

ORIGINAL ARTICLE

Universal proposal strategies of anti-HPV vaccination for adolescents: comparative analysis between school-based and clinic immunization programs

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Keywords

HPV • School-based • Adolescents • Prevention

Summary

Introduction. A promising approach to increase teenager's adherence to immunization against HPV is the administration of vaccinations within the school facilities. The Local Health Unit of Taranto experienced two different vaccine strategy proposals in the twelve-year-olds: the first one was the usual active call strategy in the outpatient clinic, while the second one provided the involvement of the schools in the area. The aim of the study is to evaluate the results of the proposed vaccination strategies in both sexes and in towns of different sizes in order to identify an effective path for achieving vaccine coverage improvement.

Methods. To estimate the number of anti-HPV vaccine doses administered in adolescents of the 2003 cohort, we used the computerized vaccination system data of the Apulia Region. Then, once analyzed, the data for anti-HPV vaccine were broken down by gender, vaccine strategy and size of the town of residence. Analyses performed by using STATA SE 14.

Results. The multiple logistic regression points out that, females (OR = 3.2; $p < 0.01$), living in small towns (OR = 1.3; $p < 0.01$) and school vaccination strategy (OR = 2; $p < 0.01$) increase the likelihood of completing the anti-HPV vaccine cycle in adolescents. The comparative assessment of anti-HPV coverage strategies, suggests that school vaccination has resulted in significantly better outcomes than outpatient clinic one, for all the groups considered (overall 72.3% vs 55.6%).

Conclusions. The involvement of school institutes can define a winning organizational model to get a wider adolescent's adherence to immunization programs, especially in bigger towns. The school vaccination strategy could improve anti-HPV vaccine adherence also in males, who perceives a lower HPV-related diseases risk than females.

Introduction

The human papillomavirus (HPV) infection is the more frequent sexually transmitted disease (STD) in the world [1]. A meta-analysis conducted on over one million women estimated that HPV infection worldwide was 11.7%, with a very high peak in the population under the age of 25 [2].

It has been amply described that the role of HPV in determining uterine cervix cancer [3-7] is the fourth cause of cancer among women and is responsible for approximately 275,000 deaths per year [8]. Recently it has developed a great interest in the relationship between HPV infection and some diseases in males, as invasive penile cancer. It has been estimated that 30% of the HPV-related cancers affects males, corresponding to 17,000 cancer cases per year in the European population [9].

The availability of effective vaccines against HPV offers the possibility to decrease morbidity and mortality rates associated with this pathology: an estimation based on 179 countries shows that the vaccination of 12 years old girls only (for a total of 58 million) would be

able to prevent 690,000 cancer cases, including 420,000 deaths [10]. Indeed, since the very first years of the introduction of HPV vaccination, various international organizations and scientific associations such as World Health Organization (WHO), the Atlanta Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP), the European Centre for Disease Prevention and Control (ECDC), recommended the administration to 11-12 years old girls with a catch-up between the age of 13 and 18 [11].

Subsequently, the quadrivalent vaccine demonstrated its effectiveness in preventing more than 90% of HPV-related male genital lesions [12] and different organizations have extended this indication to teenager males [13-15]. However this group is not considered by the WHO as a priority, especially in contexts with limited resources [16]. Currently, with about 120 national anti-HPV immunization programs for women [17], only USA, Canada, Australia, Austria, Croatia, Liechtenstein, Saxony and Czech Republic (the latter only for the catch-up) extended to the males the vaccination program [13, 18-21]. This is due to the fact that the cost-

benefit ratio of the anti-HPV vaccination in males varies considerably in relation to the duration of the protective effect induced by the vaccination, to the coverings reached in the female population and, of course, the cost of the vaccination [22, 23].

A promising approach in order to increase teenagers' adherence to the anti-HPV immunization is the administration of the vaccines within school institutes. In Sweden and some areas of the United Kingdom, Spain and Australia, the coverage of the complete anti-HPV vaccine cycle among teenagers reached optimal levels, mainly thanks to the school programs [24-28].

In the USA, the school programs in cooperation between local school system and public health department, greatly increased the adherence to different kinds of vaccines [29-31].

More than 50% of the European countries providing an organized anti-HPV vaccination program, mainly lean on school distribution-based strategy [32], although in the literature there are few comparative evaluations between schools and outpatient clinic interventions, in order to increase the coverage of this vaccination [33]. Particularly, the impact of the HPV vaccination program offered by schools wasn't adequately analyzed in relationship to the context the teenagers live in: the assessment of the vaccination strategy effectiveness should consider that, living in a rural area or in a big city can change the access to vaccines [34-36].

Since 2007 the Italian Health Authorities recommended the active and free anti-HPV vaccination offer for the 12 years old girls starting, entrusting the Regions with the task of deciding whether to extend the program to other categories [37]. The anti-HPV vaccine price reduction and the opportunity to reduce the number of doses needed to confer protection have allowed to expand target groups for immunization [23]. On 2014, Apulia and some other Italian Regions (Liguria, Sicily, Friuli Venezia Giulia, Molise and Veneto) introduced free vaccination for 12 year old males starting with those born in 2003, by using the quadrivalent vaccine and overlapping their vaccination schedule to the one of the female sex [38]. Currently, the goal to reach by the new National Immunization Program is the universal anti-HPV vaccination all over the Italian Regions [39].

The Local Health Unit of Taranto, experienced two different vaccine strategies: the first one is the usual active offer, performed by sending an invitation letter to target subjects' address, and the vaccine administered in the vaccine outpatient clinics; the second one involved secondary schools so that the vaccine was promoted and administrated within the school institutes.

In this context, at the end of the first year since the introduction of the universal vaccine, including teenager males, the goal of this work is to evaluate the vaccination strategies outcomes for both sexes and towns of different sizes in order to identify the most efficient path for a rapid achievement of optimal coverages.

Materials and methods

The anti-HPV vaccine has been offered to subjects born in 2003 by means of two different proposals:

10 vaccination centers, randomly selected, implemented the traditional active offer. The family of the target subjects received an invitation letter to go to the vaccination center for the immunization. The letter also contained information on benefits and risks of anti-HPV vaccination. This vaccination strategy doesn't need a date, but the teenagers and their parents can freely access to the outpatient clinic.

Other 14 vaccine centers involved the secondary schools in their jurisdiction. After acquiring the list of the enrolled students born in 2003, were organized counselling and anti-HPV vaccines promotional meetings with the participation of the Local Health Unit's healthcare professionals, the teachers, the students and their parents. During the meetings, planned outside of school time, the parents provided written consent for the vaccine administration within the schools. Both doses administration was scheduled within the schools during the class time. In order to estimate the number of anti-HPV doses administered to teenagers born in the period between January 1st and December 31st 2003, have been used the routine data of annual vaccines updated to December 31st 2016. The data were collected by infectious disease representatives of the Public Health Services and entered in the computerized vaccine registry of the Puglia region (GIAVA). To calculate the coverage has been used as reference population of those born in 2003, the one existing in the computerized vaccination registry system GIAVA, (data updated on December 31st 2016).

The anti-HPV vaccine coverage has been analyzed based on gender, vaccine strategy and size of the town. For this last feature, was considered the data of the resident population as of January 1st 2016 from the National Institute of Statistics, which allowed to classify the districts in small and big centers assuming a population of 30,000 as a cut-off (maximum limit of patients for the general medicine functional aggregation in Italy [40]).

Quantitative variables were identified as medians of the samples, with the related interquartile range, while qualitative variables were expressed as proportions with a 95% confidence interval. Mann-Whitney rank-sum test has been used for the median values comparison, while the chi-squared test has been used for the proportions comparison.

We assessed the possible correlations among the explored variables by defining double-entry contingency tables and calculating Chi-Square (Chi2) and Odds Ratio (OR) with 95% CIs. The variables considered in univariate analyses were evaluated in a logistic regression model to study the relationship between the vaccination coverage and the explanatory variables, while adjusting for confounding factors and effect modification if needed. OR with 95% CI was used to evaluate the strength of an association. The significance level was considered when $p < 0.05$. Analyses were performed by using STATA SE 14 for Mac OS.

Results

In the Local Health Unit of Taranto, there are 5720 subjects belonging to the 2003 cohort. The sample distribution by gender, town size and vaccination strategy it's quite uniform as shown in Table I.

The complete cycle administration coverage of the anti-HPV vaccine for the 2003 cohort it's 63% (n = 3603; 95% CI = 61.7-64.2%). The interval median between the 2 doses administration for those teenagers who completed the cycle is 194 days (p25-p75 = 184-225).

In the univariate analysis, the female sex, living in a small town and the school vaccine strategy increase the likelihood of anti-HPV vaccine cycle completion for teenagers (Tab. II).

The multiple logistic regression confirms the existence of these connections, that are more evident for the female sex (OR = 3.2; 95% CI = 2.8-3.5; $p < 0.01$) and for the school strategy (OR = 2; 95% CI = 1.8-2.3; $p < 0.01$), rather than small towns (OR = 1.3; 95% CI = 1.1-1.4; $p < 0.01$) (Tab. III).

The coverage for the teenagers immunized at school is 84.5% (n = 1089/1289; 95% CI = 82.5-86.5%) for the females and 59.7% (n = 741/1241; 95% CI = 57-62.4%) for the males (Fig. 1).

Tab. I. 2003 cohort teenagers characteristics. Taranto Local Health Unit (n = 5720).

Gender	N	%
Male	2861	50.02
Female	2859	49.98
District size		
Small	2404	42.03
Big	3316	57.97
Vaccine strategy		
School	2530	44.23
Clinic	3190	55.77

By considering the town size as a discriminating parameter, the coverage reached by school vaccination is 71.7% (n = 1066/1487; 95% CI = 69.4-74%) in the small towns and 73.2% (n = 764/1043; 95% CI = 70.6-75.9%) in the big ones.

The comparative evaluation of the coverage, by considering the different vaccination strategies shows that the school vaccination leads to significantly better results than the outpatient clinic one, for all the considered groups (Fig. 1).

The proportion of subjects who did not completed the vaccine cycle, after receiving the first dose, is 15% of those vaccinated in the outpatient clinics (n = 314/2087; 95% CI = 13.5-16.7%) and 8.5% of those immunized at school (n=169/1999; 95% CI = 7.3-9.8%); that is a significant difference according to the Chi square test ($\chi^2 = 42.6$; $p < 0.01$).

The median of the interval time between the two doses, for those who completed the cycle, is 184 days (p25-p75 = 183-209) for the vaccines administrated in school, and 217 (p25-p75 = 196-259) for the vaccines administrated in outpatient clinic; that is a significant difference according to the Mann-Whitney rank sum test ($p < 0.01$).

Discussion and conclusions

After one year since the introduction of the global immunization, the comparative analysis between the school and the outpatient anti-HPV immunization programs gives interesting and useful information to keep in mind for setting the most effective vaccination strategy. The anti-HPV school vaccination for the 12 year olds in the Taranto Local Health Unit has been far more effective than the outpatient one, leading to the best overall results. The gap between the coverage, got by the two strategies is 16% for both genders. This result it's aligned with the data existing in the literature, confirming that school vaccination is associated to better coverage [41], and clearly showing that school institutes could

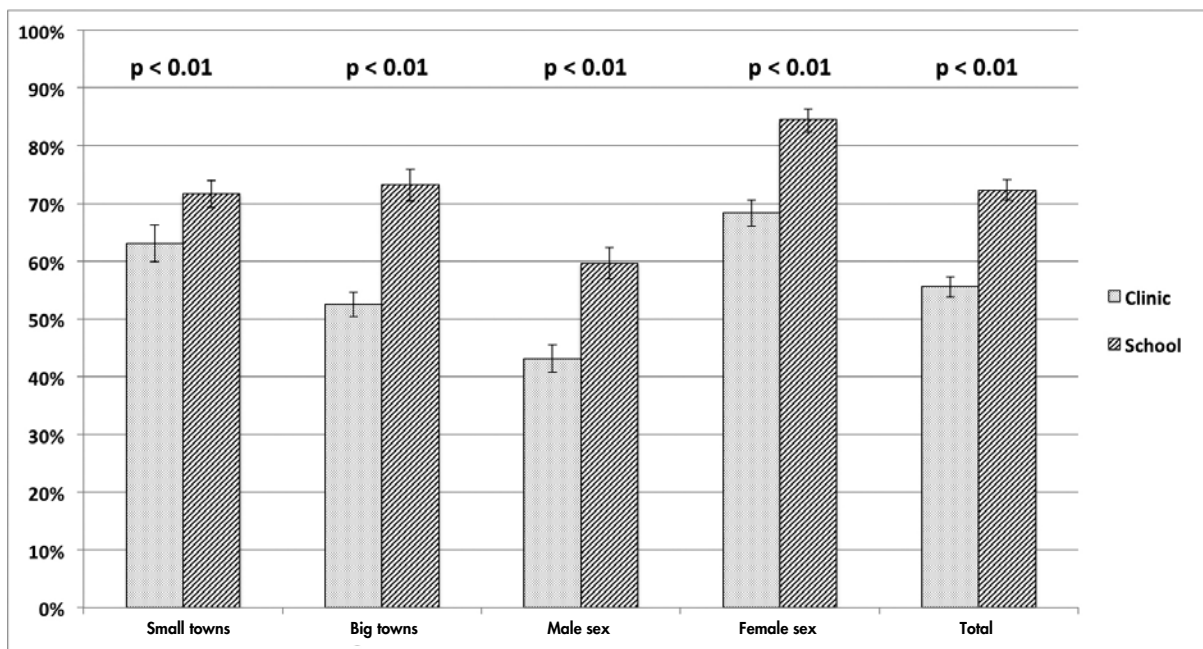
Tab. II. Univariate analysis about determinants of HPV vaccination, Taranto Local Health Unit, 2003 cohort (n = 5720).

Gender	N	%	OR (95% CI)	χ^2	P value
Female	2164	60.1%	3.1 (2.7-3.4)	392.8	0.00
Town size					
Small	1645	45.7%	1.5 (1.3-1.7)	52.6	0.00
Vaccine strategy					
School	1830	50.8%	2.1 (1.9-2.3)	169.9	0.00

Tab. III. Multivariate analysis about determinants of HPV vaccination, Taranto Local Health Unit, 2003 cohort (n = 5720).

Gender	z	OR (95% CI)	P value
Female	19.6	3.2 (2.8-3.5)	0.00
District size			
Small	3.7	1.3 (1.1-1.4)	0.00
Vaccine strategy			
School	11.5	2 (1.8-2.3)	0.00

Fig. 1. Coverage for anti-HPV complete cycle. Taranto Local Health Unit, 2003 cohort, by gender and town size.



be the key to getting greater participation to teenage vaccination programs.

That's especially important for males, since the coverage it's significantly lower than the one recorded for females. The males, according to other previous studies, are in fact associated to a lower chance of completion of the anti-HPV cycle [42]. The main limiting reason which adversely affects the prevention campaign against the HPV-infection in men, it could be the lack of risk perception connected to this STD [43]. That's why the school vaccination, by means of a more direct and effective counselling activity, could be an important promotional way to the immunization and adhesion to the anti-HPV vaccine among the teenagers [44]. Meetings with healthcare professionals about vaccine counselling represents a better approach compared to the traditional invitation letter to the outpatient clinic and allows to show in a thorough way the benefits of vaccination, especially for the males.

The impact of the anti-HPV school administration strategy it's particularly evident in towns with more than 30,000 people, where there is an increase in coverage of 20.5% compared to the outpatient vaccination. Right in those contexts in which the study found the greatest difficulties in reaching the target population of the vaccine offer, the school proposal has been undoubtedly effective. A possible interpretation may be the greater accessibility of school vaccination, this hypothesis is also supported by other data such as the reduced number of teenagers who didn't complete the vaccine cycle after receiving the first dosage and the median interval shortening between the two doses.

It should be underlined that the reported coverage estimate for school vaccination, also include the catch-up doses administrated in outpatient clinics to those school children who were absentees when the school vaccination was scheduled. In addition, those who were already privately vaccinated before 2014, were excluded from the calculation.

To set up a school vaccination campaign needs a considerable organizational effort. First, the vaccinations must be performed in compliance with the best safety standards: healthcare professionals must have Pediatric Basic Life Support and Defibrillation (P-BLSD) certifications, as well as a portable pharmacological and instrumental kit for emergencies. In the future, it will be important the cooperation with the schools to set up permanent outpatient clinics for all the students' health needs, including vaccinations. Moreover it's proper to allow real time access to the computerized vaccine registry, data entry from a laptop and a dedicated network connection.

Anyway, the school is the best place to perform health promotion and collective health education programs against vaccine-preventable diseases. Some countries included the school vaccination strategy into a wider school-based health approach, thus improving the impact of those interventions [45].

In this regard, integrating the health promotion and school vaccination programs seems to be the most sustainable solution also with regard to human resources management, especially if it's associated with teacher's involvement. Furthermore the healthcare professionals in schools could administrate much more vaccinations than

in the outpatient clinics, since they could save time by doing counselling vaccination in a single group session. The Taranto Local Health Unit experience suggests that the school is the ideal context to get the wider adherence to the anti-HPV immunization programs. The most important factors for the success of the school-based vaccination strategy are the “good” relationships between the Local Health Unit and the Local School management, the working skills improvement and the communication with the students and their parents. If the application of the aforementioned organizational model to different contexts and wider samples will confirm the outcomes, it could be adopted as a regional or national strategic plan able to oppose the hesitancy and stimulate resilience phenomena to vaccination.

Acknowledgments

We wish to thank Dr. Augusto Giorgino who coordinates the school vaccinations, all the healthcare professionals of the Taranto Local Health Unit and Dr. Antonio Mignini who revised the English version of the manuscript. This research did not receive any specific grant from any funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that there is no conflicts of interest of a financial, personal or any other nature that could affect or bias their research.

Authors' contributions

AG and MC conceived and designed the study. CR, TB and GC performed a search of the literature on epidemiology of HPV related-diseases and anti-HPV vaccination proposal strategies. FD carried out statistical analysis and wrote the first draft of the manuscript. All authors read and approved the final version of the manuscript.

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■ Received on March 19, 2017. Accepted on April 13, 2017.

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