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The optimal HPV-screening protocol in Eastern-Europe: The example of Slovenia

Erik E.L. Jansen [a,*], Urška Ivanuš [b], Tine Jerman [b], Harry J. de Koning [a], Inge M.C.M. de Kok [a]

[a] Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[b] Department of Cancer Screening, Epidemiology and Cancer Registry, Institute of Oncology Ljubljana, Ljubljana, Slovenia

HIGHLIGHTS

- 5-yearly HPV-screening from 30 to 65 is the optimal HPV-screening protocol in Eastern Europe.
- Taking the HPV genotype into account in the triage algorithm improves the cost-effectiveness.
- Socially acceptability of screening protocols can be taken into account without deteriorating cost-effectiveness.

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ABSTRACT

Objective. Eastern European countries are contemplating to introduce the high-risk Human Papillomavirus (HPV)-test as the primary screening test for their cervical cancer screening programme, but its optimal protocol is yet unknown. The aim of this study was to compare the costs, effects and cost-effectiveness of different primary HPV-screening protocols in Eastern Europe, using Slovenia as an example and with respect of local preferences for screening.

Methods. We evaluated 968 HPV-screening protocols, which varied by screening ages, triage tests (i.e. cytology, repeat HPV and/or genotyping) and strategy for women under 35 years old, using the microsimulation model MISCAN-Cervix.

Results. Within the subset of strategies that would be acceptable for Slovenian women, the optimal HPV-screening protocol is to start with two cytology tests at age 25 and 28 and switch to 5-yearly HPV screening from age 30 to 65. When also other protocols were considered, the optimal screening strategy would be 5-yearly HPV screening from age 30 to 65 only, improving the cost-effectiveness with 5%. Adding genotyping in the triage algorithm consistently improved cost-effectiveness. Sensitivity analyses showed the robustness of the results for other situations in Eastern Europe.

Conclusions. Despite differences in cervical cancer epidemiology between Eastern and Western European regions where HPV screening was evaluated, the optimal screening protocol was found to be very similar. Furthermore, strategies that were considered socially acceptable to the population were found to be almost as cost-effective as less acceptable strategies and can therefore be considered a viable alternative to prevent opportunistic screening.

1. Introduction

The World Health Organization (WHO) Director-General made a call for action to all countries to eliminate cervical cancer (CC) as a public health problem by reducing the CC age-standardized incidence rate (ASIR) to less than 4 per 100,000 women. Although ASIRs have been declining in most regions in the world, Eastern Europe is one of the exceptions with an ASIR of 16.0 in 2018 [1]. To reach the WHO goal, vaccination against high-risk human papilloma virus (HPV) is essential. Furthermore, it will take multiple decades until the majority of the population is protected by the vaccine as only young women are being vaccinated. To reach the WHO goal on a shorter term, an optimal screening programme is required, especially for unvaccinated cohorts [2].

Screening for CC using the HPV-test as the primary test has shown to be more effective and cost-effective than cytology screening in several modelling studies [3,4]. Multiple trials [5–7] have confirmed this increased effectiveness and since 2017, countries across the world have started to implement nationwide primary HPV-screening programmes [8].

* Corresponding author.
E-mail address: e.e.l.jansen@erasmusmc.nl (E.E.L. Jansen).

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Currently, Eastern European countries are contemplating to introduce the HPV-test as their primary test for CC screening programmes as well. However, what the optimal screening protocol for a country is, depends on many factors. These factors include HPV-prevalence, CC incidence and mortality, as well as screening test characteristics, costs for screening, diagnosis and treatment. Also, a new protocol must be clinically, socially and ethically acceptable to the target population, health professionals and society [9,10]. If not, users and suppliers are less likely to adhere to the protocol and the unwanted screening behaviour in terms of less screening, overuse of screening or use of not-recommended screening modalities can alter the predicted benefits to hams ratio including cost-effectiveness of organized screening [11].

As these factors are likely to be different between regions, previously conducted studies on the cost-effectiveness of primary HPV-screening in Western Europe might not be applicable to Eastern Europe.

Therefore, this study aims to compare the costs, effects and cost-effectiveness of 1) different acceptable primary HPV screening protocols in Eastern Europe and 2) all potential primary HPV-screening protocols in Eastern Europe. We will use Slovenia as an example because of the high quality data available in Slovenia as it is one among the rare countries in this region where organized CC screening is implemented and monitored. Slovenian women are currently invited for screening every three years from age 20 [12], so deviating too far from that would not be acceptable for them and could therefore lead to opportunistic screening which would deteriorate the balance between harms and benefits of screening [11].

Our analyses will focus on unvaccinated cohorts only. These analyses will aid policymakers in Eastern European countries to select a primary HPV-screening protocol that has the right balance between harms, benefits and costs of CC screening.

This modelling study is a part of the EU-TOPIA (Towards improved screening for breast, cervical and colorectal cancer in all of Europe) project in which modelling is used to quantify the harms, benefits and costs of organized screening strategies for breast, colorectal and cervical cancer in Europe.

2. Methods

To analyse the cost-effectiveness of primary HPV-screening protocols, we used the previously published microsimulation screening analysis (MISCAN-Cervix) model [13]. In this microsimulation model, a population of women is simulated individually including their natural history of CC. Women are at risk for acquiring an HPV infection, which may or may not progress to various grades of cervical intraepithelial neoplasia and eventually to CC (Fig. 1). Then, a screening protocol can be applied to this population to quantify the harms, benefits and costs of that screening protocol.

2.1. Model development

To represent Eastern Europe best, we adapted the existing model to Slovenia because of the high quality data available in that Eastern European country. The effects of potential differences with other European countries will be quantified in sensitivity analyses [3].

First, the natural history of CC was recalibrated to Slovenian data by simulating the Slovenian female population between 2006 and 2015. All adjusted model parts are indicated in bold in Fig. 1. Population characteristics such as life expectancy, and probabilities of having a hysterectomy were adapted to the Slovenian population in that time period and the screening participation was informed by data from National Cervical Cancer Screening Programme ZORA ('Zgodnje Odkrivanje predRAkavih sprememb materničnega vratu', which means 'Early detection of precancerous changes of the cervix') [12]. The HPV prevalence was calibrated to positivity rates from Učakar et al. in 2013 [14]. The age-specific and stage-specific CC incidence was calibrated to data from the Cancer Registry of Slovenia as well as the age-specific and stage-specific CC survival probabilities [15]. Test characteristics of cytology were calibrated using detection rates during the first years of ZORA [12]. The fit of the model predictions with the observed data is presented in Appendix Figs. S1-S3.

Second, the characteristics of the population were adapted so that it would represent the unvaccinated Slovenian female population between 23 and 65 years old on 1 January 2020. These characteristics include age distribution, remaining life expectancy, hysterectomy probabilities and screening history as described in the appendix. Younger age cohorts were not evaluated because they were offered HPV vaccination and therefore are at lower risk for CC.

2.2. Base case assumptions on screening behaviour and test characteristics

We assumed that attendance rates in primary screening will stay stable over time regardless of the screening protocol and would be similar to the current attendance rates in Slovenia. This means that about 10% of the population never attends screening and that the remaining

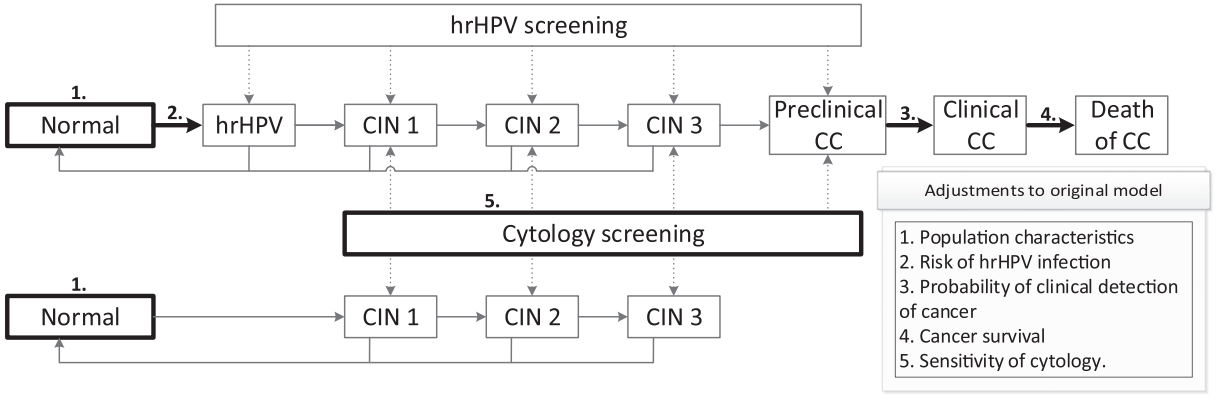

Fig. 1. Schematic representation of MISCAN-Cervix. Women are simulated individually and followed up until death. Each women is at risk for acquiring one or multiple HPV-infections, which may or may not progress sequentially into a pre-invasive CIN grade 1, CIN2, CIN3 and CC. These progression probabilities are dependent on age and on HPV-genotype. HPV-negative CIN lesions may or may not progress sequentially to CIN2 and CIN3 but will never progress to cancer. When screening is performed, the test will have a probability to be positive, depending on the type of test and the progression of the disease at that moment of time. The parts indicated in bold were adjusted during calibration to the Slovenian situation: 1. Population characteristics with regards to age distribution, life expectancy, hysterectomy rates and screening behaviour; 2. Age-specific hazard rates of acquiring an HPV infection; 3. Age specific probability of CC being clinically detected because of symptoms; 4. Stage- and age-specific survival of CC; 5. Sensitivity of cytology (was varied in a sensitivity analysis). HPV, high-risk human papillomavirus; CIN, cervical intraepithelial neoplasia; CC, cervical cancer.

90% of the population attends 83% of the screening rounds, so that the average participation in the country is 75% per screening round [12]. Adherence to repeat testing and colposcopy referral was assumed to be 90%, as is currently the case in Slovenia (Table 1).

As the sensitivity and specificity of cytology in Slovenia have much improved in the last decade [12,15], using the test characteristics from the period over which the model was calibrated (2006–2015) would not be representative for what can be expected for the future. Therefore, we applied the sensitivity and specificity of cytology in the Netherlands [13].

2.3. Screening protocols

We simulated 968 unique scenarios in which all women were invited to primary HPV-screening. The screening protocols in those scenarios differed on five domains (Table 1). First, the starting age of screening could be 25, 27 or 30. Because of the high HPV prevalence in young women, screening under age 30 would always start with primary cytology screening. Women with a high grade cytology result are referred to colposcopy, while women with a low grade positive cytology result are invited for a repeat cytology test. Second, the switching age from primary cytology screening to primary HPV-screening could either be 30, which is directly in protocols where the starting age is 30, or 35. Third, the maximum age of the last screening round could either be 55, 60, 65 or 70. Fourth, the screening interval could be either 3, 4, 5, 6, 7, 8 or 10 years. Also, protocols were simulated that started with 5-yearly screening from age 30 and switched to a 10-year interval at age 45, 50, 55 or 60. All protocols starting with cytology screening were evaluated with both a 3-year and a 5-year interval between the cytology tests. Fifth, the triage strategy after a positive primary HPV-test could either use genotyping complementary to the reflex cytology test or not and women who are not directly referred could be followed up by either a repeat cytology test or a repeat HPV-test (Appendix Fig. S4).

Screening programs should be socially and ethically acceptable to screening participants [9,10]. Therefore we categorized each protocol as either currently acceptable or not (Table 1). Based on expert opinion, we assumed a starting age of 25, a maximum interval for cytology screening of 3 years and a maximum interval for HPV-testing of 6 years to be acceptable for unvaccinated Slovenian women as it would not deviate too far from current practice.

2.4. Cost-effectiveness analyses

For each scenario, we simulated 10 million unvaccinated women alive at 1 January 2020 and followed them up until death of CC or of other causes. When all simulations were completed, we counted for each scenario several key outcomes. These outcomes include the number of screening tests, repeat tests, referrals to colposcopy, CIN2+ detection by screening, CC incidence, CC mortality and lifeyears gained compared to the scenario in which screening would be stopped. These outcomes were then multiplied with the corresponding costs and/or disutility loss if applicable to obtain the total costs and the quality adjusted lifeyears (QALYs) gained (Table 1) [4,16,17]. The costs are presented in euros (€) and are indexed to 1 January 2020. The costs of screening tests include costs for testkits, smeartaker fees, laboraty costs and costs for organization of the screening programme. Because the costs of the screening HPV-test when implemented on a national level in Slovenia is yet unknown, we assumed for the base-case analysis that the price of the HPV-test would be the same as in the Netherlands, where primary HPV-screening has been implemented in an organized

Table 1
Base case assumptions on screening behaviour, screening scenarios, costs and disutilities.

Variable	Value
Screening participation	75%[a]
Adherence to repeat testing	90%
Adherence to colposcopy referral	90%
Starting ages[b,c]	25 (27, 30)
Switching ages to primary HPV screening	30, 35
Maximum screening ages	55, 60, 65, 70
Screening intervals primary HPV screening(years)[c]	3, 4, 5, 6 (7, 8, 10)[d]
Screening intervals primary cytology before switching age (years)	3 (5)

Variable	Disutility (%)[4]	Duration (months)[4]	Costs	
			€ (2020)	Source
Screening				Dutch public health subsidy scheme.[13]
Primary cytology test	0.006	0.5	71.90[e]	
Primary HPV-test	0.006	0.5	57.59[e]	
Reflex cytology after HPV-test	0	0	25.61[e]	
Repeat cytology test	0.006	12	53.40[e]	
Repeat HPV-test	0.006	12	39.09[e]	
Diagnosis and treatment				Report on the effects and costs of cervical cancer
No CIN detected	0.005	6	224	screening in the Netherlands in 2006 [16] corrected for
CIN1	0.03	6	699	wage differences between the Netherlands and Slovenia.[22]
CIN2	0.07	12	1035	
CIN3	0.07	12	1211	
FIGO1A	0.062	60	3967	
FIGO1B	0.28	60	9408	
FIGO2+ clinically detected	0.28	60	8660	
FIGO2+ screen detected	0.28	60	9273	
Terminal care	0.712	1	21,068	

HPV, high-risk human papillomavirus; CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynaecology and Obstetrics.
[a] Distributed over 90% of the population. The remaining 10% of the population is assumed never to participate in screening.
[b] Because of the high HPV prevalence in young ages, cytology was always used as the primary screening test for women under age 30.
[c] Values outside brackets are considered socially acceptable to the Slovenian population.
[d] Both strategies using a screening interval of 10 years for all screening ages as well as strategies starting with a screening interval of 5 years from age 30 and switching to a 10-year interval at age 45,50,55 or 60 were simulated.
[e] Costs for screening include the test kit, laboratory costs, fees for smear takers and costs for organization of the screening programme.

setting in January 2017. Utility losses were based on a previously applied disutility set [3,4]. An annual discounting rate of 3% was used for both costs and effects, as stated in the recommendations for cost-effectiveness analyses by Sanders and colleagues in 2016 [18].

For calculating the incremental cost-effectiveness ratio (ICER), we used a two-step approach: In the first step, we only included protocols that would be considered as currently acceptable for Slovenian women (Table 1) and calculated the ICER for those strategies. As a second step, we added the remaining protocols (Table 1) to evaluate to what extend the cost-effectiveness can be improved if those restrictions would be overcome.

An ICER is calculated by first removing all considered strategies that are more costly and less effective than an alternative strategy or a combination of alternative strategies as they are not efficient. This remaining set of strategies form the efficient frontier. Next, each strategy is compared to the previous most effective strategy by dividing the extra costs by the extra QALYs gained, resulting in the ICER.

In general, protocols with an ICER below the gross domestic product (GDP) per capita are considered very cost-effective while protocols with an ICER above three times the GDP per capita are generally no longer considered cost-effective [19]. To select the optimal screening protocol in each of the two steps, we applied a willingness to pay (WTP) threshold of €50,000 per QALY gained. This threshold is frequently used in international literature [20,21] and is 1.4 times the GDP per capita in Slovenia [22], which is at the conservative end of the 1–3 GDP per capita range. However, because the ICERs of all strategies on the efficient frontiers will be presented, countries can apply their own WTP threshold. We defined the optimal screening protocol as the screening protocol on the efficient frontier with the highest number of QALYs gained with an ICER below the WTP threshold.

2.5. Sensitivity analyses

We performed several univariate sensitivity analyses to analyse the robustness of our results and because some of those sensitivity analyses might be more representative for specific other Eastern European countries. First, we applied a lower sensitivity of cytology to detect a cervical intraepithelial neoplasia grade 3 or cervical cancer ($CIN3^+$). Because screening programs in some Eastern European countries have not been running for a long time or screening has no extensive quality assurance and control, the quality of cytology might not be optimal yet. We applied a sensitivity of 53% for cytology being atypical squamous cells of undetermined significance $(ASC\text{-}US)^+$ in women with $CIN3^+$, as this was the lowest reported sensitivity available in situations

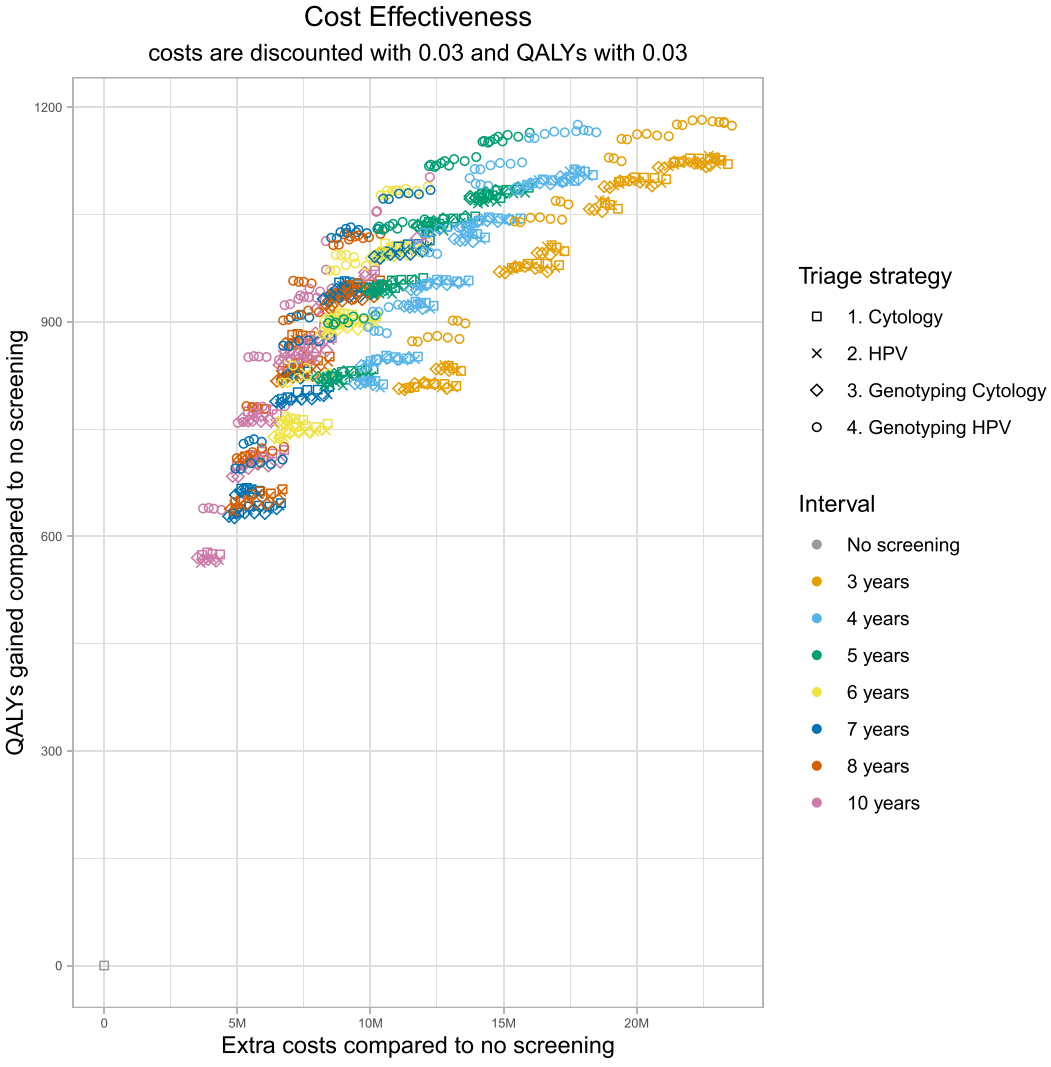

Fig. 2a. Costs and effects of the screening protocols per 100,000 women simulated and followed until death. For each protocol it is displayed how many QALYs are gained compared to a scenario where screening would be stopped, as well as the extra costs that screening would incur. QALY, quality adjusted life year.

where the HPV status is unknown [23]. Second, we applied an alternative set of published disutilities because these are dependent on the preferences of women regarding screening, diagnosis and treatment [24]. Third, we increased the price of the HPV-test with €42.31 to show the cost-effectiveness of all protocols in case the current price difference between the HPV-test and cytology in Slovenia could not be reduced. Fourth, we varied screening participation by lowering the attendance with 10 and 25 percentage points to 65% and 50% respectively and by increasing the attendance with 10 percentage points to 85% because attendance to primary screening might be different between countries and might be affected by the implemented screening protocol. Lastly, we simulated the scenarios with perfect screening attendance and follow-up adherence to find what the optimal screening protocol would be for women who perfectly adhere to the guidelines.

3. Results

Fig. 2a shows the discounted total net costs and total QALYs gained of all 968 simulated protocols per 100,000 unvaccinated Slovenian women alive on 1 January 2020 and followed lifelong.

The protocols with the largest screening intervals, and therefore the least screening rounds, are the cheapest protocols but also gain the least QALYs and are therefore on the bottom left of the spectrum. The opposite is true for protocols with the shortest screening intervals.

Cost efficient screening protocols gain the maximum number of QALYs for a given amount of costs. Those protocols lie on the efficient frontier (Fig. 2b). The black dots represent seven protocols that are on the efficient frontier of protocols that are considered acceptable for Slovenian women. The grey dots represent the thirteen protocols on

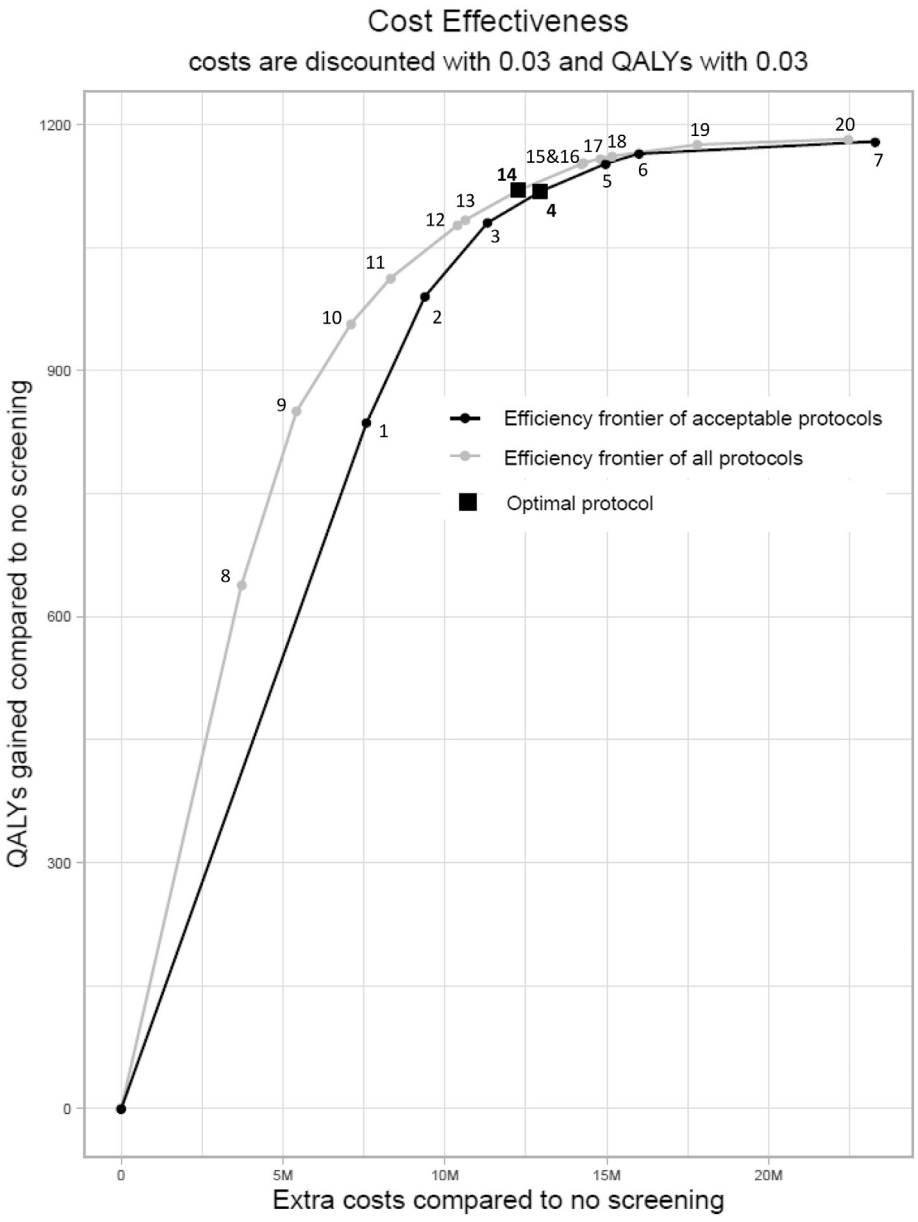

Fig. 2b. Costs and effects per 100,000 women simulated and followed until death of the screening protocols on the efficient frontier of acceptable protocols or on the efficient frontier of all simulated protocols. The efficient frontiers are indicated by the solid lines and do not contain strategies that gain less health for more costs than alternative strategies or a combination of alternative strategies. For each strategy on the frontier it is displayed how many QALYs are gained compared to a scenario where screening would be stopped, as well as the extra costs that screening would incur. The numbers next to the protocols refer to the strategy numbers as listed in Tables 2a and 2b which also include the ICER of each strategy. The strategies on each frontier indicated by a red square represent the optimal strategies for a willingness to pay threshold of €50,000. QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

Table 2a
Primary HPV-screening protocols on the efficiency frontier of acceptable protocols (see Fig. 2b). Bold indicates the optimal protocol under the cost-effectiveness threshold of €50.000 per QALY gained.

Protocol number	Age range	Screening interval	Number of Screening rounds	QALYs gained[a,b]	Extra costs[a,b] (x million €)	ICER within acceptable strategies[b] (€/QALY gained)
1	25–28[c]	3	7	836	7.6	9060
	30–54	6				
2	25–28[c]	3	8	990	9.4	11,703
	30–60	6				
3	25–28[c]	3	9	1080	11.3	21,467
	30–66	6				
4	**25–28[c]**	**3**	**10**	**1119**	**13.0**	**42,864**
	30–65	**5**				
5	25–28[c]	3	11	1152	15.0	59,392
	30–70	5				
6	25–34[c]	3	12	1165	16.0	84,879
	35–70	5				
7	25–34[c]	3	16	1180	23.3	486,371
	35–68	3				

QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
[a] Per 100,000 women simulated lifetime, compared to a no screening scenario.
[b] Discounted annually by 3%.
[c] This age range is screened with the primary cytology strategy.

the efficient frontier of all simulated protocols. The frontiers deviate from each other at the left of the graph where the cheapest protocols are located and almost merge again halfway from where they stay close to each other towards the right of the graph, but they never cross.

The characteristics of the protocols on both of the efficient frontiers are described in Table 2a and Table 2b, including their corresponding discounted net cost, QALYs gained and ICER. All strategies on the frontier apply genotyping as a direct triage strategy and use the HPV-test as the repeat test (Appendix Fig. S4, strategy 4).

Based on a WTP threshold of €50,000 per QALY gained, the optimal screening protocol within the set of acceptable strategies would be to start 3-yearly cytology screening from age 25 to 28 and switch to 5-yearly HPV-screening from age 30 to 65, leading to a total of 10 lifetime screens (ICER within acceptable strategies: €42,864 per QALY gained, Table 2a). When considering all simulated protocols, the optimal screening protocol is 5-yearly HPV-screening from age 30 to 65 (ICER: €45,406 per QALY gained, Table 2b).

If a WTP threshold of three times the GDP per capita in Slovenia would be applied (€106,853), the optimal screening protocol would become 5-yearly HPV-screening from age 35 to 70, with cytology screening at ages 27 and 32. Within the acceptable screening protocols, also 5-yearly HPV-screening from age 35 to 70 would become the optimal strategy, but with 3-yearly cytology screening from age 25 to 34.

For all protocols on both frontiers, the undiscounted main results as well as other important indicators are presented in Table 3a and Table 3b. Both tables show that with increasing screening intensity, the number of primary screens increases (70,482–507,628) as well as the number of repeat tests (4459–22,056), colposcopies (2969–10,454) and CIN2+ lesions detected by screening (1542–3431). The only exception is the number of referrals for colposcopy of strategy 6. Furthermore,

Table 2b
Primary HPV-screening protocols on the efficiency frontier of all simulated protocols (see Fig. 2b). Bold indicates the optimal scenario under the cost-effectiveness threshold of €50.000 per QALY gained.

Protocol number	Age range	Screening interval	Number of Screening rounds	QALYs gained[a,b]	Extra costs[a,b] (x million €)	ICER[b] (€/QALY gained)
8	30–50	10	3	639	3.7	5814
9	30–60	10	4	851	5.4	8035
10	30–62	8	5	958	7.1	15,747
11	30–40	5	6	1013	8.3	22,092
	45–65	10				
12	30[c]	5	7	1077	10.4	32,040
	35–65	6				
13	30–66	6	7	1084	10.6	37,757
14	**30–65**	**5**	**8**	**1120**	**12.3**	**45,406**
15	30[c]	5	9	1152	14.2	60,368
	35–70	5				
16	30–70	5	9	1153	14.3	62,833
17	27–32[c]	5	10	1159	14.8	89,529
	35–70	5				
18	30–33[c]	3	10	1161	15.2	140,466
	35–70	5				
19	30–70	4	11	1176	17.8	186,240
20	30–33[c]	3	14	1183	22.5	672,519
	35–68	3				

QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
[a] Per 100,000 women simulated lifetime, compared to a no screening scenario.
[b] Discounted annually by 3%.
[c] This age (range) is screened with the primary cytology protocol.

with increasing screening intensity the cancer incidence (429–217) as well as the cancer mortality (237–112) go down and the number of lifeyears gained (2000–3849) and QALYs gained (2078–3872) go up. The total costs go up as well (€15.4 million – €42.1 million) because of the increasing costs of screening. This while the costs of diagnosis and treatment remain more or less constant because although the costs of cancer diagnosis and treatment decrease, the costs of CIN diagnosis and treatment increase.

3.1. Sensitivity analyses

The results of the sensitivity analyses are presented in Table 4. It shows for all alternative screening assumptions what the optimal HPV screening protocol would be when considering all simulated screening protocols and applying a WTP threshold of €50,000. The optimal starting age of screening remains 30 for all sensitivity analyses although in case of the alternative disutility assumptions or higher costs for the HPV-test, that first screening would be a cytology test instead of an HPV-test. The end age of screening varies between 63 and 70 across the sensitivity analyses and the optimal screening interval increases from 4 years in case of 25% lower attendance to primary screening up to 8 years in case of perfect screening attendance and adherence to follow-up. The protocols to the direct left and right of the optimal screening protocol on the efficient frontier are also presented in Table 4. These protocols represent the optimal screening strategy if screening needs to be either less costly or more effective. All screening protocols on the efficient frontier of the sensitivity analyses are presented in Appendix Fig. S5 and Tables S1–S8 including the associated costs, QALYs gained and ICER.

4. Discussion

Our modelling analyses show that for a WTP threshold of €50,000, the optimal HPV screening protocol for Eastern Europe would be 5-yearly screening from age 30 to 65 where HPV-positive women would be triaged depending on the HPV genotype and cytology result. If this does not warrant a direct referral, repeat testing should be performed with an HPV-test. If it would not be acceptable for the population to start screening later than at age 25 and if the screening interval of primary cytology should not exceed 3 years, a cytology screen at age 25 and 28 can be added to that HPV screening protocol, although this will incur 5% extra costs without an additional gain in QALYs.

It is advised to add an extra screening round at age 70 in Eastern European countries where either the sensitivity of cytology or the attendance in primary screening is lower than assumed for Slovenia. If the attendance in primary screening would become 25% lower, the screening interval would be lowered to 4 years as well. If either the screening attendance or the costs of the HPV-test would be higher, the screening protocol can become less intensive than in the base case.

Furthermore, our analyses show that the optimal screening protocol is dependent on preferences of the population, reflected by the disutility weights of screening, diagnosis and treatment as well as acceptability of target ages for screening and screening intervals. Both of these preferences are dependent on the culture and values of women within a country and should be considered when selecting the optimal screening protocol. The effect of applying different disutility assumptions on the optimal screening protocol has been demonstrated in a previous study [24]. Our study shows that the efficient frontier of acceptable protocols is very close to the efficient frontier of all simulated protocols. This implies that the loss in cost-effectiveness by restricting to protocols that are acceptable is relatively small and should therefore be considered.

Lastly, the WTP threshold is an important factor in selecting the optimal screening protocol. This threshold is country specific and dependent on the severity of the disease, other available interventions and the maximum budget that can be spent on health [19].

4.1. Strengths and limitations

This study has some noteworthy strengths and limitations. One strength is that we evaluated many different screening protocols, including those with longer screening intervals. By including sufficient comparator strategies, especially around the WTP threshold, we avoided an underestimation of the ICER of the optimal strategy [25]. A second strength is that we evaluated those strategies with a microsimulation model that was specifically calibrated to an Eastern

Table 3a
Undiscounted Base case results of the protocols on the efficiency frontier of acceptable protocols (see Fig. 2b) per 100,000 women simulated lifelong.

protocol number	*Target ages*	*Screening interval (years)*	Effects (numbers, undiscounted)								Costs (€ millions, undiscounted)			CE[a] (€/QALY gained, undiscounted)
			Primary screen tests	Repeat tests[b]	Referrals to colposcopy	CIN2+ detections by screening	CC incidence	CC mortality	Life-years gained[a]	QALY's gained[a]	Screening costs	Diagnosis and treatment	Total costs	
0	–	–	–	–	–	–	567	326	–	–	–	12.0	12.0	–
1	25–28[c]	3	140,372	8443	4912	2268	366	204	2664	2736	8.8	11.1	19.9	2889
	30–54	6												
2	25–28[c]	3	192,337	10,293	5784	2504	314	168	3093	3206	11.9	10.4	22.3	3211
	30–60	6												
3	25–28[c]	3	250,431	12,159	6547	2652	283	141	3338	3473	15.4	9.9	25.3	3816
	30–66	6												
4	25–28[c]	3	280,517	13,638	7293	2866	269	136	3485	3601	17.3	10.1	27.4	4266
	30–65	5												
5	25–28[c]	3	340,995	15,456	7943	2948	255	122	3594	3707	20.9	9.9	30.8	5072
	30–70	5												
6	25–34[c]	3	356,180	16,012	7819	2962	253	121	3637	3744	22.1	9.9	32.0	5332
	35–70	5												
7	25–34[c]	3	507,628	22,056	10,454	3431	217	112	3849	3872	31.2	10.9	42.1	7783
	35–68	3												

CC, cervical cancer; CIN, cervical intraepithelial neoplasm; QALY, quality-adjusted life year; CE, cost-effectiveness.
[a] compared to a no screening scenario.
[b] women are only counted once per attended repeat test, if this repeat test would incur a reflex test, the costs of this reflex test are added to the screening costs, but not to the number of repeat tests as this does not cause extra harms to women.
[c] This age (range) is screened with the primary cytology protocol.

Table 3b
Undiscounted Base case results of the protocols on the efficiency frontier of all simulated protocols (see Fig. 2b) per 100,000 women simulated lifelong.

Protocol number	*Target ages*	*Screening interval (years)*	Effects (numbers, undiscounted)								Costs (€ millions, undiscounted)			CE[a] (€/QALY gained), undiscounted)
			Primary screen tests	Repeat tests[b]	Referrals to colposcopy	CIN2+ detections by screening	CC incidence	CC mortality	Life-years gained[a]	QALY's gained[a]	Screening costs	Diagnosis and treatment	Total costs	
0	–	–	–	–	–	–	567	326	–	–	–	12.0	12.0	–
8	30–50	10	70,482	4459	2969	1542	429	237	2000	2078	4.4	11.0	15.4	1647
9	30–60	10	122,369	6341	3918	1851	364	188	2583	2725	7.5	10.0	17.5	2009
10	30–62	8	159,989	8015	4789	2163	331	169	2916	3065	9.8	9.8	19.6	2488
11	30–40	5	181,918	9385	5499	2412	315	158	3104	3248	11.2	9.9	21.1	2788
	45–65	10												
12	30[c]	5	234,372	10,854	5985	2553	289	144	3297	3444	14.4	9.7	24.1	3512
	35–65	6												
13	30–66	6	242,428	11,312	6356	2602	285	141	3323	3467	14.8	9.8	24.6	3619
14	30–65	5	272,523	12,789	7104	2814	270	136	3464	3590	16.6	10.0	26.7	4081
15	30[c]	5	332,896	14,232	7393	2839	260	123	3552	3678	20.3	9.7	30.0	4901
	35–70	5												
16	30–70	5	332,997	14,609	7756	2896	256	122	3572	3693	20.2	9.9	30.1	4899
17	27–32[c]	5	340,328	14,876	7561	2896	257	122	3589	3709	20.9	9.8	30.7	5030
	35–70	5												
18	30–33	3	345,574	15,153	7629	2912	254	121	3605	3722	21.3	9.8	31.1	5123
	35–70	5												
19	30–70	4	407,917	17,744	9128	3165	234	115	3715	3799	24.8	10.3	35.1	6073
20	30–33[c]	3	497,004	21,200	10,271	3386	218	112	3833	3865	30.4	10.8	41.3	7564
	35–68	3												

CC, cervical cancer; CIN, cervical intraepithelial neoplasm; QALY, quality-adjusted life year; CE, cost-effectiveness.
[a] compared to a no screening scenario.
[b] women are only counted once per attended repeat test, if this repeat test would incur a reflex test, the costs of this reflex test are added to the screening costs, but not to the number of repeat tests as this does not cause extra harms to women.
[c] This age (range) is screened with the primary cytology protocol.

European country, which, to the best of the author's knowledge, was never done before.

A third strength is that we did not only take cost-effectiveness into account, but also considered which protocols would be acceptable to a population that is currently intensively screened. By doing this, we provide policymakers with added information on how much the cost-effectiveness would deteriorate if they would adhere to specific preferences of the population. To the best of the authors' knowledge, this is the first study to present both the ICERs of an extensive spectrum of CC screening protocols as well as ICERs of a selection of acceptable strategies. A limitation of our study is that the assumptions on costs could not directly be informed by observed costs in Eastern Europe, partly because there is no primary HPV-screening programme in place yet. The costs of an HPV-test can affect the conclusions substantially as shown in the sensitivity analyses. In case the current price difference between cytology and the HPV-test would be maintained, the optimal screening strategy would contain only 6 screening rounds instead of 8 under base case assumptions. Eastern European countries should therefore carefully check whether the cost assumptions would be valid for them as well before utilizing the results. A second limitation of the study is that opportunistic screening was not taken into account. The costs and effects of all protocols were compared to a no screening scenario. However, in absence of organized screening there is often opportunistic screening present, which does not promote equity, causes more harms and is not monitored for quality assurance, all making screening less cost-effective [11]. If organized screening would replace the inefficient opportunistic screening activities, the simulated screening protocols would be even more cost-effective than indicated in this study. Lastly, a stable HPV prevalence was assumed over time. If the HPV prevalence would increase, the risk for CC could increase as well and a more intense

Table 4
Sensitivity analyses. The Optimal target age range and screening interval are presented for each of the alternative screening assumptions assuming a WTP threshold of €50,000. Also the protocols are presented which are on the efficiency frontier and are either one step less costly and less effective, or more costly and more effective.

Scenario	Optimal protocol (age range and screening interval by test type)				Less costly, less effective (age range and screening interval by test type)				More costly, more effective (age range and screening interval by test type)			
	Age cyt.[a]	Int. Cyt.	Age HPV	Int. HPV	Age cyt.[a]	Int. Cyt.	Age HPV	Int. HPV	Age cyt.[a]	Int. Cyt.	Age HPV	Int. HPV
Base case	–	–	30–65	5	–	–	30–66	6	27–32	5	35–70	5
Lower sensitivity cytology	–	–	30–70	5	–	–	30–65	5	–	–	30–70	4
Alternative disutility assumptions	30	–	35–65	6	30	–	35–63	7	30	–	35–65	5
Higher costs of HPV-test	30	–	35–63	7	–	–	30–63	8	30	–	35–65	6
Attendance primary screening −10%	–	–	30–70	5	–	–	30–65	5	30–33	3	35–70	5
Attendance primary screening +10%	–	–	30–66	6	–	–	30–45	5	–	–	30–70	5
							45–65	10				
Attendance primary screening −25%	–	–	30–70	4	30	–	35–67	4	27–33	3	35–68	3
Perfect attendance and adherence to follow-up	–	–	30–70	8	30	–	35–67	8	30	–	35–70	7

WTP, willingness-to-pay; cyt., cytology; Int., interval; HPV, human papillomavirus.
[a] This age (range) is screened with the primary cytology protocol.

screening protocol might become optimal. However, if only the HPV prevalence increases and the CC risk not, the optimal screening intensity will not change that much.

Although it was shown that the conclusions might be dependent on specific model assumptions, it is clear from our results that when primary HPV-screening would be implemented, the screening interval should be at least 5 years. Although we assumed this would be an acceptable interval for women in Eastern Europe, some of them might be used to shorter screening intervals in current programmes. Shorter screening intervals with HPV screening will gain only few extra QALYs while incurring considerably more costs. Therefore, it is especially important to minimize opportunistic screening when implementing primary HPV screening. This might be more challenging if screening intervals are longer.

Our findings are in line with analyses performed in other regions. Van Rosmalen et al. showed that for the Netherlands 6-yearly primary HPV-screening from age 30 to 66 would be the optimal protocol applying a WTP threshold of €50,000 when considering a wide range of protocols [4]. A study for the setting of New Zealand reported an optimal protocol of 5-yearly HPV-screening in women aged 25–69, although protocols with a higher starting age were not considered in this study [26].

Screening vaccinated cohorts of women was outside the scope of this study. However, these vaccinated women will enter the ages that are eligible for screening in several Eastern European countries (including Slovenia) very soon. These vaccinated women are at lower risk for CC and because of that will require less intensive screening [27]. Therefore separate analyses should be performed on optimizing screening in vaccinated cohorts in Eastern Europe.

5. Conclusion

Although Eastern Europe differs from Western Europe on many factors that influence the cost-effectiveness of screening programmes, we showed that the optimal HPV screening programme is similar to that of Western Europe. The optimal screening protocol for individual Eastern European countries depends on preferences of women, the WTP threshold and screening attendance. However, it can be concluded that if HPV screening is implemented, the screening interval should be at least five years and should be continued until an age between 60 and 70.

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CRediT authorship contribution statement

Erik E.L. Jansen: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Visualization. **Urška Ivanuš:** Conceptualization, Methodology, Writing - review & editing. **Tine Jerman:** Methodology, Validation, Writing - review & editing. **Harry J. de Koning:** Writing - review & editing, Supervision, Funding acquisition. Inge **M.C.M. de Kok:** Conceptualization, Methodology, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

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Appendix A. Supplementary data

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