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Health and economic impact associated with a quadrivalent HPV vaccine in Italy

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ABSTRACT

Objective. The aim of this study was to determine the health impact and cost-effectiveness of introducing a human papillomavirus (HPV) vaccination programme with a quadrivalent vaccine alongside the existing cervical cancer screening programme in comparison to the current context in Italy.

Methods. A US Markov model was adapted to the Italian context, assuming under base case 80% vaccine coverage rate, lifetime duration of protection in a cohort of girls aged 12 years and discount rates of 1.5% and 3% for health benefits and costs, respectively, and estimating direct medical costs.

Results. The HPV vaccination in association with the current screening programme would allow to avoid 1432 cases of cervical cancer (−63.3%) and 513 deaths (−63.4%) compared to screening only, with an incremental cost-effectiveness ratio (ICER) of €9569 per additional quality-adjusted life-year (QALY) gained. The sensitivity analysis highlighted that this model was robust to all parameters presenting uncertainties as the ICERs ranged from €2,781 to €48,122 per QALY gained.

Conclusion. This study showed that HPV vaccination in adolescent girls would be a beneficial and cost-effective public health programme in Italy.

Introduction

Worldwide, cervical cancer is the second most common cancer in women [1]. Each year, 500,000 new cases of cervical cancer are estimated to occur, resulting in 260,000 deaths in 2005 [2].

HPV is a necessary cause of cervical cancer [3] and contributes to the development of a number of other cancers including anogenital carcinomas (vulvar, vaginal, anal and penile) and head/neck cancers [4], as well as genital warts [5]. In particular, high-oncogenic risk HPV types 16 and 18 are the most common cause of anogenital carcinomas and account for approximately 75% of all cervical cancers [6]. Low risk HPV types 6 and 11 are responsible for about 90% of genital warts [7], but are not commonly associated with cancer [8].

In Italy, a cervical cancer screening programme has been implemented to reduce the rates of cervical cancer incidence and the associated mortality. Women aged between 25 and 64 years are recommended to be screened every 3 years to detect and treat precancerous cervical lesions (cervical intraepithelial neoplasia or CIN) before the development of cervical cancer [9]. Despite important benefits due to the cervical cancer screening programme, about 3000 cervical cancers are still annually diagnosed [8,10] and about 1200 women die from this disease in Italy [8]. This screening programme nevertheless presents some limits as 29% of Italian women are never screened over their life [11].

Two prophylactic vaccines, which target HPV types 16 and 18 (Cervarix®[1]) and HPV types 6, 11, 16 and 18 (Gardasil®[2]) have been shown to be highly effective in clinical trials [12–14]. As clinical benefits are expected to occur in different time perspectives (short, medium and long terms), the use of a mathematical model could be particularly helpful for policymakers in order to make recommendations on HPV vaccination programme. Thus, several studies on the cost-effectiveness of HPV vaccination programmes were developed worldwide to assess the impact of local HPV prevention strategies, like in the US [15], Canada [16], the UK [17,18] and Switzerland [19]. In Italy, Capri et al. [20] studied the impact of introducing a HPV vaccination programme with a bivalent vaccine in association with the current local screening context. As a quadrivalent vaccine was also available, the objective of this study was to determine the health impact and cost-effectiveness of an HPV vaccination programme with a quadrivalent vaccine in addition to the existing cervical cancer screening programme in Italy.

Materials and methods

Model design

A previously published and validated US Markov model [21,22], simulating the natural history of HPV infection and cervical cancer as

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[1] Cervarix® is a registered trademark of GlaxoSmithKline.
[2] Gardasil® is a registered trademark of Merck & Co., Inc.

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well as estimating the economic consequences of HPV-related diseases, was recently adapted to the UK [17]. The structure of this revised model was subsequently adapted to Italy in order to reflect the local screening and treatment patterns. The model was programmed using the software TreeAge Pro®[3].

In this model, a cohort of 280,000 girls aged 12 years [23] moved during their lifetime in annual cycles through different health states based on cervical cytology and histology. These health states are defined from the natural history of HPV infection: well state, non cervical cancer-related hysterectomy, HPV infection, mild cervical intraepithelial neoplasia (CIN 1), moderate cervical intraepithelial neoplasia (CIN 2), severe cervical intraepithelial neoplasia or carcinoma in-situ (CIN 3), undiagnosed and diagnosed invasive cervical cancer (stages I–IV defined by the Fédération Internationale de Gynécologie et d'Obstétrique-FIGO), cervical cancer survival, death from cervical cancer and death from other causes. Movements through the health states were based on yearly transition probabilities derived from published literature (Table 1) and calibrated to reflect Italian epidemiology. Women who did not have CIN or cervical cancer were faced to an age-specific risk for developing genital warts.

Model outcomes

The model compared two scenarios:

- cervical cancer screening alone (current context),
- HPV vaccination with a quadrivalent vaccine in association with the existing Italian cervical cancer screening.

The model estimated the incidences of detected precancerous lesions and cervical cancer, cervical cancer mortality rate, lifetime risks of precancerous lesions and cervical cancer, deaths due to cervical cancer, remaining life expectancy and quality-adjusted life-years (QALYs). The model also estimated the total direct medical costs related to the cervical cancer screening, the HPV vaccination programme and the HPV-related diseases management. Annual discount rates of 3% and 1.5% were respectively used for costs and benefits.

The incremental cost-effectiveness ratios (ICERs) were obtained by dividing the incremental costs by the incremental health outcomes (number of life-year gained (LYG) or QALY gained). The LYG was calculated as the difference in the number of estimated deaths between both strategies multiplied by the remaining life expectancy. The QALY combined, in a single measure, gains or losses in both quantity of life (mortality) and quality of life (morbidity).

Costs were presented from the Italian Health Care Provider perspective, including only collective payments by the Italian Health Care System.

Data sources and inputs

Natural history of HPV

This model has been previously adjusted from a US study to the UK [17]. Then to make it suitable for the Italian situation, we first customized its structure in order to reflect the local screening and treatment patterns. In a second step, the model was populated with Italian epidemiological data when available in the published literature. Then, it was empirically calibrated in a hierarchical way to fit HPV prevalence rate [24] as well as age-specific incidence and mortality rates of cervical cancer, as observed among the Italian screened population [25]. Although it has been assumed that the underlying natural history of cervical cancer is fundamentally the same across countries, it is well acknowledged that the patterns of sexual behaviour and the age of sexual debut may vary [26]. To reflect this variation, we adjusted the incidence rates of HPV infection. Yearly transition probabilities used in the model were derived from Kulasingam et al. [17] and are presented in Table 1.

Epidemiological parameters

Women who underwent non cervical cancer-related hysterectomy would not develop cervical cancer and were controlled for in the model. Age-specific incidence rates of hysterectomy in Italy were drawn from Materia et al. [27] and estimated to be 0% below the age of 35, 0.504% between 35 and 49 years of age and 0.295% for 50 years of age and older.

No data concerning yearly survival rates were available for patients with cervical cancer in Italy. Therefore, these parameters were derived from the UK as the 5 years survival rates reported for these two countries in EUROCARE-3 study were similar [28]. Age-specific

Table 1
HPV natural history parameters

Parameters	Ages (years)	Annual transition probabilities
HPV infection		
Well to HPV infected state [54]	16	0.0200
	17	0.0500
	18	0.0700
	19	0.1300
	20–21	0.1600
	22	0.1200
	23–29	0.1100
	30–33	0.0400
	34–49	0.0330
	50+	0.0100
HPV infection to CIN 1 or CIN 2 [54]	All	0.0959
HPV infected state to well [21,54]	12–29	0.5333
	30–34	0.3333
	35–39	0.2733
	40–49	0.1800
	50+	0.0666
Proportion of SIL that are CIN 2 [21,54]	All	0.1350
CIN		
CIN 1 to CIN 2 [54]	16–34	0.0297
	35+	0.1485
CIN 1 to CIN 3 [54]	All	0.0301
CIN 1 to HPV infected state [54]	16–34	0.2248
	35+	0.1124
Proportion CIN 1 regressing directly to well [54]	All	0.9000
CIN 2 to CIN 3 [54]	16–34	0.0389
	35–44	0.0800
	45+	0.1062
CIN 2 to CIN 1 [54]	All	0.2430
CIN 2 to well or HPV infected state [54]	All	0.1901
Proportion CIN 2 regressing directly to well [54]	All	0.9000
CIN 3 to CIN 1 [54]	All	0.0000
CIN 3 to CIN 2 [54]	All	0.0135
CIN 3 to well or HPV infected state [54]	16–24	0.0150
	25–44	0.0135
	45+	0.0100
Proportion CIN 3 regressing directly to well [54]	All	0.5000
CIN 3 to invasive cervical cancer [54,55]	All	0.0105
Cervical cancer		
Probability of symptoms [21,54]		
Figo stage I		0.12
Figo stage II		0.21
Figo stage III		0.60
Figo stage IV		0.90
Progression and time of progression between [21,54]		
Figo stage I and II		0.90/48 months
Figo stage II and III		0.90/36 months
Figo stage III and IV		0.90/24 months

CIN: cervical intraepithelial neoplasia; SIL: squamous intraepithelial lesion.

[3] TreeAge Software Inc., Williamstown , MA, USA.

Table 2
Sensitivity and specificity of screening, unit costs and utility values

Sensitivity and specificity of tests used	
Pap test	
Sensitivity [26]	0.610
Specificity [22,26,56]	0.957
HPV DNA test [57]	
Sensitivity	0.948
Specificity	0.673
Colposcopy	
Sensitivity [58]	0.900
Specificity [22,58,59]	0.480
Biopsy	
Sensitivity [58]	0.900
Specificity [22,58,59]	1.000
Cost parameters (in €)	
Unit costs including gynaecologist visit [60]	
Pap test	24.70
Colposcopy	101.00
Biopsy	24.80
Treatment costs [60]	
CIN 1	686.00
CIN 2	1242.00
CIN 3	1763.00
FIGO I	7736.00
FIGO II	12,836.00
FIGO III	13,485.00
FIGO IV7	9278.00
Genital warts [41]	385.00
Vaccine and administration cost (per dose): [42,43]	
Vaccine cost	106.00
Vaccine administration	5.30
Utility values and duration [61,62]	
Genital warts	0.91 (85 days)
CIN 1	0.93 (2 months)
CIN 2/3	0.87 (2 months)
FIGO I–IV	0.67 (5 years)

ASCUS: atypical squamous intraepithelial lesion, LSIL: low-grade intraepithelial lesion, HSIL: high-grade intraepithelial lesion, CIN: cervical intraepithelial neoplasia.

mortality rates from all causes in the general female population were based on World Health Organization (WHO) estimates [29].

Owing to a lack of age-specific incidence rates for genital warts in Italy, we used figures based on a French prospective, multi-centre, observational cross-sectional study [30].

Impact of HPV-related diseases on Quality of Life (QoL)

Utility scores are necessary to calculate QALY. Since no Italian data were available at the time of the analysis, we therefore used utility scores derived from a US study [31].

Cervical cancer screening programme

In Italy, cervical cancer screening is recommended every 3 years for women aged 25–64 years [9]. Age-specific screening coverage rates were extracted from a recent survey conducted by the Institute of National Statistics (ISTAT) for the year 2004–2005 [9]. For women aged less than 25 years, we assumed a screening coverage rate of 10%. Moreover, we took into account that 29% of Italian women are never screened over their life [11].

Vaccine efficacy and vaccine coverage rate

In clinical trials, the quadrivalent HPV vaccine prevented up to 100% of cervical cancer, cervical, vulvar and vaginal precancerous lesions and genital warts due to HPV types 6, 11, 16 and 18 [32,33]. Based on these results, we used a 100% efficacy of the vaccine against cervical cancer, CIN 1–3 and genital warts caused solely by HPV types 6, 11, 16 and 18. Moreover, considering the efficacy data reported with 4 years of follow-up in phase III trials, and demonstration of immune memory [34], it appeared very likely that duration of protection could be lifelong without the need for a booster. This assumption was consistent with recently published modelling analysis [16,35]. Vaccine coverage was assumed to be 80% for the entire cohort of Italian girls aged 12 years.

Costs parameters

Only direct medical costs, including physician visits, exams, drugs and hospitalizations were considered in our analyses. Data concerning management and costs of cervical cancer, CIN, genital warts and screening in Italy were obtained from different sources (Table 2).

A survey collecting epidemiological data related to the number of positive, negative and unsatisfactory Pap tests as well as the number of CIN 1, 2 and 3 confirmed by biopsy was performed by the Italian Group for Cervical Cancer Screening (GISCi) [36]. The typical disease management implemented after an abnormal Pap test was derived from the screening guidelines of Emilia Romagna Region [37] and Società Italiana di Colposcopia e Patologia Cervico-Vaginale [38]. Then, collected epidemiological information was combined with unit costs to assess the costs related to Pap tests and the treatment of CINs.

Despite the limits of this method, the costs of cervical cancer by FIGO stage was based on a typical management derived from national and international guidelines [10]. The annual costs of treating cervical cancer include the treatment and follow-up during the first year. Inpatient unit costs were drawn from fees (based on diagnosis-related group) reimbursed in the Lazio Hospital Discharge

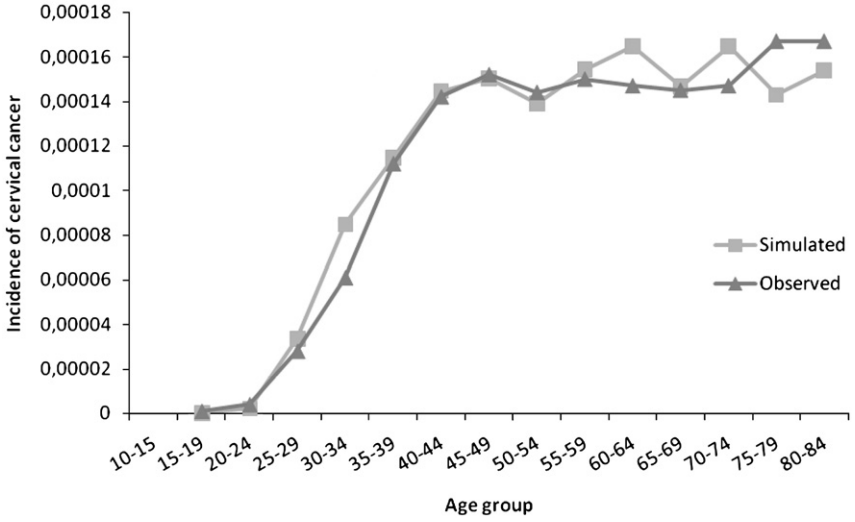

Fig. 1. Model-predicted and observed cervical cancer incidence in a screened population in Italy [25].

Table 3
Health outcomes and cost-effectiveness results

Outcomes	Current screening	HPV vaccination +current screening	Incremental outcomes	Variations (%)
Health outcomes (per cohort)				
Abnormal Pap test	148,238	128,437	19,801	−13.4%
Genital warts	20,989	6178	14,810	−70.6%
CIN 1	21,888	17,633	4255	−19.4%
CIN 2	9582	5150	4432	−46.3%
CIN 3	10,976	5771	5205	−47.4%
Cervical cancers	2262	830	1432	−63.3%
Cervical cancer deaths	809	296	513	−63.4%
Cost-effectiveness outcomes				
Total direct costs (€ per patient)	179.10	394.40	215.30	–
LYG (per patient)	42.0973	42.1148	0.0175	–
ICER (€/LYG)	–	–	12,303	–
QALY (per patient)	42.0889	42.1114	0.0225	–
ICER (€/QALY)	–	–	9,569	–

CIN: cervical intraepithelial neoplasia, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year.

Registry [39], whereas outpatient procedure costs from National Tariff Formularies [40].

A national study was conducted to assess the cost of genital warts in Italy. In this study involving a total of 28 investigators and 152 women aged 14–64 years, with newly diagnosed, recurrent or resistant genital warts [41], mean annual direct medical costs per women were estimated to be €332 for new cases.

The price of one dose of the quadrivalent HPV vaccine was assumed to be €106. As three doses are required to complete a course, the total vaccine cost for each individual is €318. The cost of administration per dose was estimated to be €5.30 [42,43]. A separate scenario examined the impact of adding a booster vaccine after 10 years. A single booster vaccine was assumed to cost €106. This would be administered within the primary care setting at a cost of €5.30.

Sensitivity analysis

One-way sensitivity analyses were performed since some parameters, such as vaccine efficacy, duration of efficacy, screening coverage rate, discount rates, administration and treatment costs, Pap test sensitivity and utilities, present some uncertainties.

Results

Validation of the model

Probabilities of becoming infected with HPV and yearly transition probabilities from CIN 3 to cervical cancer health states were calibrated empirically to fit with epidemiological data observed in Italy. Our model predicted an HPV infection prevalence of 8.7% in women aged between 25 and 70 years, which is consistent with the 8.8% observed in the same age group in Ronco et al. [24]. Projections of the model also indicated comparable age-specific cervical cancer incidence (Fig. 1) and mortality rates in Italy. Indeed, our model estimated an age standardised incidence rate of 9.5/100,000 for cervical cancer in a screened population whereas the observed rate was 9.7/100,000 [25].

Table 4
Health impact of different cervical cancer screening strategies

Strategies	Cancer cases	Δ*	Deaths	Δ*
Current screening programme	2262	–	809	–
Screening+20%	2045	218	722	86
Vaccine+Screening every 5 years	967	1295	351	457
Vaccine+Screening −20%	898	1364	323	485
Vaccine+Screening base	830	1432	296	513
Vaccine+Screening+20%	751	1512	264	544

* In comparison to the current screening programme. A coverage rate of 80% and lifelong duration of protection were assumed.

Table 5
Impact of sensitivity analysis on ICER

Parameters	ICER (€/QALY gained)
Base case	9569
Vaccine efficacy duration	
20 years protection with booster	30,341
Lifetime protection with booster	15,830
20 years	19,636
Vaccine efficacy	
80%	11,759
Screening coverage rate	
−20%	10,090
+20%	9029
Discount rates (for cost/benefits)	
0/0%	2781
5/0%	4912
3/0%	4485
3/3%	19,053
5/5%	48,122
Administration costs	
−20%	9450
+20%	9672
CIN and CC treatment costs	
−20%	7769
+20%	11,369
Pap sensitivity for detection of CIN 1	
50%	9499
Pap sensitivity for detection of CIN 2/3	
55%	9157
75%	10,381
Exclusion of genital warts	10,507
Utilities	
Cervical cancer utilities from Goldie et al. [63]	9280
Genital warts utilities (duration of 6 months)	9162
Time with disease −50%	9698
Time with disease +50%	9443

Base case

Health impact of a quadrivalent HPV vaccination programme

Under base case assumptions, the model projected that a quadrivalent HPV vaccine would prevent 1432 cervical cancer cases (−63.3%), 513 deaths from cervical cancer (−63.4%), 5205 diagnosed CIN 3 (−47.4%), 4432 diagnosed CIN 2 (−46.3%), 4255 diagnosed CIN 1 (−19.4%), 14,810 genital warts (−70.6%) and 128,437 abnormal Pap tests (−13.4%) (Table 3).

Although this study was not specifically designed to estimate the number needed to vaccinate (NNV) to avoid one HPV-related outcome, the model predicted a NNV corresponding to 148 to prevent one cervical cancer case. Moreover, values of NNV equal to 21 and 15 for CIN 2/CIN 3 and genital warts have been outputted, respectively.

Incremental cost-effectiveness ratios (ICERs)

Introducing a vaccination programme with a quadrivalent HPV vaccine alongside the current cervical cancer screening programme in Italy would result in ICERs of €12,303 per LYG and €9569 per QALY gained from direct health care cost perspective (Table 3).

Health impact of a quadrivalent HPV vaccination programme observed with different cervical cancer screening scenarios

The impact of different screening strategies associated or not with vaccination was also considered. In our base case analysis, 1432 incremental cases of cervical cancer and 513 incremental deaths could be avoided thanks to the introduction of HPV vaccination compared to the current screening programme alone (Table 4). If the screening

coverage rate was increased by 20% without HPV vaccination, only 218 incremental cases of cervical cancer and 86 incremental deaths from cervical cancer could be avoided. If the screening coverage rate decreased by 20% after the vaccination programme implementation, 1364 additional cancer cases and 485 additional deaths could be avoided.

Sensitivity analyses

Several one-way sensitivity analyses were performed by varying key parameters. The results of these analyses, summarized in Table 5, highlighted that the cost per QALY gained ranged from €2781 to €48,122 and remained under the commonly acceptable threshold of €50,000.

Cost-effectiveness results are relatively insensitive to the variation of vaccine efficacy, screening coverage rate, administration and treatment costs, sensitivity of Pap tests and utilities. Cost-effectiveness is however very sensitive to discount rates, as the greatest benefits related to HPV vaccination (i.e. cervical cancer-related death) occur decades after vaccination, and to a lower extent to vaccine efficacy duration (Table 5).

Discussion

The implementation of an HPV vaccination programme with a quadrivalent vaccine (Gardasil®) alongside the current cervical cancer screening programme in Italy would provide important health benefits to local population. Based on a coverage rate of 80%, assuming lifetime duration of protection and discount rates of 1.5% and 3% for health benefits and costs respectively, the implementation of HPV vaccination among a cohort of girls aged 12 years would avoid 1432 incremental cases of cervical cancer (−63.3%) and 513 related deaths (−63.4%) compared to screening programme only. This new preventive strategy would be a cost-effective public health programme, as the cost per additional QALY gained reached €9,569, which is considered as an acceptable threshold [20].

To date, there is much debate regarding the value of the discount rate used, particularly when evaluating public health programmes such as vaccination [44]. There are many arguments that both discount rates for health benefits and costs should not necessarily be the same [45]. Often, discounting health benefits provided by vaccines with long-term effects can negatively affect the true benefit of the intervention and make a cost-effective vaccine cost-ineffective [15,46,47]. In this context, annual discount rates of 1.5% for health benefits and of 3% for costs were assumed in the model. Nevertheless, cost and benefit discount rates were varied from 0% to 5% in sensitivity analysis. Both discount rates showed a substantial influence on the estimated cost-effectiveness of vaccination. But, despite the variation of both health benefits and costs discount rates, HPV vaccination always remained cost-effective.

Our model probably underestimates the clinical and economic benefits of HPV vaccination in Italy. First of all, our model was a "cohort model", so that it did not take into account the "herd immunity" effect as a dynamic model does. For example, Chesson et al. [15] showed that "herd immunity" could reduce by 37.9% the ICER. Moreover, our model did not consider the reduction of other diseases associated with HPV types 6, 11, 16 and 18, such as anogenital carcinomas (vulvar, vaginal, anal and penile) and head/neck cancers [4]. At least, the cross-protection effect was not included in our model. Recently published clinical data [48] showed that administration of a quadrivalent vaccine reduced the incidence of persistent infection and CIN2/3 caused by other oncogenic types, responsible for 10% of cervical cancer cases.

Despite the limits discussed above, our model provides estimates of HPV vaccination cost-effectiveness in Italy which are consistent with data reported in another Italian study. Indeed, Capri et al. [20] highlighted similar conclusions on the cost-effectiveness of HPV vaccination alongside screening strategies in Italy, but their ICERs were slightly higher (€34,676 per LYG and €26,361 per QALY gained). The main differences with our study were related to the discount rate used for benefits (1.5% in our analysis versus 3%) and the impact of the vaccination on genital warts, which was not included in Capri et al.

According to a dynamic model published in the UK [18], 97% of the HPV disease events avoided in the first 5 years after vaccine course would be attributable to the prevention of HPV types 6 and 11 infection. Our model considered health benefits and costs related to HPV types 6 and 11, including the prevention of genital warts and CIN 1, but probably underestimated these benefits because of the structure of the model. When benefits of the vaccine on genital warts were considered, the cost-effectiveness ratio was decreased by 10% in our model. Others analyses showed that a vaccination programme with a quadrivalent vaccine appeared more cost-effective than that of a bivalent one. The cost per QALY gained was estimated to decrease by 33 to 48% in dynamic model [15,16,18], and by 32% in a cohort model [15], versus the ICERs obtained with a bivalent vaccine.

Finally, it is interesting to assess the impact of adding a HPV vaccination programme to a cervical cancer screening strategy. Our study showed that targeting a better screening strategy (+20% screening coverage rate) without vaccine would be less efficient than a lower screening strategy (−20% screening coverage rate) with vaccination, under the condition that vaccination coverage and screening coverage are independent. Indeed if vaccine and screening cover the same women and a part of the population is not be reached by any intervention, the burden of disease will be slightly reduced. In this context, HPV vaccination in combination with cervical cancer screening seems to be the most relevant way to prevent cervical cancer. Our results also underlined the effect of HPV vaccination on the quality of life of screened women. Indeed, we showed that vaccination was expected to reduce by 13.4% the number of abnormal Pap tests overall, which was consistent with other studies [49,50]. On the other hand, while the number of high grade lesions could decrease by 46–47% with a vaccination programme, the positive predictive value of the Pap test will decrease by more than 50% [49,51]. This may lead to overdiagnosis (false positive results) and overtreatment, as well as a potential increase of related costs.

In this study, the impact of vaccination was evaluated considering the current screening strategy. In the coming years, it will be relevant to enhance the efficacy and the efficiency of the current screening programme, particularly with the introduction of vaccination [52]. For example, the increase of screening intervals or the use of new screening tests could be considered. In this context, a US team [53] recently evaluated different screening strategies in association with a HPV vaccination programme. They suggested that replacing Pap test by HPV test "as a triage test for equivocal results in younger women and as a primary screening test in older women" could be more cost-effective than the current US screening programme. Thus, further full-fledged investigations are needed in Italy to highlight the best way to improve the local screening programme.

In conclusion, our study provides strong evidence regarding the health benefits associated with the implementation of a HPV vaccination policy with a quadrivalent vaccine among 12 years old girls and the need to maintain the current screening programme for women aged 25–64 years. Introducing a quadrivalent HPV vaccine would likely be a cost-effective public health intervention in Italy.

Conflict of interest

PGR, FP and FM received financial support for their participation in 4 workshops and the validation of data and results. NL is an employee of Sanofi Pasteur MSD.

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References

[1] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
[2] World Health Organization. Technical information for policy markers and health professionals, WHO/IVB/07.05. Available at: http://www.who.int/vaccines-documents/DocsPDF07/866.pdf; 2007.
[3] Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189(1):12–9.
[4] Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. Epidemiol Rev 1988;10:122–63.
[5] Insinga RP, Dasbach EJ, Elbasha EH. Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US: analytic framework and review of the literature. Pharmacoeconomics 2005;23:1107–22.
[6] Clifford GM, Smith JS, Plummer M, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer 2003;88(1):63–73.
[7] Von Krogh G. Management of anogenital warts (condylomata acuminata). Eur J Dermatol 2001;11(6):598–603.
[8] Ferlay J, Bray F, Pisani P, Parkin DM. Globocan 2002: Cancer incidence, mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon (France): IARC Press; 2004.
[9] Istituto nazionale di statistica (ISTAT). La prevenzione dei tumori femminili in Italia; il ricorso a pap test e mammogragia: anni 2004–2005. Available at: http://www.istat.it/salastampa/comunicati/non_calendario/20061204_00/testointegrale.pdf; 2006.
[10] Ricciardi A, Largeron N, Giorgi Rossi P, Raffaele M, Cohet C, Federici A, Palazzo F. Incidence of invasive cervical cancer and direct costs associated with its management in Italy. in press [Tumori].
[11] Istituto nazionale di statistica (ISTAT) - Fattori di rischio e tutela della salute — Indagine multiscopo sulle famiglie italiane "Prevenzione dei tumori femminili: ricorso a pap test e mammografia" anni 2004/2005. Available at: http://www.istat.it/salastampa/comunicati/non_calendario/20061204_00/2006; 2006.
[12] Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al, Proof of Principle Study Investigators. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med 2002;347(21):1645–51.
[13] Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al, GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004;364(9447):1757–65.
[14] Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al, HPV Vaccine Study group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367(9518):1247–55.
[15] Chesson HW, Ekwueme DU, Saraiya M, Markowitz LE. Cost-effectiveness of human papillomavirus vaccination in the United States. Emerg Infect Dis 2008;14:244–51.
[16] Brisson M, Van de Velde N, De Wals P, Boily MC. Potential cost-effectiveness of prophylactic human papillomavirus vaccines in Canada. Vaccine 2007;25(29):5399–408.
[17] Kulasingam SL, Benard S, Barnabas R, Largeron N, Myers ER. Adding a quadrivalent human papillomavirus vaccine to the UK cervical cancer screening programme: a cost-effectiveness analysis. Cost Eff Resour Alloc 2008;6:4.
[18] Dasbach E, Insinga R, Elbasha E. Assessment of the health and economic impact of a Quadrivalent HPV vaccine in the United Kingdom using a transmission dynamic model. BJOG 2008. In press.
[19] Szucs TD, Largeron N, Dedes KJ, Rafia R, Bénard S. Cost-effectiveness analysis of adding a quadrivalent HPV vaccine to the cervical cancer screening programme in Switzerland. Curr Med Res Opin 2008;24(5):1473–83 May.
[20] Capri S, Bamfi F, Marocco A. Impatto clinico ed economiuco della vaccinazione anti-HPV. Ital J Publich Health 2007(Suppl 1):59–85.
[21] Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol 2000;151(12):1158–71.
[22] Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. JAMA 2003;290(6):781–9.
[23] ISTAT, Demografia in cifre. Available at: http://demo.istat.it.
[24] Ronco G, Ghisetti V, Segnan N, Snijders PJ, Gillio-Tos A, Meijer CJ, et al. Prevalence of human papillomavirus infection in women in Turin, Italy. Eur J Cancer 2005;41(2):297–305.
[25] Italian Network of Cancer Registries Work Group. Italian cancer figures — report 2006. Incidence, mortality and estimates. Epidemiol Prev 2006;30:1–130.
[26] Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy. J Natl Cancer Inst 2005;97(12):888–95.
[27] Materia E, Rossi L, Spadea T, Cacciani L, Baglio G, Cesaroni G, et al. Hysterectomy and socioeconomic position in Rome, Italy. J Epidemiol Community Health 2002;56(6):461–5.
[28] Coleman MP, Gatta G, Verdecchia A, Estève J, Sant M, Storm H, et al. EUROCARE Working Group. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Ann Oncol 2003;14(Suppl 5):v128–49.
[29] WHO Statistical Information System (WHOSIS). Mortality database — Italy. Available at: http://www3.who.int/whosis/mort/table1_process.cfm; 2001.
[30] Monsonego J, Breugelmans JG, Bouee S, Lafuma A, Benard S, Remy V. Incidence, prise en charge et coût des condylomes acumines anogénitaux chez les femmes consultant leur gynécologue en France. Gynecol Obstet Fertil 2007;35(2):107–13.
[31] Insinga RP, Glass AG, Myers ER, Rush BB. Abnormal outcomes following cervical cancer screening: event duration and health utility loss. Med Decis Mak 2007;27:414–22.
[32] Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al, Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. The New England Journal of Medicine 2007;356(19):1928–43.
[33] The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356(19):1915–27.
[34] Olsson S-E, Villa LL, Costa RLR y cols. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine 2007;25:4931–9.
[35] Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerging Infectious Disease 2007;13:28–41.
[36] Ronco G, Giubilato P, Naldoni C, Zorzi M, Anghinoni E, Scalisi A, et al. Activity level and process indicators of organised programmes for cervical cancer screening in Italy. Epidemiol Prev 2006;30(suppl 3):27–40.
[37] Regione Emilia Romagna (RER). Protocollo diagnostico-terapeutico dello screening per la prevenzione dei tumori del collo dell'utero nella regione. Bologna: Emilia-Romagna; 2004.
[38] Società Italiana di Colposcopia e Patologia Cervico-Vaginale (SICPCV). Gestione della paziente con pap test anormale Linee Guida Edizione 2006. Available at: http://www.colposcopiaitaliana.it/pdf07/Linee-Guida-2006.pdf last access April 24th 2008.
[39] Hospital information system, Lazio Region 2007. Available at: http://www.asplazio.it/asp_online/att_ospedaliera/sio_newr/sio_index.php?menu=s21, last access April 24th 2008.
[40] Ministero della salute. Nomenclatore delle prestazioni di assistenza specialistica. Available at: http://www.ministerosalute.it/resources/static/news/880/ultimo_corretta_finanziaria_specialistica.pdf, last access April 24th 2008.
[41] Merito M, Largeron N, Cohet C, et al. Treatment patterns and associated costs for genital warts in Italy. Curr Med Res Opin 2008 [Oct 10].
[42] Azzari C, Massai C, Poggiolesi C, Indolfi G, Spagnolo G, De Luca M, et al. Cost of varicella-related hospitalizations in an Italian paediatric hospital: comparison with possible vaccination expenses. Current Medical Research and Opinion 2007;23(12):2945–54.
[43] Coudeville L, Brunot A, Giaquinto C, Lucioni C, Dervaux B. Varicella vaccination in Italy: an economic evaluation of different scenarios. Pharmacoeconomics 2004;22(13):839–55.
[44] Bonneux L, Birnie E. The discount rate in the economic evaluation of prevention: a thought experiment. J Epidemiol Community Health 2001;55(2):123–5.
[45] Bos JM, Postma MJ, Annemans L. Discounting health effects in pharmacoeconomic evaluations: current controversies. Pharmacoeconomics 2005;23(7):639–49.
[46] Beutels P, Edmunds WJ, Antoñanzas F, De Wit GA, Evans D, Feilden R, et al, Viral Hepatitis Prevention Board. Economic evaluation of vaccination programmes: a consensus statement focusing on viral hepatitis. Pharmacoeconomics 2002;20(1):1–7.
[47] Torgerson DJ, Raftery J. Economic notes. Discounting. BMJ 1999;319(7214):914–5.
[48] Villa L, Villa L. The FUTURE I and II study group; Quadrivalent human papillomavirus (HPV) type 6,11,16,18 L1 virus-like particle vaccine: an analysis of cross-protection against cervical intraepithelial neoplasia caused by non-vaccine types: oral presentation. EUROGIN. 2–4 October 2007-Monte-Carlo-Monaco; 2007.
[49] Schiffman M. Integration of human papillomavirus vaccination, cytology, and human papillomavirus testing. Cancer 2007;111:145–53.
[50] Haupt RM. GARDASIL update. 2007 CDC Cancer Conference Program of Events; 2007 Aug 13–17; Atlanta. Atlanta: Centers for Disease Control and Prevention.
[51] Franco EL, Ferenczy A. Cervical cancer screening following the implementation of prophylactic human papillomavirus vaccination. Future Oncol 2007;3(3):319–27.
[52] Jit M, Choi YH, Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. BMJ 2008;17:337–a769.
[53] Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16,18 vaccination. J Natl Cancer Inst 2008;100:308–20.
[54] Canfell K, Barnabas R, Patnick J, Beral V. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. Br J Cancer 2004;91(3):530–6.
[55] Siebert U, Sroczynski G, Hillemanns P. The German cervical cancer screening model: development and validation of a decision-analytic model for cervical cancer screening in Germany. European Journal of Public Health 2006;16(2):185–92.
[56] Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med 2000;132(10):810–9.
[57] Arbyn M, Buntinx F, Van Ranst M, Paraskevaidis E, Martin-Hirsch P, Dillner J. Virologic versus cytologic triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. J Natl Cancer Inst 2004;96(4):280–93.
[58] Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol 1998;91(4):626–31.
[59] Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N. Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis. Health Technol Assess 2004;8(20):iii,1–iii,78.

[60] Giorgi Rossi P, Largeron N, Cohet C, Palazzo F, Mennini FS, Furnari G, et al. Impact and cost of the cervical cancer screening prevention in Italy. Barcelona, Spain: HTAi; 2007.
[61] Bergeron B, Largeron N, Mcallister M, Mathevet M, Remy R. Cost-effectiveness analysis of the introduction of a quadrivalent human papillomavirus vaccine in France. Int J Technol Assess Health Care 2008;24:10–9.
[62] Myers ER, Green S, Lipkus I. Patient preferences for health states related to HPV infection: visual analogue scales vs time trade-off elicitation. Proceedings of the 21st International Papillomavirus Conference Mexico City, Mexico 2004.
[63] Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst 2004;96(8):604–15.