HPV Vaccination in Switzerland: Knowledge, Attitude, and Effectiveness

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"HPV Vaccination in Switzerland: Knowledge, Attitude, and Effectiveness"

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HPV Vaccination in Switzerland: Knowledge, Attitude, and Effectiveness

Doctorate Thesis

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List of publications, manuscripts in preparation, submitted manuscripts, oral and poster communications related to the thesis.

I. Publications Peer Reviews composing this thesis:

- **Jeannot E**, Viviano M, de Pree C, Amadane M, Kabengele E, Vassilakos P, et al. Prevalence of Vaccine Type Infections in Vaccinated and Non-Vaccinated Young Women: HPV-IMPACT, a Self-Sampling Study. *Int J Environ Res Public Health. 2018;15(7)*. Impact Factor : **2.4**
- **Jeannot E**, Viviano M, Follonier MC, Kaech C, Oberhauser N, Mpinga EK, et al. Human Papillomavirus Infection and Vaccination: Knowledge, Attitude and Perception among Undergraduate Men and Women Healthcare University Students in Switzerland. *Vaccines*. *2019;7(4)*. Impact Factor : **4.7**
- Amadane M, de Pree C, Viviano M, Vassilakos P, **Jeannot E**, Petignat P. Characteristics of HPV-unvaccinated undergraduate health students in Switzerland, a cross sectional study. *Arch Public Health. 2019;77:29.*

II. Other Publications Peer Reviews related to this thesis:

1. Viviano M, Catarino R, **Jeannot E**, Boulvain M, Malinverno MU, Vassilakos P, et al. Self-sampling to improve cervical cancer screening coverage in Switzerland: a randomised controlled trial. Br J Cancer. 2017;116(11):1382-8. Impact Factor : **5.4**

2. **Jeannot E**, Huber T, Casillas A, Wolff H, Getaz L. Immunisation coverage among adolescents in a Swiss juvenile correctional facility. Acta Paediatr. 2016;105(12):e600-e2. Impact Factor : **2.26**

3. **Jeannot E**, Petignat P, Sudre P. Successful implementation and results of an HPV vaccination program in Geneva Canton, Switzerland. Public Health Rep. 2015;130(3):202-6. Impact Factor : **2.039**

III. Other manuscripts submitted for publication peer review related to this thesis:

1. Balla C, Viviano M, Vassilakos P and Petignat P and **Jeannot E**. Should we vaccinate boys against HPV? *Vaccines (2019)*

2. **Jeannot E,** Benski AC, Viviano M, Vassilakos P and Petignat P. Digital visual inspection using smartphone application: an innovative tool to cervical screening in low- and middle-income countries. *BMJ Innovations (2019)*

IV. Oral communications and posters related to the thesis:

1. **Jeannot Emilien,** and al. Human Papillomavirus infection and vaccination: knowledge, attitude and perception among undergraduate men and women healthcare university student in Switzerland. *Geneva Health Forum, 2020*

2. **Jeannot Emilien,** and al. Comparison of HPV prevalence between HPV-vaccinated and non-vaccinated young adult women. Clinical Research Day. *University Hospital of Geneva, 2019.*

3. **Jeannot Emilien,** and al. Acceptability and effectiveness of HPV self-sampling for monitoring the early impact of the HPV vaccination program on public health in Switzerland: HPV- IMPACT study. *Swiss Francophone Group of the Swiss Society of Gynecology and Obstetrics, 2018*

4. **Jeannot Emilien,** and al. Prevalence of vaccine type infections in vaccinated and non-vaccinated young women: HPV- IMPACT, a self-sampling study. *Geneva Health Forum, 2018*

5. **Jeannot Emilien,** and al. Evolution of Prevalence of vaccine type infections in vaccinated and non-vaccinated young women. *Swiss Public Health Conference, 2018*

Abstract

Background:

Human Papillomavirus (HPV) accounts for nearly all cases of cervical cancer and is responsible for causing several other cancers including: penile, vaginal, vulval, anal and oropharynx including base of the tongue and tonsils. There are over 200 types of HPV, which are categorized into high risk, and low risk groups according to their oncogenic potential. Among high risk HPV types, type 16 and type 18 are the most common and carcinogenic. Combined, these two HPV types are responsible for about 70% of cervical cancer cases in developed country.

Every year in Switzerland, 260 women develop cervical cancer, nearly 90 of them dying of the disease. It is a cancer that affects young women, ranking fourth in order of frequency of female cancers in the 20 to 49 age group. Several vaccines have been put on the market to prevent this infection. HPV vaccinations began in Switzerland in 2007, and progressively, vaccinated girls arrived at the age of their first screening. The next challenge will be to reconcile these two prevention methods, vaccination and screening, which are the pillars of primary and secondary HPV prevention.

There are numerous purposes for this research: We wanted to know if, since its introduction in vaccination programs in 2007, we could observe a reduction in the prevalence of oncogenic HPV in vaccinated populations compared to unvaccinated populations. We wanted to know if, to evaluate this likely reduction in the prevalence of vaccinated young women, we could use self-sampling technology as a tool for evaluating the effectiveness of the vaccine in real population. We also wanted to assess the knowledge and attitudes on this infection and vaccination for a target audience of midwifery students and nurses. For an immunization program to be efficient, primary health care providers, including paramedics, must be involved in this program and have a basic knowledge of this vaccination to effectively inform the rest of the population.

Methods

Our research included two different studies:

The first objective was to assess the prevalence of HPV in a population of young women aged 18-31, in nursing, midwifery, and medical training. The participants carried out an HPV self-

sampling at home and sent it directly to the Geneva hospital to obtain their result without going through their gynecologist.

The second study aimed to assess the knowledge and attitudes about HPV infection and the vaccination against it in a population of student nurses and midwives in training.

Results

These two studies gave us a lot of information about HPV vaccinations in Switzerland. There is a statistically significant decline in the prevalence of HPV strains in vaccinated girls compared to those who are not vaccinated. 7.2% of unvaccinated women were HPV 16- or 18-positive, while 1.1% of vaccinated women were infected by HPV 16 or 18 ($p<0.01$). Prevalence of HPV 6 and 11 was 8.3% in non-vaccinated women versus 2.1% in vaccinated women ($p<0.02$). No particular socioeconomic profiles were identifiable among unvaccinated young women in this study. Another extremely interesting aspect is that self-sampling was shown to be a simple and powerful technology for effectively monitoring an HPV vaccination program.

In the second study, we found that nurses and midwives had little knowledge to misinformation about HPV infection and the vaccination against it when they are a primary target of this vaccination and important future stakeholders for its promotion within the general population.

Conclusion:

The conclusions of this research work are that, given the effectiveness of this vaccine for reducing the prevalence of HPV strains, it must be better implanted and promoted in the general population. The target population must be better informed about HPV-related infections and the benefit from getting vaccinated against it in order to increase the vaccination coverage rate. Finally, the use of self-sampling will have to be part of a broader program to monitor the effectiveness of vaccination.

Résumé

Abstract

Contexte

Le virus du papillome humain (VPH) représente presque tous les cas de cancer du col de l'utérus et il est le responsable de plusieurs autres cancers, dont celui du pénis, du vagin, de la vulve, de l'anus et de l'oropharynx, dont la base de la langue et les amygdales. Il existe plus de 200 types de VPH, qui sont classés en groupes à risque élevé et à faible risque selon leur potentiel oncogène. Parmi les types de VPH à risque élevé, les types 16 et 18 sont les plus courants et les plus cancérigènes. Ensemble, ces deux types de VPH sont responsables d'environ 70 % des cas de cancer du col de l'utérus dans les pays développés.

Chaque année en Suisse, 260 femmes développent un cancer du col utérin et près de 90 d'entre elles décéderont de la maladie. Il s'agit d'un cancer qui touche les femmes jeunes, ce qui le place en quatrième position par ordre de fréquence des cancers féminins dans la tranche d'âge entre 20 et 49 ans. Plusieurs vaccins ont été mis sur le marché pour prévenir cette infection. La vaccination anti-HPV a débuté en Suisse en 2007 et, progressivement, les jeunes filles vaccinées arriveront à l'âge de leur premier dépistage. Le défi à venir sera de réussir à concilier ces deux modes de prévention que sont la vaccination et le dépistage, qui sont les piliers de la prévention primaire et secondaire contre le HPV.

Le but de ce travail de recherche était multiple, nous voulions savoir, si depuis son introduction dans les programmes de vaccination en 2007, nous pouvions observer une réduction de la prévalence des HPV oncogènes dans les populations vaccinées comparées aux populations non vaccinées. Nous voulions savoir si pour évaluer cette probable réduction de la prévalence chez les jeunes femmes vaccinées, nous pourrions utiliser la technologie du self sampling comme outil d'évaluation de l'efficacité du vaccin en population réel. Nous avons voulu également évaluer les connaissances et attitudes concernant cette infection et cette vaccination pour un public cible d'étudiants-es sage-femme et infirmières. Pour qu'un programme de vaccination soit efficient, il faut que les acteurs primaires de santé, notamment paramédicaux, soient engagés dans ce programme et disposent des connaissances de base sur cette vaccination pour informer efficacement le reste de la population.

Méthodes

Notre recherche a compris deux études différentes :
La première avait pour objectif d'évaluer la prévalence des HPV dans une population de jeunes femmes de 18-31 ans, en formation d'infirmière, sage-femme et de médecin. Les participantes réalisaient un auto-prélèvement HPV à domicile et l'envoyaient directement à l'hôpital de Genève pour avoir leur résultat sans passer par leur gynécologue.
La deuxième étude avait pour objectifs d'évaluer les connaissances et attitudes au sujet de l'infection aux HPV et de sa vaccination dans une population d'étudiants hommes et femmes infirmiers et sage-femme en cours de formation.

Résultats

Ces deux études nous ont donné beaucoup d'information sur la vaccination HPV en Suisse. On peut observer une baisse statistiquement significative de la prévalence des souches HPV chez les jeunes filles vaccinées comparé à celles qui ne sont pas vaccinées. 7,2 % des femmes non vaccinées étaient positives pour le VPH 16 ou 18, tandis que 1,1 % des femmes vaccinées étaient infectées par le VPH 16 ou 18 ($p<0,01$). La prévalence des VPH 6 et 11 était de 8,3 % chez les femmes non vaccinées contre 2,1 % chez les femmes vaccinées ($p<0,02$). Nous n'avons pas observé de profil socio-économique particulier identifiable chez les jeunes femmes non vaccinées lors de cette étude. Un autre aspect extrêmement intéressant est que nous avons observé que le self sampling est une technologie simple et performante permettant de monitorer efficacement un programme de vaccination HPV.

Dans la deuxième étude, nous avons constaté une faible connaissance des jeunes hommes et femmes infirmièr-eres et sage-femme concernant cette infection par HPV et sa vaccination voire même des connaissances erronées alors qu'ils sont une cible principale de cette vaccination et des futurs acteurs important pour sa promotion dans la population générale.

Conclusion

Les conclusions de ce travail de recherche sont que, vu l'efficacité de ce vaccin pour la réduction de la prévalence des souches HPV, il faut que celui-ci soit mieux implanté et promut dans la population générale. Une meilleure information du public cible sur les infections liées aux HPV et le bénéfice de sa vaccination doit être fait pour pouvoir augmenter le taux de

couverture vaccinal. Enfin l'utilisation du self sampling devra s'inscrire dans un programme plus large de monitoring de l'efficacité de la vaccination

OUTLINE

Introduction

HPV's Natural History

Papillomaviruses are responsible for a wide variety of cutaneous and mucosal lesions in human beings. Similar lesions induced by related viruses are also known in the animal kingdom: in rats/mice, rabbits, sheep, oxen, horses, deer, fallow deer, dogs, monkeys, as well as birds and turtles(1).

In the last 20 years, more than 200 genotypes of human papillomavirus (HPV) have been identified. Genotypes are classified according to their tropism (skin, mucous membranes) and their oncogenic potential (2). Two major classes are listed:

- HPV preferentially associated with cutaneous lesions. HPV types 1 and 4, for example, are frequently found in warts, while HPV types 5 and 8 are implicated in verruciform epidermodysplasia (3).

- HPV infecting anogenital mucosa (cervix, vulva, vagina, penis, and anus) and oropharyngeal mucosa. Among the forty viruses with this tropism, some are said to have low risk or low oncogenic potential: this is the case of HPV 6 and 11, commonly found in genital warts, while others are said to be high risk: this is the case of HPV 16 and 18 involved in the carcinogenesis of the cervix. This latter group also includes so-called intermediate risk HPV: HPV 31, 33, 35, 51... frequently found in anogenital lesions(4).

The diversity of HPV types probably results from their evolution in different human epithelia.

Characteristics of Papillomaviruses

Papillomaviruses are small (45-55 nm in diameter), non-enveloped viruses, composed of 72 capsomers arranged in icosahedral symmetry. Their genome consists of a circular double-stranded DNA molecule of approximately 8,000 base pairs (5). (see Figure 1)

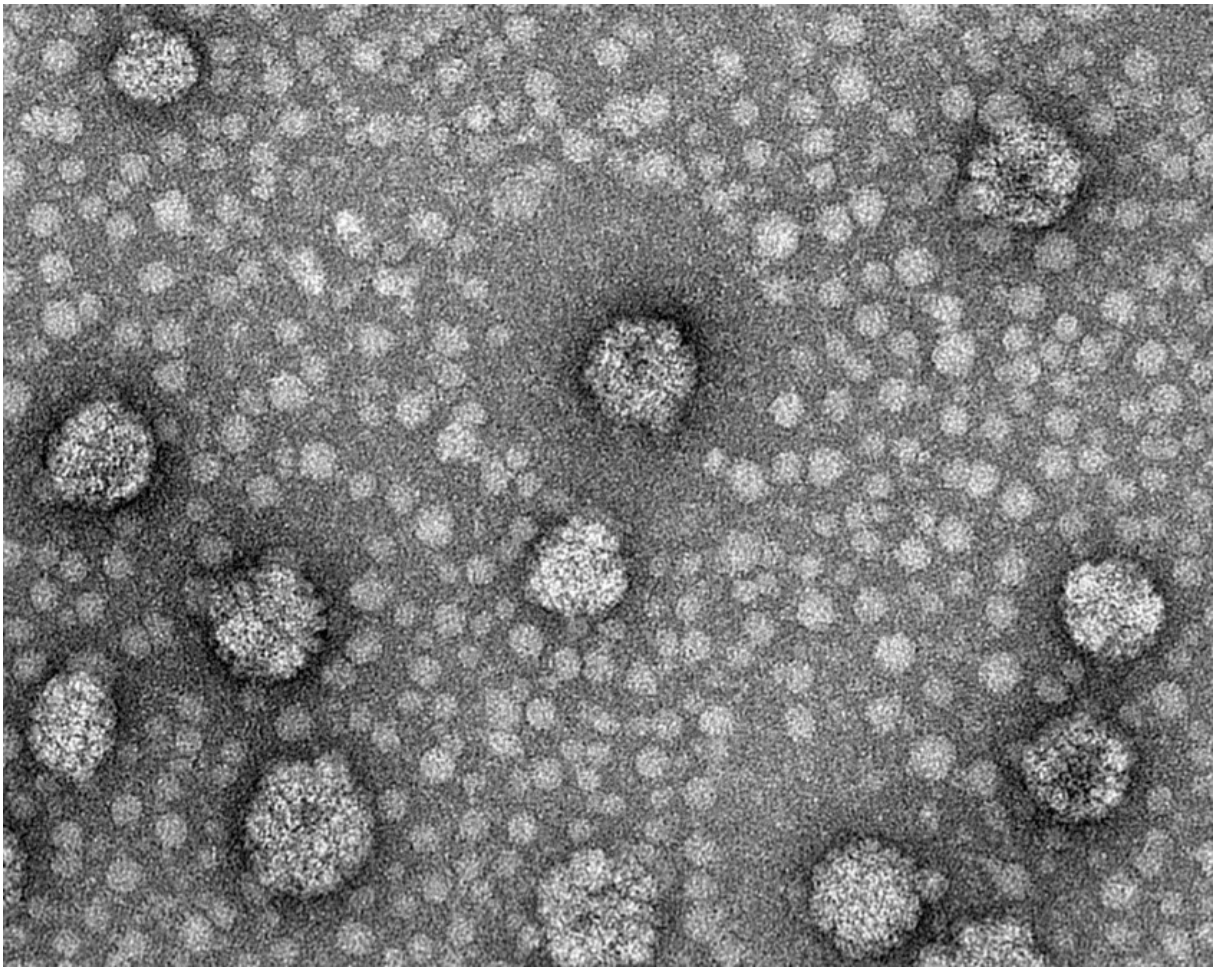

Figure 1 - Virus-Like Particles of HPV - 16 L1 Protein (copyright BMJ publishing group)

Comparative analysis of the nucleotide sequences of papillomaviruses in different species revealed a common genetic organization. About ten open reading frames carried by only one of the two DNA strands are grouped into an E *(early)* region encoding nonstructural proteins and an L *(late)* region encoding the capsid proteins. The non-coding region (NCR) comprising 400 to 1,000 nucleotides and located between the POL L1 and POL E6/E7 sequences. It contains an ori site (site of origin of viral replication), promoters of early genes, and regulatory sequences of replication and transcription. These sequences are sites recognized by factors of cellular or viral origin. Some cellular factors (for example: steroid receptors) activate the transcription of viral genes, while others (for example: retinoic acid receptors) inhibit it. E2 viral protein is involved in both replication and modulation of HPV genome transcription (6). Viral replication is tightly controlled by the E1 protein, coupled to the E2 protein. The heterodimer E1-E2 binds to the ori sequence which has a binding site for E1 (E1BS: E1 *binding*

site), itself flanked by several E2 binding sites (E2BS). A mutation in the E1BS site or mutations of the E1 and/or E2 proteins are accompanied by a decrease or even a stop of the viral replication(7).

The E2 protein, acting as a homodimer, modulates the transcription of the E6/E7 genes; it blocks the expression of these genes. As for the E4 protein, it is expressed differently in cutaneous lesions and mucosal lesions. In palmar and plantar warts related to HPV 1, it is synthesized in large quantities. It is present in a much smaller amount in mucosal lesions. It allows the production of viral particles, facilitating the encapsidation of the genome and promoting the diffusion and release of virions by destruction of the network of cytokeratin filaments. E5, E6 and E7 proteins are involved in cellular immortalization and transformation processes (8).

L1 protein is the major capsid protein. Capable of self-assembling in the absence of other viral proteins to form viral capsid-like viral particles known as virus-like *particles (VLPs)*, these L1 proteins have the same conformational epitopes as the native protein and are highly immunogenic. They are a source of antigens for the development of ELISA serological tests and for the production of vaccines. The L2 protein, a minor capsid protein, is capable of binding viral DNA and positioning it correctly within the capsid. In combination with the L1 protein, it allows the assembly of the virus and the stabilization of the capsid (9) (See Figure 2).

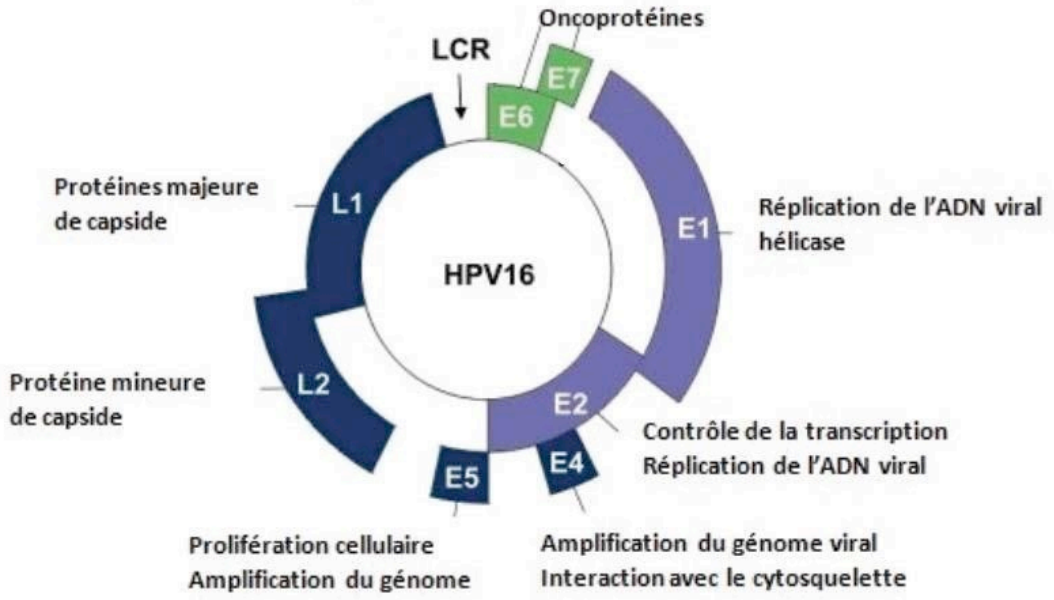

Figure 2 - HPV 16 Circular Genome Diagram

The HPV Infection's Natural History

Infection occurs in three major stages: infection of cells by HPV, implosion of the cell with the appearance of virions, and finally, infection of cells by these virions.

The infections of the cells by the virus and the virions are the same. The only difference is that virions are viral particles resulting from the implosion of cells due to infection by viruses. There are six major steps in the infection of a cell regardless of the genome of the virus. We have an attachment, a penetration, a decapsidation, a replication, an encapsidation, and then a release. It is with replication that the genome of the virus brings a slight modification to the mechanism(10). In fact, when the genome is RNA, it is immediately read by the ribosomes as is: it is the translation of the viral messenger RNA. But the papillomavirus is a DNA virus. This means that it does not use RNA during its replication but instead it's DNA polymerase. DNA polymerase is an enzymatic complex that allows the replication of DNA and therefore of the virus. These viruses must therefore first go through a transcription step before the translation of their viral messenger RNA. The cell releases the virions after infection(11).

The infection can evolve according to 2 modes: the clearance or the persistence. The majority of risky HPV infections evolve in clearance mode, particularly in young people under 30 years of age, as it progresses to persistence after this age, especially for HPV 16, 9, 10. The persistence means morphological transformations testifying to the expression of the E6 and E7 genes of the papillomaviruses at risk and thus cellular anomalies. At this stage, HPV is episomal or integrated with the genome of the cells (12).

After the infection of several cells, we have dysplasias. Low grade dysplasia occurs when only one third of the cells are infected and "high grade" dysplasias if two-thirds or all of the cells are infected. The "low grade" dysplasia corresponds to grade 1, "high grade" corresponding to grades 2 and 3. These last two grades are distinguished by the number of lesions, i.e. the extent of the dysplasias(13). (see Figure 3)

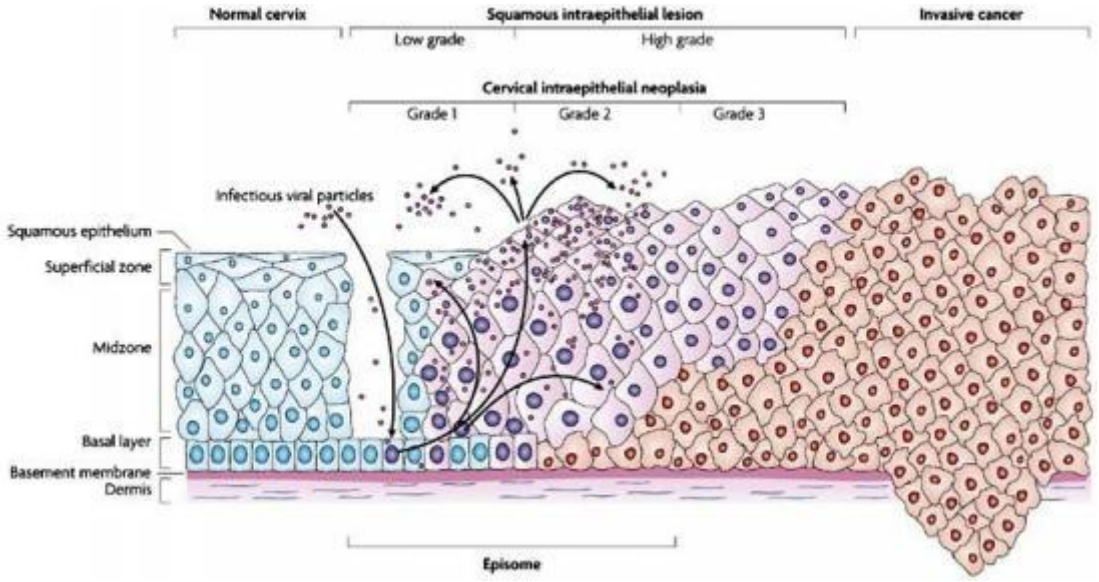

Figure 3 - Epithelial Degradation Graph

How does an HPV infection result in cervical cancer?

After the onset of sexual activity, infection with one or more HPV of different types occurs quickly in most individuals. HPV infection is almost always transient: more than 90% of HPV infections are eliminated within 1-2 years. In <10% of those infected, the virus persists and can lead to precancerous lesions (cervical, vaginal, vulvar, anal, abbreviated CIN, VAIN, VIN, AIN) and, if left untreated, cancer. An average of 20-30 years (and at least 5-10 years) separate the infection and development of cervical cancer(14) (see Figure 4). No specific antiviral treatment is available.

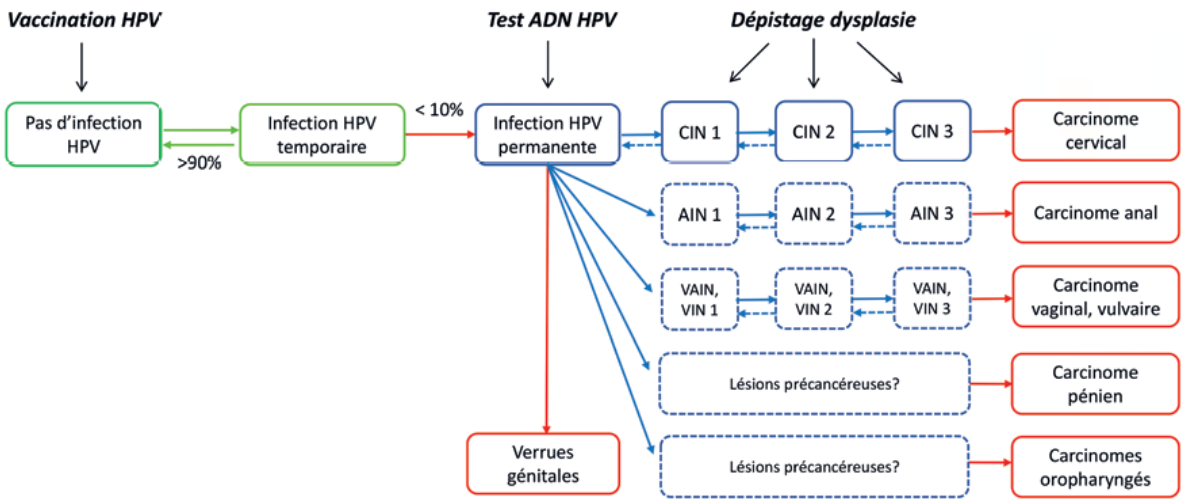

Figure 4 - Natural Evolution of the HPV Infection

History of HPV Vaccines

The identification of the causal agent of cervical cancer was developed in the 1970s with large epidemiological cohorts that demonstrated the major risk of cervical cancer attributed to at-risk HPV and the carcinogenic role of these viruses on the host cells, followed by the use of the viral test in clinical practice to optimize the management and screening (15).

It has long been difficult to develop, in practice, HPV vaccines because these viruses cannot reproduce in cell culture. Live attenuated vaccines from this manufacturing process would have contained potentially oncogenic viral genes that precluded their preventive use in healthy women. Progress emerged as soon as it became possible to produce a recombinant protein of the virus envelope in mammalian cells(16). Attention has therefore turned to the development of subunit vaccines based on the production of a protein that makes up the viral envelope, the L1 protein. Early attempts to produce this protein from bacteria failed because the purified protein was most often malformed and did not induce sufficient antibody production in animal models. Progress came with the discovery of the phenomenon of the unfolding and spontaneous self-assembly of the L1 envelope protein. It has been observed that once produced, this protein has the spontaneous capacity to self-arrange to form a spherical envelope, quite similar to that of the virus. These pseudoviral particles resembled the virus, but did not contain its genetic material. In fact, whether inoculated to animals or humans, they do not cause the disease, but instead, elicit an immune response strong enough to eliminate the virus. It is from this important innovation based on the production of VLPs *(Virus Like Particle*- viral particles that mimic the virus) that the principle of vaccination against papillomavirus was born. These particles are not infective because they contain no genetic material. They deceive the immune system which sees them as viruses and produces high levels of antibodies without generating the disease (17-19).

HPV Preventive Vaccines

The development of vaccines is based on the discovery of the phenomenon of spontaneous self-assembly of the major protein of the L1 capsid. Thus, this protein can be produced in order to generate particles reminiscent of the virus (virus like particles). They are non-infectious, but

induce an immune response with antibody production in the hosts. Two preventive vaccines against papillomavirus have been developed through clinical trials phase I, II, and III (20):

A. Cervarix® (GlaxoSmithKline Biologics, Rixensart, Belgium): This is a bivalent vaccine against types 16 and 18 of the virus; this vaccine is little used and no longer available in Switzerland.

B. Gardasil® (Merck & Co., Inc., Whitehouse Station, NJ): This is a quadrivalent vaccine directed against types 6, 11, 16, and 18 of the virus, the former two being responsible for most of the condyloma acuminata.

These vaccines are non-infectious because they do not contain viral DNA. The vaccine is administered by intramuscular dose, 0.5 ml. The vaccines are generally well tolerated, highly immunogenic with a much higher level of antibodies produced than those observed during natural infection. After four to five years, these antibody levels persist (21).

Another vaccine against 9 types HPV infections (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) has also been available since 2018 in Switzerland. It is called Gardasil 9. This nonavalent vaccine is added to Gardasil 4, the quadrivalent vaccine (HPV 6, 11, 16, 18) marketed since 2007 and Cervarix, the bivalent vaccine (HPV 16, 18) available since March 2008.

Gardasil 9 is indicated for the active immunization of individuals as of 11 years old. According to current vaccination recommendations, HPV vaccination initiations for unvaccinated girls and young women should now be conducted with Gardasil 9. In the long term, Gardasil 9 is intended to replace Gardasil 4. The latter however remains on the market as long as necessary so that individuals who started with this vaccine can finish it. The Gardasil 4, Gardasil 9, and Cervarix vaccines are actually not interchangeable and any vaccination initiated with one must be completed with the same vaccine (22, 23).

HPV Vaccination Efficiency

In countries where HPV vaccinations have been introduced for a long time and has achieved high vaccination coverage (i.e. Australia), HPV infections in the vaccine have, in 3 years, almost completely disappeared from cervical smears. In women who had been vaccinated

before first intercourse, there was 85% to 90% reduction in HPV 16/18-related higher grade dysplasias in the cervix (CIN2 or higher), vulva, and vagina. This reduction seems clearly attributable to HPV vaccination and not to a change in screening or sexual behavior (24, 25).

Currently, the effect of vaccination on the reduction of precancerous lesions is proven. The first data on the prevention of cervical cancer by vaccination is expected around 2020. However, the importance of the effect of vaccination on dysplasia should not be underestimated as the diagnosis of a precancerous lesion can trigger stress and anxiety when dysplasia is discovered, and dysplasiac interventions of the cervix also increase the risk of spontaneous abortion or premature birth (24, 26).

In 2018, the Australian government said that Australia is eradicating cervical cancer and that this goal will be achieved in the next 20 years. "Australia is likely to be the first country to reach the HPV elimination threshold," says Megan Smith, co-author of a study in Lancet Public Heath modeling HPV eradication in Australia (27, 28).

HPV Vaccine Safety

Led by the Global Advisory Committee on Vaccine Safety (GACVS) at the World Health Organization (WHO), all agencies that review and monitor the safety of the HPV vaccine continue to conclude that HPV vaccines are safe and effective and that the benefits of its use are significantly greater than the risks.

Global and national review and surveillance systems for the safety of new vaccines are complex. Before a vaccine is approved by WHO or a national licensing agency, objective experts examine its efficacy, safety, and adverse events through extensive clinical trial data. If this data is sufficiently substantiated, the product is licensed. A second phase of surveillance begins once the product is available to the public(29).

Data on the safety of HPV vaccines prior to authorization came from clinical trials that included more than 10,000 girls and young women for each of the two vaccines. Between authorization in June 2006 and May 2009, 24 million doses of Gardasil 4 were distributed in the United States and more than 40 million doses were distributed worldwide. Seven million doses of Cervarix® were distributed worldwide in May 2009.Since the introduction of HPV vaccines in the United States, Australia, Europe, and a growing number of middle-income countries, many national and international agencies have been rigorously monitoring the safety of the HPV vaccine.

These agencies track all reports of adverse events to determine if the problem was caused by the vaccination or not (30-32). They are also working together to ensure that recommendations around the use of the HPV vaccine take into account the latest safety results.

HPV Vaccinations in the World

Since HPV vaccines first licensure in 2006, at least 82 countries have included HPV vaccines in their national immunization programs (see Figure 5). The introduction has been progressive, predominantly in high-income western countries first, followed by Latin American countries alongside scattered countries from the remainder of the regions. Its addition to the national schedules of so many countries can be thus considered a significant achievement (24, 33).

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Americas	**USA**	**Canada**	Panama			Argentina Guyana Peru	Colombia Mexico	Paraguay Suriname **Trinidad & Tobago** **Uruguay**	**Barbados** Brazil **Chile**	**Bahamas** Ecuador	**Antigua& Barbuda** Belize Honduras
Europe		**Belgium** **France** **Germany** **Italy** **Spain**	**Greece** **Liechenstein** **Luxembourg** **Portugal** Romania **San Marino** **Switzerland** **UK**	**Denmark** Macedonia **Norway** **Russia(P)** **Slovenia**	**Ireland** **Latvia** **Netherland** **Sweden**	**Iceland** **Monaco**	Bulgaria **Czech Rep.** **Malta**	**Finland**	**Andorra** **Austria** Hungary **Slovakia**		**Croatia** **Cyprus** **Lithuania**
Africa						Rwanda	Lesotho Uganda	Libya	Seychelles South Africa	Botswana	Sao Tome & Principe Senegal
Asia			**United Arab Emirates (P)**		Buthan Malaysia **Singapore**	**Japan**	**Brunei**	**Israel** Kazakhstan(P)			Philippines **R.Korea** Turkmenistan
Oceania		**Australia**	Marshall Is. **New Zealand**	Micronesia Palau		Kiribati		Fiji		Vanuatu	

(P) = Partially introduced
Bold = High income countries

Figure 5 - Countries Including HPV Vaccine in their National Immunization Programs by Year of Introduction.

The Vaccination in Switzerland

Since 2007, HPV vaccinations are recommended by the Federal Office of Public Health (FOPH) and the Swiss Federal Commission for Vaccination (CFV), initially only for girls and women, though boys and men have been included since 2015. As a first step, two vaccines were available, one (Cervarix) covering the oncogenic HPVs 16 and 18, the other (Gardasil 4) also covering HPVs 11 and 6, which mainly cause genital warts (34). In recent years, there has been

a new vaccine, which protects against five other types of oncogenic HPV: 31, 33, 45, 52, and 58 (Gardasil 9). This nonavalent vaccine has been available in Switzerland since July 2018.

Girls aged 11 to 14 are the main target group for HPV vaccination (basic recommended vaccination, two-dose regimen). The FOPH and the CFV also recommend the vaccination of adolescent girls aged 15 to 19 (catch-up vaccination), as well as that of adolescents and men between 11 and 26 years old and women between 20 and 26 years of age (supplementary vaccination, three-dose treatment plan). The levels of recommendations are based, among other things, on the burden of pathologies respectively of the usefulness of vaccination for the different target groups (35).

The Thesis Objectives:

The main objective of this thesis was to study the effectiveness of the HPV vaccine (mainly Gardasil 4, which was only used in Switzerland during this research project) among young women, but also to evaluate the knowledge, attitudes, and representations on/of HPV infections and HPV vaccinations that had an audience of future midwives and nurses.

The secondary objectives of these studies were to assess whether self-sampling technology could be used as a monitoring tool for this vaccination. Finally, we wanted to know if a socio-demographic profile could emerge in unvaccinated young women to improve the promotion of this vaccination in these populations.

Methodological Contributions:

Article 1: Prevalence of Vaccine Type Infections in Vaccinated and Non-Vaccinated Young Women: HPV-IMPACT, a Self-Sampling Study

The objective of evaluating the effectiveness of HPV vaccinations in real population follows previous studies in which I participated with Professor Petignat. I had already carried out several epidemiological studies on HPV vaccination coverage in Switzerland (34-36), and I participated in a study with Pr. Petignat that focused on the detection of HPV infections using self-sampling(37). For several years, Professor Petignat's team has developed expertise on the use of self-sampling to increase the participation and effectiveness of HPV screening and cervical cancer control programs.

At the beginning of this thesis, no study in Switzerland had attempted to evaluate the effectiveness of this vaccination in the population. We therefore hypothesized that self-sampling could be used both as a screening tool and as a monitoring tool for HPV vaccinations. When this project started, only one other study in the world had used this methodology for self-sampling. This study, carried out in Canada, had obtained very positive results and opened the possibility of using self-sampling to monitor HPV vaccinations.

Self-sampling:

The self-sampling is a simple and economical technique commonly used for the detection of numerous infectious diseases and especially for HPV virus screening. It is in the form of a swab (see Figure 6). The patient performs a vaginal swab by following a simple, explained procedure. No medical training is required to perform this sample. Several meta-analyzes show that this technique is as accurate and reliable as if the sample was taken by a gynecologist (38-40). Its huge advantage is that the patient can directly send their sample to a laboratory to find out whether or not they are a carrier of HPV without the need for a gynecologist.

The use of self-sampling to improve the effectiveness of HPV screening is clearly introduced in scientific literature (41-43), but its use as a tool for assessing HPV vaccinations is yet to be demonstrated.

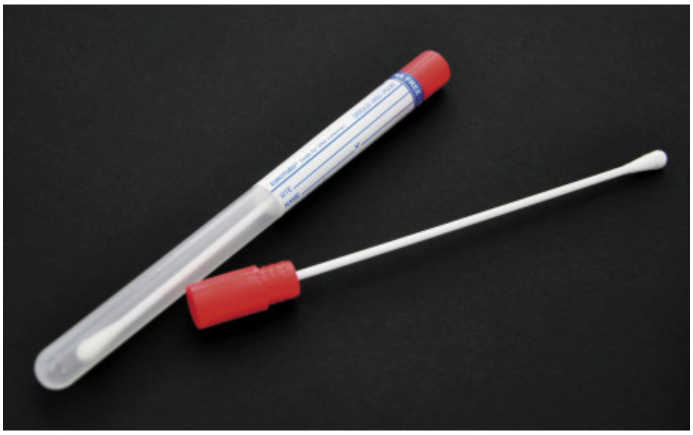

Figure 6 - Example of self-sampling for HPV Screening

My Role in This Study:

To carry out this study, we had the help of two medical Master's Degree students who were majoring on this subject. For this first study, we chose as our target population the students Geneva Graduate School of Health (Haute École de Santé de Genève), made up of student midwives, nurses, and dieticians as well as students in their 1st and 2nd year of medicine. We made this pragmatic choice because we had the support of these institutions to carry out this study.

I wrote the study protocol with Professor Petignat's research team. This protocol has been accepted by the Cantonal Commission for Research Ethics of the Canton of Geneva. This protocol, once accepted, was filed on clinicaltrial.gov to comply with current research ethics recommendations.

Data Collection:

In agreement with the research team, I took care of the data collection of the students of the Geneva Graduate School of Health. After sending the students the information about the study, the questionnaire, the self-sampling material, and getting their consent to participate, I collected the participants' swabs. The two medical students collected the data of their 1st and 2nd year colleagues.

A socio-demographic questionnaire on the participants' profile, their last vaccination and, for those who were not vaccinated, the reasons for non-vaccination accompanied the self-sampling kit. The questionnaire was made by synthesizing the questions of previous studies that seemed to be the most relevant.

Sample Size:

To estimate the sample we needed, we started from an estimate of the prevalence of HPV 16/18 of 6% in the population of young women under 30 years old from the information given by the Federal Office of Public Health. Hoping for a reduction in HPV prevalence of at least 85% in the vaccinated population, we needed 400 participants for the study.

Given the efficiency goal of this study, we decided to name it HPV-IMPACT.

Article 2: Human Papillomavirus Infection and vaccination: knowledge, attitude and perception among undergraduate men and women healthcare university student in Switzerland

This second study follows directly on the first one. One of the key findings of the HPV-IMPACT study was that a typical profile could not be identified for unvaccinated young women. The socio-demographic profile between vaccinated and unvaccinated young women was almost identical. An important finding was that a common reason cited by young women for not being vaccinated was their poor knowledge of cervical cancer and HPV vaccination.
We therefore conducted a second study on paramedical students to assess their level of knowledge about HPV infections, cervical cancer, HPV vaccination, and their attitude towards this HPV vaccine during their nursing and midwifery studies.

I was responsible for drafting the protocol for the study, which was accepted by the Cantonal Research Ethics Commission of the Canton of Geneva and filed on clinicaltrial.gov

For this study, the data collection as well as the consent of the participants was done entirely via a web platform.

Data Collection:

For practical questions, we decided to make this study 100% electronic via a secure online platform. I created the questionnaire of this study which was separated into three parts.
The first part looked at the socio-demographic characteristics of the participants, the second part at the participants' basic knowledge about HPV infection and the HPV vaccine, and the last part at the participants' attitudes towards HPV vaccinations.
The validity of this questionnaire was evaluated by three experts on the subject (a nurse, a midwife, and an epidemiologist). A pilot study of a midwife and nurse sample was conducted to test the validity and comprehension of the questionnaire. For this questionnaire, we conducted a literature review of previous studies that also aimed to assess knowledge, attitudes, and perceptions about HPV infection and HPV vaccinations.

In addition, using these two studies, we conducted a third study included in HPV Impact. The objective of this study was to compare the socio-demographic characteristics of vaccinated and unvaccinated young women in the IMPACT study. The other objectives of this study were to know the reasons given by young women for not being vaccinated and to compare the reasons given in this study with those found in other studies in Switzerland.

Publications Peer Reviews composing this thesis:

- **Jeannot E**, Viviano M, de Pree C, Amadane M, Kabengele E, Vassilakos P, et al. Prevalence of Vaccine Type Infections in Vaccinated and Non-Vaccinated Young Women: HPV-IMPACT, a Self-Sampling Study. *Int J Environ Res Public Health. 2018;15(7)*. Impact Factor : **2.4**
- **Jeannot E**, Viviano M, Follonier MC, Kaech C, Oberhauser N, Mpinga EK, et al. Human Papillomavirus Infection and Vaccination: Knowledge, Attitude and Perception among Undergraduate Men and Women Healthcare University Students in Switzerland. *Vaccines*. *2019;7(4)*. Impact Factor : **4.7**
- Amadane M, de Pree C, Viviano M, Vassilakos P, **Jeannot E**, Petignat P. Characteristics of HPV-unvaccinated undergraduate health students in Switzerland, a cross sectional study. *Arch Public Health. 2019;77:29.*

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Article

Prevalence of Vaccine Type Infections in Vaccinated and Non-Vaccinated Young Women: HPV-IMPACT, a Self-Sampling Study

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Abstract: Background: The human papillomavirus (HPV) vaccination program for young girls aged 11–26 years was introduced in Switzerland in 2008. The objective of this study was to evaluate the prevalence of high- and low-risk HPV in a population of undergraduate students using self-sampling for monitoring the HPV vaccination program's effect. **Methods:** Undergraduate women aged between 18–31 years, attending the Medical School and University of Applied Sciences in Geneva, were invited to participate in the study. Included women were asked to perform vaginal self-sampling for HPV testing using a dry cotton swab. **Results:** A total of 409 students participated in the study—aged 18–31 years—of which 69% of the participants were vaccinated with Gardasil HPV vaccine and 31% did not received the vaccine. About HPV prevalence, 7.2% of unvaccinated women were HPV 16 or 18 positive, while 1.1% of vaccinated women were infected by HPV 16 or 18 ($p < 0.01$). Prevalence of HPV 6 and 11 was 8.3% in non-vaccinated women versus 2.1% in vaccinated women ($p < 0.02$). We observed no cross-protection for the other HPV genotypes of a low- and high-risk strain. **Conclusions:** Prevalence of HPV 6/11/16/18 was lower in vaccinated women versus unvaccinated women. Continued assessment of HPV vaccine effectiveness in real population is needed.

Keywords: HPV; self-sampling; vaccination

1. Introduction

Cervical cancer is one of the leading causes of cancer-related death among women worldwide [1]. The development of cervical precancerous and cancerous lesions is a direct consequence of genital human papillomavirus (HPV) infection, which has been identified as the most common sexually transmitted infection in the world [2]. The introduction of HPV vaccinations represents a primary preventive measure, which, if given to young girls prior to the onset of sexual activity, can potentially alleviate the burden of the HPV infection [3]. Recent studies have predicted that cervical cancer rates

will be drastically reduced in about 10–15 years, thanks to the impact of the HPV vaccination and HPV-based screening [4].

In the United States, where the HPV vaccination was introduced in 2006, the population-based sentinel surveillance system has shown that the prevalence of HPV-16/18 in cervical intra-epithelial neoplasia grade 2 or worse (CIN2+) has decreased from 53.6% to 28.4% among women who have received at least one dose of the vaccine [5]. Another trial conducted in England has found HPV-16/18 prevalence to be reduced from 19.1% to 6.5% prior to and after the introduction of the vaccine, respectively [6]. In Australia, monitoring surveillance demonstrated a very low prevalence of vaccine-related HPV genotypes after eight years post-initiation of a national HPV vaccination program [7].

About 300 women in Switzerland are diagnosed with cervical cancer annually, with a risk of 2 per 100 of dying from this disease. The HPV vaccination program for young girls aged 11–26 years was launched in Switzerland in 2008 as a part of cervical cancer prevention, with the aim to prevent cervical cancer and other HPV-related disease. The quadrivalent vaccine (targeting HPV16, 18, 6, and 11) is currently administered to girls aged 11–14 years, both in schools and in healthcare centers. While it is known that the vaccination coverage rate varies widely among the different Swiss cantons, from a minimum of 20% to as much as 60% of the target population, little is known about the vaccination's direct impact on the HPV infection rates. The differences in cantonal coverage rates can be explained by the fact that each Swiss canton organizes the vaccination campaigns and the relative program on its own, thus explaining the disparities and the lack of national coordination [8]. The lack of current data on the impact of the HPV vaccination in the country, therefore, makes it difficult to monitor the program's efficacy.

The primary aim of this study was to evaluate the prevalence of high- and low-risk HPV in a population of undergraduate students using self-sampling for HPV testing. The results of this study will allow an estimation of the HPV vaccination program's effectiveness, as well as the acceptability of HPV self-sampling as a means to track down the infection among vaccinated young girls in Switzerland.

2. Methods

2.1. Study Population and Setting

This study took place in the city of Geneva, which is situated in the canton of Geneva, Switzerland, between January 2016 and October 2017. The enrolled participants were undergraduate nurse and midwife students in their first, second, or third year of studies, as well as undergraduate students attending their first through fifth year of Medical School at the University of Geneva (years 1 to 6). All women aged 18–31 years were included; exclusion criteria were history of total hysterectomy or having undergone cervical treatment in the past 12 months.

2.2. Study Procedure

Information about the trial was delivered through the University website and by the study investigators, who sent an email to the target population describing the study and then delivered a short presentation about the study after the main course's classes.

The HPV self-collection kit was directly distributed to women who expressed an interest to participate in the study at the end of class. The kit included a dry Dacron swab; a collection tube; instructions with explanatory pictures for self-sampling; a flyer explanation about HPV infection, cervical cancer screening, and cervical cancer; an informed consent form; and a questionnaire on socio-demographics. Self-sampling was performed at home, and the kit, including both the swab and filled-out questionnaire, was collected by the study investigators two to three days later. Additional information about HPV and the test results were delivered by a designated study investigator upon request. Sampling kits were provided free of charge.

2.3. Data Collection

Each participant was asked to fill out a questionnaire reporting her socio-demographic characteristics (age, nationally), sexual behaviors (number of sexual relations, use of contraception/protection device), questions about HPV vaccination (number of doses received, name of the vaccine), and questions about her acceptability of self-sampling.

2.4. Self-Sampling Procedure and Sample Preparation

Women were asked to gently insert the swab in the vagina, while being careful to avoid contact with the external genitalia, and to carefully turn it up to five times either clockwise or counter-clockwise. They were asked to then place the swab back into the dry tube, and to securely close it and put it back into its plastic bag containing the rest of the kit's material.

Each swab was then placed into a tube containing 3 mL of ThinPrep and vortexed for 45 s. A total of 350 µL of the solution was then placed into a 5-mL, cone-shaped bottom tube (Eppendorf Tube, Merck KGaA, Darmstadt, Germany). The samples were promptly sent to Buhlmann laboratories for analysis.

2.5. Laboratory Analysis

DNA extraction was performed using the NIMBUS-IVD (Hamilton, Reno, Nevada) and the extraction reagents StarMag (Seegene, Seoul, Korea). Amplification and detection was then performed with the Anyplex™ II HPV high risk (HR) Detection (Seegene, Seoul, Korea) using the CFX96™ real-time thermocycler. Data recording and interpretation were automated. Anyplex II is a semi-quantitative real-time multiplex PCR assay for screening and HPV genotyping. This test uses dual priming oligonucleotides (DPO™) and tagging oligonucleotide cleavage and extension (TOCE™) technologies and allows the simultaneous detection and genotyping of 19 high-risk HPVs (including types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, and 82) and 9 low-risk HPVs (6, 11, 40, 42, 43, 44, 54, 61, and 70). As an internal control of assay validity, the β-globin gene is also detected. By knowing the step at which the melting curve becomes positive, semi-quantification of the DNA load of the β-globin and HPV genomes is made possible; this can vary from low (+; positive after 40 PCR cycles, $<10^2$ copies/reaction), to intermediate (++; positive within 31 to 39 PCR cycles, $\geq 10^2$ and $<10^5$ copies/reaction), to high (+++; positive before 31 PCR cycles, $\geq 10^5$ copies/reaction).

Whenever the quantity of HPV genome was not high enough to be detected by the Anyplex II device after running up to 40 PCR cycles, the test result was considered invalid. Analyses were run twice before considering the test result as "invalid".

2.6. Study Sample

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 400 specimens 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%. Therefore, we estimate that a sample size of 400 women will be adequate for the analyses.

2.7. Statistical Analyses

Statistical analyses were run using STATA 13. Normality of the distribution was tested by the Kolmogorov–Smirnov test. Descriptive statistics and frequencies were analysed for all variables. Prevalence of HPV infections was evaluated for any HPV type, low vaccinated types (6 and 11), and high-risk types (16 and 18). Low- and high-risk non-vaccine types were also evaluated. *t*-test and Chi square test were used for the descriptive statistics and for the comparison between variables. A p value of less than 0.05 was considered as statistically significant.

A multivariate logistic regression was used to compare differences in HPV prevalence between vaccinated and unvaccinated women. It was also performed to identify factors associated with HPV prevalence and socio-demographic factors. The status of HPV infection (infected or not infected) was

used as the primary outcome. In multivariable models, only those covariates that were of a priori interest of univariate analysis were included.

2.8. Ethical Approval

The study was approved by the Central Ethics Committee on Human Research of the Geneva University Hospitals (approval number: 15-257). This study was 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, Brazil, October 2013). The trial was registered under cliniclatrials.gov with the identifiers: NCT03474211.

3. Results

3.1. Participants' Socio-Demographic Characteristics

A total of 409 undergraduate students performed HPV self-sampling at home for HPV DNA testing and filled out the given questionnaire, and were thus included in the study.

The participants' baseline characteristics are presented in Table 1. The mean age was 24 years (range 18–27); 55% of the participants were medical school undergraduate students (first to sixth year of medical curriculum), the other 45% were nursing students or midwives in their first, second, or third year of their Bachelor's degree). The majority of the participants were Swiss (89%), 7% of them came from France, and 3% came from other European countries or non-European countries (South America or Africa).

A total of 80% of the participants were non-smokers and 8.6% smoked on a daily basis. Overall, 2.4% of the women reported never having had sexual intercourse; these women were nevertheless included in data analyses.

Table 1. Study participants socio-characteristics. HPV—human papillomavirus.

Characteristic	Study Population (n = 409)			
	n	% or Mean	95% Confidence Interval	
Age (mean years)		24	21.1	27.2
Recruitment site				
Faculty of medicine	225	55.0%	50.2	59.8
School of health sciences	184	45.0%	40.2	49.8
Country of birth				
Switzerland	365	89.2%	85.9	92
France	30	7.3%	5.1	10.2
Other European country	10	2.4%	1.2	4.3
other country	4	1.0%	0.3	2.3
Tobacco smoking				
Yes, every day	35	8.6%	6.1	11.6
Yes, but not every day	45	11.0%	8.2	14.3
No, never	329	80.4%	76.4	84
Have you ever had sexual intercourse				
Yes	399	97.6%	95.7	98.7
No	10	2.4%	1.2	4.3
Your age at your first sexual intercourse (mean years)				
Average	17		16.7	17.2
How many sexual partners did you have in your life (mean number of partner)				
Average	5.3		4.5	6.2
Do you use condoms as a means of protection/contraception				
Never	120	29.3%	22.7	31.4
Sometimes	90	22.0%	18.2	26.2
Often	100	24.4%	20.5	28.8
Always	99	24.2%	20.2	28.4
Have you been vaccinated against HPV				

Yes	284	69.4%	64.8	73.7
No	125	30.6%	26.4	35.2
How many doses of HPV vaccine have you received (only for vaccinated women *n* = 284)				
One	20	7.0%	7.4	14.5
two	60	21.1%	16.7	26.2
Three	204	71.8%	66.4	76.8
Your age when you receive the first dose of the HPV vaccine (mean years)				
Average	14.8		14.2	15.6
Have you checked your vaccination record to answer previous questions				
Yes	220	53.8%	49	58.6
No	189	46.2%	41.4	51.1
In general, do you think that HPV vaccination is a vaccination:				
More important than others	14	3.4%	1.9	5.5
Less important than others	74	18.1%	14.6	22
As important as the others	321	78.5%	74.3	82.3
Would you recommend to your family/friends this self-sampling as monitoring vaccination				
Yes	367	89.7%	86.5	92.4
No	42	10.3%	7.6	13.5
In case of positivity of your self-collection, we authorize you to contact you again				
Yes	405	99.0%	97.6	99.7
No	4	1.0%	0.3	2.3

3.2. Vaccination Status

Overall, 69.4% of the participants were vaccinated with a minimum of one dose (284/409). Among the vaccinated participants, 72% had received all three doses of the HPV vaccine, while 21% had received two doses and 7% had received only one dose. All participants in our study were vaccinated with Gardasil.

A total of 75% of the vaccinated students were aged 18–23 years; the vaccination coverage rate was not statistically different between the medical students and the nursing students or midwives (71% versus 67%, respectively, p = NS). The mean age at the time of first vaccination dose was 14.8 years. The majority of the participants (75%) reported that the HPV vaccination was as important as the other vaccinations recommended in Switzerland, while up to 18% of them believed that this vaccination was less important than other vaccinations recommended in Switzerland.

3.3. HPV Genotype Prevalence and Distributions

Figure 1 shows the genotype and prevalence distribution of HPV infection according to the genotype. Overall, 31.1% (127/409) of the swabs were positive for the presence of HPV DNA. Gardasil-targeted HPV genotypes were detected in 6.1% of the participants, who were positive for HPV-16/18, while 6.8% of the women were positive for HPV-6/11. A total of 15% of the participants were infected by multiple HPV genotypes. The prevalence of other HPV genotypes was 5.1 for HPV-31, 3.7% for HPV-33, 4.2% for HPV-45, and 2.7% for HPV-55.

Figure 2 presents the HPV prevalence of Gardasil-targeted genotypes; we found that 7.2% of the unvaccinated population was HPV-16/18-positive, while only 1.1% of vaccinated women were infected by HPV-16/18 ($p < 0.001$). The prevalence HPV-6/11 was 8.3% among unvaccinated women versus 2.1% in the vaccinated group ($p < 0.02$). This difference was statistically significant for women of all ages. Prevalence for other HPV high-risk strains was not statistically different between vaccinated and unvaccinated women: 10.3% versus 11.2% p = NS.

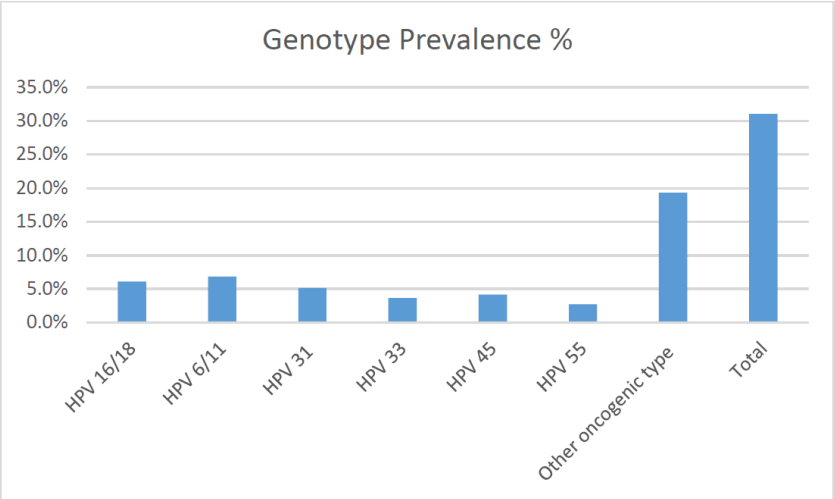

Figure 1. Human papillomavirus (HPV) genotype prevalence and distributions. In the case of multiple genotypes, each genotype was counted independently.

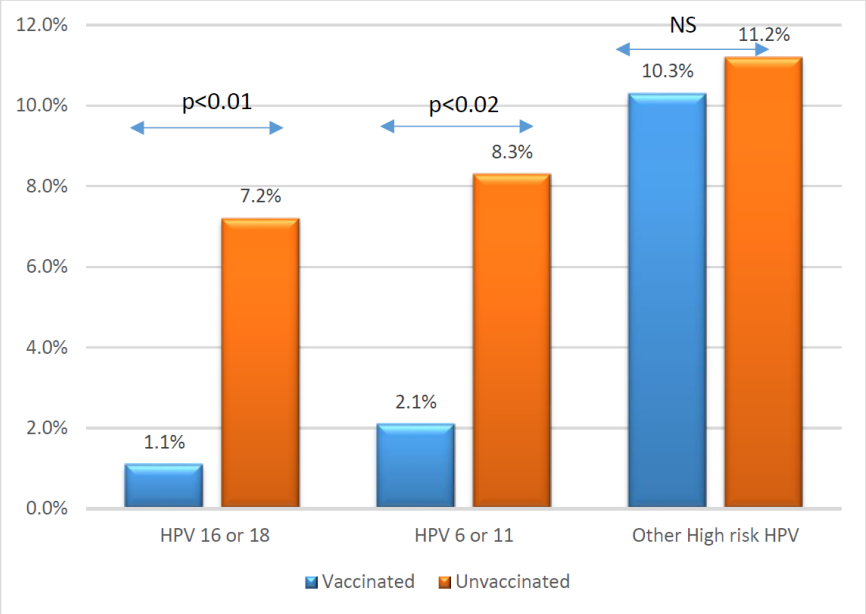

Figure 2. HPV prevalence 6/11 and 16/18, and other high-risk HPV according to vaccination status.

3.4. Relationship between HPV Infection and Sociodemographic

Table 2 reports the association between country of origin and HPV positivity. Non-Swiss women had higher odds ratios of being HPV-positive than the participants who came from Switzerland, (Adjusted OR (aOR) = 4.4 confidence interval (CI) 95% [1.3–7.6] and aOR = 3.8 CI 95% [2.4–4.1], respectively). There was also a very strong association between sexual activity and HPV positivity, as young women who reported having more than five different sexual partners throughout their sex life had higher odds of being infected with HPV when compared with women who had only one sexual partner aOR = 7.8 CI 95% [2.4–12.2]. Female students who sometimes used condoms were more likely to be HPV-infected than those who reported always using condoms aOR 7.5 CI 95% [6.3–8.7], this relationship was also found for those who never used a condom aOR 6.6 CI 95 % [4.8–8.2].

Table 2. Association between HPV positivity and socio demographic factor.

	OR	95% CI	Adjusted OR	95% CI
Recruitment site				
Faculty of medicine	1	-	1	-
School of health sciences	1.3	0.9–1.7	1.4	0.9–1.8
Country of birth				
Switzerland	1	-	1	-
France	1.2	0.5–1.9	0.9	0.3–1.6
Other European country	**3.4**	**2.1–3.7**	**3.8**	**2.4–4.1**
other country	**4.9**	**1.7–8.1**	**4.4**	**1.3–7.6**
Tobacco smoking				
yes, every day	1.7	0.7–2.7	1.5	0.5–3.1
yes, but not every day	1.5	0.8–2.7	1.7	0.9–2.8
No, never	1	-	1	-
Have you ever had sexual intercourse				
Yes	**7.8**	**6.7–8.9**	**7.2**	**6.2–8.5**
No	1	-	1	-
How many sexual partners did you have in your life (mean number of partner)				
0	0.2	0.01–0.35	0.3	0.01–0.37
1	1	-	1	-
2–5	**3.6**	**2.1–6**	**3.3**	**2.3–6.3**
>5	**9.8**	**5.4–14.2**	**7.8**	**2.4–12.2**
Do you use condoms as a means of protection/contraception				
Never	**6.3**	**4.7–7.9**	**6.6**	**4.8–8.2**
Sometimes	**7.9**	**6.8–9**	**7.5**	**6.3–8.7**
Often	2.6	0.9–5.2	**2.5**	**0.9–5.2**
Always	1	-	1	-
Have you been vaccinated against HPV				
Yes	**11.2**	**7.1–15.2**	**8.9**	**5.9–13.2**
No	1	-	1	-
How many doses of HPV vaccine have you received				
One	1.4	0.7–2.1	1.5	0.7–2.1
two	1.1	0.3–1.9	1.3	0.5–2.2
Three	1	-	1	-

Statistically significant results in **bold**.

3.5. Acceptability of Self-Sampling

Overall, 100% of the participants accepted to repeat self-sampling in order to evaluate their HPV clearance over time, and 85% of the participants reported that they would prefer self-sampling to the conventional pap smear for cervical cancer screening in the near future (p = 0.001). A total of 76% participants reported that self-sampling was not painful; only 8% found self-sampling very painful, while 97% found that self-sampling was easy to use.

4. Discussion

In this analysis performed on self-collected home samples of undergraduate medical and non-medical students, we found a low HPV prevalence of the Gardasil-targeted HPV genotypes. The canton of Geneva vaunts one of the best immunization coverage rates in Switzerland, reaching a target population coverage of nearly 80% [9]. One can assume that our results would have been very different in a canton with low immunization rates, which can go as low as less than 20% of the target population.

Our population constituted of future medical doctors, midwives, and nurses, and had a lower vaccination rate than that of the general population [9]. This under-representation of the vaccination rate among health professionals has been observed for other vaccines as well, such as the influenza vaccine [10–12].

We found a statistically significant difference in the prevalence of high-risk genotypes (6/11/16 and 18) between vaccinated and unvaccinated young women. These findings confirm the results of other studies on the effectiveness of the HPV vaccination as a means to decrease the prevalence of vaccine-targeted HPV types [13–16]. On the other hand, we observed no cross-protection for the other HPV genotypes, as we found no significant difference in the prevalence of non-Gardasil targeted genotypes between vaccinated and unvaccinated women, similar to other studies on the subject [17,18].

Other studies, however, have questioned this non-cross-protection. Saccucci et al. have shown a cross-protection in the first eight years after the HPV vaccine's introduction in the United States in 2006 [19]. Another study assessing the effect of the introduction of the vaccine on the rates of infection of non-vaccine HPV genotypes in community settings have demonstrated a possible cross-protection effect [20,21], although the clinical significance of such phenomena is not yet fully understood, nor is it sufficiently evidence-based to draw conclusions. Continuous monitoring of HPV genotypes, both vaccine-targeted and non-vaccine-targeted, is important to evaluate the possible cross-protection effect. It is possible that, with the forthcoming of the nine-valent HPV vaccine in Switzerland, the prevalence of other HPV genotypes in the population will drop.

Our results support the existence of associations between country of birth and number of sexual partners with the likelihood of HPV infection. To reduce the impact of these risk factors on the development of the relative sexually-transmitted infection, public health campaigns should be directed toward promoting a greater population awareness about the HPV infection's transmission, outcomes, and primary measures of prevention.

The use of self-sampling to measure the prevalence, distribution of HPV genotypes, and HPV vaccination effectiveness in our study population has proven to be effective. Moreover, a meta-analysis on the subject has shown that when PCR-based assays that amplify DNA viral sequences are used, the performance of HPV testing on clinician-collected samples is comparable to that of self-collected samples, such as the ones used in the present study [22]. Self-sampling has been reported to be more acceptable than physician-performed cytology testing, with women describing self-sampling as far more comfortable and practical than clinician-based sampling, which systematically entails a pelvic examination [23]. In our study, self-sampling proved to be a valid alternative to the standard vaccination program monitoring, thus proving to be a rather promising public health tool to monitor the effectiveness of HPV vaccination programs. Similarly, another study conducted in Canada has found that this strategy was a valid alternative to physician-performed vaginal sampling to evaluate the effectiveness of the HPV vaccination program [24,25].

5. Strength and Limitations

To our knowledge, this study was one of the first to directly assess the prevalence of HPV and the effectiveness of the HPV vaccination directly in the population through the use of self-sampling in Switzerland. The other studies carried out on the subject had a more modeling objective of the prevalence of this infection after the introduction of the HPV vaccination in Switzerland without trying to measure it directly in the population [26], but one large study with another methodology had shown the same results in another Swiss county [27].

Another strength was represented by the fact that we used a real-time PCR to estimate the HPV prevalence in the study population. In addition, as opposed to other trials using self-sampling, which registered between 0.5 and 0.7% of unsatisfactory HPV test results, we had no invalid results.

This study has some limitations that need to be addressed. The population sample is constituted exclusively of undergraduate students, which limits the generalization of our findings to other populations or settings. Additionally, the study sample size was not powered to detect any potential cross-protection of the vaccine-targeted HPV genotypes.

6. Conclusions

Our findings support the HPV vaccination's effectiveness as a means to lower the prevalence of the infection with most oncogenic genotypes in a population of young women. The decreasing

prevalence of the infection, therefore, represents one step closer to the prevention of the development of cervical cancer, which is the vaccination's long-term aim. As self-sampling was well accepted by participants for monitoring the effectiveness of the HPV vaccination program, such a finding may support the use of self-sampling for cervical cancer screening, in the view of alleviating the world population from the burden of cervical cancer. In this study, we observed no cross-protection for the other HPV genotypes—low- and high-risk strains—between vaccinated and unvaccinated women.

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References

1. Sabeena, S.; Bhat, P.V.; Kamath, V.; Arunkumar, G. Global human papilloma virus vaccine implementation: An update. *J. Obstet. Gynaecol. Res.* **2018**, doi:10.1111/jog.13634.
2. GLOBOCAN. Estimated Cancer Incidence, Mortality and Prevalence Worldwide. Availabe online: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (accessed on 11 February 2018).
3. Garland, S.M.; Hernandez-Avila, M.; Wheeler, C.M.; Perez, G.; Harper, D.M.; Leodolter, S.; Tang, G.W.; Ferris, D.G.; Steben, M.; Bryan, J.; et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N. Engl. J. Med.* **2007**, *356*, 1928–1943.
4. Hall, M.T.; Simms, K.T.; Lew, J.B.; Smith, M.A.; Saville, M.; Canfell, K. Projected future impact of HPV vaccination and primary HPV screening on cervical cancer rates from 2017–2035: Example from Australia. *PLoS ONE* **2018**, *13*, e0185332.
5. Hariri, S.; Bennett, N.M.; Niccolai, L.M.; Schafer, S.; Park, I.U.; Bloch, K.C.; Unger, E.R.; Whitney, E.; Julian, P.; Scahill, M.W.; et al. Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States-2008–2012. *Vaccine* **2015**, *33*, 1608–1613.
6. Mesher, D.; Soldan, K.; Howell-Jones, R.; Panwar, K.; Manyenga, P.; Jit, M.; Beddows, S.; Gill, O.N. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. *Vaccine* **2013**, *32*, 26–32.
7. Garland, S.M.; Cornall, A.M.; Brotherton, J.M.L.; Wark, J.D.; Malloy, M.J.; Tabrizi, S.N.; Group, V.S. Final analysis of a study assessing genital human papillomavirus genoprevalence in young Australian women, following eight years of a national vaccination program. *Vaccine* **2018**, *36*, 3221–3230.
8. Wymann, M.N.; Zographos, A.S.; Altpeter, E.; Spicher, V.M.; Low, N.; Mausezahl-Feuz, M. Human papillomavirus vaccine uptake in adolescence and adherence to cervical cancer screening in Switzerland: A national cross-sectional survey. *Int. J. Public Health* **2018**, *63*, 105–114.
9. Jeannot, E.; Petignat, P.; Sudre, P. Successful implementation and results of an HPV vaccination program in Geneva Canton, Switzerland. *Public Health Rep.* **2015**, *130*, 202–206.
10. Sundaram, N.; Duckett, K.; Yung, C.F.; Thoon, K.C.; Sidharta, S.; Venkatachalam, I.; Chow, A.; Yoong, J. "I wouldn't really believe statistics"—Challenges with influenza vaccine acceptance among healthcare workers in Singapore. *Vaccine* **2018**, *36*, 1996–2004.
11. Karafillakis, E.; Dinca, I.; Apfel, F.; Cecconi, S.; Wurz, A.; Takacs, J.; Suk, J.; Celentano, L.P.; Kramarz, P.; Larson, H.J. Vaccine hesitancy among healthcare workers in Europe: A qualitative study. *Vaccine* **2016**, *34*, 5013–5020.
12. Ciftci, F.; Sen, E.; Demir, N.; Ciftci, O.; Erol, S.; Kayacan, O. Beliefs, attitudes, and activities of healthcare personnel about influenza and pneumococcal vaccines. *Hum. Vaccines Immunother.* **2018**, *14*, 111–117.
13. Osborne, S.L.; Tabrizi, S.N.; Brotherton, J.M.; Cornall, A.M.; Wark, J.D.; Wrede, C.D.; Jayasinghe, Y.; Gertig, D.M.; Pitts, M.K.; Garland, S.M. Assessing genital human papillomavirus genoprevalence in young Australian women following the introduction of a national vaccination program. *Vaccine* **2015**, *33*, 201–208.
14. Kumakech, E.; Berggren, V.; Wabinga, H.; Lillsunde-Larsson, G.; Helenius, G.; Kaliff, M.; Karlsson, M.; Kirimunda, S.; Musubika, C.; Andersson, S. Significantly Reduced Genoprevalence of Vaccine-Type HPV-16/18 Infections among Vaccinated Compared to Non-Vaccinated Young Women 5.5 Years after a Bivalent HPV-16/18 Vaccine (Cervarix(R)) Pilot Project in Uganda. *PLoS ONE* **2016**, *11*, e0160099.

15. Machalek, D.A.; Garland, S.M.; Brotherton, J.M.L.; Bateson, D.; McNamee, K.; Stewart, M.; Skinner, S.R.; Liu, B.; Cornall, A.M.; Kaldor, J.M.; et al. Very low prevalence of vaccine human papillomavirus (HPV) types among 18 to 35 year old Australian women, nine years following implementation of vaccination. *J. Infect. Dis.* **2018**, *217*, 1590–1600.
16. Carozzi, F.; Puliti, D.; Ocello, C.; Anastasio, P.S.; Moliterni, E.A.; Perinetti, E.; Serradell, L.; Burroni, E.; Confortini, M.; Mantellini, P.; et al. Monitoring vaccine and non-vaccine HPV type prevalence in the post-vaccination era in women living in the Basilicata region, Italy. *BMC Infect. Dis.* **2018**, *18*, 38.
17. Woestenberg, P.J.; King, A.J.; van der Sande, M.A.; Donken, R.; Leussink, S.; van der Klis, F.R.; Hoebe, C.J.; Bogaards, J.A.; van Benthem, B.H. No evidence for cross-protection of the HPV-16/18 vaccine against HPV-6/11 positivity in female STI clinic visitors. *J. Infect.* **2017**, *74*, 393–400.
18. Markowitz, L.E.; Liu, G.; Hariri, S.; Steinau, M.; Dunne, E.F.; Unger, E.R. Prevalence of HPV After Introduction of the Vaccination Program in the United States. *Pediatrics* **2016**, *137*, e20151968.
19. Saccucci, M.; Franco, E.L.; Ding, L.; Bernstein, D.I.; Brown, D.; Kahn, J.A. Non-Vaccine-Type Human Papillomavirus Prevalence After Vaccine Introduction: No Evidence for Type Replacement but Evidence for Cross-Protection. *Sex. Transm. Dis.* **2018**, *45*, 260–265.
20. Mesher, D.; Soldan, K.; Lehtinen, M.; Beddows, S.; Brisson, M.; Brotherton, J.M.; Chow, E.P.; Cummings, T.; Drolet, M.; Fairley, C.K.; et al. Population-Level Effects of Human Papillomavirus Vaccination Programs on Infections with Nonvaccine Genotypes. *Emerg. Infect. Dis.* **2016**, *22*, 1732–1740.
21. Cameron, R.L.; Kavanagh, K.; Pan, J.; Love, J.; Cuschieri, K.; Robertson, C.; Ahmed, S.; Palmer, T.; Pollock, K.G. Human Papillomavirus Prevalence and Herd Immunity after Introduction of Vaccination Program, Scotland, 2009–2013. *Emerg. Infect. Dis.* **2016**, *22*, 56–64.
22. Arbyn, M.; Verdoodt, F.; Snijders, P.J.; Verhoef, V.M.; Suonio, E.; Dillner, L.; Minozzi, S.; Bellisario, C.; Banzi, R.; Zhao, F.H.; et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: A meta-analysis. *Lancet Oncol.* **2014**, *15*, 172–183.
23. Nelson, E.J.; Maynard, B.R.; Loux, T.; Fatla, J.; Gordon, R.; Arnold, L.D. The acceptability of self-sampled screening for HPV DNA: A systematic review and meta-analysis. *Sex. Transm. Infect.* **2017**, *93*, 56–61.
24. Goggin, P.; Sauvageau, C.; Gilca, V.; Defay, F.; Lambert, G.; Mathieu, C.S.; Guenoun, J.; Comete, E.; Coutlee, F. Low prevalence of vaccine-type HPV infections in young women following the implementation of a school-based and catch-up vaccination in Quebec, Canada. *Hum. Vaccines Immunother.* **2018**, *14*, 118–123.
25. Lam, J.U.H.; Rebolj, M.; Ejegod, D.M.; Pedersen, H.; Rygaard, C.; Lynge, E.; Harder, E.; Thomsen, L.T.; Kjaer, S.K.; Bonde, J. Prevalence of Human Papillomavirus in Self-Taken Samples from Screening Nonattenders. *J. Clin. Microbiol.* **2017**, *55*, 2913–2923.
26. Riesen, M.; Garcia, V.; Low, N.; Althaus, C.L. Modeling the consequences of regional heterogeneity in human papillomavirus (HPV) vaccination uptake on transmission in Switzerland. *Vaccine* **2017**, *35*, 7312–7321.
27. Jacot-Guillarmod, M.; Pasquier, J.; Greub, G.; Bongiovanni, M.; Achtari, C.; Sahli, R. Impact of HPV vaccination with Gardasil(R) in Switzerland. *BMC Infect. Dis.* **2017**, *17*, 790.

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Article

Human Papillomavirus Infection and Vaccination: Knowledge, Attitude and Perception among Undergraduate Men and Women Healthcare University Students in Switzerland

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Abstract: Background: Human Papillomavirus is a common sexually transmitted infection, representing the main cause of genital warts and cervical cancer. The objective of this study was to evaluate basic knowledge and beliefs regarding HPV infection and HPV vaccine among undergraduate healthcare men and women students, as well as their attitudes towards HPV vaccine. Methods: Undergraduate women and men (nursing and midwifery curses) attending three Schools of Health Sciences located in Switzerland. A total of 427 women and 223 men have completed the web questionnaire, which included questions on their socio-demographic background and about basic knowledge and attitudes toward the HPV infection and vaccination. Results: Women undergraduate students have a better knowledge of HPV infection than their men counterparts, although there was a significant gap in knowledge of the disease's mode of transmission and prevention. Among women, 72.6% of respondents reported having received at least one dose of HPV vaccines versus 31.4% for men respondents. Conclusion: The results of this study revealed a poor understanding among undergraduate healthcare men and women students about the HPV infection, its mode of transmission and its prevention. Our findings highlight the need to improve education on HPV for undergraduate healthcare students in order to increase the awareness of the disease.

Keywords: cervical cancer; human papillomavirus (HPV); undergraduate students

1. Introduction

Human papillomavirus (HPV) is the most common viral of the reproductive system. Most sexually-active men and women will be infected with HPV at some point in their lives, while some of them will be repeatedly infected [1]. Although the majority of virus types are harmless, over 40 of

them may cause cancer. Papilloma viruses can be transmitted through vaginal, oral, or anal sex. While they privilege the genital mucosae, these viruses can also reach the throat and cause pre-cancerous or cancerous lesions [2].

Two-thirds of HPV infections are asymptomatic. The persistence of high-risk HPV types, however, can cause various types of precancerous and cancerous lesions, including cervical cancer. In addition, HPV infections are responsible for other forms of cancer that can also affect men. Low-risk HPV can cause ano-genital warts (condyloma), which are common in both men and women. Over the course of life, 1 in 10 people on average will be affected [3].

In Switzerland, more than 5000 women are diagnosed with cervical pre-cancer each year and require further tests and/or surgery. They are most often young women, although cancer can sometimes only appear 20 or 30 years after the primary HPV Infection. Despite the implementation of screening, about 250 women will present cervical cancer in Switzerland every year [4].

Among over 200 HPV types, 14 of them can infect the genital organs in both women and men. Similarly to women, while infections may disappear over the years in some men, they may also persist in others. One recent study has shown that approximately three to four million cases of genital warts occur each year in men, with a peak rate of 500 per 100,000 in the 25–29 year-old men [5]. Another study conducted in the United States of America (USA) has estimated that about 2120 men in the U.S. will be diagnosed with cancer of the penis in 2017, while about 2950 men will be diagnosed with anal cancer [6].

In Switzerland, HPV infections were the main cause of anal cancer, which is diagnosed every year in 200 new cases, 90% of which are caused by HPV type 16 and 18 [7]. HPV can also take part in the development of other cancers in the genitals (penis) and throat. These cancers were, however, much rarer than those of the cervix and anus.

The introduction of the HPV vaccination represents the most important primary prevention measure against HPV-related precancer and cancer [8]. The currently available vaccines in Switzerland are Gardasil® and Cervarix®, both of which protect against HPV genotypes 16 and 18. Gardasil®, which has been available on the international market since 2007, also covers against genotypes 6 and 11, which are mostly responsible for the development of genital condylomas [9]. This 9-valent vaccine, which protects against five additional types of oncogenic HPV (HPV 31, 33, 45, 52, 58), was launched on the Swiss market in 2016. The cantonal programs, however, have integrated it in their vaccination campaigns in 2019. If vaccination is successfully started before the 15th birthday, two injections at six-month intervals are recommended, starting from the 15th birthday, three injections over a period of at least six months are necessary for optimal protection. Swiss health authorities recommend vaccination against HPV to all teenagers aged 11 to 14 years. Since HPV-related diseases occur more frequently in women than in men, vaccination is recommended for girls as one of the mandatory vaccines, while for boys it is currently considered a supplementary vaccination. Since January 2016, Gardasil® 9-valent was available and free of charge for boys in the majority of the Swiss cantons. The national coverage rates in Switzerland are assessed using the cantonal rates as part of the Swiss National Vaccination Coverage Survey (SNVCS). Concerning the HPV coverage rate, the most recent data are from the period 2014–2016. A study on the 2017–2019 period is currently underway, but the results are not yet available. For the period 2014–2016, the results were as follows: For two doses, after increasing from 24% in 2008–2010 to 54% in 2011–2013, the coverage rate no longer increased significantly during the period 2014–2016 and now stands at 56%. An analysis of the dose gap shows that during the last investigation period, only 48% of girls had received a valid two- or three-dose schema

One of the main challenges for the Swiss public health HPV vaccination program is to develop accurate forms of communication and information about the HPV infection. Research has identified that health professionals play an important role in vaccines uptake. Moreover, there is a lack of initiatives to improve education among undergraduate healthcare students about HPV infection,

consequences, and prevention [10]. For a large majority of these young adults (women or men), the internet is the main and only source of information.

In order to make a conscious, informed decision about the vaccine's uptake, the target population, which includes both women and men, should understand the importance of prevention through HPV vaccination, and the issues associated with the persistence of the infection.

Accurate knowledge about HPV infection and HPV vaccination are two critical points to make appropriate evidence-based health care choices. Consciousness about the knowledge of undergraduate health students on HPV infection and vaccination is important for the students themselves, but also for the society, as spreading the correct information about the vaccines is a fundamental point in ensuring community support [11].

Education of the community was, therefore, an essential step in the primary prevention of the HPV infection. This study aimed to evaluate (1) the basic knowledge and beliefs regarding HPV infections and HPV vaccines among undergraduate healthcare women and men students (nursing and midwifery) and (2) their attitudes towards the HPV vaccination.

2. Methods

2.1. Population

Recruitment of the study participants took place from January to March 2019 at three Schools of Health Sciences located in Switzerland. Men and women aged 18 years or older, currently attending these three Schools of Health Sciences to obtain a nursing or midwifery degree in their first year, second year, or third year, were invited to participate in the study.

2.2. Study Design

Announcements about the study were given by previously informed professors who were teaching classes at the School of Health Sciences. An email was also sent by the study investigators to the students prior to their recruitment.

The survey instrument was an online self-administrated anonymous questionnaire developed using SurveyMonkey software (Palo Alto, CA, USA). This software automatically saves responses into a secure database, thus protecting the participants' confidentiality. On the first page of the web questionnaire, the participant could view a consent form, informing him/her of the study objectives and procedures. The participants had the right to refuse or terminate their participation in the study at any moment, in which case the time of study drop-out was indicated in the questionnaire. If the participants accepted to participate in the study, they were asked to tick a box in order to accept the informed consent form. If the participants did not agree to participate, the webpage automatically closed down. Three email reminders were sent at one, two weeks and three weeks after the first invitation, unless an individual requested to be removed from the mailing list throughout the process. The web-based survey was automatically closed 10 weeks after having sent the first invitation.

2.3. Study Tool

The questionnaire included three parts. The first part contained items about the socio-demographic characteristics of the participants. The second part contained items about basic knowledge of the HPV infection (17 items), and basic knowledge about HPV vaccination (seven items), where he/she could answer either "yes" or "no". The third part contained items about the participants' attitude toward the HPV vaccination (six items). The content's validity was evaluated by three experts (nurse, midwife, and epidemiologist), and a feasibility study was previously performed on 15 nurses and five midwives (not publish). The questionnaire was developed in French, based on previous surveys evaluating HPV knowledge, attitudes and perceptions [12–17].

2.4. Sample Size

The total number of nursing and midwifery students enrolled at the three selected Schools of Health Sciences is around 1'200 students: A minimum sample size of $n = 600$ was calculated based on a confidence interval of 95%, a significance level of 0.05, a power of 80%, and response rate of 50%.

2.5. Statistical Analyses

Data collected by the Survey Monkey was exported to a Microsoft Excel database. Statistical analyses were run using STATA 13. Normality of the distribution was tested by the Kolmogorov–Smirnov test. Descriptive statistics and frequencies were analyzed for all variables. The *t*-test and Chi-square test were used for the descriptive statistics and for the comparison between variables. Logistic regression models were used to assess the associations between explicative variables and the status of the HPV vaccine's uptake. The status of HPV immunization on women and men was used as the primary outcome. For this purpose, an individual was considered as vaccinated when he/she had received at least one dose of the vaccines. At the multivariate analysis, only those covariates considered to be of interest based on the univariate analysis' results were included. All the hypotheses were two-sided, and results were considered significant at 0.05.

2.6. Ethical Approval

The study protocol was approved by the ethical cantonal board in Geneva (Commission Cantonale d'Ethique et de la Recherche—CCER) with the identification number Req-2019-00118. All participants signed an informed consent form prior to taking part in the study. The trial was registered under cliniclatrials.gov with the identifiers: NCT03888599.

3. Results

3.1. Participants Socio-Demographic Characteristics

A total of 650 men and women undergraduate students accepted to participate in the study and answered the entire questionnaire online and were thus included in the study.

The participants' baseline characteristics are presented in Table 1. The mean of age was 23.1 years (range 18–35), 66% of the participants were nursing women students or midwives in their first year, second year or third year of Bachelor's degree, the other 34% were nursing men students in either their first year, second year or third of Bachelor's degree, while no midwifery man student took part in the study. The majority of the participants were Swiss (77%), 14% of them came from Europe (mainly France 10%) and 9% came from non-European countries (mainly either South America or Africa). The vast majority of the participants were not married (85%). A total of 65% of the participants were non-smokers. Overall, 9.2% of the women and men reported never having had sexual intercourse. The reported age of first intercourse of 17.5 years was the same for both women and men. A total of 14% of women students declared that they did not use a contraceptive method, 9.5% of the entire group had never used a condom, and 82% of them were sexually active.

Table 1. Socio-demographic characteristics of the study population.

	N	%
Total	**650**	
Age (mean/SD)	23.1	8.16
Range (min-max)	18–35	
Gender		
Women	427	65.7%
Men	223	34.3%
Birthplace		
Switzerland	502	77.2%
Europe	90	13.8%
Other	58	8.9%
Relationship status		
Married	554	85.2%
Not married	96	14.8%
Smoker		
Yes	423	65.1%
No	227	34.9%
Ever had sexual Intercourse		
Yes	559	86.0%
No	60	9.2%
Missing	31	4.8%
Age of first sex encounter (mean/SD)	17.5	1.83
Number of sexual partners in lifetime (mean/SD)	5.3	0.043
Women	3.6	7.8
Men	8.7	5.9
Contraceptive method (question only for women *N* = 427)		
vaginal ring	128	30.0%
hormonal IUD	16	3.7%
Injectable	2	0.5%
withdrawal	50	11.7%
condom	171	40.0%
no method	60	14.1%
Condom use during sexual intercourse		
Never	62	9.5%
Occasional	231	35.5%
Always	357	54.9%
Currently sexually active		
Yes	533	82.0%
No	117	18.0%

3.2. Students Basic Knowledge about HPV

Table 2 shows the basic knowledge and beliefs about HPV infection and vaccination. Most of the students (women and men) knew that cervical cancer was strongly linked to the HPV infection (over 90% of positive responses), a vast majority of them was aware that HPV could to be sexually transmitted (86% of women and only 67% of men obtained positive response). The majority of women (84%) knew that HPV was responsible for genital warts, while only 61% of men answered this question. Overall, 75% of men and 42% of women believed that HPV infection could be treated with antibiotics. Nearly 50% of men students believed that men could not be infected with HPV.

Table 2. Knowledge and beliefs regarding HPV infections and HPV vaccines.

		Women *N* = 427				Men *N* = 223			
	Correct Answer	True Response		False Response		True Response		False Response	
HPV Knowledge Questions		*N*	%	*N*	%	*N*	%	*N*	%
The type of cancer highly associated with HPV infection is uterine cancer	True	400	93.7%	27	6.3%	205	91.9%	18	8.1%
HPV can be sexually transmitted	True	368	86.2%	59	13.8%	150	67.3%	73	32.7%
Having many sexual partners increases the risk of getting HPV	True	334	78.2%	93	21.8%	135	60.5%	88	39.5%
HPV can be passed on during sexual intercourse	True	298	69.8%	129	30.2%	125	56.1%	98	43.9%
A person could have HPV for many years without knowing it	True	267	62.5%	160	37.5%	135	60.5%	88	39.5%
HPV always has visible signs or symptoms	False	231	54.1%	196	45.9%	150	67.3%	73	32.7%
HPV is very rare infection	False	285	66.7%	142	33.3%	138	61.9%	85	38.1%
There are many types of HPV	True	306	71.7%	121	28.3%	147	65.9%	76	34.1%
Using condoms reduces the risk of getting HPV	True	370	86.7%	57	13.3%	187	83.9%	36	16.1%
HPV can be passed on by genital skin to skin contact	True	214	50.1%	213	49.9%	147	65.9%	76	34.1%
HPV can cause genital warts	True	360	84.3%	67	15.7%	136	61.0%	87	39.0%
HPV can cause herpes	False	258	60.4%	169	39.6%	141	63.2%	82	36.8%
HPV can be cured with antibiotics	False	245	57.4%	182	42.6%	54	24.2%	169	75.8%
Most sexually active people will get HPV at some point in their lives	True	201	47.1%	226	52.9%	157	70.4%	66	29.6%
Having sex at an early age increases the risk of getting HPV	True	220	51.5%	207	48.5%	109	48.9%	114	51.1%
HPV usually doesn't need any treatment	True	235	55.0%	192	45.0%	104	46.6%	119	53.4%
Men cannot get HPV	False	350	82.0%	77	18.0%	120	53.8%	103	46.2%
HPV Vaccine Knowledge Questions									
There is a vaccine to protect women from HPV	True	405	94.8%	22	5.2%	173	77.6%	50	22.4%
There is a vaccine to protect men from HPV	True	302	70.7%	125	29.3%	157	70.4%	66	29.6%
The HPV vaccines offer protection against all sexually transmitted infections	False	258	60.4%	169	39.6%	124	55.6%	99	44.4%
Someone who has had HPV vaccine cannot develop cervical cancer	False	390	91.3%	37	8.7%	168	75.3%	55	24.7%
The HPV vaccines are most effective if given to people who have never had sex	True	367	85.9%	60	14.1%	162	72.6%	61	27.4%
The HPV vaccines offer protection against most cervical cancers	True	361	84.5%	66	15.5%	158	70.9%	65	29.1%
The HPV vaccine offers protection against genital warts	True	347	81.3%	80	18.7%	147	65.9%	76	34.1%

3.3. HPV Vaccination's Knowledge

The participants' attitudes toward HPV vaccination are reported in Table 3. We observed that nearly 95% of women and 77% of men were aware of the existence of vaccines to protect women from HPV. Over 70.7% and 70.4% of women and men students, respectively, were aware of the existence of vaccines for both women and men. A total of 60.4% of women and 55.6% of men students believed that the HPV vaccine provided protection against most sexually transmitted infections.

Table 3. Attitudes toward HPV vaccines.

	Women *N* = 427		Men *N* = 223		*p*
	N	%	*N*	%	
HPV vaccination status					
Vaccinated (min 1 dose)	310	72.6%	70	31.4%	**<0.001** *
Not vaccinated	117	27.4%	153	68.6%	
Who should pay for this vaccination					
Private Insurance	269	63.0%	126	56.5%	0.08
State health system	100	23.4%	61	27.4%	
From my pocket	23	5.4%	10	4.5%	
Others	10	2.3%	6	2.7%	
Don't know	25	5.9%	20	9.0%	
Who should get vaccinated					
Women only	301	70.5%	185	83.0%	**0.0003**
Men and women	121	28.3%	37	16.6%	
Men only	5	1.2%	1	0.4%	
When vaccine should be given					
Before the first sex encounter	126	29.5%	94	42.2%	**0.0009**
Casual relationship	139	32.6%	67	30.0%	
If more than one partner	112	26.2%	43	19.3%	
Any time	50	11.7%	19	8.5%	
Would you recommend the HPV vaccine?					
Yes	382	89.5%	201	90.1%	0.69
No	45	10.5%	22	9.9%	
Do you think that the vaccine should be offered free of charge					
Yes	415	97.2%	220	98.7%	0.45
No	12	2.8%	3	1.3%	

* Bold font indicates a statistical significance.

3.4. Attitude toward the HPV Vaccines

The participants' attitudes toward HPV vaccines are reported in Table 3. A total of 72.6% and 31.4% of women and men students, respectively, had received at least one dose of the vaccines. Overall, 29.5% of women and 42.2% of men students believed that the vaccination should be administered before the first sexual intercourse. Only 28.3% and 16.6% of the women and men students, respectively, knew that the vaccines were available for both women and men. A total of 89.5% of women and 90.1% of men students responded that they would recommend the HPV vaccination to their peers.

3.5. Predictors of HPV Vaccination

The results of the logistic regression predicting HPV vaccination are presented in Table 4.

Women participants were five times more likely to be vaccinated than their men counterparts (aOR: 5.79, 4.06–8.25 CI 95%). Participants with a European nationality also had higher vaccination rates than those with a Swiss nationality (aOR: 1.65, 1.42–1.92 CI 95%). Not being married, never having had sexual intercourse and not being sexually active at the moment were all predictive factors for having lower vaccination rates (aOR: 0.68, 0.22–0.72 CI 95%, aOR: 0.50, 0.30–0.83 CI 95% and aOR: 0.31, 0.10–0.95 CI 95%). A non-smoking status was also a predictor of a greater likelihood of being vaccinated for HPV (aor: 1.51, 1.05 - 2.81 CI 95%).

Table 4. Logistic regression predicting HPV vaccination (min one dose).

	aOR (95 CI)
Gender	
Men	Referent
Women	**5.79 (4.0 6–8.25)**
Birthplace	
Switzerland	Referent
Europe	**1.65 (1.42–1.92)**
Other	0.81 (0.66–1.03)
Relationship status	
Married	Referent
Not married	**0.68 (0.22–0.72)**
Smoker	
Yes	Referent
No	**1.51 (1.05–2.81)**
Ever had sexual Intercourse	
Yes	Referent
No	**0.50 (0.30–0.83)**
Currently sexually active	
Yes	Referent
No	**0.31 (0.10–0.95)**

Only odds ratio significant in the univariate model is presented in this table aOR adjusted OR for significant univariate predictors. Bold font indicates a statistical significance and a 95% confidence interval.

4. Discussion

This was the first study to assess knowledge about HPV infection and vaccination in a population of undergraduate men and women healthcare students in Switzerland. Previously published studies have sought to assess the prevalence of different HPV strains (only in nurses and midwife women) and the reasons and socio-demographic characteristics of the unvaccinated women [18,19]. This study also represents the first effort in evaluating the HPV vaccination coverage rate in a population of young men.

Our findings highlight a general lack of knowledge of the HPV infection's natural history and its prevention among future Swiss nurses (men and women) and midwives (women only). The knowledge gaps of future health professionals have also been documented by studies conducted in other countries, such as Pakistan, Turkey, Lebanon, Germany, and USA [11,13,15,16,20].

Such knowledge gaps may be explained by the fact that among the three Schools of Health Sciences that participated in this study, none includes in their nursing curriculum a specific course about sexuality and HPV infection, with the exception of an optional course only available during their third year of bachelor. There is also no specific course about vaccinations in the nursing curriculum in these three schools. The topic of HPV is studied in the curriculum of midwives in a little more detail (about 2 h on their entire curriculum), two schools out of the three included in this study have a specific course (only 1 h) on vaccinations in their midwifery training curriculum.

This lack of education on HPV and other vaccines among future health professionals on the subject of vaccination (HPV, measles, and others) seems to be more frequent and is becoming a major problem due to the increasing hostility towards vaccination, particularly in the current context in Europe and the United States [21–23], where there is a growing mistrust towards vaccinations parallel to the increased incidence of vaccine-preventable diseases [24,25].

Our study indicates that young women have a higher level of knowledge about HPV than young men. This difference can be explained by the habit of girls to go for an annual check-up with the gynecologist or physician starting at puberty. Such consultations are aimed at providing girls with information about family planning, menstruation-related issues such as dysmenorrhea, and sexually

transmitted diseases [26–28]. When asked about the source of their information about sexuality in general, young girls in Switzerland tend to turn to other girls, then, secondly, to magazines for young people and finally, to the Internet, while boys cite the Internet first and other young men as second [29]. While a study conducted in the United States found that the use of video messages was a potential tool to increase knowledge about HPV [30], other trials have also shown that social networks (e.g., Facebook, Instagram, Twitter etc.) can be used as complementary tools to deliver conventional prevention messages [31–33].

Strength and Limitations of the Study

One of the strengths of our study is that it is the first in Switzerland to evaluate knowledge about HPV infection and HPV vaccination on such a large sample size. It is also the first to ask men about this problem in Switzerland and to have a first approach to HPV vaccination coverage for young men.

This study has some limitations that need to be addressed. The population sample was constituted of exclusively undergraduate students, which limits the generalization of our findings to the general population. As data were also collected through a questionnaire with self-reported answers, the reliability of which could not be directly verified by the study investigators, the results could also have been altered by such means of data collection.

HPV vaccination coverage rate was calculated using self-reporting of the number of doses received by participants to be sure of the number of doses people received, a copy of their vaccination carnet should have been requested, which was not possible in the context of this study. In the absence of a blood test, we cannot be sure of their HPV immunological status. It can, therefore, be assumed that the HPV vaccination coverage rate was calculated even if it was only a secondary objective of this study underestimates or on the contrary overestimates the right vaccination coverage rate. A final limitation of our study was the fact that the sample collected was not selected randomly, but according to the participation in the study by the students. This problem limits the generalization of our results.

5. Conclusions

The results of this study revealed a poor understanding among healthcare undergraduate men and women students about the HPV infection, its mode of transmission and its prevention. Nurses and midwives play a crucial role in shaping public views of HPV transmissions, prevention and vaccination. They represent a privileged channel to spread information about HPV to the target audience [34]. Future education campaigns and courses for healthcare students need to clarify multiple points about the modes of transmission of the infection, the means of prevention, including vaccination and other lesions induced by HPV in both men and women, in the view of increasing the vaccination coverage rate, and subsequently, reduce the rate of HPV-related cancers. In the future, those involved in prevention will have to make more use of the new communication channels in order to disseminate their message. Clear and targeted messages can positively influence adherence to primary and secondary preventive strategies, such as reduced risk-taking in sexual behavior or participation in HPV vaccination and cervical cancer screening.

The findings highlight the need for more HPV education among undergraduate healthcare student. It must be done to increase HPV knowledge and vaccination rates in this population.

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References

1. Boda, D.; Docea, A.O.; Calina, D.; Ilie, M.A.; Caruntu, C.; Zurac, S.; Neagu, M.; Constantin, C.; Branisteanu, D.E.; Voiculescu, V.; et al. Human papilloma virus: Apprehending the link with carcinogenesis and unveiling new research avenues. *Int. J. Oncol.* **2018**, *52*, 637–655. [CrossRef] [PubMed]
2. Alizon, S.; Murall, C.L.; Bravo, I.G. Why Human Papillomavirus Acute Infections Matter. *Viruses* **2017**, *9*, 293. [CrossRef] [PubMed]
3. Office Fédéral de la Santé Publique. *Cancers et Verrues Génitales dus aux Papillomavirus Humains*; Office Fédéral de la Santé Publique: Bern, Switzerland, 2016.
4. Burton-Jeangros, C.; Cullati, S.; Manor, O.; Courvoisier, D.S.; Bouchardy, C.; Guessous, I. Cervical cancer screening in Switzerland: Cross-sectional trends (1992–2012) in social inequalities. *Eur. J. Public Health* **2017**, *27*, 167–173. [CrossRef] [PubMed]
5. Moscicki, A.B.; Palefsky, J.M. Human papillomavirus in men: An update. *J. Low. Genit. Tract Dis.* **2011**, *15*, 231–234. [CrossRef] [PubMed]
6. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer Statistics, 2017. *CA Cancer J. Clin.* **2017**, *67*, 7–30. [CrossRef]
7. Duvoisin, C.C.; Clerc, D.; Vanoni, A.; Pache, B.; Hubner, M.; Demartines, N.; Hahnloser, D. Screening for anal cancer: Is it the same as for cervical cancer? *Rev. Med. Suisse* **2018**, *14*, 1230–1236.
8. Office Fédéral de la Santé Publique. *Vaccination Contre les HPV: Recommandations de l'OFSP et de la CFV Concernant le Nouveau Vaccin Gardasil 9®*; Office Fédéral de la Santé Publique: Bern, Switzerland, 2018.
9. Jeannot, E.; Sudre, P.; Chastonay, P. HPV vaccination coverage within 3 years of program launching (2008–2011) at Geneva State, Switzerland. *Int. J. Public Health* **2012**, *57*, 629–632. [CrossRef]
10. Thomas, T.L. Cancer Prevention: HPV Vaccination. *Semin. Oncol. Nurs.* **2016**, *32*, 273–280. [CrossRef]
11. Kasymova, S.; Harrison, S.E.; Pascal, C. Knowledge and Awareness of Human Papillomavirus Among College Students in South Carolina. *Infect. Dis.* **2019**, *12*. [CrossRef]
12. Canon, C.; Effoe, V.; Shetty, V.; Shetty, A.K. Knowledge and Attitudes Towards Human Papillomavirus (HPV) Among Academic and Community Physicians in Mangalore, India. *J. Cancer Educ.* **2017**, *32*, 382–391. [CrossRef]
13. Khan, T.M.; Buksh, M.A.; Rehman, I.U.; Saleem, A. Knowledge, attitudes, and perception towards human papillomavirus among university students in Pakistan. *Papillomavirus Res.* **2016**, *2*, 122–127. [CrossRef] [PubMed]
14. Sherman, S.M.; Bartholomew, K.; Denison, H.J.; Patel, H.; Moss, E.L.; Douwes, J.; Bromhead, C. Knowledge, attitudes and awareness of the human papillomavirus among health professionals in New Zealand. *PLoS ONE* **2018**, *13*, e0197648. [CrossRef] [PubMed]
15. Karasu, A.F.G.; Adanir, I.; Aydin, S.; Ilhan, G.K.; Ofli, T. Nurses' Knowledge and Opinions on HPV Vaccination: A Cross-Sectional Study from Istanbul. *J. Cancer Educ.* **2019**, *34*, 98–104. [CrossRef] [PubMed]
16. Dany, M.; Chidiac, A.; Nassar, A.H. Human papillomavirus vaccination: Assessing knowledge, attitudes, and intentions of college female students in Lebanon, a developing country. *Vaccine* **2015**, *33*, 1001–1007. [CrossRef] [PubMed]
17. Schmotzer, G.L.; Reding, K.W. Knowledge and beliefs regarding human papillomavirus among college nursing students at a minority-serving institution. *J. Community Health* **2013**, *38*, 1106–1114. [CrossRef]
18. Jeannot, E.; Viviano, M.; de Pree, C.; Amadane, M.; Kabengele, E.; Vassilakos, P.; Petignat, P. Prevalence of Vaccine Type Infections in Vaccinated and Non-Vaccinated Young Women: HPV-IMPACT, a Self-Sampling Study. *Int. J. Environ. Res. Public Health* **2018**, *15*, 1447. [CrossRef] [PubMed]
19. Amadane, M.; de Pree, C.; Viviano, M.; Vassilakos, P.; Jeannot, E.; Petignat, P. Characteristics of HPV-unvaccinated undergraduate health students in Switzerland, a cross sectional study. *Arch. Public Health* **2019**, *77*, 29. [CrossRef]
20. Blodt, S.; Holmberg, C.; Muller-Nordhorn, J.; Rieckmann, N. Human Papillomavirus awareness, knowledge and vaccine acceptance: A survey among 18–25 year old male and female vocational school students in Berlin, Germany. *Eur. J. Public Health* **2012**, *22*, 808–813. [CrossRef]
21. Karafillakis, E.; Simas, C.; Jarrett, C.; Verger, P.; Peretti-Watel, P.; Dib, F.; De Angelis, S.; Takacs, J.; Ali, K.A.; Pastore Celentano, L.; et al. HPV vaccination in a context of public mistrust and uncertainty: A systematic literature review of determinants of HPV vaccine hesitancy in Europe. *Hum. Vaccines Immunother.* **2019**, *15*, 1615–1627. [CrossRef]

22. Maltezou, H.C.; Theodoridou, K.; Ledda, C.; Rapisarda, V.; Theodoridou, M. Vaccination of healthcare workers: Is mandatory vaccination needed? *Expert Rev. Vaccines* **2019**, *18*, 5–13. [CrossRef]
23. Givaudan, M.; Pala, K.C. Vaccination: When providence becomes mistrust. *Rev. Med. Suisse* **2017**, *13*, 1641–1644. [PubMed]
24. Cousins, S. Measles: A global resurgence. *Lancet Infect. Dis.* **2019**, *19*, 362–363. [CrossRef]
25. Paules, C.I.; Marston, H.D.; Fauci, A.S. Measles in 2019—Going Backward. *N. Engl. J. Med.* **2019**, *380*, 2185–2187. [CrossRef] [PubMed]
26. Lutringer-Magnin, D.; Kalecinski, J.; Barone, G.; Borne, H.; Regnier, V.; Vanhems, P.; Chauvin, F.; Lasset, C. Gynaecologists' attitudes and practices towards HPV vaccination: A quantitative-qualitative study in Rhone-Alpes. *Gynecol. Obstet. Fertil.* **2011**, *39*, 687–693. [CrossRef] [PubMed]
27. Young, J.L.; Bernheim, R.G.; Korte, J.E.; Stoler, M.H.; Guterbock, T.M.; Rice, L.W. Human papillomavirus vaccination recommendation may be linked to reimbursement: A survey of Virginia family practitioners and gynecologists. *J. Pediatr. Adolesc. Gynecol.* **2011**, *24*, 380–385. [CrossRef] [PubMed]
28. Lutringer-Magnin, D.; Kalecinski, J.; Barone, G.; Leocmach, Y.; Regnier, V.; Jacquard, A.C.; Soubeyrand, B.; Vanhems, P.; Chauvin, F.; Lasset, C. Human papillomavirus (HPV) vaccination: Perception and practice among French general practitioners in the year since licensing. *Vaccine* **2011**, *29*, 5322–5328. [CrossRef] [PubMed]
29. Commission fédérale pour l'enfance et la jeunesse. *La Sexualité des Jeunes au fil du Temps: Evolution, Influences et Perspectives*; Commission Fédérale Pour L'enfance et la Jeunesse: Bern, Switzerland, 2009.
30. Sheaves, C.G. Influence of education strategies on young women's knowledge and attitudes about the HPV vaccine. *Womens Heal.* **2016**, *4*, 4.
31. Lee, M.J.; Cho, J. Promoting HPV Vaccination Online: Message Design and Media Choice. *Health Promot. Pract.* **2017**, *18*, 645–653. [CrossRef]
32. Angioli, R.; Casciello, M.; Lopez, S.; Plotti, F.; Minco, L.D.; Frati, P.; Fineschi, V.; Panici, P.B.; Scaletta, G.; Capriglione, S.; et al. Assessing HPV vaccination perceptions with online social media in Italy. *Int. J. Gynecol. Cancer* **2019**, *29*, 453–458. [CrossRef]
33. Tu, Y.C.; Lin, Y.J.; Fan, L.W.; Tsai, T.I.; Wang, H.H. Effects of Multimedia Framed Messages on Human Papillomavirus Prevention Among Adolescents. *West J. Nurs. Res.* **2019**, *41*, 58–77. [CrossRef]
34. Barras, V.; Jacot-Guillarmod, M. Human papillomavirus: What do young people really know about it? *Rev. Med. Suisse* **2014**, *10*, 1297–1301.

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Characteristics of HPV-unvaccinated undergraduate health students in Switzerland, a cross sectional study

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Abstract

Background: Human Papillomavirus (HPV) vaccination, intended for young women aged 11–14 years old, has been introduced in Switzerland in 2007. Ten years after its introduction, only a few studies have explored the reasons associated with uptake and non-uptake of the vaccination. Our objective was to identify the sociodemographic characteristics of a population of vaccinated and unvaccinated undergraduate healthcare female students, to define the reasons of non-uptake of vaccination, and compare our findings with those found in other Swiss cantons.

Methods: Between January and November 2017, women studying in Health Sciences School and Medical School in Geneva, aged 18–31 years old, were recruited in a large trial assessing HPV prevalence. As part of a smaller, observational study nested in this larger trial, women were invited to complete a questionnaire. Self-reported HPV vaccination uptake or non-uptake, as well as knowledge and attitude about HPV vaccination were assessed. T-Test and Chi square test were used to compare characteristics of vaccinated and unvaccinated women.

Results: Overall, 409 women were recruited in the study. The majority of them (69.1%) reported having been vaccinated for HPV, while 30.9% of them had never received any dose of the HPV vaccine. The only factor associated with a higher vaccination rate was the participants' origin, as women from Geneva were more represented in the vaccinated group than women from other Swiss regions or countries. Unvaccinated women were more likely to consider HPV vaccination as less important than the vaccinated ones (50.4% vs 3.5% $p < 0.001$).

Conclusion: Although no typical profile can be established in this studied population of unvaccinated women, a lack of information was a major reason of non-uptake of vaccination among the study participants. An effort by health authorities and carefully designed messages are essential to increase the population's awareness over cervical cancer and its prevention.

Trial registration: The trial was registered under cliniclatrials.gov with the identifier: NCT03474211.

Keywords: Cervical cancer, Human papillomavirus (HPV), Undergraduate students, Unvaccinated

Background

Human Papillomavirus (HPV) is responsible for the most prevalent sexually transmitted infection worldwide, which represents a major public health challenge [1]. It is estimated that up to 70% of the sexually active population will be infected with HPV at least once in their life [2]. The highest infection rate is found among 16–25-year-old women. While up to 70% of HPV infections are spontaneously cleared after a few months [3], the persistence of the virus is responsible for the development of cervical cancer, which is associated to HPV in nearly 100% of cases [4]. Cervical cancer is the fifth most common cancer among women aged 20–49 years living in Switzerland [5]. Every year, Switzerland counts as many as 250 cervical cancer and 5′000 cervical precancerous lesion diagnoses [6].

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HPV vaccination represents a fundamental primary prevention measure for the development of cervical cancer. The currently available vaccines in Switzerland are Gardasil® and Cervarix®, both of which protect against HPV genotypes 16 and 18, which are responsible for the development of cervical cancer in over 70% of cases [7]. Gardasil®, which has been available on the market since 2007, also covers against genotypes 6 and 11, which are mostly responsible for the development of genital condylomas [8].

The Swiss recommendations for HPV vaccination were first published in 2007, advising the vaccination for all females between the ages of 11 and 14 years while also recommending a catch-up vaccination for women aged 15 to 19 years [9]. The aim of such primary prevention measure is to cover over 80% of the target population. Such recommendations, however, were implemented by each federal canton individually. Such individualized implementation has resulted in disparities in the campaigns and, therefore, in vaccination rates across the country (from 17 to 75% of the targeted population in 2014) [10].

In the Canton of Geneva, the first HPV vaccination campaign tookplace in September 2008. The greatest asset of the campaign in Geneva is the strong involvement of school health services, such as the *Service de L'Enfant et de la Jeunesse* (SSJ) in public schools, which inform families and offer vaccination to all female school children aged 11–19 years old. According to a study on HPV vaccination carried out 4 years after the first campaign, the majority of 13–14 year-old girls had been vaccinated through the SSJ, thus proving its efficiency [11]. Despite this institutional effort, however, the targeted coverage rate of 80% has yet to be reached. Only a few studies have been carried out with the aim of understanding the reasons for non-vaccination in Switzerland. Moreover, as the campaigns are organised individually by each canton, it is difficult to make generalisations based on the other cantons' experience and statistics.

The aim of this study was (i) to compare the sociodemographic characteristics of a population of vaccinated and unvaccinated undergraduate female healtcare students in the Geneva canton, (ii) to define the reasons for not having undergone vaccination in the latter group, and (iii) to compare the reasons for non-vaccination to those found in other Swiss cantons.

Material and methods

Population

Recruitement of the study participants took place from January to November 2017 at the Medical school and at the School of Health Sciences of the Medical University of Geneva, located in the city of Geneva, Switzerland. Women aged 18–31 years, currently attending either Medical School to obtain a medical doctor degree or the School of Health Sciences in Geneva to obtain a nurse or midwife degree, were invited to participate in the study.

Study design

This study has been carried out as a nested, observational study within a larger trial evaluating the HPV vaccine's effectiveness by analyzing the HPV prevalence using a cervico-vaginal self-sampling method [12].

Announcements about the study were given by previously-informed professors teaching classes at the School of Health Sciences and at the Medical School in Geneva. An email was also sent by the study investigators to the students prior to their recruitement. After having delivered a short presentation about the HPV infection and the project's design, the study investigators distributed the kits to those students who expressed an interest to participate in the study. The kits contained a cotton swab for HPV self-sampling (ClassiqSwab, COPAN, Brescia, Italy), illustrated instructions on how to use the swab for self-sampling, an informed consent form, an explanatory document about the HPV infection and a questionnaire on sociodemographics and their reasons of non vaccinated choice. Each kit also contained an identification number, to which the participants could refer to obtain their HPV test results. The students were given 1 week to return the kit and the questionnaire to the study investigators. The results of the HPV analysis were given to the students by a designated study investigator upon request.

The questionnaire which women were invited to complete in order to fulfill the aim of this study included questions about the HPV vaccination uptake or non-uptake, the participants' knowledge and attitudes over the HPV vaccination, their sexual behavior and country or Swiss canton of origin.

Sample size

The sample size was calculated based on the primary outcome of the main study [12]. It was obtained based on an estimated prevalence of 6% of HPV 16/18 infection in the Swiss population aged less than 30 years. A total of 400 specimens were 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%. We therefore estimated that a sample size of 400 women would be adequate for the analyses.

Statistical analyses

Statistical analyses were run using STATA 13. The normality of the distribution was tested by the Kolmogorov-Smirnov test. Descriptive statistics and

frequencies were analysed for all variables. The T-test and Chi square test were used for the descriptive statistics and for the comparaison between variables. A p value of less than 0.05 was considered as statistically significant.

Ethical approval

The study protocol was approved by the ethical cantonal board in Geneva (Commission Cantonale d'Ethique et de la Recherche – CCER) with the identification number 15–357. All participants signed an informed consent form prior to taking part in the study. The trial was registered under cliniclatrials.gov with the identifiers: NCT03474211.

Results

Sociodemographic and clinical characteristics

Out of 500 kits distributed, a total of 409 were given back, thus obtaining a response rate of 81.8% (409/500). Among the 409 participants included in the study, 55% of them (225/409) were enrolled in Medical School while 45% (184/409) of them attended the School of Health Sciences. A total of 46% of the study participants reported their vaccination status based on their own personal notion, without verifying such data on their vaccination booklet. Women coming from the Geneva canton were more represented in the vaccinated (71.1%, 202/284) than in the nonvaccinated group of participants (59.2%, 74/125), whereas women coming from other Swiss cantons, who were grouped together with women coming from other countries (France, Portugal, Spain ect..) were more represented in the nonvaccinated group (40.8%, 51/125) than in the vaccinated one (28.9%, 82/284, $p = 0.017$). We found that only 2.8% (8/284) of vaccinated women were infected by the HPV strains 6, 11, 16 and 18, while up to 11% (17/125) of the unvaccinated participants were infected by these same 4 strains. The participants' sociodemographic and clinical characteristics are reported in Table 1.

Beliefs regarding the importance of the HPV vaccination

Overall, 91.9% (261/284) of the vaccinated women believed that the HPV vaccination was as important as other vaccinations, while only 48.8% (61/125) of the unvaccinated participants believed that the HPV vaccination was as important as the others ($p < 0.001$). A total of 4.6% (13/284) and 0.8% (1/125) vaccinated and unvaccinated women, respectively, believed that the HPV vaccination was more important than other types of vaccination. There were 3.5% (10/284) and 50.4% (63/125) of vaccinated and unvaccinated women, respectively, who believed that the HPV vaccination was less important than others. The participants' perceptions of the importance of the HPV vaccination are reported in Table 2.

Table 1 Sociodemographic characteristics and HPV test results of the study population

Variable	vaccinated		unvaccinated		*p value*
	n=284		n=125		
	n	%	n	%	
Age, y					
Mean	22.5 SD (±) 2.9		21.9 SD (±) 2.6		0.16
< 20	110	38.7	50	40	**0.03**[#]
20-23	101	35.6	57	45.6	
> 23	73	25.7	18	14.4	
Origin					**0.017**
Geneva	202	71.1	74	59.2	
Other*	82	28.9	51	40.8	
Tobacco smoking					0.31
Yes	53	18.7	27	21.6	
No	231	81.3	98	78.4	
Age at your first sexual intercourse, mean (y)	17.1 SD (±) 2.4		17 SD (±) 2.8		0.14
Total number of sexual partners					
Mean	5.3 SD (±) 1.26		5.1 SD (±) 1.33		0.42
None	10	3.5	4	3.2	0.98
≤ 5	135	47.5	60	48	
> 5	139	48.9	61	48.8	
Use of condoms					0.6
Never/sometimes	142	50	66	52.8	
Often/always	142	50	59	47.2	
HPV prevalence					
Types 6, 11, 16, 18	8	2.8	17	11	**0.0002**
Other HR and LR HPV types	41	14	25	20	0.12

Abbreviations: *HPV* Human Papillomavirus, *y* years, *N* number, *HR* high risk HPV, *LR* low-risk HPV
*Includes women coming either from other Swiss cantons or from other countries
[#]*p* value in boldface are statistically significant

Association between opinion on the HPV vaccination and sociodemographics characteristics

Among unvaccinated participants, the proportion of women who believed that the HPV vaccination was less important than others decreased as the women's age

Table 2 Participants' beliefs about the HPV vaccination

In general, do you think that HPV vaccination is a vaccination:	Vaccinated		Unvaccinated		*P value*
	N	%	N	%	
More important than others	13	4.60	1	0.80	**< 0.001**[#]
Less important than others	10	3.50	63	50.40	**< 0.001**
As important as the others	261	91.90	61	48.80	**< 0.001**

Abbreviations: *HPV* Human Papillomavirus, *N* number
[#]*p* value in boldface are statistically significant

increased (62% of the < 20 years group (31/50), 45.6% of the 20–23 years (26/57), 38.9% of the > 23 years (7/18); $p = 0.35$). On the contrary, the proportion of women who believed that the HPV vaccination was either more than or as important as other vaccinations increased with the women's age (< 20 years: 38% (19/50); 20–23 years: 54.4% (31/57); > 23 years: 61.1% (11/18); $p = 0.07$).

Association between opinion about the HPV vaccination and condom use

Among unvaccinated participants who believed that the HPV vaccination was less important (50.4%; 63/125), 57.1% of them (36/63) used the condom sometimes/never, whereas 42.9% (27/63) of them used it often/always. Among women who considered the HPV vaccination as/more important than other vaccinations (49.6%; 62/125), 51.2% (32/62) used the condom often or always, while 48.8% (30/62) used it sometimes/never. The association between the participants' opinion about the HPV vaccination and their frequency of condom use is reported in Fig. 1.

Reasons for not having been vaccinated

A total of 41.6% (52/125) of the unvaccinated women did not give any information or did not know why they had not been vaccinated. Among women who gave a reason for not having been vaccinated (58.4%, 73/125), the reported reasons included: fear of side effects (21.6%, 27/125); parents being against the vaccination, either in general or the HPV-one (14.4%; 18/125); the physician in private practice being against the HPV vaccination (8.8%; 11/125); the vaccination not being considered as useful (2.4%; 3/125); the person being against vaccinations in general (2.4%; 3/125); sexual inactivity (1.6%; 2/125); insufficient evidence on the vaccine's efficacy and side effects (1.6%; 2/125). The reasons for not having been vaccinated are reported in Table 3.

Discussion

This is the first study to evaluate the acceptability of the HPV vaccine in Geneva since the introduction of the HPV vaccination in the canton. Our results revealed that 69.4% of our study population was vaccinated against HPV, a rate higher than the rest of Switzerland where, according to the results of a survey conducted in 2016, only 53.6% of women aged 18–24 years were vaccinated [13]. Another study conducted in 2014 found that the French-speaking Swiss regions vaunt a vaccination rate of 68.1%, which is consistent with the rate found in our trial [10]. Moreover, a recent systematic review collecting data from 28 countries pointed out the heterogeneity of vaccination rates worlwide, varing from 2.4 to 94.4% [14].

However, Our results reflect a reality in which, despite the remarkable efforts to reach the optimal vaccination coverage rate, the resistance to the vaccination prevents public health workers from reaching the optimal coverage rate. When looking at reasons for non-vaccination, three of them stood out: fear of side effects (21.6%), parents being against the HPV vaccination (14.4%) and the physician being against the vaccination (8.8%). Similarly, in a study including women aged 18–24 years living in the French-speaking region in Switzerland [10], the main reasons for not having been vaccinated were: thinking it was too late (due to either age, sexual activity, or pathological smear) (52%), fear of side effects (26%), not having received enough information (19%), being against all kinds of vaccination (17%) and having discouraging relatives and friends (15%). Furthermore, a study

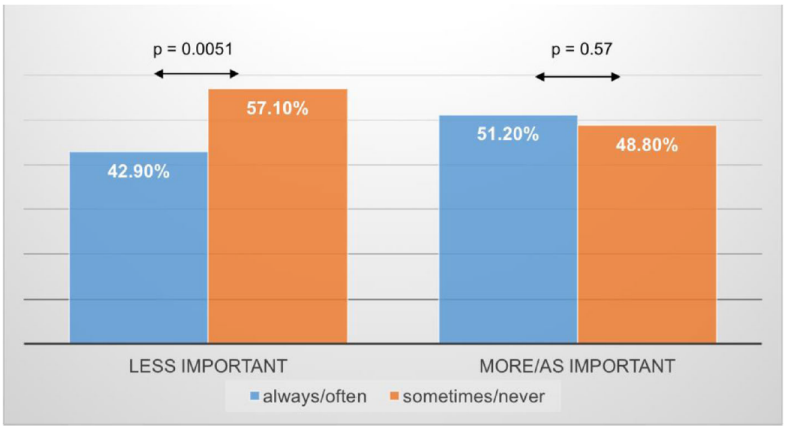

Fig. 1 Association between use of condom and opinion about HPV-vaccination among the unvaccinated group of participants

Table 3 Reasons for not having been vaccinated among unvaccinated women

Variable	n	%
No reason given or doesn't know	52	41.6
Reason given :	73	58.4
Fear of side effects	27	21.6
Parent against HPV vaccination	18	14.4
Physician in private practice against HPV vaccination	11	8.8
Not considered useful	3	2.4
Against vaccinations in general	3	2.4
No sexual activity	2	1.6
Only 1 sexual partner	2	1.6
No efficacy	2	1.6
Insufficient evidence	2	1.6
Other	3	2.4

Abbreviations: *N* number, *HPV* Human Papillomavirus

including 16–20 year-olds living in the Canton of Vaud [9] revealed a lack of information about the HPV infection's natural history and prevention, as over 70% of the interviewed population felt insufficiently informed about the disease. Moreover, one of the issues highlighted by 29% of the physicians working in private practice in the French-speaking region of Switzerland [8] was the lack of information and support brought by their cantons. A recent study conducted in Switzerland following the first 2 years after the vaccination's introduction reported that only 117 cases of Gardasil®-associated side effects were found among 420′000 vaccine doses. The same study estimated that 93–98% of CIN2+ lesions caused by 16 and 18 genotypes and 46–70% of the CIN2+ lesions caused by other HPV genotypes could be avoided with vaccination [15]. Such results, which can be used by public health workers to improve the future vaccination campaigns, demonstrate that the lack of information about the HPV infection and its prevention concerns not only the general population, but also health professionals.

Concerning the opinion about the importance of the HPV vaccination, we found that the difference between vaccinated and unvaccinated women was compatible with their immunization status. Over 50.4% of unvaccinated women considered the vaccination as less important than other vaccinations, while 91.9% of vaccinated women considered it as as important as other vaccinations. Another study carried out in Italy obtained similar results among women aged 18–21 years old, thus demonstrating that one of the factors associated with not having been vaccinated was the lower perception of its benefits [16].

A small majority (51.1%) of our population sample had been vaccinated between the ages of 15 and 19 years old, although vaccination for women in this age range was meant to be a catch-up for those who had missed their opportunity to be vaccinated in the first place. Knowing that the moment for the ideal vaccination is before first sexual intercourse, which in our population took place at a median age of 17.2 years old, baseline vaccination for all 15–19 years-olds seems to be a reasonable target to improve prevention. Nevertheless, the median age when receiving the first vaccine dose in our study population was 14.8 years old. The small percentage of vaccinated women after the age of 20 years old (4.2%) is not surprising considering that the campaign mainly targets the younger part of the population. Such results are in line with those of a study [6] evaluating the age at the first dose of HPV vaccine in a population of Swiss women, which found that the vaccination rates were 54.4% for women between aged 15–19 years old, 39.8% for women aged 11–14 years old, and 5.8% for women older than 20.

When studying the sociodemographic characteristics of our population, only nationality was found to be significantly associated to vaccination status, as a greater proportion of women coming from Geneva and its surroundings were vaccinated when compared to women coming from other cantons and countries. Given the difference of the vaccination campaigns and policies in other cantons and countries, such finding highlights the efficacy of the vaccination campaign in the canton of Geneva, where a particularly active role was played by the SSJ in public and private schools. Other studies have confirmed that, when the SSJ was involved in vaccination campaigns, as is the case in other French-speaking cantons in Switzerland, such finding resulted in better vaccination rates than those in the German-speaking part of Switzerland [9].

One strength of our study was given by the fact that we chose a population of young, future healthcare providers, whose opinion is fundamental in the view of spreading the vaccination uptakein the near future. In addition, this population sample of young adults has never been studied in such geographical area.

One limitation of our study was the sample's relatively small size, which limited the power of some of our observations. A selection bias also may have occurred, as all the participants not only had a high educational degree but also studied medical and health sciences, which does not reflect the heterogeneity of the general population. Additionally, the HPV kits were offered to the students who proactively expressed an interest to participate in the study, excluding the girls possibly having another opinion about the HPV vaccination. Finally, 46.3% of our participants had not checked their

vaccination record to answer the questionnaire, an aspect which may have altered some of the study results.

Conclusion

The suboptimal HPV vaccination rate among our study population of undergraduate women shows that, despite the vaccine's proven efficacy, the coverage rate is still far from reaching 80%. The majority of vaccinated women in our study population came from the Geneva Canton, a finding which further highlights the discrepancies in vaccination campaigns in the country. Proactive education about the HPV infection's natural history and the vaccination's role, to be delievered by the women's personal healthcare providers, represents a fundamental step in increasing the vaccination coverage rate across the country.

Abbreviations

CCER: Commission Cantonale d'Ethique et de la Recherche; HPV: Human PapillomaVirus; SSJ: Service de L'Enfant et de la Jeunesse

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Availability of data and materials

The databases are not publically available.

Authors' contributions

JE, VM, VP and PP conceived and designed the study; JE, VM, dPC, AM collected data; JE, VM analyzed the data; JE, VM, dPC, AM, KE, VP and PP wrote the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the ethical cantonal board in Geneva (Commission Cantonale d'Ethique et de la Recherche – CCER) with the identification number 15–357.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Carmona-Gutierrez D, Kainz K, Madeo F. Sexually transmitted infections: old foes on the rise. Microb Cell. 2016;3(9):361–2.
2. Wang CJ, Palefsky JM. Human papillomavirus (HPV) infections and the importance of HPV vaccination. Curr Epidemiol Rep. 2015;2(2):101–9.
3. Ingles DJ, Lin HY, Fulp WJ, Sudenga SL, Lu B, Schabath MB, et al. An analysis of HPV infection incidence and clearance by genotype and age in men: the HPV infection in men (HIM) study. Papillomavirus Res. 2015;1:126–35.
4. Ault KA. Epidemiology and natural history of human papillomavirus infections in the female genital tract. Infect Dis Obstet Gynecol. 2006; 2006(Suppl):40470.
5. Burton-Jeangros C, Cullati S, Manor O, Courvoisier DS, Bouchardy C, Guessous I. Cervical cancer screening in Switzerland: cross-sectional trends (1992-2012) in social inequalities. Eur J Pub Health. 2017;27(1):167–73.
6. Ochs K, Meili G, Diebold J, Arndt V, Gunthert A. Incidence trends of cervical Cancer and its precancerous lesions in women of Central Switzerland from 2000 until 2014. Front Med (Lausanne). 2018;5:58.
7. Maine D, Hurlburt S, Greeson D. Cervical cancer prevention in the 21st century: cost is not the only issue. Am J Public Health. 2011;101(9):1549–55.
8. Bonanni P, Bechini A, Donato R, Capei R, Sacco C, Levi M, et al. Human papilloma virus vaccination: impact and recommendations across the world. Ther Adv Vaccines. 2015;3(1):3–12.
9. Jeannot E, Petignat P, Sudre P. Successful implementation and results of an HPV vaccination program in Geneva Canton, Switzerland. Public Health Rep. 2015;130(3):202–6.
10. Office Fédérale de la Santé Publique. La vaccination contre le HPV en Suisse: résultats d'une enquête nationale réalisée en 2014. 2015.
11. Jeannot E, Sudre P, Chastonay P. HPV vaccination coverage within 3 years of program launching (2008-2011) at Geneva State, Switzerland. Int J Public Health. 2012;57(3):629–32.
12. Jeannot E, Viviano M, de Pree C, Amadane M, Kabengele E, Vassilakos P, et al. Prevalence of vaccine type infections in vaccinated and non-vaccinated young women: HPV-IMPACT, a self-sampling study. Int J Environ Res Public Health. 2018;15(7):1447.
13. Wymann MN, Zographos AS, Altpeter E, Spicher VM, Low N, Mausezahl-Feuz M. Human papillomavirus vaccine uptake in adolescence and adherence to cervical cancer screening in Switzerland: a national cross-sectional survey. Int J Public Health. 2018;63(1):105–14.
14. Loke AY, Kwan ML, Wong YT, Wong AKY. The uptake of human papillomavirus vaccination and its associated factors among adolescents: a systematic review. J Prim Care Community Health. 2017;8(4):349–62.
15. Office Fédérale de la Santé Publique. Programmes de vaccination contre les HPV en Suisse: synthèse des années 2007 à 2010. Office Fédéral de la Santé Publique; 2010.
16. Restivo V, Costantino C, Fazio TF, Casuccio N, D'Angelo C, Vitale F, et al. Factors associated with HPV vaccine refusal among young adult women after ten years of vaccine implementation. Int J Environ Res Public Health. 2018;15(4):770.

Other Publications Peer Reviews related to this thesis:

1. Viviano M, Catarino R, **Jeannot E**, Boulvain M, Malinverno MU, Vassilakos P, et al. Self-sampling to improve cervical cancer screening coverage in Switzerland: a randomised controlled trial. Br J Cancer. 2017;116(11):1382-8. Impact Factor : **5.4**

2. **Jeannot E**, Huber T, Casillas A, Wolff H, Getaz L. Immunisation coverage among adolescents in a Swiss juvenile correctional facility. Acta Paediatr. 2016;105(12):e600-e2. Impact Factor : **2.26**

3. **Jeannot E**, Petignat P, Sudre P. Successful implementation and results of an HPV vaccination program in Geneva Canton, Switzerland. Public Health Rep. 2015;130(3):202-6. Impact Factor : **2.039**

FULL PAPER

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Keywords: cervical cancer; screening; HPV self-sampling; HPV testing; screening participation; follow-up

Self-sampling to improve cervical cancer screening coverage in Switzerland: a randomised controlled trial

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Background: The aim of this study is to evaluate whether self-sampling can increase screening attendance of women who do not attend regular screening in Switzerland.

Methods: Participants were proactively recruited in Geneva between September 2011 and November 2015. Women (25–69 years) who had not undergone CC screening in the last 3 years were considered eligible. Through a 1 : 1 ratio randomisation, enrolled participants were invited to either undergo liquid-based cytology, which was performed by a health-care provider (control group, CG) or to take a self-sample for HPV-testing, which was mailed to their home (intervention group, IG).

Results: A total of 331 and 336 women were randomised in the CG and in the IG, respectively. Overall, 7.3% (95% CI: 4.9–10.6) women in the CG and 5.7% (95% CI: 3.6–8.7) women in the IG did not undergo the initial screening ($P=0.400$). There were 1.95% (95% CI: 0.8–4.3) women in the CG and 5.05% (95% CI: 3.1–8.1) women in the IG with a positive screen who did not attend triage and colposcopy ($P=0.036$).

Conclusions: The participation in CC screening in women offered self-sampling was not higher than among those offered specimen collection by a clinician. Compliance with further follow-up for women with a positive HPV test on the self-sample requires further attention.

The successful implementation of cytology-based screening has rendered cervical cancer (CC) preventable and has led to a decrease in the incidence, morbidity and mortality from this disease (Kitchener *et al*, 2006; Arbyn *et al*, 2009). Gynecologists and general physicians (GPs) in Switzerland have been promoting CC screening since the late 1960s, in this way achieving a reduction of the CC incidence by ~60% (Bouchardy *et al*, 1990; Petignat *et al*, 2012). The country has an opportunistic screening system, which is essentially based on the gynecologists' and GPs' invitation for a periodic control (Petignat *et al*, 2012). This means that, in the absence of an organised screening program, women are only screened based on their own initiative and that of their physician (Vassilakos *et al*, 2015). As it is an opportunistic system, the relative statistics are difficult to monitor and the only available data come from population-based surveys conducted by the Swiss Federal Office of Public Health (FOPH) and the National Institute for Cancer Epidemiology (NICER; Petignat *et al*, 2012).

According to these sources, approximately 70% of eligible women have had a Pap smear in the last 3 years (Burton-Jeangros *et al*, 2017). The latest recommendations of the SSGO (*Société Suisse de Gynécologie et d'Obstétrique*) propose that, in the absence of cervical abnormalities, women aged 21–29 years should be

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screened with cytology every 2 years, while women aged 30–70 years should be screened on a 3-year basis (Gerber *et al*, 2012). Women from lower socioeconomic groups and living in rural areas are less likely to undergo screening, which exposes them to a higher risk of developing CC (Rodriguez *et al*, 2005; Bischoff *et al*, 2009). The main obstacles to screening participation include absence of insurance coverage, low income, lack of time, and human/emotional factors, such as lack of knowledge about CC and fear of a positive test result (Catarino *et al*, 2016). One of the aims of the Swiss National Cancer Control Program 2011–2015 is the implementation of a CC screening system across the nation, together with the maximisation of the screening coverage rate (National Cancer Programme for Switzerland, 2011–2015). In an effort to extend their participation rate, CC screening policies in Switzerland should take into account the main practical and emotional barriers that stand in the way of regular screening attendance, as well as the socio-demographic and cultural diversity that characterise women across the country (Bischoff *et al*, 2009).

When compared to cytology-based screening, Human Papillomavirus (HPV) testing has proven to be more sensitive in detecting cervical intra-epithelial neoplasia grade 2 or worse (CIN2+), therefore improving the identification of women at risk for CC (Arbyn *et al*, 2012; Ronco *et al*, 2014). In addition, as it can be performed on self-collected samples (self-sampling), HPV testing has the potential to overcome some of the obstacles to conventional cytology-based screening (Arbyn *et al*, 2014). By avoiding the need of a clinic-based visit, HPV testing could reach women who would not otherwise attend the traditional screening program and, therefore, increase the effectiveness of CC screening (Feldman, 2014; Arbyn and Castle, 2015; Giorgi-Rossi *et al*, 2015).

Although several clinical trials support the use of HPV testing for primary CC screening, the use of this new strategy has to be adapted to the specific context in which it is being implemented (Verdoodt *et al*, 2015). Given the heterogeneity in health and screening systems, as well as in the follow-up strategies worldwide, it is crucial to determine the feasibility and population compliance with HPV-based screening in each setting (Arbyn and Castle, 2015).

We conducted a randomised controlled trial to determine (i) whether Self-sampling is a feasible and effective method to reach women who do not regularly attend CC screening with the traditional strategy in Switzerland and (ii) the proportion of women with a positive screening test that underwent the recommended follow-up clinical investigations.

MATERIALS AND METHODS

General study design. This randomised controlled clinical trial took place in Geneva between September 2011 and December 2015. Recruitment took place mainly via newspaper and web-based advertisements, as well as through flyers distributed by physicians working both at the public hospital and in private practice. A web page dedicated to the study was also created on a social network. Women from immigrant communities were also recruited in order to maximise the socio-demographic and ethnical heterogeneity of our study sample. Women interested in taking part in the study could either return a coupon in a pre-paid envelope or contact the referent medical staff via e-mail. These women were then contacted by telephone by a research nurse who checked for eligibility criteria, gave them further information and instructions regarding the study procedure and, if possible, registered them in the study. Inclusion criteria were as follows: women aged between 25 and 69 years, who had never taken part in a CC screening program or who had not undergone Pap testing in the preceding 3 years. Exclusion criteria were pregnancy or previous hysterectomy.

An online statistical software (www.randomization.com) was used to generate the randomisation list, with randomly permuted blocks of varying size (4, 6 and 8). On the basis of this list, consecutively numbered, sealed opaque envelopes containing the group allocation were prepared. When a new participant consented to participate in the study, the study nurse opened the next available envelope.

The study was approved by the Central Ethics Committee on Human Research of the Geneva University Hospitals (approval number: CER 11-034 MAT-PED 11-010). All enrolled women have given written informed consent.

Control group. Women assigned to the control group (CG) received an invitation letter to undergo liquid-based cytology testing, which was performed by a clinician. The sample for cytology was collected using the Thin Prep Pap tests (HOLOGIC, Marlborough, MA, USA). Cervical cells were collected using the Cervex-Brush Combi (Rovers, Oss, the Netherlands) as recommended by the European guidelines (Arbyn *et al*, 2007) and introduced into a PreservCyt solution vial. If the Pap test result showed no signs of dyskaryosis, women were invited to repeat CC screening after a 3-year interval. If cytology showed either atypical squamous cells, cannot exclude HSIL (ASC-H), or a low-grade (LSIL) or high-grade squamous intra-epithelial lesion (HSIL), women were referred to colposcopy. In case of ASC-US, triage by HPV testing was performed. The sample for HPV testing was taken directly from the PreservCyt solution vial, therefore not requiring participants to return to the clinic for an additional visit. The HPV test was performed with the Roche Cobas 4800 HPV test (Roche Molecular Diagnostics, Pleasanton, CA, USA), which consists of a qualitative, multiplex, real-time PCR assay that provides pooled results on 12 high-risk HPV (HR-HPV) genotypes and individual results on the highest-risk genotypes, HPV 16 and HPV 18. If the HPV test was negative, women were advised to repeat CC screening after one year. If the HPV test was positive, regardless of the HPV genotype, they were referred to colposcopy.

Intervention group. Participants in the intervention group (IG) received a self-sampling kit at home. This included written instructions and drawings explaining them how to perform Self-sampling, and a sterile flocked swab that came in a transportation tube containing 1 ml of Liquid Amies (ESwab; Copan, Brescia, Italy). Women performed Self-sampling at home and returned it by mail in a pre-paid envelope within 7 days after sample collection. The HPV test was performed with the Roche Cobas 4800 HPV test, as described above. The test results were communicated to each participant by telephone. HPV-negative women were advised to repeat screening after 5 years. Women who tested positive for HPV-16 and/or 18 were referred to colposcopy. Participants who were positive for other HR-HPV genotypes were invited to undergo triage with Pap testing. Women with a cytological diagnosis of ASC-US or worse (ASC-US+) were referred to colposcopy, while the others were advised to repeat screening within a year.

Financial aspects. The costs associated with baseline screening were fully covered by the study for women in both groups. The costs of HPV testing triage and those of colposcopy for women in the CG were covered by the participant's insurance or by the participant herself in the absence of insurance coverage. Similarly, the costs of cytology triage and those of colposcopy for women in the IG were covered by the participants' insurance or by the participant herself in the absence of insurance coverage.

Data collection. Each participant completed a questionnaire on demographics, obstetric and gynecological history, and reasons for previous non-attendance in CC screening. The detailed results of this analysis are reported in two previously published articles (Catarino *et al*, 2015, 2016).

Statistical analysis. Statistical analyses were performed using Stata IC, version 14.0 (StataCorp, College Station, TX, USA). Descriptive statistics and frequencies were analysed for all variables.

For the primary outcome, we estimated the proportion of women who did not complete baseline testing. For the secondary outcome, we estimated the proportion of participants who tested positive at either self-sampling or cytology and who did not undergo the following recommended clinical investigations to obtain a diagnosis.

We also calculated the rate of histologically-confirmed Cervical Intra-epithelial Neoplasia grade 1 (CIN1), grade 2 (CIN2), grade 3 (CIN3) and grade 2 or worse (CIN2+).

Differences between mean values were assessed using the T-Student test, whereas differences between percentages were tested with the Pearson X^2-test.

Results were considered statistically significant at $P \leqslant 0.05$.

The sample size was set to 550 women in each group and was calculated to be able to detect a 10% difference in the response rate between the IG (60%) and the CG (50%) with a power of 90% and a 95% confidence level.

RESULTS

Sample characteristics. The baseline characteristics of women in the two groups were similar (see Table 1). The mean and s.d. of the age of the participants were 42.0 (10.8) years and 42.3 (10.9) years in the CG and IG, respectively. The majority of women in the two groups had previously undergone CC screening, with the last screening test dating back to at least four years (80.8% and 82.4% in the CG and in the IG, respectively). A high proportion of women in both groups were Latin American (31.7% and 31.3% in the CG and in the IG, respectively) and 42.3% of women in the CG and 35.8% of women in the IG did not have a health insurance.

Main study results. A total of 941 women were assessed for eligibility; of these, 667 (70.9%) fulfilled the eligibility criteria and were enrolled in the study (see Figure 1).

Following randomisation, 331 women were assigned to the CG and were thus invited for a clinician-performed liquid-based cytology testing. Among these, 307 (92.7%) participants attended at a clinic-based Pap testing. There were 252 (82.1%) women with a normal cytology and 55 (17.9%) women with ASC-US or worse. Out of the 55 women (17.9%) with an ASC-US+ result, 23 (41.8%) had an ASC-H+ cytology result and were referred to colposcopy. The cytology samples of the 32 women (58.2%) with an ASC-US diagnosis were processed for HPV testing. Among these, 7 (25.0%) women were HPV-positive and were also referred to colposcopy for further evaluation.

Three-hundred and thirty-six women were randomised in the IG and were thus invited to perform Self-sampling. Of these women, 317 (94.3%) participants performed and returned their self-sample. Overall, 242 (76.3%) women were HPV-negative, and 75 (23.7%) were HPV-positive. Among the 75 (72.0%) women who tested positive for HPV, 21 (28.0%) were positive for HPV-16 and/or HPV-18 and were referred directly to colposcopy. Fifty-four women (72.0%) were positive to other HR-HPV types and therefore underwent triage by cytology. Six women positive for other HR-HPV types did not undergo Pap testing. Among the participants who underwent cytology triage, 15 of them (34.9%) were ASC-US+ and were therefore addressed to colposcopy. Women positive at HPV testing with a negative cytology were recalled for repeat HPV testing at 1 year.

Primary and secondary outcomes. Overall, 24/331 (7.3%, 95% CI: 4.9–10.6) women in the CG and 19/336 (5.6%, 95% CI: 3.6–8.7) women in the IG did not attend the initial screening ($P = 0.400$). A total of 6/307 (1.95%, 95% CI: 0.8–4.3) women in the CG and 16/317 (5.05%, 95% CI: 3.1–8.1) women in the IG with a positive screening test were lost between baseline screening and colposcopy ($P = 0.036$). The overall proportion of women who missed either the initial screening or the follow-up was 30/331 (9.1%; 95% CI: 6.4–12.7) participants in the CG and 35/336 (10.4%, 95% CI: 7.6–14.2) participants in the IG ($P = 0.650$; See Table 2).

Among these women, 10/30 (33.3%, 95% CI: 19.1–51.3) and 13/35 (37.1%, 95% CI: 23.1–53.7) did not have a health insurance in the CG and in the IG, respectively ($P = 0.87$). Overall, 22/30 (73.3%, 95% CI: 55.4–86.0) and 25/35 (71.4%, 95% CI: 54.8–83.8) of women who exited the study had a part or full-time job in the CG and in the IG, respectively ($P = 0.84$). Among women who dropped out between baseline screening and colposcopy in the IG, 12/17 (70.6%, 95% CI: 46.6–87.0) of them had part- or full-time job.

Table 1. Demographic characteristics of the study participants

	Control group (n = 331)		Intervention, group (n = 336)	
Age, mean ± s.d.	42.1 ± 10.8		42.3 ± 10.9	
Previous CC screening				
Yes, *n* (%)	268	81.0	277	82.4
No	63	19.0	59	17.6
Relationship status				
With a partner	154	46.5	161	47.9
Single	177	53.5	175	52.1
Nationality				
Swiss	47	14.2	47	14
Other European	58	17.5	66	19.6
Asian	61	18.4	45	13.4
African	33	10	30	8.9
Latin American	106	32.0	105	31.3
Other	26	7.9	40	12.1
Religion				
Christians	158	47.7	157	46.7
Muslims	21	6.3	24	7.1
Other	92	28.1	75	22.3
Atheists	59	17.8	77	22.9
Unknown	1	0.3	3	0.9
Number of children, mean ± s.d.	1.4 ± 1.4		1.6 ± 1.6	
Education				
Apprenticeship/high school	150	45.3	169	50.3
University	176	53.2	159	47.3
None	5	1.5	3	0.9
Employment status				
Unemployed	58	17.5	60	18
Employed part or full time	242	73.1	253	76
Retired	7	2.1	8	2.4
Student	12	3.6	10	3
Insurance				
Yes	192	58.0	215	64.2
No	139	42.0	120	35.8

Abbreviations: CC = cervical cancer; HPV = Human Papillomavirus; *n* = number.

Histological diagnoses. A total of 25 women underwent colposcopy in the CG. The detection rate of CIN2+ in this group was 4/331 (1.3%, 95% CI: 0.4–3.2). All of these women had CIN grade 3 (CIN3).

Thirty women underwent colposcopy in the IG. The CIN2+ detection rate was 10/336 (3.0%, 95% CI: 1.6–5.5); of these, 6 women had a CIN3 and 4 had a CIN3 (Table 3).

The difference between the detection rate of CIN2+ in the CG (1.2%) and in the IG (3.0%) was not statistically significant ($P = 0.110$).

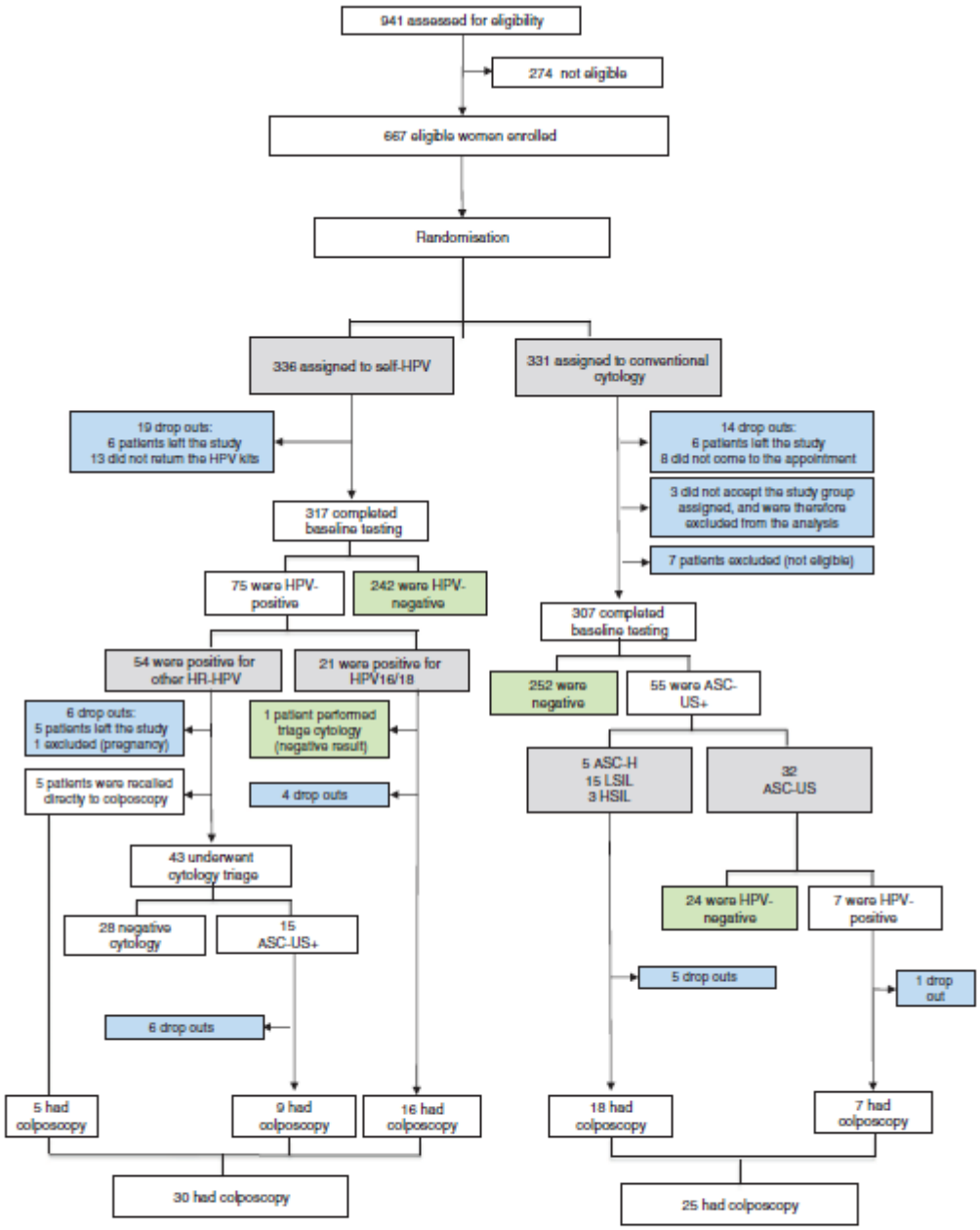

Figure 1. Study flowchart. HPV = Human Papillomavirus; ASC-US = Atypical squamous cells of undetermined significance; ASC-US + = Atypical squamous cells of undetermined significance or worse; ASC-H = Atypical squamous cells of undetermined significance cannot exclude HSIL; L-SIL = Low-grade squamous intra-epithelial lesion; HSIL = High-grade squamous intra-epithelial lesion.

Table 2. Participants who exited the study

	Control group N (%)	Intervention group N (%)	P
Baseline screening	24/331 (7.1)	19/336 (5.6)	0.400
Between baseline screening and colposcopy	6/307 (1.95)	16/317 (5.05)	0.036
Overall	30/331 (9.1)	35/336 (10.4)	0.650

Table 3. Histological diagnoses' distribution in the two study groups

	Control group (n) %	Intervention group % (n)	P
CIN1	2.4% (8/331)	0.3% (1/336)	0.17
CIN2	0 (0%)	1.2% (4/336)	
CIN3	1.2% (4/331)	1.8% (6/336)	0.54
CIN2+	1.2% (4/331)	3.0% (10/336)	0.11

Abbreviations: CIN1 = cervical intraepithelial neoplasia grade 1; CIN2 = cervical intraepithelial neoplasia grade 2; CIN3 = cervical intraepithelial neoplasia grade 3; CIN2+ = cervical intraepithelial neoplasia grade 2 or more severe; n = number.

DISCUSSION

Our results show that Self-sampling does not improve screening uptake among non- and under-screened women willing to participate in a study on CC screening in Switzerland. Clinic-based Pap testing and home-performed Self-sampling achieved a comparable initial attendance. In contrast with our results, other studies found that inviting women to perform Self-sampling by mailing them the HPV kit directly at home results in a greater participation when compared to that obtained with an invitation letter for a clinic-based Pap test (Huynh *et al*, 2010; Penaranda *et al*, 2015; Sultana *et al*, 2016). The recruitment strategy, could partly explain the difference between our findings and those of other trials. While our study population of non- and under-screened women was proactively recruited through advertisements, the participants in other trials, such as the iPap in Australia, were selected directly through the national register (Sultana *et al*, 2016). Therefore, women included in our study were possibly more willing to attend CC screening, regardless of the method. A systematic review and meta-analysis reported that the overall participation was similar for self- and clinician-performed cervical sampling when women had to 'opt-in' screening, as in our trial (Verdoodt *et al*, 2015). Women in the CG with a positive screening test went directly to colposcopy, resulting in a lower drop-out rate compared to that of participants in the IG, who had to undergo clinic-based cytology triage. The significant difference between these two proportions suggests a certain reluctance to undergo further clinic-based investigations when a screening test is positive. It is worth mentioning that about half of the women in the two groups did not have a health insurance. This means that while the possibility to benefit of a free primary screening service may have contributed to their recruitment, the fact that the costs of the clinical management that followed a positive screening test were at their charge may have discouraged them from undergoing further clinical management. Considering that one of the main obstacles to screening participation is its cost, this aspect may have influenced the higher loss to follow-up rate in the IG, where an additional clinical step was required (Loerzel and Bushy, 2005; Catarino *et al*, 2015). Furthermore, as another barrier to screening attendance is lack of time, the time-consuming aspect of an additional clinical visit may explain the higher dropout rate in the IG (Catarino *et al*, 2016). This concept is reinforced by the finding that the majority of participants who dropped out between the baseline screening results and colposcopy were working women, who may have lacked the time to undergo multiple clinical visits.

We found that HPV testing for CC screening led to an increased detection of CIN2+ lesions in the IG when compared to the CG. Although in our case they are compatible with a random fluctuation, these results are in line with previous studies conducted in other industrialised countries (Cuzick *et al*, 2006; Bulkmans *et al*, 2007; Naucler *et al*, 2007; Ronco *et al*, 2010; Rijkaart *et al*, 2012; Ronco *et al*, 2014), which support the use of HPV testing as a primary screening tool. A meta-analysis on the subject suggests that, when PCR-based assays that amplify DNA viral sequences are used, the performance of HPV testing on clinician-collected samples is comparable to that of Self-sampling (Arbyn *et al*, 2014). Although recent results from a qualitative study conducted in Switzerland have shown a certain degree of skepticism toward the Self-sampling test, the majority of women in favor of this technique were the unscreened ones (Fargnoli *et al*, 2015). Furthermore, the absence of invalid HPV test results supports the simplicity and feasibility of this technique when performed by women themselves, outside the clinical setting.

One of the main problems of opportunistic screening systems, such as the one in Switzerland, is that they can easily miss people who have limited access to information and health services, thus not adequately covering the entire targeted population (Bischoff *et al*, 2009). The first step in building a strong screening service in Switzerland should be the implementation of a coordinating service in each Canton, with the aim of establishing a screening program in order to inform and raise the population's level of awareness of CC and its prevention. In addition, in order to increase the program's effectiveness, the cost of primary screening should be covered by federal funds, at least for women whose annual income does not exceed a certain threshold. Further studies are needed in order to validate the proactive screening strategy *vs* the opportunistic one in Switzerland.

One promising way to increase follow-up compliance would be by incorporating HPV testing in a 'screen-and-treat' strategy, which would simplify the clinical management that follows a positive test result. By reducing the number of clinical visits, the 'screen-and-treat' strategy may be preferable in developing countries, where some of the main factors influencing the success of CC screening campaigns are low patient compliance and loss to follow-up. The more promising option for industrialised countries such as Switzerland appears to be the one which, by reducing the number of clinical visits while alleviating the costs of CC screening, would allow to break down the main barriers to CC screening attendance.

Strengths and limitations. One strength of this study was the participation of ethnically diverse women, which reflects the real-life population in the Swiss canton of Geneva. Another strength is represented by the fact that we used a real-time PCR that allowed distinguishing the HPV-16/18 genotypes, which are associated to a higher risk of developing CC, from other 12 HR-HPV types. In addition, as opposed to other trials using Self-sampling, which registered between 0.5 and 0.7% of unsatisfactory HPV test results, we had no invalid results (Bosgraaf *et al*, 2015; Giorgi-Rossi *et al*, 2015).

Our study has some limitations that need to be addressed. We were able to recruit fewer participants than expected by the sample size estimation. The assumptions used to estimated the sample size

were different from the actual recruitment process of the trial, thus limiting the power to obtain statistically significant difference between the two options for initial screening. In addition, our study was conducted in an urban setting, which limits the generalisation of our results to the population living in Switzerland. Another reason for which the study group was not entirely representative of the population living in Geneva and its surroundings is the proportion of women with previous CC screening, which was rather high as compared with the lower rates in Geneva and its surroundings. Additionally, an important pre-selection bias is likely to have occurred. Since we selected women who had actively responded to the campaign's advertisements, participants were possibly more willing to accept any CC screening approach than the general population.

CONCLUSION

When compared to Pap testing, Self-sampling does not increase screening participation for non- and under-screened women who are motivated to participate in a CC screening campaign in Switzerland. The clinical management of HPV-positive women requires further attention in order to define the most acceptable algorithm in terms of women compliance, financial and clinical aspects.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Arbyn M, Rebolj M, De Kok IM, Fender M, Becker N, O'Reilly M, Andrae B (2009) The challenges of organising cervical screening programmes in the 15 old member states of the European Union. *Eur J Cancer* **45**: 2671–2678.

Arbyn M, Castle PE (2015) Offering self-sampling kits for HPV testing to reach women who do not attend in the regular cervical cancer screening program. *Cancer Epidemiol Biomarkers Prev* **24**: 769–772.

Arbyn M, Herbert A, Schenck U, Nieminen P, Jordan J, Mcgoogan E, Patnick J, Bergeron C, Baldauf JJ, Klinkhamer P, Bulten J, Martin-Hirsch P (2007) European guidelines for quality assurance in cervical cancer screening: recommendations for collecting samples for conventional and liquid-based cytology. *Cytopathology* **18**: 133–139.

Arbyn M, Ronco G, Anttila A, Meijer CJ, Poljak M, Ogilvie G, Koliopoulos G, Naucler P, Sankaranarayanan R, Peto J (2012) Evidence regarding HPV testing in secondary prevention of cervical cancer. *Vaccine* **30**(Suppl 5): F88–F99.

Arbyn M, Verdoot F, Snijders PJ, Verhoef VM, Suonio E, Dillner L, Minozzi S, Bellisario C, Banzi R, Zhao FH, Hillemanns P, Anttila A (2014) Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* **15**: 172–183.

Bischoff A, Greuter U, Fontana M, Wanner P (2009) Cervical cancer screening among immigrants in Switzerland. *Divers Health Care* **6**: 159–169.

Bosgraaf RP, Verhoef VM, Massuger LF, Siebers AG, Bulten J, de Kuyper-de-Ridder GM, Meijer CJ, Snijders PJ, Heideman DA, IntHout J, van Kemenade FJ, Melchers WJ, Bekkers RL (2015) Comparative performance of novel self-sampling methods in detecting high-risk human papillomavirus in 30,130 women not attending cervical screening. *Int J Cancer* **136**: 646–655.

Bouchardy C, Fioretta G, Raymond L, Vassilakos P (1990) Age differentials in trends of uterine cervical cancer incidence from 1970 to 1987 in Geneva. *Rev Epidemiol Sante Publique* **38**: 261–262.

Bulkmans NWJ, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJ, Bulk S, Voorhorst FJ, Verheijen RH, van Groningen K, Boon ME, Ruitinga W, van Ballegooijen M, Snijders PJ, Meijer CJ (2007) Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet* **370**: 1764–1772.

Burton-Jeangros C, Cullati S, Manor O, Courvoisier DS, Bouchardy C, Guessous I (2017) Cervical cancer screening in Switzerland: cross-sectional trends (1992–2012) in social inequalities. *Eur J Public Health* **27**(1): 167–173.

Catarino R, Vassilakos P, Stadali-Ullrich H, Royannez-Drevard I, Guillot C, Petignat P (2015) Feasibility of at-home self-sampling for HPV testing as an appropriate screening strategy for nonparticipants in Switzerland: preliminary results of the DEPIST study. *J Low Genit Tract Dis* **19**: 27–34.

Catarino R, Vassilakos P, Royannez-Drevard I, Guillot C, Alzuphar S, Fehlmann A, Meyer-Hamme U, Petignat P (2016) Barriers to Cervical Cancer Screening in Geneva (DEPIST Study). *J Low Genit Tract Dis* **20**: 135–138.

Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, Szarewski A, Birembaut P, Kulasingam S, Sasieni P, Iftner T (2006) Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer* **119**: 1095–1101.

Fargnoli V, Petignat P, Burton-Jeangros C (2015) To what extent will women accept self-sampling for cervical cancer screening? A qualitative study conducted in Switzerland. *Int J Womens Health* **7**: 883–888.

Feldman S (2014) Human papillomavirus testing for primary cervical cancer screening: is it time to abandon Papanicolau testing? *JAMA Intern Med* **174**: 1539–1540.

Gerber S, Heinzl S, Canonica C, Fehr M, Frey Tirri B, Mueller M, Obwegeser J, Seydoux J, Wight E (2012) Mise á jour du dépistage du cancer du col et du suivi en colposcopie. *Avis d'expert No 40*. Bern, Switzerland.

Giorgi-Rossi P, Arbyn M, Meijer CJ (2015) Cervical cancer screening by human papillomavirus testing followed by cytology triage. *JAMA Intern Med* **175**: 1068.

Huynh J, Howard M, Lytwyn A (2010) Self-collection for vaginal human papillomavirus testing: systematic review of studies asking women their perceptions. *J Low Genit Tract Dis* **14**: 356–362.

Kitchener HC, Castle PE, Cox JT (2006) Achievements and limitations of cervical cytology screening. *Vaccine* **24**(suppl 3): S63–S70.

Loerzel VW, Bushy A (2005) Interventions that address cancer health disparities in women. *Fam Community Health* **28**: 79–89.

Naucler P, Walter R, Törnberg S, Strand A, Wadell G, Elfgren K, Radberg T, Strander B, Johansson B, Forslund O, Hansson B-G, Rylander E, Dillner J (2007) Human papillomavirus and papanicolau tests to screen for cervical cancer. *N Engl J Med* **357**: 1589–1597.

National Cancer Programme for Switzerland (2011–2015) *Communication NCP*. Bern January 2011: Oncosuisse.

Penaranda E, Mololwu J, Flores S, Byrd T, Brown L, Shokar N (2015) Women's attitudes toward cervicovaginal self-sampling for high-risk HPV infection on the US-Mexico border. *J Low Genit Tract Dis* **19**: 323–328.

Petignat P, Untiet S, Vassilakos P (2012) How to improve cervical cancer screening in Switzerland? *Swiss Med Wkly* **142**: w13663.

Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NW, Heideman DA, Kenter GG, Cuzick J, Snijders PJ, Meijer CJ (2012) Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. *Lancet Oncol* **13**: 78–88.

Rodriguez A, Ward LM, Pérez-Stable EJ (2005) Breast and cervical cancer screening: impact of health insurance status, ethnicity, and nativity of latinas. *Ann Fam Med* **3**: 235–241.

Ronco G, Dillner J, Elfström KM, TUnesi S, Snijders PJ, Arbyn M, Kitchener H, Segnan N, Gilham C, Giorgi-Rossi P, Berkhof J, Peto J, Meijer CJ, International HPV screening working group (2014) Efficacy of HPV-based screeningfor prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet* **383**: 524–532.

Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, Ghiringhello B, Girlando S, Gillio-Tos A, De Marco L,

Naldoni C, Pierotti P, Rizzolo R, Schincaglia P, Zorzi M, Zappa M, Segnan N, Cuzick J, New Technologies for Cervical Cancer screening (NTCC) working group (2010) Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol* **11**: 249–257.

Sultana F, English DR, Simpson JA, Drennan KT, Mullins R, Brotherton JM, Wrede CD, Heley S, Saville M, Gertig DM (2016) Home-based HPV self-sampling improves participation by never-screened and under-screened women: results from a large randomised trial (iPap) in Australia. *Int J Cancer* **139**: 281–290.

Vassilakos P, Catarino R, Frey Tirri B, Petignat P (2015) Cervical cancer screening in Switzerland: time to rethink the guidelines. *Swiss Med Wkly* **145**: w14112.

Verdoodt F, Jentschke M, Hillemanns P, Racey CS, Snijders PJ, Arbyn M (2015) Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials. *Eur J Cancer* **51**: 2375–2385.

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SHORT COMMUNICATION

Immunisation coverage among adolescents in a Swiss juvenile correctional facility

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The risk of acquiring vaccine-preventable diseases is higher among incarcerated populations, compared to the general population. Factors associated with this are: history of social precarity/vulnerability, risky behaviours and the baseline prevalence of communicable diseases within these populations (1). Adolescents in juvenile correctional facilities are a particularly vulnerable population in regards to vaccine-preventable diseases. Therefore, vaccination is a key health promotion activity towards adolescent well-being and healthy development, especially for incarcerated youth (2). A juvenile corrections facility environment provides a vaccination window for an at-risk population whose access to healthcare is otherwise limited in the community. This study analysed immunisation data among incarcerated adolescents in Geneva, Switzerland. Our objectives were to examine vaccination coverage and compare these data to a community adolescent population in Geneva.

All adolescents admitted to the 'Clairière' for a consecutive duration of at least three months, between January 2009 and December 2011 were eligible for the study. The Clairière is a juvenile correctional facility for adolescents (ages 12–18 years) awaiting trial or sentenced to an educational placement in detention. All admits undergo an intake history and physical examination at entry. Immunisation records for participants were systematically retrieved by at least one of the following mechanisms: existing vaccination charts in the personal health record, communication with paediatrician and/or by serologic examination (with consent from the adolescent). Some information was also obtained from legal parental guardians, letter was automatically sent to all guardians asking about immunisation records/history.

Immunisation history for the study focused on the following vaccination dose completion: tetanus, diphtheria and pertussis (DTaP), polio (IPV) (for DTaP and IPV, between three and six doses according to age of initial immunisation), measles mumps rubella (MMR) two doses, hepatitis B (HBV) (two or three doses according to vaccination schedule) and Human papilloma virus (HPV)-three doses (3). For those individuals with multiple admissions into the juvenile correctional facility, vaccination history was computed as a tally of their cumulative entry examinations and considered here as a single data point. We also collected socio-demographic data (age, sex, place of origin).

The study was approved by the ethical research committee (CER 12-238-R) from the University Hospitals of Geneva. Informed consent was obtained from all individual participants included in the study.

We used the binomial proportions test and the Wilcoxon two-samples test to compare coverage between incarcerated youth and the general adolescent population. The significance level was set at $p < 0.05$. Statistical analysis was performed using Stata 10.

We compared these results to a sample of community-living adolescents in Geneva, using 2007 vaccine prevalence data from the youth health service/'Service santé Jeunesse' (SSJ) from 2007. Service santé Jeunesse conducted vaccination surveys among 16-year-old students enrolled at secondary schools in the Geneva canton. The SSJ survey methodology regarding students' immunisation history is described elsewhere (4).

For the 36-month study period, 116 eligible adolescents (93 boys and 23 girls) detained for at least 3 months were

enrolled in the study (100% participation rate). Mean age was 15.35 years (SD = 0.11). We can observe that fifty-five percent (63/116) of participants were Swiss, and 45% (53/116) were foreign-born (18 from Southern European countries, two from Eastern Europe, three from the American continents, four from Asia and five from Africa). Of the 116 participants, 36% (IC95%: 27.5–45.3) were vaccinated on schedule (againstTdap, Polio, MMR and HBV), in line with the recommendations from the Swiss Federal office of Public Health (3). Specific immunisation rates are shown in Table 1.

Compared to a community adolescent population in Geneva in 2007 (the SSJ study), these incarcerated adolescents had significantly lower immunisation rates for all vaccines ($p < 0.0001$), except for the HPV vaccine ($p = 0.71$) (Table 1). Furthermore, immunisation rates according to origin were mostly similar. However, Hepatitis B immunisation rates of Swiss-born adolescents (60.3%) were significantly higher than foreign-born adolescents (7.9%) ($p = 0.0001$). There was no statistically significant difference in vaccination rates according to sex (Table 2).

Eighty-nine vaccine injections were administered during detention; 32 adolescents became up-to-date on their vaccines during detention.

There are few studies that examine the vaccine status of adolescents in custodial detention. Similar to our findings, two surveys in North America showed a deficit in vaccination coverage among incarcerated adolescents. A study from the United States showed that the baseline immunisation coverage of adolescents entering the juvenile justice system was lower than the general adolescent population (5). A Canadian study observed that 73% of adolescents under detention had incomplete immunisations according to Canadian National Advisory Committee on Immunizations; 49% were missing tetanus, diphtheria and acellular pertussis immunisations; 33%, meningococcus; 2%, measles, mumps and rubella; and 37% (55 of 148), hepatitis B. Routine vaccine evaluation and access to medical services in detention increased vaccine coverage from 27% to 65% in this juvenile population (2). Nevertheless the severity of this problem depends on region: a study in Spain showed that only 16.8% of adolescents admitted to a juvenile correctional facility were incompletely immunised (6).

One notable finding was that HBV and HPV immunisation rates were low in the study population (37% and 52%, respectively). This is of increased importance given that incarcerated adolescents have an elevated risk of sexually transmitted infections (7). Gaskin et al. have already demonstrated that immunisation programs in the juvenile justice setting increase coverage rates to levels that are comparable to an adolescent population in the community (5). Thus, vaccination programs for incarcerated adolescents should also focus on 'catch-up' vaccine boosters that prevent sexually transmitted infections.

In terms of limitations, the findings may not be readily generalisable to other settings and/or populations as the study took place at one detention facility in Geneva. It is also possible that vaccination history abstracted from medical records did not reflect true immunisation status. Nevertheless, subsequent efforts were made to systematically corroborate vaccine record information with communication with adolescents' parents and/or their primary care physicians This study demonstrated significantly lower rates of vaccination coverage among Geneva's incarcerated adolescents, compared to a population of adolescents in the community. Medical service during detention is a health-promoting opportunity for these at-risk youth. Such services include screening examinations that review vaccination records and proactive vaccine administration

Table 1 Vaccine coverage rates for 2009–2011 Clairière adolescents versus 2007 SSJ Geneva study population

	Clairière N = 116			SSJ N = 912			
	N	%	95 CI%	N	%	95 CI%	p
Tdap	42	36.2	27.8–45.2	771	84.5	82.1–86.8	<0.0001
Polio	55	47.4	38.4–56.5	770	84.4	82.1–86.8	<0.0001
MMR	71	61.2	52.1–69.7	768	84.2	81.9–86.7	<0.0001
Hep B	43	37.0	28.6–46.1	561	61.5	58.3–64.6	<0.0001
HPV*	12/23	52.2	32.1–71.7	250/446	56.1	51.4–60.6	0.71

*Administered only to females.
SSJ = Service santé Jeunesse.

Table 2 Vaccine coverage across origin and sex, at Clairière custodial facility in 2009–2011

	Place of origin			Sex		
Vaccination schedule completed	Swiss-born n = 63	Foreign-born n = 53	p	Male n = 93	Female n = 23	p
'DTaP/Tdap'	26/63 (41.2%)	16/53 (30.1%)	0.21	31/93 (33.3%)	11/23 (47.8%)	0.19
Polio	31/63 (49.2%)	24/53 (45.2%)	0.67	41/93 (44.0%)	14/23 (60.8%)	0.15
MMR	39/63 (61.9%)	32/53 (60%)	0.86	57/93 (62.3%)	14/23 (60.8%)	0.97
Hep B	38/63 (60.3%)	5/53 (7.9%)	<0.001	32/93 (34.4%)	11/23 (47.8%)	0.23
HPV*	4/10 (40%)	8/13 (61.5%)	0.49	–	12/23 (52.1%)	
ALL Vaccines	23/63 (36.5%)	14/53 (26.4%)	0.52	31 (33.3%)	11/23 (47.8%)	0.19

*Administered only to females.
MMR = Measles mumps rubella.

('catch-up' the patient to the recommended national schedule). In the long-term, these public health measures not only protect this vulnerable population, but also the community at large.

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The authors indicated they have no potential conflict of interest to disclose.

References

1. Sequera VG, Garcia-Basteiro AL, Bayas JM. The role of vaccination in prisoners' health. *Expert Rev Vaccines* 2013; 12: 469–71.
2. Bartlett L, Kanellos-Sutton M, van Wylick R. Immunization rates in a Canadian juvenile corrections facility. *J Adolesc Health* 2008; 43: 609–11.
3. Office fédéral de la Santé Publique. Plan de vaccination 2011. 2011; Available at: http://www.bag.admin.ch/themen/medizin/00682/00684/02535/index.html?lang=fr (accessed on July 20, 2011).
4. Jeannot E, Wyler CA, Duperrex O, Chastonay P. [Evolution of the immunization coverage of 13 to 14 year-old adolescents in Geneva between four years]. *Sante Publique* 2009; 21: 605–11. Epub 2010/05/01. Evolution a quatre ans de la couverture vaccinale chez les 13–14 ans a Geneve.
5. Gaskin GL, Glanz JM, Binswanger IA, Anoshiravani A. Immunization coverage among juvenile justice detainees. *J Correct Health Care* 2015; 21: 265–75.
6. Olivan G. The health profile of Spanish incarcerated delinquent youths. *J Adolesc Health* 2001; 29: 384.
7. Belenko S, Dembo R, Rollie M, Childs K, Salvatore C. Detecting, preventing, and treating sexually transmitted diseases among adolescent arrestees: an unmet public health need. *Am J Public Health* 2009; 99: 1032–41.

Successful Implementation and Results of an HPV Vaccination Program in Geneva Canton, Switzerland

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ABSTRACT

We describe a human papillomavirus (HPV) vaccination program implemented since 2007 in Geneva Canton, Switzerland, that used school services, a public hospital, and private physicians as vaccination providers. We assessed program performance with the evolution of immunization coverage during the first four years of program implementation. We measured vaccination coverage of the target population using individual records of vaccination status collected by service providers and transmitted to the Geneva Canton Medical Office. The target population was 20,541 adolescent girls aged 11–19 years as of September 1, 2008, who resided in the canton when the program began. As of June 30, 2012, HPV vaccination coverage was 72.6% and 74.8% in targeted cohorts for three and two doses, respectively. The global coverage for three doses increased by 27 percentage points from December 2009 to June 2012. Coverage for girls aged 16–18 years at the beginning of the program reached 80% or more four years into the program. High coverage by this HPV vaccination program in Geneva was likely related to free vaccination and easy access to the vaccine using a combination of delivery services, including school health services, a public hospital, and private physicians, covering most eligible adolescent girls.

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Human papillomavirus (HPV) represents a group of sexually transmitted viruses of particular interest because of their high prevalence and strong causal association with cervical cancer.[1] Cervical cancer is the second most frequently occurring cancer in the world for women.[2] Every year in Switzerland, 5,000 women present with a precancerous lesion of the cervix or an in situ carcinoma, and 320 women present with an invasive cervical carcinoma requiring surgical or laser treatment.[1] Half of the women presenting with a precancerous lesion of the cervix or an in situ carcinoma are <50 years of age at the time of diagnosis.[3] In Geneva, Switzerland, 400 cases of in situ and 30 cases of invasive cervical cancer are diagnosed annually, resulting in 5–10 deaths per year.[4] Both morbidity and mortality associated with this infection can be reduced through vaccination.[5]

Two vaccines to prevent HPV infections have been developed by two companies, Sanofi Pasteur MSD and GSK,[6–8] that decrease the incidence of precancerous lesions of the cervix and also that of genital warts, another HPV-related infection.[9] Since 2006, following the European Medicine Agency approval of Cervarix® and Gardasil®, these two vaccines have been used in most European countries.[5] Cervarix targets HPV-16, -18, -31, -33, and -45, the five most common cancer-causing viral types, including most causes of adenocarcinoma. Gardasil targets HPV-16, -18, and -31, the three common squamous cell cancer-causing viral types, as well as HPV-6 and -11, which are associated with genital warts and respiratory papillomatosis.[10] As in the United States, national recommendations on immunization in Switzerland are implemented by states (cantons), which have a wide level of autonomy on health-related matters. In Geneva Canton, the operational strategy was to vaccinate as many eligible (i.e., aged 11–18 years) adolescent girls as possible by sending them individual letters and making vaccination free of charge through all potential health-care providers of this age group (e.g., pediatricians, general practitioners, gynecologists, public hospital clinics, and school health services). This article provides an overview of the establishment of a publicly funded HPV vaccination program in Geneva Canton, preliminary coverage results, and key features of success.

METHODS

Implementation of the HPV vaccination program in Geneva

In Switzerland, immunization policy is defined by the federal immunization commission. Vaccines for children are provided free of charge through the mandatory universal health insurance program. Vaccinations are mostly administered by private physicians and school health services in public schools. In some cantons, state-employed public health nurses and physicians provide preventive services such as vaccination and health education in publicly funded schools. Since 2007, the Swiss Federal Vaccination Commission has recommended HPV vaccination free of charge for adolescent girls aged 11–19 years[11] through a cantonal vaccination program. During the 2007–2008 school year, Geneva Canton was among the first cantons in Switzerland to plan and implement such a canton-wide HPV vaccination program through three different and complementary service providers: in public schools, by private physicians, and by the Geneva University Hospital.

During the first year of the program (2007–2008), only the 2,150 girls in seventh grade in public schools of the canton (i.e., aged 11–12 years) could be vaccinated by the School Health Service (i.e., Service Santé de la Jeunesse [SSJ]). Since the 2008–2009 school year, vaccination has been offered free of charge to adolescent girls aged 11–19 years, amounting to approximately 4,000 eligible adolescent girls each year. Girls can be vaccinated by one of three service providers: in public schools (since 2007–2008), by private physicians, or by the Geneva University Hospital.

Vaccination data monitoring was available through a list of girls who had received their first, second, and third shots and were sent three times per year to the State Medical Office. Participating private practitioners (i.e., pediatricians, gynecologists, internists, and general practitioners) received the vaccine doses free of charge. Every three months, they transmitted individual electronic vaccination forms—including name; date of birth; and number and date of first, second, or third dose—to the State Medical Office. Geneva University Hospital offered vaccination to those who did not have a private physician or who could not or did not want to use SSJ. They applied the same procedure as private practitioners and submitted vaccination forms to the State Medical Office every three months.

Program promotion

Geneva University Hospital vaccination was offered on a voluntary basis. Public information and the vaccine promotion were therefore essential to reach the targeted coverage of 80% with three doses. All service providers contributed to this activity and received promotional documents, including posters and brochures prepared and printed locally or by the Federal Office of Public Health. On the basis of the federal immunization commission positioning, the Federal Office of Public Health

makes official recommendations and ensures that recommended vaccines are included in the list of services covered free of charge by the national insurance plan. All eligible adolescent girls (or their parents if they were <16 years of age) received a letter from the State Medical Office containing three vaccination vouchers for the first, second, and third injections. When the state HPV vaccination program was launched, all teen girls aged 16–19 years—16 being the age of sexual majority in Switzerland—or their parents if they were 11–15 years of age received a letter with information on the HPV vaccine. This letter included three vouchers to complete and present at the time of vaccination. These vouchers were sent by the health-care provider to the HPV program coordinator and used for their reimbursement and statistics. The SSJ sent a separate mailing offering vaccination in schools. The mailing for girls <16 years of age included a parental consent form. A reminder letter was sent to all eligible girls. An automated electronic reminder via short messaging service and an individual letter were also sent to the eligible girls owning a mobile phone who had received their first injection at the Geneva University Hospital vaccination center.[12]

Estimation of HPV vaccination coverage of the target population

At the beginning of the Geneva vaccination program in September 2007, 20,541 adolescent girls aged 11–19 years were eligible for vaccination, with a new yearly cohort of approximately 2,400 11-year-old girls. This number was used as the denominator to estimate immunization coverage with two and three doses of vaccine; this yearly denominator was supplied by the Service for Research in Education of the canton of Geneva based on an official government database. To determine the numerator, each service provider transmitted a nominal list of the people who had received their first, second, or third doses of HPV vaccine to the State Medical Office on a quarterly basis. Coverage for these cohorts was measured three times: on December 31, 2009, a year and a half after the program started; on June 30, 2011, after three years; and on June 30, 2012, four years into the program. We conducted statistical analysis using Stata® version 10.0.[13] All personal identifiers were removed prior to the analysis.

OUTCOMES

A year and a half into the program, three-dose HPV coverage for the 1989–1997 birth cohort was 45.6% (Table). Coverage had progressed to 61.4% after three years and 72.6% after four years, a 27-percentage-point increase in 2.5 years. Two-dose HPV coverage increased from 47.9% to 63.2% to 74.8% at the 1.5-, 3-, and 4-year marks, an increase of 27 percentage points in 2.5 years for the target population (data not shown). The vast majority of girls who received their second dose also received the third dose, with an average difference of only two points (data not shown). To date, the highest coverage was reached among girls born between 1994 and 1996 (aged 16–18 years at the beginning of the program), and at least 80% of them had received three doses of vaccine four years into the program (Table).

Service providers covered different age groups. SSJ vaccinated 80% of the 14-year-old girls, 60% of the 13-year-old girls, and <10% of those aged 16–21 years. Medical doctors in private practice vaccinated 50%–70% of the target population except in the 13- to 14-year-old age group. Geneva University Hospital (ad hoc vaccination center) vaccinated about 50% of girls aged 18–19 years and a much lower proportion

Table. Evolution of third-dose HPV coverage from December 31, 2009, to June 30, 2012, for adolescent girls born between 1989 and 1997 in Geneva Canton, Switzerland

Birth year	*Eligible girls* N	*Third-dose HPV coverage as of December 31, 2009* Percent	*Third-dose HPV coverage as of June 30, 2011* Percent	*Third-dose HPV coverage as of June 30, 2012* Percent
1989	2,282	35.0	40.9	45.0
1990	2,421	38.3	51.8	58.1
1991	2,342	50.2	62.6	68.0
1992	2,256	54.5	67.8	72.8
1993	2,297	55.9	74.9	76.9
1994	2,228	61.9	78.0	80.1
1995	2,307	65.1	79.2	82.3
1996	2,218	54.2	78.1	82.0
1997	2,190	16.1	64.7	75.0
Total 1989–1997	20,541	45.6	61.4	72.6

HPV = human papillomavirus

(5%–15%) of those aged 11–14 years. The proportion of eligible girls who did not get the second and/or third dose after receiving the first dose was similar for all age groups regardless of the service providers, with the exception of the SSJ (data not shown).

LESSONS LEARNED

Within a fairly short period of time, the HPV vaccination program implemented in Geneva has achieved immunization coverage as high as 82% in the main target group. One reason for this success could be related to the opportunity given the target audience to be vaccinated by different providers (e.g., school health service, Geneva University Hospital, and physicians in private practice). Media interest, public promotion of the vaccination program, and direct mailing with free vouchers have also played an important role in the program's success. Although the monitoring system was relatively complex for vaccination providers, it helped to improve coordination and collaboration between the various stakeholders and the State Medical Office. In Geneva, the State Medical Office coordinated the HPV vaccination program, imposing for management purposes a strict registration system for monitoring financial and HPV vaccine flow. This monitoring scheme made it possible to follow trends in vaccination uptake in the target population during the four-year period.

To date, Geneva Canton is the only canton in Switzerland that has published comprehensive, population-based coverage data.[12] A first estimation of HPV coverage for the entire Swiss population was conducted in 2013 (Personal communication, Claire Anne Wyler, School Health Service, Geneva, January 2014), indicating a rate of 51% (95% confidence interval 48.4, 52.9) for three doses of vaccine in girls aged 16 years. Unfortunately, many Swiss cantons, especially Geneva Canton, did not participate in this study; as such, comparison with our results was difficult.

If cervical cancer is to be eliminated as a public health problem, increasing and maintaining high HPV vaccination coverage of new cohorts remains the main programmatic challenge. In 19 out of 29 European Union countries that have launched HPV vaccination programs, coverage rates vary widely from only 17% in Luxembourg to 84% in Portugal for three doses. In 2010, of seven countries reporting coverage data, only Portugal and the United Kingdom had full vaccination coverage rates >80% for their target groups.[14] In the U.S., vaccination coverage for adolescents aged 13–17 years with two and three doses significantly increased annually for the 2007–2012 period: from 16.9% to 43.4% for two doses and from 5.9% to 33.4% for three doses. However, this coverage rate is still lower than results in Europe or Geneva.[15]

There is no explanation for the better acceptability of HPV vaccination in Switzerland than in other countries. As for Geneva Canton, there might be less hesitation about immunization compared with other countries. To better understand these differences, further research will be conducted to determine the motivation and reason for nonvaccination in our context.

Vaccination in boys is expected to facilitate the eradication of cervical cancer, reduce transmission of the virus, increase herd immunity, and contribute to the prevention of HPV-associated diseases in both genders. However, the Swiss Federal Office of Public Health does not yet recommend HPV vaccination for men. This issue remains important, as more incremental benefits are expected through the inclusion of boys in the vaccine program.[16]

Limitations

Our study was subject to several limitations. First, we could not follow individuals' vaccination history and use the number of eligible residents, as it was known in cantonal statistics at the beginning of the program, as the denominator of coverage calculation. However, this methodological choice should only have had a marginal impact on the coverage estimate and its trend because the cohort of eligible patients remained fairly stable during this short period of time. Second, not all service providers transmitted the nominal lists of vaccinated people for monitoring. Thus, there was a bias in the evaluation of our coverage.

CONCLUSION

Although estimated HPV vaccination coverage has not yet reached 80% in all eligible age groups, it has been increasing over time and a favorable trend seems to be emerging. Easy and free access to vaccination; well-coordinated delivery services, including school health, public hospitals, and private physicians; and general and individual information played a major role in this program's success. In the future, an important challenge will be determining if this strategy is the best one for maintaining and further increasing coverage with younger cohorts and expanding the target population to young men.

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REFERENCES

1. Berchtold A, Michaud PA, Nardelli-Haefliger D, Suris JC. Vaccination against human papillomavirus in Switzerland: simulation of the impact on infection rates. Int J Public Health 2010;55:25-34.
2. World Health Organization. Report of the consultation on human papillomavirus vaccines. Geneva: WHO; 2005. Also available from: URL: http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.16.pdf [cited 2013 May 7].
3. Judson PL, Habermann EB, Baxter NN, Durham SB, Virnig BA. Trends in the incidence of invasive and in situ vulvar carcinoma. Obstet Gynecol 2006;107:1018-22.
4. University of Geneva. [Cancer in Geneva: incidence, mortality, survey, and prevalance, 2003–2006]. Geneva: University of Geneva; 2009. Also available from: URL: http://www.unige.ch/medecine/rgt/publicationquadriennale/publication_1970_2006.pdf [cited 2013 Jun 10].
5. Lugarini J, Maddalo F. Results of a vaccination campaign against human papillomavirus in the province of La Spezia, Liguria, Italy, March–December 2008. Euro Surveill 2009;14:19342.
6. Petignat P, Bouchardy C, Sauthier P. [Cervical cancer screening: current status and perspectives]. Rev Med Suisse 2006;2:1308-9, 1311-2.
7. Petignat P, Untiet S, Vassilakos P. How to improve cervical cancer screening in Switzerland? Swiss Med Wkly 2012;142:w13663.
8. Federal Office of Public Health. Human papilloma virus (HPV) [cited 2013 Jun 15]. Available from: URL: http://www.bag.admin.ch/themen/medizin/00682/00684/03853/index.html?lang=en
9. Tomljenovic L, Spinosa JP, Shaw CA. Human papillomavirus (HPV) vaccines as an option for preventing cervical malignancies: (how) effective and safe? Curr Pharm Des 2013;19:1466-87.
10. Harper DM. Currently approved prophylactic HPV vaccines. Expert Rev Vaccines 2009;8:1663-79.
11. Federal Office of Public Health. Factsheets [cited 2013 Jun 15]. Available from: URL: http://www.bag.admin.ch/themen/medizin/00682/00685/03212/index.html?lang=en
12. Jeannot E, Sudre P, Chastonay P. HPV vaccination coverage within 3 years of program launching (2008–2011) at Geneva State, Switzerland. Int J Public Health 2012;57:629-32.
13. StataCorp. Stata®: Version 10.0. College Station (TX): StataCorp; 2007.
14. European Center of Disease and Control. ECDC guidance on HPV vaccination: focus on reaching all girls. 2012 [cited 2013 Jul 11]. Available from: URL: http://www.ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?ID=497&List=8db7286c-fe2d-476c-9133-18ff4cb1b568
15. Stokley S, Curtis CR, Jeyarajah J, Harrington T, Gee J, Markowitz L. Human papillomavirus vaccination coverage among adolescent girls, 2007–2012, and postlicensure vaccine safety monitoring, 2006–2013—United States. MMWR Morb Mortal Wkly Rep 2013;62(29):591-5.
16. Crosignani P, De Stefani A, Fara GM, Isidori AM, Lenzi A, Liverani CA, et al. Towards the eradication of HPV infection through universal specific vaccination. BMC Public Health 2013;13:642.

Other manuscript submitted for publication peer review related to this thesis

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Should we vaccinate boys against HPV?

Human papillomaviruses (HPV) are small, non-enveloped DNA viruses with a tropism for squamous epithelia. Due to the virus's malignant potential, the infection can cause cervical, vaginal, vulvar and anal cancer in women, as well as penile and anal cancer in men. The viral infection is also responsible for oropharyngeal cancer, recurrent respiratory papillomatosis and genital warts in both sexes. High-risk (HR) HPV infections account for 95% of anal cancers, 70% of oropharyngeal cancers, 60% of vaginal cancers, 50% of vulvar cancers, and for 35% of penile cancers (Harden and Munger 2017). The overall prevalence of anogenital warts based on genital examinations (in both sexes) is reported to be between 0.2 and 5% (Patel et al. 2013).

The prophylactic (they do not protect those who are already infected) HPV vaccine is produced with recombinant technology using virus-like particles (VLPs), which induce the production of type-specific antibodies. There are currently three types of HPV vaccines available: the bivalent one, offering protection against virus types 16 and 18 (which types account for about 70% of cervical cancer cases (Winer et al. 2006), the quadrivalent one, offering additional protection against low-risk (LR) types 6 and 11 (which types are responsible for the majority of genital warts), and the nonavalent vaccine for further frequent HR HPV types like 31, 33, 45, 52 and 58 (MMWR Weekly Report 2015).

The Center for Disease Control and Prevention recommends routine HPV vaccination at age 11 or 12 years for both sexes. Vaccination is also recommended for females aged 13 through 26 years, and males aged 13 through 21 years. As for MSM (men who have sex with men) and immunocompromised persons, the vaccine is recommended up until the age of 27 years if they not have been previously immunized (MMWR Weekly Report 2015).

In some countries, the HPV vaccine is offered free-of-charge to boys and is included in the routine vaccination program. In Australia, girls and boys up to 19 years-of-age can receive two-doses of the nonavalent vaccine (three doses for the immunocompromised) and the vaccine is routinely given in school-based programs at age 12-13 (NCIRS 2018). In 2014, Austria also introduced a gender-neutral immunization program by offering 4th graders two doses of the quadrivalent vaccine (Borena et al. 2016). In the UK, the HPV vaccination program will also be extended to include boys aged 12-13 years (Green 2018).

The extension of the vaccination to the male population has multiple dimensions to it, including clinical, socio-economical and ethical aspects. From a purely clinical approach, the HPV vaccine can directly decrease the prevalence of virus-related pathologies among men, especially among high-risk groups like MSM who do not benefit from the "herd-immunity" provided by women, or patients presenting immunodeficiency; and indirectly have an impact on the prevalence of HPV-related

lesions in women. From a socio-economic approach, vaccination of boys might not be the most cost-effective tool to drastically diminish the burden of the HPV-induced diseases whilst the vaccination of women is suboptimal, as “herd immunity” for boys may occur where coverage is above 80% (Favato et al. 2017). According to Choi et al., assuming that vaccine protection lasts 20 years on average, selective immunization of 12-year-old school girls could significantly reduce, even eliminate cervical cancer and anogenital warts incidence among women after 60 years of an ongoing immunization program (Choi et al. 2010). However, findings of the systematic review of Favato et al. indicate that the selective immunization of pre-pubertal girls is likely to fail to achieve expected level of “herd immunity” at a population level. They also suggest that population characteristics and sexual behavior should be aligned more closely to real-life scenarios in modelled populations (Favato et al. 2017). Ethically, as HPV infection is an STI, sharing the responsibility of the viral transmission can be an argument for a gender-neutral vaccination.

To achieve optimal vaccine coverage, whether our primary target population is pre-teen girls or boys, as HPV vaccination is currently non-mandatory, parental consent is necessary to administer the vaccine. Therefore, the success of HPV-immunization programs at a population level (HPV vaccine uptake among minors), partially relies on the awareness of HPV-related diseases and the acceptance of the HPV vaccine among parents. Simultaneously, while optimizing any pre-existing or implementing new vaccination programs, the knowledge of the general population concerning HPV infection should be increased in order to obtain a favorable attitude and response towards vaccination. Previous studies have shown that the knowledge about HPV is insufficient, especially among men (Patel et al. 2016). With the introduction of specific health educational programs, vaccination rates could be increased. At the level of primary prevention, it is necessary to mention that prophylactic vaccination is not the only existing mean of prevention; sexual behavior has a considerable impact on the risk of infection. Sexual educational programs may have an effect on this factor well.

References

Borena W, Luckner-Hornischer A, Katzgraber F et al (2016) Factors affecting HPV vaccine acceptance in west Austria: Do we need to revise the current immunization scheme? Papillomavirus Res 2:173-177

Choi YH, Jit M, Gay N et al (2010) Transmission dynamic modelling of the impact of human papillomavirus vaccination in the United Kingdom Vaccine 28(24):4091-102

Favato G, Easton T, Vecchiato R et al (2017) Ecological validity of cost-effectiveness models of universal HPV vaccination: A systematic literature review.Vaccine 35(20):2622-2632

Green A (2018) HPV vaccine to be offered to boys in England. 392(10145):374

Harden ME, Munger K (2017) Human papillomavirus molecular biology. Mutat Res 772:3–12

Mortality and Morbidity Weekly Report (2015) Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. 64(11);300-304

National Centre for Immunisation and Research&Surveillence (2018) Human papillomavirus (HPV) vaccines for Australians. Available at: http://www.ncirs.org.au/sites/default/files/2018-12/HPV%20Factsheet_2018%20Aug%20Update_final%20for%20web.pdf Accessed: 25.04.2019

Patel H, Wagner M, Singhal P et al (2013) Systematic review of the incidence and prevalence of genital warts. BMC Infect Dis 13:39

Patel H, Jeve YB, Sherman SM et al (2016) Knowledge of human papillomavirus and the human papillomavirus vaccine in European adolescents: a systematic review. Sex Transm Infect 92(6):474–479

Winer RL, Hughes JP, Feng Q et al (2006) Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med 354(25):2645-54

Digital visual inspection using smartphone application: an innovative tool to cervical screening in low and middle income countries.

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Background

Cervical Cancer (CC) is one of the most common cancers in women, ranking second in developing country, with an incidence of 445 000 news cases per year, in comparison in develops country this cancer was only on the 11th ranks, with 83 000 new cases per year(44). HPV infections are very common and one of the most common sexually transmitted diseases in the world, they are common in young people. HPV infections are usually cleared by the immune system but for a part of the infected women, infection can persist (45).

Screening of cervical cancer

The implementation of cytology-based screening programmes has resulted in a considerable reduction in disease burden in high-income countries; however, economically poor geographic areas fail to provide efficient CC screening services because of a lack of human and material resources. Indeed, the success of cytology-based screening programmes depends on well-organised and complex infrastructure with well-trained personnel, including cytopathologists, colposcopy specialists, and pathologists, and an adequate laboratory infrastructure to manage women with positive test results.

Colposcopes are expensive, difficult to transport, and require specialized technicians for maintenance, as well as electric supply. Therefore, the implementation of colposcopes in low and middle income countries (LMIC) is difficult and alternative system is required (46)

Screening of CC in low and middle income country

To overcome this difficulty, the options recommended by the World Health Organization (WHO) include human papillomavirus (HPV) testing followed by visual inspection with acetic acid (VIA) as a triage test, followed by the application Lugol's iodine (VILI)(47). The VIA is positive when there is appearance of thick whitish patches with sharp edges, called acidophilic. VILI, which immediately follows is a confirmation test. It is positive when there is appearance of colored regions in saffron yellow or mustard yellow, called iodine-negative. Integrating HPV-based screening with VIA/VILI (visual inspection after application of acetic acid/lugol's iodine) offers the dual benefit of optimizing both HPV detection and VIA/VILI for triage of HPV-positive women.

All healthcare professionals (doctors, nurses, midwives) can perform this exam. However, in order to perform the VIA / VILI successfully while being effective in reducing the incidence of cervical cancer, health personnel must receive formal and practical VIA / VILI training.
One of the limitations of the use of visual screening by VIA / VILI is that the results depend to a large extent on the individual interpretation of the person performing the VIA / VILI. Inter-observer variability remains a limiting factor, hence the importance of good initial training and continuous quality control (48).

Smart phone applications "exam" as adjuvant tools for cervical Cancer Screening and CCPS app for improving Data collection and electronical patient record.

Concerns about the lack of a quality assurance system and important inter-observer variability, a possible way is to develop the use of digital smartphone application (D-VIA and D-VILI for Digital VIA and digital VILI). This is a promising choice for developing countries to improve their quality and efficiency. In this context, smartphone application development can help clinicians to diagnose pre-cancers and can be an important step towards improving visual eye inspection techniques (49). This approach opens up new possibilities, thanks to its accessibility, user-friendly interfaces and high-definition cameras to visualize the cervix. In addition, sharing real-time images with long-distance experts allows health professionals to seek advice and improve the quality of their work. The use of smartphone applications as a tool to minimize the subjectivity of the diagnosis has been tested in other medical fields, such as that of dermatology for the detection of cutaneous melanoma with promising results(50).

The procedure of D-VIA/D-VILI

This smartphone application has been developed in order to use the digital images for the evaluation of VIA and VILI method. With this application it is possible to take good quality cervical pictures, magnify the lesions using the zoom and to compare native to VIA and VILI by sliding through pictures.

The procedure is user friendly and it consists in different steps, full description of the procedure for performing D-VIA/D-VILI is detailed on other article(49).

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To use easily this procedure an application for smartphones called “Exam” has been developed. It is an android application specifically designed to obtain high-quality images by the Signal

Processing Laboratory of the Swiss Federal Institute of Technology in Lausanne, Switzerland. This application's functioning is based on the fact that the changes of the cervical surface induced by the application of acetic acid and Lugol's iodine can be captured by inexpensive smartphone cameras simply by recording multiple sequential images of the cervix immediately after the application of each solution. The image capture, featured extraction and classification methods are implemented to run directly on an Android smartphone, using the Software Development Kit made available by Google to develop Android applications.

All the pictures collected by the smartphone application are sent to a central database and automatically saved and classified in the patient's file by date and type (native, VIA, VILI, posttreatment). Written comments can be added to each patient's visual file. Finally, the biopsy site was marked on the VIA picture with a cross mark. The VIA picture can also be viewed without the marked biopsy site.

For security and privacy, data transfer to the central database was accomplished using an encrypted key. Authentication was required to access the patients' file, and only the caregivers who received accreditation with a personal identifier and password could log into the smartphone application or the respective database. Access to patient data was only possible after scanning a bar code unique for each patient or by entering the patient's identification number and the date of the VIA/VILI assessment. This ensured patients' information to be protected. Finally, it is possible to slide between pictures on the Smartphone to compare them to one another and find the diagnosis. It is a simple reproducible procedure that facilitates the identification of the lesion and it allows a second opinion with telemedicine. Expert from all over the world can give their opinion in real time.

Digital imaging of VIA is an adjunctive procedure to improve diagnosis performance and there is a tutorial on Geneva Foundation for Medical and Education Research (GFMER) website where it is possible to learn the procedure and practice exercises. The tutorial is divided in five modules: the first module consists in learning anatomy of the cervix, SC junction, the second for basic knowledge for CC screening using VIA and VILI and HPV test, the third module to learn how to treat VIA/VILI positive cases, the fourth how to proceed and the last to learn how to perform digital VIA and VILI for quality insurance of visual inspection of the cervix using a smartphone (51).

In addition of digital VIA and VILI, a system to create a digitalized patient record called Cervical Cancer Prevention System (CCPS) has been developed. It is an m-Health application that allows the registration of clinical data while women are undergoing cervical cancer screening. All data registered in the smartphone were transmitted onto a secure, Web-based platform through the use of an Internet connection. Healthcare providers had access to the central database and could use it for the follow-up visits. Quality of data was assessed by computing the percentage of key data missing(52).

Performances of smart phone based digital images: "EXAM"

Some studies have been done to evaluate the sensitivity and specificity for D-VIA and D-VILI and also the quality of the photos and the quality control in order to improve cervical cancer screening and precancerous lesions treatment. We have extracted sensitivity and specificity reported in each study using our application tool, after we have pooled these sensitivity and specificity using a bivariate normal model to account for the logit transforms of sensitivity and specificity.

Table 1 shows the pooled sensitivity and specificity for D-VIA and D-VILI. The pooled sensitivity and specificity of D-VIA is 69 % (95% confidence interval, 95% CI 61-77) and 88% (95% CI 84-89) respectively. D-VILI pooled sensitivity is 85% (73-97), and 86 % (83-89) for the specificity. This pooled sensitivity and specificity of D-VIA and D-VILI is substantially comparable to the classic VIA and VILI, a recent meta analyse included 101 273 women show a pooled sensitivity and specificity of VIA 78% and 88 % respectively, and a pooled sensitivity and specificity of VILI of 88% and 86 %(48).

A first pilot study was conducted in Madagascar in 2014, women aged between 30-65 years were recruited through a cervical cancer screening campaign. Each women was testing positive (N=95) for HPV were referred for VIA followed by D-VIA, the same day the D-via was e-mailed to a tertiary care center for immediate assessment. Each of the three off-site physicians were blinded to the results reported by one on suite physician and each gave their individual assessment followed by a consensus diagnosis. The on-site physician had a sensitivity of 66.7% (95%CI: 30.0-90.3) and a specificity of 85.7% (95%CI: 76.7-91.6); the off-site physician consensus sensitivity was 66.7% (95%CI: 30.0-90.3) with a specificity of 82.3% (95%CI: 72.4-89.1). This first studies has shown that off-site detection of cervical lesions based on the evaluation of smartphone photographs was more reliable than on-site diagnosis alone (53).

A second study always in Madagascar assessed the clinical performance of D-VIA and D-VILI examinations for diagnosing cervical lesions in LMIC. The aim of this study was to evaluate the feasibility and performance of smartphone digital images for the detection of cervical intraepithelial neoplasia of grade 2 or worse (CIN2+) as an adjunct to a conventional visual inspection approach with acetic acid (VIA) and Lugol's iodine (VILI), in comparison with detection by histopathologic examination. This studies was included 88 HPV-positive women. The on-site physician obtained a sensitivity of 28.6% (95% confidence interval [95% CI], 3.7-71) and a specificity of 87.2% (95% CI, 77.7- 93.7). The off-site physicians obtained a

sensitivity ranging between 42.9% (95% CI, 9.9-81.6; p = 0.1) and 85.7% (95% CI, 42.1-99.6; p = 0.13) and a specificity between 48.1% (95% CI, 36.5- 59.7; p < .001) and 79.2% (95% CI, 68.5-87.6; p = 0.10). Conclusion of this studies was that the use of digital images for triaging HPV-positive women by using Smartphones allows detection of most precancerous and cancerous lesions and can improve cervical cancer in low-resource settings (50).

After those two studies, two other studies were performed in Madagascar in 2015 using Exam application to evaluate the quality of smartphone images in order to assess the feasibility and usability of this mobile application for CC screening in LMIC. On the first study, HPV positive women were invited to undergo VIA/VILI assessment. Pictures of their cervix were taken using a Samsung Galaxy S5 with our application "Exam", which was designed to obtain high-quality images and to classify them in the following sequence: native, VIA, VILI and posttreatment. Experts in colposcopy were asked to evaluate if the quality of the pictures was sufficient to establish the diagnosis and to assess sharpness, focus and zoom. A total of 208 photos were evaluated by three physicians, resulting in 624 evaluations. The quality was judged as adequate for diagnosis in 93.3 % of cases. All criteria were fulfilled in the majority of pictures. The aspect fulfilled in most cases was the focus (89.1%), followed by the diagnostic utility (83.7%), the sharpness (77.7%) and the zoom (73.7%). Study show that "Exam" smartphone application was able to capture high-quality images and was an efficient method for storing the patients' data. As the overall pictures' quality was judged as good, this smartphone-based approach can potentially be integrated in the context of CC screening (49). The second studies confirmed this previous results, during this study 15 clinicians assessed 240 images recorded by Exam application. Sensitivity was higher for the D-VIA interpretations (94.1%; 95% CI 81.6-98.3) than for the D-VILI interpretations (78.8%; 95% CI 54.1-92.1; P=.009). In contrast, the

specificity was higher for the D-VILI interpretations (56.4%; 95% CI 38.3-72.9) than for the D-VIA interpretations (50.4%; 95% CI 35.9-64.8; P=.005) (54).

Performances of smart phone data collections images: "CCPS"

The last study we performed in Madagascar in 2016 was to assess the feasibility of the CCPS: Cervical Cancer Prevention System mobile health (m-Health) data collection system to facilitate monitoring of women participating to cervical cancer screening campaign. This CCPS was designed to enable healthcare providers to monitor women undergoing cervical cancer screening, treatment, and follow-up via an icon-based application for smartphones, The CCPS application collected a total of 44 items, including information about the women's identity, medical, and obstetrical history. All the information collected were directly transmitted to a electronic platform creating immediately a digital medical record for each patient.

With this telemedicine system it was possible to have a medical distance supervision for management decisions.

We practice a teaching session of two days onsite and the use of the application was well accepted by the medical team on site; they quickly learned how to use it and were overall satisfied with it. The clinical visits' duration using CCPS was similar to that of the visits performed using handwritten files, taking*20 min.

Only one datum concerning the employment status of one patient was not transferred onto the Medical Unit and was therefore lost, probably due to a transient crash of the application. This represents a data loss of less than 0.02% of all recorded data (1/6,644 recorded data: 44 data for each patient 151 patients). Conclusion of this study was that the quality of the data was satisfactory and allowed monitoring of cervical cancer screening data of participants(52), but Larger studies evaluating the efficacy of the system for the women's follow-up are needed in order to confirm its efficiency on a long-term scale.

Discussion

The introduction of a smartphone-based approach for cervical cancer screening and treatment in such settings allow to overcome some of the barriers to the implementation of screening and treatments programs in developing countries. The capture of cervical images with the smartphone camera guarantee a good quality system of screening and management decisions using expert medical distance supervision and allows to create an electronical medical record with all the image for each patient in order to ensure a good follow up.

This systems allows also the user to look back in real time at either the native, post-VIA, or post-VILI cervix and to magnify the pictures in order to see them more closely before deciding whether or not to treat. In addition, the automatic saving of digital images on the smartphone allows the on-site, often less experienced and less qualified healthcare worker, to seek advice from long-distance off-site specialists.

Moreover, the use of automated phone applications is on the rise and might improve and facilitate CC screening strategy in LMICs by providing a system to classify the images and to guide health workers through their decision-making algorithm. Such mobile health tools are either free of charge or come at a very low price and can be easily installed on a smartphone without requiring any additional equipment. Their low cost and practicality distinguish them from other mobile colposcopy systems, such as the MobileODT (EVA system, enhanced visual assessment; Tel Aviv, Israel) for which the digital images' increased sharpness comes at the cost of a far more expensive and elaborate type of equipment. A study in Kenya using MobileODT technology show that the implementation of the decision support job aid, coupled with integration on the back end, enabled real time M&E of the VIA screening program was a

succesful and this another devices holds promise for improving the quality of care at the health system, organizational, and practitioner level(55)

There are many other tools for using smartphone camera technology as a tool for DC screening. We can mention the ColpPHON in India for example which also showed the feasibility of its use for improving cervical cancer screening in resource poor countries (56). Other study show using telecytology (via whatapp application) are also possible and that the developments in the smartphone camera technology and transfer software make them efficient telepathology and telecytology tools(57), study in osaka using only camera of a Iphone 5 S (8 megapixels camera, with an aperture size of F2.2, focal length of 30 mm and a pixel size of 1.5 μm) had also promising results(58).

To finish this medical device can be used for the continuing education of the healthcare worker performing VIA to prevent their skills decreases. In Ghana a mHealth application has been used to support continuous VIA training. Result show an improving skills of the healthcare worker about cervical cancer screening(59).

Conclusion

These aspects make the use of images taken by mobile phone a promising option for cervical cancer screening in low-income countries. Further prospective studies are needed in order to assess the performance of D-VIA and D-VILI as a single, co-testing or triage screening tool.

Table 1 – Summary pooled Sensitivity and Specificity of D-VIA and D-VILI using a bivariate random effects model

	Pooled Sensitivity (95 % CI)	Variance logit (sensitivity)	Pooled Specificity (95 % CI)	Variance logit (Specificity)
D-VIA	69 (61-77)	0.85	88 (84-92)	0.83
D-VILI	85 (73-97)	1.12	86 (83-89)	0.63

Conclusions:

Reductions in Prevalence Among Vaccinated Persons:

The main conclusion of this research is that we can in fact observe a statistically significant decrease in the prevalence of strains covered by Gardasil 4 in the study population. This reduction in the prevalence of HPV strains targeted by vaccination is found in many studies around the world. The effectiveness of the vaccine varies between studies, but they all point to a reduction in the prevalence of HPV covered by vaccination (60-66). Examples include studies in Europe, particularly in Luxembourg, where there is significant protection against oncogenic HPV, mainly 16/18 strains, with an 87% reduction in prevalence among vaccines (Odds ratio = 0.13 95% CI 0.03-0.63) and a reduction of 84% for strains 6/11(67). The large Australian studies also show results of great importance for public health. Studies that compared the prevalence of HPV covered by HPV vaccination before and after the introduction of this vaccine in 2007 in Australia have shown quite spectacular results. In fact, it was observed that the HPV prevalence of HPV types decreased from 22.7% (2005-2007) and 7.3% (2010-2012), to 1.5% (2015) (P trend <.001) among women aged 18-24, and from 11.8% (2005-2007) to 1.1% (2015) (P = .001) among women aged 25-35(63, 68-70).

As far as Switzerland is concerned, apart from this research work, few studies have been carried out for the time being to evaluate the effectiveness of HPV vaccination. Nonetheless, the CIN 3+ study, which aimed to examine the distribution of oncogenic HPV genotypes in biopsies with cervical intraepithelial neoplasia stage 3 or more severe lesions (CIN3 +) at the beginning of HPV vaccination programs. 768 biopsies from 767 women were included in this study. The results showed that four hundred and seventy-five (61.8%) biopsies were positive for HPV 16 and/or 18, 687 (89.5%) were positive for oncogenic HPV genotypes 16, 18, 31, 33, 45, 52, and/or or 58 and five (0.7%) were HPV negative. There was also an extremely low immunization coverage rate with only 10% of women reporting having received at least one dose of the vaccine. The conclusion of this study was that, potentially, a 90% reduction in CIN 3+ lesions could be expected with the introduction of the monovalent vaccine and a 60% reduction for the quadrivalent vaccine in Switzerland (71).

Only one other study was done to estimate the effectiveness of HPV vaccination in the general population in Switzerland. This is based on patient records. Jacot-Guillarmod et al. have shown that the prevalence of high-risk vaccine-type HPV decreased significantly (59%, $P = 0.0048$)

for participants during the post-vaccination era, which may be less than 26 years (P <0.0001) (72).

A recent Cochrane review conducted in 2018 and including 26 clinical studies for a total of 73,428 participants clearly shows a significant reduction in the risk of precancerous lesions in vaccinated young women. All trials evaluated the safety of vaccines over a period of 0.5 to 7 years with follow-up ranging from 3.5 to 8 years. Most of the recruits were under 26 years old. Three trials recruited women aged 25 to 45 years. The studies compared the HPV vaccine to a placebo. It can be seen that HPV vaccines reduce the risk of precancerous cervical lesions associated with HPV 16/18 from 164 cases to 2 cases/10,000 women. They also reduce all precancerous lesions from 287 cases to 106 cases/10,000 women. The conclusion of this review is that there is evidence of a high degree of certainty that HPV vaccines protect against precancerous cervical lesions in adolescent girls and women who are vaccinated between ages 15 and 26. Protection is lower when part of the population is already infected with HPV (45).

Another objective of this review was to know the risk of serious adverse events related to this vaccination. The risk of serious adverse events is comparable between the HPV vaccine and the control vaccine (a placebo or a vaccine against an infection other than HPV). The mortality rate is globally comparable (11/10,000 in the control group, 14/10,000 in the HPV vaccine group). Therefore, these vaccines do not increase the risk of serious adverse events, miscarriage, or termination of pregnancy (45, 73-75).

It is important to note the important debate or even the controversy that currently exists over the results of this Cochrane review (76-78). In an article published in the BMJ Evidence Based Medicine in July 2018, a few weeks after the publication of this review, Professor Peter Goetzsche from Denmark and member of the Governing Board of the Review Cochrane questioned the results of this systematic review (76). Here are Professor Goetzsche's criticisms:

- The Cochrane Review forgot about half of the eligible tests
- The included trials used composite substitution criteria for cervical cancer
- The review did not correctly and completely evaluate the side effects
- The review did not correctly evaluate warning signals related to the HPV vaccine
- Industrial trials were included with conflicts of interest not taken into account

This thesis has no claim to respond to this debate, but it was important to point it out.

Cross Protection Against Other HPV Strains.

This research did not show cross-protection in people vaccinated with other strains not covered by the tetravalent vaccine. Other studies on the subject have, for their part, shown that such cross-protection could exist.

A study in Scotland was the first to observe this cross-protection in the vaccinated population. A population-based study of vaccine-infected women with the bivalent vaccine at the age of 13 years, 85.1% (95% confidence interval, 77.3% - 90.9%) compared with HPV 31, 33, and 45(79). In 2018, another study, carried out this time in Holland, showed a vaccine efficacy against strains 31, 33, and 45 of 61.8% (95% CI, 16.7% - 82.5%). The authors suggest that cross-protection has no reason to reduce over time and will persist in the vaccinated population (80). In Luxembourg, cross-protection against HPV 31/33/45 was also observed with a statistically significant odds ratio (Odds Ratio = 0.41, 95% CI 0.18 - 0.94) (67).

For the moment, there is little solid evidence to support cross-protection with the tetravalent vaccine. On the other hand, it may be thought that this protection exists for the bivalent vaccine (81, 82).

Using Self-Sampling to Evaluate HPV Vaccinations

The use of self-sampling as an effective tool for screening for HPV and pre-cancerous lesions is clearly introduced in the scientific literature. However, its use as a tool to monitor the effectiveness of vaccination has yet to be demonstrated.

Our HPV-impact study showed that its use was easy and well-accepted by young women. Since our research, several other studies have used self-sampling with this objective to monitor the effectiveness of HPV vaccination in the population. These studies in Canada, Italy, Australia, and Germany had different vaccine efficiencies, but all recognized that self-sampling was an effective tool for monitoring the effectiveness of this vaccination in real population (60, 61, 63, 83).

Increasing Knowledge of Target Audiences About HPV Infection and HPV Vaccinations

Our second study showed that there were significant gaps in the knowledge that people in the health care profession had about HPV infections and HPV vaccination. These shortcomings, which are found in many studies around the world, illustrate the effort health professionals must

make to better inform the target population of the benefits and risks of this vaccination (84-88). In recent years, there has been a significant increase in mistrust of vaccination, particularly against HPV vaccination. A systematic review including 103 quantitative and qualitative studies done in Europe shows that the main determinants of not getting vaccinated are insufficient and inadequate information about HPV vaccination; potential side effects of the vaccine; issues around trust of health authorities, doctors, and new vaccines; and perceived low vaccine effectiveness (see Figure 7). Many of these determinants could be improved by adequate communication and training around this vaccination, including improved training for health professionals on the effectiveness of this vaccination and these potential risks (89).

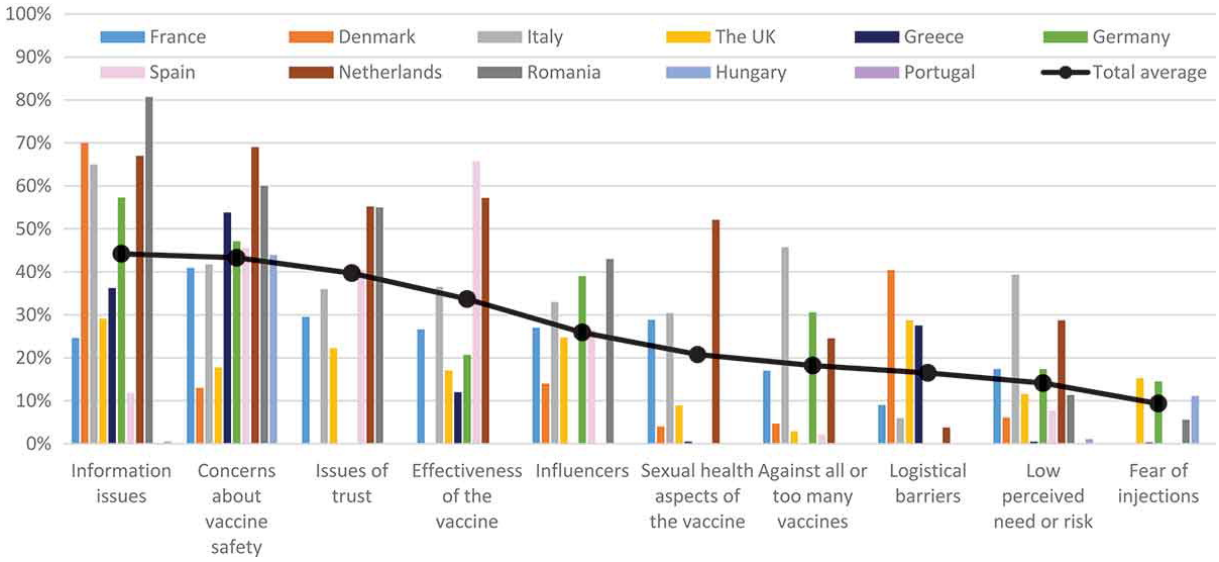

Figure 7: Average proportions of hesitant participants who reported certain categories of determinants of HPV vaccine hesitancy, by country.

Efforts in this area have been made by the World Health Organization to provide a guideline to states including the HPV vaccine in their immunization program. This good practice guide is an aid to follow when communicating about the HPV vaccine.

The World Health Organization's guide line clearly repeats the importance of both epidemiological and social immunization and the crucial role of information and communication for the promotion of these vaccines "*Immunization should be a social norm, for which demand and access by all members of each community is a normal, socially acceptable health behavior. The introduction of the HPV vaccine should be considered as a long-term strategy to prevent cervical cancer and communities should demand it as a social norm for their adolescent girls. This standard can be put in place thanks to communication strategies*"

The knowledge gaps that we have highlighted are often linked to the lack of knowledge of the virus and vaccines leading to reluctance or fear to vaccinate. The WHO guide proposes a whole process of change for HPV vaccination based on communication and education (see Figure 8) (90)

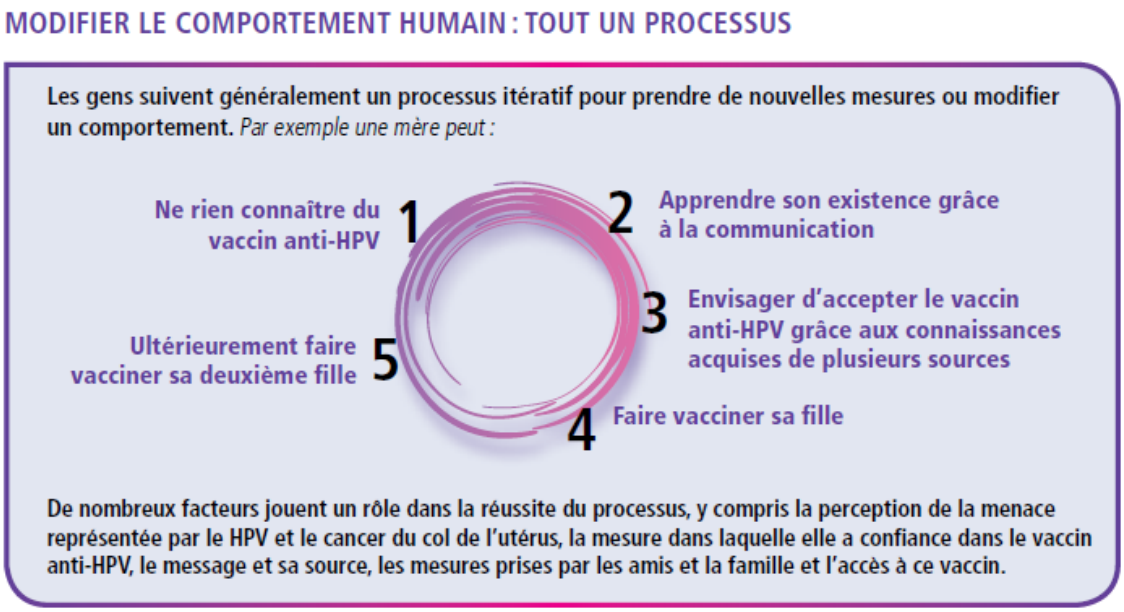

Figure 8: Modification of Human Behavior towards HPV vaccination

Future Perspectives

HPV Vaccinations with the Gardasil 9 Vaccine

Due to its increased ability to protect against other strains of HPV (6, 11, 16, 18, 31, 33, 45, 52, and 58), Gardasil 9 will be a very powerful public health tool to further reduce the incidence of HPV infections. Early studies suggest that the Gardasil 9 vaccine is expected to prevent up to 90% of cervical and 96% of anal cancers in the world (91). Knowing that finding oncogenic HPV varies from one country to another, we can nevertheless estimate that Gardasil 9 will offer protection against 87.7% of cervical cancers in Asia, 91.7% in Africa, 92% in North America, 90.9% in Europe, 89.5% in Latin America & the Caribbeans, and 86.5% in Australia (92, 93) (see Figure 9).

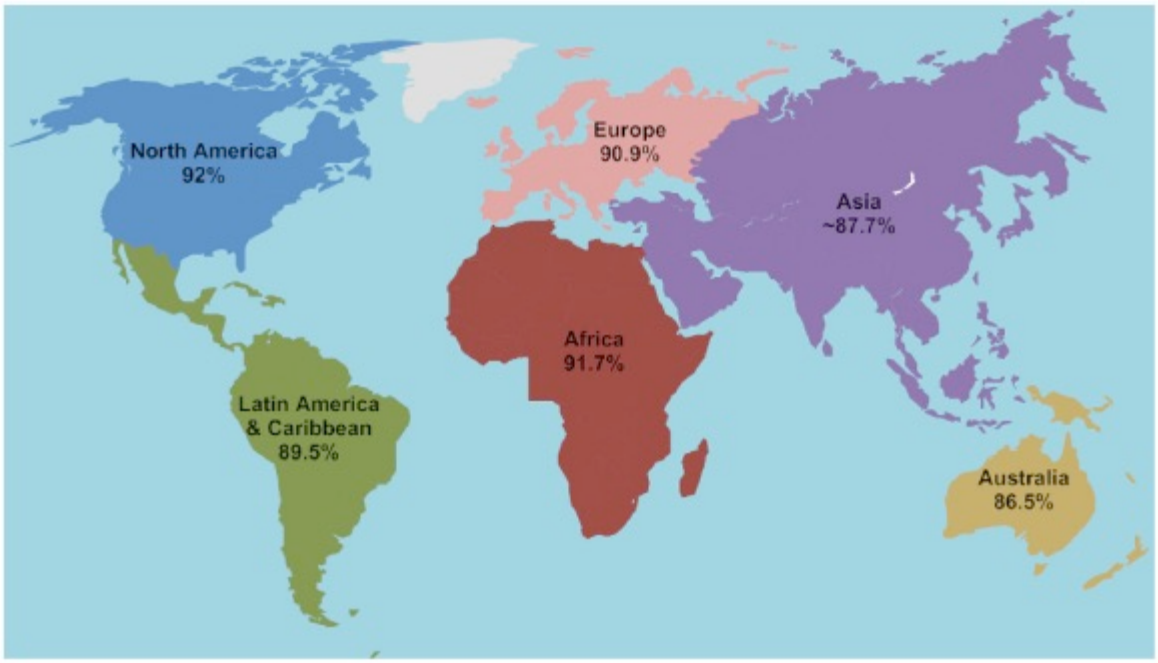

Figure 9: Expected regional percentages of HPV protection by Gardasil-9. Estimates are based on the prevalence and the sum of percent contributions of vaccine HPV types to HPV-associated cervical cancers in different regions

The composition of Gardasil 9 against HPV is comparable to that of the quadrivalent vaccine in that the vaccine uses virus-like particles to elicit an immune response. This one is injected the same way with the same treatment plan (94). Side effects also exist. There may be injection site pain, such as swelling and erythema. Individuals receiving Gardasil 9 are slightly more likely to experience these side effects than individuals receiving the quadrivalent vaccine, possibly because of the increased number of virus-related particles and adjuvants in Gardasil 9. The rate of systemic events, such as headaches, pyrexia, nausea, and fatigue, are comparable for both vaccines (95, 96).

Vaccinations for Men

Thirty countries have already decided to extend vaccination to young male adolescents (as young as 11 years old) as is the case in the US, Australia, Germany, and Great Britain, in order to reduce the incidence, which has increased since 1974, of HPV-related cancers in men(97-100). Although this vaccination is free of charge in Switzerland since July 1, 2016, we currently have little information on vaccination coverage among young men aged 11 to 26 who correspond to the target population of this vaccination (101).

Final Recommendation:

The conclusions of this research work are that, given the effectiveness of this vaccine for reducing the prevalence of HPV strains, it must be better introduced and promoted in the general population. Better information and education of the target population regarding HPV infection and the benefit of this vaccination should be available in order to increase the coverage rate of this vaccine. Finally, the use of self-sampling will have to be part of a larger program to monitor the effectiveness of vaccination and in particular the effectiveness of Gardasil 9.

Bibliography:

1. Mistry N, Wibom C, Evander M. Cutaneous and mucosal human papillomaviruses differ in net surface charge, potential impact on tropism. Virol J. 2008;5:118.
2. Egawa N, Egawa K, Griffin H, Doorbar J. Human Papillomaviruses; Epithelial Tropisms, and the Development of Neoplasia. Viruses. 2015;7(7):3863-90.
3. Aldabagh B, Angeles JG, Cardones AR, Arron ST. Cutaneous squamous cell carcinoma and human papillomavirus: is there an association? Dermatol Surg. 2013;39(1 Pt 1):1-23.
4. Kim SM. Human papilloma virus in oral cancer. J Korean Assoc Oral Maxillofac Surg. 2016;42(6):327-36.
5. Gelderblom HR. Structure and Classification of Viruses. In: th, Baron S, editors. Medical Microbiology. Galveston (TX)1996.
6. Harari A, Chen Z, Burk RD. Human papillomavirus genomics: past, present and future. Curr Probl Dermatol. 2014;45:1-18.
7. Sverdrup F, Khan SA. Two E2 binding sites alone are sufficient to function as the minimal origin of replication of human papillomavirus type 18 DNA. J Virol. 1995;69(2):1319-23.
8. Lazarczyk M, Cassonnet P, Pons C, Jacob Y, Favre M. The EVER proteins as a natural barrier against papillomaviruses: a new insight into the pathogenesis of human papillomavirus infections. Microbiol Mol Biol Rev. 2009;73(2):348-70.
9. Finnen RL, Erickson KD, Chen XS, Garcea RL. Interactions between papillomavirus L1 and L2 capsid proteins. J Virol. 2003;77(8):4818-26.
10. Puck TT, Lee HH. Mechanism of cell wall penetration by viruses. II. Demonstration of cyclic permeability change accompanying virus infection of Escherichia coli B cells. J Exp Med. 1955;101(2):151-75.
11. Grove J, Marsh M. The cell biology of receptor-mediated virus entry. J Cell Biol. 2011;195(7):1071-82.
12. Erickson BK, Alvarez RD, Huh WK. Human papillomavirus: what every provider should know. Am J Obstet Gynecol. 2013;208(3):169-75.
13. Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;16(1):1-17.
14. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002;55(4):244-65.
15. Chrysostomou AC, Stylianou DC, Constantinidou A, Kostrikis LG. Cervical Cancer Screening Programs in Europe: The Transition Towards HPV Vaccination and Population-Based HPV Testing. Viruses. 2018;10(12).
16. Nayereh KG, Khadem G. Preventive and Therapeutic Vaccines against Human Papillomaviruses Associated Cervical Cancers. Iran J Basic Med Sci. 2012;15(1):585-601.
17. Nascimento IP, Leite LC. Recombinant vaccines and the development of new vaccine strategies. Braz J Med Biol Res. 2012;45(12):1102-11.
18. Lauring AS, Jones JO, Andino R. Rationalizing the development of live attenuated virus vaccines. Nat Biotechnol. 2010;28(6):573-9.
19. Loomis RJ, Johnson PR. Emerging Vaccine Technologies. Vaccines (Basel). 2015;3(2):429-47.
20. Wang JW, Roden RB. Virus-like particles for the prevention of human papillomavirus-associated malignancies. Expert Rev Vaccines. 2013;12(2):129-41.
21. Zhang L, Wang W, Wang S. Effect of vaccine administration modality on immunogenicity and efficacy. Expert Rev Vaccines. 2015;14(11):1509-23.
22. Lopalco PL. Spotlight on the 9-valent HPV vaccine. Drug Des Devel Ther. 2017;11:35-44.
23. Pinto LA, Dillner J, Beddows S, Unger ER. Immunogenicity of HPV prophylactic vaccines: Serology assays and their use in HPV vaccine evaluation and development. Vaccine. 2018;36(32 Pt A):4792-9.

24. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health. 2016;4(7):e453-63.
25. de Sanjose S, Delany-Moretlwe S. HPV vaccines can be the hallmark of cancer prevention. Lancet. 2019;394(10197):450-1.
26. Senkomago V, Duran D, Loharikar A, Hyde TB, Markowitz LE, Unger ER, et al. CDC Activities for Improving Implementation of Human Papillomavirus Vaccination, Cervical Cancer Screening, and Surveillance Worldwide. Emerg Infect Dis. 2017;23(13).
27. Hall MT, Simms KT, Lew JB, Smith MA, Brotherton JM, Saville M, et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. Lancet Public Health. 2019;4(1):e19-e27.
28. Simms KT, Laprise JF, Smith MA, Lew JB, Caruana M, Brisson M, et al. Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis. Lancet Public Health. 2016;1(2):e66-e75.
29. Organization WH. Safety of HPV vaccines. 2016.
30. Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine. 2012;30 Suppl 5:F123-38.
31. Gee J, Weinbaum C, Sukumaran L, Markowitz LE. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. Hum Vaccin Immunother. 2016;12(6):1406-17.
32. Arana JE, Harrington T, Cano M, Lewis P, Mba-Jonas A, Rongxia L, et al. Post-licensure safety monitoring of quadrivalent human papillomavirus vaccine in the Vaccine Adverse Event Reporting System (VAERS), 2009-2015. Vaccine. 2018;36(13):1781-8.
33. Gallagher KE, Howard N, Kabakama S, Mounier-Jack S, Burchett HED, LaMontagne DS, et al. Human papillomavirus (HPV) vaccine coverage achievements in low and middle-income countries 2007-2016. Papillomavirus Res. 2017;4:72-8.
34. Jeannot E, Sudre P, Chastonay P. HPV vaccination coverage within 3 years of program launching (2008-2011) at Geneva State, Switzerland. Int J Public Health. 2012;57(3):629-32.
35. Jeannot E, Petignat P, Sudre P. Successful implementation and results of an HPV vaccination program in Geneva Canton, Switzerland. Public Health Rep. 2015;130(3):202-6.
36. Jeannot E, Wyler CA, Meynard A, Kaiser B, Sudre P, Alvarin J, et al. [Factors associated with HPV immunization for 13-14-year-old girls in the Geneva district, Switzerland]. Rev Epidemiol Sante Publique. 2013;61(6):513-8.
37. Viviano M, Catarino R, Jeannot E, Boulvain M, Malinverno MU, Vassilakos P, et al. Self-sampling to improve cervical cancer screening coverage in Switzerland: a randomised controlled trial. Br J Cancer. 2017;116(11):1382-8.
38. Yeh PT, Kennedy CE, de Vuyst H, Narasimhan M. Self-sampling for human papillomavirus (HPV) testing: a systematic review and meta-analysis. BMJ Glob Health. 2019;4(3):e001351.
39. Arbyn M, Smith SB, Temin S, Sultana F, Castle P, Collaboration on S-S, et al. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ. 2018;363:k4823.
40. 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. Lancet Oncol. 2014;15(2):172-83.
41. Verdoodt F, Jentschke M, Hillemanns P, Racey CS, Snijders PJ, Arbyn M. Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials. Eur J Cancer. 2015;51(16):2375-85.
42. Madzima TR, Vahabi M, Lofters A. Emerging role of HPV self-sampling in cervical cancer screening for hard-to-reach women: Focused literature review. Can Fam Physician. 2017;63(8):597-601.

43. Racey CS, Withrow DR, Gesink D. Self-collected HPV testing improves participation in cervical cancer screening: a systematic review and meta-analysis. Can J Public Health. 2013;104(2):e159-66.
44. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global Cancer in Women: Burden and Trends. Cancer Epidemiol Biomarkers Prev. 2017;26(4):444-57.
45. Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database Syst Rev. 2018;5:CD009069.
46. Kunckler M, Schumacher F, Kenfack B, Catarino R, Viviano M, Tincho E, et al. Cervical cancer screening in a low-resource setting: a pilot study on an HPV-based screen-and-treat approach. Cancer Med. 2017;6(7):1752-61.
47. Toliman PJ, Kaldor JM, Tabrizi SN, Vallely AJ. Innovative approaches to cervical cancer screening in low- and middle-income countries. Climacteric. 2018;21(3):235-8.
48. Catarino R, Schafer S, Vassilakos P, Petignat P, Arbyn M. Accuracy of combinations of visual inspection using acetic acid or lugol iodine to detect cervical precancer: a meta-analysis. BJOG. 2018;125(5):545-53.
49. Gallay C, Girardet A, Viviano M, Catarino R, Benski AC, Tran PL, et al. Cervical cancer screening in low-resource settings: a smartphone image application as an alternative to colposcopy. Int J Womens Health. 2017;9:455-61.
50. Ricard-Gauthier D, Wisniak A, Catarino R, van Rossum AF, Meyer-Hamme U, Negulescu R, et al. Use of Smartphones as Adjuvant Tools for Cervical Cancer Screening in Low-Resource Settings. J Low Genit Tract Dis. 2015;19(4):295-300.
51. Negulescu RA, Catarino R, De Vuyst H, Undurraga-Malinverno M, Meyer-Hamme U, Alec M, et al. Web-based instrument to assess skills in visual inspection of the cervix among healthcare providers. Int J Gynaecol Obstet. 2016;134(1):107-13.
52. Quercia K, Tran PL, Jinoro J, Herniainasolo JL, Viviano M, Vassilakos P, et al. A Mobile Health Data Collection System for Remote Areas to Monitor Women Participating in a Cervical Cancer Screening Campaign. Telemed J E Health. 2018;24(4):277-82.
53. Catarino R, Vassilakos P, Scaringella S, Undurraga-Malinverno M, Meyer-Hamme U, Ricard-Gauthier D, et al. Smartphone Use for Cervical Cancer Screening in Low-Resource Countries: A Pilot Study Conducted in Madagascar. PLoS One. 2015;10(7):e0134309.
54. Urner E, Delavy M, Catarino R, Viviano M, Meyer-Hamme U, Benski AC, et al. A Smartphone-Based Approach for Triage of Human Papillomavirus-Positive Sub-Saharan African Women: A Prospective Study. JMIR Mhealth Uhealth. 2017;5(5):e72.
55. Peterson CW, Rose D, Mink J, Levitz D. Real-Time Monitoring and Evaluation of a Visual-Based Cervical Cancer Screening Program Using a Decision Support Job Aid. Diagnostics (Basel). 2016;6(2).
56. Sharma D, Rohilla L, Bagga R, Srinivasan R, Jindal HA, Sharma N, et al. Feasibility of implementing cervical cancer screening program using smartphone imaging as a training aid for nurses in rural India. Public Health Nurs. 2018;35(6):526-33.
57. Sahin D, Hacisalihoglu UP, Kirimlioglu SH. Telecytology: Is it possible with smartphone images? Diagn Cytopathol. 2018;46(1):40-6.
58. Tanaka Y, Ueda Y, Okazawa A, Kakuda M, Matsuzaki S, Kobayashi E, et al. 'Smartscopy' as an alternative device for cervical cancer screening: a pilot study. BMJ Innov. 2017;3(2):123-6.
59. Asgary R, Adongo PB, Nwameme A, Cole HV, Maya E, Liu M, et al. mHealth to Train Community Health Nurses in Visual Inspection With Acetic Acid for Cervical Cancer Screening in Ghana. J Low Genit Tract Dis. 2016;20(3):239-42.
60. Goggin P, Sauvageau C, Gilca V, Defay F, Lambert G, Mathieu CS, et al. Low prevalence of vaccine-type HPV infections in young women following the implementation of a school-based and catch-up vaccination in Quebec, Canada. Hum Vaccin Immunother. 2018;14(1):118-23.
61. Carozzi F, Puliti D, Ocello C, Anastasio PS, Moliterni EA, Perinetti E, et al. Monitoring vaccine and non-vaccine HPV type prevalence in the post-vaccination era in women living in the Basilicata region, Italy. BMC Infect Dis. 2018;18(1):38.

62. Kumakech E, Berggren V, Wabinga H, Lillsunde-Larsson G, Helenius G, Kaliff M, et al. Significantly Reduced Genoprevalence of Vaccine-Type HPV-16/18 Infections among Vaccinated Compared to Non-Vaccinated Young Women 5.5 Years after a Bivalent HPV-16/18 Vaccine (Cervarix(R)) Pilot Project in Uganda. PLoS One. 2016;11(8):e0160099.
63. Garland SM, Cornall AM, Brotherton JML, Wark JD, Malloy MJ, Tabrizi SN, et al. Final analysis of a study assessing genital human papillomavirus genoprevalence in young Australian women, following eight years of a national vaccination program. Vaccine. 2018;36(23):3221-30.
64. Osborne SL, Tabrizi SN, Brotherton JM, Cornall AM, Wark JD, Wrede CD, et al. Assessing genital human papillomavirus genoprevalence in young Australian women following the introduction of a national vaccination program. Vaccine. 2015;33(1):201-8.
65. Guo F, Hirth JM, Berenson AB. Comparison of HPV prevalence between HPV-vaccinated and non-vaccinated young adult women (20-26 years). Hum Vaccin Immunother. 2015;11(10):2337-44.
66. Feiring B, Laake I, Christiansen IK, Hansen M, Stalcrantz J, Ambur OH, et al. Substantial Decline in Prevalence of Vaccine-Type and Nonvaccine-Type Human Papillomavirus (HPV) in Vaccinated and Unvaccinated Girls 5 Years After Implementing HPV Vaccine in Norway. J Infect Dis. 2018;218(12):1900-10.
67. Latsuzbaia A, Arbyn M, Tapp J, Fischer M, Weyers S, Pesch P, et al. Effectiveness of bivalent and quadrivalent human papillomavirus vaccination in Luxembourg. Cancer Epidemiol. 2019;63:101593.
68. Machalek DA, Garland SM, Brotherton JML, Bateson D, McNamee K, Stewart M, et al. Very Low Prevalence of Vaccine Human Papillomavirus Types Among 18- to 35-Year Old Australian Women 9 Years Following Implementation of Vaccination. J Infect Dis. 2018;217(10):1590-600.
69. McGregor S, Saulo D, Brotherton JML, Liu B, Phillips S, Skinner SR, et al. Decline in prevalence of human papillomavirus infection following vaccination among Australian Indigenous women, a population at higher risk of cervical cancer: The VIP-I study. Vaccine. 2018;36(29):4311-6.
70. 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.
71. Egli-Gany D, Spaar Zographos A, Diebold J, Masserey Spicher V, Frey Tirri B, Heusser R, et al. Human papillomavirus genotype distribution and socio-behavioural characteristics in women with cervical pre-cancer and cancer at the start of a human papillomavirus vaccination programme: the CIN3+ plus study. BMC Cancer. 2019;19(1):111.
72. Jacot-Guillarmod M, Pasquier J, Greub G, Bongiovanni M, Achtari C, Sahli R. Impact of HPV vaccination with Gardasil(R) in Switzerland. BMC Infect Dis. 2017;17(1):790.
73. Scavone C, Di Mauro C, Brusco S, Bertini M, di Mauro G, Rafaniello C, et al. Surveillance of adverse events following immunization related to human papillomavirus vaccines: 12 years of vaccinovigilance in Southern Italy. Expert Opin Drug Saf. 2019;18(5):427-33.
74. Schartau S, Heering Holt D, Lutzen T, Rytter D, Molbak K. On the contextual nature of vaccine safety monitoring: Adverse events reporting after HPV-vaccination in Denmark, 2015. Vaccine. 2019;37(19):2580-5.
75. Bonaldo G, Vaccheri A, D'Annibali O, Motola D. Safety profile of human papilloma virus vaccines: an analysis of the US Vaccine Adverse Event Reporting System from 2007 to 2017. Br J Clin Pharmacol. 2019;85(3):634-43.
76. Jorgensen L, Gotzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. BMJ Evid Based Med. 2018;23(5):165-8.
77. Riva C, Tinari S, Spinosa JP. Lessons learnt on transparency, scientific process and publication ethics. The short story of a long journey to get into the public domain unpublished data, methodological flaws and bias of the Cochrane HPV vaccines review. BMJ Evid Based Med. 2019;24(2):80-1.
78. Jorgensen L, Gotzsche PC, Jefferson T. Index of the human papillomavirus (HPV) vaccine industry clinical study programmes and non-industry funded studies: a necessary basis to address reporting bias in a systematic review. Syst Rev. 2018;7(1):8.

79. Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. Lancet Infect Dis. 2017;17(12):1293-302.
80. Woestenberg PJ, King AJ, van Benthem BHB, Donken R, Leussink S, van der Klis FRM, et al. Bivalent Vaccine Effectiveness Against Type-Specific HPV Positivity: Evidence for Cross-Protection Against Oncogenic Types Among Dutch STI Clinic Visitors. J Infect Dis. 2018;217(2):213-22.
81. Brotherton JML. Confirming cross-protection of bivalent HPV vaccine. Lancet Infect Dis. 2017;17(12):1227-8.
82. Pollock KGJ. Sustained Cross-protection of the Bivalent Human Papillomavirus Vaccine. J Infect Dis. 2018;217(10):1515-6.
83. Delere Y, Remschmidt C, Leuschner J, Schuster M, Fesenfeld M, Schneider A, et al. Human Papillomavirus prevalence and probable first effects of vaccination in 20 to 25 year-old women in Germany: a population-based cross-sectional study via home-based self-sampling. BMC Infect Dis. 2014;14:87.
84. Makwe CC, Anorlu RI, Odeyemi KA. Human papillomavirus (HPV) infection and vaccines: knowledge, attitude and perception among female students at the University of Lagos, Lagos, Nigeria. J Epidemiol Glob Health. 2012;2(4):199-206.
85. Blodt S, Holmberg C, Muller-Nordhorn J, Rieckmann N. Human Papillomavirus awareness, knowledge and vaccine acceptance: a survey among 18-25 year old male and female vocational school students in Berlin, Germany. Eur J Public Health. 2012;22(6):808-13.
86. Rathfisch G, Gungor I, Uzun E, Keskin O, Tencere Z. Human papillomavirus vaccines and cervical cancer: awareness, knowledge, and risk perception among Turkish undergraduate students. J Cancer Educ. 2015;30(1):116-23.
87. Dany M, Chidiac A, Nassar AH. Human papillomavirus vaccination: assessing knowledge, attitudes, and intentions of college female students in Lebanon, a developing country. Vaccine. 2015;33(8):1001-7.
88. Fernandes R, Potter BK, Little J. Attitudes of undergraduate university women towards HPV vaccination: a cross-sectional study in Ottawa, Canada. BMC Womens Health. 2018;18(1):134.
89. Karafillakis E, Simas C, Jarrett C, Verger P, Peretti-Watel P, Dib F, et al. HPV vaccination in a context of public mistrust and uncertainty: a systematic literature review of determinants of HPV vaccine hesitancy in Europe. Hum Vaccin Immunother. 2019;15(7-8):1615-27.
90. Santé OMdl. Communication sur le Vaccin Anti-HPV: Considérations particulières pour un vaccin unique. 2006.
91. Patel C, Brotherton JM, Pillsbury A, Jayasinghe S, Donovan B, Macartney K, et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent? Euro Surveill. 2018;23(41).
92. Zhai L, Tumban E. Gardasil-9: A global survey of projected efficacy. Antiviral Res. 2016;130:101-9.
93. Toh ZQ, Kosasih J, Russell FM, Garland SM, Mulholland EK, Licciardi PV. Recombinant human papillomavirus nonavalent vaccine in the prevention of cancers caused by human papillomavirus. Infect Drug Resist. 2019;12:1951-67.
94. Yang DY, Bracken K. Update on the new 9-valent vaccine for human papillomavirus prevention. Can Fam Physician. 2016;62(5):399-402.
95. Costa APF, Cobucci RNO, da Silva JM, da Costa Lima PH, Giraldo PC, Goncalves AK. Safety of Human Papillomavirus 9-Valent Vaccine: A Meta-Analysis of Randomized Trials. J Immunol Res. 2017;2017:3736201.
96. Genovese C, V LAF, Squeri A, Trimarchi G, Squeri R. HPV vaccine and autoimmune diseases: systematic review and meta-analysis of the literature. J Prev Med Hyg. 2018;59(3):E194-E9.
97. Pollock KG, Wallace LA, Wrigglesworth S, McMaster D, Steedman N. HPV vaccine uptake in men who have sex with men in Scotland. Vaccine. 2019;37(37):5513-4.

98. Widdice LE, Bernstein DI, Franco EL, Ding L, Brown DR, Ermel AC, et al. Decline in vaccine-type human papillomavirus prevalence in young men from a Midwest metropolitan area of the United States over the six years after vaccine introduction. Vaccine. 2019;37(45):6832-41.
99. Chandler E, Ding L, Gorbach P, Franco EL, Brown DA, Widdice LE, et al. Epidemiology of Any and Vaccine-Type Anogenital Human Papillomavirus Among 13-26-Year-Old Young Men After HPV Vaccine Introduction. J Adolesc Health. 2018;63(1):43-9.
100. Chow EPF, Machalek DA, Tabrizi SN, Danielewski JA, Fehler G, Bradshaw CS, et al. Quadrivalent vaccine-targeted human papillomavirus genotypes in heterosexual men after the Australian female human papillomavirus vaccination programme: a retrospective observational study. Lancet Infect Dis. 2017;17(1):68-77.
101. Office Fédérale de la Santé Publique. Vaccination contre les HPV : recommandations de l'OFSP et de la CFV concernant le nouveau vaccin Gardasil 9®. 2018.