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A cost-effectiveness analysis of adult human papillomavirus vaccination strategies in Italy

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ABSTRACT

Vaccination can reduce the public health and economic burden of human papillomavirus (HPV)-associated diseases. In 2023, the Italian national immunization program (NIP) was updated to include HPV vaccination of females ≤26 and males ≤18 years. However, the cost-effectiveness of this update along with proposals to include additional cohorts is unknown. This study evaluates the cost-effectiveness of different HPV vaccination strategies in Italy over a 100-year period, using a published dynamic transmission model with Italy-specific input data. We modeled vaccination of the primary cohort (11 years of age) for 100 years, alone and supplemented with vaccination of additional cohorts for 5–100 years. We found that vaccination of the primary adolescent cohort resulted in substantial, sustained decreases in the incidence and mortality rates of all HPV-related cancers, but smaller, transient decreases in genital warts and recurrent respiratory papillomatosis. Adding supplementary vaccination of additional cohorts for 5–10 years had minor additional public health benefits, while continuing any of the modeled supplementary vaccination strategies for 100 years resulted in more substantial incremental benefits. For example, implementing the 2023–2025 NIP strategy for 100 years averted an additional 21,495 cases of cervical cancer compared to vaccination of the primary cohort alone. All supplementary vaccination strategies that were continued for 10 or 100 years were cost-effective compared to vaccination of the primary cohort alone at a willingness-to-pay threshold of €40,000 per quality-adjusted life year (QALY) gained. The benefits deriving from vaccinating additional cohorts should be considered when developing and updating NIPs.

PLAIN LANGUAGE SUMMARY

The human papillomavirus (HPV) is a common sexually transmitted infection, and persistent infections with some HPV genotypes can cause diseases including anogenital and head and neck cancers, genital warts, and recurrent respiratory papillomatosis. Three HPV vaccines have been approved by the European Medicines Agency, and the introduction of HPV vaccination in Italy has been associated with a reduced public health and economic burden of HPV-related diseases. However, HPV vaccine uptake among the primary cohort has been well below the target, making HPV-related diseases a major source of morbidity, mortality, and health care costs in Italy. In this study, we modeled the public health and economic impacts of various supplementary HPV vaccination strategies in Italy over a 100-year period compared to vaccination of the primary adolescent cohort (11 years of age) alone, from the health care system perspective. The analysis incorporates all diseases attributable to HPV genotypes included in the 9vHPV vaccine, in both sexes, and compares supplementary vaccination strategies that include different age groups and that run for different durations. We found that vaccination of the primary adolescent cohort over a 100-year period resulted in substantial, sustained reductions in the incidence and mortality rates of all HPV-related cancers compared to no vaccination, but smaller, transient decreases in genital warts and recurrent respiratory papillomatosis. Adding supplementary vaccination of additional cohorts for 5- or 10-year durations had minor additional public health benefits, while continuing any of the modeled supplementary vaccination strategies for 100 years resulted in more substantial and sustained benefits compared to vaccination of the primary cohort alone. The incremental benefits of 100-year supplementary vaccination programs were particularly large for anal, head and neck, penile, and vulvar cancers; genital warts; and RRP. These benefits deriving from additional targets of vaccination programs could be taken into account when considering vaccination strategies. The implementation of policies strategies including additional cohorts should be performed together with awareness campaigns, routine vaccination reminders, and possible government subsidies to accelerate HPV elimination.

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Introduction

The human papillomavirus (HPV) is a common sexually transmitted infection. Most infections are cleared by the immune system, but persistent infections with some HPV genotypes can cause diseases including anogenital and head and neck cancers, genital warts, and recurrent respiratory papillomatosis (RRP).[1,2] In Europe, HPV is estimated to cause 2.5% of all cancers (4.4% among women and 0.9% among men); in Italy, this equates to approximately 15,000 cases and 6,000 deaths each year from potentially HPV-related cancers.[1,3] Globally, there is evidence for an increasing incidence of HPV-related head and neck cancers in both men and women and of all HPV-related cancers among men.[4,5]

Three HPV vaccines have been approved by the European Medicines Agency and have proven to be safe and effective in reducing the incidence of HPV infection and HPV-related diseases.[6–9] In 2007, Italy introduced fully funded HPV vaccination with a bivalent vaccine against HPV-16 and 18 (2vHPV) and a quadrivalent vaccine against HPV-6, 11, 16, and 18 (4vHPV) into its national immunization program (NIP).[10] As in many other countries, these vaccines were originally indicated for the prevention of cervical cancer and were administered only to girls. The initial primary cohort comprised girls 11–12 years of age, although some Italian regions also contextually offered vaccination to older girls and young women (≤15 years of age in 3 regions, ≤16 in 4 regions, ≤18 in 3 regions, and ≤25 in 1 region), extending the beneficiary cohorts.[11,12] Increasing evidence for the role of HPV in other cancers and the importance of high levels of overall population immunity, as well as favorable cost-effectiveness analyses in Italy and other countries, subsequently prompted a switch to universal vaccination of adolescents (i.e., vaccination of both girls and boys) in some Italian regions as early as 2015 and nationwide by 2017.[13–18]

With the introduction of the 2017–2019 NIP, Italy switched to fully reimbursed universal vaccination of female and male adolescents 12 years of age with 2 doses of a nonavalent vaccine (9vHPV) which provides broader protection against HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58.[19] The 2017–2019 NIP also recommended vaccination of women 25 years of age upon their first cervical cancer screening appointment since these cohorts had been eligible for vaccination during adolescence in most, but not all, regions. Due to the COVID-19 pandemic, the 2017–2019 NIP was extended until August 2023, when the new 2023–2025 NIP was approved.[20] The current NIP acknowledges the World Health Organization's HPV vaccination strategy,[6] the European Commission's commitment to cervical cancer elimination,[21] and the impact of the COVID-19 pandemic, which caused a decrease in HPV vaccine uptake in Italy and elsewhere, especially in 2020.[20,22–25] As such, the 2023–2025 NIP continues universal primary cohort vaccination at 11 years of age, and also recommends catch-up vaccination for girls/women at least until the age of 26 years (actively promoted at routine cervical cancer screening appointments) and of boys at least until the age of 18 years. In addition, HPV vaccination is recommended for women treated for cervical lesions and for other high-risk populations, such as HIV-positive individuals and men who have sex with men.[20]

The introduction of HPV vaccination in Italy has been associated with a reduced public health and economic burden of HPV-related diseases.[26,27] However, HPV vaccine uptake among the primary cohort has been well below the target of 95%, at 38.7% for girls and 31.8% for boys in 2022 (the vaccination coverage rates [VCRs] are higher when observed at 14 years of age, with a consolidated average of 70% for girls).[28] Vaccine hesitancy is one possible explanation for this immunization gap. A cross-sectional survey of parents of adolescents aged 12 and 13 years in Italy found that 33.3% of the parents were hesitant toward HPV vaccination for their children.[29] Factors associated with hesitancy included attitudes and knowledge gaps with parents who had not heard of HPV infection, did not know that vaccination was a preventive measure, or needed more information, and those who did not believe that the vaccination was useful for the prevention of HPV-related cancers associated with hesitancy.[29] Estimated crude incidence rates in 2020 per 100,000 population for HPV-related cancers among women were 10.2, 5.38, and 3.88 for cervical, oral, and vulvar cancers.[3] Among men, the estimated 2020 crude incidence rates of HPV-related cancers were 9.42, 8.04, and 3.61 for laryngeal, oral, and oropharyngeal cancers.[3] Raising VCRs across sexes is essential to reduce transmission, protect from HPV-related diseases, and achieve herd immunity.[15] As a result of low VCRs, diseases attributable to HPV remain a major source of morbidity, mortality, and health care costs in both females and males in Italy.[22,30–34] In 2018, the total annual direct costs of HPV-related diseases in Italy were €542.7 million, with 61% of the costs attributable to diseases caused by the 9vHPV vaccine genotypes.[34]

Since the release of the 2017–2019 NIP, some academics and working groups have been advocating for HPV vaccination extension to all women of potentially fertile age, independent of individual risk.[35–37] However, while previous changes to the NIP – the introduction of HPV vaccination in Italy, the extension of vaccination to include boys, and the use of the 9vHPV vaccine – were supported by cost-effectiveness analyses,[11,15,16,38,39] the cost-effectiveness of supplementary vaccination of older age groups is unknown in the Italian context. A 2015 analysis estimated the public health impact of supplementary vaccination of girls 15 years of age or women 25 years of age, compared to female-only or universal vaccination of adolescents, and concluded that supplementary vaccination would prevent more cases of cervical cancer than would universal vaccination of adolescents, but only when ≥31% of the 15-year-old cohort or ≥43% of the 25-year-old cohort were vaccinated.[11] Another Italian study estimated that adding vaccination of women 25 years of age would reduce the incidence of HPV-related cervical cancer and precancer by 9.6% compared to vaccination of adolescents alone.[39] However, cost-effectiveness was not assessed in these studies; further, both analyses were based on vaccination with 2vHPV and considered only cervical cancer prevention, and thus did not account for vaccine-mediated prevention of other HPV-related diseases or of cervical cancers caused by genotypes other than HPV-16 and 18.[11,39]

A comprehensive analysis is needed of the costs and benefits of female and male supplementary vaccination in the context of the current Italian NIP. The objective of the current

study was thus to assess the public health benefits and cost-effectiveness of supplementary 9vHPV vaccination in Italy over a 100-year period. The analysis incorporates all diseases attributable to HPV genotypes included in the 9vHPV vaccine in both sexes and compares supplementary vaccination strategies that include different age groups and that run for different durations. These results will help policymakers and healthcare stakeholders make informed decisions about resource allocation and vaccination strategies.

Methods

Study design and model structure

The incidence and mortality of diseases related to HPV genotypes that are included in the 9vHPV vaccine and the associated health care costs were estimated for the Italian population over a 100-year time horizon for various HPV vaccination strategies. We modified a previously published deterministic population-based dynamic transmission model (see Supplementary Text and Supplementary Figure S1) by incorporating Italy-specific input data and model parameters (see below) and calibrated it against Italian demographic and epidemiological data.[18,40–48]

Briefly, the demographic component of the model stratified the entire Italian population by 23 age groups, binary sex (as recorded at birth), and sexual activity level (low and high activity categories). The force of infection with each HPV genotype included in the 9vHPV vaccine was estimated for each age/sex group based on its sexual partnerships within and between groups, HPV prevalence, and sexual activity levels. Some infections were assumed to resolve, triggering seroconversion that would prevent subsequent infections with the same HPV genotype, while the remaining infections were assumed to become persistent.

For HPV-related cancers, a portion of persistent infections was assumed to progress to precancerous and then cancerous disease. Diseases were initially undetected but progressed to detected status via routine screening (cervical cancer only) or symptom recognition (all cancers). Cancers progressed from local to regional and then distant disease stages; later stages were associated with increased rates of symptom recognition, loss of quality of life, and mortality.[18,43,44,49] A portion of cancer was successfully treated. Sexually transmitted HPV infections could also progress to adult-onset RRP (AORRP) or genital warts. A portion of genital warts was assumed to remain asymptomatic. A portion of the individuals born to mothers with prevalent HPV-6 or 11 infections (rates based on the prevalence of these genotypes among women in each age group) were assumed to progress to juvenile-onset RRP (JORRP).

Model inputs, parameters, calculations, and calibration

The Italian population size (female 30,974,780; male 29,384,766), all-cause mortality rates by age group and sex (Supplementary Table S1), and health utility values for individuals without HPV-related disease by age group (Supplementary Table S2) were derived from United Nations and Italian data.[50–53] The proportion of the Italian population with low (<5 partners) and high (≥5 partners) sexual activity was computed from published sources[54–56] and estimated at 74.35% low for men and 88.9% low for women.

Data on the overall proportion of Italian women screened for cervical cancer within the last 3 years were obtained from national surveillance data on health behaviors, stratified by age group: 73.9% of women 25–29 years of age were assumed to have undergone screening, 82.8% of those 30–49 years of age, and 78.8% of those 50–64 years of age.[57] Women who have undergone a hysterectomy (numbers and rates obtained from national hospital care statistics;[58] Supplementary Table S3) were assumed in the model to be excluded from cervical cancer screening programs and to have zero cervical disease incidence or progression but were still able to acquire and transmit HPV infections.

The HPV genotype attribution rates for each modeled disease are shown in Supplementary Table S4, stratified by sex for diseases that are not sex specific. Published attribution rates from Europe were used as a proxy and scaled according to the incidence of each disease in Italy compared to the European average.[59–64] Weighted average attribution rates for cancers of the oropharynx, larynx, and oral cavities were used in the model as the attribution rates for all head and neck cancers. Age-specific incidence and mortality rates for RRP were derived from a previous model;[40] age-specific incidence rates for all other modeled diseases, and mortality rates for all other diseases except genital warts, are shown in Supplementary Tables S5–9.

Supplementary Tables 10 and 11 show the vaccine efficacy estimates used in the model and the estimated degree of vaccine-mediated protection against persistent infections and HPV-related diseases, stratified by infection site, disease, HPV genotype, and sex. Protection against the HPV genotypes included in the 9vHPV vaccine was assumed to be lifelong. Historical HPV VCR estimates from 2015 to 2021 were obtained from the Ministry of Health[65] and used to compute the VCR for girls and boys born between 1994 and 2009 (Supplementary Table S12). The model for each combination of HPV genotype and HPV-related disease was independently calibrated by comparing the model's estimates to published age-specific disease incidence and mortality rates and minimizing the least square error, as before.[40]

The modeled costs (in 2019 euros, €) included vaccination costs (2- or 3-dose cycle at a vaccine cost of €63.00 and administration cost of €6.18 per dose),[15,66,67] the costs associated with the cervical cancer screening program (cytological and DNA screening and office visit, €31.82; diagnostic biopsy, €38.22; colposcopy, €10.74),[68] and the direct costs of diagnosis and treatment of HPV-related disease (Supplementary Table S13). The latter data were obtained from government sources and previously published work and represent lifetime inpatient and outpatient costs, stratified by disease severity (i.e., local, regional, or distal disease for HPV-related cancers).[15,16,34,38,68] Health utility values associated with each HPV-related disease were derived from published sources and stratified by sex and disease severity (Supplementary Table S13).[15,34]

Analyses

The base case analysis compared universal vaccination of a primary cohort 12 years of age (corresponding to the Italian 2017–2019 NIP recommendation), with a baseline VCR of ~30% for girls and ~27% for boys, to 3 vaccination strategies that comprise universal vaccination of a primary cohort 11 years of age as well as different supplementary vaccination strategies. The first strategy represented the new '2023–2025 NIP,' which recommends free vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age. To estimate supplementary vaccination uptake, we applied the average public cervical cancer screening adherence rate of 48.7%[57] to the estimated number of unvaccinated women in each eligible birth cohort and assumed that 70% of unvaccinated women who attended a screening would choose to receive the promoted HPV vaccine, based on the current average VCR of 63.0% among girls and women 12–26 years of age.[65] We assumed a vaccination rate of 50% among unvaccinated boys/men ≤18 years of age. The second strategy modeled a 'Single cohorts' approach and assumed the vaccination of 3 cohorts of women at 30, 35, and 40 years of age upon attending fully funded routine HPV DNA screening. Screening adherence and vaccine uptake were estimated as above, except that all women 27–45 years of age were assumed to be unvaccinated. Finally, the third immunization strategy, 'Mid-adult,' modeled the vaccination of women up to 45 years of age and boys up to 18 years of age. Vaccination uptake assumptions were as above, except that all women 27–45 years of age were assumed to be unvaccinated. All strategies assumed that all vaccinated individuals received a full course of the 9vHPV vaccine (2 doses for those ≤14 years of age and 3 doses for those >14 years of age), and all strategies ramped up the vaccination uptake rate in a linear fashion over a 3-year period. Outcomes were modeled for each of the 3 strategies according to different durations of their supplementary vaccination components (3, 5, 10, or 100 years) in order to evaluate the short- and long-term impacts of each strategy; the results of the 3-year duration analyses are not included in all tables in the current manuscript as they were very similar to the 5-year duration results, but are available upon request. Universal vaccination of the primary cohort continued for the full 100-year modeled period in all analyses.

All outcomes were estimated over a 100-year time horizon to capture the impacts of long-term sequelae of HPV infection. Public health outcomes were obtained by modeling the incidence and cumulative number of cases of and deaths from HPV-related diseases under each of the vaccination strategies outlined above. Health economics outcomes were derived by calculating the direct costs associated with vaccination, screening, and treatment of diseases related to HPV genotypes included in the 9vHPV vaccine for each vaccination strategy, as well as the quality-adjusted life years (QALYs) gained from the averted cases of and deaths from HPV-related diseases. Incremental cost-effectiveness ratios (ICERs) were calculated as the difference between vaccination strategies in the cost per QALY gained. A discount rate of 3% was applied to costs and life years.[69] Only the public national health care system perspective was considered; no indirect or societal costs were included in the analysis.

One-way sensitivity analyses were conducted to assess the dependence of the ICER of each vaccination strategy on variations in vaccine price, treatment cost, health utility, disease disutility (all ±20%), and the discount rate (0–5%). We also conducted a scenario analysis to examine the effect of higher sub-cohort VCRs on the cost-effectiveness of each vaccination strategy, and to determine whether the incremental public health benefits of further increasing the VCRs above the base case levels remained cost-effective. In this analysis, the female and male VCRs for the primary and supplementary vaccination cohorts were linearly increased over 3 years to the values shown in Supplementary Table S14 and compared to the base case.

Results

Model fit

Model fit curves for each disease are shown in Supplementary Figures S2–4. Overall, the calibrated model fits were close to the target data, particularly for the disease incidence data. The model fits were also close to the age-specific mortality data, although the model did not closely match the mortality rates for head and neck and vulvar cancers.

Public health outcomes

The incidence and mortality rates for diseases attributable to the HPV genotypes included in the 9vHPV vaccine were modeled over a 100-year period. Incidence curves for the '2023–2025 NIP' vaccination strategy compared to the base case are shown in Figure 1 (cancers) and Figure 2 (RRP and genital warts); the incidence curves for the other modeled vaccination strategies are generally similar and are shown in Supplementary Figures S5–8. The mortality curves that were generated for all diseases other than genital warts were highly similar to the respective incidence curves and are available upon request. For all HPV-related cancers, the universal vaccination of the primary cohort alone (base case; '2017–2019 NIP') resulted in substantial and sustained decreases in incidence and mortality. Incorporating any of the 3 modeled supplementary vaccination programs resulted in additional decreases in both outcomes, with greater benefits for longer supplementary program durations, although for some diseases (notably cervical and vaginal cancer) these decreases were small compared to the difference between no vaccination and universal vaccination of the primary cohort. In contrast, the incidence and mortality of HPV-related cancers of the anus, head and neck, penis, and vulva decreased substantially compared to universal vaccination of the primary cohort alone when any of the 3 supplementary campaigns were included and maintained for the full 100-year modeled period.

For AORRP, JORRP, and genital warts, universal vaccination of the primary cohort alone ('2017–2019 NIP') resulted in relatively small and temporary decreases in incidence and/or mortality, with the lowest incidences observed around Year 10. Including any of the modeled supplementary programs for 3, 5, or 10 years resulted in a larger and more prolonged decrease in incidence and mortality, with greater benefits observed for longer supplementary program durations; however, as with

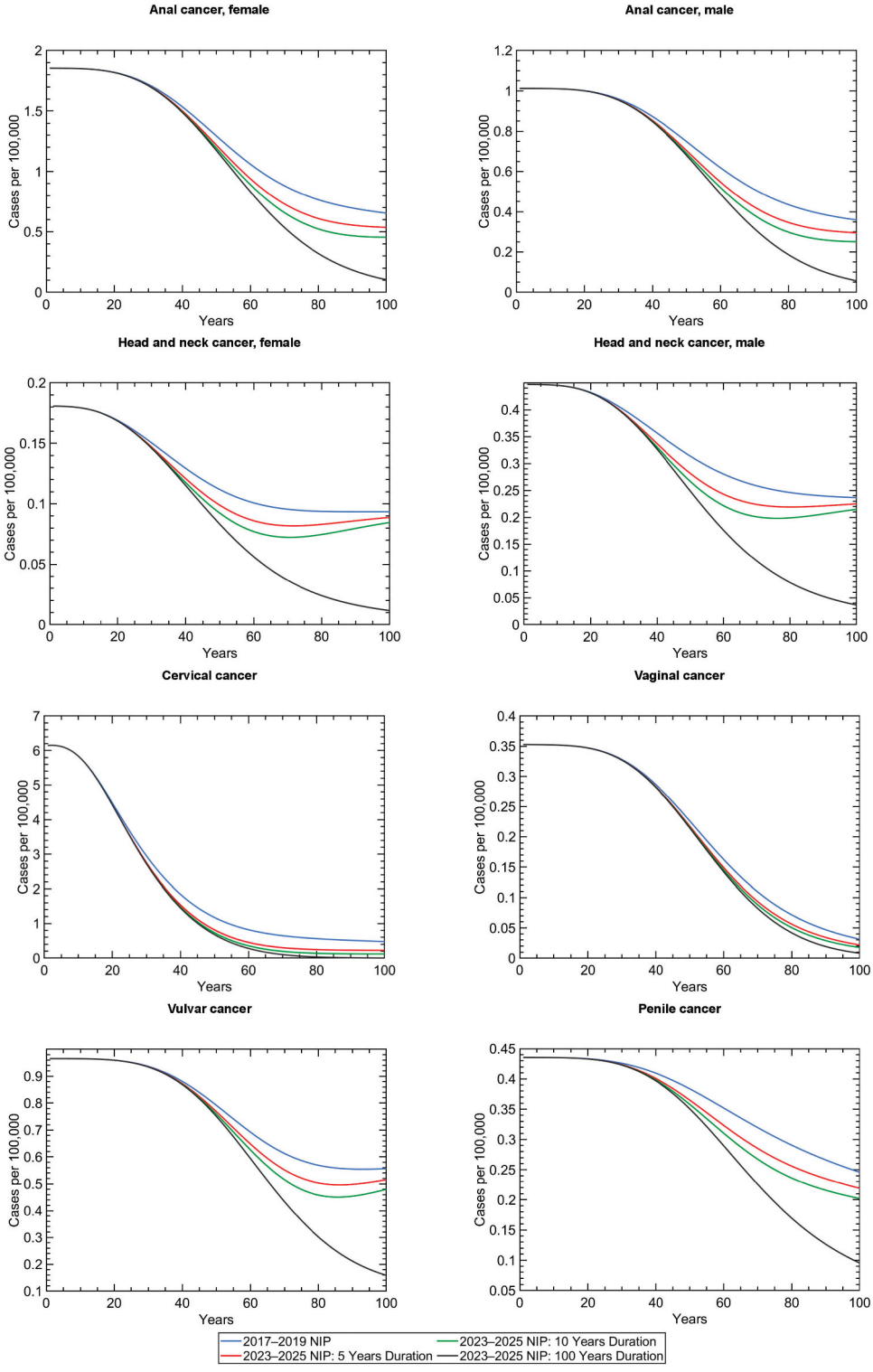

Figure 1. Estimated incidence per 100,000 people of human papillomavirus-related cancers in Italy over a 100-year period, under the '2023–2025 NIP' human papillomavirus vaccination strategy. NIP, national immunization program. Incidence rates are for diseases attributable to the HPV genotypes included in the 9vHPV vaccine. Both strategies use the 9vHPV vaccine and include universal vaccination of the primary cohort (adolescents 11 years of age) for the full 100-year modeled period. Durations relate only to the supplementary vaccination component of the '2023–2025 NIP' strategy (i.e., supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age).

universal vaccination of the primary cohort alone, the incidence and mortality rates subsequently increased to at or near the baseline level. Persistent decreases in the incidence and/or mortality of these 3 diseases were observed only when any of the 3 supplementary programs was continued for the full 100-year modeled period.

All modeled strategies averted substantial numbers of cases of (Table 1) and deaths from (Table 2) diseases related to the

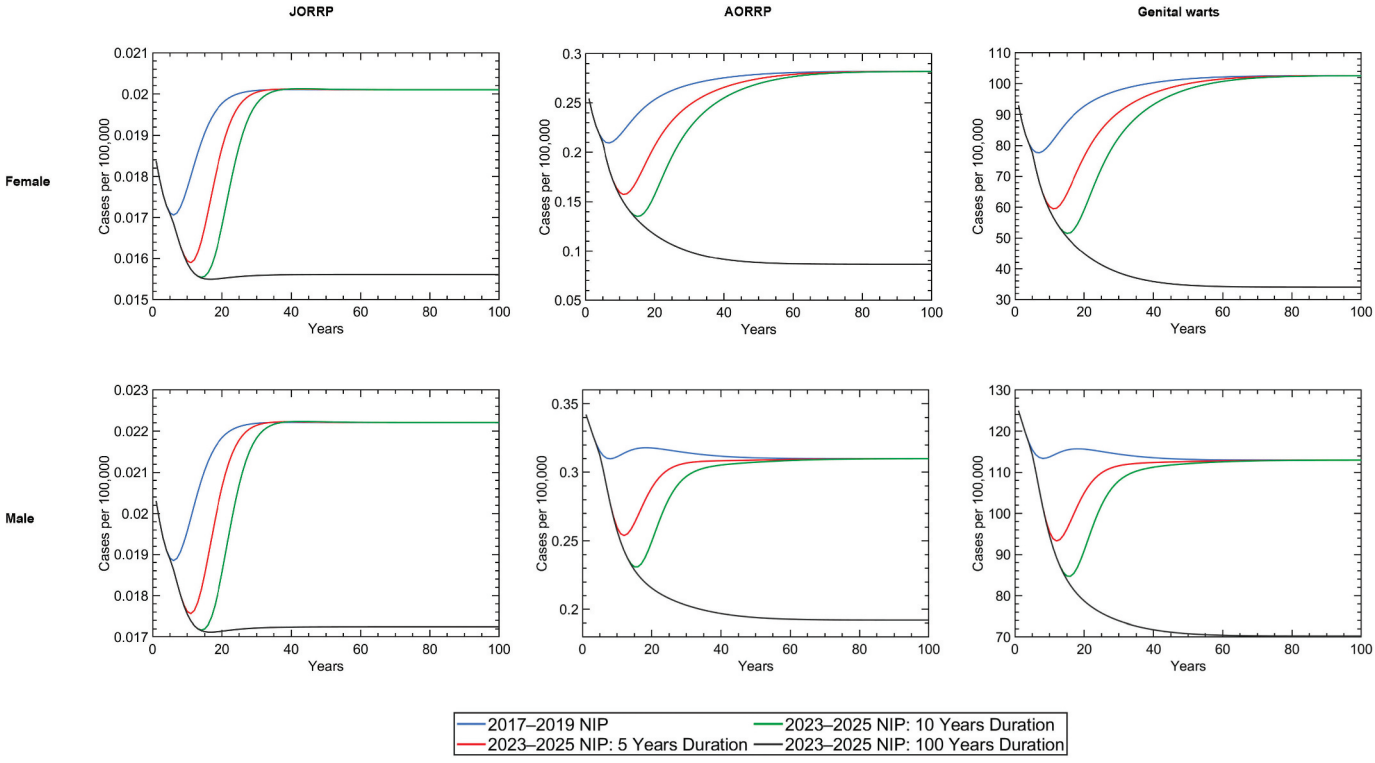

Figure 2. Estimated incidence per 100,000 people of human papillomavirus-related juvenile- and adult-onset recurrent respiratory papillomatosis and genital warts in Italy over a 100-year period, under the '2023–2025 NIP' human papillomavirus vaccination strategy. AORRP, adult-onset recurrent respiratory papillomatosis; JORRP, juvenile-onset recurrent respiratory papillomatosis; NIP, national immunization program. Incidence rates are for diseases attributable to the HPV genotypes included in the 9vHPV vaccine. Both strategies use the 9vHPV vaccine and include universal vaccination of the primary cohort (adolescents 11 years of age) for the full 100-year modeled period. Durations relate only to the supplementary vaccination component of the '2023–2025 NIP' strategy (i.e., supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age).

Table 1. Averted cases of human papillomavirus-related diseases in Italy over a 100-year period under different human papillomavirus vaccination strategies.

	Disease															
	Anal cancer					Head & neck cancer					JORRP		AORRP		Genital warts	
Vaccination strategy[A]	F	M	Cervical cancer	CIN 1	CIN 2/3	F	M	Penile cancer	Vaginal cancer	Vulvar cancer	F	M	F	M	F	M
2023–2025 NIP[B]																
5 years	4,546	2,602	14,337	9,863	32,974	451	1,107	1,050	458	1,718	17	18	822	531	284,911	190,382
10 years	6,814	3,856	18,245	12,800	42,888	731	1,760	1,588	610	2,803	30	33	1,416	892	493,127	320,616
100 years	12,134	6,767	21,495	15,496	51,982	2,069	4,902	3,308	818	6,984	241	266	9,793	6,210	3,434,433	2,252,292
Single cohorts[C]																
5 years	4,784	2,638	14,671	10,105	33,710	467	1,110	1,026	513	1,739	17	19	888	535	308,030	191,454
10 years	6,890	3,865	18,312	12,848	43,030	736	1,760	1,580	626	2,809	30	33	1,440	893	501,298	320,984
100 years	12,441	6,808	21,856	15,758	52,735	2,090	4,905	3,284	886	7,013	241	267	9,878	6,215	3,463,883	2,253,768
Mid-adult[D]																
5 years	5,033	2,685	15,196	10,488	34,870	483	1,115	1,004	576	1,768	18	20	942	538	326,803	192,370
10 years	7,291	3,934	18,976	13,336	44,482	763	1,767	1,544	722	2,852	31	34	1,536	899	534,658	322,610
100 years	12,588	6,833	22,125	15,952	53,305	2,101	4,908	3,274	922	7,031	242	267	9,910	6,217	3,475,330	2,254,362

AORRP, adult-onset recurrent respiratory papillomatosis; CIN, cervical intraepithelial neoplasia (numbers refer to grade); F, female; JORRP, juvenile-onset recurrent respiratory papillomatosis; M, male; NIP, national immunization program. Data represent averted cases of diseases attributable to the HPV genotypes included in the 9vHPV vaccine, compared to universal vaccination of the primary cohort alone.

[A]All strategies use the 9vHPV vaccine and include universal vaccination of the primary cohort (adolescents 11 years of age) for the full 100-year modeled period. Durations relate only to the supplementary vaccination components of each strategy.

[B]Includes supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age.

[C]Includes supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age, plus opportunistic vaccination of single cohorts of women at 30, 35, and 40 years of age upon HPV DNA screening.

[D]Includes supplementary vaccination of girls/women ≤45 years of age and boys/men ≤18 years of age.

HPV genotypes that are included in the 9vHPV vaccine, compared to universal vaccination of the primary cohort alone. For example, the number of additional cervical cancers averted compared to the 2017–2019 NIP strategy ranged from 11,762 ('2023–2025 NIP' strategy, 3-year duration) to 22,125 ('Mid-adult' strategy, 100-year duration) and the number of additional averted deaths from cervical cancer ranged from 179 to 1,105. Supplementary vaccination strategies that included more people for longer averted more cases and deaths, with the 'Mid-adult' strategy (supplementary vaccination of girls/women ≤45 years

Table 2. Averted deaths from human papillomavirus-related diseases in Italy over a 100-year period under different human papillomavirus vaccination strategies.

	Disease											
	Anal cancer			Head & neck cancer					JORRP		AORRP	
Vaccination strategy[A]	Female	Male	Cervical cancer	Female	Male	Penile cancer	Vaginal cancer	Vulvar cancer	Female	Male	Female	Male
2023–2025 NIP[B]												
5 years	1,244	709	4,656	243	591	320	250	888	1	1	39	25
10 years	1,862	1,049	5,895	394	938	483	332	1,449	1	1	68	43
100 years	3,290	1,826	6,892	1,088	2,549	993	444	3,581	10	11	442	281
Single cohorts[C]												
5 years	1,308	719	4,783	251	593	312	279	899	1	1	42	26
10 years	1,882	1,052	5,921	396	938	481	340	1,452	1	1	69	43
100 years	3,373	1,838	7,037	1,099	2,551	985	481	3,596	10	11	446	281
Mid-adult[D]												
5 years	1,376	732	4,977	260	595	306	313	914	1	1	45	26
10 years	1,992	1,070	6,174	410	942	470	393	1,474	1	1	73	43
100 years	3,413	1,844	7,140	1,105	2,552	982	501	3,605	10	11	447	281

AORRP, adult-onset recurrent respiratory papillomatosis; JORRP, juvenile-onset recurrent respiratory papillomatosis; NIP, national immunization program. Data represent averted deaths from diseases attributable to the HPV genotypes included in the 9vHPV vaccine, compared to universal vaccination of the primary cohort alone.

[A]All strategies use the 9vHPV vaccine and include universal vaccination of the primary cohort (adolescents 11 years of age) for the full 100-year modeled period. Durations relate only to the supplementary vaccination components of each strategy.

[B]Includes supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age.

[C]Includes supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age, plus opportunistic vaccination of single cohorts of women at 30, 35, and 40 years of age upon HPV DNA screening.

[D]Includes supplementary vaccination of girls/women ≤45 years of age and boys/men ≤18 years of age.

of age and boys/men ≤18 years of age) averting the most negative outcomes and the '2023–2025 NIP' (supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age) averting the fewest. Within each strategy, continuing the supplementary vaccination component(s) for longer averted more cases and deaths.

Health economic outcomes

The total costs (costs of treatment of diseases related to HPV genotypes included in the 9vHPV vaccine, cervical cancer/HPV DNA screening, and vaccines) and benefits (QALYs gained) of each strategy were estimated per 100,000 people and used to calculate the ICER for each supplementary vaccination strategy (Table 3). Compared to the universal vaccination of the primary cohort alone, the current Italian vaccination strategy ('2023–2025 NIP') was cost-effective (i.e., below the conventional [although unofficial] Italian willingness-to-pay [WTP] threshold of 40,000 €/QALY)[69] for all modeled durations of the supplementary vaccination component of the strategy. The lowest ICER for this strategy was 25,700 €/QALY (10-year supplementary vaccination duration), and the highest was 30,382 €/QALY (100-year supplementary vaccination duration). Adding opportunistic vaccination of single cohorts of women ('Single cohorts') to this strategy became cost-effective when supplementary vaccination was continued beyond 5 years, with a 10-year duration resulting in the lowest ICER for this strategy, at 29,108 €/QALY. The 'Mid-adult' strategy, which extended female supplementary vaccination to women ≤45 years of age but without opportunistic vaccination of single cohorts, became cost-effective when supplementary vaccination was continued for 10 or 100 years, with a 100-year duration resulting in the lowest ICER (35,365 €/QALY).

Table 3. Estimated health economic outcomes per 100,000 people of different human papillomavirus vaccination strategies in Italy over a 100-year period.

Vaccination strategy[A]	Treatment costs (€)	Screening costs (€)	Vaccine costs (€)	Total cost (€)	QALYs	ICER (€/QALY)
Primary cohort only	10,510,017	16,786,400	5,094,220	32,390,637	2,135	Comparator
2023–2025 NIP[B]						
5 years	9,984,044	16,750,500	7,259,330	33,993,874	2,075	26,184
10 years	9,746,983	16,741,700	8,239,100	34,727,783	2,045	25,700
100 years	8,690,598	16,735,400	13,933,300	39,359,297	1,907	30,382
Single cohorts[C]						
5 years	9,958,420	16,748,600	8,114,970	34,821,990	2,072	38,127
10 years	9,739,482	16,741,300	8,578,760	35,059,542	2,044	29,108
100 years	8,656,305	16,732,700	15,012,000	40,401,005	1,903	34,412
Mid-adult[D]						
5 years	9,927,541	16,745,100	8,646,610	35,319,251	2,069	43,868
10 years	9,692,403	16,736,600	9,626,370	36,055,373	2,040	38,051
100 years	8,637,421	16,730,500	15,320,500	40,688,421	1,901	35,365

ICER, incremental cost-effectiveness ratio; NIP, national immunization program; QALY, quality-adjusted life year. Treatment costs and QALY data represent diseases attributable to the HPV genotypes included in the 9vHPV vaccine. Costs are in 2019 euros.

[A]All strategies use the 9vHPV vaccine and include universal vaccination of the primary cohort (adolescents 11 years of age) for the full 100-year modeled period. Durations relate only to the supplementary vaccination components of each strategy.

[B]Includes supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age.

[C]Includes supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age, plus opportunistic vaccination of single cohorts of women at 30, 35, and 40 years of age upon HPV DNA screening.

[D]Includes supplementary vaccination of girls/women ≤45 years of age and boys/men ≤18 years of age.

Sensitivity analyses

A one-way deterministic sensitivity analysis was conducted to determine the effect of key input parameters on the model's economic predictions. For all modeled supplementary vaccination strategies that were continued for 5 or 10 years, the parameter with the greatest impact on the health economic outputs of the model was the discount rate (Figure 3, Supplementary Table S15). For example, for a 10-year supplementary vaccination program duration, varying the discount rate from 0% to 5% resulted in an ICER range of 3,301.48–44,157.95 €/QALY for the '2023–2025 NIP' strategy, 4,489.62–49,223.46 €/QALY for the 'Single cohorts' strategy, and 7,111.78–64,149.41 €/QALY for the 'Mid-adult' strategy. However, when supplementary vaccination was continued for the entire 100-year modeled period, the parameter with the greatest impact on the model's outputs was disease disutility, for which a variance of ± 20% resulted in an ICER range of 19,835.15–64,885.65 €/QALY for the '2023–-2025 NIP' strategy 22,460.18–73,549.87 €/QALY for the 'Single cohorts' strategy, and 23,085.77–75,559.19 €/QALY for the 'Mid-adult' strategy. Treatment costs had the smallest impact on the ICER for all supplementary vaccination strategies of all durations, followed by the health utility parameter.

Scenario analyses

A scenario analysis was conducted to explore the public health impact and cost-effectiveness of increasing the VCRs of the male and female primary and supplementary vaccination cohorts (Supplementary Table S16, Supplementary Figure S9). Across 10 scenarios that simulated high VCRs in the supplementary cohorts, the ICER remained below the WTP threshold of 40,000 €/QALY in all analyses except the 'Single cohorts' vaccination strategy scenario with the highest VCRs (95% in all 4 cohorts) and longest modeled duration (10 years). The 'Single cohorts' strategy was the most sensitive of the 3 strategies to these variations in VCR.

Discussion

In this study, we modeled the public health and economic impacts of various supplementary HPV vaccination strategies in Italy compared to vaccination of the primary adolescent cohort alone, from the health care system perspective. Vaccination of the primary cohort over a 100-year period resulted in substantial, sustained reductions in the incidence and mortality rates of all HPV-related cancers compared to no

Figure 3. Deterministic one-way sensitivity analysis of estimated health economic outcomes of different human papillomavirus vaccination strategies in Italy over a 100-year period. ICER, incremental cost-effectiveness ratio; NIP, national immunization program; QALY, quality-adjusted life year. Data represent diseases attributable to the HPV genotypes included in the 9vHPV vaccine. All strategies use the 9vHPV vaccine and include universal vaccination of the primary cohort (adolescents 11 years of age) for the full 100-year modeled period. Durations relate only to the supplementary vaccination components of each strategy. Costs are in 2019 euros. a) Includes supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age. b) Includes supplementary vaccination of girls/women ≤26 years of age and boys/men ≤18 years of age, plus opportunistic vaccination of single cohorts of women at 30, 35, and 40 years of age upon HPV DNA screening. c) Includes supplementary vaccination of girls/women ≤45 years of age and boys/men ≤18 years of age.

vaccination, but only a temporary reduction in the burden of genital warts and RRP. Supplementary vaccination programs with a 5- or 10-year duration had further incremental public health benefits, whereas continuing any of the modeled supplementary vaccination programs for 100 years resulted in more substantial and sustained decreases in the burden of HPV-related diseases compared to vaccination of the primary cohort alone. The incremental benefits of 100-year supplementary vaccination programs were particularly large for anal, head and neck, penile, and vulvar cancers; genital warts; and RRP. These benefits deriving from additional targets of vaccination programs could be taken into account when considering vaccination strategies. Compared to vaccination of the primary cohort alone, all supplementary vaccination strategies were cost-effective (ICER <40,000 €/QALY) when continued for 10 or 100 years. Expanding supplementary vaccination beyond the groups included in the 2023–2025 NIP (i.e., girls/women ≤26 years of age and boys/men ≤18 years of age) – either by increasing the female age limit to 45 years or by adding opportunistic vaccination of single cohorts of women 30, 35, and 40 years of age – averted additional cases of and deaths from HPV-related diseases, with minimal impact on the ICER. The discount rate parameter had the greatest effect on the model's ICER estimations at supplementary vaccination program durations of 5 and 10 years, while disease disutility became the most impactful parameter at a 100-year duration. Scenario analyses predicted that all vaccination strategies would remain cost-effective at higher sub-cohort VCRs, except for a 10-year 'Single cohorts' program with a universal VCR of 95%. In particular, maintaining high VCRs in the long-term projections could have a relevant impact on the results in terms of cost-effectiveness.

To our knowledge, this is the first published analysis of the cost-effectiveness of supplementary vaccination in Italy according to the 2023–2025 NIP recommendation. Our findings are consistent with those of earlier Italian studies that modeled the impact of vaccination with 2vHPV on cervical cancer incidence, which concluded that supplementary vaccination of women 25 years of age would avert additional cases compared to vaccination of the primary cohort alone; however, the current study incorporates additional HPV genotypes and HPV-related disease outcomes and adds a cost-effectiveness analysis.[11,39]

The public health benefits and cost-effectiveness of single-sex supplementary HPV vaccination have been assessed in other countries. Analyses conducted for Belgium, China, the Netherlands, the UK, and the USA using 2vHPV or 4vHPV, and for Japan using 9vHPV, found that catch-up vaccination of older female cohorts would avert additional cases of cervical cancer (and other cancers in both men and women, in the Japanese study) compared to vaccination of adolescent girls alone, albeit with diminishing incremental benefits among older cohorts.[44,70–74] Catch-up vaccination of women ≤25 or ≤26 years of age was estimated to be cost-effective in China, the Netherlands, and Japan, while the Belgian study concluded that catch-up vaccination would be highly cost-effective for women ≤33 years of age and cost-effective for women ≤40 years of age and beyond.[44,70,72,73] In contrast, the US study found that vaccination of screened women >30 years of age to prevent cervical cancer was less cost-effective than screening-based interventions.[71] The UK analysis found that incorporating an assumption that vaccination with 2vHPV would benefit women with prior exposure to HPV substantially improved the cost-effectiveness of catch-up vaccination; no similar assumptions were included in the current model.[74] Finally, an analysis of male catch-up vaccination in the Netherlands found that vaccinating boys and men ≤26 years of age with 2vHPV would avert additional cases of HPV-related diseases among men compared to universal vaccination of the primary cohort alone and was only slightly over the Dutch cost-effectiveness threshold.[75]

Most of the above studies measured a limited set of HPV-related disease outcomes for a single sex (e.g., 5 studies only assessed cervical cancer) and thus did not capture the full benefits of HPV vaccination.[44,70–75] The current analysis incorporated the incidence, mortality, and health care costs of all HPV diseases related to genotypes included in the 9vHPV vaccine in both sexes. Further, by including both males and females in vaccination efforts, we contribute to community-wide immunity. This broader strategy enhances public health by reducing the incidence of HPV-related diseases. Vaccinating males directly reduces their risk of HPV-related diseases, including penile cancer, anal cancer, and genital warts while also decreasing HPV transmission to females, indirectly lowering their risk of HPV-related diseases like cervical cancer, and vice versa. Promoting high vaccination coverage fosters herd immunity, ultimately benefiting everyone, especially those vulnerable to infection. Therefore, implementing inclusive vaccination strategies is vital to mitigating the HPV burden and maximizing the public health impact of vaccination programs. This comprehensive approach is necessary to estimate the true population-level cost-effectiveness of HPV vaccination and likely accounts for our finding that supplementary vaccination in Italy would remain cost-effective for women ≤45 years of age, compared to ≤25 or ≤26 years of age in most previous studies.[44,71–74]

Our approach also incorporated a comparison of the costs and benefits of supplementary vaccination strategies that included different age cohorts and continued for different durations. As expected, strategies that included more individuals for longer durations averted more additional cases of and deaths from HPV-related diseases. However, only the strategies that continued their supplementary component for the full 100-year modeled period resulted in substantial and sustained incremental public health benefits compared to vaccination of the primary cohort alone. A 100-year supplementary program duration was particularly important for genital warts and RRP, as the incidence and/or mortality rates for these diseases rebounded to at or near baseline levels in approximately 10–50 years when shorter (or no) supplementary programs were modeled. Among the 3 modeled 100-year supplementary programs, the 'Mid-adult' strategy averted the most additional cases of and deaths from most HPV-related diseases but had the highest ICER (35,365 €/QALY), while the '2023–2025 NIP' strategy averted fewer additional cases and deaths but with a slightly lower ICER of 30,382 €/QALY.

Our finding that the current model was generally most sensitive to variations in the discount rate is consistent with similar analyses conducted in Japan and Belgium,[44,70] although

not with a US analysis of the cost-effectiveness of HPV vaccination to prevent cervical cancer among women 35–45 years of age, in which the model was robust to this parameter.[71] The model became more sensitive to variations in disease disutility when the supplementary vaccination programs were continued for 100 years. This finding, as well as the model's relative robustness to disease treatment costs, suggests that quality of life benefits contribute more to the economic value of HPV vaccination than do direct health care cost savings.

This study is subject to some known limitations. The analysis used Italy-specific input data and parameters whenever possible, but suitable Italian data were not available for all variables. We attempted to minimize the impact of these input data gaps by using and adjusting the closest equivalent available proxy data (e.g., European or regional Italian data for HPV genotype attribution rates and sexual behavior) and validated population-independent parameters (e.g., variables related to disease natural history). Further, we did not include geographic population-specific differences in our analysis, such as varying HPV infection rates and healthcare access across regions. In Italy, there is not sufficient and detailed data to conduct a stratified analysis based on socioeconomic status. While we recognize that a stratified approach could enhance the model's accuracy and support targeted vaccination strategies and address potential disparities in the population, the current limitations in data availability restrict our ability to perform such analyses. The model assumed a constant rate of HPV vaccine and screening uptake and did not account for changes in vaccine technology, advancements in cancer treatment, and changes in health care and HPV strain evolution or genotypic prevalence shifts to non-vaccine HPV genotypes due to vaccination;[76] future changes in these parameters could affect disease progression and survival rates, thus affecting the model's outputs. The model does, however, include survival improvements over time, and, thus, if there are advancements in treatment technology that influences survival rates, these improvements would be reflected in the model. Our health economic analyses used the conventional Italian WTP threshold of €40,000 euros per QALY, but this value has not been officially updated since 2009.[69] Direct health care costs were obtained from the official hospital and specialist tariffs, which are from 2013;[68] as a result, all costs are likely underestimates. Further, the results presented here represent the payer's cost and did not account for indirect costs or the societal perspective such as productive losses or caregiver costs; including these data would have increased the cost-effectiveness of the modeled vaccination strategies. Additionally, implementing supplementary vaccination programs over 100 years presents several potential practical challenges not explicitly modeled in this study. Potential challenges, including declining vaccination rates over time, funding challenges, and vaccine hesitancy, should be considered and explored in future research. Finally, the complexity of the model precluded any probabilistic sensitivity analyses. However, we were able to conduct deterministic sensitivity analyses to assess the robustness of the model's outputs to uncertainty in key input variables.

In conclusion, the Italian 2023–2025 NIP continues the universal vaccination of adolescents and recommends supplementary immunization up to the age of 26 for girls/women and 18 for boys/men. In this study, we found that, compared to vaccination of adolescents alone, the current Italian NIP would reduce the burden of HPV-related diseases and would already be highly cost-effective within 5 years, even when considering only direct health care costs from the payer's perspective. Expanding immunization to cohorts of women attending routine fully funded cervical screening appointments (~47% of eligible women) would also be a cost-effective strategy although expanding immunization to all women ≤45 years of age was predicted to be the strategy with the greatest public health benefits while remaining cost-effective if continued for 10 or 100 years. The implementation of policies and strategies including additional cohorts should be performed together with awareness campaigns, routine vaccination reminders, and possible government subsidies to accelerate HPV elimination.

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AC, CP, and FS are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and may own restricted stock units and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. CS and SB have no conflicts of interest. The study was funded by a research grant from MSD Italy with PIN S.c.r.l. (Polo Universitario di Prato available online: https://www.pin.unifi.it/); AB and PB were principal investigators of the research.

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Ethics approval

Since this was a modeling study using de-identified published data as model inputs, no ethical approval or informed consent was required.

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