HPV vaccination and screening to preventing cervical cancer: the road to elimination

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" *HPV vaccination and screening to preventing cervical cancer: the road to elimination"*

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by

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TABLE OF CONTENTS

Summary ***3***

Introduction ***5***

- **The cost of cervical cancer worldwide and in Switzerland:** **9**
- **Cervical cancer prevention:** **12**

Original Article 1: ***20***

Original Article 2: ***31***

Original Article 3: ***43***

Original Article 4: ***53***

Original Article 5: ***61***

Discussion and conclusion ***74***

Reduction of HPV infections and cancers linked to these viruses through vaccination: the first step to elimination **74**

Evolution of screening and future prospects: The second step to elimination **75**

Scientific conclusion and perspective: ***79***

References ***81***

SUMMARY

INTRODUCTION :We can estimated that there are nearly 45 million deaths from cervical cancer and other HPV-related cancers worldwide, all of which could be prevented if a sufficient preventive measures for HPV screening and vaccination can be implemented.

OBJECTIVES :The aim of the present habilitiation thesis is to present a synthesis of the research work that I have published on the subject of HPV vaccination and HPV screening.

RESULTS AND DISCUSSION :Study 1 aimed to assess the coverage of HPV vaccination among a group of future health professionals, including midwives and nurses, through using a self-sampling technique. The findings here indicated that the prevalence of HPV6/11/16/18 was lower in vaccinated women versus unvaccinated women. Study 2 therefore sought to follow on by developing an understanding of knowledge and attitudes towards the HPV vaccine for healthcare undergraduates (both male and female). The findings indicated a poor understanding of the HPV infection and its prevention, which were then further investigated. Study 3 therefore focused on identifying the factors hindering or promoting HPV vaccination. Taken together, all 3 studies indicate that average vaccination rates are closely related to the information provided on HPV infection and prevention.Study 4 included a randomized controlled trial which revealed that self-sampling is an alternative to conventional cervical cancer screening, by increasing participation and adherence to screening. Subsequently, study 5 involved a systematic review to investigate the use of self-sampling in Latin America (a country that has high incidence and mortality rates relating to cervical cancer). The findings indicate that self-sampling is an acceptable screening method amongst Latin American women, being associated with important factors such as comfort and privacy.

CONCLUSION :Taken together, the studies reviewed demonstrate the need to provide increased access to key prevention strategies through vaccination and self-screening. There is also a clear need to provide information to the vaccine audience, which should be a key focus for prevention programmes. These findings can be used to inform public health policy on HPV prevention efforts.

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Cervical cancer is the fourth most common cancer in women worldwide, with approximately 600,000 new cases diagnosed each year. The majority of cases occur in developing countries, where access to preventive measures is often limited(1).Measures to prevent cervical cancer include vaccination against Human Papillomavirus (HPV), regular screening tests and safe sex practices(2).

We will begin with a general presentation of HPV viruses, and their epidemiology. Next, I will present information on cervical cancer globally and in Switzerland. Additionally, we will consider primary and secondary prevention methods in place to eliminate this disease. This will introduce the articles summarising my extensive research on this theme for the last five years, which make up this Privatdocent thesis.

Biological characteristics and descriptions of different HPV viruses

Human Papillomaviruses (HPV) are non-enveloped, icosahedral capsid viruses belonging to the Papillomaviridae family. The virus genome is a circular, double-stranded deoxyribonucleic acid molecule comprising several open reading frames divided into three regions called the early (E), late (L), and upstream regulatory region (URR) or long control region (LCR)(3). (Figure 1)

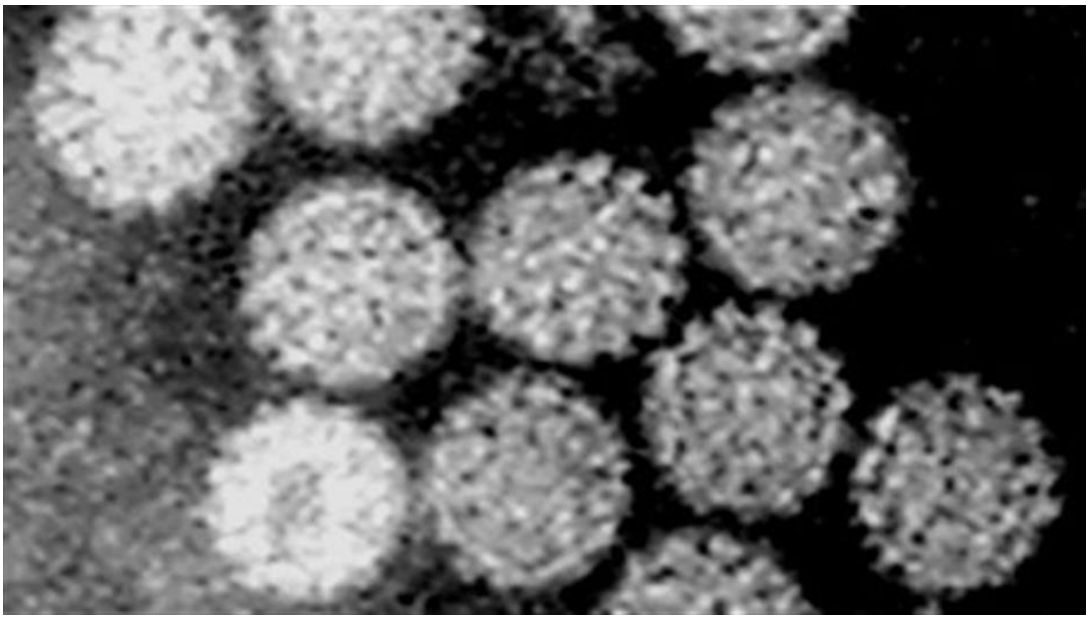

Figure 1: Electron microscope image of Papillomavirus. Adapted from Dr. Graham Beards

Human Papillomaviruses are a set of DNA viruses of the Papillomaviridae family. There are more than 200 types, classified according to their tropism and pathogenicity(4).

Thus, two different tropisms can be distinguished in humans:

- HPV with skin tropism; these infect the epithelial cells of the skin. They can cause benign tumours such as plantar warts but also promote certain malignant tumours such as squamous cell carcinoma (skin cancer).

- HPV with mucosal tropism; these infect the epithelial cells of the genital and oral mucous membranes. They are separated into two subgroups:
    - HPV with a low carcinogenic risk (HPV 6 and 11, for example). Infection with these viruses can cause the appearance of benign tumours or condylomas (genital warts). These can be disabling, requiring long treatment and recurring frequently.

    - HPV with a high carcinogenic risk is also called oncogenic HPV (HPV 16, 18, 31, 33, 45, 52, 58, and in particular HPV 16 and 18). They can cause the development of precancerous lesions, particularly of the cervix, which can develop into cancers after several years or even decades.

- A brief history of HPV :

The first animal papillomavirus was described in 1933 by Richard Shope, who studied papillomas in "warty" wild rabbits, and then the first clinical descriptions of HPV viruses in humans date back to the second part of the 20th century(5). In fact Dr Zur Hausen's first work on the role of HPV viruses in cervical cancer dates back to the 1970s, when the majority of researchers focused on the involvement of Herpes virus infections or other sexually transmitted

infections as a cause of cervical cancer(6). This research shows that HPV 16 and 18 DNA are found in the vast majority of biopsy samples of cervical cancer and precancerous lesions. Harald zur Hausen subsequently demonstrated that viral infection and expression of the viral gene in the infected cell was necessary but not sufficient. Genetic modifications are necessary for the tumour transformation of the infected cell(7). They are associated with the expression of HPV E6 and E7 proteins, which are considered "high-risk". This results in chromosomal instability, mutation accumulation, and the progression of cancerous lesions(8).

Nevertheless, long before Harald zur Hausen's discoveries on the etiology of cervical cancers, the Greek cytologist George Nicholas Papanicolaou had developed a screening technique. At a conference in 1928, he made a presentation on the possibility of diagnosing cervical cancer by means of a vaginal smear(9). However, because he was unable to rely on a sufficient number of cases, his work was not appreciated at the time. In 1943 Herbert Frederik Traut published "The Diagnosis of Uterine Cancer by the Vaginal Smear", and in 1944, he published "Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus". The Pap smear test (Papanicolaou staining) was derived from the work of Georges Nicholas Papanicolaou, which immediately led to extensive developments. He is the inventor of the Pap smear test, which is used worldwide for the detection and prevention of cancer and other cellular disorders of the female reproductive system(10). This particular screening technique will be detailed later.

- Natural history of HPV infections:

As previously reported, there are more than 200 identified human genotypes of HPV, including 40 with anogenital tropism(11). They are characterised by narrow host specificity and cutaneomucosal epithelial tropism. Transmission is mainly direct (through sexual contact) and can also be indirect. Infections are often plurifocal, asymptomatic and recurrent(12).

The clinical aspects are varied: skin warts, condyloma, papillomas, epidermodysplasia verruciformis and dysplasia. Some so-called "High Risk (HR)" genotypes are directly associated with cancers (of the cervix, anal canal, vulva, oropharynx...); the closest association

is that of squamous cell carcinoma of the cervix, which is considered as a viral-induced cancer(13). Of the 200 human papillomaviruses described to date, 13 to 15 genotypes of the genus alpha, classified as high-risk HPV, are recognised as being the etiological factors for cervical cancer(14).

The natural history of HPV HR infection is closely related to that of precancerous and cancerous lesions of the cervix. The peak incidence of HPV HR infections, observed for the age group 15–25 years, precedes that of precancerous lesions, noted a decade later (group 25–35 years), which itself precedes the peak incidence of invasive cancers observed 10 years later (group 35–45 years). HPV HR infections are transient in more than 90% of cases and eliminated in 12 to 16 months(15) (see figure 2). Only persistent infections are likely to lead to the appearance of intraepithelial lesions of the cervix and then invasive cancer. Among HPV HR, HPV 16 and HPV 18 persist more than other HPV HR and are associated with a higher risk of cervical cancer. The prevalence of these two viruses also increases with the severity of cervical lesions; it reaches about 70% for HPV 16 and 19% for HPV 18(16).

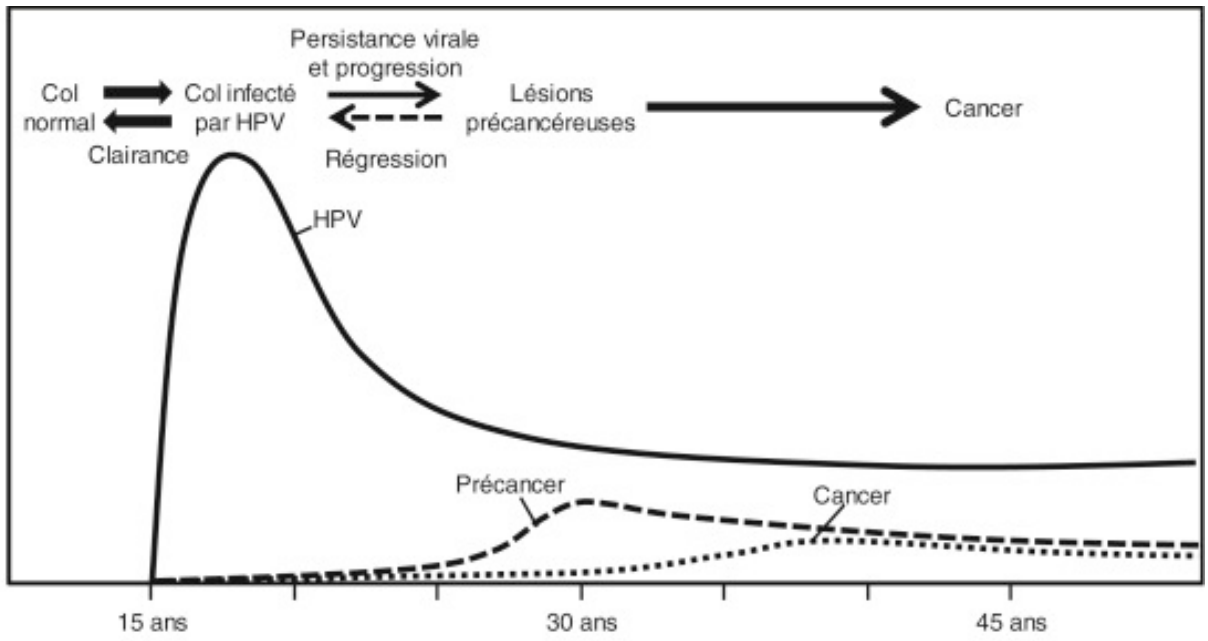

Figure 2. Natural history of HPV infection and cervical cancer (adapted from Schiffman and Castle).

- The cost of cervical cancer worldwide and in Switzerland:

***Cervical cancer worldwide**:*

It is estimated that there are nearly 45 million deaths from cervical cancer and other HPV-related cancers worldwide, including vaginal cancer, laryngeal cancer and anal cancer, all of which could be prevented if, as recommended by the World Health Organization, its goal of a sufficiently high prophylactic HPV vaccination by 2036 could be achieved(17).

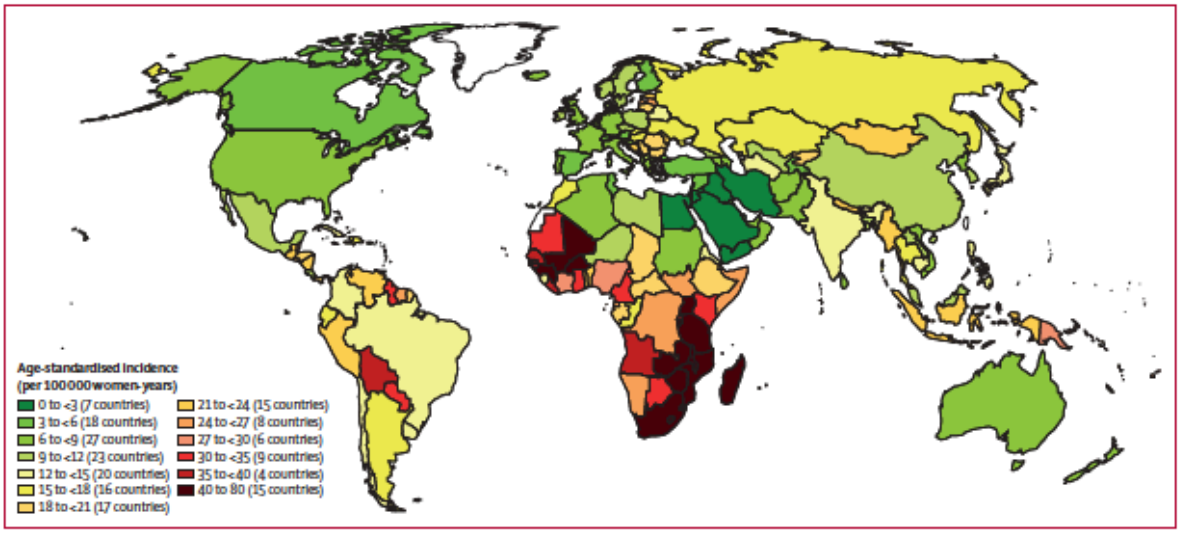

Figure 1: Geographical distribution of world age-standardised incidence of cervical cancer by country, estimated for 2018

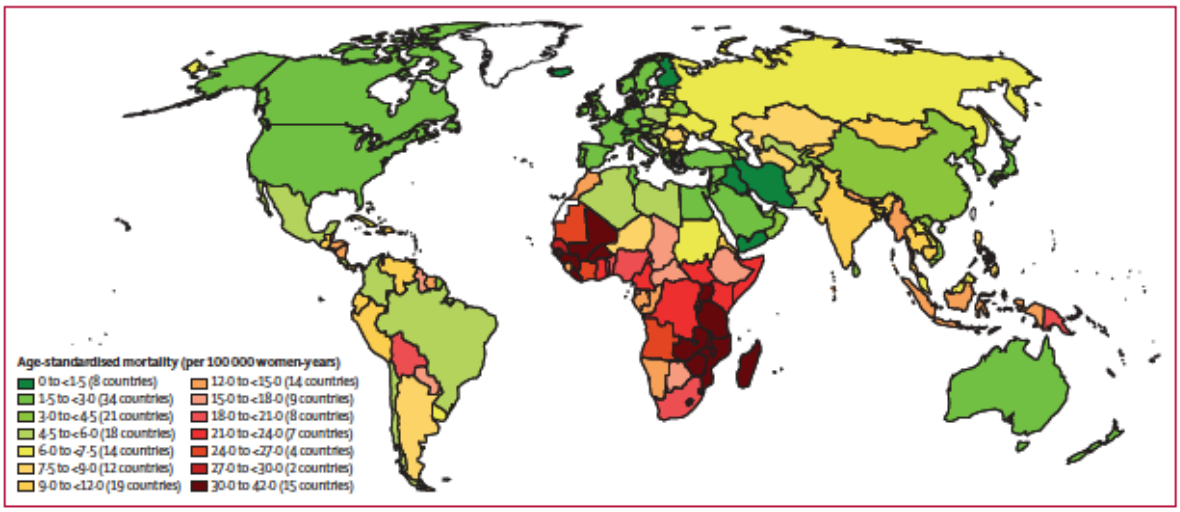

Figure 3: Global distribution of cervical cancer incidence and mortality in 2018. (Source Lancet Global Health)(17)

Cervical cancer in Switzerland:

Some 250 new cases of uterine cancer and about 5,000 precancerous lesions are diagnosed annually in Switzerland (18). Cervical cancer is the fifth most common cancer in the country, for women between 20 and 49 years old (Figure 4) (19). Warts and precancerous lesions can be removed surgically, andthe earlier the therapy is initiated, the more likely the treatment is to be successful.

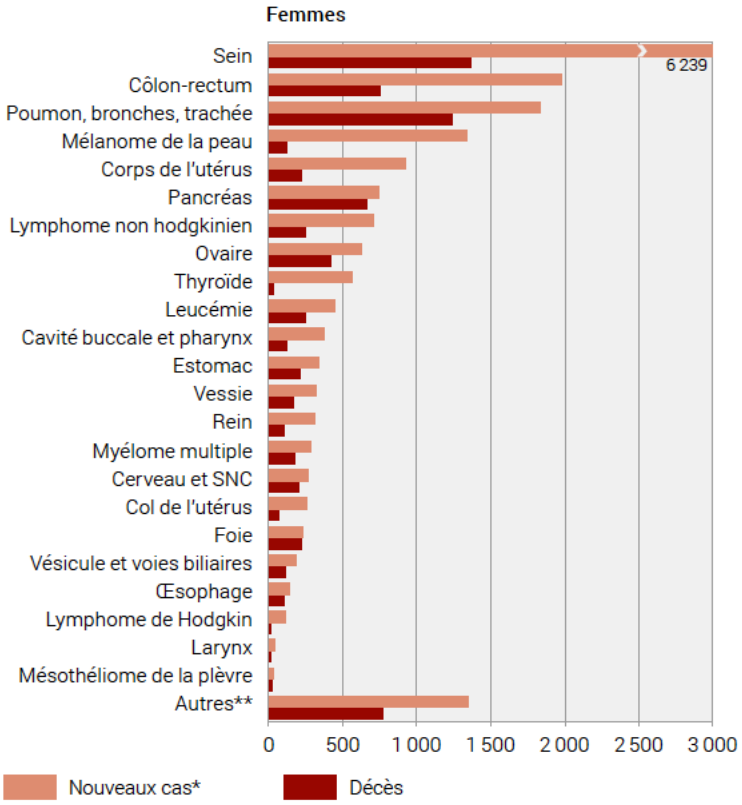

Figure 4: Number of new cancer cases and deaths in Switzerland between 2017 and 2021. (Source Federal Office of Statistics)(19)

Figure 5 demonstrates that cervical cancer can develop in women from as early as 24 yearsof age. Although the mortality rate is low at this age, it is not zero. The incidence of cervical cancer increases up to the age of 79 years, then decreases. Mortality, on the other hand, increases continuously with age. Half of all cancers of the uterus are diagnosed for women aged 68 years and above, and fifty percent of cervical cancer-related deaths are recorded for women aged 78 years and over (19).

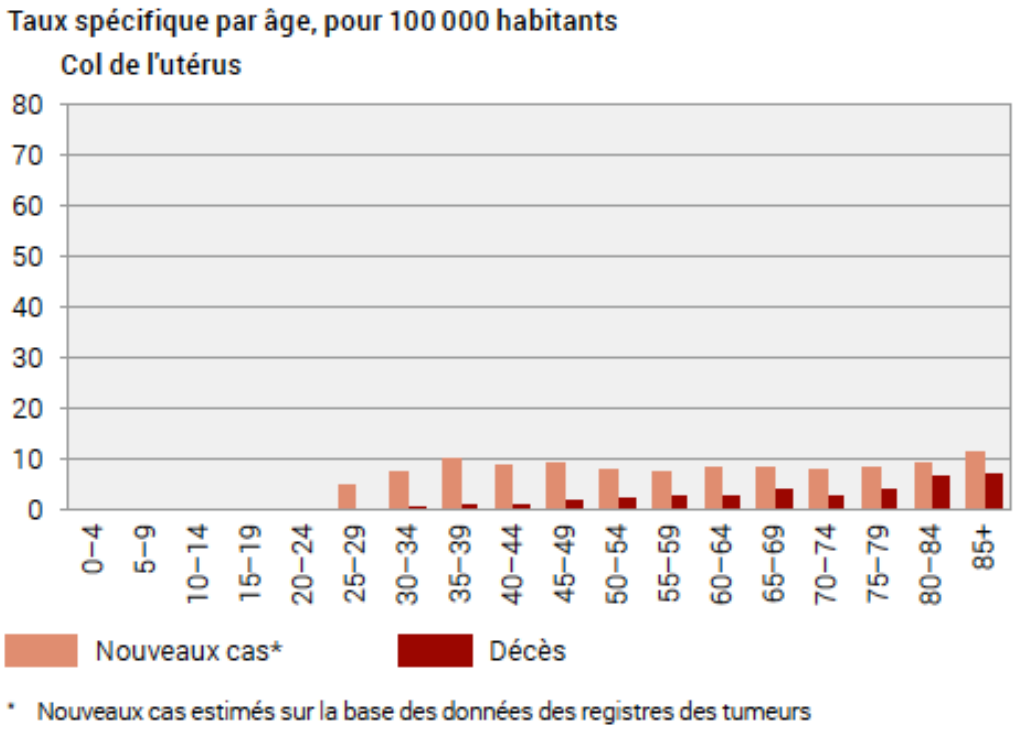

Figure 5: Number of new cervical cancer cases and deaths in Switzerland between 2017 and 2021 by age. (Source Federal Office of Statistics)(19)

It is important to note that although cervical cancer is a female cancer, the problem of HPV infection and this oncological consequence affects both sexes. Indeed, it is often falsely believed that HPV and these consequences are solely a female problem(20). Indeed, when we think of papillomavirus, we think of cervical cancer. And therefore, it is commonly perceived as a public health problem that only affects women. However, the public health threat concerns both sexes, and researchers are increasingly identifying this. A meta-analysis published in the journal "The Lancet Global Health" shows that globally, nearly a third of males over 15 years old are infected with Human Papillomavirus(21). This is not surprising, according to specialists, because HPV is the most common sexually transmitted infection in the world, and half of these infections affect young people aged between 15 and 24 years old(22). Any adult (man or woman) who is sexually active during his or her lifetime will have more than an 80% risk of being infected with Human Papilloma Virus at any given time. In most cases, HPV infections do not present symptoms and are eliminated naturally by the body. They also do not systematically lead to serious diseases(23).

The best way to protect against HPV is vaccination; ideally, both girls and boys should get vaccinated before they are 15 years old and before their first sexual experience(24). However, catch-up vaccination can be offered later as well. This catch-up option is less common among men and women over 26 years old, perhaps because the vaccine is expensive (200 Swiss Francs per dose, and requires three doses in total) and payable by the person who requests it.

I will now detail HPV screening and HPV prophylactic vaccination, which are the 2 most effective means for preventing HPV infections and, at the same time, avoiding uterine cancers (and other HPV-related cancers): .

- Cervical cancer prevention:

HPV screening

HPVs are small, non-enveloped viruses harbouring double-stranded DNA of about 8,000 base pairs. The genome comprises an E (*early*) region encoding early proteins, an L (*late*) region encoding late capsid proteins and a *long control region* (LCR) controlling the expression and replication of the viral genome(25).

The HPV HR-induced neoplastic transformation process is partly related to the integration of the viral genome into the host cell genome. This integration follows the cleavage of viral DNA in E2 and/or E1(26). As a result, the E2 protein is no longer expressed and no longer performs its function as a transcription regulator, and this results in increased expression of the viral oncoproteins E6 and E7. Epigenetic mechanisms, and in particular the methylation of viral DNA, can also participate in the deregulation of viral protein expression and play a role in the progression of HPV-associated diseases. In the end, it is the pleiotropic effects of E6 and E7 that lead to the activation of proliferation, an alteration of cell cycle control, immortalisation and then transformation of cells(27).

Since the replication cycle of HPVs depends closely on the differentiation of epithelial cells, detecting them on cell culture is not easy, and thus, this approach is not used for diagnosis. In

fact, HPV detection is essentially based on the detection of their genome and, more recently, on the detection of viral transcripts using molecular hybridisation techniques(28). There are currently several tests available for detecting HPV, which can detect different HPV spectra (High-Risk HPV and Low-Risk HPV). These tests use various detection formats, such as combined detection of several HPVs without genotype identification, partial genotyping and complete genotyping. Additionally, they detect targets of different natures, such as DNA and RNA and implement highly variable detection/revelation methods such as target amplification, signal amplification and reverse hybridisation(29).

HPV screening in public health:

Public health screening for cervical cancer involves detecting an HPV infection to detect precancerous lesions and cancer and then treating them appropriately. Screening is carried out in women who have no symptoms and who may feel perfectly healthy. When screening detects HPV infection or precancerous lesions, these can easily be treated, and cancer can be prevented. Screening can detect cancer in its early stages, increasing the chances of successful treatment(30).

The World Health Organization is now encouraging countries to use HPV screening tests for cervical cancer screening, including tests based on HPV DNA and mRNA(31).

- HPV DNA tests detect high-risk HPV strains, which are responsible for almost all cervical cancers.

- HPV mRNA-based tests detect HPV infections leading to cell transformation.

Unlike tests that rely on a visual inspection (VIA/VILI), these HPV screening tests are objective tests. They have proven to be simpler, preventing more precancerous lesions and cancers and saving more lives. They are also more effective at lower cost than visual inspection techniques or cytology (Pap test or vaginal smear)(32).

Screening should begin from 30 years of age in the general population of women, with regular screening by means of an HPV test validated every 5 to 10 years, and from 25 years of age for women living with HIV, who must also be screened more frequently i.e., every 3 to 5 years(33).

The process of obtaining a cervico-uterine sample by a health professional is similar to that of a cytology or an HPV screening test. However, the WHO indicates that self-collection can be used to provide samples for HPV DNA-based tests but not for HPV mRNA-based tests. Women need appropriate support to feel confident in the process(34).

Screening must be linked to treatment and management in case of positive screening tests. HPV-positive women can be treated without diagnosis verification in places where resources are limited.

HPV vaccination

- *The HPV vaccination worldwide*

The WHO regularly updates its recommendations for the Human Papillomavirus vaccine. To summarize their recommendation, it is important to know that a single-dose vaccination regimen using the nonavalent vaccine that protects against strains 6, 11, 16, 18, 31, 33, 45, 52, and 58 is available as an off-label single-dose alternative. This alternative regimen can offer comparable efficacy and duration of protection to the two-dose regimen(35). The single-dose alternative regimen was initially recommended in April 2022 by the WHO Independent Expert Advisory Group, but these new recommendations are timely, and issued in the very worrying context of declining HPV vaccination coverage worldwide(36). In 2019 and 2021, coverage with the first dose of the HPV vaccine decreased from 25% to 15%. This means that in 2021, 3.5 million more girls were unable to benefit from this vaccine than in 2019(37).

Optimizing the HPV vaccination schedule is expected to improve access to the vaccine, providing countries with the opportunity to vaccinate more girls and alleviate the often complicated and costly follow-up burden of two-dose vaccination. It is vital that countries strengthen their HPV vaccination programmes, accelerate their implementation and reverse the decline in vaccination coverage.

The updated WHO recommendations in 2023 are(36):

- **One or two-dose regimen** for girls aged **9 to 14 years**;
- **One or two-dose regimen** for girls and young women aged **15 to 20 years**;
- Two-dose regimen administered 6 months apart for **women over 21 years old**.

The recommendation stresses the importance of prioritizing vaccination for individuals who are immunocompromised or living with HPV. Immunocompromised people should receive at least two doses and, where possible, three doses.

The primary target for vaccination is girls aged 9 to 14 years before the start of sexual activity. Vaccination of secondary targets, namely older boys and girls is recommended where practical and economically feasible(38).

The intensification of adolescent vaccination against HPV will have a significant effect on the prevention of cervical cancer and related mortality.

As part of its global strategy to eliminate cervical cancer, the World Health Organization has set a goal to vaccinate 90% of young girls against papillomavirus before they reach the age of 15(39).

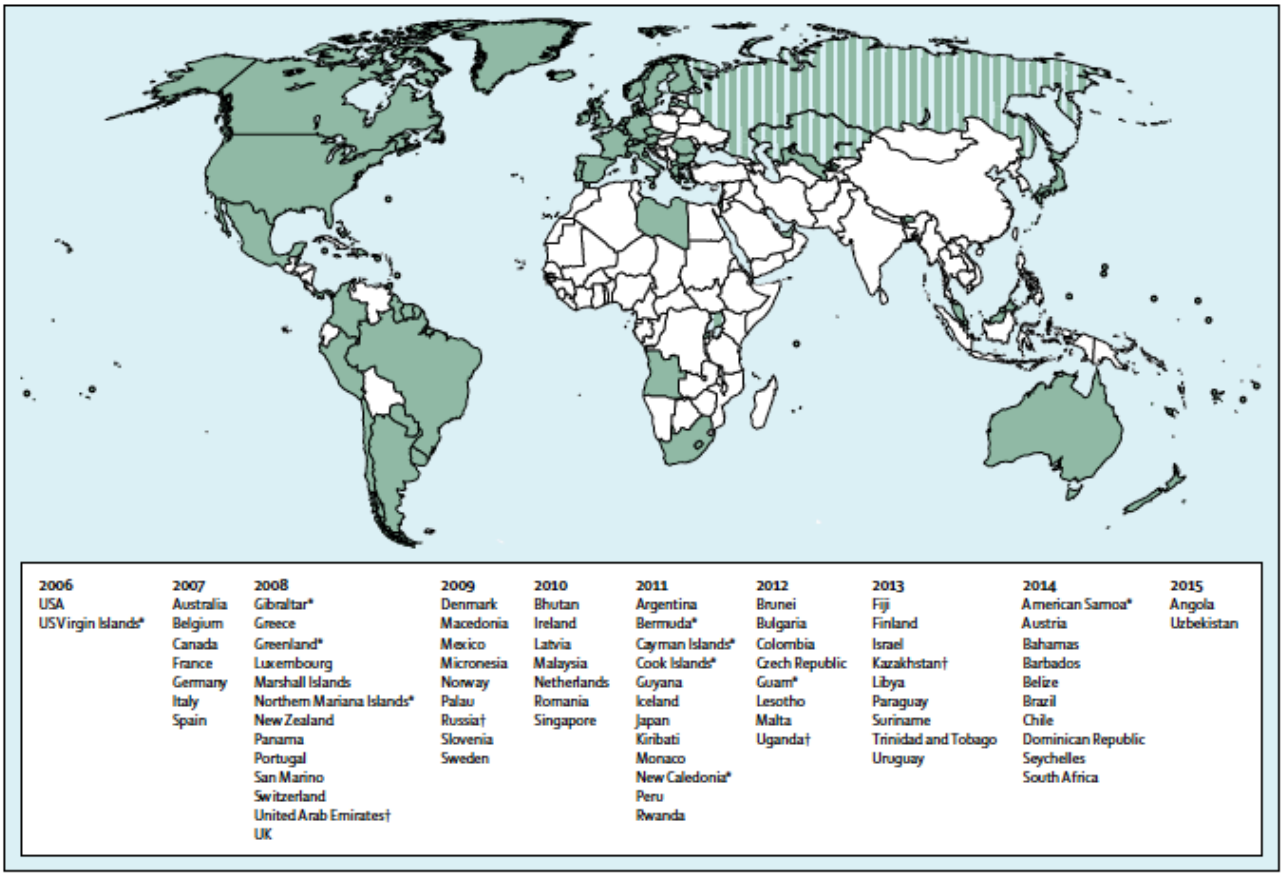

Figure 6: Mapping of countries that have introduced HPV vaccine into their vaccination programmes. (Source Lancet)(40)

Although we find the highest incidence density of cervical cancer and the main mortality burden on the African continent, Figure 6 clearly shows that Western countries benefit the most from HPV vaccination programmes(40).

- *HPV vaccination in Switzerland:*

Since 2008, vaccination against Human Papillomaviruses (HPV) has been recommended in Switzerland as a basic vaccination for all girls aged 11 to 14 years. Since 2019, it has been possible to use a nonavalent vaccine. The "basic vaccination" category applies to vaccinations essential for individual and public health. The introduction of this vaccination aimed to reduce the burden of disease associated with cervical cancer. Papillomaviruses can, however, also

cause other cancerous diseases and genital warts that affect both sexes(41). In 2015, the Federal Commission for Vaccinations (CFV) and the Federal Office of Public Health (FOPH) updated their guidelines and now recommend vaccination against HPV for boys and men aged between 11 and 26 years old. This falls under the "complementary vaccination" category, which aims to provide personal protection. For optimal protection, the vaccine should be administered before the start of sexual activity. A two-dose regimen is applied to girls and boys between the ages of 11 and 14. When vaccination begins at 15 years of age or older, or is administered to adolescent girls who have an immune deficiency, a three-dose regimen is recommended(42).

Tableau 1 :
Taux de vaccination nationaux contre les HPV chez les filles et garçons de 16 ans, Suisse, périodes d'enquête 2017–2019 et 2020–2022

		Pourcentage d'adolescents vaccinés (%) *intervalle de confiance à 95 %*		Fourchettes cantonales (%)	
Période d'enquête	Nombre de doses	Filles	Garçons	Filles	Garçons
2017–2019	1 dose	64 *56–61*	20 *18–22*	19–76	0–56
	2 doses	**59** *62–67*	**17** *15–19*	**19–74**	**0–55**
2020–2022	1 dose	74 *71–76*	52 *49–54*	28–82	8–74
	2 doses	**71** *68–73*	**49** *46–51*	**26–82**	**6–71**

Source des données : monitorage cantonal de la couverture vaccinale

Source (Federal Office of Public Health)(43)

Although vaccination coverage has increased since the introduction of the HPV vaccine in Switzerland, it continues to be sub-optimal to prevent the spread of the virus and significantly reduce new HPV infections. Indeed, less than 1 in 2 boys in the target population is vaccinated against HPV. For girls, the coverage rate increases to 71%, but this rate is still largely insufficient (Table 1)(43).

In Switzerland, reaching sufficient HPV vaccination coverage could theoretically prevent 80 to 180 new cancer cases per year in men and about 300 cases in women(44).

One of the main obstacles to increasing vaccination coverage, and thus reinforcing its effectiveness in the general population, is the reluctance of some people to be vaccinated, linked

to a high level of vaccine hesitancy. This phenomenon is particularly prevalent among future healthcare professionals (nurses, midwives ....)(45-47). According to the WHO, “vaccine hesitancy” can be defined as delaying or refusing a safe vaccination despite its availability. It's a complex problem, depending on the circumstances, as well as the time, place and vaccines in question. Many factors come into play, including misinformation, complacency, convenience and trust. This notion is often used to describe a heterogeneous category of people with varying degrees and reasons for indecision about vaccines. This heterogeneity does not, however, facilitate research into understanding these phenomena or designing interventions to remedy them. We can see that this phenomenon has been amplified since the Covid 19 pandemic and the ever-increasing use of social networks as vectors of information and also of false/counter-information on vaccination(48-50).

To change this behavior, several behavior change models exist, including the COM B model, used in particular by the WHO. The COM-B model for behavior change cites capability (C), opportunity (O), and motivation (M) as three key factors capable of changing behavior (B). Capability refers to an individual's psychological and physical ability to participate in an activity. Opportunity refers to external factors that make a behavior possible. Lastly, motivation refers to the conscious and unconscious cognitive processes that direct and inspire behavior. This model recognizes that behavior is influenced by many factors, and that behavior changes are induced by modifying at least one of these components. The COM-B model is particularly important when considering intervention methods, as interveners need to ensure the sustainability of learned behavior. The model can be summarized as follows:

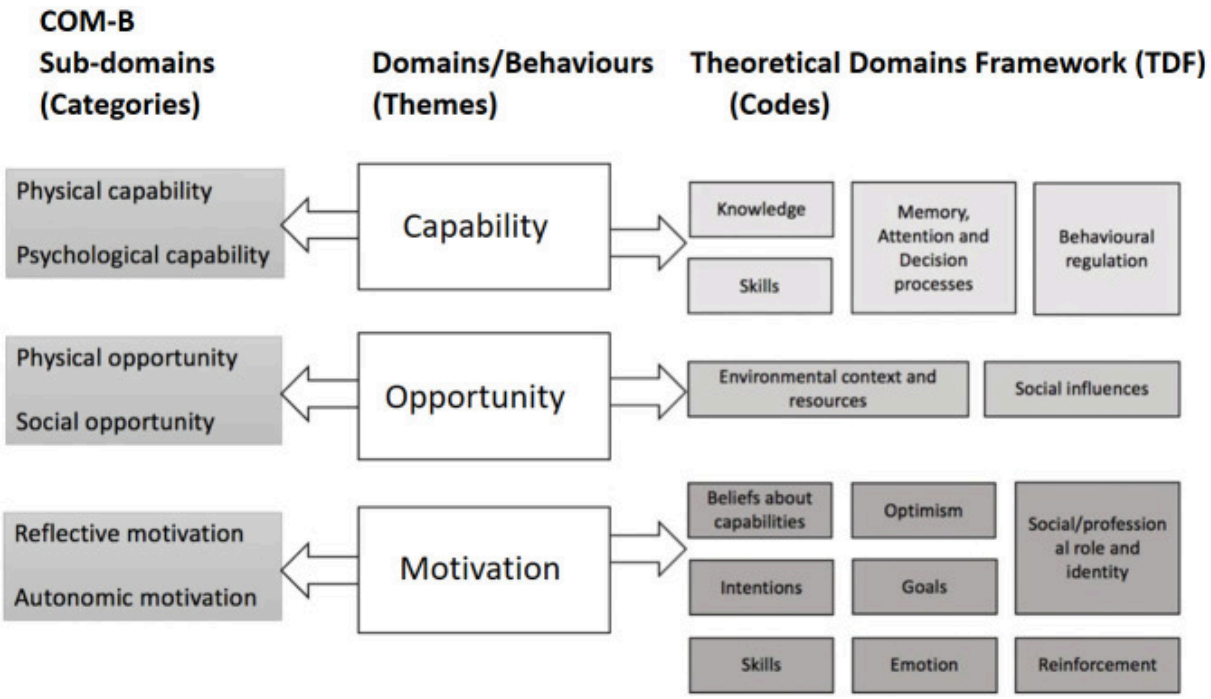

Figure 7 : The COM – B modeled map

Several studies on the subject of HPV vaccine hesitancy have used the COM-B model, clearly showing a lack of knowledge, poor information and even mistrust of vaccination(51-53).

In 2024, we conducted a national study on HPV vaccine hesitancy among future healthcare professionals, the results of which will be available by the end of 2024.

In the continuation of this habilitation (Privatdocent) thesis, I will present the extensive research work that I have carried out on this theme of cervical cancer prevention via HPV vaccination and early detection. First, we will look at three studies on HPV vaccination (vaccinale coverage, knowledge, attitude ect…) and its effectiveness in the general population, and then we will consider two articles on HPV screening and the different screening strategies that can be implemented.

ORIGINAL ARTICLE 1: PREVALENCE OF VACCINE TYPE INFECTIONS IN VACCINATED AND NON-VACCINATED YOUNG WOMEN: HPV-IMPACT, A SELF-SAMPLING STUDY(54)

Before carrying out this study (study 1), we had conducted several prior studies on the evaluation of HPV vaccination coverage in Switzerland. The prior studies had shown a regular increase in HPV vaccination coverage within the framework of the vaccination programmes proposed by the cantons since its introduction(44, 55, 56). In study 1, the first of its kind in Switzerland, we aimed to assess the coverage of HPV vaccination among a group of future health professionals, including midwives and nurses. We were curious to find out if there has been a decline in the prevalence of HPV infections among vaccinated populations since the introduction of the vaccine, compared to an identical but unvaccinated population, in fact, unvaccinated people are almost 9 times more likely to be HPV carriers than vaccinated people (aOR =8.9 IC 95% 5,9-13,2). To measure this prevalence and the effect of the vaccination, we used the self-sampling technique to see if it could be used both as a screening technique and as a vaccination monitoring tool.

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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.

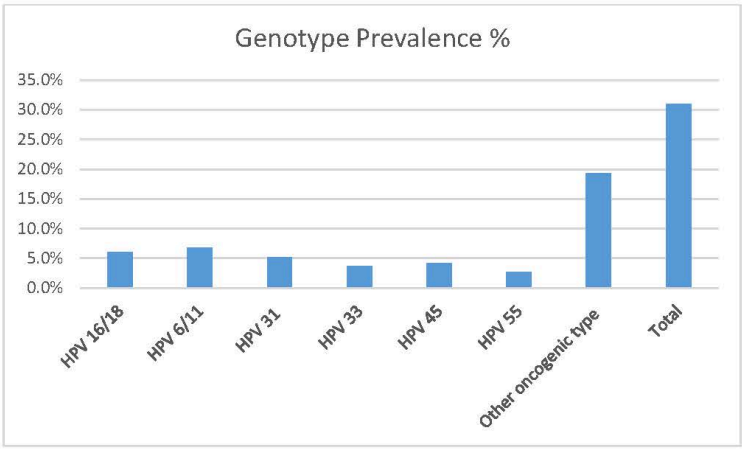

Figure 1. Human papillomavirus (HPV) genotype prevalence and distributions. In the case of multiple genotypes, each genotype was counted independently.

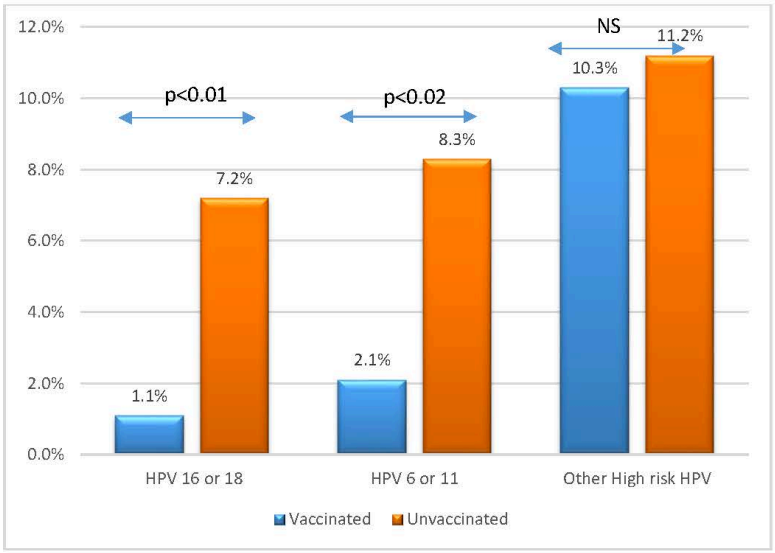

Figure 2. HPV prevalence 6/11 and 16/18, and other high-risk HPV according to vaccination status.

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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ORIGINAL ARTICLE 2: HUMAN PAPILLOMAVIRUS INFECTION AND VACCINATION: KNOWLEDGE, ATTITUDE AND PERCEPTION AMONG UNDERGRADUATE MEN AND WOMEN HEALTHCARE UNIVERSITY STUDENTS IN SWITZERLAND (57).

In the previous study (study 1, presented above) we were surprised by the relatively average vaccination coverage of these future health professionals. We therefore conducted a study (study 2) to explore the knowledge, attitudes, and perceptions of young adult women and men in pre-graduate healthcare training regarding HPV-related infections and vaccination. We hypothesised that despite receiving health training, many of these young adults had limited or incorrect knowledge about HPV infections, lacked confidence and held false beliefs about the HPV vaccine. These factors could potentially explain the relatively average rates of vaccination coverage that we had observed previously. In this study, we also interviewed young men to get an initial idea of their vaccination coverage.

vaccines

MDPI

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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ORIGINAL ARTICLE 3: FACTORS INFLUENCING THE DECISION TO VACCINATE AGAINST HPV AMONG A POPULATION OF FEMALE HEALTH STUDENTS (58)

As a follow-up to the two previous studies, we conducted a study involving a comprehensive questionnaire (study 3), which aimed to understand the factors that either hinder or promote HPV vaccination in young women. This time, the study focused solely on young women. We sought to identify the barriers to initiating HPV vaccination and the reasons for refusal of vaccination by a population of future health professionals. The refusal could be linked to participants` decisions alone or influenced by outside people (family or their doctor in particular).

The purpose of this particular study is to improve vaccination policies as well as to improve prevention and promotion messages for HPV vaccination. Thus, it could be integrated into cantonal programmes to increase vaccination coverage.

vaccines

MDPI

Article

Factors Influencing the Decision to Vaccinate against HPV amongst a Population of Female Health Students

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Abstract: Background: In Switzerland, HPV vaccination has been recommended since 2007 for all adolescent girls aged between 11 and 14 years. More than 10 years after the introduction of this recommendation, immunization coverage targets have not been met. Very few studies at a national level describe the reasons for the reluctance of some young women to become vaccinated. The aim of this study is to describe the socio-demographic characteristics of a population of vaccinated and unvaccinated female health students and then to compare the different factors that may have influenced their vaccine choice. Method: Female health students in the French-speaking part of Switzerland, aged between 18 and 31, were invited to participate in the study. A total of 234 female students completed a questionnaire that included questions about their socio-demographic data, sexual behavior and vaccination status. Results: 69% of the participants received at least one dose of the vaccine. Women who had not yet had sex were less likely to be vaccinated than sexually active women (ORa: 0.1, 0.0–0.4, 95% CI), the same as those who did not express an opinion about the importance of vaccination (ORa: 0.1: 0.0–0.6, 95% CI). The main reasons given for refusing vaccination were fear of side effects (26.0%), parental opposition (24.6%) and reluctance of the attending physician (13.6%). Conclusions: The main results of this study highlight a good rate of vaccine coverage in the sample population. Reasons for nonvaccination demonstrate the need to provide information on the vaccine to the target audience, as well as to parents and health professionals.

Keywords: human papillomavirus; vaccination; invasive cervical cancer; student population

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1. Introduction

Human papillomavirus (HPV) is a group of sexually transmitted viruses, of which there are more than a hundred genotypes. These viruses infect the skin and genital mucous membranes. Although most infections are self-resolving, some genotypes can cause genital warts (6 and 11) as well as precancerous lesions and invasive cancers [1]. Both types 16 and 18 are responsible for 70% of invasive cervical cancer [2]. The development of such cancer is preceded by precancerous lesions.

Globally, cervical cancer is the 4th most diagnosed cancer and the 4th leading cause of cancer-related death in women [3]. For the year 2020, 604,000 new cases and 342,000 deaths were recorded [3]. In Switzerland, around 5000 women a year are diagnosed with precervical cancer, leading to additional examinations and sometimes surgery. Around 260 types of cancer are diagnosed each year in Switzerland [4]. In terms of frequency, cervical cancer is ranked as the fifth most common type of cancer found among Swiss women aged 20 to 49 [5].

The primary prevention strategy to reduce the risk of invasive cervical cancer is to vaccinate young women, ideally before they are sexually active. The vaccinal goal is to effectively reduce the burden of disease by avoiding the onset of precancerous stages [6].

The development of vaccines against human papillomavirus has therefore represented a major advancement in prevention. A Swedish study demonstrated a significant reduction in the risk of invasive cervical cancer. Specifically, an 88% reduction was found for young women vaccinated before the age of 17 and 50% for those vaccinated between ages 17 and 30, when compared with an unvaccinated sample [7].

In Switzerland, vaccination has been recommended since 2007 to all adolescent girls aged between 11 and 14 years (before they become sexually active) [8]. It is also offered to adolescent girls aged 15 to 26 years as a catch-up vaccination. Since 2007, two vaccines protecting against oncogenic genotypes 16 and 18 have been available: Cervarix® and Gardasil® [9]. Gardasil® also offers protection against genotypes 6 and 11 which are responsible for genital warts. The effectiveness of these two vaccines against invasive cervical cancers is estimated to be 70% [10]. Since 2019, a new vaccine has been used, Gardasil 9®, as it offers additional protection against five other oncogenic papillomavirus genotypes [11].

Since autumn 2008, all of the 26 Swiss cantons have implemented vaccination programs. The aim of these campaigns was to achieve vaccination coverage rates of 80% for girls aged 11 to 14 years and 50% amongst those aged 15 to 19 years [12]. A study published in 2019 shows an estimated vaccination coverage of 54% amongst 18- to 20-year-olds and 34% amongst 21- to 24-year-olds, with significant regional differences. These results indicate that six years after the start of the program these objectives had not yet been achieved [13]. Cantons in which vaccination is carried out through school programs have higher vaccination coverage rates than other cantons [14].

In the Swiss French-speaking cantons, 3 years after the start of the campaign, the vaccination coverage rate was 63% for vaccination with one or two doses and 61% with three doses [15]. This result, which is higher than the national average, is largely due to good coordination at a cantonal level. The involvement of child and adolescent health services has contributed to increasing vaccination coverage. However, this rate remains low compared with the 80% target initially set [12]. Very few studies at a national level describe the reasons for the reluctance of some young women to become vaccinated. In order to improve and further target prevention programs, it is essential to understand the individual factors influencing the choice to vaccinate. A study of 16 to 20 year olds living in French-speaking Swiss cantons revealed a perceived lack of information about the history of and prevention approaches towards HPV. In particular, over 70% of the target population reported feeling insufficiently informed about these issues. The lack of information about HPV and its vaccine was not restricted to Switzerland and affects many other countries.

Another study in Sweden has shown that HPV vaccination among young girls was associated with a European background and high maternal education level, as well as more favorable beliefs about HPV prevention and less sexual risk taking.

Research has identified that health professionals play an important role in vaccine uptake. Moreover, there is a lack of initiatives to improve education among undergraduate healthcare students about HPV infection, its associated consequences and methods of prevention.

The aim of this study is to describe the socio-demographic characteristics of a population of female health students in two Swiss French-speaking cantons (Vaud and Geneva). A comparison is then made between the vaccinated and unvaccinated groups to determine whether certain factors may influence a decision in favor of vaccination.

2. Method

2.1. Population and Context

This study was carried out between September 2019 and January 2020 in the cities of Geneva and Lausanne in Switzerland. The participants were female students of nursing, midwifery and dietetics (in years 1 to 3 of a bachelor's degree). All students aged between 18 and 31 who agreed to participate in the study were included. Students were excluded if they had a history of hysterectomy or treatment targeting the cervix in the past 12 months.

All individuals who fully completed the questionnaire and agreed to participate in the study were included in our sample.

2.2. Procedure of the Study

This study was conducted as a cross-sectional observational study. Information about the study was communicated to the students via the University of Geneva and University of Lausanne websites as well as by the investigators themselves via email. In addition, a presentation of the study was made to the participants during class hours.

At the end of the course, the questionnaire was distributed to students interested in participating in the study. Participants completed the questionnaire at home. The completed questionnaires were returned to the investigators within one week of distribution. Alternatively, participants could complete the socio-demographic questionnaire online via a web platform. The survey instrument was an online self-administrated, anonymous questionnaire developed using SurveyMonkey software (https://de.surveymonkey.com/, accessed on 1 July 2019). This software automatically saves responses to a secure database, thus protecting the participants' confidentiality. On the first page of the web questionnaire, the participants were presented with a consent form informing them of the objectives of the study and its procedures. The students 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 they agreed to participate in the study, they were asked to tick a box in order to declare their informed consent. If the individuals did not agree, the webpage automatically closed. Three email reminders were sent at 1, 2 and 3 weeks after the first invitation, unless an individual requested to be removed from the mailing list during the process. The web-based survey was automatically closed 10 weeks after the first invitation was sent.

2.3. Data Collection

In this study, data obtained through a questionnaire were analyzed. All participants answered questions about their socio-demographic profile (age and nationality), sexual behavior (number of sexual relationships and condom use) and HPV vaccination status (number of doses received, age at first dose and opinion on the vaccination). The questionnaire used for data collection was developed and validated in a previous study using the same population type [16].

2.4. Statistical Analysis

Statistical analyses were carried out using STATA 14. Descriptive statistics and frequencies were analyzed for all variables with a 95% confidence interval. The Kolmogorov–Smirnov test was used to analyze the normality of distribution for the continuous variables. Normally distributed continuous variables were reported as means and standard deviations (SDs), and categorical variables were reported as frequencies (%). A p value of at least 0.05 was considered to be statistically significant. Multivariate logistic regression was performed to identify factors influencing vaccine choice. Vaccination status was used as the primary outcome. Only variables identified to be of interest in the univariate analysis were included in the multivariate analysis. The final model was selected with a stepwise procedure based on Akaikes information criterion, and the results were reported as odds ratios with 95% confidence intervals.

2.5. Ethical Approval

The study protocol was approved by the University Hospital of Geneva's Cantonal Commission for Ethics and Research on Human Beings (approval number 19-357). This study was conducted in accordance with all laws and regulations relating to Good Practice in Clinical Trials (ICH E6-1996) and the Declaration of Helsinki (Fortaleza, Brazil, October 2013). All participants signed a consent form before taking part in the study.

3. Results

3.1. Sociodemographic Data

Data from the questionnaires of 234 female students was analyzed in this study. Characteristics of the participants are presented in Table 1.

Table 1. Sociodemographic characteristics.

Characteristic	Sample Population (n = 234)		
	n *	% or Mean	95% CI
Age			
Mean age	218	21.0	20.7–21.3
Nationality			
Swiss	63	26.9%	21.6–33.0
Other	171	73.1%	67.0–78.4
Tobacco consumption			
Never	19	8.1%	5.2–12.4
Sometimes	33	14.1%	10.2–19.2
Often	182	77.8%	72.0–82.7
Already had first sexual intercourse			
Yes	214	91.5%	87.1–94.4
No	20	8.6%	5.6–12.9
Age at first sexual intercourse			
Mean age	213	17.0	16.7–17.3
Number of sexual partners			
Mean number	234	5.4	4.5–6.2
Condom use as contraception			
Never/rarely	60	28.0%	22.4–34.5
Sometimes	52	24.3%	19.0–30.5
Often	52	24.3%	19.0–30.5
Always	50	23.4%	18.1–27.6
HPV carrier			
No	179	76.5%	70.6–81.5
Yes (types 6, 11, 16, 18)	4	1.7%	0.6–4.5
Yes (other type)	51	21.8%	16.9–27.6
Vaccinated against HPV			
Yes	161	68.8%	62.5–74.4
No	73	31.2%	25.6–37.5
Vaccine doses received			
1	10	6.2%	3.4–11.2
2	15	9.3%	5.7–14.9
3	135	83.9%	77.3–88.8
Do not know	1	6.0%	0.1–4.3
Age at first dose			
Mean age	158	14.6	14.2–15.0
Consultation of vaccination record			
Yes	120	51.5%	45.1–57.9
No	113	48.5%	42.1–54.9
Opinion about HPV vaccination			
More important than others	7	3.0%	1.4–6.2
Less important than others	38	16.2%	21.0–21.6
As important as others	167	71.4%	65.2–76.8
Do not know	22	9.4%	6.3–13.9

* The value of n varies between the variables based on the number of no-responses and questions addressed only to a subgroup of participants.

Participants' mean age at the start of the study was 21 years (range 17 to 29 years). The majority of participants were of foreign nationality (73%) compared with Swiss women, who represented 27% of the sample. Of the students surveyed, 78% reported consuming tobacco regularly, 14% sometimes and 8% never. The majority of participants (92%) had already had a first experience of sexual intercourse. The average age reported at the time

of the first experience was 17 years (range 10 to 24 years). The average number of sexual partners reported by female students was 5.4.

In terms of condom use as a means of contraception, 28% of participants reported that they rarely or never used a condom. In total, 24% stated that they sometimes used one, 24% often used a condom and 23% always used one. A total of 8% of the females surveyed had never had sex and therefore did not answer the question about contraception.

Following vaginal self-sampling, 77% of participants were not carriers of a human papillomavirus. Four students (2%) were found to be carriers of a human papillomavirus type 6, 11, 16 or 18, and 51 students (22%) were carriers of another genotype of the virus.

3.2. Vaccination Status

Regarding the vaccination rate, 161 students (69%) had received at least one dose of HPV vaccine. Of these, 84% had received three doses, 9% two doses and 6% only one dose. All participants had been vaccinated with the Gardasil® vaccine. The average age at the time of receiving the first dose was 14.6 years (range 9 to 26 years). A total of 52% of the participants consulted their vaccination record in order to answer the questionnaire.

Regarding the participants' opinions on HPV vaccination, 71% thought that this vaccination was as important as other vaccinations, 16% thought it was less important, 3% thought it was more important and 9% had no opinion on the issue.

3.3. Association between HPV Vaccination and Sociodemographic Characteristics

Table 2 presents the association between the HPV vaccination and sociodemographic characteristics. The results show that young women who had not yet had sexual intercourse were significantly less vaccinated than sexually active young women (ORa: 0.1, 0.0–0.4 95% CI).

Table 2. Association between vaccination and sociodemographic characteristics: results of univariate and multivariate analyses.

Sociodemographic Characteristics	OR	95% CI	Adjusted OR	95% CI
Nationality				
Swiss	1.0	-	1.0	-
Other	0.6	0.3–1.2	0.5	0.2–1.1
Tobacco consumption				
Never	1.0	-	1.0	-
Sometimes	0.4	0.1–1.5	0.5	0.1–2.3
Often	0.9	0.3–2.5	0.8	0.2–3.2
Already had first sexual intercourse				
Yes	1.0	-	1.0	-
No	0.4	0.2–1.1	**0.1**	**0.0–0.4**
Number of sexual partners				
1	1.0	-	1.0	-
2 to 5	1.0	0.5–2.1	1.4	0.6–3.3
>5	0.9	0.4–2.0	2.1	0.7–5.8
Opinion about HPV vaccination				
More important than others	1.0	-	1.0	-
Less important than others	0.4	0.1–2.3	0.2	0.0–1.7
As important as others	1.5	0.3–8.1	1.2	0.2–7.3
Do not know	**0.1**	**0.0–0.8**	**0.1**	**0.0–0.6**
HPV carrier				
No	1.0	-	1.0	-
Yes (types 6, 11, 16, 18)	0.4	0.6–3.0	0.1	0.0–1.2
Yes (other type)	0.7	0.4–1.3	0.5	0.2–1.1

Statistically significant results in **bold**. The odds ratios were adjusted according to the following variables: nationality, tobacco consumption, already had first sexual intercourse, number of sexual partners and opinions about HPV vaccination and HPV carrier.

One particularly important finding is that participants who did not express an opinion about vaccination had a lower probability of being vaccinated (ORa: 0.1, 0.0–0.6 95% CI).

There was no statistically significant difference between the two groups in terms of nationality, tobacco consumption, number of sexual partners and HPV test positivity.

3.4. Reasons Given for Vaccination Refusal

Table 3 shows that of the 73 participants who had not been vaccinated, 62 had mentioned the reason for their refusal of the vaccine. These different reasons are presented in Table 3. The most common reason given for refusing vaccination was fear of side effects, reported by 26% of unvaccinated young women. Parental opposition (24%) was also among the most frequently cited reasons, alongside that of the attending physician (13%). The attending physicians were general practitioners, pediatricians or gynecologists.

Table 3. Reasons given for refusal of vaccination.

Reason	Sample Population (n = 73)	
	N	%
No reason given	11	15.1
Reason given n = 62:		
Fear of side-effects	19	26.0
Parental opposition	18	24.6
Physician opposition	10	13.6
Never had sexual intercourse	3	4.1
Absence of hindsight	2	2.7
Lack of information	2	2.7
Other	8	10.9

Three other reasons were less frequently mentioned: namely the absence of sexual intercourse (4%), the absence of hindsight (2%) and lack of information (2%). The reasons categorized as "other" were extraneous to the analysis and included comments such as "I do not want to vaccinate myself" or "I never have vaccines".

4. Discussion

In this study, 69% of participants received at least one dose of the HPV vaccine. Although lower than the initial vaccination target of 80% [12], this percentage is quite acceptable in comparison with the existing vaccination coverage rate among 18 to 20 yearolds in Switzerland, which is estimated to be 54% [13]. A study published in 2011 reported a vaccination rate of 64% for a single dose amongst 11- to 19-year-old girls in the canton of Geneva [15]. This good coverage rate can be explained, in particular, by a cantonal campaign aimed at easier access to vaccinations. The campaign offers teenagers the opportunity to be vaccinated as part of compulsory schooling. Several studies have already shown that countries with school-based information programs have higher vaccination coverage rates [17,18]. In the present study, the good vaccination coverage rate cannot be linked solely to the efforts of the cantonal campaign as a high proportion of the participants are not Swiss.

The average age at the time of injection of the first dose was 14.6 years. This is in line with the recommendations that vaccination be given before the age of 15 [8]. The age of the participants at the time of vaccination suggests that they were vaccinated in a school setting or by their pediatrician.

Regarding factors that may influence participants' decision to vaccinate, a significant association could be found for the onset of sexual activity. Indeed, young women who had not yet had sexual intercourse were 10 times less likely to be vaccinated than those who had already had intercourse. This result suggests that women who do not have sex feel less concerned by vaccination. However, analysis of the reasons given for vaccine refusal indicates that only 4% of unvaccinated women cite not yet having had sex as the main reason. Their vaccine refusal does not therefore seem to be related to this single factor.

Evidence from the literature suggests mixed results concerning the relationship between vaccination and the onset of sexual activity. One Swedish study shows that a high number of sexual partners as well as an onset of sexual activity at a young age are predictors for vaccination [19]. However, the results of the Swiss study by Wymann et al. show that women who have had more than 10 sexual partners are less often vaccinated than those with only 1 or 2 [13]. These contradictory results demonstrate the need to continue efforts to inform adolescents of the importance of vaccination before the onset of sexual activity.

The other statistically significant variable in this analysis is participants' opinions about the importance of vaccination. Women without an opinion are 10 times less likely to be vaccinated than those who reported an opinion on the issue. This lack of position from a significant proportion of female students is surprising and could suggest a lack of information or interest in the HPV vaccination. The link between lack of knowledge about the benefits of vaccination and vaccine refusal has already been studied. Particularly, an Italian study by Restivo et al. shows that women with less knowledge of the HPV vaccination are less likely to be vaccinated than others [20].

In relation to vaccination uptake, 85% of unvaccinated participants cited a reason for refusing the vaccine. The three main reasons given are the fear of side effects, opposition from parents or that of the attending physician. The reasons given in the literature depend very much on the country and the psychosocial context. One systematic review published in 2017 highlights parents' views and lack of information as the main barriers to vaccination [21]. However, it notes the importance of physician recommendations and parental acceptance as facilitating factors. Other studies also put the source of information as a key element in encouraging vaccination [22]. Young women with unofficial (nonprofessional) sources of information, such as friends for example, have a higher probability of not getting vaccinated [23].

Strengths and Limitations of the Study

The key strength of this study is that it analyses the data of future health professionals. The participants of this study will probably have to give information to their future patients, and it is therefore essential that they are made aware of issues relating to HPV and vaccination.

However, certain limitations should be taken into account when interpreting the results. Firstly, as this study had a cross-sectional design, we could not determine a causal relationship but only hypotheses and reflections about factors that might encourage or discourage vaccination. Secondly, this sample concerns a very specific population, mostly foreign health students in two cities, and is therefore not representative of the general Swiss population. Another limitation is that our sample is relatively small, resulting in low statistical power. Thus, we cannot know whether a larger sample would have allowed us to find statistically significant associations between the socioeconomic variables and decision on whether to vaccinate.

In order to have a more precise and complete idea of the influence of factors facilitating vaccination, the use of a standardized tool such as the CHIAS (Caroline HPV Immunization Attitudes Scale) [24] could be considered for data collection.

5. Conclusions

The main results of this study show that in this population of undergraduate healthcare students a good level of HPV vaccination coverage has been achieved, even if it does not yet reach the level desired by the health authorities. The results demonstrate the need to provide information on vaccination. Specifically, if we increase the knowledge and awareness level of the target audience, this should reduce the reluctance for HPV vaccinations and increase the coverage rate. The reasons given for nonvaccination demonstrate that public health programs should also include health professionals and parents in order to achieve the objectives set. The results of this study, as well as the existing literature, indicate the need for further large studies with longitudinal follow-up, ideally using mixed

and qualitative methods. These would enable confirmation of the link between various factors and the decision to vaccinate, in order to provide prevention programs that promote vaccination. Additional studies could also be carried out to evaluate the effectiveness of interventions encouraging vaccination among young Swiss women.

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Informed Consent Statement: The participants were requested to give their informed consent. Participation was voluntary and no compensation was given to respondents.

Data Availability Statement: Data will be made available by the authors upon reasonable request.

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ORIGINAL ARTICLE 4: SELF-SAMPLING TO IMPROVE CERVICAL CANCER SCREENING COVERAGE IN SWITZERLAND: A RANDOMISED CONTROLLED TRIAL (59)

In the first part of this thesis, we have seen work on the primary prevention of HPV and cervical cancer infections via vaccination. In this 2nd part, we will look at two pieces of work on secondary prevention via the early detection of cervical cancer through the use of self-sampling.

In the first of these two studies (study 4), we conducted a randomised controlled trial to assess whether self-sampling would increase screening coverage in women with low screening rates. This work aimed to demonstrate that self-sampling is an effective alternative to conventional cervical cancer screening by increasing participation and adherence to screening, especially in low-screening populations, for a lower financial cost.

FULL PAPER

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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 ($P=0.110$).

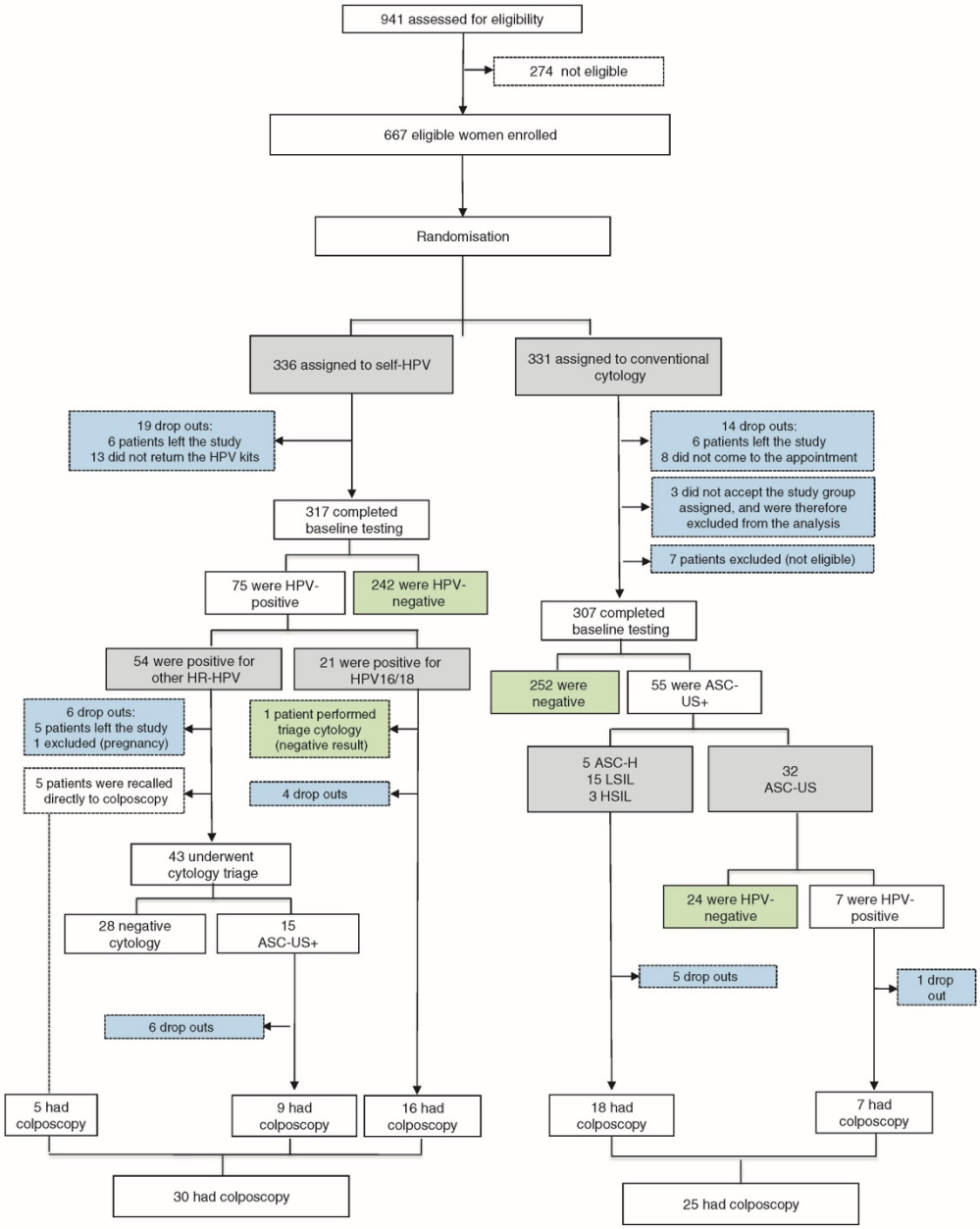

Figure 1. Study flowchart. HPV = Human Papillomavirus; ASC-US = Atypical squamous cells of undetermined significance; ASC-US + = Atypical squamous cells of undetermined significance or worse; ASC-H = Atypical squamous cells of undetermined significance cannot exclude HSIL; L-SIL = Low-grade squamous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

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ORIGINAL ARTICLE 5: THE ACCEPTABILITY OF HPV VAGINAL SELF-SAMPLING FOR CERVICAL CANCER SCREENING IN LATIN AMERICA: A SYSTEMATIC REVIEW (60)

As the randomised controlled trial (study 4) showed that self-sampling was an effective strategy to increase the coverage rate of cervical cancer screening, we decided to carry out a systematic review concerning its use in a context other than that of Switzerland (study 5). That is to say, one with a high incidence of cervical cancer and significant mortality related to this cancer but with little logistical and financial means to set up this screening. We showed in the introduction to this work that Latin America suffers from a high incidence of cervical cancer, so we chose this continent as a study area. We wanted to use this systematic review to make a complete map of the use of self-sampling as a screening technique in Latin America, as well as to summarise its acceptability and possibility of in-depth dissemination within this continent.

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The acceptability of HPV vaginal self-sampling for cervical cancer screening in Latin America: A systematic review

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ABSTRACT

Objective: This review summarizes women's acceptability of vaginal self-sampling for cervical cancer screening in Latin America.
Study design: Systematic review
Method: A systematic literature search was performed in PubMed, Web of Science, and Embase regarding the acceptance of HPV vaginal self-sampling by women over 18 years old. Articles were selected for research that was conducted in Latin America and published between January 1st, 1993, and December 31st, 2022.
Results: Fifteen publications were included. Eight publications reported an acceptance of HPV self-sampling as high as 80%, six papers found an acceptance rate between 50 and 80% and only one found an acceptance rate of less than 50%. Based on non-standardized questionnaires, women considered self-sampling more comfortable, easier, and less painful than conventional cytology. The procedure was associated with less embarrassment and a greater sense of privacy.
Conclusion: HPV vaginal-self sampling appears to be an acceptable screening method amongst eligible Latin American women.

1. Introduction

Cervical cancer is a malignant tumor of the cervix, the most distal part of the uterus which connects with the vagina [1,2]. It is the fourth most common gynecologic malignancy and the fourth leading cause of cancer death worldwide [3]. Incidence and mortality vary widely with geographic location [4]; recent reports ranked cervical cancer as the third most common neoplasia affecting women in Latin America and in the Caribbean region [3]. In 2020, there were 59,439 estimated new cases of cervical cancer and 31,582 deaths due to this malignancy in this region [5]. Approximately 85% of the new cases and deaths occur in low- and middle-income countries (LMICs) [3,6]. Persistent infection with high-risk types of Human Papillomavirus (hrHPV) -such as 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 [7] - has been identified as the leading risk factor of cervical cancer, being responsible for up to 90% of cases of squamous cell carcinoma, where the hrHPV types 16 and 18 are the most prevalent isolated (70%) of cervical cancer samples worldwide [1,8,9].

Cervical cancer is largely preventable disease due to the highly effective HPV vaccine [4] and secondary prevention measures. Standard secondary measures include Pap smears (cervical cytology), visual inspection with acetic acid (VIA), and Lugol's iodine, which can detect precursor and early-stage disease [3]. However, access to HPV immunization is insufficient, especially in LMICs [10,11].

The coverage and access to a screening programme are limited outside high-income countries, due to the limited access to health services, paucity of resources, and social, economic, and political issues. In Latin America, several countries have attempted to establish national screening programs without achieving high quality and coverage [12]. In addition, ethnic, religious, and cultural challenges combined with women's subjective experiences of shame, pain, and discomfort from cervical cancer screening tests result in a reduced number of screening women, which leads to the high incidence of this disease in LMICs, which is why it continues to be an important cause of cancer morbidity and mortality [4,13,14].

A promising strategy to overcome multiple barriers to cervical cancer screening, particularly in low-resource settings, is the Human Papillomavirus (HPV) vaginal self-sampling method. This novel alternative has

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been developed to decrease cervical cancer mortality worldwide with a considerable impact on decreasing the disease burden and overall health inequalities [15]. Since 2013, the World Health Organization (WHO) has recommended HPV self-sampling as a cost-effective option for initial screening. If the woman desires, she can perform it in the comfort of her own home and send the sample to the health center or laboratory for processing; those screened positive will undergo more extensive testing. HPV DNA Self-sampling test has the potential to reach under screened women, such as those who have never been screened and the ones who do not attend screening regularly [16].

Despite the high disease burden, limited studies have been conducted to evaluate the acceptance of HPV self-testing in Latin America. To our knowledge, no systematic review has been published on this specific subject. The aim of this review is to investigate women's acceptability of HPV vaginal self-sampling for cervical cancer screening in Latin America, as reported by articles published between January 1st, 1993, and December 31st, 2021. This systematic review will constitute valuable reference materials for epidemiologists, health policymakers, stakeholders, and researchers on cervical cancer to show if this screening method can increase adherence to cervical cancer screening in Latin America. This may be applicable to other LMICs.

2. Method

2.1. Vaginal HPV self-sampling testing definition

The HPV self-sampling test is a feasible and accurate collection method used by the patient who wishes to know if an HPV infection is present [17]. This process can be carried out alone in private, at home, or at a health facility center. Vaginal self-sampling involves the patient obtaining a kit (a single-use swab or cervical brush and a tube containing a transport medium to collect a cervicovaginal sample) and collecting instructions. The patient gently inserts the swab or brush into the vagina and delicately rotates it for 10 to 30 s to take the sample. After removing the swab, it is transferred into the tube with the transport medium, where the shaft of the swab is broken off and discarded, the tube is sealed and labeled and, finally, is sent to be analyzed at a certified laboratory. The patient receives the results directly at the health facility center, or by telephone by a nurse or doctor from the health center or transmitted by the community health workers. HPV DNA testing identifies the users with a higher risk of developing HPV-related cervical cancer in the future; in the case of positive test results, the women are invited to attend and appropriate health facility for further assessments [18,19].

2.2. Literature search strategy

Following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, a focused electronic systematic literature search was carried out in PubMed, Web of Science, and Embase for studies conducted in any Latin-American country (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Uruguay, and Venezuela)

and published between January 1st, 1993, and December 31st, 2022, - 1993 was chosen as the cut-off year because it was the year of the first report on HPV self-sampling [20].

The Keywords used for the research were (HPV[tw] OR "Human Papillomavirus"[tw] OR "Human Papilloma Virus*"[tw] OR "HPV, Human Papilloma Virus*"[tw] OR "Papillomavirus Infections"[Mesh] OR "Papillomavirus Infection*"[tw] OR "Human Papillomavirus Infection*"[tw] OR "HPV Infection*"[tw]) AND ("Vagina"[Mesh] OR "Vaginal"[tw] OR "Cervico-vaginal"[tw] OR "Cervicovaginal"[tw]) AND ("Self-Examination"[Mesh] OR "Self-Examination*"[tw] OR "Self Examination*"[tw] OR Self-sampl*[tw] OR "self sampl*"[tw] OR "Self-collect*"[tw] OR "Self collect*"[tw] OR "Self-test*"[tw] OR "Self test*"[tw] OR "Self-administ*"[tw] OR "Self administ*"[tw] OR "Self-obtained"[tw] OR "Self obtained"[tw] OR "Self-assessment"[tw] OR "Self assessment"[tw]) AND ("Cervical Cancer"[tw] OR "Uterine Cervical Cancer*"[tw] OR "Cancer of the Cervix"[tw] OR "Cancer of Cervix"[tw] OR "Cancer Cervix"[tw] OR "Cancer of the Uterine Cervix"[tw] OR "Cervix neoplasm*"[tw]) AND ("Early Detection of Cancer"[Mesh] OR "Cancer Early Detection"[tw] OR "Cancer Screening"[tw] OR "Screening, Cancer"[tw] OR "Cancer Screening Test*"[tw] OR "Early Diagnosis of Cancer"[tw] OR "Cancer Early Diagnosis"[tw]) AND ("Argentina"[tw] OR "Bolivia"[tw] OR "Brazil"[tw] OR "Chile"[tw] OR "Colombia"[tw] OR "Costa Rica"[tw] OR "Cuba"[tw] OR "Dominican Republic"[tw] OR "Ecuador"[tw] OR "El Salvador"[tw] OR "Guatemala"[tw] OR "Haiti"[tw] OR "Honduras"[tw] OR "Mexico"[tw] OR "Nicaragua"[tw] OR "Paraguay"[tw] OR "Panama"[tw] OR "Peru"[tw] OR "Puerto Rico"[tw] OR "Uruguay"[tw] OR "Venezuela"[tw] OR "Latin America"[Mesh] OR "Hispanic or Latino"[Mesh] OR "Latinas"[tw]) AND ("Women"[Mesh] OR "Female"[Mesh]). Each search strategy was adapted to consider the differences in the controlled vocabulary and the syntax rules.

2.3. Study selection criteria

Studies meeting the following inclusion criteria were selected: 1) Studies conducted in Latin American countries; 2) Studies conducted with Latin American women; 3) Studies in women of at least 18 years of age who had completed self-sampling tests; 4) Studies involving pregnant or non-pregnant women, with or without HIV infection and minority ethnicities; 5) Studies measuring the acceptability of vaginal HPV self-sampling test; 6) Studies conducted on primary cervical cancer screening; 7) Studies using a vaginal self-sampling device including swab, brush or tampons; 8) Both quantitative and qualitative studies; 9) Articles reported in English, Spanish, French, and Portuguese due to the linguistic competence of the researcher. Duplicate papers, articles with unclear or lacking methodology, and publications that did not provide sufficient data on the Latin American population were excluded.

2.4. Data collection and analysis

Search results were exported to Zotero software, version 5.0. A standardized data abstraction form created on Microsoft Excel, version 16.56, recorded the relevant information for each study: country location, authors, publication year, study design, sample size, population characteristics, intervention, setting, general acceptability, and global experience.

2.5. Study quality assessment

Table 1 presents the study quality criteria based on the National Heart, Lung and Blood Institute (NHLBI) guidelines [21]. One researcher assessed the articles according to the aforementioned quality criteria and observed that out of the fifteen included manuscripts, only one was rated as high quality. Seven papers were classified as moderate quality, and an additional seven were considered low to moderate quality. Notably, none of the publications met the criteria for being classified as low or moderate to high quality.

3. Results

3.1. Study characteristics

Fig. 1 shows the selection process for studies included in the review. A total of 335 citations were yielded in the search using the keywords previously described. After removing duplicate reports, a total of 235 articles remained. Through an initial reading of titles and abstracts meeting the inclusion criteria, 58 potential articles of interest were

Table 1
The National Heart, Lung and Blood Institute - based study quality criteria [21]

Authors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality
Arrossi et al. (19)	G	G	G	G	G	R	R	Y	G	Y	G	G	G	G	Moderate
Surriabre et al. (20)	G	G	G	G	R	R	R	Y	G	Y	G	R	G	Y	Low - moderate
Allende et al. (21)	G	G	G	G	R	R	R	Y	G	Y	G	R	G	Y	Low - moderate
Lorenzi et al. (22)	G	G	G	G	G	R	R	Y	G	Y	G	R	G	G	Moderate
Léniz et al. (23)	G	G	G	G	G	R	R	Y	G	Y	G	G	G	R	Moderate
Torrado-Garcia et al. (24)	G	G	G	G	R	R	R	Y	G	Y	G	R	Y	G	Low - moderate
Rosenbaum et al. (25)	G	G	R	G	G	R	R	Y	G	Y	G	R	Y	R	Low - moderate
Laskow et al. (26)	G	G	G	G	R	R	R	Y	G	Y	G	R	Y	G	Low - moderate
Maza et al. (27)	G	G	G	G	G	R	R	Y	G	Y	G	R	G	G	Moderate
Gottschlich et al. (28)	G	G	R	G	G	R	R	Y	G	Y	G	G	G	G	Moderate
Murchland et al. (29)	G	G	G	G	G	R	R	Y	G	Y	G	G	G	G	High
Dzuba et al. (30)	G	G	G	G	R	R	R	Y	G	Y	G	G	G	G	Moderate
Quincy et al. (31)	G	G	G	G	R	R	R	Y	G	Y	G	R	G	G	Low-moderate
Morán et al. (32)	G	G	G	G	G	R	R	Y	G	Y	G	G	G	R	Moderate
Ortiz et al. (33)	G	G	G	G	R	R	R	Y	G	Y	G	R	G	R	Low-moderate

Green = Yes Yellow = Not applicable Red = No

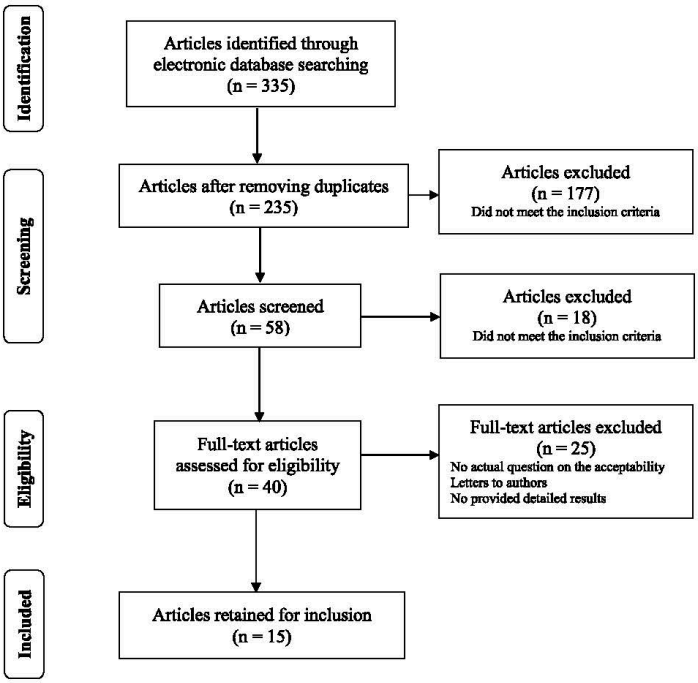

Fig. 1. Study selection flow chart.

selected. Finally, 40 full-text articles were obtained and read using the same selection criteria; specific articles were selected for further review and final analysis. Of these, 15 articles were included in this review.

Table 2 summarizes the fifteen included articles published between 2002 and 2020 [22–36]. Three of the studies were conducted in El Salvador [28–30], two in Bolivia [23,24] and Guatemala [31,32], and one each in Argentina [22], Brazil [25], Chile [26], Colombia [27], Mexico [33], Nicaragua [34], Peru [35] and Puerto Rico [36]. 60% were conducted in Central America [28–34,36]. El Salvador and Guatemala have the highest publications, with 20% [28–30] and 13.3% [31,32]. The studies were carried out among women living in urban, peri-urban, and rural areas, the latest the most studied. All the publications were cross-sectional studies, two of which used a mixed methodology [22, 35].

A total of 10,004 women who performed the HPV self-testing were surveyed. Regarding inclusion criteria, the enrolled women were 18

Table 2
Summary of the fifteen included articles.

Country	Authors, Year	Study design	Women, *n*	Population characteristics	Intervention	Setting	Acceptability	Experience
Argentina, Jujuy (Urban and rural area)	Arrossi et al., 2016 [22]	Cross-sectional/ Mixed method	3049	**Inclusion criteria:** ***Age:*** 30 years + Living in a home visited by community health workers **Exclusion criteria:** Have a previous HPV DNA test History of hysterectomy History of treatment for premalignant or malignant disease Pregnancy Have a mental disability	Self-sampling **Offered by:** Community Health Workers (CHWs) **Specimen collection instructions:** offered but not described **Device:** cervical sampler kit (Qiagen, Gaithersburg, MD, USA), brush. **Quantitative component** ***Questionnaire:*** 7-item closed-ended questions regarding education level, health insurance, cervical cancer screening history, and reasons for screening method choice. **Qualitative component** Two focus groups (n = 30) Interview for HPV knowledge, reasons for accepting or rejecting self-sampling tests. Experience, satisfaction, and circumstances surrounding the test. The possibility of changing their minds in the future to accept self-collection.	Home	85.8% for self-sampling	Majority accepted for being comfortable, easy, fast, painless, voluntary, and free.
Bolivia, Cochabamba (Urban, peri-urban, and rural area)	Surriabre et al., 2017 [23]	Cross-sectional	222	**Inclusion criteria:** ***Age:*** 25 -59 years old Living in urban, peri-urban, and rural areas of Cochabamba.	Self-sampling and clinician-sampling. **Offered by:** a health professional **Specimen collection instructions:** written and visual (video) **Device:** cotton swab and vaginal tampon ***Questionnaire:*** evaluate the experience with self-sampling and the preference for a specific device	Health center	64% for self-sampling	Comparing the two self-sampling devices: Cotton swab is 77% easier to use, and 80% more comfortable to use than a vaginal tampon.
Bolivia, Cochabamba and Chapare (Urban, peri-urban, and rural area)	Allende et al., 2019 [24]	Cross-sectional	221	**Inclusion criteria:** ***Age:*** 25 -64 years old Living in urban, peri-urban areas of Cochabamba and rural Chapare Signed informed consent **Exclusion criteria:** Pregnant women over 20 weeks History of hysterectomy	Vaginal self-sampling and physician-sampling **Offered by:** a health professional **Specimen collection instructions:** offered but not described **Device:** cotton swab ***Questionnaire:*** 8-item closed-ended questions after self-sampling and physician-sampling	Health center	High acceptance of self-sampling	89.7% easy to use 81.7% comfortable 67.2.% painless
Brazil, São Paulo (Urban area)	Lorenzi et al., 2019 [25]	Cross-sectional	116	**Inclusion criteria:** ***Age:*** 21 years + Were referred for colposcopy due to an abnormal Pap smear. **Exclusion criteria:** Women under 21 years of age Pregnant women Women unwilling to participate in the research protocol	Vaginal self-sampling **Offered by:** a health professional **Specimen collection instructions:** verbal and visual (illustrations) **Device:** Evalyn Brush® (Rovers®, Oss, the Netherlands). ***Questionnaire:*** 7-item regarding ease of understanding of the method's use, ease of the use the self-collection brush, discomfort or pain,	Health center	76.70% for self-sampling (95% CI, 68.40–83.70) vs. 12.9% for health professional sampling (95% CI, 7.8–19.9%) vs. 10.3% for both tests acceptable (95% CI, 5.8–16.9%)	Easy to understand how to use and use it. Practicality, minor embarrassment, Discomfort or pain perception decreased as the age increased (p = 0.080).

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Table 2 (*continued*)

Country	Authors, Year	Study design	Women, *n*	Population characteristics	Intervention	Setting	Acceptability	Experience
					embarrassment or shame, fear of hurting oneself, preference between self-sampling vs. health professional collection. Reason to choose self-sampling (less pain or discomfort, less shame or embarrassment, practicality, Self-sampling at home/Basic Health Facility/ Laboratory; afraid of not collecting it correctly, the health professional can do it better)			
Chile, Santiago (Urban area)	Léniz et al., 2013 [26]	Cross-sectional	1085	**Inclusion criteria:** ***Age:*** 30–64 years Residents of the geographic area covered by the Alejandro del Río health center in the Puente Alto County Have not attended Pap screening in the previous three years. **Exclusion criteria:** History of hysterectomy Pregnant women	Vaginal self-sampling **Offered by:** Community Health monitor **Specimen collection instructions:** verbal **Device:** HC2 Collection Device (brush) ***Questionnaire:*** regarding socio-educational characteristics, reproductive history, Pap test history, smoking, sexual habits, satisfaction with the procedure, and future test preference	Home	High acceptability for self-sampling	93.4% slightly or not at all uncomfortable 91.6% considered vaginal self-sampling less uncomfortable than Pap testing
Colombia, Bucaramanga (Urban area)	Torrado-Garcia et al. 2020 [27]	Cross-sectional	423	**Inclusion criteria:** ***Age:*** 35–65 years Living in the northern part of Bucaramanga Have a moderate to high risk of developing cervical cancer **Exclusion criteria:** History of hysterectomy Pregnant women	Cervico-vaginal self-sampling and physician-sampling **Offered by: a** health professional **Specimen collection instructions:** visual and verbal **Device:** brush ***Questionnaire:*** 10 questions regarding experience, comfort, the safety of the procedure, preference between the self-sampling method and conventional cytology, and the reasons why they had chosen one of the two methods	Health center	88.5% for self-collected sampling vs. 4% for conventional cytology vs. 7.3% no preference over any method	40.1% Privacy 29.7% comfortability 14% easier to use 29.7% painless 12.4% reliability
El Salvador, San Pedro Perulapan, San Rafael Cedros, Apastepeque and San Sebastian (Rural area)	Rosenbaum et al., 2014 [28]	Cross-sectional	518	**Inclusion criteria:** ***Age:*** 30–49 years Under-screening women in the last 3 years Women capable of providing informed consent **Exclusion criteria:** Pregnant women History of hysterectomy, cryotherapy, or loop electrosurgical excision procedure	Provider-collected sampling and cervicovaginal self-sampling **Specimen collection instructions:** verbal **Offered by:** Health provider **Device:** careHPV QIAGEN Gaithersburg, Gaithersburg, MD, USA) ***Questionnaire***: regarding demographic information (age, education, marital status, household size, and the number of children), sexual history (age of first intercourse, lifetime sexual partners, and current birth control method), smoking history, cervical cancer screening history, and knowledge of HPV and cervical cancer. Open-	Health center	38.8% for self-collection; (95% CI, 34.6–43.2) vs. 31.9% for provider-collected sampling (95% CI, 27.9–36.1) vs. 29.3% no preference over any method. (95% CI, 29.3–33.5)	29.9% Privacy/ embarrassment 19.9% ease 18.9% pain 14.9% comfort 8.5% time/ convenience

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Table 2 (*continued*)

Country	Authors, Year	Study design	Women, *n*	Population characteristics	Intervention	Setting	Acceptability	Experience
					ended question regarding the preference between self-sampling or provider-collected sampling, preferred method and during a future screening visit, the preferred screening location (home vs. clinic).			
El Salvador, San Pedro Perulapan, San Sebastian, Apastepeque, San Rafael Cedros, Candelaria, San Vicente, Tecoluca, and Suchitoto (Rural area)	Laskow et al., 2017 [29]	Cross-sectional	60	**Inclusion criteria:** ***Age:*** 30–59 years Non-attenders women to scheduled appointments for cervical cancer screening of the CAPE program Women capable of providing informed consent **Exclusion criteria:** Pregnant women Women screened within the past 2 years history of hysterectomy, cryotherapy, or loop electrosurgical excision procedure.	Vaginal self-sampling **Specimen collection instructions:** visual and verbal **Offered by:** Health researchers **Device:** Digene Hc2 DNA test, Gaithersburg, MD, USA) (Brush) ***Questionnaire***: regarding sociodemographic characteristics (age, education, marital status, household size, and number of children), sexual history (age at first intercourse, number of lifetime sexual partners, and birth control method), smoking history, previous cervical cancer screening, knowledge and risk perception of HPV and cervical cancer, and reasons for non-attendance, and reasons for agreeing to self-sampling	Home	68% for self-sampling	90% easy process, could be performed at home, save time, little discomfort. and less embarrassment.
El Salvador, San Vicente, La Paz, Cabañas, and Cuscatlán (Rural area)	Maza et al., 2018 [30]	Cross-sectional	1869	**Inclusion criteria:** ***Age:*** 30–59 years Underscreening women (No cytology screening in the last three years, HPV screening within the last five years or had never been screened) **Exclusion criteria:** History of hysterectomy, cryotherapy, cold knife conization History of cervical cancer	Vaginal self-sampling **Specimen collection instructions:** visual and verbal **Offered by:** Community Health promoter and research assistant. **Device:** CareHPV test (QIAGEN, Gaithersburg, MD, USA) ***Questionnaire***: collected sociodemographic information, health, sexual history, previous screening history, cervical cancer and HPV risk perception, and reasons for non-participation in previous screening programs. Finally, separate sets of questions were administered to women who accepted and those who declined self-sampling to explore the underlying reasons.	Home	99.8% for self-sampling	Most women agreed with statements highlighting positive aspects of the test (e.g., it is easy to perform, can be performed at home, and is more comfortable to do the exam oneself).
Guatemala, Santiago Atitlán, (Rural and rural area)	Gottschlich et al., 2017 [31]	Cross-sectional	178	**Inclusion criteria:** ***Age:*** 25–54 years **Exclusion criteria:** Pregnant women Women currently menstruating	Cervical self-sampling **Specimen collection instructions:** visual and verbal **Offered by:** Community Health Workers (CHWs): Tz'utujil language **Device:** Eve Medical HerSwab self-collection HPV kits	Home	High acceptability for self-sampling	78.7% comfortable to use 91% easy to use 80% screening at home

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Table 2 (*continued*)

Country	Authors, Year	Study design	Women, *n*	Population characteristics	Intervention	Setting	Acceptability	Experience
					Questionnaire: 143 questions regarding demographics, preventive health care practices, HPV and cervical cancer knowledge, and risk factors. Finally, questions assessing the acceptability and feelings toward HPV self-collection.			
Guatemala, Santiago Atitlán, and Livingston (Rural area)	Murchland et al., 2019 [32]	Cross-sectional	760	**Inclusion criteria:** ***Age:*** 25–54 years **Exclusion criteria:** History of hysterectomy, History of previous cervical cancer Pregnant women Women currently menstruating Women who had never been sexually active.	Cervical self-sampling **Specimen collection instructions:** visual and verbal **Offered by:** Community Health Workers (CHWs) (bilingual: Spanish and Tz'utujil or Q'eqchi, Kaqif language) **Device:** HerSwab kits (brush) ***Questionnaire***: 153 questions regarding demographics, risk factors for cervical cancer and HPV, self-reported attitudes towards screening, health care service use, and knowledge of cervical cancer and HPV. Finally, a post-sample survey of 3 questions regarding ease, comfort, and acceptability of the sampling method:	Home	High acceptability for self-sampling	82.3% comfortable 84% easy to use 96.7% willing to use it as a form of cervical cancer screening
Mexico, Morelos (Unspecified area)	Dzuba et al., 2002 [33]	Cross-sectional	1061	**Inclusion criteria:** ***Age:*** 20 years + Use of the Mexican Institute of Social Security services in Morelos Are registered in the parent study [50]	Vaginal self-sampling and health professional sampling **Specimen collection instructions:** visual, written, and verbal **Offered by:** Female nurses (self-sampling and pelvic examination) **Device:** Cotton-tipped sterile Dacron swab ***Questionnaire***: 65 questions regarding socioeconomic and demographic status; sexual, reproductive, and Pap histories; and the acceptability (discomfort, pain, embarrassment, and privacy) perceived during the self-sampling and Pap test procedure.	Health center	65.6% for self-sampling vs. 11.3% for Pap test vs. 23% for both procedures Overall self-sampling acceptability score was 21.7 ($p < 0.001$) for a maximum total score of 25.	71% more comfortable 55.3% less embarrassing
Nicaragua, Leon (Unspecified area)	Quincy et al., 2012 [34]	Cross-sectional	245	**Inclusion criteria:** ***Age:*** 25–60 years Women living in Leon, Nicaragua Women with intact uteri **Exclusion criteria** Pregnant women	Vaginal self-sampling and clinician-collected specimen **Specimen collection instructions:** none reported **Offered by: a** health professional **Device:** vaginal swab and brush ***Questionnaire***: questions regarding demographic information, past medical and reproductive history, and perceptions of	Health center	High acceptance of self-sampling Self-collected brush acceptability Score index for a maximum total score of 20 Self-collected brush (M = 18.40, SD = 2.73) Self-collected swab (*M* = 18.48, *SD* =	76.3% no pain with self-sampling using the swab 73.1% no pain with self-sampling using the brush 76.3% very comfortable with self-sampling using the swab 73.1% very comfortable with self-sampling using the brush 90.2% no

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Table 2 (*continued*)

Country	Authors, Year	Study design	Women, *n*	Population characteristics	Intervention	Setting	Acceptability	Experience
					experiences with self-collection and the clinician examinations. The questionnaire included items about the comfort, pain, privacy, and level of embarrassment associated with the self-collection and pelvic examination. There were also questions about the preference of testing method, the reason for the preference and willingness to self-collect in the future.		2.41), $t(238) = 4.27$, $p < 0.01$. Clinician-collection ($M = 17.56$, $SD = 2.92$), $t(235) = 3.81$, $p < 0.01$	embarrassment with self-sampling using the swab 88.2% no embarrassment with self-sampling using the brush 90% high privacy for all methods self-sampling using brush and swab were statistically significantly high than those for the clinician-collection
Peru, Ventanilla (Unspecified area)	Morán et al., 2017 [35]	Cross-sectional / Mixed method	97	**Inclusion criteria:** ***Age:*** 25–59 years Have performed a previous vaginal self-sampling test at the HOPE program (Women who help women to fight cervical cancer)	**Previous vaginal self-sampling** **Offered by:** Community Health Workers (CHWs) **Device:** *Care*HPV (QIAGEN, Gaithersburg, MD, USA) ***Questionnaire***: 29 questions regarding sociodemographic information and variables of preferences regarding self-administration of the test.	Home	68% for self-sampling	It requires less time, privacy. very few women reporting pain or discomfort.
Puerto Rico, San Juan (Urban area)	Ortiz et al., 2012 [36]	Cross-sectional	100	**Inclusion criteria:** ***Age:*** 18–34 years Women undergoing routine Pap smears in the University of Puerto Rico Gynecology Clinic. Women with an intact uterus, No history of cervical cancer No recent cervical procedures **Exclusion criteria:** HIV-positive Cognitively or physically impaired	Cervicovaginal clinician-collected specimens and cervicovaginal self-sampling **Specimen collection instructions:** written and verbal **Offered by:** physician **Device: Sterile collection kit** - Dacron swab and Cytobrush® (Cooper Surgical, Inc; Connecticut, USA) ***Questionnaire***: 16-item questions regarding demographic, lifestyle, and reproductive characteristics. Sexual practices and acceptability (comfort, pain, privacy, and embarrassment) and the reasons for this preference for the self-sampling for HPV testing	Health center	50% for self-sampling. vs. 22% for clinician-collection vs. 28% for both sampling methods (MD = −0.71, p<0.05). MD: mean difference	Less embarrassment (MD − 0.36) Less pain (MD − 0.23) Women felt that the techniques were equally acceptable in terms of pain (58%), embarrassment (71%), discomfort (47%), and privacy (94%).

years or older; however, most studies screened women with an average of 25 to 59 years of age for screening with the self-testing method; the selected age range varied according to the characteristics of each study and guidelines for cervical cancer prevention in each country. Several studies focused on including under-screened women within the previous three years at the time of the study and non-attendees to cervical cancer screening appointments fixed by local prevention programs. Only one study focused on women having a moderate to high risk of developing cervical cancer [27]. The studies conducted in Guatemala focused on indigenous women [31,32]. The most frequently employed exclusion criteria were being pregnant, having a history of cervical cancer, undergoing a hysterectomy, or receiving other treatments for cervical abnormalities. The primary language of the studies was Spanish; the indigenous communities spoke Tz'utujil, Q'eqchi, or Karif. Therefore, bilingual community health workers assisted them in facilitating their understanding of the information provided during the studies.

The proportion of studies that evaluated the self-sampling method alone was 53.3%, compared to 46.7% of the remaining publications, which used both methods (self-sampling and health professional sampling). Health professionals offered for 60% of the HPV self-tests, as they also conducted cervical cytology in certain cases, whereas the remaining 40% were offered by Community Health Workers (CHWs). Similar rates were observed with regard to the choice of screening setting (health center 53.3% vs. home 46.7%).

Concerning the type of device tested, various brands were used. Up to 53.3% of women were offered to use a brush as a collector, and 26.7% opted to use the swab. Two studies employed both brushes and swabs simultaneously [34,36]; a single study incorporated the vaginal tampon and swab in its evaluation [23]. The self-sampling instructions were given both verbally and visually (at the same time) in 40% of cases, the

instructions were only given verbally in 13.3% of cases, a combination of both written and visual, written and verbal, or oral, written, and visual instructions were reported in 6.7% of cases, respectively. The remaining studies did not describe the instructions for the self-sampling method. After performing the test, all studies were based on non-standardized questionnaires with heterogeneous questions to assess the acceptability of the HPV self-sampling test among women. Two studies relied additionally on a qualitative component with focus groups and guided interviews [22,35].

Eight papers reported a high acceptance of HPV self-sampling. Among these, three papers reported an acceptance of the self-testing greater than 80% [22,27,30], of which Maza et al. [30] reported near 100% acceptability. Additionally, the other five publications reported the acceptance of HPV self-sampling as "high" without specifying it directly in terms of percentages [24,26,31,32,34]. Six papers found an acceptance level of between 50 and 80% [23,25,29,33,35,36]. Only one study found an acceptance level of lower than 50% [28]. Five publications examined the acceptability of self-sampling vs. provider sampling collection vs. the two methods simultaneously; among which Torrado-Garcia et al. [27], Lorenzi et al. [25], and Dzuba et al. [33] evidenced self-sampling acceptability rates of 88.5%, 76.7%, and 65.6% respectively over the health professional collection or the two methods equally. Rosenbaum et al. [28] and Ortiz et al. [36] indicated a self-sampling acceptance of 38.8% and 50%, respectively. Although acceptance was lower than 50%, there is a greater proportion of women who conduct self-testing than those who choose the physician-collection method or use a combination of both approaches. The results of Rosenbaum et al. [28] tend towards similar acceptance rates among those who select self-sampling (38.8%), samples collected by a health professional (31.9%), and those who accept both methods (29.3%). Dzuba et al. [33] show that in spite of the high acceptance of self-testing, 23% of women accept both methods equally, compared to 11.3% who accept only the test de Papanicolaou (Pap test) a Physician-collected method.

The leading indicators for assessing the acceptability of each method were comfort, ease of use, pain, embarrassment, and privacy. Around 66% of the women considered self-testing to be a comfortable method when compared to the physician-collected method [23,24,26–28,31–34,36], and referred to it as an easy [22–25,27–32] method. In terms of pain, roughly 50% of the women considered it less painful [22,24,27,28,34–36] than conventional physician-collected method, they also felt less embarrassed [28,29,33,34,36], and felt it gave them more privacy [27,28,34–36] than the routine procedure, involving a gynecological examination. Among these indicators, Quincy et al. [34] found that comfort, pain, and embarrassment showed a statistically significant ($p < 0.001$) predictive relationship for the uptake of vaginal self-testing. However, other indicators analyzed more infrequently were screening rapidity [22,28,29,35], ease of understanding screening instructions [25,27], fear of hurting themselves [25], the willingness to undertake self-testing as a screening method in the future [28,30–33], and the possibility of undertaking self-testing at home [28–31]. Nevertheless, Laskow et al. [29] and Maza et al. [30] used women's Likert scores to evaluate the experience with vaginal self-testing, and they found that women reported being highly satisfied with the experience, with an average of 9.5 on a 10-point scale and between 4.2 and 4.6 on a 5-point scale, respectively.

Furthermore, various studies tested different devices, such as swabs, brushes, and tampons; the results showed that women thought that the swab was more comfortable (80% vs. 56%) and easier to use (77% vs. 59) than the vaginal tampon [23]. Regarding the acceptance of self-testing performed with a swab or a brush, Quincy et al. [34] revealed a slightly higher acceptability of the swab ($M = 18.48$, $SD = 2.41$) over the brush ($M = 18.40$, $SD = 2.73$) when measuring the acceptability index over a maximum score of 20 points.

3.2. Reasons limiting the acceptance of cervical cancer screening

Table 3. Summarizes the reasons that may limit the acceptance of HPV self-sampling or other cervical screening methods. The primary reasons for not accepting the HPV self-sampling screening test were related to beliefs about the inaccuracy of its results [28,29,34,35], concerns over the ability to correctly use the self-sampling tool [22,24,30], beliefs about the possibility of getting hurt [22,25,30], or concerns about feeling discomfort or pain during self-sampling [25,28,30], a lack of interest in one's own health [22,26,29], and the perception of not having the disease, due to the absence of self-observed symptoms [22,29,30]. Other reasons, which were not often mentioned, were associated with the perception of, and beliefs about the self-sampling test, including; the fear of contaminating the sample [22,28,36], the possibility of having a cervical cancer diagnosis [22,35], the lack of confidentiality in healthcare facilities [22,30], the belief that cancer is a dormant disease that can be provoked by introducing a sample-taking device in the vagina or cervix [22]. Elsewhere, studies have revealed that women may refuse the self-sample test because they prefer attending a health center [26,29], can be embarrassed by self-sampling, and feel uncomfortable touching themselves. In addition, some women have reported having greater confidence in the Pap test [33] and the knowledge and expertise of the test provider [28]. Furthermore, Maza et al. [30] reported that women may not attend screening appointments because they feel embarrassed to be examined by a male physician, believe that cervical cancer screening is unnecessary, and fear that treatment would be needed.

4. Discussion

Cervical cancer continues to be a significant public health problem affecting women worldwide [3–5]. The effort to detect women at high risk of cervical cancer is challenging as there are several difficulties establishing a screening programme and access to ad hoc cervical testing in LMICs. This is the first review to summarize the acceptance of HPV vaginal self-sampling as a screening method for cervical cancer in Latin America [22–36].

The different research studies included in this review have demonstrated high acceptability of HPV self-sampling compared to the clinician-collection, despite the different devices used; these results are consistent with Nodjikouambaye et al. [37]studies previously conducted in the African context. Even though the acceptance of this methodology in Latin America was subjective because no standardized questionnaire for evaluating vaginal self-sampling acceptability exists, the authors demonstrated the common points of acceptance and the facility of approaching women who had not wanted to be screened by conventional physician-collected method. However, women highlighted the simplicity of vaginal self-sampling because of the limited time required to perform it and the possibility of performing it at home [22,25,28–30,35].

In addition, the Community Health Workers (CHWs) support played an essential role in the approach of the women who have impairments in approaching health centers provided for the traditional cervical cancer screening tests, and also when women have linguistic communication barriers because they speak regional dialects and do not speak Spanish [22,26,30–32,35]. The literature demonstrates that offering HVP testing through CHWs during home visits effectively increases cervical cancer screening coverage [38,39].

Nevertheless, this systematic review highlighted some reasons that can limit the acceptance of the self-sampling approach; mainly women's perceptions of and beliefs about this screening method. The most outstanding reason was related to beliefs about the accuracy of results. HPV self-sampling has no statistically different specificity or sensitivity compared with clinician-collection samples [40]. Some studies have previously demonstrated a high level of agreement for the detection of HPV DNA through self-sampling testing and clinician-collection samples

Table 3
Reasons limiting the acceptance of HPV self-sampling.

Country, Authors	Reasons to not accept HPV self-sampling or other screening test
Argentina, Arrossi et al. [22]	Insecurity in their ability to correctly use the self-sampling test Possibility of self-injury using the self-sampling test Fear of contaminating the sample Lack of confidentiality in healthcare facilities Perception of the health-disease status defined as the absence or presence of symptoms (pain, inflammation, or vaginal discharge) Lack of interest in their health The possibility that screening could result in cancer diagnosis frightened women The belief that cancer is a dormant disease that can be awaken by introducing a sample-taking device in the vagina or cervix
Bolivia, Surriabre et al. [23]	NR
Bolivia, Allende et al. [24]	NR
Brazil, Lorenzi et al. [25]	Fear of self-injury using the self-sampling test Discomfort or pain using the self-sampling test
Chile, Léniz et al. [26]	Lack of interest (38.2%) Preference to attend health center (26.5%) Fear of the procedure (19.6%) Lack of time (15.7%)
Colombia, Torrado-Garcia et al. [27]	NR
El Salvador, Rosenbaum et al. [28]	Result accuracy (33.3%) Provider's knowledge confidence (24.2%) Confidence in the provider's expertise in performing the test (16.4%) Fear of improper sampling (13.3%) Comfort (33.0%) The availability of assistance/equipment (25.2%) The sanitation of the facilities (12.4%) Privacy (11.0%)
El Salvador, Laskow et al. [29]	Disinterest to be screened ($p = 0.001$) Belief that the results might not be correct Discomfort with touching themselves ($p = 0.001$) Felt embarrassed by self-sampling ($p = 0.001$) Preferred that a clinician take the sample ($p = 0.001$) Not having the time or privacy in their own home ($p = 0.001$) Perception to be at low risk of cervical cancer to not have symptoms
El Salvador, Maza et al. [30]	Were embarrassed at being seen by a male physician (55.6%) * Lack of symptoms (38.9%) * Belief that the test was not necessary (27.5%) * Long clinic waits times (22.5%) * Belief that the screening would be painful (27.1%) * Fear that treatment would be needed (20.5%) * Belief that tests results would not be kept confidential (20.1%) * Fear that the person might lose part of the uterus during treatment (22.9%) *
Guatemala, Gottschlich et al. [31]	NR
Guatemala, Murchland et al. [32]	NR
Mexico, Dzuba et al. [33]	More confidence in the Pap test (93.1%)
Nicaragua, Quincy et al. [34]	More confident of the result from clinician-sampling
Peru, Morán et al. [35]	Fear of knowing they are diseased Confidence that self-sampling will be administered correctly Distrust in the validity of self-sampling results
Puerto Rico, Ortiz et al. [36]	More confident that the sample would be more properly taken (85.6%)

NR: Not reported.
* Reasons for not attending a cervical cancer screening appointment.

[41,42]. These results are similar to those reported by Surriabre et al. [23] in Bolivia and Torrado-Garcia et al. [27] in Colombia, where similar identification levels were found for the two screening methods with a Cohen's Kappa = 0.71 (95% CI 0.55 -0.88) and 0.9774, respectively.

Despite the cultural barriers mentioned above, there are other barriers such as religious, socioeconomic, demographic, and geographical factors. However, none of these other barriers were identified in the current review, probably due to the structure of the questionnaires used in the selected articles. A previous study by Allen-Leigh et al. [43] revealed a series of barriers to cervical cancer screening among indigenous Mexican women in rural communities; these barriers related to the lack of knowledge about self-sampling and human papillomavirus, male partner opposition, and organizational barriers such as the distance to the clinic, use of comprehensive language and long waiting times in receiving test results. In addition, this study also refers to the lack of confidence to perform the self-sampling procedure correctly, in keeping with concerns revealed by our systematic review.

Finally, women consider some reasons such as the reliability of the sample taken, the experience or performance of the clinician, fear of injury, discomfort of touching their own vulva, and hygiene at the time of screening, to be particularly important. Such concerns highlight the need for a clinician-collection sampling option, alongside that of self-sampling [28,29,35,36].

The HPV self-sampling procedure is a useful solution to reduce barriers to access for screening programs in LMICs. Moreover, increasing the use of self-sampling methods in LMICs may help ration the more resource intensive physician-collected methods to those women who are determined to be higher risk based on the self-sampling results. In Bolivia - one of the countries with the highest incidence and mortality rates of cervical cancer in Latin America - Allende et al. observed a 4.7 fold increase in self-sampling by women living in a peri-urban area, when compared to rates from the previous year [24]. These data were similar to others obtained in Argentina, Guatemala, and Mexico, where a 4-fold increase in self-sampling screening coverage was observed [31, 38,43]. In addition, HPV self-sampling is a cost-effective screening method, especially in LMICs, compared to an average cost of a Physician collected method in Latin America, it can range from 13.00 to 72.00 US Dollars (USD) on average [44]. Particularly, Surriabre et al. [23], reported that an HPV self-sampling kit containing a pair of sterile gloves, a cotton swab, and a sterile glass slide covered in a cardboard box could have an accessible price of around 0.5 USD. Other results were obtained recently in Peru in a real-world implementation of HPV self-sampling; the cost per HPV self-sampling kit distributed door-to-door by community health workers to women with a socioeconomic disadvantage for around 3.00 USD, this same kit could be obtained and tested for women of higher socioeconomic status for around 45·39 USD [45,46]. Self-sampling therefore costs less than cytological screening and treating a premalignant lesion or the same cervical cancer [46].

In May 2018, a global call for action to eliminate cervical cancer was announced by the Director-General of the World Health Organization (WHO) [47]; in August 2020, The World Health Assembly adopted the Global Strategy to eliminate this disease, in which they pointed out that providing women with the option of self-sampling contributes to acceptability and access to health services [15]. According to the facts mentioned above and to the experience gained after the effects of the COVID-19 pandemic, where traditional cervical cancer screening programs were disrupted, the self-screening initiatives can change the perspectives of vaginal self-sampling as a screening method for women worldwide [48,49].

This review has some limitations that need to be addressed. 1) The heterogeneity of the populations in terms of demographic data and sample size varied among the studies. It can be explained by the vast age range of the participants included in each study, the number of patients ranging from 60 to 3049, and the difficulty of generalizing the results to some populations, such as indigenous communities. 2) No standardized

questionnaire was used. Therefore, the variety of questions in the studies make it difficult to compare them. In a few studies, the authors asked about the reasons for refusing self-sampling, the possibility of changing their minds about this screening method, and their cervical cancer knowledge. For this reason, it is necessary to create a standardized and validated questionnaire to carry out further research and obtain more accurate results on the acceptability of vaginal self-sampling by women in the Latin American context. 3) Most publications were carried out in El Salvador, Guatemala, and Nicaragua - three out of the six Latin American countries located in Central American countries - with one of the highest prevalence of cervical cancer in Latin America. In this region, different investigations have been carried out to introduce HPV testing for cervical cancer, such as the Scale-Up project in Guatemala, Honduras, and Nicaragua [50]; and the CAPE project (The Cervical Cancer Prevention in El Salvador) for El Salvador [51]. We note that the acceptability of HPV self-sampling was not investigated at the time these projects were introduced. Nevertheless, evaluation of the Scale-Up project has shown a positive impact, with an 85.5% target coverage of HPV-based screening, where 75,1% of the total women screened for HPV used the self-sampling collection. In this regard, it is also essential to conduct future studies that explore the acceptance of vaginal self-sampling in other countries and settings with greater inclusion of indigenous groups and women with HIV infection. 4). Finally, the fact that only one researcher has performed the quality analysis of the articles may lead to selection and information bias. Finally, certain studies mixed up the terminology of acceptability with test preference, making it difficult to interpret the results in some cases.

5. Conclusion

Vaginal HPV self-sampling is an additional screening method, a helpful cost-effective tool [52] with a high acceptance among Latin American women that can achieve a higher rate of screening vulnerable populations and ethnic minorities at risk of cervical cancer. This strategy increases women's opportunities to participate actively in cervical cancer prevention and increases screening coverage and greater adherence to screening programs. In addition, early diagnosis of the disease will allow timely initiation of treatment and follow-up care.

Considering that self-sampling is an effective screening method that provides privacy, autonomy, and confidentiality, it is essential to continue the education campaigns about the existence of the human papillomavirus, its relationship with cervical cancer, the possibility and advantage of vaccination for HPV, the methods and frequency of the screening test, in the aim of e reducing cervical cancer's incidence and related deaths worldwide.

Ethics approval and consent to participate

This article does not require ethical approval for being based on previously published data.

Data availability statement

The authors will make available data upon a reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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DISCUSSION AND CONCLUSION.

REDUCTION OF HPV INFECTIONS AND CANCERS LINKED TO THESE VIRUSES THROUGH VACCINATION: THE FIRST STEP TO ELIMINATION

The purpose of HPV vaccination is to reduce or even completely prevent the transmission of the virus, thus limiting new infections and ultimately reducing new cases of precancer and cancer. From a public health perspective, it is important that these effects can be observed in the target populations in order to have observable and quantifiable evidence of the effectiveness of this vaccination. This evidence is important for health policies to maintain and increase efforts to promote this vaccination, but also to convince sceptical groups of the positive effect of this vaccination on their health(61, 62). Until now, it has been assumed that this vaccination was effective, thanks to the clinical studies that had made it possible to develop the vaccines, but without being certain of the effects within the general population. The issue was the inability to observe its effectiveness due to a lack of temporal hindsight. The studies carried out by the manufacturers have found a decline in the number of so-called precancerous lesions during their clinical studies. However, it takes about 20 years to observe an impact on the development of cancers in the general population. However, since the marketing of these vaccines, and in particular of nonavalent Gardasil, studies have multiplied, demonstrating the real effectiveness of this vaccination in the general population(63-66). Vaccines against HPV infections have been introduced in many countries around the world since 2006/2007 (86 countries introduced this vaccine in their vaccination schedule in 2018). In 2018, all countries in Europe introduced HPV vaccination into their national programmes. Thanks to this, there is now solid epidemiological data from the general population demonstrating the effectiveness of vaccines in reducing the incidence of invasive cervical cancers, precancerous lesions, HPV infections and anogenital warts compared to the pre-vaccine situation.

The first observation of an association between vaccination and cervical cancer risk-reduction was published in the Swedish Cancer Registry in 2020. Over the period between 2006 and2017, the observation of cancers in females aged 10 to 30 years highlighted that the risk of invasive cervical cancer was substantially reduced in young women who had received at least a dose of quadrivalent vaccine against HPV(39, 67). Moreover, in Sweden, a 75% reduction in

precancerous lesions was observed in young women who had been vaccinated before the age of 17, compared to other young women. In addition, the reduction in the number of new cases of invasive cervical cancers is greater in women vaccinated at a younger age (68).

An Australian study showed that the number of people infected with HPV (which causes cervical cancer) has decreased thanks to vaccination; from 22.7% in 2005-2007 to 1.5% in 2015 among young women aged 18-24(69). These results led the International Papillomavirus Society to declare that extensive HPV vaccination coverage combined with high participation in cervical cancer screening and appropriate treatments, can lead to the elimination (less than 4 cases per 100,000 women per year) of cervical cancer as a public health problem(21). Meanwhile the English National Health Service has declared that cervical cancer can be eliminated from England by 2040 (70). For the moment it is quite difficult to observe thes same effects in Switzerland, as seen in Sweden or England, nevertheless discussions with the various cantonal cancer registries are underway. The objectives would be to assess the reduction in precancer and cervical cancer following the routine introduction of this vaccination in Switzerland via the cases of precancer and cancer recorded in the various cantonal cancer registries in Switzerland. It can be noted that, for the moment, no date for a potential elimination of cervical cancer in Switzerland has been mentioned.

Although studies indicate a clear reduction in precancer and cervical cancer in Europe and Western countries, the burden of cervical cancer remains heavy in many parts of the world. In most countries, the incidence and mortality of the disease remain well above the threshold set by the WHO initiative on the elimination of cervical cancer(4 cases per 100,000 women per year). A systematic review published in The Lancet Global Health in 2023 indicates that there are still significant geographical and socio-economic inequalities in the elimination of cervical cancer worldwide, with a cancer rate for developing countries that is still far too high(21, 71).

Numerous studies indicate that the impact of vaccination will be all the greater if the number of young women and men vaccinated (vaccination coverage) is high, whether in Western or developing countries. The vaccination is, by its primary preventative action, the 1st step for the elimination of cervical cancer from a global point of view, but many efforts remain to be made to have optimal vaccination coverage and still succeed in convincing the many people who doubt the usefulness of this vaccination (2, 72).

There are different strategies and techniques for screening for HPV infections and cervical cancer, and we specifically researched screening via self-sampling, inthe studies I have included in this thesis. We found through our randomised controlled trial and systematic review that this method led to an increase in screening participation, with the quality of screening being equivalent to that carried out by a gynaecologist. However, we are yet to determine its effectiveness from a global perspective and what the next steps should be regarding this subject (73-75).

A meta-analysis of 33 randomised control trials on the subject published in the British Journal of Cancer clearly indicates that with an intention-to-treat analysis, self-sampling was very effective in reaching under-screened women. The associated data showed an increase from 13% to 39% in the coverage rate(76) (see figure 7). Several other observational studies have shown that self-sampling allowed an increase in coverage rate, regardless of the socio-economic category of women screened and regardless of whether the screening was carried out in Western or developing countries. In 2023, we published a review showing that self-sampling was the most accepted screening method, and which allowed the highest coverage rate among sex workers(77); a population that is relatively difficult to involve in screening programmes.

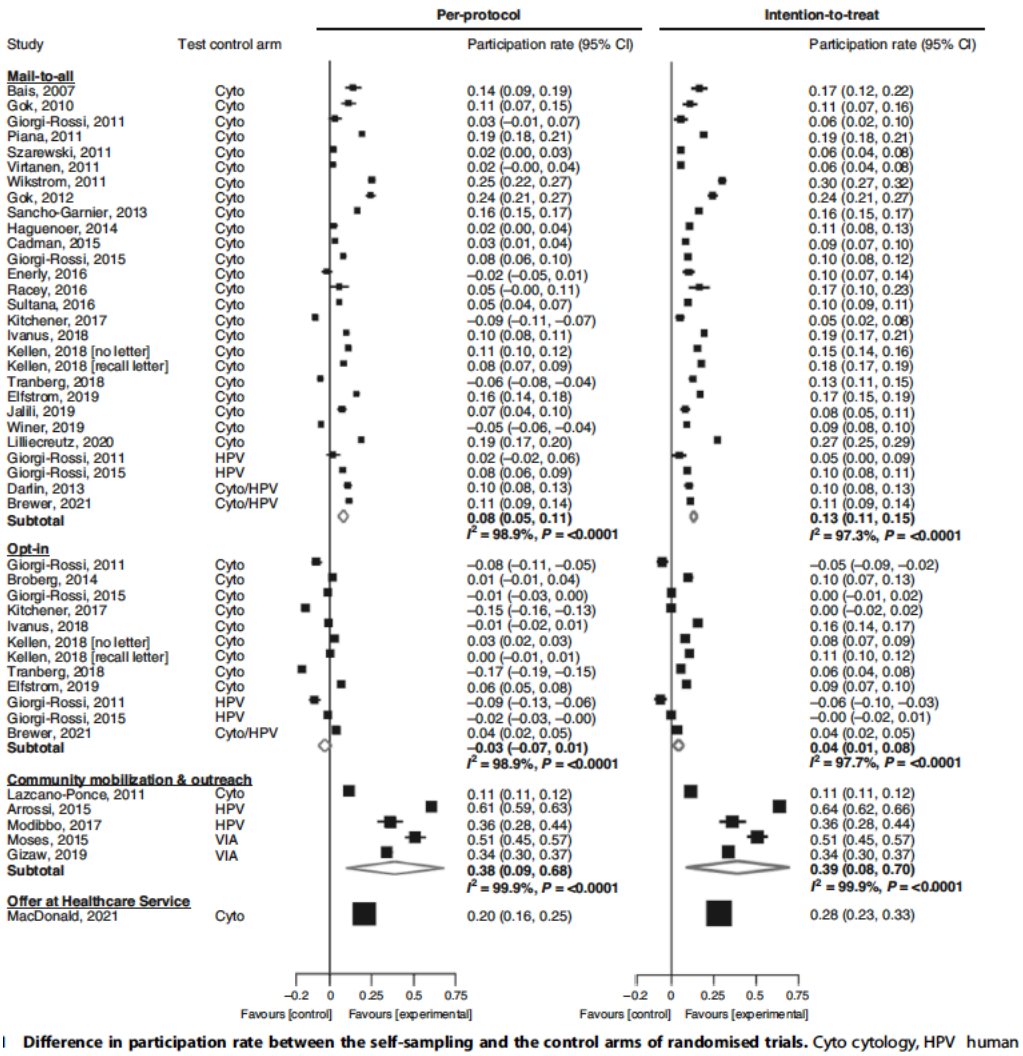

Figure 8: Effectiveness of self-sampling versus conventional screening on increasing the participation rate in HPV screening(76).

We have observed that many epidemiological studies have produced evidence supporting the efficacy and cost-effectiveness of self-sampling as a primary screening strategy(75, 78-80). The next public health step would be for this strategy to be implemented and used nationally as a screening strategy in Switzerland or abroad. For the moment, few countries make this choice despite the scientific evidence. In Switzerland, the Swiss Society of Gynaecology and Obstetrics' latest recommendations do not include self-sampling as a screening strategy for first recourse. Their current recommendations are as follows(81):

- "*Screening every 3 years from 21 to 70 years of age; cytological screening every 3 years from 21 to 29 years; first-line cytological or HPV screening every 3 years from 30 to 70 years. Please note: at present, the first-line HPV test is not yet covered by basic*

insurance. Therefore, we recommend cytological screening until the costs are legally covered.

- *If first-line HPV screening reveals a high-risk type of HPV, cervical cytology is performed*. »

In 2023, HPV tests are still not reimbursed by the mandatory Lamal insurance; the situation remains in an economic rather than scientific status quo. Nevertheless, the Swiss Society of Gynaecology and Obstetrics mentions that:

"*Participation in a screening examination, regardless of the method, is the most important approach. This is why the establishment of an organised screening programme is recommended. In Switzerland, with its federalist health system, such a programme is not currently planned. The HPV test has a significantly higher sensitivity. In contrast, cytology offers slightly higher specificity, and the costs of the HPV test are higher to date. With the wide introduction of the HPV test, test prices are expected to fall significantly in Switzerland as well*. It is possible that in the near future, a change in the reimbursement offer could allow the use of self-sampling as the primary screening strategy in organised screening programmes. This method can be used in programmes such as those already in place for breast cancer or colon cancer screening.

It is nevertheless important to note that some Western countries such as Australia, (first) but also Italy, Belgium, the United Kingdom, Sweden, the Netherlands and Turkey have decided to adopt the HPV test in primary screening and the smear as a complement if the test is positive. The combination of the two techniques makes it possible to obtain a reliability of 98%. The United States and Germany have chosen to carry out both methods simultaneously(82).

The map below (see figure 8), dating from 2020, shows that for the moment, apart from a rare exception (Ghana), countries with high incidence and high mortality related to cervical cancer do not have organised screening and little experience in using self-sampling as screening as a 1st resort(83).

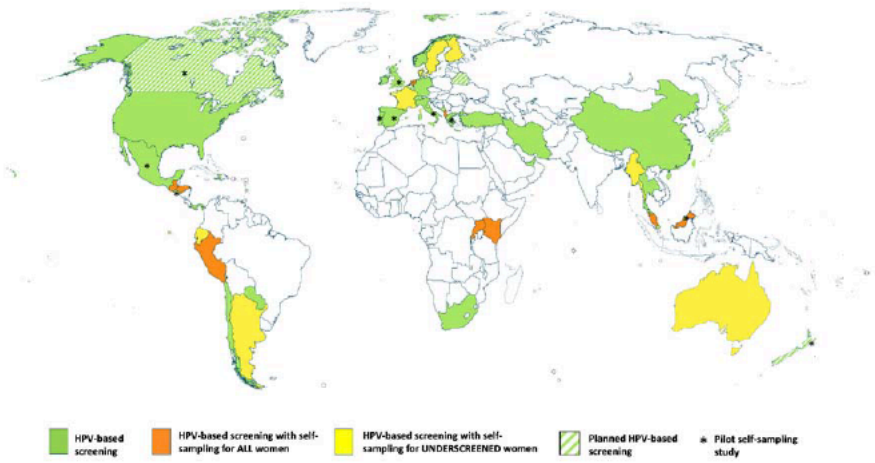

Figure 3. Map showing the self-sampling approach in countries that officially recommend HPV-based screening. As of October 2020, few countries had introduced HPV primary screening, and most were concentrated in high-income countries. Only 17 countries had introduced HPV self-sampling into their national programs or guidelines and of those, half reserved the use of self-sampling for under-screened populations only. Reprinted from Serrano B et al. 2022. *Preventive Medicine* **154**:106900.

Figure 9: Map of countries that officially recommend HPV based screening(83).

SCIENTIFIC CONCLUSION AND PERSPECTIVE:

As demonstrated through scientific evidence, there is no doubt, that joint use of HPV vaccination and screening would make it possible in the medium to long-term, to plan an elimination of cervical cancer (less than 4 cases per 100,000 women per year) at least in Western countries (84).

This will require maintaining a high vaccination coverage rate for women (but also coverage for men, to a lesser extent). Ambitious and coordinated public health policies must therefore be put in place. Better information and promotion of vaccination, particularly in Switzerland, should be implemented so that the target populations are better aware of the benefit of this vaccination on their health and that some of the obstacles and barriers to this vaccination are overcome. To achieve this objective, since the end of 2023, we have been conducting a national

survey of all paramedical students in training in Switzerland on their hesitation with HPV vaccination(85). The results of the survey will be available in the spring of 2024.

The other aspect allowing the elimination of this disease will be to continue to offer effective and early detection and, above all, to increase the rate of participation in screening. After evaluating different strategies, we believe that self-sampling is the most appropriate approach to achieve this objective. We are currently planning a study evaluating the possibility and effectiveness of a screening strategy proposed by general practitioners during their outpatient consultation. They will be proposing self-sampling during their consultation, thus making it possible to reach populations who do not go to their gynaecologists and who do not get screened. This study is at the protocol stage, and will not begin before the end of 2024.

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