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Cost-effectiveness of human papillomavirus vaccination and screening in Spain

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ABSTRACT

Background: In Spain, prophylactic vaccination against human papillomavirus (HPV) types 16 and 18 is being offered free-of-charge to one birth cohort of girls aged 11–14. Screening is opportunistic (annual/biannual) contributing to social and geographical disparities.

Methods: A multi-HPV-type microsimulation model was calibrated to epidemiologic data from Spain utilising likelihood-based methods to assess the health and economic impact of adding HPV vaccination to cervical cancer screening. Strategies included (1) screening alone of women over age 25, varying frequency (every 1–5 years) and test (cytology, HPV DNA testing); (2) HPV vaccination of 11-year-old girls combined with screening. Outcomes included lifetime cancer risk, life expectancy, lifetime costs, number of clinical procedures and incremental cost-effectiveness ratios.

Results: After the introduction of HPV vaccination, screening will need to continue, and strategies that incorporated HPV testing are more effective and cost-effective than those with cytology alone. For vaccinated girls, 5-year organised cytology with HPV testing as triage from ages 30 to 65 costs 24,350€ per year of life saved (YLS), assuming life-long vaccine immunity against HPV-16/18 by 3 doses with 90% coverage. Unvaccinated girls would benefit from organised cytology screening with HPV testing as triage; 5-year screening from ages 30 to 65 costs 16,060€/YLS and 4-year screening from ages 30 to 85 costs 38,250€/YLS. Interventions would be cost-effective depending on the cost-effectiveness threshold and the vaccine price.

Conclusions: In Spain, inequitable coverage and overuse of cytology make screening programmes inefficient. If high vaccination coverage among pre-adolescent girls is achieved, organised cytology screening with HPV triage starting at ages 30 to at least 65 every 4–5 years represents the best balance between costs and benefits.

1. Introduction

Over the past several years, the introduction of more accurate cervical cancer screening and diagnostic tests and the development of efficacious prophylactic vaccines against human papillomavirus (HPV), the necessary cause of cervical cancer, have stirred debate in countries with secondary prevention programmes. The effectiveness of cytology screening in

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reducing cervical cancer incidence and mortality rates has varied across different settings. In countries that have achieved population-wide coverage of cytology-based screening and access to treatment for women at highest risk, the benefit of screening is unquestionable.[1,2] The efficiency of this screening policy has been thoroughly demonstrated for the Nordic countries, but despite the efforts only Finland has achieved an 80% decrease in incidence after 46 years of wide organised screening.[2,3] Opportunistic screening of variable quality has generally been less effective and less cost-effective.[2,4,5] At present, two vaccines protect against two of the 15 oncogenic genital HPV types that cause the majority of cervical cancers and have demonstrated high efficacy against persistent type-specific infection and precancerous lesions; however, roughly 30% of cervical cancer cases are attributable to HPV types not targeted by the vaccines. Moreover, with pre-adolescent girls being the primary target group for vaccination, older women beyond the recommended age of vaccination will not benefit from the vaccines. Screening, therefore, cannot be discontinued, even with high vaccination uptake in the population. In many countries, high-frequency screening with cytology in conjunction with widespread HPV vaccination may be too costly and inefficient, although new approaches using HPV DNA testing may help.[2,6]

In Spain, cervical cancer incidence and mortality are 7.6 and 2.2 per 100,000 woman-year, respectively.[7] Although a low-risk country with only slightly lower screening coverage rates than Finland, Spain, still experiences twice the incidence of Finland; however, changes in sexual lifestyles in young Spanish cohorts have been associated with a higher risk of HPV infection in recent years and consequently higher incidence of cervical cancer.[8,9] Cervical cancer screening in Spain is opportunistic, contributing to social and geographical disparities in screening practices,[10] as is experienced in other industrialised countries. Conventional cytology is the reference method and colposcopy is often performed as a complementary evaluation. Despite recommendations for triennial screening based on regional protocols, annual or biannual cytology has been largely established, primarily among those of high and middle social classes, leading to an overuse of cytology and a low incidence of abnormal results.[4,5,9,10] Correcting these deviations from protocols offers opportunities to improve preventive efforts in a more efficient manner. HPV vaccination was approved in October 2007 by Spain's Interterritorial Council of the National Health System with planned implementation by each autonomous region before the end of 2010. Prophylactic vaccination is being offered free-of-charge for one cohort of girls ranging in age from 11 to 14 years as a part of the regular immunisation schedule in most regions. School-based immunisation programmes are available in several regions with traditional high vaccination coverage (i.e. for HBV vaccines).

The introduction of HPV vaccination in countries with ongoing secondary prevention is not straightforward and healthcare decision makers will have to reprioritise health expenditures and accommodate the fiscal space.[11] Decision-analytic models that synthesise the best epidemiologic, clinical and economic data can project long-term health and economic outcomes simulating different cancer prevention strategies that integrate vaccination-screening approaches.[12] Using a decision-analytic approach, a cost-effectiveness analysis is presented to address novel screening protocols for vaccinated girls and adapted screening guidelines for screening women who were not vaccinated in preadolescence.

2. Model and methods

2.1. Analytic approach

A multi-HPV-type microsimulation model of cervical cancer was adapted from a previously published model[13–15] and calibrated to the best epidemiologic, clinical and economic data available from Spain. Using the calibrated model, we assessed the health and economic impact of introducing a pre-adolescent HPV vaccination programme in the context of cervical cancer screening in Spain. We evaluated a range of relevant uncertainties by conducting one- and two-way sensitivity analyses and a probabilistic sensitivity analysis.

For the purpose of addressing timely policy questions in Spain, we performed three general analyses. The first was addressed to propose screening guidelines for women who were not vaccinated in preadolescence, considering all screening strategies in the absence of vaccination. The second analysis focused on novel screening protocols for women who were vaccinated in preadolescence, considering strategies with HPV vaccination followed by screening in adulthood. The third analysis considers all screening strategies with and without vaccination.

Analyses were conducted from the societal perspective, with future costs and health outcomes discounted annually at 3%. Outcomes related to cervical cancer prevention included lifetime cancer risk, life expectancy, lifetime costs and number of clinical procedures (cytologies, HPV tests and colposcopies). Performance of alternative strategies was measured using incremental cost-effectiveness ratios (ICERs), calculated as the additional Euro (€) divided by the additional life year saved (YLS) of a strategy in relation to the next most costly strategy. Strategies that were more costly and less effective or less costly and less cost-effective than an alternative strategy were eliminated from the cost-effectiveness calculations. There is no universal willingness-to-pay threshold, below which an intervention would be considered 'good value for money'; however, several benchmarks have been used in the European Union, ranging from 20,000€/quality-adjusted life year (QALY) in the Netherlands[16] to 50,000€/QALY in France.[17] The National Institute for Clinical Excellence[18] has adopted a cost-effectiveness threshold range of 20,000£/QALY to 30,000£/QALY. The World Health Organisation's Commission on Macroeconomics and Health recommends that an intervention be considered very cost-effective if the ICER is less than the country's per capita gross domestic product (GDP; 23,069€ for Spain in 2005) and cost-effective if the ICER is less than three times the per capita GDP (69,207€ for Spain in 2005).[19] A review of economic evaluations of health technologies published in Spain suggests that health interventions with a cost per QALY of 30,000€ are efficient.[20]

2.2. Model

The individual-based stochastic model has been previously described.[13–15] In short, individual girls representing a single

birth cohort are followed from age 9 years throughout their lifetime as they transition monthly between mutually exclusive health states. Transitions depend on HPV type (categorised as high-risk type 16, high-risk type 18, other high-risk types and low-risk types[21]), age and history of prior type-specific infection (i.e. natural immunity). Incidence of

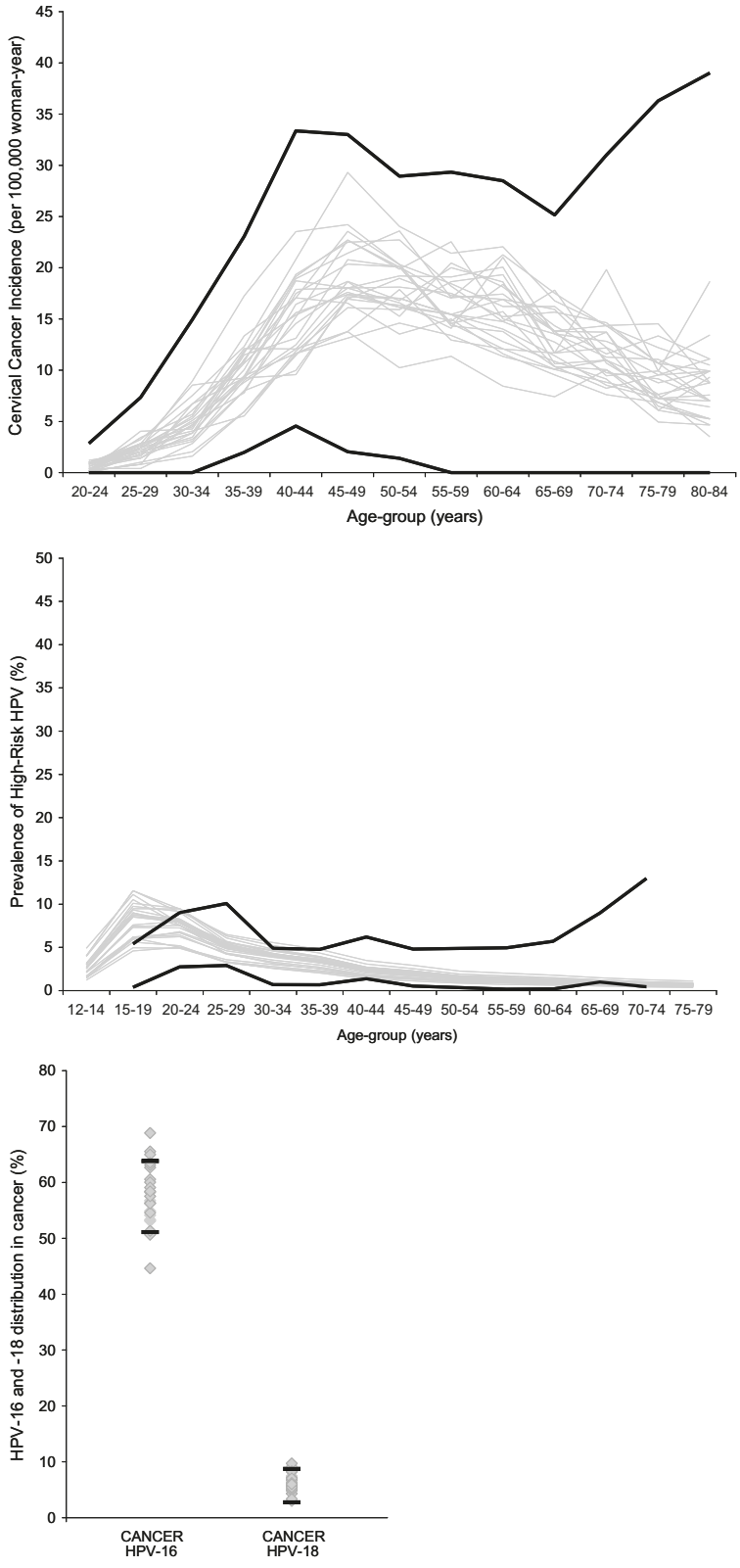


Fig. 1 – Model calibration outputs. Sample of good-fitting parameter sets of model simulation (grey curves) compared with the 95% confidence interval of the empirical data (bold curves) from Spain for cervical cancer incidence, prevalence of high-risk HPV and HPV-16 and -18 distribution.

HPV infection is a function of age and individual-level characteristics, but does not change over time in response to sexual activity or HPV prevalence in the population. Women with HPV infection can progress to low- or high-grade cervical disease, classified as cervical intraepithelial neoplasia grade 1 (CIN 1) or grades 2, 3 (CIN 2, 3), respectively, but most regress on their own. Women with persistent infection with high-risk types and high-grade lesions may progress to invasive cancer, and then can be detected through symptoms or screening, be diagnosed and treated, or progress to the next stage of cancer. Women with cancer are subject to stage-specific survival rates, although all women face all-cause age-specific competing mortality risks from other causes.

2.3. *Epidemiologic data*

Baseline natural history model inputs were based on the best available data, assuming the mechanism of cervical carcinogenesis is not different between countries. The model was then calibrated to empirical data from published literature on Spain—largely based on the results generated by ICO/IARC collaborative studies—since we assumed that epidemiology, risk factors and age-specific cervical cancer rates differ between settings. Age-specific prevalence of high-risk HPV types in women with normal cytology was from two studies carried out in the Barcelona province[22,23]; HPV types 16 and 18 distribution in cervical cancer was from four studies carried out in different Spanish regions[24–27]; and age-specific cancer incidence was from 12 population-based registries from Spain reported in the cancer incidence in five continents (CI5C).[28,29]

Details of the model parameterisation process can be found in previous publications[13–15] and in the Supplementary material. Briefly, plausible ranges for each input parameter were determined, and multiple simulations were undertaken with different combinations of these values, creating over 2 million unique parameter sets. The outcomes produced by each parameter set were scored according to their fit with multiple calibration targets using a likelihood-based approach. A composite goodness-of-fit score was computed for each parameter set by summing the log likelihood of each model outcome. Fig. 1 shows examples of model output from a sample of a good-fitting parameter sets compared with the 95% confidence intervals of empirical calibration target data. Cost-effectiveness analyses were conducted with a sample of good-fitting parameter sets to incorporate the effect of parameter uncertainty. Results were reported as the mean and range of outcomes, and incremental cost-effectiveness ratios were calculated as the incremental mean costs divided by the incremental mean effects of two strategies.[30]

2.4. *Cost data*

Costs included direct medical and non-medical costs from Spain in 2005€ associated with screening, diagnosis and treatment (e.g. tests, procedures and hospitalisations) (Table 1). Costs of vaccination included the costs of three doses, administration, supplies and wastage. We assumed a cost per dose of 104€ according to the maximum price established by the Interdepartmental Committee on Pharmaceutical Prices.

Table 1 – Selected model assumptions and direct costs of screening and vaccination.[a]

Variable	Value
Performance characteristics of diagnostics	
Cytology performance for detection of CIN[b,c]	
Probability of abnormal cytology result given CIN 1	70%
Probability of abnormal cytology result given CIN 2, 3 or worse	80%
Probability of normal cytology result given no CIN	95%
HPV DNA test performance for detection of CIN[c,d]	
Probability of HR HPV DNA positivity given CIN 1	78%
Probability of HR HPV DNA positivity given CIN 2, 3 or worse	88%
Probability of HR HPV DNA negativity given no CIN (specificity)	93%
Total medical and non-medical direct costs (€)	
Screening test	
Initial office visit	28€
Subsequent office visit	23€
Cytology screening test (Pap smear)	34€
HPV DNA test (hybrid-capture II)	48€
Patient time and transport	17€
Diagnostic follow-up	
Office visit	22€
Colposcopy	130€
Biopsy	67€
Patient time and transport	18€
Treatment of CIN 1, 2, 3	
Office visit	167€
Procedure for CIN 1	941€
Procedure for CIN2, 3	1367€
Cancer treatment	
Stage I	5435€
Stage II	12,633€
Stage III	22,715€
Stage IV	33,079€
HPV vaccine cost per dose	
Vaccine[e]	104€
Administration and supplies	5€

[a] Parameters shown represent the values used in the base case. CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; DNA = deoxyribonucleic acid; HR = high risk.
[b] Abnormal cytology is defined as low-grade intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) or cancer.
[c] Tests for screening include cytologic examination of cervical cells on a Papanicolaou smear and DNA testing for HPV in cervical cell samples with the use of the hybrid-capture method (hybrid-capture II HPV DNA test, HCII).
[d] Probability of HR HPV DNA positivity given high-risk HPV is assumed to be 100%, however, we define the clinically-relevant sensitivity of HPV DNA testing to be the probability of HR HPV DNA positivity given CIN 1 and CIN 2, 3+. Note that these are implied values, not inputs to the model.
[e] Cost per dose according to the maximum price established by the Interdepartmental Committee on Pharmaceutical Prices.

Since the price of the vaccine can vary based on sales volume by autonomous region, we varied it from 50€ to 200€ in sensitivity analysis. Direct medical and non-medical costs were ob-

tained from the published literature.[31] In sensitivity analyses, costs of cancer, cytology and colposcopy were varied widely.

2.5. *Vaccination strategies*

For the base case, we assumed 90% coverage of vaccination in girls aged 11 years—before sexual debut—in combination with different screening strategies in adulthood. We considered such coverage based on the Spain National Health Ministry which reports coverage of infant vaccines between 90% and 95%. All vaccinated girls were assumed to receive the recommended three doses of vaccine, which provided life-long protection against HPV-16 and -18 but kept the same rate of infection for other high-risk HPV types as girls who were not vaccinated. Given the uncertainty in vaccine properties, we explored the implications of duration of protection (10 years to lifetime), efficacy (70–100%), price (50€–200€) and different levels of coverage (50–100%) in sensitivity analyses.

2.6. *Screening strategies*

Screening strategies differed by age of initiation (18, 25 and 30 years), age of termination (50 and 65 years, lifetime), combination of the primary and triage tests (cytology, HPV DNA testing) for atypical squamous cells of uncertain significance (ASCUS), frequency of screening events (every 1–5 years) and switch age for protocols that allow different tests in younger and older women (35 and 40 years). All screening strategies were assessed with and without HPV vaccination.

Three specific screening protocols were selected to consider plausible alternatives by local experts and clinical societies and included (1) cytologic evaluation of cervical cells with a Pap test with repeated cytology triage for ASCUS ('cytology alone'); (2) cytology followed by HPV DNA testing of cervical specimens for ASCUS ('cytology with HPV testing triage'); (3) cytology with HPV testing triage for ASCUS for younger women and HPV testing in combination with cytology for older women ('combined cytology and HPV'). Other assumptions regarding screening strategies are provided in the Supplementary material.

For the base case, we assumed 90% coverage of both vaccination and screening to enable a balanced comparison of primary and secondary prevention strategies. Since the implementation of HPV vaccination and cervical screening system in Spain differ by autonomous region, we modelled various levels of screening and vaccination coverage along with vaccine price to reflect these differences.

3. Results

3.1. *Epidemiological impact of screening alternatives*

3.1.1. *Reduction in lifetime risk of cervical cancer*

Fig. 2 shows the reductions in lifetime risk of cervical cancer for screening alone (lower bars), vaccination alone (central

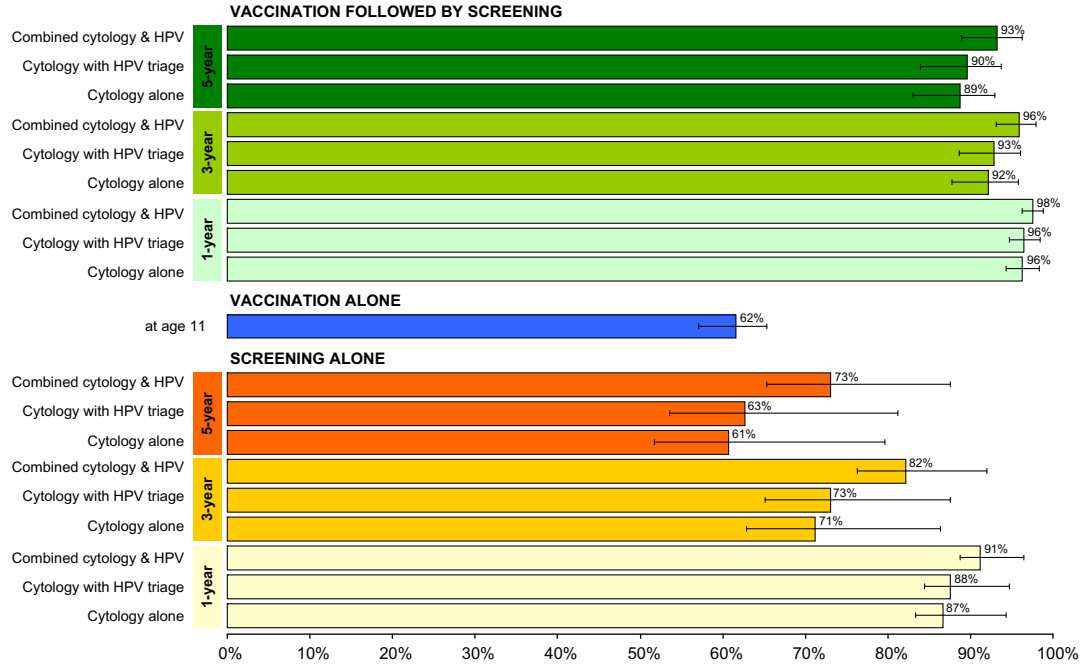
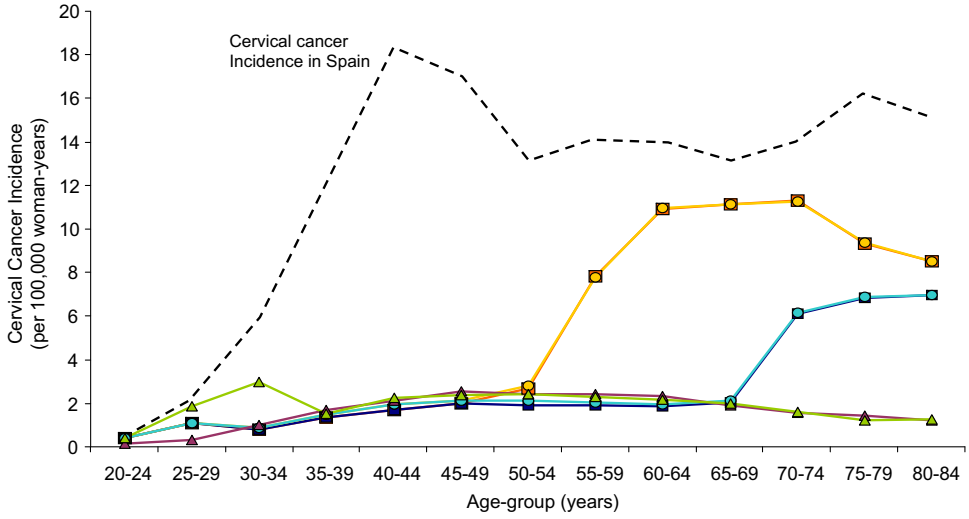


Fig. 2 – Mean reduction in lifetime risk of cervical cancer. The length of the bars represents the mean values, and the error bars represent the minimum and maximum values, across the 50 parameter sets. Strategies considered are screening alone (lower bars), vaccination alone (central bar) and combined strategies (upper bars). Screening starts at age 25 years for lifetime and switch age occurred at age 35 years. Both screening and vaccination coverage were assumed to be 100% and efficacy was 100% with life-long protection. Cytology alone: conventional cytology with repeated cytology triage for ASCUS; cytology with HPV triage: conventional cytology followed by HPV DNA testing triage for ASCUS; combined cytology and HPV: conventional cytology with HPV testing triage for ASCUS for younger women and HPV testing in combination with cytology for older women.

bar) and combined strategies (upper bars). Screening is assumed to start at age 25 years and continue over the lifetime with a switch age (when relevant) at age 35 years. Both screening and vaccination coverage are assumed to be 100% to provide a comparison of the maximum benefits for each approach, and vaccine efficacy is 100% for types HPV-16 and -18 with life-long protection. Strategies that incorporate HPV DNA testing are more effective than those with cytology alone assuming the same screening frequency. Strategies that include both pre-adolescent vaccination and screening are always more effective than vaccination or screening alone, irrespective of screening frequency and with less uncertainty. A strategy of pre-adolescent vaccination followed by every 5-year cytology with HPV testing triage for ASCUS in women younger than 35 years old and HPV testing with cytology in older women is more effective than either modality alone and with less uncertainty (93%; range = 89–96%).

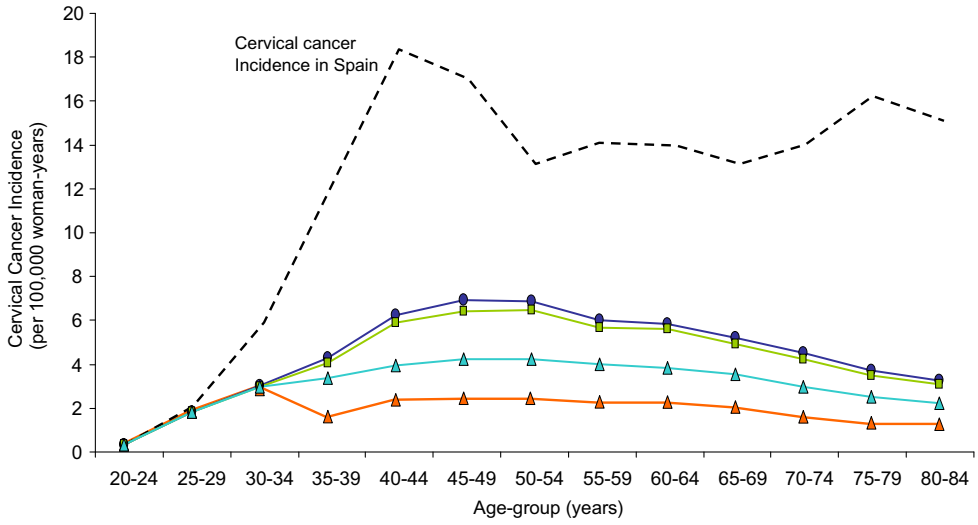
3.1.2. *Cervical cancer incidence*

The observed and predicted age-specific cervical cancer incidences for different scenarios are shown in Figs. 3 and 4. The tables displayed below the graphs depict the total cost per woman discounted at 3% per year and the number of cytologies, HPV tests and colposcopies per 1000 woman-years for each strategy. In Fig. 3, all predicted curves represent an annual screening strategy using cytology alone with 90% coverage and varying the age interval of screening and number of follow-up visits for women with ASCUS cytology. Screening ASCUS women every 3 months for 3 years (12 follow-up visits) prevents nearly equal as screening every 6 months for 2 years (four follow-up visits) at the same age interval, but costs more (1287€ versus 1021€ at age interval 25–50 and 1648€ versus 1309€ at age interval 25–65) and results in more diagnostic procedures. Starting screening before age 30 reduces incidence marginally, though the total cost per woman changes considerably (1776€ starting at age 18 versus 1137€ at age 30) with a similar number of diagnostic procedures per 1000 woman-years. However, extending the age of screening beyond age 50 has a large influence on preventing incidence at older ages. Fig. 4 illustrates age-specific cervical cancer incidences for different screening strategies, all with 90% coverage and starting at age 30 until 85 years. A strategy of 5-year cytology alone results in similar cancer rates with a total cost per woman somewhat higher than a strategy that integrates HPV DNA testing as a triage for ASCUS at the same screening frequency. A strategy that involves 5-year cytology with HPV triage for ASCUS with a switch at age 35 to combined cytology with HPV testing prevents 15% more cervical cancer than either 5-year strategy above, but costs nearly double (414€). Screening with cytology alone every year instead of every 5 years further reduces the overall incidence rates by less than 2 per 100,000 woman-years, but increases the total cost per woman fourfold (1137€ versus 287€). Extending the age interval of screening to younger women is unattractive (data not shown); for instance, 5-year cytology with HPV triage for ASCUS between ages 30–85 achieves similar cancer reduction



	Follow-up frequency in ASCUS cytology results	Age interval of screening	Total cost-woman (€)	No. of cytologies per 1000 woman-years	No. of colposcopies per 1000 woman-years
	Screening every 3 month for 3 years	25-50	1287 €	1314	54
		25-65	1648 €	1268	47
	Screening every 6 months for 2 years	25-50	1021 €	1049	38
		25-65	1309 €	1016	33
	Screening every 12 months for 3 years	18-85	1776 €	881	25
		30-85	1137 €	869	23

Fig. 3 – Impact on cervical cancer incidence and clinical procedures of interval age of screening and follow-up frequency of women having ASCUS cytology results. All strategies are conventional cytology with repeat cytology triage for ASCUS assuming 90% coverage. We consider women with ASCUS cytology results screened every 3 months for 3 years (12 follow-up visits), every 6 months for 2 years (four follow-up visits) or every 12 months for 3 years (three follow-up visits).



	Screening strategy	Age interval of screening	Total cost-woman (€)	No. of cytologies per 1000 woman-years	No. of HPV tests per 1000 woman-years	No. of colposcopies per 1000 woman-years
	5-year cytology alone [a]	30-85	€ 287	201	0	6
	5-year cytology with HPV triage for ASCUS [b]	30-85	€ 280	192	8	6
	5-year combined cytology and HPV [c]	30-85	€ 414	199	182	7
	1-year cytology alone [a]	30-85	€ 1137	869	0	23

Fig. 4 – Impact on cervical cancer incidence and clinical outcomes of different screening strategies. All strategies assume 90% coverage from ages 30 to 85 years and switch age occurred at age 35 years. Follow-up frequency for women with positive cytology results is every 12 months and after two negative results women return to the routine screening interval. [a]Cytology alone: conventional cytology with repeated cytology triage for ASCUS; [b]cytology with HPV triage: conventional cytology followed by HPV DNA testing triage for ASCUS; [c]combined cytology and HPV: conventional cytology with HPV testing triage for ASCUS for younger women and HPV testing in combination with cytology for older women.

as screening women between ages 25 and 85 (58% and 59%, respectively), but increases the total cost per woman by 20% (280€ and 337€, respectively). In contrast, restricting the age interval of screening from 30–85 to 30–65, reduces both health benefits and cost in similar magnitudes.

3.2. *Economic impact*

3.2.1. *Cost-effectiveness of screening*

For women who were not vaccinated in preadolescence, screening strategies that employ new HPV testing technology are consistently found to be efficient; in contrast, cytology alone at any frequency and age interval is always dominated by strategies that include HPV testing. Cytology screening with HPV triage for ASCUS every 5 years starting at age 30 until 65 has a cost of 16,060€/YLS, compared to no intervention (Table 2A). Screening with this same strategy every 4 years between the ages of 30 and 85 has an incremental cost of 38,250€/YLS, compared with the next best alternative. Allowing for different screening approaches with HPV testing in younger and older women between ages 25 and at least 65 every 3 or 2 years costs more than 100,000€/YLS. Other combinations of these strategies are less attractive; for example, both strategies at annual screening frequency starting at age 18 years and continuing for the lifetime exceed 1 million €/YLS.

3.2.2. *Cost-effectiveness of vaccination plus screening*

For women who were vaccinated in preadolescence, screening with cytology alone regardless of the frequency and age interval are also dominated by strategies that include HPV testing. Under assumptions of 90% vaccination and screening coverage and 100% efficacy with life-long vaccine immunity against HPV-16/18 by 3 doses for women who were vaccinated in preadolescence, screening with cytology and HPV triage every 5 years ages 30–65 has an expected incremental cost-effectiveness ratio of 24,350€/YLS, compared to no intervention (Table 2B). Increasing the screening frequency to less than every 5 years results in all strategies exceeding 90,000€/YLS and reaching nearly 5 million €/YLS for annual screening starting at age 18 years over the lifetime.

3.3. *Sensitivity analysis*

Fig. 5 shows the impact of varying parameters and assumptions on the cost-effectiveness results for a strategy of vaccination followed by cytology with HPV triage for ASCUS every 5 years at 90% coverage for both, compared to no intervention (ICER = 24,350€/YLS in the base case). The most influential factors are the per dose cost of the vaccine, low vaccination or low screening coverage and a reduction of the average duration of vaccine immunity without a booster. Ratios are more sensitive to screening coverage than vaccination

Table 2 – Total lifetime costs, lifetime risk of cervical cancer and incremental cost-effectiveness ratio for screening strategies.

Strategy[a]	Screening frequency (years)	Age interval of screening	Total expected lifetime cost[b]	% Reduction in cervical cancer	ICER
Natural history			€18		
(A) Women who were not vaccinated in preadolescence					
Cytology alone	1–5	25/30–65/lifetime			Dominated[c]
Cytology with HPV triage	5	30–65	€246	51.0	€16,060
Cytology with HPV triage	4	30–85	€346	67.7	€38,250
Combined cytology and HPV	3	25–65	€605	68.0	€123,730
Combined cytology and HPV	3	25–85	€705	78.3	€194,400
Combined cytology and HPV	2	25–85	€1031	83.8	€286,350
Combined cytology and HPV	2	18-lifetime	€1254	85.2	€538,435
Cytology with HPV triage	1	18-lifetime	€1768	86.2	€1,070,990
Combined cytology and HPV	1	18-lifetime	€2300	90.1	€1,098,120
(B) Women who were vaccinated in preadolescence					
Vaccination + cytology alone	1–5	25/30–65/lifetime			Dominated[c]
Vaccination + cytology with HPV triage	5	30–65	€513	80.4	€24,350
Vaccination + cytology with HPV triage	4	30–65	€550	81.3	€97,000
Vaccination + combined cytology and HPV	4	30–65	€655	84.3	€162,030
Vaccination + combined cytology and HPV	4	30-lifetime	€747	91.0	€308,785
Vaccination + combined cytology and HPV	4	25–85	€812	91.0	€330,865
Vaccination + combined cytology and HPV	3	25–85	€960	92.8	€449,560
Vaccination + combined cytology and HPV	2	25–85	€1281	94.6	€1,047,620
Vaccination + combined cytology and HPV	2	18-lifetime	€1500	95.2	€2,066,255
Vaccination + combined cytology and HPV	1	18-lifetime	€2547	96.5	€4,803,795
(C) Comprehensive analysis[d]					
Cytology with HPV triage	5	30–65	€246	51.0	€16,060
Vaccination + cytology with HPV triage	5	30–65	€513	80.4	€43,390
Vaccination + cytology with HPV triage	4	30–65	€550	81.3	€97,000
Vaccination + combined cytology and HPV	4	30–65	€655	84.3	€162,030
Vaccination + combined cytology and HPV	4	30-lifetime	€747	91.0	€308,785
Vaccination + combined cytology and HPV	4	25–85	€812	91.0	€330,865
Vaccination + combined cytology and HPV	3	25–85	€960	92.8	€449,560
Vaccination + combined cytology and HPV	2	25–85	€1281	94.6	€1,047,620
Vaccination + combined cytology and HPV	2	18-lifetime	€1500	95.2	€2,066,255
Vaccination + combined cytology and HPV	1	18-lifetime	€2547	96.5	€4,803,795

This table shows the costs, benefits and incremental cost-effectiveness ratios (ICERs) associated with strategies of screening only and vaccination plus screening.

[a] Strategies included in the analysis were 'cytology alone', 'cytology with HPV triage' and 'combined cytology and HPV' at screening frequency between 1 and 5 years and age interval of screening of 18-lifetime, 25-lifetime, 30-lifetime, 25–85 and 25–65. The switch age for combined cytology and HPV strategies that allow different test in younger and older women was 35 or 40-year-olds. We assumed 90% coverage for vaccination and screening and life-long vaccine immunity against HPV-16/18 by 3 doses. Strategies not shown in the table were dominated.

[b] Costs were discounted at an annual rate of 3%.

[c] Dominated: strategies that were more costly and less effective (i.e. strongly dominated) or less costly and less cost-effective (i.e. weakly dominated) than an alternative strategy.

[d] The comprehensive analysis includes screening alone, vaccination alone and vaccination plus screening.

coverage and especially when both are changed simultaneously. If vaccine-induced immunity lasts only 10 years, vaccination plus screening has a ratio of nearly 30,000€/YLS. When the vaccine per dose cost decreases by half, the strategy becomes increasingly attractive at a cost of 16,715€/YLS; in contrast, the ratio increases to around 36,000€/YLS when the per dose cost is doubled.

3.3.1. *Cost-effectiveness of screening alone versus vaccination plus screening*

We also conducted a more comprehensive analysis in which we compared all strategies, including screening alone, vaccination alone and vaccination plus screening (Table 2C). Cytology screening with HPV triage for ASCUS every 5 years starting at age 30 until 65 has a cost of 16,060€/YLS, compared to no intervention. Combining this screening strategy with vaccination in preadolescence has an incremental cost of 43,390€/YLS. Vaccination alone and other combinations of screening alone are dominated. The remaining cost-effective strategies combining vaccination and screening exceed 90,000€/YLS.

In order to reflect variations among autonomous regions within Spain, we modelled different levels of vaccination and screening coverage in combination with vaccine price and the ICERs were evaluated according to different cost-effectiveness thresholds. Fig. 6 shows the ICERs (€/YLS) for vaccination plus 5-year cytology with HPV triage for ASCUS considering combinations of 50% and 90% coverages for vaccination and screening, at different levels of cost per dose

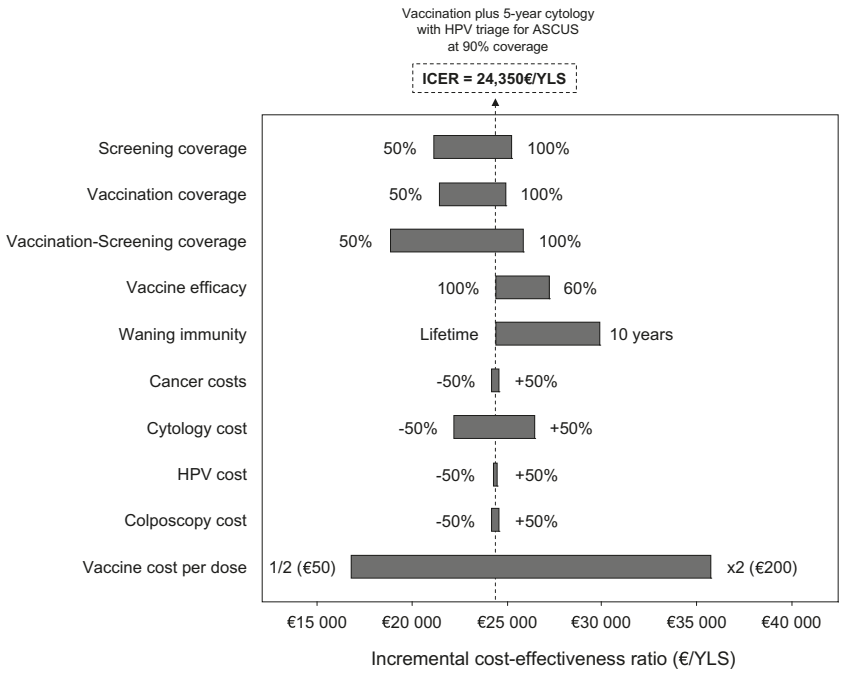


Fig. 5 – One-way sensitivity analysis. Shown is the range of the incremental cost-effectiveness ratios (ICERs) as a result of varying parameters and assumptions for a strategy of vaccination plus 5-year cytology with HPV triage for ASCUS at 90% coverage for both. The ICER assuming base case assumptions is 24,350€/YLS.

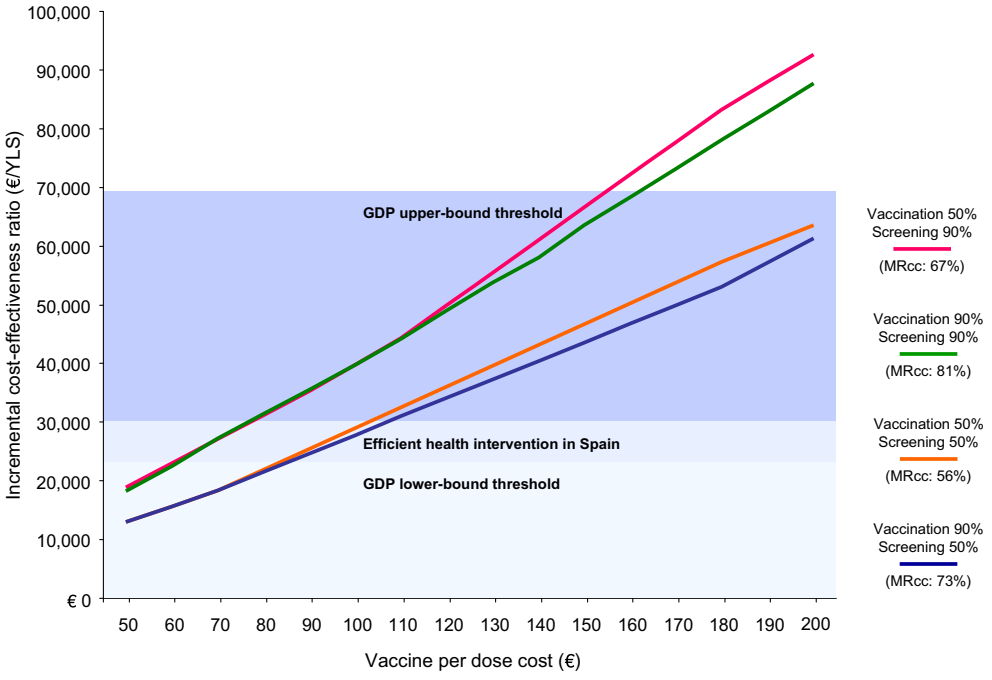


Fig. 6 – Cost-effectiveness of vaccination plus 5-year cytology with HPV triage for ASCUS. Different levels of vaccination coverage (50% and 90%) and screening coverage (50% and 90%) in combination with vaccine price (from 50€ to 200€). The interval age for all strategies is from 30 to 65 years. Different cost-effectiveness thresholds are shaded (per capita gross domestic product (GDP) lower-bound: 23,069€/YLS; efficient health intervention in Spain: 30,000€/YLS; per capita GDP upper-bound: 69,207€/YLS). Mean reduction in lifetime risk of cervical cancer (MRcc) is shown in brackets.

from 50€ to 200€, compared to the next best strategy. When screening coverage is 50%, the combined strategy is cost-effective at a per dose cost below 90€ based on the GDP lower-bound threshold (23,069€) and 110€ based on the threshold defined for efficient health interventions in Spain (30,000€). When screening coverage is 90%, the costs per dose at which

the strategy exceeds the cost-effectiveness thresholds in Spain are lower; for example, the strategy exceeds the GDP upper-bound threshold when the per dose cost reaches 150€, whereas at the lower screening coverage rate, the strategies exceed the upper-bound threshold at a per dose cost greater than 200€. While this combined strategy is cost-effective under different assumptions of coverage depending on the threshold, only vaccination plus 5-year cytology with HPV triage for ASCUS at 90% coverage for both vaccination and screening achieves a lifetime cervical cancer reduction of 80% (green line); and costs 47,200€/YLS compared to 4-year cytology with HPV triage for ASCUS assuming the base case per dose vaccine cost.

4. Discussion

Our analysis suggests that organised screening in Spain can result in greater reductions in cervical cancer incidence, even in the absence of HPV vaccination and especially when screening incorporates HPV DNA testing technology. When strategies include HPV vaccination, reductions in cancer incidence are even greater, ranging from 89% to 98%, assuming 100% coverage for both vaccination and screening. These results favour a national immunisation programme achieving high coverage rates.[32] Newer strategies for screening are being considered in light of HPV vaccination, including HPV testing for primary screening with cytology triage; however, we purposefully restricted the analysis to evaluate screening strategies used in current practice and therefore did not include possible future strategies.

Issues related to screening start and stop ages and how often to screen women with ASCUS were evaluated. Given low cancer incidence rates before age 30 years, starting screening at earlier ages increases costs with little health benefit. Spain has one of the longest average life expectancies among women worldwide (84 years in 2006)[33] and cancer incidence rates remain high until older ages[7,28]; therefore extending the age of screening beyond 50 years results in a major decline in cervical cancer incidence. Our results also suggest that intensive follow-up of women with ASCUS over a long period does not contribute to a relevant reduction in cervical cancer cases but increases costs by up to 25%.

One of the most important questions with regard to cervical screening is how to efficiently screen women who have been vaccinated in preadolescence. There are several reasons why screening needs to be continued after the introduction of HPV vaccination: current vaccines do not protect against all HPV types, although included high-risk HPV types 16 and 18 are responsible for most cases of cervical lesions and some degree of cross-protection against other HPV types is likely; the duration of immunity is unknown; and HPV vaccination in pre-adolescent girls will not have immediate impact on older women. Therefore, it will be essential to instruct young adolescents about the importance of continuing screening after vaccination according to age-based protocols. Our model suggests that in Spain, women who have been vaccinated in preadolescence would benefit from organised screening every 5 years using cytology with HPV triage for ASCUS, beginning at age 30 until 65. These interventions are potentially cost-effective, compared to no intervention considering a threshold range of 23,000€/YLS–69,000€/YLS as suggested by WHO and at a willingness-to-pay threshold of 30,000€/YLS defined for efficient health interventions in Spain. The cost-effectiveness results are robust under a variety of scenarios, although waning vaccine efficacy and vaccination and screening coverage are influential. Several CEA analyses have been performed in Europe[16,17,34–37] with different modelling approaches and assumptions, screening strategies, epidemiological and economic data that cannot easily be reconciled without a formal comparison. Despite these differences, pre-adolescent vaccination of girls has been consistently found to be attractive in the context of current screening practices, provided there is complete and life-long vaccine immunity and high vaccination coverage. Incremental cost-effectiveness ratios of adding HPV vaccination to screening strategies are higher than considering screening alone. Assuming the base case per dose cost of 104€, vaccination plus 5-year cytology with HPV triage for ASCUS at 90% coverage for both vaccination and screening costs 24,350€/YLS, compared to no intervention. This ICER is cost-effective at a threshold range of 23,000€/YLS–69,000€/YLS, but if we consider the most restrictive benchmark, less than 23,000€/YLS, the price of vaccination should be below 60€–70€ per dose to be cost-effective which probably is already the case under competitive selling to the public sector. These findings are consistent with a study[38] in the Netherlands that noted that the price of the vaccine and the threshold are determinant to consider HPV vaccination cost-effective.

Another important question in Spain focuses on women who are older and not eligible to be vaccinated. For those women, we found that strategies that capitalise on new HPV testing technology as a triage for ASCUS or in combination with conventional cytology allowing for different screening approaches in younger and older women and utilise screening intervals of 4–5 years, would be more attractive than screening involving cytology alone. Our results suggest that increasing the frequency of screening beyond every 3 years makes cost-effectiveness ratios increasingly unattractive.

To date, three published articles[39–41] have evaluated the impact of introducing HPV vaccination in the context of Spanish screening practices and all three predict clinical benefits associated with HPV vaccination. Unlike the three studies, we used a model that was empirically calibrated to epidemiological data from Spain and incorporates uncertainty about the natural history of HPV and cervical cancer into the policy results. In addition, our individual-based stochastic model allows for health states to be distinguished by HPV type, for transitions between states to differ from woman to woman due to chance and for women to adopt different screening patterns given their particular vaccination status. Furthermore, our analysis is the first to evaluate the cost-effectiveness of alternative cervical cancer prevention strategies in Spain, including prophylactic vaccination in addition to different screening strategies.

There are several limitations associated with our model that have already been described in previous publications.[13–15] The data used for calibration were extracted from heterogeneous sources and from specific regions not necessarily representing the national variability, thus we may have

underestimated uncertainty in model outcomes. To address this possibility, we conducted all analyses using 50 parameter sets that fit well within the range of uncertainty within the data to explore the robustness of our results. Also, we made a purposeful tradeoff in choosing a detailed microsimulation model that accommodates complex screening strategies and individual history, at the expense of omitting transmission dynamics of HPV-16 and HPV-18, which may underestimate the benefits of vaccination. We also did not include the potential benefits of vaccination on other non-cervical HPV-16/18-related cancers or on HPV 6/11-related genital warts or the impact of cross-protection against other HPV types than HPV 6, 11, 16 and 18. Their exclusion leads to an underestimation of the health outcomes and thereby the cost-effectiveness of vaccination. With the exception of the impact on HPV 6 and 11, for which there is strong evidence of protection against genital warts,[42,43] there is still limited evidence on the quantitative impact of cross-protection, as well as on duration of vaccine immunity and the need of a booster to obtain long-term protection. Clinical trials published to date do not suggest waning vaccine efficacy over time,[44] but life-long protection remains to be established. While the main analysis was conducted under the favourable assumption of life-long protection against HPV-16 and -18 we also performed sensitivity analysis under assumptions of waning immunity, which resulted in less attractive cost-effectiveness ratios. Although we did not consider the administration of boosters, their requirement would lead to less favourable cost-effectiveness results. Benefits could also be lower than expected if vaccinated girls have already had sexual contacts and exposure to HPV before vaccination, if efficacy is lower in risk groups such as human immunodeficiency virus (HIV)-infected adolescents or if there is an increase in the prevalence of non-vaccine-targeted HPV types and their associated diseases. We acknowledge the importance of reporting quality-adjusted life year (QALY) but information on health state utilities associated with cervical disease has yet to be published in Spain; therefore, we elected to express our results as Euros per year of life saved. We aimed to inform policy questions regarding screening strategies for both vaccinated girls and women who will not have access to vaccination, but future work focuses on assessing the cost-effectiveness of immunising boys in addition to girls and the optimal age range for a catch-up vaccination programme in Spain. Furthermore, screening strategies that utilise HPV DNA testing as a primary screening test should be further explored.

This cost-effectiveness analysis is intended to inform policy decisions being made in Spain today. Decision makers require information on the relative value of vaccination and screening strategies compared with alternative uses of resources (i.e. cost-effectiveness), as well as information on its affordability (i.e. budgetary impact).[45] Both aspects of current HPV vaccines must be favourable since it competes for Euros earmarked for current immunisation or screening programmes or initiatives for scale-up. Even so, decisions about vaccine implementation should consider other dimensions, such as the capacity to achieve wide coverage and equity, the capability of educating stakeholders, healthcare professionals, parents and adolescents on the degree of vaccine protection and the feasibility of organising and improving screening programmes. While most strategies would be considered attractive according to commonly cited cost-effectiveness thresholds, the financial requirements in Euros for vaccinating just five consecutive birth cohorts of 11-year-old girls at 90% coverage would be 174 million Euros at 60€ per dose and 292 million Euros at 104€ per dose. There are more than 3.1 million girls under age 14 years in Spain, who will be eligible for HPV vaccination now or in the near future.[46] Our model predicts that in Spain, we will prevent one case of cervical cancer by vaccinating 198 of these young girls and prevent one death from cervical cancer by vaccinating 287, assuming 90% vaccination coverage and 100% efficacy with life-long protection. However, there are more than 20.8 million women over 14 years of age who will not receive HPV vaccination, and in spite of current screening efforts they still generate some 2000 new cases of invasive disease per year. These women require more effective and cost-effective organised screening with national adherence to protocols that start screening at age 30 until at least age 65 years with cytology-based primary testing and systematic HPV DNA testing for triage of women with an ASCUS result.

As there are several studies currently underway in Spain on HPV prevalence, screening programmes and the HPV vaccination programme—and as ongoing clinical trials provide new information on vaccine efficacy and duration of immunity—we expect to iteratively revisit model assumptions and analyses to continue to inform cervical cancer prevention efforts in Spain. The similitude of screening scenarios in various countries in the region anticipates that these results will also be of more general interest.

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Conflict of interest statement

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.06.016.

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