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23 **Threshold cost-effectiveness analysis for a**
24 **therapeutic vaccine against HPV-16/18-positive**
25 **Cervical Intraepithelial Neoplasia in the Netherlands**

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28

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30

31 **Abstract**

32 In this study, (yauponery.weebly.com) the potential price for a therapeutic vaccine against
33 Human Papilloma Virus (HPV)-16 & 18 (pre)-malignant cervical lesions is examined. A model
34 was built in the context of the new Dutch cervical cancer-screening program. This renewed
35 screening will be introduced in (www.eurogin.com) 2016 and includes a primary test for the
36 presence of high risk human papilloma virus (HPV). (www.cwru.edu) Based on data of
37 cervical cancer screening and HPV prevalence in the Netherlands, (www.eurogin.com)
38 cohorts for cervical intraepithelial neoplasia (CIN) 2 and 3 and cervical cancer stage 1A
39 (FIGO 1A) were created with women positive for HPV-16 or 18. In the base case, the
40 potential vaccine price was based on parity in cost and an equal number of effective
41 treatments between the simulation with a therapeutic vaccine and the standard treatments.
42 Scenario analyses were performed taking quality adjusted life years (QALYs) into account
43 with €20000/QALY, €50000/QALY and €80000/QALY thresholds as cut-offs. Sensitivity
44 analyses were specifically targeted at the characteristics of the type-specific HPV test in the
45 screening practice and vaccine efficacy. A probabilistic sensitivity analysis (PSA) was
46 performed to quantify the level of confidence of the results found in the base case. In the

47 base case, break-even vaccine prices of €555, €794 and €2982 were found for CIN 2, CIN 3
48 and FIGO 1A, respectively. The PSA showed vaccine pricing below €462, €702 and €2886
49 will be cost saving with a likelihood of 95% for CIN 2, CIN 3 and FIGO 1A, respectively. The
50 vaccine price proved to be very sensitive for inclusion of QALY gains and including the HPV-
51 type specific test into the Dutch screening practice. Treating CIN 2, CIN 3 and FIGO 1A with
52 a therapeutic vaccine costing €400, can save about 1.4 million euro in the Netherlands,
53 annually.

54

55 Introduction

56 Screening for (pre)-malignant lesions of the cervix has lowered the number of cervical
57 cancers in the Netherlands. Despite screening, approximately 700 women are still diagnosed
58 with cervical cancer and about 200 women die of cervical cancer in the Netherlands every
59 year [1]. To further reduce the number of cervical cancers the prophylactic bivalent **vaccine**
60 **against infection with human papillomavirus (www.uptodate.com)** (HPV) type 16 and 18 was
61 implemented in the national immunization program in 2009, offering vaccination to twelve-
62 year-old girls. The HPV high risk (HR) types are considered the cause of cervical cancers,
63 with HR-HPV **types 16 and 18 (www.uptodate.com)** being responsible for about 70% of all
64 cervical cancers[1,2]. The first significant effects of vaccination on cervical cancers numbers
65 can only be expected and being measured in more than a decade, when the first cohort of
66 vaccinated women may encounter increased risks and enters cervical screening. The results
67 of the prophylactic vaccination can be expected far from optimal given the low vaccination
68 coverage of 59% in the Netherlands in 2014 [3].

69 In 2016, the Dutch cervical screening program is intended to change. Cytology as primary
70 test is replaced by an HR HPV-DNA test, cytology will be used as a triage test in case of a
71 positive HR-HPV-test [4]. The HR-HPV test is more sensitive than cytology for detection of
72 **cervical intraepithelial neoplasia (CIN) grade 2 or worse (grade 3 and cancer) [5]. It is**
73 **expected that (worldwidescience.org)** the new screening program will detect an extra of 75

74 women with CIN or cervical cancer and prevent 18 deaths in contrast with the current
75 screening. The specificity of the HR-HPV-test is lower than cytology though. The test
76 provides information about whether or not a woman has an infection with a HR-HPV type, but
77 it does not provide information on the degree of transformation of cervical cells. Cytology will
78 be used as a triage test when a woman has a positive HR-HPV-test [6]. If a woman has a
79 PAP3A2 or worse, she will be referred to a gynecologist [7]. A colposcopy is performed and
80 an additional biopsy is taken to assess the state of the lesion. Notably, despite the
81 introduction of vaccination and an improved screening program, (pre)malignant cervical
82 neoplasia will remain to exist and better treatment options are needed.

83 Therapeutic HPV-vaccines may improve the treatment of (pre)malignant cervical neoplasia
84 as no surgical treatment is needed [8]. Therapeutic HPV-vaccines can trigger the immune
85 system to recognize HPV-infected cells and enhance the immune system eliminate these
86 cells. A major difference between a therapeutic HPV-vaccine and a prophylactic HPV-
87 vaccine concerns the **specific immune response** that is evoked against different HPV
88 proteins. The prophylactic vaccines induce antibodies against a viral capsid protein, **which**
89 **can neutralize the virus and** thus inhibit infection of cells. The current prophylactic vaccines
90 are however not capable of clearing already existing infections. Upon infection of cells with
91 HPV, the cells express non-structural proteins of HPV, e.g. E1, E2, E6 and E7. Notably,
92 therapeutic HPV vaccines that have entered clinical trials mostly target HPV E6 and E7 [8].
93 The therapeutic HPV vaccines tested so far show varying results with regression or reduction
94 of HPV-induced lesions with an efficacy of around 40-70%. The best results were found
95 using a microencapsulated DNA vaccine; in younger patients a 70% reduction of lesions was
96 detected [8].

97 Economic aspects are becoming increasingly important in the assessment of any health-care
98 technology, (therapeutic) vaccines included. The aim of this study is to explore potential
99 pricing of a therapeutic HPV vaccine for women identified with HPV-induced cervical lesions
100 in the Netherlands.

101

102 **Methods**

103 We analyzed three cohorts of women with detected HPV-16/18 positive CIN 2, CIN 3 and
104 cancer (notably, early stage FIGO 1A). It is assumed that therapeutic vaccines are of less
105 use in later stages of cancer. The sizes of the CIN cohorts are estimated for the whole of the
106 Netherlands based on the annually detected number of CIN 2 and CIN 3 in current screening
107 setting [9,10]. With data on the prevalence on HR-HPV CIN 2/3 in the Netherlands, the total
108 number of HR-positive women could be calculated that in the new screening practice would
109 have been detected when an HR-HPV test would be used as primary test [11]. The cohort
110 size for HPV-16/18 positive CIN 2 and CIN 3 is calculated using the prevalence of HPV-
111 16/18 in CIN 2 and CIN 3, assuming all HR-positive CINs are detected in the new screening
112 settings the detection of HPV-16/18 an HPV-type specific test was modeled on top of the
113 screening program. Due to the selectivity of the test, also HPV-16/18 false-positive women
114 enter the cohort [12]. The false positive HPV-16/18 women are kept in the cohort and treated
115 as true positives. The cohort size for FIGO 1A is based on a Dutch report on the national
116 cervical screening program and the prevalence of HPV-16/18 in cervical cancer [11,13]. In
117 the base case, the sizes of the cohorts for HPV-16/18 positive CIN 2, CIN 3 and FIGO 1a are
118 1455, 3496 and 102 women, respectively.

119 To estimate potential vaccine pricing, a comparison was made based on parity in cost. The
120 same cohort was simulated twice, once treating the women with the current treatments and
121 once treating the women with an HPV-16&18 therapeutic vaccine. In the base case,
122 calculation of the maximum vaccine price was based on equal costs between the two
123 simulations and the same number of effective treatments in both simulations.

124

125 **Effectiveness of treatments**

126 Although the efficacy of therapeutic vaccines is not established yet, it is obvious that the
127 vaccine must have effectiveness in the same ball park area as the current surgical
128 interventions, to present a realistic alternative. The effectiveness for the current treatments,
129 Loop Excision of the Transformation Zone (LETZ), conization and hysterectomy are
130 presented in Table 1 [13]. The efficacy of the vaccine was assumed at 90% to reflect similar
131 efficacy. In the model, false positive diagnosed women in the vaccine simulation are
132 retreated with one of the surgical treatments in order to offer the same number of effective
133 treatments in both. The same goes for women who would normally be treated with
134 hysterectomy and ineffectively treated by the vaccine; they are retreated with a
135 hysterectomy.

136 **Table 1.** Input parameters relating to costs, treatment effectiveness, QALY loss and HPV-
137 16/18 test characteristics.

Parameter	Value (min-max) ^a	One-way sensitivity/ Scenario analysis	Source
CIN 2	€788 ^b (688-888)		[13]
CIN 3	€990 ^b (890-1090)		[13]
FIGO 1A	€3400 ^b (3300-3500)		[13]
Hysterectomy	€4976 ^b		[13]
Radical hysterectomy	€6951 ^b		[13]
Treatment effectiveness LETZ & Conization	90%		[13]
Treatment effectiveness therapeutic vaccine	90%	95% ^c	[13]
Treatment effectiveness hysterectomy	100%		Assumption
QALY loss CIN 2/3	0 ^d	0.007, 0.0375, 0.07 ^e	[14]
QALY loss hysterectomy	0 ^d	0.0175, 0.0875, 0.175 ^e	[15]
QALY loss FIGO 1A	0 ^d	0.03, 0.15, 0.30 ^{e,1}	[14]
HR-HPV prevalence CIN 2	93.2% (79.55-100%)		[11]
HR-HPV prevalence CIN 3	98.7% (98.3-100%)		[11]
HR-HPV prevalence FIGO 1A	86.7%(61.5-100%)		[11]
HPV-16/18 prevalence CIN 2 ^g	54.6% (52.2-56.8%)		[11]
HPV-16/18 prevalence CIN 3 ^g	72.1%(69.8-74.4%)		[11]
HPV-16/18 prevalence FIGO 1A ^g	76.9% (69.2-84.6%)		[11]
Specificity HPV test for HPV-16/18	97.8% (95.1-99.2%)		[12]
Sensitivity HPV test for HPV-16/18	73.7% (63.7-78.7%)	80%, 90%, 95% and 100% ^c	[12]
Cost HPV test for HPV-16/18	€83.86		[16]

^a Minimal and maximal values between parentheses are used in a probabilistic sensitivity analysis.

^b Updated with the consumer price index to 2015 [17]

^c Used in a one-way sensitivity analysis

^d In the base-case and in the probabilistic sensitivity analysis no QALY loss due to treatment of (pre)-malignant lesions was assumed.

^e In a one-way sensitivity analysis 10, 50 and 100% of the QALY loss was assumed to be prevented by

using a vaccine. This gain in QALY was used to calculate a vaccine price using the Dutch willingness-to-pay threshold of €20000/QALY. The vaccine price was further explored using different thresholds. Also a PSA was performed taking the QALY gain into account.

^f Discounted according to Dutch Pharmacoeconomic guidelines [18]

^g HPV-16/18 prevalence is presented as a proportion of the HR-HPV prevalence

138

139 The cost comparison between the vaccine and the current treatments was made on one
140 round of effective treatment only, i.e. women who were diagnosed false positive or normal
141 would be treated with hysterectomy and are not effectively treated by the vaccine are
142 retreated to match the number of effective treatments of the current treatments simulations.
143 The authors believe that taking multiple rounds of treatment into account would make the
144 estimation of the vaccine price unnecessarily complex, whereas this simplification does not
145 invalidate our model.

146

147 **Costs**

148 The simulation of the cohort with the surgical treatments was calculated by multiplying the
149 number of women in the cohort with the treatments cost, see Table 1. The treatments cost
150 were calculated based on a Dutch report and updated to 2015 price level using the consumer
151 price indices [13,17]. The break-even vaccine price was calculated based on the costs of
152 surgical treatment, HPV-16/18-test costs for the group of HR-HPV women, retreatment costs
153 for false-positive women and costs of retreating women who would normally get a
154 hysterectomy and are not effectively treated by the vaccine.

155

156 **Analyses**

157 Besides the base case, a number of analyses were performed. A probabilistic sensitivity
158 analysis (PSA) was performed to determine the uncertainty in the vaccine prices. In a PSA,
159 statistical distributions are assigned to the parameters in a model. The ranges used in the

160 PSA for the HPV prevalence and the type specific HPV test are presented in able 1. Due to
161 the skewed distributions, for all the parameters varied in the PSA a beta PERT distribution
162 was used. The ranges of the confidence intervals were used as minimum and maximum
163 values for creating the beta distributions. For the cost of CIN 2, CIN 3 and FIGO 1A a uniform
164 distribution was chosen with ranges of cost of +/- €100. In the model, a thousand repeat
165 drawings were simulated, where the model randomly draws values from each distribution
166 and the vaccine prices with those values were calculated. Besides the PSA, two univariate
167 sensitivity analyses were performed to see to what extend the potential vaccine price is
168 sensitive to the vaccine efficacy and an increase of sensitivity of the HPV-test.

169 We also performed two scenario analyses. The first scenario investigated the effect of
170 inclusion of [quality adjusted life year \(web.mit.edu\)](#) (QALY) gains into the calculation of the
171 vaccine price. In the base case, conservatively [quality of life](#) was not taken into account to
172 calculate the vaccine prices. [Quality of life \(web.mit.edu\)](#) (QoL) obviously decreases when a
173 woman is diagnosed with CIN 2/3, but data lack on how much of this decrease is due to
174 surgical treatment. It is suggested that most QoL loss is due to the fear of having cancer and
175 not due to the surgical treatment [7]. Therefore, no good estimates for the possible gain in
176 QOL could be deducted if women are treated with a vaccine rather than surgical treatment.
177 To overcome the lack of insight in the QoL, we calculated the potential vaccine price for
178 scenarios of 10%, 50% and 100% gains in quality adjusted life years (QALYs) for CIN2, CIN
179 3, FIGO 1A and hysterectomy. In this calculation, the various suggested Dutch willingness-
180 to-pay thresholds of €20 000, 50 000 and 80 000 per QALY are used as cut-offs [19-21]. In a
181 PSA the uncertainty of the found vaccine prices is established. In Table 1 the maximum
182 QALY losses for CIN 2/3, FIGO 1A and hysterectomy are presented [14,15].

183 The second scenario analyzed a therapeutic vaccine as an alternative for hysterectomy. The
184 price of therapeutic vaccines is unknown since none of these vaccines have entered the
185 market yet. High production costs for a therapeutic vaccine may cause the vaccine to be too
186 expensive to be an alternative for CIN 2 or 3. A third scenario analysis was performed,

187 investigating the maximum vaccine price when the primary HPV test is replaced by an HPV-
188 type specific test, making the cost of testing for HPV-16/18 part of screening.

189 Finally, in a budget-impact analysis was the vaccine price was varied to calculate the
190 possible cost savings in the Dutch setting. This scenario was divided into two sub-analyses:
191 use of the vaccine against CIN 2 and CIN3 and use of the vaccine against CIN 2, CIN 3 and
192 FIGO 1A. In this analysis the base case assumptions were used.

193 **Results**

194 The potential vaccine prices for the (pre)malignant cervical lesions increase with severity of
195 the lesions. Maximum vaccine prices are €555, €794 and €2982 for CIN 2, CIN 3 and FIGO
196 1A respectively. Potential prices of a therapeutic vaccine are very sensitive to whether or not
197 costs of an HPV-test are included in the calculations. In the new screening program the
198 women will be identified as HR-positive, but for the HPV-16/18 therapeutic vaccine
199 identification of these types is necessary. In the future the HR-test may be replaced by a
200 HPV-type specific test. Including the HPV-type-specific test into screening will increase the
201 potential vaccine prices to €759, €957 and €3089 for CIN 2, CIN 3 and FIGO 1A respectively.
202 The potential price goes up with about €200, roughly twice the HPV-test price. Notably, for
203 identifying a HPV-16/18 positive woman approximately two women have to be tested with the
204 HPV-16/18 test.

205 Figure 1 shows the results of the PSA. The figure shows [the probability of \(web.mit.edu\)](#) cost
206 savings per value for the vaccine price. A vaccine price below €462, €702 and €2886 will be
207 cost saving with a likelihood of 95% for CIN 2, CIN 3 and FIGO 1A respectively.

208 Fig. 1. Effect of the vaccine price on the probability that the vaccine will be cost saving for the
209 (pre)malignant CIN 2, CIN 3 and FIGO 1A.

210 Table 2 shows the results of the sensitivity analyses on the vaccine efficacy and the
211 sensitivity of the HPV-test. When the vaccine efficacy is slightly increased, the vaccine prices

212 increases also as a higher efficacy lowers [the number of \(web.mit.edu\)](#) women that need
 213 retreatment with a hysterectomy. A higher sensitivity of the HPV-test increases the vaccine
 214 price, as more HPV-16/18 positive women with an (pre)malignant cervical lesion will be
 215 detected the ratio of women tested for HPV-16/18 [and the number of \(web.mit.edu\)](#) women
 216 treated by the vaccine will decrease.

217 Table 2. Results of sensitivity analyses on vaccine efficacy and sensitivity of the modelled
 218 HPV-test

Vaccine efficacy	CIN 2	CIN 3	FIGO 1A
95%	€560	€804	€3124
100%	€564	€813	€3266
Sensitivity			
80%	€572	€807	€2992
90%	€594	€825	€3005
95%	€603	€833	€3011
100%	€612	€840	€3016

219

220 Inclusion of QALY-gains for the vaccine over the current treatments leads to higher
 221 maximum vaccine prices, see Table 3. The maximum vaccine price almost doubles, when
 222 half of the maximal QALY gain is achieved by vaccinating instead of surgery for the
 223 €20,000/QALY threshold.

224 Table 3. Results of probabilistic sensitivity analyses on the potential vaccine price for three
 225 cost-effectiveness thresholds

226

QALY savings		€20,000/QALY			€50,000/QALY			€80,000/QALY		
		Deterministic vaccine price	0.95 probability cost saving	0.05 probability cost saving	Deterministic vaccine price	0.95 probability cost saving	0.05 probability cost saving	Deterministic vaccine price	0.95 probability cost saving	0.05 probability cost saving
CIN 2	10%	€668	€558	€754	€852	€761	€937	€1036	€944	€1128
	50%	€1159	€1066	€1246	€2081	€1981	€2172	€3003	€2896	€3098
	100%	€1774	€1679	€1859	€3617	€3504	€3711	€5461	€5324	€5564
CIN 3	10%	€909	€818	€994	€1095	€1003	€1181	€1282	€1189	€1367
	50%	€140	€1313	€1494	€2338	€2243	€2425	€3271	€3173	€3359
	100%	€2027	€1934	€2114	€3892	€3796	€3981	€5757	€5651	€5850
FIGO 1A	10%	€3829	€3734	€3920	€4682	€4539	€4725	€5436	€5339	€5531

	50%	€5972	€5881	€6071	€9991	€9888	€10103	€14009	€13894	€14137
	100 %	€8651	€8559	€8760	€16688	€16568	€16828	€24725	€24568	€24900

227

228 The deterministic maximum price for the vaccine as an alternative for hysterectomy and
 229 radical hysterectomy are €4347 and €6124 respectively. As an alternative for these
 230 expensive treatments pricing of a therapeutic vaccine is found to be high compared to CIN 2,
 231 CIN 3 and FIGO 1A. Table 4 shows the results of taking QALY gain into account. The
 232 potential therapeutic vaccine price is very sensitive for gain in QALYs.

233 Table 4. Results of calculating the vaccine price as an alternative for (radical) hysterectomies
 234 taking QALY gain into account for different willingness-to-pay thresholds.

Gains in QALY	Hysterectomy			Radical hysterectomy		
	€20 000 / QALY	€ (workspace.imperial.ac.uk) 50,000/ QALY	€ 80,000/ QALY	€ 20,000/ QALY	€ 50,000/ QALY	€ 80,000/ QALY
10%	€4697	€5222	€5747	€6474	€6999	€7524
50%	€6097	€8722	€11347	€7874	€10499	€13124
100%	€7847	€13097	€18347	€9624	€14874	€20124

235

236 In the budget impact analysis, the annual cost savings are calculated for 2 scenarios, see
 237 Table 5. The analysis shows maximal achievable cost saving for a therapeutic HPV-16/18
 238 vaccine against CIN 2&3 and CIN 2, CIN 3 and FIGO 1A. Vaccine prices of €710 and €760
 239 are breakeven points for the CIN 2&3 and CIN 2, CIN 3 and FIGO 1A scenario respectively.

240

241 Table 5. Annual cost savings in the Netherlands for a series of vaccine prices and two
 242 scenarios for applying the vaccine (CIN only and FIGO 1A as well as
 243 (workspace.imperial.ac.uk) CIN)

Vaccine price	CIN 2 & CIN 3	CIN 2, CIN 3 and FIGO 1A
€0	€2 763 464	€2 992 831
€100	€2 378 999	€2 600 674

€200	€1 994 534	€2 208 548
€300	€1 610 069	€1 816 362
€400	€1 225 604	€1 424 206
€600	€456 675	€639 894 ⁵
€800	€-312 255	€- 144 419

246

247

248

249 Discussion

250 Cervical (pre)cancer is still a major threat for women worldwide and new treatments are
251 necessary to further reduce the number of cervical cancers. In this study, we examined the
252 potential pricing of a therapeutic vaccine against HPV-16/18 positive CIN 2, CIN 3 and FIGO
253 1A. A conservative approach was chosen to arrive at a maximum vaccine price for the
254 therapeutic vaccine in the Netherlands. The conservative approach is reflected in the
255 assumption of equal effectiveness of the vaccine and the current treatments, including an
256 extra HPV-test for detecting HPV-16/18 positive women and not taking prolonged protection
257 against HPV-infections and cross-protections into account. Notably, the deterministic
258 maximum vaccine price is lower than the average treatment cost for the stages investigated
259 due to retreated false-positive diagnosed women, costs of an additional HPV test and re-
260 treated women who would normally be treated by hysterectomy and are ineffectively treated
261 by the vaccine. Obviously, a type-specific HPV-test for HPV-16/18 identification is essential
262 for treating women with a therapeutic HPV-16/18 vaccine effectively. The maximum vaccine
263 price is very sensitive to the costs of the additional HPV test. Replacing the primary HPV-
264 DNA test in the cervical cancer screening with a type-specific test would increase the
265 acceptable maximum vaccine price drastically as these costs would no longer be needed in
266 the vaccination strategy. However, it will obviously affect the cost-effectiveness of screening
267 as the ICER of screening is sensitive for [the cost of \(workspace.imperial.ac.uk\)](#) the primary
268 HPV-test [14]. Another solution to the problem of requiring an additional type-specific HPV-

269 test is to broaden the spectrum of a therapeutic vaccine against multiple HR-HPV-types, as
270 is being done for the prophylactic vaccines.

271 The probabilistic sensitivity analysis shows considerable uncertainty in value for the vaccine
272 price for CIN 2, CIN 3 and FIGO 1A. Despite the uncertainty, a vaccine price around the
273 €400 will most likely be cost saving for all (pre)-malignant cervical lesions and annually a
274 possible 1.2 million euro can be saved when the vaccine is used against CIN 2&3. When the
275 vaccine is also used against FIGO 1A savings can possibly be 1.4 million euro. This saving is
276 of course very sensitive to the total number of HVP-16/18 positive CIN 2/3 and FIGO 1A.
277 When the incidence and prevalence of these lesions drops, the possible monetary gains also
278 drop.

279 Women diagnosed with abnormal cervical cells experience a reduced QOL. This reduction is
280 mostly due to the fear of having or getting cancer and not necessarily due to the surgical
281 treatment of abnormal cells. A study in the Netherlands on the QOL of women referred for
282 colposcopy showed that the reduction in QOL is likely irrespective of the CIN-grade [7]. It is
283 likely though, that treating women with a vaccine instead of surgically decreases the QOL
284 loss of these women. Already a small gain in QALYs in comparison to the current treatments
285 leads to a big increase in the maximum vaccine price. Further research into the QOL of (pre)-
286 malignant lesions is needed in order to justify inclusion of exact gains in QOL by the vaccine.
287 Beside a possible reduction in QOL using a therapeutic HPV-vaccine is likely beneficial when
288 it comes to pre-term births. Studies have shown that excision of the cervix causes an
289 increased risk of pre-term pregnancies. The risk of a pre-term pregnancy after excision is not
290 restricted to the first birth after excision, but the woman may have an increased risk
291 throughout her reproductive years [22,23].

292 Sensitivity analysis showed that vaccine efficacy has moderate **impact on the**
293 workspace.imperial.ac.uk maximum vaccine price for CIN2/3 within the plausible range
294 investigated. In the model, increasing vaccine efficacy leads to a small decrease in the

295 number of retreated women who would normally be treated with hysterectomy. Although
296 hysterectomies are expensive, [the percentage of \(workspace.imperial.ac.uk\)](#) women having
297 this treatment is low, while the decrease in retreatment is low as mentioned. [The impact of](#)
298 increasing vaccine efficacy has a bigger [impact on the \(workspace.imperial.ac.uk\)](#) vaccine
299 price for FIGO 1A, as the percentage hysterectomies in this disease state is much higher.

300 The modeled type-specific HPV-test has a far from ideal sensitivity. Therefore, [a sensitivity](#)
301 [analysis was \(workspace.imperial.ac.uk\)](#) performed on the sensitivity of the test. A poor
302 sensitivity leads to high numbers of undetected HPV-16/18 positive women. A type-specific
303 test with a better sensitivity will lead to more women positive for HPV-16/18 CIN 2/3 or FIGO
304 1A treated by the vaccine, therefore reducing the number of true positive women treated
305 surgically. However, a type-specific HPV-test with a higher sensitivity will only slightly
306 increase the vaccine price, but it can offer more women a choice between vaccination and
307 conventional treatments.

308 Hysterectomies are major procedures leading to a decreased QOL. If therapeutic vaccines
309 can be an alternative for hysterectomies, major cost savings and QALY gains can be
310 expected, allowing a threshold vaccine price at almost €4500 for this setting.

311

312 **Conclusion**

313 In this study, the pricing of a potential therapeutic HPV vaccine against HPV-16/18-positive
314 CIN 2, CIN 3 and FIGO stage 1A cervical cancer was explored in the Dutch setting. If no gain
315 in QALYs was assumed, maximum vaccine prices resulted of €555, €794 and €2982 for CIN
316 2, CIN 3 and FIGO 1A, respectively. The PSA showed vaccine pricing below €462, €702 and
317 €2886 will be cost saving at 95% likelihood or more. Taking QALY gains into account
318 increases the maximum vaccine price, although for CIN 2 and CIN 3 only small gains in
319 QALYs may be reasonable. The vaccine pricing is also sensitive to the inclusion of a type-

320 specific HPV-test. Treating CIN 2, CIN 3 and FIGO 1a with a therapeutic vaccine costing
321 €400, can save about 1.4 million euro in the Netherlands annually.

322 **Conflict of interest**

323 Prof Maarten J Postma received grants and honoraria from various pharmaceutical
324 companies, inclusive those developing, producing and marketing (prophylactic HPV)
325 vaccines. Also, Prof Postma holds stocks in Ingress Health (Rotterdam, Netherlands /
326 Wismar, Germany). J Luttjeboer MSc has no conflicts of interest to report. Prof Toos
327 Daemen is founder of ViciniVax, a spin-off from the UMCG developing cancer vaccines.

328

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