

Burden and Prevention of HPV. Knowledge, Practices and Attitude Assessment Among Pre-Adolescents and their Parents in Italy

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Abstract: Despite infections due to HPV nowadays represent the most common sexually transmitted diseases worldwide with recognized effective and safe preventive strategies, knowledge, attitudes; however, awareness on HPV is considerably low. The present study has two main objectives: 1. To conduct a literature review to analyze the evolution of preventive tools, the complexity of the vaccine choice process, and the challenges posed by HPV vaccine hesitancy and refusal among pre-adolescents and their parents; 2. To assess knowledge, practices and attitudes toward HPV infection and vaccination in a sample of Italian pre-adolescents and their parents. The observational study was carried out through the use of two anonymous and self-administered pre- and post-intervention questionnaires dedicated to the target populations. Between the administrations of the pre- and post-intervention questionnaires, an educational intervention on HPV infection and related diseases, and prevention strategies was conducted. All participants demonstrated suboptimal knowledge and positive attitudes in the pre-intervention questionnaire. Higher levels of knowledge and attitudes were observed among pre-adolescents that used social networks and had heard of sexually transmitted diseases at home/school/physician and from parents and also who had heard of HPV from General Practitioners, Gynecologists, family members and newspapers. A significant increase in HPV vaccination awareness was observed among pre-adolescents after the educational sessions. Health education programs aimed at increasing knowledge, attitudes and awareness on HPV are needed to implement the outcomes of HPV immunization programs, especially if supported by the physicians involved in counselling and recommendation processes.

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1. INTRODUCTION

HPV infection is one of the most common sexually transmitted infections worldwide [1], with an estimated prevalence of approximately 12%, in a population of over one million asymptomatic women from 194 studies [2].

Around 90% of infected individuals are asymptomatic and clear the infection within two years [3]. Nevertheless, a small proportion develops a persistent infection that can lead to a wide range of diseases, from benign lesions to cancers in the anogenital area as well as some benign and cancerous oropharyngeal diseases [4].

More than 100 HPV genotypes with a different tropism and pathogenesis have been identified to date. Mucosal HPV types can be classified into high- and low-risk types according to their capacity to induce cancer [4-6].

The low-risk types, HPV 6 and HPV 11, cause 90% of anogenital warts and benign/low-grade abnormalities in the genital

areas [7, 8], and are also responsible for causing recurrent respiratory papillomatosis, a proliferative disease of the upper aerodigestive tract [9-11].

Carcinogenic types are responsible for up to 4.5% (630,000 cases) of all new cases (8.6% in females; 0.9% in males) and cause 29.5% of all HPV-related cancers [12-14]. In particular, HPV 16 and 18 cause 70% of the cervical cancers, and a relevant proportion of vaginal (78%) and anal (88%), as well as some vulvar (25%) and penile (50%) cancers and, together with HPV types 31/33/45/52/58, are responsible for about 90% of HPV-related cancers worldwide [12, 15-17].

Cervical cancer remains the fourth most common female cancer globally, with an estimated 570,000 cases and 311,000 deaths yearly [16, 18].

There is evidence that the protection elicited by HPV vaccines to prevent HPV persistence and HPV-associated diseases in women and men is robust and long-lasting and widespread immunization campaigns could lead to substantial health economic benefits [19, 20].

Since 2006, HPV vaccination has been introduced globally into national immunization programs for girls in 71 countries, and for boys in 11 countries [21].

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In Italy, the HPV vaccine has been included in Italy's national vaccination program since 2008, when the recommendation and offer targeted girls aged between 11 and 12 years [22]. The current National Vaccine Prevention Plan 2017-2019 extended the vaccination program to include pre-adolescent males (aged between 11 and 12 years) and at-risk subjects (men who engage in same-sex sexual behaviors) [23] since the vaccine is also recommended for adults [21].

Many countries with national immunization programs experienced difficulties in reaching HPV vaccination coverage goals due to several HPV vaccination uptake barriers, such as lack of knowledge about HPV infection and related diseases in vaccine targets, parents of pre-adolescents and multidisciplinary providers, vaccination safety concerns, criticisms in the accessibility to HPV vaccine due to the high cost, limited healthcare services, organizational aspects of HPV vaccine campaigns and difficulties in vaccine schedule completion for patients and providers [24-28]. These barriers are of particular concern in low- and middle-income countries, which bear the greatest global burden of HPV-related cancers, particularly cervical cancer [29-31].

Given the relevance of HPV infection and the burden of related diseases, the complexity of factors influencing the compliance to HPV vaccine, and the suboptimal results in terms of gained vaccine coverage also observed in Italy, we conducted the present study in order to discuss the evolution of preventive tools, the complexity of the vaccine choice process, and the challenges posed by HPV vaccine hesitancy and refusal [32]. Furthermore, we focused on the primary HPV vaccine target by assessing the knowledge, practices and attitudes toward HPV infection and vaccination, as well as the willingness to accept HPV vaccine among Italian pre-adolescents and parents.

2. HPV VACCINES: THE PROGRESSIVE INTEGRATION OF PREVENTIVE TOOLS, INDICATIONS AND TARGETS

There are currently three licensed HPV vaccines with high efficacy, effectiveness and safety profile in the prevention of vaccine-type HPV infections and diseases [4, 17]. The first-generation of HPV vaccines, quadrivalent (4vHPV) and bivalent (2vHPV), were licensed in 2006 and 2007, respectively [4].

The 2vHPV protects against infections caused by HPV types 16 and 18, while 4vHPV also prevents against HPV types 6 and 11 [4].

Both 4vHPV and 2vHPV showed an efficacy higher than 90% against cervical intraepithelial lesions (from grade 1 to 3), adenocarcinoma in situ, and invasive cervical carcinoma due to HPV types 16 and 18 in women aged 15-26 years [33-36]. Even though, both the first-generation vaccines might protect against other HPV-related cancers such as vulvar, vaginal, and anal [37], only 4vHPV is licensed against these cancers as well as against HPV 6- and HPV 11-related genital warts by FDA. Therapeutic indications of the 2vHPV have been progressively expanded by the EMA including the prevention of premalignant anogenital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers [38]. In 2013 and 2014, the EMA approved a new schedule of 2vHPV and 4vHPV, respectively, targeting pre-adolescents (from 9 to 14 years for 2vHPV and from 9 to 13 years for 4vHPV). The reduction from 3 to 2 in the number of doses represents a relevant opportunity to improve vaccine uptake and completion.

Recently, a nonavalent HPV vaccine (9vHPV), which contains five additional HR genotypes (HPV 31/33/45/52/58) and has the potential to prevent up to 93% of cervical cancers, has been developed [16, 39, 40].

The second-generation HPV vaccine (9vHPV) was licensed by the United States (U.S.) Food and Drug Administration (FDA) in 2014 for individuals aged 9-26 years, and subsequently extended to women up to the age of 45 years in 2018. In Europe, the 9vHPV was licensed in 2015 and recommended for males and females from the

age of nine years. The schedule of the 9vHPV vaccine is identical to the 4vHPV vaccine [41].

As of early 2019, 115 countries and territories have introduced HPV vaccine into their national immunization programs and, among these, 20 countries and 4 territories have a gender-neutral HPV vaccination schedule [42].

In Europe, by 2018, all countries had introduced HPV vaccination in their national immunization programs [43, 44]. Fifty percent of the countries introduced HPV vaccination within the first three years after the European Commission granted a license for human use of the first HPV vaccines in 2006-2007, and the remaining countries have progressively introduced the vaccination in the last 5 years. Many countries initially adopted a multiple age-cohort vaccination strategy accompanied by temporary catch-up programs for older-aged people, in order to maintain catch-up programs for targeted cohorts that missed vaccination at the recommended ages. Several countries (22%), including Italy, have also expanded or will soon expand vaccination to boys of the same age and also other EU/EEA Member States are considering expanding the program to include boys.

3. THE INVOLVEMENT OF MULTIDISCIPLINARY TEAMS, PARENTS AND PRE-ADOLESCENTS THEMSELVES IN HPV VACCINATION CHOICE

The most current HPV vaccination programs target preadolescent girls within the age range of 9-14 years, either through organized school-based vaccination plans or delivery through primary care services (including family doctors, nurses and gynecologists).

A recently published study by Martakis K *et al.* revealed significant differences in practices in primary health-care services targeting children throughout the EU [45]. In Europe, with the exception of Finland, parents decide if a child should be immunized or not, including HPV vaccination. In case of disagreement between the daughter and her parents, there were different approaches in Southern, Western, Eastern and Northern Europe, which either gave priority to the parent's or to the child's decision.

The health professionals that offer HPV vaccination play a role in providing correct information for children and parents, negotiating in cases of disagreement and, in some EU countries, overruling the child's refusal. Processes of vaccine provision may vary substantially across the national vaccination programs in Europe, from authoritarian paternalistic models, imposing a passive role on the child, to libertarian models, where mutual participation of both actors is needed. Further ethical issues should be considered according to the age-based HPV vaccination strategies. A delay of a couple of years in offering the HPV vaccine (after 14 y.o. as in the UK) may seem to be boosting children's autonomy and acceptance, although it should be taken into account that this vaccination needs to be provided before the start of sexual activity [45].

In general, high HPV vaccine coverage could be achieved through a school-based strategy, as applied for adolescent hepatitis B vaccination in the UK and other European Countries [46].

HPV vaccine acceptance or refusal depends on taking part or not in school informative meetings about HPV and school-based vaccination campaigns, further suggesting the key role of schools in the promotion of correct information about HPV vaccination [47].

In Italy, the results of the 'Valore project' suggested that pre-adolescents are interested in acquiring information about HPV vaccination, identifying the school as an ideal setting for the freedom of expression without fear of being judged, especially with teachers [48]. Multidisciplinary teams of health professionals could play a key role in the school-based HPV immunization program. In the UK, according to different local authorities, vaccines were provided as part of a 'broader school nursing service' or by a 'stand-alone immunization team' [45].

A close collaboration between commissioners, service providers and data system managers, together with a proactive engagement with schools played a key role for successful HPV school-based vaccination programs [49].

Information regarding HPV vaccination and infection provided by healthcare workers (HCWs) is more complete and trustworthy than those given by parents who may have unconsolidated and partial knowledge [50].

4. RESULTS OBTAINED BY HPV VACCINE CAMPAIGNS TARGETING PRE-ADOLESCENTS: WHICH CRITICISMS PERSIST?

Despite the documented effectiveness and safety of HPV vaccination programs, according to the latest available data, HPV vaccination coverage in the EU Region remains substantially lower than recommended (about 50% in the primary target) [51].

HPV vaccination was offered actively and free of charge to all female adolescents starting from the age of 12 since 2007, and to all male adolescents since 2015. Nevertheless, vaccination coverage against HPV is considerably lower than recommended by the Italian National Vaccination Plan (PNPV) 2017-2019 (target 95%) among girls and boys [52, 53].

Several studies have analyzed the possible barriers for HPV vaccination uptake in the recent years [54].

Race and ethnicity, sex and income factors could considerably affect vaccination coverages in adolescence [55].

Moreover, organizational factors linked to vaccination offer and strategies should also be taken into account in the analysis of the criticisms against HPV vaccination. In Italy, a recent study demonstrated that higher vaccination coverages were observed in Local Health Units that implemented incentive strategies in HPV vaccination campaigns such as: free access to vaccination centers, reminders for subjects who missed vaccination doses, appointment planning systems and presence of an immunization registry [24].

Forster *et al.* conducted a randomized controlled trial to test the efficacy and feasibility of an incentive intervention to improve HPV vaccination uptake among girls. Data suggested that the incentive (a £50 shopping voucher) may improve consent form return rates (+21%) and vaccination uptake (+15%) in the intervention arm [56].

In general, implementing vaccination requirements in schools and sending reminders for adolescent vaccinations, has the potential to improve immunization uptake [57].

Teeter *et al.* have been investigating in the United States the possible role of community pharmacies in the promotion of HPV vaccination. Usually, community pharmacies are more accessible in terms of working hours and distance from home, when compared to vaccination centers [58].

Recently, another research has shown that only half of the community pharmacies surveyed in eight US States offered HPV vaccination to adolescents, highlighting an underutilization of these highly accessible sites [59].

Finally, also a game-based learning tool ("Fight HPV"), dedicated to mobile technology users, has been developed and evaluated recently. This mobile app which focused on HPV infection and related diseases, cancer risks associated with HPV infection and preventive methods, such as vaccination and screening, has been appreciated by a focus group of 16-18 years old adolescents and has increased awareness among participants about HPV infection and preventive measures [60].

5. COUNTERING VACCINE HESITANCY AND REFUSAL: A FOCUS ON HPV VACCINE

The development and widespread adoption of vaccines is one of the most important developments of the 20th century for public health.

Vaccination strategies have contributed substantially to the eradication of diseases such as smallpox, to prevent the re-emergence of diseases that were common like polio and to limit highly contagious diseases, such as measles, mumps, and rubella [61].

Vaccines are universally recognized as one of the most effective instruments for the primary prevention of infectious diseases, but, in recent years, vaccination delay or refusal is putting at risk the high level of immunization rates achieved in the past. This phenomenon, namely vaccine hesitancy, could be due to multiple levels of factors that influence parental vaccine confidence and acceptance [62].

Apart from the risk perception of the diseases and the confidence on vaccines, the WHO SAGE Working Group on Vaccine Hesitancy pointed out "convenience" as a possible explanation related to the ease of access to immunization in terms of location and time [63].

Especially with regard to HPV vaccination, which requires two or three accesses to the vaccination services, logistical reasons for not completing the vaccination schedule, such as the distance from the vaccination centers and the lack of time to administer HPV vaccines, should be considered [64].

Only a correct counselling on the benefits of HPV schedule completion and an improvement of the accessibility to vaccination services for adolescents (for instance, opening on weekends or late in the afternoon) could increase HPV vaccination coverages [65].

Regarding HPV vaccination, public health professionals should consider the impact of education levels on hesitancy. A discordant association emerged from the literature. Some studies confirmed that more deprived subjects had higher rates of HPV vaccination and cycle completion [65, 66].

On the other hand, another research conducted in Greece demonstrated higher vaccination coverage for female students who attended a University course compared to school students of a Technological Institute [67].

In general, subjects with a lower perception about HPV vaccination benefits were more likely to be unvaccinated and usually young women who were not vaccinated showed a consistent lack of knowledge about HPV vaccination and disease [65].

Fear of vaccine adverse events, especially long-term side effects, was often reported as the main reason to refuse HPV vaccination. Furthermore, the same subjects were critical about the roles of pharmaceutical industry in HPV vaccination [68].

Recognizing the main reasons for HPV vaccine hesitancy is fundamental to develop tailored public health strategies in order to improve vaccination adherence. Regarding HPV vaccination, HCWs are one of the main and most reliable sources of information for adolescents, but the type of vaccination counselling provided has often been unsatisfactory, representing an important reason for hesitancy [50].

More updated and adequate information, aimed at dispelling false myths regarding HPV vaccination, should be provided by public health care professionals not only during "face-to-face" counselling interventions, but also in school-based informative programs for adolescents and parents [65].

6. OUR RESULTS

6.1. Materials and Methods

6.1.1. Study Design and Participants

A cross-sectional survey about HPV and its prevention, addressed to pre-adolescents and parents of pre-adolescents, was conducted during the 2017/2018 school year.

The inclusion criteria consisted of pre-adolescent school students attending first-grade secondary schools and parents living in

the provinces of Palermo and Lecce, in the Regions of Sicily and Apulia. These represent two of the Southern Italian Regions with the highest number of inhabitants (1,260,193 and 798,891, respectively) and the lowest mean age [69].

The sample size was calculated considering the number of subjects belonging to the target study population, the at risk subjects and healthcare personnel, the available evidences about the HPV vaccine acceptability fixing the confidence interval 95%, a margin of error (+/-) of 2.5% and adding a quote of 5%, in consideration of the possible drop-outs and missed answers.

6.1.2. Data Collection and Questionnaire

The survey consisted of anonymous questionnaires. The questionnaire addressing parents of pre-adolescents was self-administered and conducted using the Google Drive platform. Google Drive automatically populates and saves digital responses into a secure Microsoft Excel database protecting participant confidentiality throughout the surveying process. Participants were shown a consent page informing them of the study aims and objectives as well as the participant's right to refuse or terminate their participation in the study at any time and without disadvantages.

Participant pre-adolescents filled in two written questionnaires, the first one before the educational session on HPV infection and related diseases conducted by the research team, and the second one after it. Participant pre-adolescents and their parents were shown and subscribed assent and consent documents, respectively, informing them of the study's aims and objectives as well as the participant's right to refuse or terminate their participation in the study at any time and with no disadvantages.

The questionnaires targeting pre-adolescents and parents included 28 and 50 items, respectively, in a total of three sections. The first section investigated the general characteristics of the participants, the source of information on sexually transmitted diseases (STDs), including HPV and the knowledge of vaccines received during childhood. The general characteristics investigated in pre-adolescents included gender, country of birth, use of social networks, professed religion and educational qualification of parents. Parents were asked for age, family relationship with the pre-adolescent, country of birth, school qualification level of education, occupation, professed religion, number of sons/daughters, compliance with cervical screening (for mothers), occurrence of HPV-related lesions in participating subjects and of cancers in their own family, compliance to the national vaccine program by their sons/daughters, knowledge about HPV infections and prevention, and, if yes, the main sources of information.

The first section also included a 10-point Likert scale on how much the participant is willing to receive or to have their son/daughter receive the HPV vaccine before continuing the survey.

The second section included 7 and 15 'True' or 'False' knowledge statements about HPV infection or HPV vaccination addressed to pre-adolescents and parents of pre-adolescents, respectively.

After completing the knowledge section, participants were given information about HPV and its vaccine (an educational session in the school setting for pre-adolescents conducted by the research group and a written text for the pre-adolescents' parents, respectively) before proceeding to the third section, which assessed their attitude using 9 statements with a 5-point Likert scale for each one (0 points- Strongly Agree, 1 points-Agree, 2 points-Neutral, 3 points-Disagree, 4 points-Strongly Disagree). Finally, the last section was a 10-point scale that measured the willingness of the participant to get vaccinated or to have their son/daughter vaccinated against HPV after completing all the survey sections and after receiving the educational intervention or the written information.

6.1.3. Statistical Analyses

Data collected through written questionnaires and Google Drive, which were exported to JMP software, version 13. Data are

presented as mean \pm standard deviation or median and 25-75p for continuous variables and as percentages for categorical variables.

Based on the participants' responses, the knowledge, attitude and intention scores were calculated. The 'knowledge' score summarizes the percentage of correct answers the participants gave. For each knowledge statement, one point was given for a correct answer (True or False) and zero points if they selected a wrong answer or "Do not know". The attitude score was obtained by calculating the average of the participants' responses to the statements on a 5-point Likert scale.

The 'intention' score reflects the willingness of each participant to receive or have their sons/daughters receive the HPV vaccine. The 'intention' score was estimated both at the beginning and at the end of the survey, when the information about HPV infection and vaccination had been given. The score is a scale from 1 to 10, where 10 reflects the highest intention to receive the HPV vaccine.

Each score is presented as mean \pm standard deviation and median (25-75p) for pre-adolescents and parents, respectively.

The possible association of baseline characteristics of pre-adolescents and parents with knowledge and attitude scores higher than 75 percentiles was tested through univariable logistic regression.

A p-value less than 0.05 was considered significant throughout the study.

6.2. Results

6.2.1. Participants' Characteristics and Sources of Information about HPV/HPV Vaccines

6.2.1.1. Pre-adolescents

A total of 1,160 pre-adolescents participated in the study; 969 (83.53%) pre-adolescents responded to both pre- and post-educational session questionnaires, while 191 (16.46%) adolescents responded either only to the pre- or the post- educational session questionnaire.

Table 1 reports the baseline characteristics of pre-adolescent participants. Both genders were equally represented, since about 53% of the participants were girls, who were almost all Italian and Catholic (98.2% and 91.2%, respectively). Regarding the use of social networks, the mostly used ones were Instagram and Facebook (53% and 31%, respectively).

The educational level of the parents was investigated: about 40% of the mothers and 38% of fathers had a high school diploma.

Regarding the source of information about STDs, the most cited was the school (58.9% of cases) and 70.3% of subjects knew about HPV infection, mostly from parents and their physicians (32.3% and 28.2%, respectively). Furthermore, almost all participants declared that they were informed about vaccines and remembered receiving them during childhood.

6.2.1.2. Parents of Pre-adolescents

Table 2 summarizes the baseline demographics and characteristics of the 161 participating parents of pre-adolescents. The median age of the enrolled parents was 44 years (25-75p = 40-53), with a median number of children equal to 2 (25-75p = 2-2). Almost all subjects were Italian and Catholics. The majority of the participants had a secondary school diploma (32.9%) and only 47.8% of subjects had an employment.

Of the total sample, 85.7% were mothers, of which 72.2% declared having Pap tests regularly. Of all the respondents, 6.2% had an HPV related disease.

The majority of the parents declared that their children received the recommended vaccinations during childhood and have heard about HPV before participating in the study (93.2% and 87%, respectively). Nevertheless, only 60.2% knew that HPV vaccines could also be administered to males.

Table 1. Baseline characteristics of the pre-adolescent participants.

Variables	N	%
Sex	-	-
<i>Female</i>	559	52.84
Birthplace	-	-
<i>Italy</i>	1043	98.2
Social Network usage	935	88
<i>Instagram</i>	494	52.9
<i>Facebook</i>	289	31
<i>Whatsapp</i>	141	15.1
<i>Musical.ly</i>	23	2.5
<i>Youtube</i>	14	1.5
<i>Twitter</i>	4	0.4
<i>Tik Tok</i>	2	0.2
<i>Snapchat</i>	1	0.1
Religion	1002	93.9
<i>Catholics</i>	966	96.4
<i>Evangelical</i>	21	2.1
<i>Orthodox</i>	10	1.0
<i>Muslims</i>	5	0.5
Educational qualification of mothers	-	-
<i>Primary School Certificate</i>	48	5.2
<i>Secondary School Certificate</i>	304	33.1
<i>High School Diploma</i>	365	39.8
<i>University Degree</i>	198	21.6
<i>Other</i>	3	0.3
Educational qualification of fathers	-	-
<i>Primary School Certificate</i>	42	4.6
<i>Secondary School Certificate</i>	335	36.5
<i>High School Diploma</i>	344	37.5
<i>University Degree</i>	193	21.0
<i>Other</i>	3	0.3
Have you ever been told about STD at home?	347	32.6
Have you ever been told about STD at school?	625	58.9
Has your doctor ever told you about STD?	201	18.9
Do you know what vaccines are?	1025	96.2
Do you remember receiving vaccinations during your childhood?	1029	96.4
Have you ever heard of HPV?	749	70.3

Table 1 contd....

Variables	N	%
If yes, who told you about HPV?	-	-
<i>Parents</i>	243	32.3
<i>Physician</i>	212	28.2
<i>TV</i>	108	14.4
<i>Internet</i>	78	10.4
<i>Friends</i>	43	5.7
<i>Newspapers</i>	11	1.5
<i>Radio</i>	6	0.8
<i>Teacher</i>	2	0.3
<i>Other</i>	99	13.2

Table 2. Baseline characteristics of the study’s parents of pre-adolescents participants.

Variables	N	%
Age, median (25-75p)	44 (40-49)	
Parenthood	-	-
<i>Mother</i>	138	85.7
<i>Father</i>	21	13.0
<i>Legal tutor</i>	2	1.2
Nationality	-	-
<i>Italian</i>	1581	98.1
Level of education	-	-
<i>Primary School Certificate</i>	11	6.8
<i>Secondary School Certificate</i>	53	32.9
<i>Professional-Technical Institute Diploma</i>	29	18.0
<i>High School Diploma</i>	41	25.5
<i>University Degree</i>	27	16.8
Worker	77	47.8
Religion	146	90.7
<i>Catholics</i>	145	90.1
Sons/daughters, median (25-75p)	2 (2-2)	
If female, do you have a Pap-test regularly?	112	80.0
Have you ever had an HPV-related disease?	10	6.2
<i>Genital warts</i>	9	90.0
<i>Cancer</i>	1	10.0
Have your family members ever been diagnosed for cancer (any location and cause)?	68	42.2
Have your children received all the recommended vaccinations during childhood?	150	93.2
Before participating in this project, had you ever heard of HPV infections?	142	88.2

Table 2 contd....

Variables	N	%
Before participating in this project, had you ever heard of HPV vaccines?	140	87.0
If yes, who told you about HPV?	-	-
<i>Family member</i>	11	7.9
<i>Friends</i>	30	21.6
<i>General Practitioner</i>	22	15.8
<i>Pediatrician</i>	68	48.9
<i>Gynecologist</i>	28	20.1
<i>Pharmacist</i>	4	2.9
<i>Newspaper</i>	9	6.5
<i>TV/Radio</i>	12	8.6
<i>Internet</i>	19	13.7
<i>Healthcare workers of a vaccine center</i>	24	17.3
<i>Information material of the local health agency</i>	15	10.8
Before participating in this project, were you aware that vaccines preventing HPV infections could also be given to males?	97	60.2

Table 3. Answers given by pre-adolescents to knowledge statements about HPV infection, related diseases, and prevention.

Knowledge Statement	Response	Correct		Do not Know		Wrong	
		n	%	n	%	n	%
HPV infection is transmitted through sexual intercourse.	true	904	84.9	31	2.9	130	12.2
HPV infection is widespread.	true	422	39.6	589	55.3	54	5.1
HPV infection can cause diseases such as cancers in both males and females.	true	504	47.3	497	46.7	64	6.0
HPV can cause genital warts.	true	181	17.0	837	78.6	47	4.4
Both males and females can be vaccinated against HPV.	true	923	86.7	3	0.3	139	13.0
The best age to be vaccinated against HPV is 11-12 years.	true	1,032	96.9	2	0.2	31	2.9
Subjects vaccinated against HPV can avoid using precautions (e.g. condom) during sexual intercourse.	false	531	49.9	13	1.2	521	48.9

6.3. Knowledge About HPV Infection and Vaccination at Baseline

6.3.1. Pre-adolescents

The majority of participating pre-adolescents knew at what age it was best to be vaccinated against HPV, the targets and the main transmission mode of HPV infection (96.9%, 86.7% and 84.9%, respectively) (Table 3).

The subjects showed suboptimal knowledge about the other investigated items, in particular the role of HPV in causing genital warts (only 17% answered correctly).

The overall mean knowledge score (number of correct answers/total of questions) was 0.6 ± 0.19 (95% C.I. = 0.59 - 0.61).

Table 7 shows the results of univariable logistic regression investigating the possible association between the characteristics of the participant pre-adolescent and the knowledge score. Pre-adolescent characteristics significantly related to knowledge scores higher than the 75th percentile were ‘the use of social networks’

($p=0.0076$), such as Instagram ($p=0.0136$), the educational level of parents, with lower scores related to primary school graduation ($p=0.0318$ estimated among mothers) and having heard about STDs at home and at school ($p<0.001$).

6.3.2. Parents of Pre-adolescents

Table 4 shows the parents’ answers to the 15 questions about their knowledge on HPV infection, its related diseases and prevention. The majority of the correct answers were about the HPV transmission mode and the asymptomatic nature of the majority of HPV infections (67.08% and 65.22% of subjects, respectively). Only 13.7% of the parents knew that HPV does not cause genital herpes and about one-third replied correctly to questions about the role of HPV in causing genital warts and their occurrence in both genders.

With respect to malignant diseases, only 54% of the participants reported cervical cancer as related to HPV.

Recommendation for HPV vaccine in adults and both genders was known by about 50% of the participants.

Table 4. Answers given by parents to knowledge statements about HPV infection, related diseases, and prevention.

Knowledge Statement	Response	Correct		Do not know		Wrong	
		n	%	n	%	n	%
Most people contract HPV infection during their lifetime.	true	50	31.1	93	57.8	18	11.2
Type of female cancer strongly associated with HPV: cervical cancer.	true	87	54.0	34	21.1	40	24.8
HPV can cause genital herpes.	false	22	13.7	100	62.1	39	24.2
HPV can cause genital warts.	true	55	34.2	96	59.6	10	6.2
Genital warts can only occur in females and not in males.	false	57	35.4	79	49.1	25	15.5
HPV is mainly transmitted through sexual intercourse or intimate mucosal contacts.	true	108	67.1	31	19.2	22	13.7
A person may have an HPV infection and not be aware of it.	true	105	65.22	43	26.7	13	8.1
HPV infection can be transmitted from mother to child during pregnancy and at the time of delivery.	true	33	20.5	84	52.2	44	27.3
HPV infection can only be transmitted if the carrier has the symptoms of the disease.	false	76	47.2	66	41.0	19	11.8
A Pap test with a normal result means you don't have HPV infection.	false	33	20.50	73	45.3	55	34.2
To avoid contracting HPV infection, it is sufficient to use condoms during sexual intercourse.	false	36	22.4	62	38.5	63	39.1
There are no specific therapies for HPV infection.	true	39	24.2	75	46.6	47	29.2
An HPV vaccine is available for the prevention of HPV-induced carcinomas in both males and females.	true	74	46.0	71	44.1	16	9.9
HPV vaccines can also be given to adults.	true	77	47.8	51	31.7	33	20.5
HPV vaccine is effective only if administered to subjects who are 12 years-old.	true	75	46.6	48	29.8	38	23.6

The overall mean knowledge score was 0.38 ± 0.20 (95% C.I. = 0.35 - 0.41).

Table 8 shows the results of univariable logistic regression investigating the possible association between characteristics of participating parents and knowledge score. Pre-adolescent characteristics significantly related to knowledge scores higher than the 75th percentile were a previous diagnosis of an HPV-related disease ($p=0.0002$), and a family member, the General Practitioner, the Gynecologist or newspapers as source of information about HPV infections and vaccine ($p=0.0377$, $p=0.0444$, $p<0.0001$ and $p=0.0148$, respectively).

6.3.3. The Effect of Education Interventions on Attitudes toward HPV Infection, Related Diseases and Prevention

6.3.3.1. Pre-adolescents

Of the adolescents, 84% showed a positive attitude (agreed or strongly agreed) about the role of HPV in causing serious diseases (Table 5). Also, the sentences “anti-HPV vaccines usefulness in preventing cervical cancer and warts” and “the importance that both males and females get vaccinated” obtained a strongly positive attitude by 89.5% and 90.7% respectively.

Instead, of the adolescents, 35.1% exhibited a neutral attitude and 18.8% were negative (disagree or strongly disagree) about the possibility of being exposed to HPV infection during their lives.

The majority of the participants showed a positive attitude toward the usefulness utility of talking about HPV infections and other STDs at home, at school and with their doctor.

The overall average attitude score resulted as being equal to 3.12 ± 0.52 (95% C.I. = 3.09 - 3.15).

Table 7 shows the results of univariable logistic regression analysis investigating the possible association between characteristics of pre-adolescent participants and attitude score. Pre-adolescent characteristics significantly related to knowledge scores higher than the 75th percentile were having heard about STDs at home, at school and from their physician ($p=0.0024$, $p<0.001$ and $p=0.0437$, respectively).

6.3.3.2. Parents of Pre-adolescents

The best positive attitude of parents was toward the importance of protecting their own child from any HPV related disease (85.1%) (Table 6). Other positive attitudes were related to the usefulness of discussing about HPV with a gynecologist (83.2%), the importance of vaccination before being sexually active to maximize its effectiveness (83.8%) and the importance of the ministerial recommendation for HPV vaccination for all pre-adolescents to comply with the vaccination program (83.2%). Parents demonstrated a neutral attitude (35.4%) or a negative attitude (disagree or strongly disagree) (19.2%) toward the chances of their daughter being exposed to HPV infection during lifetime.

Overall, the median attitude score was 3.05 (25-75 $p=2.8-3.4$).

Table 8 shows the results of univariable logistic regression investigating the possible association between characteristics of participant parents and attitude score. Pre-adolescent characteristics

Table 5. Attitudes of pre-adolescents toward HPV infections, related diseases, and prevention statements.

Attitude Statement	Strongly Agree		Agree		Neutral		Disagree		Strongly Disagree	
	n	%	n	%	n	%	n	%	n	%
I think that Papillomavirus (HPV) can cause serious diseases.	618	58.2	368	34.6	44	4.1	12	1.13	20	1.9
I think that over the course of my life I will be exposed to HPV infection.	128	12.1	362	34.1	372	35.1	141	13.3	58	5.5
I think it is useful to talk about HPV infections and other sexually transmitted infections at home.	356	33.55	403	38.0	219	20.6	54	5.1	29	2.7
I think it is useful to talk about HPV infections and other sexually transmitted infections at school.	362	34.1	420	39.6	190	17.9	56	5.3	34	3.2
I think it would be useful to talk to my doctor / pediatrician about HPV infections and other sexually transmitted infections.	344	32.4	426	40.1	244	23.0	34	3.2	14	1.3
I think anti-HPV vaccines are useful for preventing cervical cancer and warts.	634	59.7	316	29.8	77	7.2	21	2.0	14	1.3
I think the HPV vaccine is safe.	483	45.5	421	39.7	128	12.1	17	1.6	12	1.1
I think boys and girls of my age should be vaccinated against HPV.	688	64.8	275	25.9	75	7.1	9	0.8	15	1.4

Table 6. Attitudes of parents toward HPV related diseases and prevention statements.

Attitude Statement	Strongly Agree		Agree		Neutral		Disagree		Strongly Disagree	
	n	%	n	%	n	%	n	%	n	%
I think HPV is the main cause of cervical cancer.	31	19.2	83	51.5	37	23.0	9	5.6	1	0.6
I think my daughter has a high chance of being exposed to HPV infection during her lifetime.	15	9.3	58	36.0	57	35.4	22	13.7	9	5.6
I think it is possible that during my life I could be exposed to HPV infection.	37	23.0	80	49.7	33	20.5	9	5.6	2	1.2
I think that both males and females have a role in the transmission of HPV infection.	55	34.16	73	45.3	30	18.6	2	1.2	1	0.6
I think HPV can cause cancer in the anogenital area in both males and females.	53	32.9	68	42.2	35	21.7	4	2.5	1	0.6
I think it is important for me to be able to transmit to my child the information regarding HPV infection and the ways to prevent it taking into account my child's level of understanding.	70	43.5	56	34.8	30	18.6	3	1.9	2	1.2
I think my son/daughter's opinion on HPV vaccination is important in the decision to receive HPV vaccination.	45	27.95	62	38.5	36	22.4	11	6.8	7	4.3
I think it is important to acquire information about HPV infection and ways to prevent it to discuss these matters with other parents on the basis of objective data and without bias.	61	37.9	67	41.6	31	19.2	1	0.6	1	0.6
I think talking to the pediatrician / general practitioner about the HPV vaccine is useful.	55	34.2	72	44.7	30	18.6	3	1.9	1	0.6

Table 6 contd....

Attitude Statement	Strongly Agree		Agree		Neutral		Disagree		Strongly Disagree	
	n	%	n	%	n	%	n	%	n	%
I think talking to the Gynecologist about HPV vaccine is useful.	58	37.4	71	45.8	24	15.5	1	0.6	1	0.6
I think talking to healthcare professionals who are experts in vaccines at my local health agency on HPV vaccine is useful.	58	36.0	75	46.6	25	15.5	2	1.2	1	0.6
I think my son/daughter should receive information regarding HPV diseases and the related vaccine at school.	85	52.8	52	32.3	21	13.0	2	1.2	1	0.6
I think the recommendation to vaccinate all pre-adolescent males and females against HPV by the Ministry of Health through the National Vaccine Prevention Plan is important to facilitate the compliance.	76	47.2	58	36.0	20	12.4	6	3.7	1	0.6
I think vaccination against HPV before the start of sexual activity is important to obtain the best effectiveness.	74	46.0	61	37.9	24	14.9	2	1.2	0	0
I think it is important to protect my son/daughter from the development of HPV genital warts and carcinomas through HPV vaccine.	75	46.6	62	38.5	22	13.7	1	0.6	1	0.6
I think it is important to protect the future partner of my son/daughter from the development of genital warts and carcinomas caused by HPV through vaccination.	67	41.6	57	35.4	29	18.0	6	3.7	2	1.2
I think the reduction in the number of vaccine doses from three to two for pre-adolescent subjects improves compliance to HPV vaccine.	31	19.2	64	39.7	62	38.5	4	2.5	0	0
I think that receiving a proposal for an appointment by the vaccination service for the administration of both HPV vaccine doses instead of contacting the vaccination center to make the reservation improves compliance to the vaccination.	53	32.9	65	40.4	40	24.8	3	1.9	0	0
I think the available HPV vaccines are safe.	36	22.4	84	52.2	37	23.0	4	2.5	0	0
I think the available HPV vaccines are also effective for males.	44	27.3	83	51.5	28	17.4	5	3.1	1	0.6

significantly related to attitude scores higher than the 75th percentile were a previous diagnosis of an HPV-related disease (p=0.0002), and a family member, the General Practitioner, the Gynecologist and newspapers as source of information about HPV infections and vaccine (p=0.0377, p=0.0444, p<0.0001 and p=0.0148, respectively).

6.3.3.3. Intention to have one’s Son/daughter Receive the HPV Vaccine

Each group was asked to express to what level they intended to be vaccinated against HPV (on a scale from 0 to 10) both before and after an educational session/intervention. The pre- and post-intervention items were completed by 969 pre-adolescents and 161 parents.

The first group obtained an average score of 8.59 ± 1.70 (CI 95% 8.49 - 8.69) and 9.10 ± 1.43 (CI 95% 9.01 – 9.19) at the pre- and post-educational intervention, showing a statistically significant increase (p<0.0001).

The median pre-intervention score estimated in parents was 10 (25-75p = 8-10) and remained high after providing written information (median, 25-75p = 10, 7.8-10).

7. DISCUSSION

To our knowledge, this is the first study that examines, using the same methodology and an overall approach, knowledge, practices and attitudes toward HPV infection, its related diseases and STDs prevention in pre-adolescents of both genders and their parents in a developed country such as Italy, where an evolution in HPV vaccine target and public health objectives has been observed since its introduction in 2007. This has enabled us to understand and compare educational needs and attitudes toward HPV infection and prevention among the main HPV vaccine targets and their parents, since both of them are fundamental for the HPV decision-making process [70-74]. Previous studies have mainly focused on females and their mothers and revealed a somewhat passive approach by girls and a desire of acquiring information about HPV although mirroring their mother’s position [72]. Based on the current

Table 7. Knowledge and attitude scores stratified by pre-adolescent characteristics.

Characteristics	Knowledge Score >75 p		Knowledge Score <75 p		p-value	Attitude Score >75 p		Attitude Score <75 p		p-value
	N	%	N	%		N	%	N	%	
Sex										
<i>Female</i>	240	52.9	319	53.0	0.967	356	53.4	154	52.4	0.7764
Birthplace										
<i>Italy</i>	446	98.4	595	98.0	0.6003	661	98.7	286	96.9	0.0709
Social Network Use										
<i>Instagram</i>	238	57.3	254	49.2	0.0136	306	52.0	139	53.5	0.7025
<i>Facebook</i>	120	28.9	169	32.7	0.2086	193	32.8	70	26.9	0.0868
<i>Whatsapp</i>	57	13.7	84	16.2	0.2818	85	14.5	48	18.5	0.1391
<i>Musical.ly</i>	5	1.2	18	3.5	0.0257	19	3.2	4	1.5	0.1617
<i>Youtube</i>	5	1.2	9	1.7	0.5015	13	2.2	1	0.4	0.0543
<i>Twitter</i>	2	0.5	2	0.4	0.8269	0	-	2	0.8	0.0332
<i>Tik Tok</i>	0	-	2	0.4	0.2042	1	0.2	1	0.4	0.5526
<i>Snapchat</i>	1	0.2	0		0.2646	1	0.2	0	-	0.5058
Religion										
<i>Catholics</i>	413	96.3	551	96.5	0.8457	616	96.6	261	96.3	0.8416
<i>Evangelical</i>	10	2.3	11	1.9	0.6618	13	2.0	5	1.8	0.8782
<i>Orthodox</i>	4	0.9	6	1.0	0.8706	7	1.1	2	0.7	0.6652
<i>Muslims</i>	2	0.5	3	0.5	0.9197	2	0.3	3	1.1	0.1897
Educational qualification of mothers										
<i>Primary School Certificate</i>	15	3.5	33	6.7	0.0318	30	5.2	14	5.6	0.8152
<i>Secondary School Certificate</i>	134	31.5	170	34.5	0.3431	188	32.9	85	34.3	0.6945
<i>High School Diploma</i>	171	40.2	194	39.3	0.7848	239	41.8	95	38.3	0.3520
<i>University Degree</i>	103	24.2	95	19.3	0.0682	114	19.9	54	21.8	0.5479
<i>Other</i>	2	0.5	1	0.5	0.4785	1	0.2	0	-	0.5100
Educational qualification of fathers										
<i>Primary School Certificate</i>	16	3.8	26	5.3	0.2661	26	4.6	15	6.0	0.3644
<i>Secondary School Certificate</i>	146	34.3	189	38.5	0.1856	213	37.2	90	36.3	0.7963
<i>High School Diploma</i>	161	37.8	183	37.3	0.8705	209	36.5	98	39.5	0.4184
<i>University Degree</i>	101	23.7	92	18.7	0.0655	124	21.7	44	17.7	0.1996
<i>Other</i>	2	0.5	1	0.2	0.4820	0	-	1	0.4	0.1286

Table 7 contd....

Characteristics	Knowledge Score >75 p		Knowledge Score <75 p		p-value	Attitude Score >75 p		Attitude Score <75 p		p-value
	N	%	N	%		N	%	N	%	
Have you ever heard of STD at home?	203	44.5	144	23.7	<0.0001	240	35.7	76	25.8	0.0024
Have you ever heard of STD at school?	324	71.2	301	49.7	<0.0001	419	62.6	141	47.8	<0.0001
Has your doctor ever told you about STD?	96	21.0	103	17.0	0.0911	134	20.0	43	14.5	0.0437
Do you know what vaccines are?	444	97.4	579	95.2	0.0729	649	96.4	281	95.2	0.3844
Do you remember receiving vaccinations during your childhood?	448	98.2	579	95.1	0.0058	655	97.3	281	94.9	0.0585
Have you ever heard of HPV?	376	82.6	373	61.2	<0.0001	476	70.8	199	67.2	0.2608
If yes, who told you about HPV?										
<i>Parents</i>	135	35.4	108	29.1	0.0638	161	33.5	58	29.3	0.2821
<i>Physician</i>	100	26.2	112	30.2	0.2297	137	28.5	52	26.3	0.5473
<i>TV</i>	47	12.3	61	16.4	0.1084	71	14.8	29	14.6	0.9613
<i>Internet</i>	36	9.4	42	11.3	0.3999	46	9.6	27	13.6	0.1216
<i>Teacher</i>	0	-	2	0.5	0.1513	1	0.2	1	0.2	0.5171
<i>Friends</i>	19	5.0	24	6.5	0.3815	22	4.6	13	6.6	0.2888
<i>Newspapers</i>	4	1.1	7	1.9	0.3392	9	1.9	2	1.0	0.4176
<i>Radio</i>	2	0.5	4	1.1	0.3939	4	0.8	2	1.0	0.8232
<i>Other</i>	53	13.9	46	12.4	0.5398	66	13.8	27	13.6	0.9688

Table 8. Knowledge and attitude scores stratified by parent characteristics.

Characteristics	Knowledge Score >75 p		Knowledge Score <75 p		p-value	Attitude Score >75 p		Attitude Score <75 p		p-value
	N	%	N	%		N	%	N	%	
Age (median, 25-75p)	42 (34-51)		44 (40-49)		0.4569	44 (40-49)		45 (40-50)		0.5028
Parenthood	-	-	-	-	0.4958	-	-	-	-	0.1785
<i>Mother</i>	8	100	130	85	-	88	89.8	50	79.4	-
<i>Father</i>	0	-	21	13.7	-	9	9.2	12	19.1	-
<i>Legal Tutor</i>	0	-	2	1.3	-	1	1.0	1	1.6	-
Nationality	-	-	-	-	-	-	-	-	-	-
<i>Italian</i>	8	100	150	98.0	0.6893	95	96.9	63	100	0.1610
Scholarship	-	-	-	-	-	-	-	-	-	-

Table 8 contd....

Characteristics	Knowledge Score >75 p		Knowledge Score <75 p		p-value	Attitude Score >75 p		Attitude Score <75 p		p-value
	N	%	N	%		N	%	N	%	
<i>Primary School Certificate</i>	0	-	11	7.2	0.4320	5	5.1	6	9.5	0.2778
<i>Secondary School Certificate</i>	1	12.5	52	34	0.2074	18	18.4	35	55.6	<0.0001
<i>High School Diploma</i>	3	37.5	38	24.8	0.4229	29	29.6	12	19.1	0.1339
<i>Professional-Technical Institute Diploma</i>	1	12.5	28	18.3	0.6773	23	23.5	6	9.5	0.0246
<i>University Degree</i>	3	37.5	24	15.7	0.1074	23	23.5	4	6.4	0.0045
Worker	6	75	71	46.4	0.1145	52	53.1	25	39.7	0.0972
Religion	6	75	140	91.5	0.1175	93	94.9	53	84.1	0.0217
<i>Catholics</i>	-	-	-	-	-	-	-	-	-	-
Sons/daughters (median, 25-75p)	2 (1-2)		2 (2-3)		0.0510	2 (2-2)		2 (2-3)		0.7368
If female, do you have a Pap-test regularly?	6	75	106	80.3	0.8780	79	88.8	33	64.7	0.0028
Have you ever had an HPV-related disease?	3	37.5	7	4.6	0.0002	7	7.2	3	4.8	0.5309
Have your family members ever been diagnosed for cancer (any site and cause)?	2	25	66	43.1	0.3113	47	48	21	33.3	0.0667
Have your children received all the recommended vaccinations during childhood?	7	87.5	143	93.5	0.5145	94	95.9	56	88.9	0.0845
Before participating in this project, have you ever heard of HPV infections?	8	100	134	87.6	0.2885	88	89.8	54	85.7	0.4334
Before participating in this project, have you ever heard of the HPV vaccine?	7	87.5	133	86.9	0.9627	85	86.7	55	87.3	0.9170
Source of information?	-	-	-	-	-	-	-	-	-	-
<i>Family member</i>	2	28.6	9	6.8	0.0377	6	7.1	5	9.1	0.6774
<i>Friend</i>	1	14.3	29	22	0.6301	19	22.6	11	20	0.7136
<i>General Practitioner</i>	3	42.9	19	14.4	0.0444	11	13.1	11	20	0.2754
<i>Pediatrician</i>	2	28.6	66	50	0.2691	45	53.6	23	41.8	0.1753
<i>Gynecologist</i>	6	85.7	22	16.7	<0.0001	24	28.6	4	7.3	0.0022
<i>Pharmacist</i>	0	-	4	3.0	0.6403	3	3.6	1	1.8	0.5454
<i>Newspaper</i>	2	28.6	7	5.3	0.0148	9	10.7	0	-	0.0121
<i>TV/Radio</i>	1	14.3	11	8.3	0.5848	10	11.9	2	3.6	0.0896
<i>Internet</i>	2	28.6	17	12.9	0.2389	14	16.7	5	9.1	0.2036
<i>Healthcare worker of vaccine center</i>	1	14.3	23	17.4	0.8305	10	11.9	14	25.5	0.0387
<i>Informative material of the local health agency</i>	1	14.3	14	10.6	0.7598	12	14.3	3	5.5	0.1008
Before participating in this project, were you aware that vaccines preventing HPV infections could also be given to males?	5	62.5	92	60.1	0.8938	63	64.3	34	54	0.1917

universal HPV vaccine strategy and the need to increase the evidence base about pre-adolescent males, an overall approach is desirable.

Furthermore, HPV vaccine uptake rates have recently decreased in both genders and in many developed countries, including Italy [24]. Therefore, it has become crucial to educate pre-adolescents and their parents since better knowledge and a positive attitude are

proven to be positively associated with higher vaccine coverage [47].

With respect to pre-adolescents, our results revealed that, even though there is a moderate knowledge of HPV infection, its related diseases and vaccination in parents and pre-adolescents, there is a general positive attitude toward the importance of obtaining the vaccine and the seriousness of HPV related diseases even before the educational sessions. Moderate knowledge was especially found in

relation to the spread of HPV infection and the role of HPV in causing genital warts (39.6 and 17%, respectively). Statements on attitudes confirmed the suboptimal awareness in pre-adolescents of being exposed to HPV infection during their lifetime (53.8% were neutral or disagreed).

Furthermore, our data highlighted a higher proportion (70.3%) of school students reporting to have heard about HPV at baseline, than data recently reported in literature, such as comparable studies conducted in China by Liu CR *et al.* and Xue L *et al.*, who found that only 15.1% and 15.5% of subjects had heard about HPV, respectively [71, 75]. This result is quite in line with the mean knowledge score estimated through our survey ($60\% \pm 19\%$).

The willingness of pre-adolescents to receive information about STDs and HPV at home, at school, and by their physician was confirmed by the survey results. It is noteworthy that only 18.9% and 28.2% had heard about STDs and HPV, respectively, by their own physician and 72.5% declared that it was useful. This finding is interesting, since available evidence shows that healthcare provider recommendations is one of the major predictors of young subjects' willingness to get vaccinated [76-78].

The use of social networks was widespread (88% of the school students) and one of the main factors significantly associated with a higher knowledge score. This finding confirms the relevant role of Internet through which adolescents get health information and, in particular, of social media [79, 80]. Thus, providing correct and effective health information through social media may represent a helpful strategy to reach adolescents who are willing to improve their knowledge about health *via* social networks.

In addition, the intention score to obtain the HPV vaccine was high both at the beginning and at the end of the study and equally among pre-adolescents and their parents, and it increased significantly after the pre-adolescents had completed the post intervention questionnaire. This finding confirms the available evidence about the effectiveness of school-based education in increasing acceptability toward HPV vaccination in pre-adolescents [71].

The answers given by participating parents showed a largely suboptimal knowledge in the field of HPV infection and prevention, although the majority declared having heard about HPV infection and vaccine at baseline.

The lack of awareness about the spread of HPV infection observed in pre-adolescents was confirmed in adults through both knowledge and attitude statements (31.1% of correct answers and 46.2% of agreeing subjects). Only about one-third of the parents knew that HPV can cause common diseases such as genital warts and that genital warts can occur in both genders, showing only slightly better knowledge compared to pre-adolescents.

Of note, that indication for HPV vaccine in adult subjects was known only by about the half of participants.

Nevertheless, parents exhibited very high median attitude and intention scores (3.1 and 10) towards HPV and a high propensity toward primary and secondary prevention tools in general, since 80% of the participating mothers declared their regular adherence to cervical cancer screening and 93.2% of parents had their children vaccinated. These variables were consistently associated with higher attitude scores ($p=0.0028$ and $p=0.0845$, respectively). Our results were higher than those obtained in another Sicilian town where a survey investigating the attitudes in a sample of parents about vaccinations showed that 60% were favorable towards HPV vaccine [81].

Parents confirmed the interest shown by pre-adolescents in talking about HPV with physicians, such as General Practitioners/Pediatricians, Gynecologists and healthcare workers at immunization centers, with 78.9%, 83.2% and 82.6% of the subjects agreeing or strongly agreeing with the respective statements. This interest was aimed at transmitting correct information to their own

child and discussing with other parents about this topic, since only 66.5% of the parents take into account their son/daughter's opinion about the choice for vaccination. This is in line with the findings published by Perez S *et al.* who investigated Canadian parents' involvement in HPV vaccination decision for their children [82]: these authors found that the child's involvement was moderate. Family members and physicians as source of information about HPV were found to be statistically significantly associated with higher knowledge scores, thus demonstrating their educational role. Parents' attitudes were found to be strongly influenced by the favorable opinion of the physician also in a study recently conducted by Facciola *et al.* [81] and other similar studies [83-86].

Of relevance, a non-negligible and higher proportion (about 20%) of parents than pre-adolescents had a neutral attitude toward the performance of HPV vaccine in terms of effectiveness and safety. This finding is interesting because there is evidence that the perceived effectiveness and safety of vaccines have been described as relevant factors that contribute to vaccine hesitancy [63].

The main limits of the present study are the representativeness of the study population, since the results refer to two Southern Italian regions and are preliminary for parents, whose enrollment was particularly difficult. Furthermore, selection bias could have an impact on the participation of school students whose parents were more prone to vaccine compliance. Since few school students refused to participate in the study, the reasons for refusal were not investigated.

Nevertheless, relevant data useful to address counselling and vaccine hesitancy have been collected and further indepth investigations have been planned.

CONCLUSION

In conclusion, this study suggests that health education programs aimed at increasing knowledge and awareness about HPV infection, its related diseases and prevention of male and female pre-adolescents are needed to implement the outcomes of HPV immunization programs. The inclusion of parents in the evaluation of knowledge gaps and attitudes about HPV should be encouraged in order to obtain an exhaustive list of the factors that influence the decision-making process.

The role of physicians in providing counselling and recommendations for HPV vaccine target populations plays a crucial role together with school-based vaccination programs and social media in the case of pre-adolescents.

These results could support Public Health policymakers in implementing multicomponent interventions including organizational and educational strategies, which warrant a comprehensive approach to improve HPV vaccine compliance [24, 87].

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

In complying with the highest ethical standards, participants were informed that their participation was entirely voluntary and that they could withdraw at any moment. All data obtained through their participation was kept strictly confidential among the research team. In addition, an informed consent was obtained after explaining the nature of the study and its possible consequences.

The study protocol was approved by the Liguria Regional Ethics Committee (P.R. 162REG2017) for the study coordination center; and acknowledged by the Ethics Committee "Palermo 1" (Report n. 06/2017) and the Ethics Committee of the Local Health Agency "Lecce" (Report n. 19/2018).

HUMAN AND ANIMAL RIGHTS

No animals were used for this study and no experiments on human were conducted.

CONSENT FOR PUBLICATION

The written informed consent form included information about the possible use of data collected through the study questionnaires for research purposes.

AVAILABILITY OF DATA AND MATERIALS

The data used to support the findings of this study are available from the corresponding authors upon request.

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None.

CONFLICT OF INTEREST

Giancarlo Icardi is the principal investigator of this national multicentre study. The research staff included the fixed-term assistant professor funded by Sanofi Pasteur MSD. The other authors have no known competing financial interests nor personal relationships that could have appeared to influence the work reported in this paper.

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