Vaccine 31S (2013) H71–H79

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Cost-Effectiveness of Cervical Cancer Prevention in Central and Eastern Europe and Central Asia

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ARTICLE INFO

*Article history:*
Received 22 February 2012
Received in revised form 9 April 2013
Accepted 26 April 2013

*Keywords:*
Central Europe
Eastern Europe
Central Asia
HPV
Vaccination
Screening
Cost effectiveness
Mathematical model

ABSTRACT

We studied the cost-effectiveness of cervical cancer prevention strategies in the Central and Eastern Europe and Central Asia (CEECA) region. The cost-effectiveness of human papillomavirus (HPV)16/18 vaccination of 12 year-old girls was calculated for 28 countries, under the assumption that vaccination prevents 70% of all cervical cancer cases and that cervical cancer and all-cause mortality rates are stable without vaccination. At three-dose vaccination costs of I$ 100 per vaccinated girl (currency 2005 international dollars), HPV16/18 vaccination was very cost-effective in 25 out of 28 countries using the country's gross domestic product (GDP) per capita as cost-effectiveness threshold (criterion by World Health Organization). A three-dose vaccination cost of I$ 100 is within the current range of vaccine costs in European immunization programs, and therefore our results indicate that HPV vaccination may be good value for money. To evaluate the cost-effectiveness of cervical cancer screening combined with vaccination, we calibrated a published simulation model to HPV genotype data collected in Slovenia, Poland, and Georgia. The screening interval was varied at 3, 6, and 10 years starting at age 25 or 30 and ending at age 60. In Slovenia and Poland, combined vaccination and 10-yearly HPV (DNA) screening (vaccination coverage 70%, screening coverage per round 70%) was very cost-effective when the cost of three-dose vaccination was I$ 100 per vaccinated girl. More intensive screening was very cost-effective when the screening coverage per round was 30% or 50%. In Georgia, 10-yearly Pap screening was very cost-effective in unvaccinated women. Vaccination combined with 10-yearly HPV screening was likely to be cost-effective if the three-dose vaccination cost was I$ 50 per vaccinated girl. To conclude, cervical cancer prevention strategies utilizing both HPV16/18 vaccination and HPV screening are very cost-effective in countries with sufficient resources. In low-resource settings, low vaccine pricing is essential for strategies of combined vaccination and screening to be cost-effective.

This article forms part of a regional report entitled *"Comprehensive Control of HPV Infections and Related Diseases in the Central and Eastern Europe and Central Asia Region"* Vaccine Volume 31, Supplement 7, 2013. Updates of the progress in the field are presented in a separate monograph entitled *"Comprehensive Control of HPV Infections and Related Diseases"* Vaccine Volume 30, Supplement 5, 2012.



## 1. Introduction

Countries in the Central and Eastern Europe and Central Asia (CEECA) region show a high incidence of cervical cancer compared to countries in Western and Northern Europe [1,2]. Organized screening programs have been successfully implemented in Western and Northern European countries [3], but few programs have been established in CEECA, where screening is largely opportunistic (Poljak M *et al*, Vaccine, this issue and Rogovskaya SI *et al.*, Vaccine, this issue [4,5]). Such programs typically reach a minority of the population who are not necessarily at highest risk of disease. Moreover, screening intervals, follow-up procedures, and treatment protocols are often not well-defined in such programs. Higher coverage and increased efficiency may be achieved by standardization of screening programs, and cervical cancer burden could be further reduced by adding human papillomavirus (HPV)16/18 vaccination [6]. However, considering the limited resources available for disease prevention programs, it remains uncertain whether the incidence of cervical cancer can be reduced to levels comparable to those in Western and Northern Europe.

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http://dx.doi.org/10.1016/j.vaccine.2013.04.086

**Table 1**
Country-specific profiles of seven selected countries.

| | Georgia | Kazakhstan | Latvia | Poland | Romania | Slovenia | Uzbekistan |
|---|---|---|---|---|---|---|---|
| Total population (in millions) [15] | 4.49 | 16.59 | 2.22 | 38.22 | 21.39 | 2.05 | 29.34 |
| Rural population (% of total population) [15] | 47 | 46 | 32 | 39 | 47 | 50 | 64 |
| Population density (people per sq km) [15] | 78 | 6 | 36 | 126 | 93 | 102 | 67 |
| Life expectancy at birth, female (years) [15] | 77 | 73 | 78 | 81 | 77 | 83 | 71 |
| Cervical cancer incidence (ASR) [16] | 9.4 | 19.1 | 12.4 | 11.6 | 23.9 | 11.1 | 10.8 |
| Persistence to grade 5 (female %) [15] | 99.0 | NA | 95.7 | 99.6 | NA | 99.6 | NA |
| Physicians per 1,000 people [15] | 4.8 | 4.1 | 3.0 | 2.2 | 2.3 | 2.5 | 2.6 |
| Prevalence of HIV (% of population ages 15-49) [15] | 0.2 | 0.2 | 0.7 | 0.1 | 0.1 | 0.1 | NA |
| Immunization, DPT (% of children ages 12-23 months) [15] | 94 | 99 | 94 | 99 | 89 | 96 | 99 |
| Percent of paved roads (%) [15] | NA | 88.5 | 20.9 | 69.9 | NA | 100 | NA |
| Percent of population living on <$2 per day, PPP (%) [15] | 32 | 1.1 | 0.37 | 0.2 | 1.7 | NA | NA |
| Inpatient tertiary hospital bed day cost (I$) [17] | 58.18 | 156.94 | 274.86 | 270.77 | 223.74 | 478.06 | 28.50 |
| Per capita GDP, PPP (2005 I$) [15] | 4546 | 10,916 | 12,948 | 17,348 | 10,921 | 25,053 | 2754 |
| GAVI-eligible[a] [18] | no | no | no | no | no | no | yes |

ASR: Age-standardized (world) incidence rate (per 100,000 person-years); DPT: diphtheria, pertussis, and tetanus; GDP: Gross domestic product; HIV: Human Immunodeficiency Virus; I$: International dollars; NA: Not available; Persistence to grade 5: The World Bank defines this as the share of children enrolled in the first grade of primary school who eventually reach grade 5 ([15]); PPP: Purchasing power parity.

[a] Countries eligible to apply for and receive vaccine funding from the Global Alliance for Vaccines and Immunisation (GAVI Alliance).

In the current screening programs in CEECA countries [4,5,7], cytology is the most commonly recommended screening instrument. Information on the accuracy of cytology in CEECA is scarce but in Western and Northern European studies, it has been shown that cytology has limited sensitivity and shows considerable heterogeneity across laboratories [8]. HPV screening has been suggested as an alternative to cytology, as it is objective and therefore expected to have better reproducibility. Moreover, in four European randomized controlled trials, HPV screening has consistently been shown to yield lower rates of cervical intraepithelial neoplasia (CIN) grade 3 (CIN3) in the following screening round compared to cytology [9–12]. This suggests that HPV screening may offer better protection than cytology against CIN3 in the following screening round. However, the HPV DNA test also detects more transient infections than cytology, which may lead to overtreatment [13].

In this paper, we evaluated the cost-effectiveness of standardized cervical cancer prevention programs in countries in the CEECA region: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Montenegro, Poland, Republic of Moldova, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Tajikistan, The Former Yugoslav Republic (FYR) of Macedonia, Ukraine, Turkmenistan, and Uzbekistan. The analyses consist of two parts. First, we calculated the cost-effectiveness of introducing HPV16/18 vaccination for 12-year old girls in 28 countries leveraging national mortality and life expectancy statistics. Second, using a simulation model of cervical cancer development [14] calibrated to epidemiologic data in three countries (Slovenia, Poland, and Georgia), we estimated the health benefits and cost-effectiveness of screening strategies with 3-, 6- or 10-yearly intervals, alone and combined with vaccination. Both cytology and the HPV (DNA) test were evaluated as the primary screening instrument. The selected countries are interesting for a comparative evaluation as they have markedly different standards of living and different levels of burden of cervical cancer. This is illustrated in Table 1, where country-specific profiles are presented for the three selected countries as well as for four other countries in the CEECA region [15–18].

## 2. Methods

### 2.1. HPV16/18 vaccination in 28 countries

We calculated the cost-effectiveness of vaccinating 12 year-old girls under the assumption that HPV16 and HPV18 are responsible for 70% of the cervical cancer cases [19] and that all HPV16/18-related cases can be prevented by vaccination. The number of life years saved by vaccination was estimated from age-specific cervical cancer mortality rates in 2008 [20]. By using recent cervical cancer mortality rates, we implicitly assumed that mortality rates will remain fixed if vaccination is not implemented. Formulas are given in the Supplementary Appendix Section 1. We did not take into account the indirect benefit of vaccination for non-vaccinated women (i.e., the herd immunity effect).

We utilized the World Health Organization (WHO) definition of cost-effectiveness, which states that a health intervention is cost-effective if the net cost required to save one life year does not exceed three times the gross domestic product (GDP) per capita. Furthermore, an intervention is very cost-effective if the net cost required to save one life year does not exceed one time the GDP per capita. The net cost per vaccinated girl is defined as the sum of the cost of vaccination minus the expected future savings per girl from treating fewer cervical cancers. The cost of vaccination includes the price of three vaccine doses and the cost of vaccine administration. We considered the vaccine price to be an endogenous, negotiable parameter and estimated the maximum three-dose vaccination cost per vaccinated girl at which vaccination is (very) cost-effective (see Supplementary Appendix Section 2 for technical details).

We determined the three-dose vaccination cost for the 28 CEECA countries. Country and age-specific estimates of cervical cancer mortality were obtained from GLOBOCAN 2008 [16], and life expectancies were obtained from United Nations World Population Prospects 2008 [21]. GDP per capita figures were from the World Bank [15]. The cost of treating cancer and GDP per capita were indexed at year 2010 and expressed in 2005 international dollars (I$), a hypothetical currency that accounts for inter-country differences in purchasing power. Future costs and life years were discounted at 3% per year [22].

### 2.2. Screening and vaccination in Slovenia, Poland, and Georgia

The cost-effectiveness of screening with and without vaccination was evaluated using an individual-based simulation model [14], calibrated to Dutch population-based screening data [23–26] and cancer registry data [27]. We considered the Dutch model [14] acceptable for describing disease development in infected women but allowed the HPV incidence rates and cancer survival rates [16,28] to vary across countries. A description of the model can be found in the Supplementary Appendix Sections 3–4. We estimated country-specific HPV incidences from population-based HPV16, HPV18, and other high-risk HPV (hrHPV) prevalences [29–31]. The estimation of the HPV incidence rates is explained in

Supplementary Appendix Section 5. The model nicely fitted the observed HPV16, HPV18, and other hrHPV prevalences (Supplementary Appendix: Fig. S1). As a form of validation, we compared the model-projected 5-yearly cancer incidence rates with incidences in GLOBOCAN 2008 [16]. If screening efforts in year 2007 were assumed for the simulated cohort, the predicted cancer incidences were comparable to those in GLOBOCAN [16] for Poland and Georgia but were much lower than GLOBOCAN incidences for Slovenia (Supplementary Appendix: Fig. S2). This may be partially explained by the recent introduction of Slovenia's organized screening program, the full impact of which has not yet been realized [32,33]. Therefore, we used the models without further adjustment.

#### 2.2.1. Prevention and treatment strategies

We studied the following strategies: treatment of cancers detected symptomatically only, screening (and treatment of screen-detected and symptomatic lesions), HPV16/18 vaccination of preadolescent 12-year old girls (and treatment of symptomatic lesions), and combined screening and preadolescent HPV16/18 vaccination (and treatment of screen-detected and symptomatic lesions). For screening strategies without vaccination, the screening interval was set at 10 years (age 30–60 years), 6 years (25–60 years), and 3 years (25–60 years). For combined vaccination and screening, the screening interval was set at 10 years (age 30–60 years) and 6 years (25–60 years). Screening modalities were cytologic examination of cervical cells on a Papanicolaou smear (Pap test) and HPV DNA test. Women with a positive screening test were referred for colposcopy and biopsy, and treated in case of CIN grade 1 or worse. However, in contrast with our model, women with CIN1 may not be treated in practice; they usually remain under the surveillance of the gynaecologist and will be treated if disease progresses. The screening program was assumed to perform similarly to the organized programs in Western and Northern Europe, both in terms of test sensitivity and achievable coverage.

We assumed coverage of 70% for vaccination and 70% for screening per round. The coverage per round of screening is the product of several probabilities. We assumed that 15% of the women never attended screening and that the screening attendance of the other 85% of the women was 82.5% per round. This corresponds to a marginal screening coverage of 70% per round ($15\% \times 0\% + 85\% \times 82.5\% = 70\%$). We assumed successful diagnosis and treatment of pre-invasive disease. We assumed that missed or unsuccessfully treated lesions were detected during follow-up, resulting in additional costs. More detail on the screening, diagnosis, and treatment parameters can be found in the Supplementary Appendix Sections 3–4.

#### 2.2.2. Base-case analyses

Results are based on simulated cohorts of 10,000,000 women. Outcome measures include lifetime risk of cervical cancer, number of quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios (ICERs). We adjusted for quality of life because screening and non-fatal cancer burden are not captured by the number of life years. The quality of life utilities of the different health states are presented in Supplementary Appendix, Table S.2. We calculated costs by summing the cost of vaccination, the cost of screening, the cost of diagnosing and treating CIN and the cost of treating cancer. As in the 28-country analysis described in Section 2.1, costs were indexed at year 2010, expressed in 2005 I$, and future costs and QALYs were discounted at 3% per year. Multiple preventive strategies were compared by means of an incremental analysis. First, strategies were ordered according to costs; dominated strategies were identified and excluded. A strategy is dominated if the number of QALYs saved can also be saved at lower costs by another strategy or a weighted combination of other strategies. Next, the ICERs of adjacent, non-dominated strategies were calculated. The ICER is defined as the extra lifetime cost of a strategy required to save one extra QALY, compared to the adjacent, less costly strategy. Very cost-effective strategies have an ICER lower than the GDP per capita (criterion by WHO). The WHO also considers strategies to be cost-effective, but not very cost-effective, at a threshold of three times GDP per capita [22]. Because some of the strategies in our analyses may be unacceptable on non-economic grounds, each strategy was also compared to the cancer treatment only strategy and the corresponding ICER was named cost-effectiveness ratio (CER). The prices of the HPV DNA test and the vaccine were considered to be negotiable. Therefore, we set the HPV DNA test cost equal to the Pap test cost, $I 10 above the Pap test cost, and I$ 20 above the Pap test cost. We set the three-dose vaccination cost at I$ 25, 50, 100, and 400.

#### 2.2.3. Sensitivity analyses

We evaluated the robustness of our results by means of univariate and multivariate sensitivity analyses. In the natural history model, we varied HPV incidences and the duration of CIN3 phase and the cancer stage I phase. The base-case HPV incidences were multiplied by 0.67 and 1.5, which roughly correspond to the bounds of the 95 percent confidence intervals of observed HPV prevalences (Supplementary Appendix: Fig. S1). The duration of CIN3 to cancer and the progression probability of CIN3 to cancer were simultaneously lowered by 50%. The duration from cancer stage I to II was lowered by 50%. The durations are functions of multiple model parameters and the new values of the model parameters are listed in Supplementary Appendix: Table S.3. We also varied several screening and treatment parameters. The base-case screening coverage of 70% per round was lowered to 50% and 30% (the percentage of women that never attended screening was kept the same as in the base-case but the attendance rate per round of the other women was lowered to achieve a marginal coverage of 50% or 30%). The sensitivity of cytology for CIN grade 1 or 2 was increased to 75%, the sensitivity of cytology for CIN3 was lowered to 50%, the specificity of the HPV DNA test for detecting an infection was lowered from 100 to 96%, and the percentage of screen-detected CIN not accurately diagnosed/treated after colposcopy referral was increased from 0 to 20%. Finally, cost, utility, and discounting parameters were varied. Base-case costs of treating CIN and cancer were doubled and halved, and the cost of screening (Pap and HPV) was lowered by I$ 10. The outcome measure QALY was replaced by life years (without quality of life adjustment). The discount rates for future costs and health benefits were varied between 0 and 5%.

### 2.3. Costing

Screening, diagnosis, and treatment costs in Slovenia and Poland were taken from the literature [34,35] and costs in Georgia were based on reimbursement fees in a state-funded opportunistic program [36]. Direct medical costs that were not available from these sources, as well as the cost of time and transportation, were extrapolated from reference countries [37]. Italy was used as a reference country for Slovenia and Poland, and Thailand was used as a reference country for Georgia. The cancer treatment costs for the other 25 countries in the 28-country analysis were obtained from a regression line with GDP per capita as covariate. See Supplementary Appendix Section 7 for details on the costing methods.

## 3. Results

### 3.1. HPV16/18 vaccination in 28 countries

The number of life years saved by vaccination and the maximum three-dose vaccination cost per vaccinated girl at which

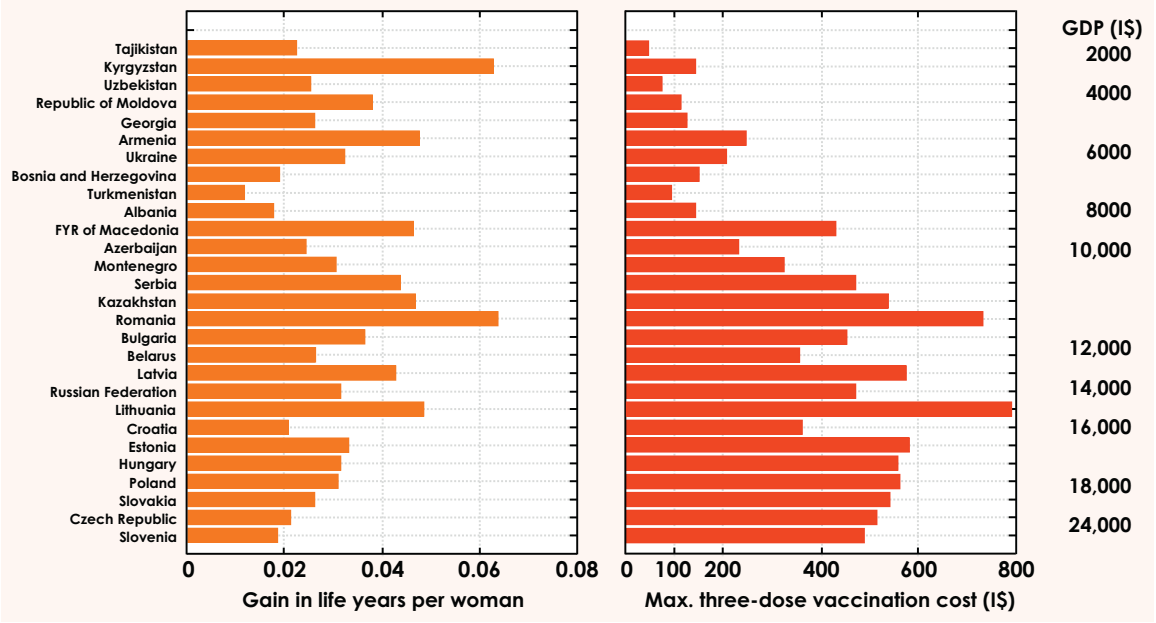


**Fig. 1.** Gain in life years (left panel) and maximum 3-dose vaccination cost per vaccinated girl at which vaccination is very cost-effective (right panel). Vaccination is very cost-effective if the incremental cost-effectiveness ratio is below gross domestic product (GDP) per capita. The costs are indexed at year 2010 and expressed in 2005 international dollars (I$). Discounting is set a 3 percent per year. Countries are ordered according to GDP per capita. FYR: Former Yugoslav Republic.

vaccination is very cost-effective are displayed in Fig. 1. The vaccination cost threshold at which vaccination is very cost-effective varied greatly across countries. Fifty-six percent of this variation could be ascribed to the variation in country's GDP per capita. At a three-dose vaccination cost of I$ 100, vaccination was very cost-effective in all countries except the Central Asian countries Tajikistan, Turkmenistan, and Uzbekistan. In those countries, vaccination was cost-effective (although not very cost-effective) at a cost per vaccinated girl of I$ 100; the corresponding vaccination cost thresholds for a cost-effective intervention were I$ 141, I$ 285, and I$ 225, respectively. At three-dose vaccination cost of I$ 200 per vaccinated girl, HPV16/18 vaccination was still very cost-effective in 20 countries (no longer very cost-effective in the Republic of Moldova, Georgia, Kyrgyzstan, Bosnia and Herzegovina, and Albania).

### 3.2. *Screening and vaccination in Slovenia, Poland, and Georgia: base-case results*

Screening alone yielded a larger reduction (69–85%) in the lifetime risk of cancer than vaccination alone (36–54%) (Supplementary Appendix Table S12). Adding vaccination to screening decreased the cancer risk by an absolute 5–15%. The effect of vaccination in Georgia was somewhat lower than in Slovenia and Poland because HPV16 and HPV18 were estimated to be less common in the Georgian population than in the Slovenian and Polish population (Supplementary Appendix: Fig. S1). The gain in quality-adjusted life years was also higher for screening alone compared to vaccination alone. The expected absolute gain in adjusted life years was markedly lower in Georgia than in Slovenia and Poland for all strategies due to a relatively low incidence of cervical cancer in the model for Georgia.

The total cost of screening, diagnosis, and treatment per woman is presented in Supplementary Appendix Table S13. Screening was not cost saving, indicating that the savings from treating fewer cancers were lower than the cost of preventing those cancers. Vaccination was cost saving for Slovenia and Poland if costs were not discounted. However, at 3% annual discounting, vaccination was not cost saving.

The cost-effectiveness results are shown in Table 2. In Slovenia and Poland, combined vaccination and 10-yearly HPV screening was very cost-effective (ICER < GDP per capita) if the three-dose vaccination cost was not higher than I$ 100 per vaccinated girl. In Georgia, combined strategies were not cost-effective, unless the vaccination cost was I$ 25, and the ICER threshold was increased to three times GDP per capita.

If vaccination strategies were excluded from the comparison, 10-yearly HPV screening was very cost-effective in Slovenia and Poland and 10-yearly Pap screening was very cost-effective in Georgia (see Supplementary Table S14). Such strategies are relevant in particular for unvaccinated cohorts of women of at least 25 years of age. Six-yearly HPV screening was cost-effective in Slovenia and Poland at an increased threshold of three times GDP per capita. Three-yearly screening, which is currently recommended in Slovenia, Poland, and Georgia for unvaccinated women, was not cost-effective in an incremental analysis. However, 3-yearly screening was very cost-effective (CER < GDP per capita) to cost-effective (CER < 3×GDP per capita) when compared to a strategy where women remain unscreened and are treated when presenting with cancer (Supplementary Appendix: Table S15).

### 3.3. *Screening and vaccination in Slovenia, Poland, and Georgia: sensitivity analyses*

The relation between lifetime cancer risk and screening and vaccination coverage is displayed in Fig. 2. The reduction in lifetime cancer risk was robust against varying levels of screening coverage for 3-yearly screening, but the risk reduction was sensitive to screening coverage levels if the interval was 6 or 10 years. This indicates that a short screening interval may compensate for poor screening attendance per round. In Supplementary Appendix Table S16, associations between lifetime cancer risk and various model parameters are presented. The lifetime cancer risk was also more stable against changes in model parameters if the screening interval was 3 years than if the screening interval was 6 or 10 years. Compared to the base-case, for 10-yearly Pap screening, the reduction in lifetime cancer risk was an absolute 16% lower when the duration

**Table 2**
Incremental cost-effectiveness ratios (ICER) of non-dominated strategies.[a]

| | Incremental cost-effectiveness ratio (I$/ QALY saved) Three-dose vaccination cost (I$ per vaccinated girl) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 25 | | | 50 | | | 100 | | | 400 | | |
| Strategies[b] | Cost HPV DNA test – cost Pap (I$) | | | Cost HPV DNA test – cost Pap (I$) | | | Cost HPV DNA test – cost Pap (I$) | | | Cost HPV DNA test – cost Pap (I$) | | |
| | +0 | +10 | +20 | +0 | +10 | +20 | +0 | +10 | +20 | +0 | +10 | +20 |
| *Slovenia* | | | | | | | | | | | | |
| Vaccination | **<0** | **<0** | **<0** | **175** | **175** | **175** | **1254** | **1254** | **1254** | - | - | - |
| 10-yearly Pap | - | - | - | - | - | - | - | - | - | **1733** | **1733** | **1733** |
| 10-yearly HPV | - | - | - | - | - | - | - | - | - | **5496** | **7337** | **9179** |
| 6-yearly Pap | - | - | - | - | - | - | - | - | - | - | - | - |
| 6-yearly HPV | - | - | - | - | - | - | - | - | - | - | - | - |
| 3-yearly Pap | - | - | - | - | - | - | - | - | - | - | - | - |
| 3-yearly HPV | - | - | - | - | - | - | - | - | - | - | - | - |
| Vaccination+10-yearly Pap | **3410** | **3410** | **3410** | **3410** | **3410** | **3410** | **3410** | **3410** | **3410** | - | - | - |
| Vaccination+10-yearly HPV | **8409** | **12,778** | **17,151** | **8409** | **12,778** | **17,151** | **8409** | **12,778** | **17,151** | 26,854 | 26,854 | 26,854 |
| Vaccination+6-yearly Pap | - | - | - | - | - | - | - | - | - | - | - | - |
| Vaccination+6-yearly HPV | 71,550 | >3xGDP | >3xGDP | 71,550 | >3xGDP | >3xGDP | 71,550 | >3xGDP | >3xGDP | 71,550 | >3xGDP | >3xGDP |
| *Poland* | | | | | | | | | | | | |
| Vaccination | **<0** | **<0** | **<0** | **316** | **316** | **316** | **1504** | **1504** | **1504** | - | - | - |
| 10-yearly Pap | - | - | - | - | - | - | **2294** | **2294** | **2294** | **1651** | **1651** | **2299** |
| 10-yearly HPV | - | - | - | - | - | - | - | - | - | **5856** | **7690** | **9524** |
| 6-yearly Pap | - | - | - | - | - | - | - | - | - | - | - | - |
| 6-yearly HPV | - | - | - | - | - | - | - | - | - | - | - | - |
| 3-yearly Pap | - | - | - | - | - | - | - | - | - | - | - | - |
| 3-yearly HPV | - | - | - | - | - | - | - | - | - | - | - | - |
| Vaccination+10-yearly Pap | **3091** | **3091** | **3091** | **3091** | **3091** | **3091** | **3619** | **3619** | **3619** | - | - | - |
| Vaccination+10-yearly HPV | **7544** | **11,539** | **15,533** | **7544** | **11,539** | **15,533** | **7544** | **11,539** | **15,533** | 32,019 | 32,019 | 32,019 |
| Vaccination+6-yearly Pap | - | - | - | - | - | - | - | - | - | - | - | - |
| Vaccination+6-yearly HPV | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP |
| *Georgia* | | | | | | | | | | | | |
| Vaccination | **1956** | **1956** | **1956** | - | - | - | - | - | - | - | - | - |
| 10-yearly Pap | - | **3206** | **3206** | **2525** | **2525** | **2525** | **2525** | **2525** | **2525** | **2525** | **2525** | **2525** |
| 10-yearly HPV | **3172** | - | - | **3067** | 7566 | 12,065 | **3067** | 7566 | 12,065 | **3067** | 7566 | 12,065 |
| 6-yearly Pap | - | - | - | - | - | - | - | - | - | - | - | - |
| 6-yearly HPV | - | - | - | - | - | - | - | - | - | >3xGDP | >3xGDP | >3xGDP |
| 3-yearly Pap | - | - | - | - | - | - | - | - | - | - | - | - |
| 3-yearly HPV | - | - | - | - | - | - | - | - | - | - | - | - |
| Vaccination+10-yearly Pap | - | 6277 | 6277 | - | - | - | - | - | - | - | - | - |
| Vaccination+10-yearly HPV | 8346 | 10,697 | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | - | - | - |
| Vaccination+6-yearly Pap | - | - | - | - | - | - | - | - | - | - | - | - |
| Vaccination+6-yearly HPV | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP | >3xGDP |

[a] The lowest ICER in each column compares the least-costly non-dominated strategy with the treatment of asymptomatically detected cancers only strategy. The other presented ICERs compare strategies to the nearest less costly, non-dominated strategy. Dominated strategies are less effective than equally expensive (combinations of) other strategies. The presented ICERs correspond to cost-effective strategies (ICER < 3xGDP per capita), ICERs in bold correspond to very cost-effective strategies (ICER < GDP per capita). The costs are indexed at year 2010 and expressed in 2005 international dollars (I$). Each column corresponds to a specific setting for the vaccination cost (25-400 I$) and the HPV DNA test cost (Pap test cost + 0, 10, 20 I$). Discounting is 3 percent per year. The effect is measured by quality-adjusted life years (QALYs).

[b] Screening and vaccination coverage was assumed to be 70%.

"-": Dominated strategy; GDP: Gross domestic product; HPV: Human papillomavirus; I$: International dollar.

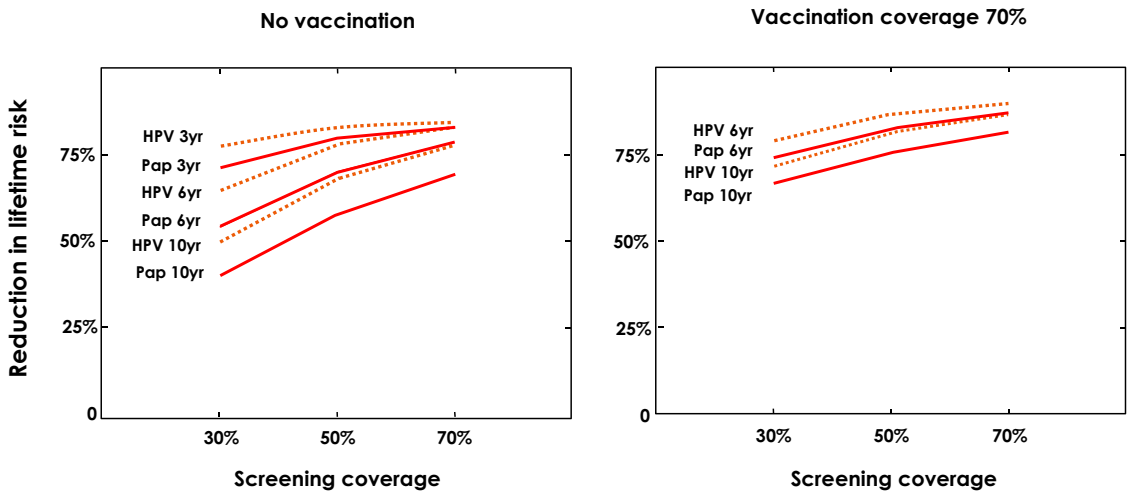


**Fig. 2.** Reduction in lifetime cervical cancer risk against screening coverage, both for an unvaccinated cohort (left panel) and a partly vaccinated cohort (right panel). Shown are the averages of risk reductions in Slovenia, Poland, and Georgia.

from CIN3 to cancer was halved, an absolute 8% lower when 20% of screen-detected CIN were not diagnosed/treated, and an absolute 13% lower when the sensitivity of the Pap test for detection of CIN3 was only 50%.

The robustness of the preferred screening strategy against changes in the model parameters is presented in Table 3. A combination of vaccination and 10-yearly HPV screening was always very cost-effective for Slovenia and, in most non base-case settings, very cost-effective for Poland; 10-yearly Pap screening was always very cost-effective for Georgia. At the increased ICER threshold of three times GDP per capita, a combination of vaccination and 6-yearly HPV screening was generally cost-effective for Slovenia and Poland and a combination of vaccination and 10-yearly HPV screening was generally cost-effective for Georgia. In unvaccinated women, 6-yearly HPV screening was very cost-effective for Slovenia in most non base-case scenarios and 10-yearly HPV screening was very cost-effective for Georgia when the sensitivity of the Pap test for detection of CIN3 was only 50%. Lowering the screening coverage led to an increase in the number of very cost-effective screening strategies.

## 4. Discussion

Cervical cancer mortality rates are up to 11 times higher in countries in the CEECA region than in Western and Northern European countries, clearly indicating the health inequality present in Europe [16,38]. The potential to narrow the inequality depends on available resources and cost-effectiveness of cervical cancer prevention strategies. We found that HPV16/18 vaccination of preadolescent girls was cost-effective in 28 CEECA countries and very cost-effective in 25 out of 28 CEECA countries at a three-dose vaccination cost of I$ 100 per vaccinated girl. For most countries, vaccination was also very cost-effective at a three-dose vaccination cost of I$ 200 per vaccinated girl. These cost levels are comparable to vaccine contract prices negotiated by national authorities in Europe. For example, Sweden and Belgium reported contract prices of about €20 per dose. Our results are also consistent with four other published analyses for Lithuania, Slovenia, Hungary, and Poland, which found that vaccination was cost-effective under local criteria [35,39–41].

For our calculations, we assumed that the current cervical cancer mortality rates remain fixed in the future. This assumption may not hold for the CEECA region, as the cancer incidences were not stable over the last decade (Bray F *et al*, Vaccine, this issue [42]). Some countries showed a decrease in cervical cancer incidence in the last 10 years (e.g., Croatia, Czech Republic, Slovenia) whereas others showed an increase (e.g., Bulgaria, Latvia, Russian Federation). The annual change in cancer incidence ranged from -2.7 to 2.8%, which indicates that there has been substantial variation in cancer incidence trends among countries. This implies that substantial variation in future cancer incidence and mortality trends cannot be ruled out and the estimated maximum vaccine prices should be interpreted cautiously.

In our calculations, the main assumption was that 70% of cervical cancer deaths were prevented by HPV16/18 vaccination. The prevalence of HPV16/18 in cancer has been assessed in large worldwide studies [19] and recent calculations indicate that HPV16 proportion in cancer is higher in Western/Central Asia and Europe than in the rest of the world [43]. The main weakness of our assumption is that the long-term protective effect against HPV16/18-related cancers can only be proven using long-term follow-up of vaccinated cohorts, which will not be available in the near future [14]. The eventual effect of vaccination on cancer deaths may also be larger than anticipated, as HPV16/18 vaccination is expected to provide herd immunity to unvaccinated girls and partial cross-protection to other oncogenic types [44]. In spite of the limitations of our analysis, our view on the cost-effectiveness of HPV16/18 vaccination is favorable, as our calculations indicated that vaccination was very cost-effective in most countries in the CEECA region for a wide range of vaccine prices. Lack of resources, reflected by a low GDP per capita, turned out to be the strongest determinant of the vaccination cost threshold for cost-effective vaccination and underlines the importance of low vaccine pricing in the CEECA region.

In countries like Slovenia, the recent implementation of organized screening is expected to lead to a further decrease in the cervical cancer mortality rate in the near future. It is therefore important to supplement predictions on the cost-effectiveness of HPV16/18 vaccination with predictions on organized screening efforts, which we have done using a Markov-type model. Our model-based predictions for Slovenia, Poland, and Georgia indicate that vaccination in combination with screening in Slovenia and Poland is very cost-effective. In Georgia, combined screening and vaccination was cost-effective only when three-dose vaccination cost was I$ 25 per vaccinated girl. The latter outcome is not surprising as Georgia has few resources and a fairly low age-standardized cervical cancer incidence of 9.4 per 100,000 woman-years [16]. The results were, however, sensitive to model assumptions and combined screening and vaccination at a three-dose vaccination cost

**Table 3**
Sensitivity analyses.[a]

| | Cost-effective strategies | | | |
|---|---|---|---|---|
| | Screening only | | Screening and/or vaccination | |
| | ICER < GDP per capita | ICER < 3xGDP per capita | ICER < GDP per capita | ICER < 3xGDP per capita |
| ***Slovenia*** | | | | |
| Base-case (vaccination costs 100 I$) | HPV 10yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 10yr |
| HPV16/18 inc x 1½ | HPV 10yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| HPV inc x 1½ (all hr types) | HPV 10yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Duration&progression HPV16/18-pos. CIN3-cancer x ½ | HPV 6yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Duration&progression CIN3-cancer x ½ | HPV 6yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Duration cancer stage I to II x ½ | HPV 6yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Coverage screening 50% | Pap 3yr | HPV 3yr | Vacc + HPV 6yr | Vacc + HPV 6yr |
| Coverage screening 30% | HPV 3yr | HPV 3yr | Vacc + HPV 6yr | Vacc + HPV 6yr |
| CIN not accurately diagnosed/treated 20% | HPV 6yr | Pap 3yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Treatment costs CIN x ½ | HPV 10yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Decrease price screening test 10I$ | HPV 10yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Discount rates 0% | HPV 6yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| ***Poland*** | | | | |
| Base-case (vaccination costs 100 I$) | HPV 10yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 10yr |
| Duration&progression HPV16/18-pos. CIN3-cancer x ½ | HPV 10yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Duration&progression CIN3-cancer x ½ | HPV 10yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Duration cancer stage I to II x ½* | HPV 10yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Coverage screening 50% | Pap 3yr | Pap 3yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Coverage screening 30% | HPV 3yr | HPV 3yr | Vacc + HPV 6yr | Vacc + HPV 6yr |
| CIN not accurately diagnosed/treated 20% | HPV 10yr | Pap 3yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Treatment costs CIN x2 | HPV 10yr | HPV 10yr | Vacc + Pap 10yr | Vacc + HPV 10yr |
| Discount rates 0% | HPV 6yr | HPV 6yr | Vacc + HPV 10yr | Vacc + HPV 6yr |
| Discount rates 5% | HPV 10yr | HPV 10yr | Vacc + Pap 10yr | Vacc + HPV 10yr |
| ***Georgia*** | | | | |
| Base-case (vaccination costs 50 I$) | Pap 10yr | HPV 10yr | Pap 10yr | HPV 10yr |
| HPV16/18 inc x 1½ | Pap 10yr | HPV 10yr | Pap 10yr | Vacc + HPV 10yr |
| All type HPV inc x 1½ (all hr types) | Pap 10yr | HPV 10yr | Pap 10yr | Vacc + HPV 10yr |
| Duration&progression HPV16/18-pos. CIN3-cancer x ½ | Pap 10yr | HPV 10yr | Pap 10yr | Vacc + HPV 10yr |
| Duration&progression CIN3-cancer x ½ | Pap 10yr | HPV 10yr | Pap 10yr | Vacc + HPV 10yr |
| Coverage screening 50% | Pap 10yr | HPV 10yr | Pap 10yr | Vacc + HPV 10yr |
| Coverage screening 30% | HPV 10yr | Pap 3yr | HPV 10yr | Vacc + HPV 6yr |
| Sensitivity cytology for CIN3+ 50% | HPV 10yr | HPV 10yr | HPV 10yr | HPV 10yr |
| Discount rates 0% | HPV 10yr | HPV 10yr | Vacc + Pap 10yr | Vacc + HPV 10yr |

CIN: Cervical intraepithelial neoplasia; GDP: Gross domestic product; HPV: Human papillomavirus; ICER: Incremental cost-effectiveness ratio; I$: International Dollar.
[a]Two types of analyses are presented: one in which only screening strategies are compared and one in which screening, vaccination, and combined strategies are compared. For the base-case parameter setting, the most costly non-dominated very cost-effective strategy (ICER < GDP per capita) and the most costly non-dominated cost-effective strategy (ICER < 3×GDP per capita) are presented. Parameter settings are different for each country; those not shown are not different from the country's base-case strategy. The strategies in red (green) are more (less) costly than the base-case strategy. A complete list of changes to the base-case parameter setting is given in the Methods section. Vaccination cost was set at 100 I$ for Slovenia and Poland and at 50 I$ for Georgia. The cost of the HPV DNA test was set 10 I$ higher than the cost of the Pap test. Discounting was set at 3% per year. The effect is measured by quality-adjusted life years (QALYs).

of I$ 50 per vaccinated girl was cost-effective when the quality of screening or screening coverage of 70% assumed in the base-case model was not achieved. We found that screening with a short interval of 3 years yielded only moderate benefits in terms of cancer risk reduction compared to screening with longer intervals. A reason for this is that HPV screening was often selected, which permits longer intervals than Pap screening [45]. Three-yearly screening may still be considered because the reduction in lifetime cancer risk for 3-yearly screening was robust against poor screening coverage, imperfect diagnosis/treatment of screen-detected lesions, and low screening test sensitivity. It is, however, debatable whether intensive screening should be advised to mitigate the effect of poor screening, diagnosis, and treatment. We also found a large impact of the assumed duration of the CIN3 phase on the reduction in lifetime cancer risk, which is somewhat troublesome as the duration is not widely documented in the literature. Our estimate was based on calibrating the model to Dutch age-specific CIN3 and cancer incidences and was similar to a recent duration estimate obtained by fitting a statistical model to doubly censored nationwide registry data [46]. Despite the uncertainty about the effect on the cancer risk, recommendations on cervical cancer prevention were fairly robust against variations in the duration of the CIN3 phase. Six- and 10-yearly screening strategies were generally found to be very cost-effective, indicating that 3-yearly screening seems safe but is not necessarily the best value for money in CEECA countries.

Our analysis has several limitations. First, we assumed in all analyses that screen-positive women were directly referred for colposcopy. In particular for HPV DNA screening strategies, it may be desirable to control the number of colposcopy referrals by additional testing of HPV-positive women. Several studies have examined this problem and have indicated that the identification of CIN3 can be improved by adding triage testing and/or follow-up testing [47–49]. Second, we did not account for indirect vaccine effects (i.e., herd immunity) among non-vaccinated women. Including herd immunity effects might have led to a shift towards less frequent screening in combination with vaccination and would also have made all strategies involving vaccination more cost-effective. Third, in our analyses we assumed that the screening program would perform similarly to the organized programs in Western and Northern Europe, both in terms of test sensitivity and achievable coverage. This may not be achievable for all countries in the CEECA region, in particular when resources are limited. Fourth, the costs of initiating a screening program were not included in the analysis and this could also influence the feasibility of its introduction. It is important to realize that our analysis is an approach to determine the cost-effectiveness of prevention programs but other aspects should be considered by decision makers, including information on affordability, potential financing mechanisms, and likelihood of uptake and acceptability. Finally, the usefulness of modeling results strongly depends on the quality of the data. We selected three countries with HPV genotype data collected in a

population-based setting. Samples were medium-sized with 4431 women from Slovenia, 834 from Poland, and 1309 from Georgia. Two different HPV DNA tests were used (for Slovenia, RealTime High Risk HPV Test, Abbott, Wiesbaden, and for Poland and Georgia, PCR GP5+/6+ EIA followed with reverse-line blot hybridization) but both tests are clinically validated [50,51]. Nevertheless, it remains uncertain whether the HPV data are representative for the whole country, whether the cancer registry data are accurate, and whether the extrapolation of some cost items from reference countries are accurate, and this may influence the results.

To conclude, we found that HPV16/18 vaccination is cost-effective in countries in the CEECA region. However, according to our model, optimal strategies identified in Slovenia, Poland, and Georgia robustly included routine screening, either alone or in combination with HPV vaccination, suggesting cervical cancer screening should also remain a priority in efforts against cervical cancer in these countries.

## Acknowledgements

The authors are grateful to Gary Clifford, Silvia Franceschi, Mario Poljak, and Salvatore Vaccarella for providing HPV prevalence data from Slovenia, Poland, and Georgia, to Laia Bruni for assisting in processing national life expectancy and mortality data, and to Levan Jugeli for providing information about screening costs in Georgia. The work was supported by public grants from the European Commission (7th Framework Programme grant HEALTH-F3-2010-242061, PREHDICT), from the Netherlands Organisation for Health Research and Development (ZonMW 121030032), from the Instituto de Salud Carlos III (Spanish Government) (grants FIS PI10/02995, RCESP C03/09, RTICESP C03/10, RTIC RD06/0020/0095, RD12/0036/0056 and CIBERESP) and from the Agència de Gestió d'Ajuts Universitaris i de Recerca - Generalitat de Catalunya (Catalonian Government) (grants AGAUR 2005SGR00695 and AGAUR 2009SGR126), who had no role in data collection, analysis or interpretation of results.

## Disclosed potential conflicts of interest

JB: Received speakers' fees from Qiagen and incidental consultancy fees from Sanofi Pasteur and GSK.

JAB, ED, MD, MS, and JJK: Have disclosed no conflict of interest. The Unit of Infections and Cancer at the ICO is involved in HPV vaccine trials and epidemiological studies sponsored by GlaxoSmithKline, Merck and Sanofi Pasteur MSD.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.04.086.

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