

## Factors associated to anti-HPV vaccine refusal among young adult women after ten year of vaccine implementation

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### Abstract

In Italy HPV vaccination was implemented for girls since 2007 but its coverage was lower than recommended level. Sicily is one of the Italian administrative regions with lower vaccination coverage, ranging in the birth cohorts 1996-1999 from 59% to 62%. Aim of the study was to investigate factors associated with refusal of anti-HPV vaccination among young adult women of Palermo, Italy. A cross-sectional study was conducted through the administration of a telephone questionnaire, consisting of 23 items on HPV infection and vaccination knowledge based on Health Belief Model framework. The eligible population were young women with at least a previous vaccination among all included in Sicilian Vaccination schedule, without starting or completing anti-HPV vaccination schedule. Overall, 141 young women were enrolled, of them 84.4% were unvaccinated and 15.6% had at least one dose of HPV vaccine. In multivariate analysis, factors associated with the failure to perform the HPV vaccination were degree as school level (OR = 10.2,  $p = 0.041$ ), lower participation at school seminar on HPV (OR = 0.2,  $p = 0.047$ ) and lower perception of anti-HPV vaccine benefits (OR = 0.4,  $p = 0.048$ ). Public health educational program focusing and tailored on benefits perception of anti-HPV vaccine and HPV disease severity, especially if carried out at school, can improve HPV vaccination uptake.

### Keywords

Human Papillomavirus, vaccine refusal, hesitancy, women, school based, Health Belief Model, gynaecologist, general practitioner, survey, catch up

## Introduction

Human Papillomavirus (HPV) vaccination represents the best strategy for primary prevention of cervical cancer. HPV vaccines have high efficacy against cervical pre-cancerous lesions, if given to females before they are exposed to the virus, therefore the World Health Organization (WHO) recommends to offer HPV vaccination to pre-adolescent girls [1].

As of January 2018, 30 of 31 European (EU) countries had implemented HPV vaccination. Target age, financing and vaccine delivery differ among countries [2]. In 2014, mean EU coverage accounted for 53% in the primary target, and organised catch-up. Even if a lower number of primary cohorts were invited, African countries reported a mean 88% HPV vaccination coverage [3].

In Italy, HPV vaccination was free and actively offered to all girls during their 12th year of life since 2007, and the National Health Department established a target vaccination coverage of 95% within 5 years of the start of the campaign [4, 5]. However, despite several promotional activities, vaccination coverage is largely unsatisfactory, ranging from 27% to 83% among administrative regions [6]. Sicily is one of the Italian administrative regions with lowest immunization coverage against HPV, with a value of 59.5%, 58.7% and 62.1% for full HPV vaccination in the 1997, 1998, and 1999 birth cohort, respectively [6]. Consistent differences were reported between subjects who received at least 1 dose of anti-HPV vaccine and who complete the full vaccination schedule. In Sicily anti-HPV vaccine coverage for at least 1 dose were 70.3%, 63.4% and 69.2% in 1997, 1998, and 1999 birth cohort, respectively [6].

Previous studies have indicated that common reasons for not receiving the HPV vaccine were the perception of low risk or not needing the vaccine, lack of vaccine awareness, doubt about the safety and efficacy of the vaccine, fear of side effects, inadequate testing of novel vaccines that may be harmful and weaken the immune system, lack of physician recommendation and cost of the vaccine [7-9].

The Health Belief Model (HBM) attempts to explain and predict health behaviours, and is used in assessing health-behaviour interventions by focussing on the attitudes and beliefs of individuals. The HBM has been used extensively to study vaccination beliefs and behaviours, and has also been used in vaccination research to identify people's perceptions of disease and vaccination [7, 10, 11].

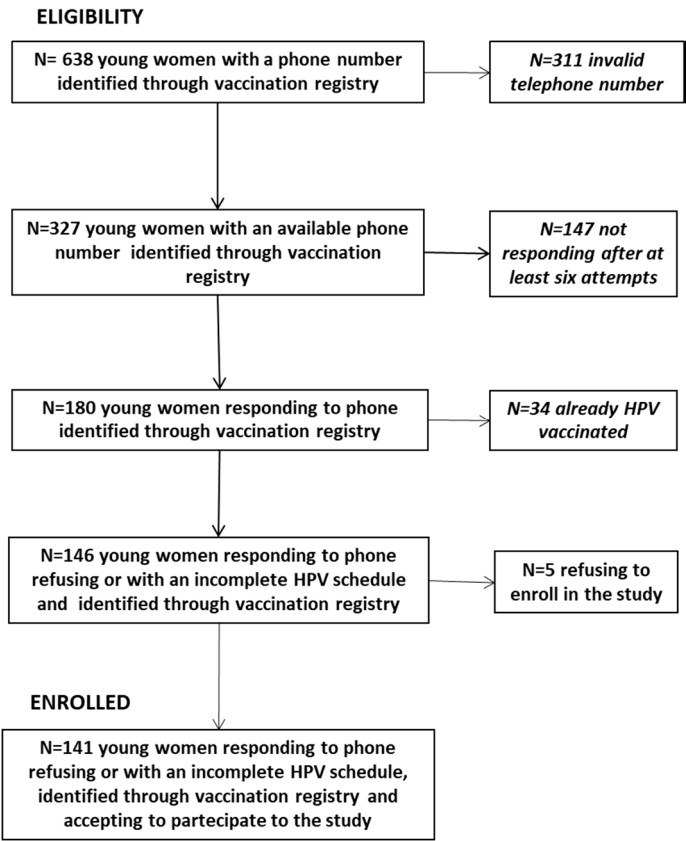
The objective of the study was to investigate factors associated with refusal of anti-HPV vaccination among young adult women of the City of Palermo, Italy, after ten year of vaccine implementation.

## Materials and Methods

An observational study was conducted among young adult women of the local health unit (LHU) of Palermo (Italy), including girls born from 1996 to 1999 (overall 1996-1999 Palermo birth cohorts  $n=26,153$ ). The sample was recruited through the vaccination registries of two public vaccination services of Palermo LHU. These services were selected to be as representative as possible of the Palermo geographical area, relatively to knowledge, attitudes and behaviours toward HPV vaccination and reliable source of information. The vaccination registry was filled in for each girl residing in the area of public vaccination services, and who had performed at least one immunization recommended by the Sicilian vaccination schedule. A structured questionnaire was administered through telephone by a trained healthcare professional from May to September 2017.

The eligible population was represented by young adult women who refused or didn't complete HPV vaccination schedule. The exclusion criteria from the study were: erroneous telephone number, not responding after at least six attempts, already vaccinated, and refusal to participate to the study. Overall 638 young women were eligible, although 72% of them did not have a useful phone number (erroneous phone number or not responding). Figure 1 describes reason for exclusion from the study. Main reasons for exclusion from the study were: to have an invalid telephone number (49%, n=311) or not available after at least six attempts (23%, n=147). Only 5% (n=34) of women had already performed anti-HPV vaccination outside Sicily.

Figure 1 Flow chart for exclusion from the study



The questionnaire consists of 23 items, divided into two sections. The first concerned demographic characteristic, HPV infection knowledge and use of gynaecologist services. The second section consist of HPV vaccination knowledge and health belief investigating: perceived susceptibility of risk of developing cervical cancer (one item), perceived severity of the disease and its consequences (one item), perceived benefits related to vaccination (four items), perceived benefits related to HPV vaccination (three items), perceived vaccination barriers (two items) and perceived HPV vaccination barriers (three items) using HBM as the theoretical framework. Young women responded using a five point Likert scale (1 = absolutely disagree, 2 = disagree, 3 = neither disagree nor agree, 4 = agree, 5 = absolutely agree). In order to make the results easier to understand, all questions were scored toward beliefs that would result in adherence to vaccination. Therefore, lower scores reflect stronger beliefs about vaccination refusal. This questionnaire was validated in a convenience sample representing approximately 10% of the young women.

At the beginning of the interview, informed consent was obtained and survey aims were explained as well as methods used to ensure confidentiality of data. The study was approved by Ethics Committee of the Policlinico “Paolo Giaccone” Hospital (Palermo 1).

Statistical analyses were performed using STATA v14.2 software. For all analyses,  $P\text{-value} \leq 0.05$  was assumed to indicate significance (two-tailed). Normal distribution and homogeneity of variables were tested with Kolmogorov-Smirnov and Levene’s test, respectively. Mean (with standard deviation) or median values (with interquartile range) were calculated for quantitative variables, while frequencies for qualitative variables. Mean data were compared by a one-way analysis of variance (ANOVA) with Scheffe’s post hoc test, while comparisons of differences in the medians were analysed with the Mann-Whitney test. An univariate logistic regression analysis was performed in order to evaluate factor associated to refuse HPV vaccination. Study covariates, which were found to be significantly associated with the study outcome after the univariate analysis ( $p < 0.1$ ), were evaluated into the multiple logistic regression models. Multivariate analysis was performed to investigate the independent effect of a risk or protective factor after adjustment for one or several other factors or to adjust for confounding variables. Only age was considered *a priori* confounder.

## Results

A total of 141 young women were enrolled in the study. Of these, 84.4% ( $n = 119$ ) were unvaccinated and 15.6% ( $n = 22$ ) received at least one dose of HPV vaccine. Demographic characteristics, HPV infection knowledge and use of gynaecologist services of young adult women were described in Table 1. The median age was 19 years (IQR = 18-20). Enrolled women had more frequently a high school diploma (66.7%) followed by graduate ones (26.2%). HPV virus was known by 93.6% of women ( $n = 132$ ), 90.8% ( $n = 128$ ) of them were aware of HPV can cause cervical cancer and 8.5% ( $n = 12$ ) didn’t know diseases caused by HPV. Furthermore 31.2% ( $n = 44$ ) of young women participated in school informative meeting about HPV. Moreover 58.2% ( $n = 82$ ) had a complete sexual intercourse, 11.3% ( $n = 16$ ) a sexually transmitted disease (STD) and 50.3% ( $n = 71$ ) a gynaecologist visit. Young women refusing vaccination had more frequently, than women with incomplete HPV vaccine schedule, a school diploma (OR = 4.56,  $p = 0.034$ ). On the other hand, young women refusing vaccination, had less commonly taken part in a school informative meeting about HPV (OR = 0.38,  $p = 0.043$ ), and they had lower gynaecologist visit (OR = 0.24,  $p = 0.009$ ).

Table 1 Demographic characteristics, HPV infection knowledge, and use of gynaecologist services of young adult women.

	<b>Total (N=141)</b>	<b>Refusal vaccination (N=119)</b>	<b>Crude OR</b>	<b>95% CI</b>	<b>p</b>
<b>Age, mean (SD)</b>	19 (18-20)	19 (18-20)	0.80	0.55-1.15	0.266
<b>Education, n (%)</b>					
<i>Secondary school</i>	10 (7.1)	6 (5.0)	1		
<i>High school</i>	94 (66.7)	82 (68.9)	4.56	1.12-18.52	<b>0.034</b>
<i>University</i>	37 (26.2)	31 (26.1)	3.44	0.74-16.03	0.155
<b>Family members, median (IQR)</b>	4 (3-5)	4 (3-5)	0.85	0.47-1.52	0.582
<b>Smoking habit, n(%)</b>					
<i>No</i>	119 (84.4)	103 (86.6)	1		
<i>Yes</i>	22 (15.6)	16 (13.4)	0.41	0.14-1.21	0.108
<b>Drinking habit, n(%)</b>					
<i>No</i>	117 (83.0)	99 (83.2)	1		
<i>Yes</i>	24 (17.0)	20 (16.8)	0.91	0.28-2.97	0.875
<b>Papillomavirus knowledge, n(%)</b>					
<i>No</i>	9 (6.4)	8 (6.7)	1		
<i>Yes</i>	132 (93.6)	111 (93.3)	0.66	0.08-5.56	0.703
<b>HPV can cause genital warts, n(%)</b>					
<i>No</i>	114 (80.9)	97 (81.5)	1		
<i>Yes</i>	27 (19.1)	22 (18.5)	0.77	0.262-3.1	0.643
<b>HPV can cause cervical cancer, n(%)</b>					
<i>No</i>	13 (9.2)	12 (10.1)	1		
<i>Yes</i>	128 (90.8)	107 (89.9)	0.42	0.05-3.44	0.422
<b>I don't know disease caused by HPV, n(%)</b>					
<i>No</i>	129 (91.5)	108 (91.8)	1		
<i>Yes</i>	12 (8.5)	11 (9.2)	2.14	0.26-17.46	0.478
<b>Taking part in a school informative meeting about HPV, n(%)</b>					
<i>No</i>	97 (68.8)	86 (72.3)	1		
<i>Yes</i>	44 (31.2)	33 (27.7)	0.38	0.16-0.97	<b>0.043</b>
<b>Current relationship status, n(%)</b>					
<i>Stable relationship</i>	80 (56.7)	66 (46.8)	1		
<i>Non-stable relationship</i>	4 (2.8)	2 (1.7)	0.21	0.03-1.63	0.137
<i>Single</i>	57 (40.5)	51 (51.5)	1.80	0.65-5.02	0.259
<b>To have had a complete sexual intercourse, n(%)</b>					
<i>No</i>	59 (41.8)	53 (44.5)	1		
<i>Yes</i>	82 (58.2)	66 (55.5)	0.47	0.17-1.28	0.138
<b>To have had STDs, n(%)</b>					
<i>No</i>	125 (88.7)	108 (91.8)	1		
<i>Yes</i>	16 (11.3)	11 (9.2)	0.35	0.11-1.12	0.077
<b>To have had a gynaecologist visit, n(%)</b>					
<i>No</i>	70 (49.7)	65 (54.6)	1		
<i>Yes</i>	71 (50.3)	54 (45.4)	0.24	0.08-0.70	<b>0.009</b>
<b>PAP test knowledge, n(%)</b>					

No	18 (12.8)	16 (13.4)	1		
Yes	123 (87.2)	103 (86.6)	0.64	0.14-3.02	0.577
<b>To have a PAP test, n(%)</b>					
No	112 (79.4)	97 (81.5)	1		
Yes	29 (20.6)	22 (18.5)	0.49	0.18-1.33	0.161

As showed in Table 2, main sources of information about anti-HPV vaccination was paediatrician/general practitioner (42.5%, n=60), followed by gynaecologist (33.3%, n=47) and parents (24.8%, n=35). The HBM answers on benefits of all vaccines had a mean score of 2.5 (SD=0.1), benefits of anti-HPV vaccine 2.5 (SD = 0.1), barriers of all vaccines 2.6 (SD=0.1), barriers of anti-HPV vaccine 2.0 (SD = 0.1), susceptibility of disease 4.3 (SD = 0.1) and disease severity 3.2 (SD = 0.1). Young women refusing vaccination had lower score on HBM question of perceived HPV vaccination benefit (OR=0.42, p=0.002), perceived HPV vaccination barrier (OR=0.46, p=0.008) and perceived severity (OR=0.50, p=0.022), compared to women with at least one vaccination dose received.

Table 2 HPV vaccination knowledge and HBM questions of young adult women

	<b>Total (N=141)</b>	<b>Refusal vaccination (N=119)</b>	<b>Crude OR</b>	<b>95% CI</b>	<b>p</b>
<b>Informative source about anti-HPV vaccination</b>					
<b>Gynaecologist, n(%)</b>					
No	94 (66.7)	81 (68.1)	1		
Yes	47 (33.3)	38 (31.9)	0.68	0.26-1.72	0.414
<b>Public vaccination services, n(%)</b>					
No	137 (97.2)	116 (77.5)	1		
Yes	4 (2.8)	3 (2.5)	0.54	0.05-5.47	0.605
<b>Parents, n(%)</b>					
No	106 (75.2)	87 (73.1)	1		
Yes	35 (24.8)	32 (26.9)	2.33	0.64-8.41	0.197
<b>Paediatrician/General Practitioner, n(%)</b>					
No	81 (57.5)	68 (48.5)	1		
Yes	60 (42.5)	51 (51.5)	1.08	0.43-2.73	0.865
<b>Social network, n(%)</b>					
No	135 (95.8)	114 (95.8)	1		
Yes	6 (4.2)	5 (4.2)	0.92	0.10-8.29	0.942
<b>Perceived vaccination benefit D1-4, mean (SD)</b>	2.5 (0.1)	2.5 (0.1)	0.76	0.34-1.68	0.494
<b>Perceived HPV vaccination benefit D5-7, mean (SD)</b>	2.5 (0.1)	2.4 (0.1)	0.42	0.23-0.75	<b>0.002</b>
<b>Perceived vaccination barrier D8-10, mean (SD)</b>	2.6 (0.1)	2.6 (0.1)	0.49	0.23-1.04	0.063
<b>Perceived HPV vaccination barrier D11-12, mean (SD)</b>	2.0 (0.1)	1.9 (0.1)	0.46	0.26-0.81	<b>0.008</b>
<b>Perceived susceptibility D13, mean (SD)</b>	4.3 (0.1)	4.2 (0.1)	0.73	0.42-1.26	0.262
<b>Perceived severity D14, mean (SD)</b>	3.2 (0.1)	3.1 (0.1)	0.50	0.28-0.91	<b>0.022</b>

In multivariate analysis, factors associated with the failure to perform HPV vaccination compared to perform at least one dose were degree as secondary school level (OR = 10.62,  $p = 0.028$ ), the lower participation at school seminar on HPV (OR = 0.25,  $p = 0.028$ ) and the lower perception of anti-HPV vaccine benefits (OR = 0.41,  $p = 0.044$ ).

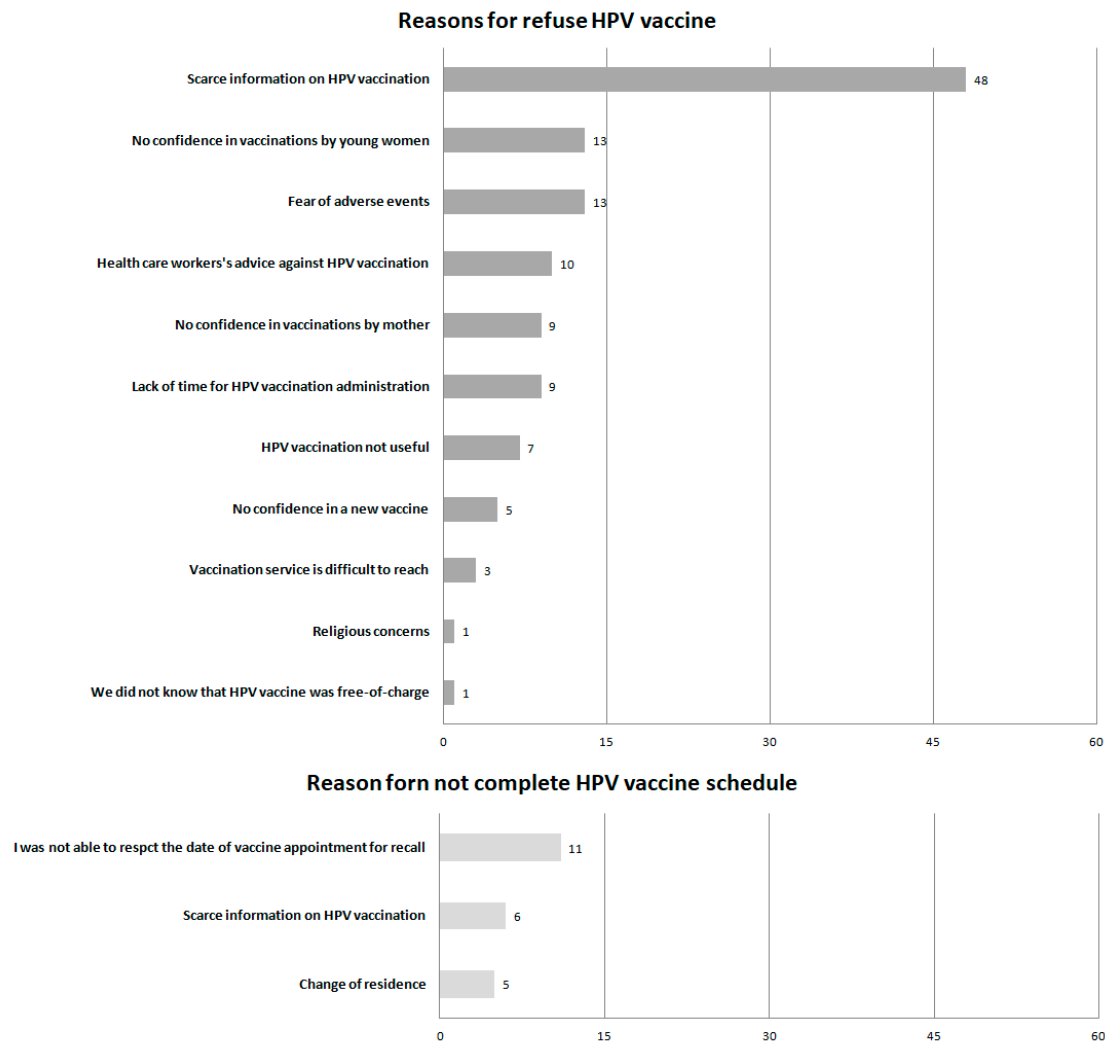
Table 3 Multivariate logistic regression of factor associated with refusal of HPV vaccine

	Adjusted OR	95% CI	p
<b>Age</b>	0.69	0.43-1.12	0.139
<b>Education</b>			
<i>Secondary school</i>	1		
<i>High school</i>	5.33	0.83-34.35	0.078
<i>University</i>	10.62	1.29-87.52	<b>0.028</b>
<b>Taking part in a school informative meeting about HPV</b>			
<i>No</i>	1		
<i>Yes</i>	0.25	0.07-0.93	<b>0.028</b>
<b>To have had a gynaecologist visit</b>			
<i>No</i>			
<i>Yes</i>	0.59	0.17-2.09	0.414
<b>To have had STDs, n(%)</b>			
<i>No</i>	1		
<i>Yes</i>	0.59	0.17-2.09	0.414
<b>Perceived HPV vaccination benefit D5-7, mean (SD)</b>	0.41	0.17-0.98	<b>0.044</b>
<b>Perceived vaccination barrier D8-10, mean (SD)</b>	0.83	0.29-2.35	0.731
<b>Perceived HPV vaccination barrier D11-12, mean (SD)</b>	0.69	0.31-1.56	0.375
<b>Perceived severity D14, mean (SD)</b>	0.80	0.31-2.00	0.635

Main reasons for vaccination refusal (Figure 2) were lack of information (40.3%  $n = 48$ ), followed by no confidence in vaccination and fear of adverse events (each 10.9%,  $n = 13$ ). Among young women who did not complete the anti-HPV vaccine schedule, the most frequent reason was the lack of time for subsequent vaccine administration (50.0%,  $n = 11$ ).



Figure 2 Reason for vaccine refusal and to have an incomplete anti-HPV vaccination schedule



Discussion

Sicily offered universal anti-HPV vaccination to all girls aged 12-years from ten years. However, there were notable variations in vaccination coverage among Sicilian LHUs and, in detail, lower vaccination coverage was reported in the LHU of Palermo. The present study investigated reasons for refusal of the HPV vaccine among young adult women of the City of Palermo, and explored their perceptions and attitudes using the HBM.

One of the main factor associated to HPV vaccine refusal was an higher education level. This finding was already showed in several studies but it has a discordant trend. In England Jan S, *et al* showed that LHU with more educational deprivation had higher rates of vaccination for all doses. In this study educational deprivation includes individuals with no qualification or the lowest levels of qualification [12]. On the other hand, in Greece Michail G *et al* observed that female students who studied at University were more likely to be vaccinated than female students who attended a Technological Institute [13]. In our setting, it was possible that young women with a higher educational level has greater access to misleading health information, for instance throughout mass media and/or social media. It is also possible that women with the lowest educational level had higher levels of health literacy, as observed by Lee C et al. In this study, young adults with lower



educational level had better HPV literacy and higher rates of both HPV vaccination initiation and completion, signalling the importance of increasing education and knowledge about HPV in the public [14].

Another predictor associated to HPV vaccine refusal was didn't take part in school informative meeting about HPV. In Italy, the HPV vaccination offer was carried out outside the school setting and therefore the organization of meetings on the HPV was carried out sporadically. Unlike Italy, the UK provides the HPV vaccine in school (offered to all girls aged 12). The UK HPV vaccination programme had several variations: some schools hold assemblies to promote and discuss the programme in advance of vaccination days, other schools offer science lessons associated with HPV vaccination [11]. In Sweden according to National law, all first year upper secondary school students (aged 16 years) are offered a health interview with the school nurse, who provides a dialogue regarding several preventive topics as sexual health and relationships [15]. In Italy, school health service was introduced in 1968 and concerned preventive and emergency medicine [16]. In 2004 this law was abrogated because it referred to an epidemiological, social, scholastic context extremely modified in its features [17]. Furthermore school health service was also superseded by the same legislation about the organization of the Italian health service by paediatrician [17]. On the other side, the 'Valore project' showed that Italian pre-adolescents were interested in acquiring additional information about HPV vaccination, and identified school as a setting where they are free to express themselves without fear of being judged, especially if the dialogue takes place with trusted teachers [18]. These results suggested the possible key role of schools in the promotion of correct information about HPV vaccination. Additionally, to achieve a higher uptake of the vaccine, it could be offered in the context of school-based voluntary vaccination and information campaigns, as already implemented in other countries [15, 19]. It has been showed that acceptance rate of the HPV vaccine is considerably lower (19–71%) in the lack of school-based programs than in the presence of the programs (65–86%) [20].

In addition, participants with a lower score for perceptions about HPV vaccinations benefits were more likely to be unvaccinated. This finding is in agreement with Marlow *et al.* where participants with a low score for HPV vaccination benefits (safety and efficacy of HPV vaccination) were more likely to be unvaccinated [7]. A possible explanation would be that a threatened individual didn't expect to accept the recommended health action unless it was perceived as feasible and efficacious. While acceptance of personal susceptibility to a condition also believed to be serious was held to produce a force leading to behaviour, the particular course of action to be taken depends upon beliefs regarding the effectiveness of the various actions available in reducing the disease threat [11]. Evaluation of the perceptions about benefits, barriers, severity and susceptibility of HPV vaccine could play a key role in the development of targeted educational campaigns that would increase the intention to uptake the HPV vaccine [12, 21]. Public Health professionals should provide tailored information to reinforce strength of recommendation regarding HPV vaccination, especially with parents of young women [21, 22].

The reasons reported among young women who reused HPV vaccination and those who did not complete the vaccination schedule differ each other. A consistent lack of information is mainly reported among young women who never performed vaccination. This data was similar to what was reported in a study conducted in the USA and other survey conducted in Italy [23]. The provisions of unambiguous information about benefits of vaccination and risks of the disease, clarifying also doubts, fears, and risk of severe side-effects, were fundamental communicative strategies in influencing awareness of young women of HPV vaccination [4]. On the other hand, women who

did not complete the schedule were more likely to not have time to perform it. In order to take on these barriers, it would be necessary to guarantee higher access to vaccination services.

The main limitations of the study are two. Firstly, the study was based on self-reported information, so personal perceptions may have been overestimated, although self-reporting was recognized as a cost-effective and feasible method for gathering data from large population samples. Secondly, the study had low participation rate therefore, the possibility of non-response bias should be taken into consideration. The low participation rate was mainly due to invalid phone number in vaccination registry, suggesting a reorganization of telephone catch-up procedure of vaccination services of Palermo.

## Conclusions

These findings suggest that educational interventions conducted in a school setting may be necessary to enhance HPV vaccination rates among Sicilian girls. Therefore, supply correct and unambiguous information to young women about vaccine efficacy and safety, and the value of vaccination in preventing cervical cancer may be needed, to increase in future HPV vaccination coverage.

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## Author Contributions

Restivo V, Costantino C, Casuccio A and Vitale F conceived and designed the study; Fazio TF, D'Angelo C and Casuccio N performed the study; Restivo V analyzed the data; Casuccio A and Vitale F wrote the paper.

## Conflicts of Interest

The authors declare no conflict of interest.