The cost-effectiveness profile of sex-neutral HPV immunisation in European tender-based settings: a model-based assessment

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Summary

Background In many European countries, human papillomavirus (HPV) vaccine uptake among girls has remained below target levels, supporting the scope for vaccination of boys. We aimed to investigate if sex-neutral HPV vaccination can be considered cost-effective compared with girls-only vaccination at uptake levels equal to those among girls and under tender-based vaccination costs achieved throughout Europe.

Methods We investigated the cost-effectiveness of sex-neutral HPV vaccination in European tender-based settings. We applied a Bayesian synthesis framework for health economic evaluation to 11 countries (Austria, Belgium, Croatia, Estonia, Italy, Latvia, the Netherlands, Poland, Slovenia, Spain, and Sweden), accommodating country-specific information on key epidemiological and economic parameters, and on current HPV vaccination programmes. We used projections from three independently developed HPV transmission models to tailor region-specific herd effects. The main outcome measures in the comparison of sex-neutral with girls-only vaccination were cancer cases prevented and incremental cost-effectiveness ratios (ICERs), defined as the cost in international dollars (I$) per life-year gained.

Findings The total number of cancer cases to be prevented by vaccinating girls at currently realised vaccine uptake varied from 318 (95% CI 197–405) per cohort of 200 000 preadolescents (100 000 girls plus 100 000 boys) in Croatia (under 20% uptake of the 9-valent vaccine) to 1904 (1741–2101) in Estonia (under 70% uptake of the 9-valent vaccine). Vaccinating boys at equal coverage increased these respective numbers by 168 (95% CI 121–213) in Croatia and 467 (391–587) in Estonia. Sex-neutral vaccination was likely to be cost-effective, with ICERs of sex-neutral compared with girls-only vaccination varying from I$4300 per life-year gained in Latvia (95% credibility interval 3450–5160; 40% uptake) to I$25 720 per life-year gained in Spain (21 380–30 330; 80% uptake). At uniform 80% uptake, a favourable cost-effectiveness profile was retained for most of the countries investigated (Austria, Belgium, Italy, Latvia, the Netherlands, Slovenia, Spain, and Sweden).

Interpretation Sex-neutral HPV vaccination is economically attractive in European tender-based settings. However, tendering mechanisms need to ensure that vaccination of boys will remain cost-effective at high vaccine uptake rates.

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Introduction

Oncogenic human papillomavirus (HPV) infections are transmitted through sexual contact and are causally related to the development of anogenital and oropharyngeal cancers. In Europe, persistent infections with oncogenic HPV account for around 73 000 anogenital and 14 000 oropharyngeal cancer cases per year.[1] Prophylactic immunisation against HPV provides an opportunity for cancer control, as HPV vaccines have proven to be highly efficacious when given before a person becomes sexually active.

On May 19, 2018, the Director-General of WHO made a global call for action aiming to eliminate cervical cancer, which has the highest HPV-related disease burden. This initiative is investigating which approaches can accomplish this mission within this century.[2,3] Two studies assessing the health effects of HPV vaccination strategies in girls found that at least 90% uptake is required to achieve WHO target levels for the elimination of cervical cancer incidence and mortality in many low-income and middle-income countries.[2,3] In Europe, most countries have already introduced female-only HPV vaccination programmes, with a main objective to prevent cervical cancer. Mathematical models have found that female-only HPV vaccination at very high uptake could suffice to halt heterosexual HPV transmission, as heterosexual male individuals would be protected via herd immunity.[4] The importance of herd immunity is becoming evident in post-vaccine surveillance.[5,6] Consequently, vaccination of girls has been consistently predicted to be cost-effective for reducing the HPV-related disease burden.[7–12]

By contrast, male HPV vaccination has been the subject of considerable debate. Mathematical models have

Research in context

Evidence before this study

Many health economic assessments have been published over the past decade to facilitate decision making concerning the optimisation of human papillomavirus (HPV) vaccination. Although most studies support routine HPV vaccination of preadolescent girls, the cost-effectiveness profile of additional vaccination of boys is debated, being highly dependent on vaccine uptake in girls. We searched PubMed for economic evaluations of sex-neutral HPV vaccination published up to Oct 1, 2019, using the search terms ("cost effectiveness" OR "economic") AND ("HPV" OR "human papillomavirus") AND ("vaccine") AND ("boys" OR "males"). The search was complemented by scanning reference lists of identified full-text articles and previously published systematic reviews on economic assessments of HPV vaccination. English language-only publications were included. Of the 20 studies identified that evaluated sex-neutral versus girls-only HPV vaccination, 13 concluded that preadolescent male vaccination would not be cost-effective, primarily owing to assumptions of high vaccine uptake among girls and high costs of vaccination. However, in most European countries, vaccine uptake among girls has been lower than anticipated, while strong vaccine price reductions have been realised via tendering procedures and adoption of reduced dosing schemes.

Added value of this study

To our knowledge, this is the first study to systematically report on cost-effectiveness of sex-neutral HPV vaccination in different European tender-based settings. We showed that the benefit of adding boys to existing girls-only programmes at current uptake levels varies widely, increasing the number of cancers prevented by 14% to 96%, depending mainly on the country-specific disease burden and realised rates of vaccine uptake. We also showed that the incremental cost-effectiveness ratios of sex-neutral vaccination remain consistently below thresholds indicative for cost-effective interventions compared with girls-only vaccination. When vaccine uptake was set at 80% in all countries, a favourable cost-effective profile was retained for most of the countries included in the study.

Implications of all the available evidence

The results of this study strengthen the case for vaccinating preadolescent boys in addition to girls, both with respect to projected health impact and cost-effectiveness. Our study also shows that tendering mechanisms for vaccine procurement must be aligned with country-specific resources to ensure a favourable cost-effectiveness profile at universally high vaccine uptake rates.

suggested that to achieve an almost zero prevalence of vaccine-targeted HPV, vaccination of both sexes at 80% uptake could be sufficient.[13] Furthermore, modelling studies have suggested that sex-neutral vaccination would make programmes more resilient to sudden drops in uptake.[14] However, vaccination of boys alongside girls has been deemed economically unattractive. This unfavourable cost-effectiveness profile is primarily attributable to the restricted incremental benefit from vaccination of boys after assuming high uptake among girls, and the presumed high HPV vaccination cost.[7–12] However, in Europe, HPV vaccine uptake among preadolescent girls has remained far below target levels in many countries.[15] Additionally, reduced dosing schemes and long-term competitive tendering have led to a substantial decline in vaccination costs.[16]

In light of these developments, many previous economic assessments of sex-neutral HPV vaccination could be considered outdated or not representative for European tender-based settings. Here, we provide a cost-effectiveness evaluation, consistent with current trends in vaccine compliance and costs, for the inclusion of boys in national HPV vaccination programmes in European tender-based settings. We used a Bayesian synthesis framework, originally developed for health economic evaluation of sex-neutral HPV vaccination in the Netherlands,[11,17] and applied this framework to 11 European countries with reliable information on vaccination cost and HPV-related cancer incidence.

Methods

Countries

We investigated the cost-effectiveness of sex-neutral HPV vaccination in European countries with established procurement procedures for HPV vaccines in public vaccination programmes. To this end, we used a recently published database that contained information on tender-based outcomes for 15 European countries from Jan 1, 2007, until Jan 31, 2018.[16] We updated data collection until Dec 31, 2018 (table 1).[16] Considering that the most substantial price drops occurred in the first few years of competitive HPV vaccine market introduction, we focused on countries with tender-based prices available since Jan 1, 2013, deeming these prices representative of the current cost.[16] Furthermore, we conditioned country inclusion on the availability of HPV-related cancer incidence data, leading to selection of the following 11 countries for the present analysis: Austria, Belgium, Croatia, Estonia, Italy, Latvia, the Netherlands, Poland, Slovenia, Spain, and Sweden.

Disease data and other input parameters

We focused on cancers that are causally related to oncogenic HPV infections according to the International Agency for Research on Cancer. In women, these are cervical, vulvar, vaginal, anal, and oropharyngeal cancers, and in men anal, oropharyngeal, and penile cancers. Country-specific cancer incidence from Jan 1, 2003, until December 31, 2012, was obtained from the last edition

	Austria	Belgium	Croatia	Estonia	Italy	Latvia	Netherlands	Poland	Slovenia	Spain	Sweden
Cervical cancer											
Cumulative risk of disease, × 10^{-5}	968 (932–1002)	1068 (1033–1103)	1373 (1315–1435)	2133 (2016–2252)	723 (707–740)	1655 (1558–1751)	812 (789–837)	1424 (1383–1466)	1268 (1201–1341)	822 (794–849)	959 (928–992)
Age at diagnosis, years	55 (54–57)	54 (53–55)	54 (53–55)	54 (52–55)	57 (56–58)	54 (53–54)	52 (51–53)	56 (55–57)	51 (50–52)	54 (53–54)	54 (53–55)
10-year relative survival	0·54 (0·53–0·56)	0·64 (0·62–0·66)	0·61 (0·60–0·63)	0·56 (0·54–0·57)	0·60 (0·58–0·61)	0·45 (0·44–0·46)	0·60 (0·58–0·61)	0·60 (0·58–0·61)	0·63 (0·61–0·65)	0·60 (0·58–0·62)	0·59 (0·57–0·61)
Cost per incident case, PPP, 2017 I$	36 400 (21 600–50 600)	14 300 (8500–19 800)	8800 (5300–12 200)	10 200 (5900–14 200)	36 200 (22 500–50 700)	10 900 (6500–15 600)	10 400 (6400–14 200)	9200 (5700–12 900)	10 200 (6400–13 900)	27 200 (16 600–37 600)	31 400 (18 800–43 100)
Cost per death, PPP, 2017 I$	20 500 (13 100–28 900)	24 700 (15 500–34 500)	6800 (4300–9500)	11 200 (6800–15 400)	15 200 (9300–21 400)	8400 (5200–11 800)	25 700 (14 800–35 500)	9400 (6000–13 000)	12 900 (7700–17 900)	14 500 (8800–20 200)	29 700 (19 000–41 500)
Vulvar cancer											
Cumulative risk of disease, × 10^{-5}	496 (464–533)	519 (487–552)	434 (389–482)	499 (419–585)	458 (440–474)	377 (321–437)	618 (590–646)	373 (341–404)	522 (460–583)	489 (457–520)	502 (471–533)
Age at diagnosis, years	70 (69–71)	70 (69–71)	70 (68–71)	71 (70–73)	74 (73–75)	70 (68–71)	69 (68–70)	71 (70–71)	68 (67–70)	73 (72–73)	71 (70–72)
10-year relative survival	0·54 (0·51–0·56)	0·68 (0·65–0·70)	0·44 (0·42–0·45)	0·60 (0·58–0·62)	0·67 (0·64–0·69)	0·48 (0·46–0·50)	0·67 (0·64–0·69)	0·66 (0·64–0·69)	0·57 (0·55–0·59)	0·67 (0·64–0·41)	0·60 (0·58–0·63)
Cost per incident case, PPP, 2017 I$	32 200 (19 300–44 100)	9400 (5900–13 200)	3400 (2100–4700)	6500 (4200–9000)	19 900 (11 900–27 300)	4300 (2700–5900)	10 300 (6100–14 700)	4700 (2800–6700)	6500 (4000–8900)	20 000 (12 000–27600)	10 000 (6100–14 000)
Cost per death, PPP, 2017 I$	21 500 (13 400–29 300)	19 700 (11 900–27 900)	7100 (4400–9800)	11 600 (7000–16 200)	15 800 (9500–22 100)	8900 (5500–12 500)	21 600 (12 900–30 100)	9800 (6300–13 700)	13 300 (8100–18 900)	15 100 (9000–20 900)	20 600 (12 900–28 500)
Vaginal cancer											
Cumulative risk of disease, × 10^{-5}	158 (140–178)	119 (104–133)	93 (73–112)	131 (97–172)	96 (88–103)	120 (87–164)	103 (91–114)	66 (54–77)	121 (95–151)	78 (67–89)	121 (107–136)
Age at diagnosis, years	71 (69–72)	68 (66–70)	66 (63–68)	63 (59–67)	70 (69–71)	69 (68–71)	69 (66–69)	66 (64–68)	64 (60–67)	69 (66–71)	71 (69–72)
10-year relative survival	0·35 (0·27–0·42)	0·42 (0·33–0·51)	0·37 (0·29–0·45)	0·36 (0·29–0·43)	0·34 (0·27–0·40)	0·40 (0·31–0·49)	0·36 (0·28–0·42)	0·37 (0·30–0·43)	0·43 (0·33–0·52)	0·35 (0·27–0·41)	0·34 (0·27–0·42)
Cost per incident case, PPP, 2017 I$	31 900 (19 600–43 700)	9600 (6000–13 100)	3400 (2100–9900)	6300 (3800–8800)	23 400 (14 500–32 500)	4300 (2600–6000)	10 500 (6800–14 100)	4700 (2900–6500)	6400 (3900–9000)	15 900 (9800–22 600)	10 000 (6000–13 900)
Cost per death case, PPP, 2017 I$	21 600 (12 700–29 500)	19 600 (11 700–27 000)	7200 (4300–9900)	11 500 (7000–16 000)	15 800 (8900–21 800)	8700 (5300–12 200)	21 400 (13 500–30 200)	9900 (6100–13 800)	13 600 (8100–18 400)	15 200 (9700–21 100)	20 700 (12 800–28 500)
Anal cancer in women											
Cumulative risk of disease, × 10^{-5}	241 (220–263)	190 (174–208)	85 (67–107)	193 (153–236)	229 (218–241)	163 (124–213)	128 (117–140)	124 (108–142)	120 (92–148)	114 (100–129)	239 (221–259)
Age at diagnosis, years	65 (64–66)	66 (65–67)	66 (63–68)	66 (63–68)	69 (68–70)	65 (61–68)	63 (62–64)	67 (65–68)	63 (60–67)	67 (65–69)	67 (66–68)
10-year relative survival	0·52 (0·47–0·57)	0·53 (0·47–0·58)	0·48 (0·43–0·53)	0·40 (0·36–0·44)	0·55 (0·50–0·60)	0·44 (0·40–0·48)	0·56 (0·50–0·60)	0·55 (0·50–0·60)	0·38 (0·35–0·42)	0·55 (0·50–0·60)	0·51 (0·45–0·56)
Cost per incident case, PPP, 2017 I$	37 600 (22 700–51 100)	6000 (3500–8300)	2100 (1300–2700)	7600 (4600–18 700)	17 400 (10 800–24 000)	2700 (1600–3700)	6500 (3900–9100)	3000 (1800–4200)	4000 (2500–5600)	12 000 (7200–16 300)	6200 (4000–8600)
Cost per death, PPP, 2017 I$	24 700 (15 000–34 300)	22 500 (14 200–32 200)	8200 (5100–11 600)	13 300 (8100–18 700)	18 300 (11 200–25 100)	10 300 (6300–13 900)	24 600 (15 100–34 700)	113 000 (7000–15 400)	15 600 (9800–21 800)	17 500 (10 800–24 100)	24 000 (14 700–33 200)

(Table 1 continues on next page)

	Austria	Belgium	Croatia	Estonia	Italy	Latvia	Netherlands	Poland	Slovenia	Spain	Sweden
(Continued from previous page)											
Anal cancer in men											
Cumulative risk of disease, × 10^{-5}	138 (118–159)	148 (130–170)	71 (51–96)	98 (62–154)	179 (166–192)	100 (63–151)	113 (100–127)	75 (59–93)	111 (78–146)	133 (118–150)	112 (98–129)
Age at diagnosis, years	63 (61–65)	64 (63–65)	60 (57–63)	60 (54–65)	67 (66–68)	61 (56–67)	62 (60–63)	65 (63–67)	60 (56–64)	63 (61–64)	67 (66–68)
10-year relative survival	0·48 (0·41–0·54)	0·54 (0·46–0·61)	0·38 (0·33–0·43)	0·20 (0·17–0·22)	0·52 (0·45–0·59)	0·50 (0·44–0·57)	0·51 (0·45–0·57)	0·52 (0·45–0·58)	0·51 (0·45–0·57)	0·51 (0·45–0·58)	0·58 (0·52–0·65)
Cost per incident case, PPP, 2017 I$	43 300 (26 800–59 900)	5900 (3600–8100)	2600 (1600–3600)	7500 (4600–10 500)	17 400 (10 500–24 000)	2700 (1600–3700)	6500 (4000–8800)	3000 (1800–4000)	4100 (2500–5500)	11 600 (7100–15 900)	6000 (3800–8500)
Cost per death, PPP, 2017 I$	24 900 (15 300–34 900)	23 000 (13 900–31 500)	8400 (4900–11 800)	13 900 (8800–19 600)	18 100 (10 900–25 300)	10 300 (6300–14 300)	24 600 (15 200–34 500)	11 400 (6800–16 100)	15 600 (9700–21 800)	11 800 (7100–16 300)	23 800 (14 300–32 800)
Oropharyngeal cancer in women											
Cumulative risk of disease, × 10^{-5}	194 (178–201)	211 (198–226)	102 (86–122)	93 (69–121)	100 (94–107)	76 (56–99)	177 (167–189)	88 (77–99)	155 (130–181)	75 (66–84)	112 (102–123)
Age at diagnosis, years	62 (60–62)	61 (60–63)	61 (59–63)	60 (54–65)	64 (63–65)	60 (58–61)	62 (61–63)	60 (59–61)	58 (57–59)	60 (58–61)	61 (59–62)
10-year relative survival	0·24 (0·21–0·26)	0·38 (0·33–0·42)	0·28 (0·24–0·32)	0·35 (0·31–0·39)	0·35 (0·31–0·39)	0·26 (0·23–0·29)	0·36 (0·28–0·42)	0·34 (0·30–0·38)	0·32 (0·29–0·36)	0·34 (0·30–0·38)	0·31 (0·27–0·34)
Cost per incident case, PPP, 2017 I$	43 900 (26 900–60 400)	7100 (4400–9800)	2600 (1600–3600)	8900 (5600–12 300)	27 100 (16 300–37 800)	3200 (2000–4400)	7700 (4700–10 500)	3600 (2100–5000)	4900 (2900–6800)	12 200 (7500–17 000)	7500 (4600–10 300)
Cost per death, PPP, 2017 I$	25 300 (16 000–35 900)	22 900 (13 400–31 800)	8500 (5200–11 700)	13 800 (8300–18 900)	18 900 (11 600–25 800)	10 300 (6300–13 900)	25 400 (15 300–34 900)	11 500 (7200–16 200)	15 900 (9000–21 500)	21 500 (13 100–30 000)	24 600 (14 600–34 100)
Oropharyngeal cancer in men											
Cumulative risk of disease, × 10^{-5}	607 (576–642)	658 (630–689)	568 (533–603)	408 (419–585)	374 (359–389)	353 (309–400)	394 (373–416)	315 (295–334)	836 (767–911)	450 (430–474)	283 (264–303)
Age at diagnosis, years	60 (59–61)	60 (59–61)	59 (58–60)	60 (58–61)	63 (62–64)	60 (58–61)	61 (60–62)	59 (58–60)	59 (58–60)	61 (60–61)	61 (60–61)
10-year relative survival	0·20 (0·18–0·22)	0·29 (0·26–0·32)	0·19 (0·17–0·21)	0·14 (0·13–0·16)	0·28 (0·25–0·30)	0·19 (0·17–0·21)	0·28 (0·25–0·31)	0·28 (0·25–0·30)	0·18 (0·16–0·19)	0·28 (0·25–0·31)	0·27 (0·24–0·29)
Cost per incident case, PPP, 2017 I$	37 300 (23 100–52 300)	7100 (4400–9800)	2200 (1300–2900)	9100 (5700–12 600)	27 200 (16 000–38 300)	3200 (2000–3700)	7800 (4700–10 800)	3600 (2200–4900)	4900 (2900–6900)	12 200 (7500–17 000)	7400 (4600–10 400)
Cost per death, PPP, 2017 I$	24 800 (15 000–35 200)	23 000 (13 400–31 800)	8300 (5100–11 600)	13 500 (8300–18 900)	18 500 (11 300–26 000)	10 300 (6100–14 400)	25 100 (15 200–35 300)	11 500 (7000–16 100)	15 700 (9400–22 300)	18 000 (10 500–24 600)	23 800 (15 200–33 100)
Penile cancer											
Cumulative risk of disease, × 10^{-5}	200 (176–228)	222 (199–248)	166 (129–207)	230 (164–315)	197 (183–211)	159 (124–200)	307 (280–333)	160 (137–184)	165 (127–213)	304 (278–334)	275 (248–303)
Age at diagnosis, years	65 (64–66)	67 (65–68)	63 (61–65)	61 (58–64)	68 (67–69)	61 (58–64)	68 (67–69)	64 (62–65)	61 (58–64)	69 (68–70)	67 (66–68)
10-year relative survival	0·68 (0·64–0·72)	0·75 (0·70–0·79)	0·58 (0·55–0·62)	0·53 (0·50–0·57)	0·70 (0·65–0·75)	0·49 (0·45–0·52)	0·70 (0·65–0·74)	0·69 (0·65–0·74)	0·53 (0·49–0·56)	0·70 (0·66–0·74)	0·62 (0·58–0·66)
Cost per incident case, PPP, 2017 I$	26 100 (15 400–36 800)	4700 (2700–6400)	1700 (1000–2300)	2800 (1700–3800)	15 000 (9300–20 500)	2100 (1300–2900)	5200 (2900–7200)	2400 (1500–3300)	3200 (1900–4500)	9700 (5800–13 400)	5000 (2900–6900)
Cost per death, PPP, 2017 I$	25 200 (15 000–35 300)	22 900 (14 300–31 800)	8500 (5100–11 500)	13 700 (8300–18 900)	18 400 (11 700–26 300)	10 500 (5700–14 300)	25 500 (15 100–35 400)	11 600 (7100–15 800)	15 800 (9500–22 000)	17 900 (11 100–25 000)	23 700 (14 500–33 600)

(Table 1 continues on next page)

of the Cancer Incidence in Five Continents (CI5). Site-specific cancers in CI5 are coded according to the International Classification of Diseases 10th revision and are stratified by age and sex. Disease-specific and background mortality were obtained from WHO databases, Cause of Death Query, and Global Health Observatory Data Repository.

Table 1 presents the main disease-specific inputs of our Bayesian framework with median values of the prior distributions and their 95% credible intervals (CrIs). Cancer-specific HPV-attributable fractions were obtained from international studies that used a validated protocol to analyse specimens and were based on European estimates (table 2). We assumed the same vaccine efficacy of 0·98 (95% CrI 0·95–0·99) against HPV-16 and HPV-18 or HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58, depending on the vaccine used, and disregarded vaccine cross-protection from the 2-valent and 4-valent vaccines.[11,17] Low-risk HPV-6 and HPV-11 primarily cause anogenital warts and recurrent respiratory papillomatosis, which are associated with reduced quality of life but not with mortality. Hence, protection against HPV-6 and HPV-11 was not included, as we quantified the vaccination benefit in life-years to be gained.

Model

We used a previously published Bayesian synthesis framework that was developed to estimate the health and economic impact of HPV vaccination in the Netherlands. This framework meets the HPV-FRAME reporting criteria for models of preadolescent HPV vaccination (appendix p 39).[11,17,18] The model equations and inputs, based on non-informative priors, are summarised in the appendix (pp 2–28), and have been described in detail elsewhere.[11,17] Briefly, the model allows for lifetime evaluation of an HPV-naive birth cohort in terms of life-years lost and medical costs incurred because of cancer incidence. We estimated the expected gain in life-years due to prevention of HPV-associated cancers in vaccine-eligible cohorts for each country included in the analysis using country-specific data for disease parameters. Herd effects from vaccination were incorporated by using projections from three independently developed heterosexual transmission models, fitted to prevaccination HPV infection data from Finland, Italy, and the Netherlands.[19–21] These models were used to project infection risk reductions from HPV vaccination onto regions for which the transmission models were considered to be representative based on sexual activity indicators (appendix pp 22–27). To obtain projections for eastern European countries (Poland and Latvia) included in the study, we recalibrated the Dutch model to Polish data based on HPV-type prevalence and detailed sexual activity information from Polish surveys.

	Austria	Belgium	Croatia	Estonia	Italy	Latvia	Netherlands	Poland	Slovenia	Spain	Sweden
(Continued from previous page)											
Other parameters											
Per capita gross domestic product, PPP, 2017 I$	52 398	47 840	25 264	31 742	39 427	27 598	52 503	29 026	34 868	37 998	50 208
PPP conversion factor 2017	0·80	0·80	3·48	0·55	0·72	0·50	0·82	1·80	0·60	0·66	9·10
Price per vaccine dose (local currency unit)	66·8 (2016 EUR)	42·0 (2018 EUR)	332·5 (2014 HRK)	43·4 (2017 EUR)	35·0/63·0 (2017 EUR)*	16·9 (2013 LVL)	17·2 (2013 EUR)	98·3 (2017 PLN)	49·0 (2016 EUR)	29·2/ 38·0 (2017 EUR)*	150·6 (2014 SEK)
Price per vaccine dose (2017 I$)	83·5	52·5	95·5	78·9	48·6/87·5*	33·8	21·0	54·6	81·7	44·2/57·6*	16·5
Administration cost per dose (2017 I$)	15	31	31	53	8	29	22	35	29	7	7
Vaccine type (baseline scenario)	9-valent	9-valent	9-valent	9-valent	2-valent, 4-valent, or 9-valent	2-valent	2-valent	2-valent or 4-valent	9-valent	2-valent, 4-valent, or 9-valent	4-valent
Vaccine uptake	60%	70%	20%	70%	70%	40%	50%	20%	50%	80%	80%

Summary measures for input parameters on human papillomavirus-related cancer sites are medians and 95% credible intervals. A version of the table with relevant reference citations is supplied in the appendix (pp 7–13). I$=international dollars. EUR=Euros. HRK=Croatian kuna. LVL=Latvian lats. PLN=Polish złoty. PPP=purchasing power parity. SEK=Swedish krona. *The first price refers to the average price of the 2-valent or 4-valent vaccines over regions per country, and the second refers to the price of the 9-valent vaccine.

Table 1: **Input parameters for human papillomavirus-related cancer sites, and economic and vaccine parameters**

	Women	Men
Cervix		
HPV attributable fractions %	96%	..
HPV-16	60·6 (59·6–61·6)	..
HPV-18	10·2 (9·6–10·9)	..
HPV-31	3·7 (3·4–4·1)	..
HPV-33	3·8 (3·5–4·2)	..
HPV-45	5·9 (5·4–6·4)	..
HPV-52	2·8 (2·5–3·2)	..
HPV-58	2·3 (2·0–2·6)	..
Anus		
HPV attributable fractions %	87·5 (82·1–91·9)	87·5 (82·1–91·9)
HPV-16	75·8 (71·6–79·6)	75·8 (71·6–79·6)
HPV-18	3·5 (2·0–5·5)	3·5 (2·0–5·5)
HPV-31	1·2 (0·4–2·5)	1·2 (0·4–2·5)
HPV-33	2·4 (1·2–4·0)	2·4 (1·2–4·0)
HPV-45	1·0 (0·3–2·3)	1·0 (0·3–2·3)
HPV-52	0·5 (0·1–1·4)	0·5 (0·1–1·4)
HPV-58	1·9 (0·9–3·4)	1·9 (0·9–3·4)
Oropharynx		
HPV attributable fractions %		
Western Europe	32·9 (29·4–36·4)	32·9 (29·4–36·4)
Central and eastern Europe	36·8 (30·2–43·1)	36·0 (29·7–42·7)
Northern Europe	49·4 (46·3–52·1)	49·4 (46·3–52·1)
Southern Europe	20·8 (16·5–25·7)	20·8 (16·5–25·7)
HPV-16	86·5 (84·9–87·9)	86·5 (84·9–87·9)
HPV-18	1·7 (1·2–2·4)	1·7 (1·2–2·4)
HPV-31	0·3 (0·1–0·7)	0·3 (0·1–0·7)
HPV-33	2·3 (1·7–3·0)	2·3 (1·7–3·0)
HPV-45	0·4 (0·2–0·7)	0·4 (0·2–0·7)
HPV-52	0·2 (0·01–0·4)	0·2 (0·01–0·4)
HPV-58	0·6 (0·3–1·0)	0·6 (0·3–1·0)
Odds ratio for HPV positivity*	0·29 (0·12–0·71)	3·5 (1·4–8·6)
HR for HPV positivity†	0·47 (0·35–0·63)	0·47 (0·35–0·63)
Vulva		
HPV attributable fractions %	18·3 (15·9–20·1)	..
HPV-16	72·8 (68·4–76·9)	..
HPV-18	4·7 (3·0–7·0)	..
HPV-31	1·0 (0·3–2·1)	..
HPV-33	6·6 (4·5–9·2)	..
HPV-45	3·3 (1·9–5·1)	..
HPV-52	1·9 (0·9–3·5)	..
HPV-58	1·0 (0·3–2·3)	..
Vagina		
HPV attributable fractions %	71·0 (63·5–77·8)	..
HPV-16	57·4 (51·8–62·9)	..
HPV-18	5·0 (2·9–7·8)	..
HPV-31	5·4 (3·1–8·1)	..
HPV-33	4·7 (2·8–7·6)	..
HPV-45	3·4 (1·7–5·7)	..
HPV-52	2·7 (1·3–4·9)	..
HPV-58	3·7 (1·8–6·2)	..
Penis		
HPV attributable fractions %	..	32·3 (28·2–36·7)
HPV-16	..	62·8 (57·6–67·9)
HPV-18	..	1·2 (0·4–2·8)
HPV-31	..	0·7 (0·1–1·9)
HPV-33	..	2·4 (1·2–4·5)
HPV-45	..	2·8 (1·4–4·7)
HPV-52	..	1·2 (0·4–2·8)
HPV-58	..	1·0 (0·3–2·2)
HR for HPV positivity†	..	0·2 (0·1–0·9)

Data are median (95% CrI), unless otherwise indicated. A detailed description of the methods for the selection of the attributable fractions is included in the appendix (p 14). A version of the table with relevant reference citations is supplied in the appendix (pp 14–16). Type-specific attributable fractions are conditioned on HPV-positive cancers. CrI=credible interval. HPV=human papillomavirus. HR=hazard ratio. *Odds ratio was used to correct for the higher incidence of HPV-related oropharyngeal cancers among men compared with women. †HRs were used to account for the relatively favourable survival of HPV-positive carcinomas compared with HPV-negative carcinomas

Table 2: **Site-specific HPV-related attributable fractions**

Economic assumptions and scenarios investigated

We evaluated the incremental cost-effectiveness ratios (ICERs) of girls-only vaccination compared with no vaccination and of sex-neutral vaccination compared with girls-only vaccination. Lifetime costs from a health-care provider perspective and life-years gained were evaluated for birth cohorts of 100 000 women and 100 000 men, assuming post-vaccination equilibrium infection risks for the vaccinated cohorts.

To use uniform conditions for cost-effectiveness assessment, we discounted costs and life-years at a yearly rate of 3%, as recommended by WHO for economic evaluations.[22] We set the cost-effectiveness threshold equal to the WHO threshold for a very cost-effective intervention as the annual per capita gross domestic product (GDP),[22] and we also considered an opportunity cost-based threshold, estimated at 0·8 times (per capita GDP) for the countries under consideration (appendix pp 28–30).

In the baseline scenario, vaccine uptake among boys was set as equal to uptake among girls in years 2016–17 (table 1). Vaccination effect in the baseline scenario considered prevention against HPV-16 and HPV-18 or HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58, depending on the vaccine type decided in the latest available tender contract (table 1). For Italy, Poland, and Spain, vaccine choice is a regional matter, but most regions have used 2-valent or 4-valent vaccination in recent years. Hence, in the baseline scenario of these three countries, we used the average tender-based price of the 2-valent and 4-valent vaccines over regions per country.[16] However, as some regions in Italy and Spain use the 9-valent vaccine, the cost-

effectiveness of HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 prevention was also estimated for these countries.

Vaccination costs were calculated using tender-based prices and local two-dose administration cost (table 1). For Croatia, Latvia, and Poland, local administration costs were not available and they were set equal to the average costs in other countries (€15 per dose). Medical costs incurred because of cervical cancer diagnosis were obtained from local studies that estimated treatment costs per cancer case, using unit costs and use patterns of health-care services paid by public health-care payers (table 1). These data were sourced from national health insurance funds and expert opinion. Medical costs attributable to cervical cancer deaths were added to cancer incidence costs and were also obtained from local studies whenever available. These costs included palliative care costs, including procedural and pharmacological treatment at home and hospice care for patients with terminal stage cervical cancer. For non-cervical HPV-related cancers, costs were collected from local studies or were imputed. All costs were in local currencies, inflated to 2017 prices using the Organisation for Economic Co-operation and Development GDP deflator and converted to 2017 international dollars (I$) using 2017 purchasing power parity.

Sensitivity analysis

To identify determinants of variation in the ICER of sex-neutral vaccination between countries, we sampled 1000 posterior draws per country and did a multiple regression analysis of ICERs on economic and disease-specific parameters. For continuous parameters, we calculated standardised regression coefficients to signify how the estimated ICER changed with one SD increase in the corresponding parameter. Regarding herd immunity, we considered first-order herd effect parameters for HPV-16 and HPV-18 (ie, the infection risk reduction in men from vaccinating girls and the incremental risk reduction in women from additionally vaccinating boys).

The ICERs of sex-neutral HPV vaccination were re-evaluated using discount rates at 3% and 1·5% for costs and health effects, respectively, and by using country-specific discount rates and cost-effectiveness thresholds (appendix pp 29–30). We also reassessed sex-neutral HPV vaccination by assuming an annual change of 2% and 5% up to 2020 in oropharyngeal cancer incidence, similar to the annual percentage change observed in some European countries during the past decade.[23,24] Furthermore, we determined the ICERs of sex-neutral vaccination under 80% uptake in both sexes in all countries, which is the highest HPV vaccine uptake reported in the included countries.[15] Finally, to examine the effect of using three transmission models, we re-evaluated our results using the mean risk reductions from the three transmission models.

All statistical analyses were performed with R version 3.6.1.

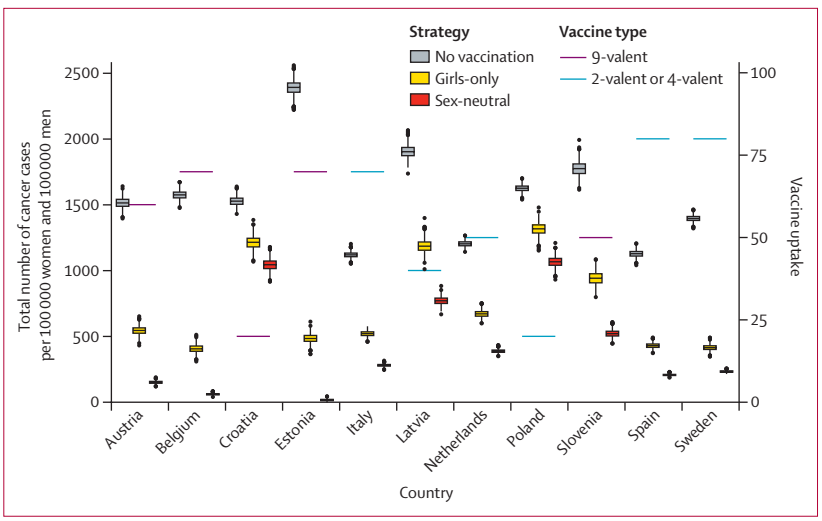

Figure 1: **Total number of cancer cases per 100 000 women and 100 000 men, per country in absence of HPV vaccination, under girls-only HPV vaccination, and under sex-neutral HPV vaccination**
Horizontal lines indicate realised vaccine uptake among girls (secondary y-axis), which was assumed to be equal among girls and boys in the sex-neutral vaccination scenarios, and different colours represent different vaccines used. The midline of the boxplot is the median value, with the upper and lower limits of the box being the third and first quartile (75th and 25th percentile), and the whiskers covering 1·5 times the IQR. HPV=human papillomavirus.

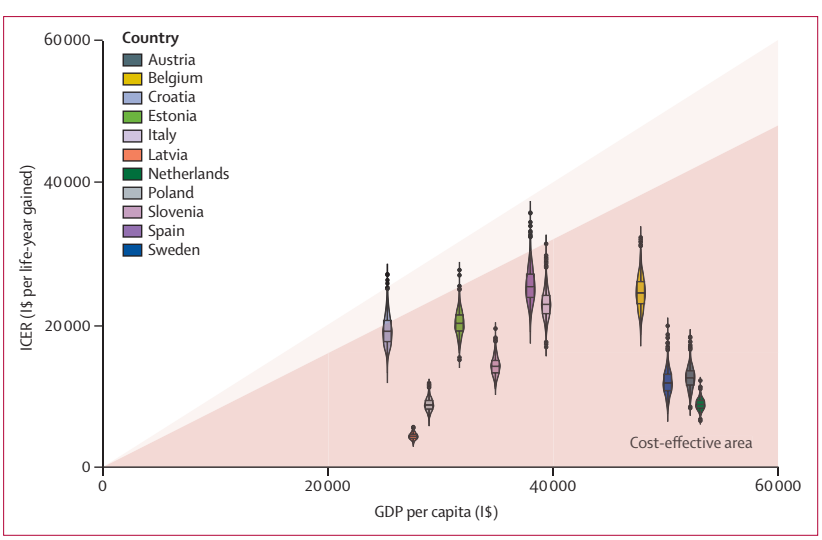

Figure 2: **ICERs of sex-neutral HPV vaccination under equal vaccine uptake among boys and girls compared with girls-only vaccination**
Countries are ordered by per capita GDP. The shaded diagonal area indicates the cost-effective area when the ICERs lie below 1 (lighter shading) and 0·8 times (darker shading) the respective country-specific GDP level. The midline of the boxplot is the median value, with the upper and lower limits of the box being the third and first quartile (75th and 25th percentile), and the whiskers covering 1·5 times the IQR. The coloured violin plot represents the kernel probability density (ie, the width of the shaded area represents the density of ICER values). ICER=incremental cost-effectiveness ratio. HPV=human papillomavirus. GDP=gross domestic product. I$=international dollars.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

See Online for appendix

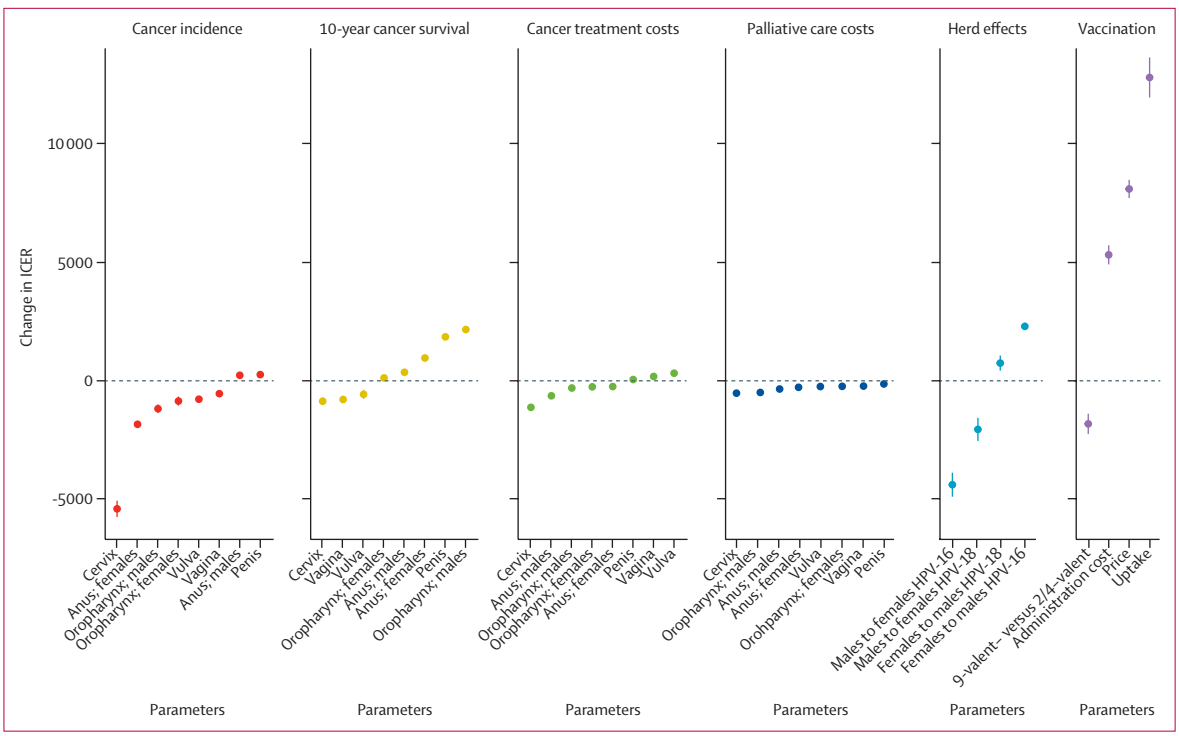

Figure 3: **Sensitivity analysis of the estimated ICER of sex-neutral HPV vaccination relative to girls-only vaccination**
Circles for continuous covariates denote the change in ICER with an increase of one SD in the model parameters, whereas the circles for the vaccine type denote the change in ICER using the 9-valent vaccine compared with the 2-valent or 4-valent vaccine. Error bars denote 95% CIs obtained when fitting a multiple regression model to 1000 posterior draws. ICER=incremental cost-effectiveness ratio. HPV=human papillomavirus.

Results

The country-specific prevaccination HPV-related disease burden in lifetime numbers of incident cancers per cohort of 100 000 women and 100 000 men is presented in the appendix (pp 40–41). The numbers of cancer cases attributable to HPV-16 and HPV-18 varied from 942 (95% CrI 888–1004) in Spain to 1966 (1821–2119) in Estonia, whereas the respective numbers attributable to HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 were 1129 (1070–1196) in Spain and 2388 (2193–2572) in Estonia. The greatest disease burden among women occurred in Estonia and Latvia, due to relatively high cervical cancer incidence, whereas men had the greatest disease burden in Slovenia due to relatively high oropharyngeal cancer incidence. We recorded country-specific estimates for the lifetime number of cancers per cohort of 100 000 women and 100 000 men attributable to HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 under the following three scenarios: no vaccination, girls-only vaccination, and sex-neutral vaccination (figure 1; appendix pp 42–43). The lowest impact of girls-only vaccination was estimated in Croatia, with total cancer cases reduced by 318 (95% CI 197–405) under 20% uptake of the 9-valent vaccine, whereas the highest impact was estimated in Estonia, with total cancer cases reduced by 1904 (1741–2101) under 70% uptake of the 9-valent vaccine. Vaccinating boys at equal uptake as girls increased the cancer cases prevented by 168 (121–213) in Croatia and 467 (391–587) in Estonia. The decrease in residual disease burden attributable to HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 by vaccination of boys ranged from 14% (12–16) in Croatia to 96% (94–98) in Estonia.

The ICERs of girls-only vaccination compared with no vaccination under realised uptake in girls, vaccine type, and tender-based price were cost-saving in Sweden and Austria (ICERs below 0). In other countries, the ICER ranged from I$1470 per life-year gained (867–2124) in Latvia to I$9390 per life-year gained (7060–13 040) in Croatia (appendix p 33), and remained below the per capita GDP. The ICERs of sex-neutral vaccination compared with girls-only vaccination varied from I$4300 (3450–5160) per life-year gained in Latvia to I$25 720 (21 380–30 330) per life-year gained in Spain, remaining below the WHO and opportunity cost-based threshold (figure 2). Repeating this analysis to account for sex-neutral vaccination with the 9-valent vaccine in Italy and Spain did not alter the results (appendix p 33). The strongest determinants of the ICERs of sex-neutral vaccination were, in descending order of absolute standardised effect size, vaccine uptake, price and administration cost, cervical cancer incidence, incremental herd protection against HPV-16 in women

and girls from vaccination of boys, and herd protection against HPV-16 in men and boys from vaccination of girls (figure 3). Increases in vaccine uptake, cost of vaccination, and herd protection from girls-only vaccination were associated with higher ICERs for sex-neutral vaccination, whereas higher cervical cancer incidence and herd protection from men and boys to women and girls were associated with lower ICERs. Combined, these explained 60% of the variation in the ICERs (appendix pp 44–45).

The cost-effectiveness of sex-neutral vaccination slightly improved under the scenario of increased oropharyngeal cancer incidence (appendix p 34), whereas ICERs dropped to almost half of their base case values when using 3% and 1·5% discount rates, remaining below I$15 000 for all countries (appendix p 35). When using national guidelines, the cost-effectiveness profile was unfavourable for Croatia, Estonia, and Slovenia, which are the countries that recommend 5% discounting for future health effects (appendix p 30). Assuming 80% uptake, sex-neutral vaccination remained cost-effective in most of the 11 European countries (Austria, Belgium, Italy, Latvia, the Netherlands, Slovenia, Spain, and Sweden when using 1 times the respective country-specific GDP level and Austria, Italy, the Netherlands, Slovenia, Spain, and Sweden when using 0·8 times the respective country-specific GDP level; figure 4). Under 80% uptake in all countries and 3% and 1·5% discount rates, ICERs of sex-neutral HPV vaccination remained below I$25 000 (appendix p 35). These results did not alter when using the mean risk reductions from the three transmission models for all countries (appendix pp 36–37).

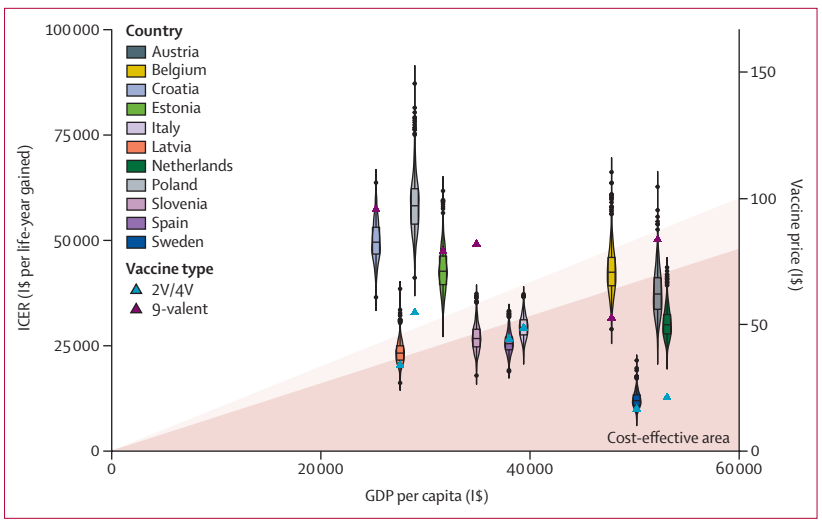

Figure 4: **ICERs of sex-neutral HPV vaccination under 80% vaccine uptake in both girls and boys compared with girls-only vaccination**

Countries are ordered according to per capita GDP. The shaded diagonal area indicates the cost-effective area (ie, where the ICERs lie below 1 [lighter shading] and 0·8 times [darker shading] the respective country-specific GDP level). The triangles indicate the tender-based vaccine price per dose (right y-axis scale), with different colours representing the HPV vaccine chosen in procurement procedures during 2013–18. The midline of the boxplot is the median value, with the upper and lower limits of the box being the third and first quartile (75th and 25th percentile), and the whiskers covering 1·5 times the IQR. The coloured violin plot represents the kernel probability density (ie, the width of the shaded area represents the density of ICER values). ICER=incremental cost-effectiveness ratio. HPV=human papillomavirus. GDP=gross domestic product. I$=international dollars.

Discussion

Compared with previous economic assessments of sex-neutral HPV vaccination, we found that the incremental benefit of vaccinating preadolescent boys was cost-effective in all European tender-based settings considered. Differences compared with previous assessments derive from the inclusion of non-cervical HPV-related cancers, the use of realised vaccine uptake levels in girls-only programmes instead of target levels, and the assumption of two-dose instead of three-dose schedules and of tender-based dose prices of HPV vaccines. A systematic data collection revealed that, in Europe, long-term procurement of HPV vaccines has reduced introductory list prices by around 50–80%.[16] Disregarding such reductions when evaluating HPV vaccination leads to inflated vaccination cost.[7] Three other independent country-specific assessments of sex-neutral HPV vaccination, which also accounted for procurement-based vaccination cost, reached similar conclusions to our study.[9,10,12] By contrast, a study commissioned by the UK Department of Health and assessed by the Joint Committee on Vaccination and Immunization concluded that sex-neutral vaccination would not be cost-effective, even if the vaccine price dropped to zero.[8] However, this study assumed vaccine uptake of 85%, which is higher than that realised in other European countries.[8] Relatively low uptake in countries other than the UK has been consistently observed during the past decade, suggesting that it might be difficult to increase vaccine uptake by national campaigns in some jurisdictions.[25] This has renewed interest in sex-neutral HPV vaccination, as inclusion of boys could substantially strengthen herd protection and facilitate elimination of HPV vaccine types.[13] The difference in outcomes between our study and the UK study is also related to the choice of the discount rate and cost-effectiveness threshold. In accordance with the guidelines of the National Institute for Health and Care Excellence,[26] the UK study employed 3·5% discount rates for both costs and effects, combined with a cost-effectiveness threshold of £20 000. These criteria might be considered stringent when compared with WHO and other countries' criteria for cost-effectiveness analyses of vaccinations. This observation is particularly relevant for HPV vaccination, as investments predate cancer prevention benefits by several decades. Therefore, differentially discounted rates for HPV vaccination have also been suggested. Indeed, at a discount rate of 1·5%, sex-neutral vaccination would be cost-effective at dose prices of £36–47,[8] which could represent realistic tender-based prices in the UK. The strong effect of the discount rate on the ICER was supported by our sensitivity analyses, since we observed unfavourable cost-effectiveness profiles for countries

with a recommended discount rate of 5%, whereas lowering the discount rate for health effect from 3% to 1·5% led to a reduction of about 50% in the ICER. Notably, countries with a discount rate of 5% also recommended sensitivity analyses with a lower discount rate as part of the cost-effectiveness evaluation.

Our study indicates that vaccination of boys is likely to remain cost-effective at high uptake among girls in most countries.[7] Four of the countries we investigated (Croatia, Estonia, Latvia, and Poland) with a less favourable cost-effectiveness profile were characterised by a relatively low per capita GDP, but still had high projected health gains. This finding indicates that even at tender-based prices, HPV vaccination cost might constitute a relatively large financial burden, underlining the importance of tiered pricing. From the public health-care payer perspective, a way to tier prices is to improve procurement mechanisms. Parameters associated with low tender-based prices include increasing contract duration and volume, centralising vaccine procurement, and organising open tenders instead of direct negotiation procedures.[16]

In our analysis, we assumed similar vaccine uptake among boys and girls. Experience with sex-neutral HPV vaccination so far has shown that HPV vaccine uptake among boys is reaching similar levels to uptake by girls or is around 20% lower than among girls.[27] Nonetheless, the cost-effectiveness of vaccinating a particular sex is most strongly affected by vaccine uptake in the opposite sex; hence, in this case the cost-effectiveness of vaccination of boys (in addition to girls) is mainly determined by vaccine uptake in girls, and not by uptake in boys.[11,12]

A strength of our model is that it is data-driven and only uses models for estimating the reduction in type-specific infection risk in unvaccinated women and men (herd effect). We assumed the same type-specific reductions in countries for which a transmission model has been used and neighbouring countries, as often used in multi-country analyses,[2] and supported by multi-country assessment of sexual behaviour indicators (appendix pp 18–21). Regarding the sexual behaviour indicators, there appears to be noticeable similarity among countries that are grouped together. Even so, there is little country-specific information on sexual activity, and differences between countries are small. This finding is in accordance with the observation that the herd effects estimated by the three country-specific models were similar, and were also similar to the mean of the three models, providing further support for the presented outcomes.

Our analysis has some limitations. First, we only considered health benefits in terms of life-years gained. Hence, the health and economic effect of vaccination on non-lethal conditions was not considered, indicating that the ICERs of sex-neutral vaccination should be considered conservative in our analysis. Second, we did not consider cross-protective effects for first-generation HPV vaccines. HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 account for around 18% of cervical cancers, with a higher contribution to precancerous lesions. By contrast, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 attribution to non-cervical HPV-related cancers is much lower. Hence, in the context of 2-valent and 4-valent vaccination, the additional cross-protection afforded by vaccination of boys will primarily enhance herd protection against cervical disease. Considering that herd effects from girls-only vaccination for non-HPV-16 and non-HPV-18 types are probably higher than for HPV-16 and HPV-18,[13] the incremental benefit from the prevention of these types under a sex-neutral programme will be particularly relevant for countries with low uptake among girls.[5] This hypothesis is in line with our sensitivity analyses, in which the maximum allowable vaccine price for sex-neutral vaccination was similar for the different vaccines at 80% uptake. Third, in our base-case analysis we disregarded cancer incidence trends, which might differ between countries due to temporal changes in sexual behaviour, cervical cancer screening strategies, access and adherence to screening, or competing risk factors such as smoking.

The HPV prevention targets set by WHO on May 19, 2018, calling for cervical cancer elimination, contributed to an increase in the worldwide demand for HPV vaccines, causing a supply shortage. Therefore, the WHO Strategic Advisory Group of Experts (SAGE) advised temporary suspension of implementation of male HPV vaccination until vaccine supply allowed equitable access to HPV vaccines by all countries, contradicting the recommendation of the European Board and College of Obstetrics and Gynaecology to introduce sex-neutral preadolescent HPV vaccination in Europe.[28] The implementation of sex-neutral HPV vaccination might be considered inequitable for low-income countries with high cervical cancer burden that struggle to secure HPV vaccine supply for girls. However, as indicated by the International Papillomavirus Society,[29] moving vaccine supplies from one country to another might not be possible in the short term because of complex regulatory rules or multi-year contracts, reducing the desired impact of the SAGE recommendations when the supply shortage is most likely only temporary, and expected to last for around 3–5 years. Furthermore, the temporary postponement of male HPV vaccination might seriously jeopardise the efficacy and efficiency of existing HPV vaccination programmes,[14] and in many high-income countries HPV vaccination programmes have been shown to be vulnerable, as reflected by the strongly variable levels of HPV vaccine uptake. Vulnerability of prevention programmes to external events has also been highlighted by the recent COVID-19 crisis, which has disrupted HPV vaccination and HPV-based screening programmes. Moreover, HPV vaccine production might be delayed further if current HPV vaccine manufacturers get a licence for administration of a COVID-19 vaccine. These considerations strengthen the case for sex-neutral vaccination in the future. It is also worth stressing that, as mentioned at the SAGE meeting from Oct 8–10, 2019, it is

the responsibility of vaccine manufacturers to be operationally and ethically responsive to global vaccine supply needs and align with the Pan American Health Organization and WHO's call for action to eliminate cervical cancer.[30] In this regard, announcements indicate that existing HPV vaccine manufacturers are rapidly scaling up vaccine production and new manufacturers from China and India are preparing to soon enter the marketplace, probably facilitating supply and pricing of HPV vaccines and expansion of HPV vaccination to boys.[29]

In conclusion, our study confirms that vaccinating boys and girls would substantially improve HPV-related cancer control throughout Europe and adhere to cost-effective investments under established tender-based vaccination costs. Although the current shortage in HPV vaccine supply might temporarily limit the implementation of sex-neutral vaccination, our findings show the potential of vaccination of boys for the prevention of HPV-related cancers and support the global WHO strategy for elimination of cervical cancer.

Contributors

VQ conceived the study through discussion with JAB and JB. VQ, JAB, and JB designed the study. VQ did the analysis and drafted the Article. JAB, IB, SV, and JB co-drafted the manuscript. VQ, JAB, FL, and SV made projections on type-specific infection risks using the three independently developed transmission models. All authors interpreted the results and critically revised the manuscript for scientific content. All authors approved the final version of the Article.

Declaration of interests

VQ is currently employed at Pharmerit International, which holds consultancy contracts with pharmaceutical companies. This study was done and submitted during the time VQ was employed at Amsterdam UMC. JB reports grants from EU 7th Framework and grants from WHO during the conduct of the study. IB reports grants from the European Commission 7th Framework programme Health 2013 Innovation 1 during the conduct of the study. All other authors declare no competing interests.

Data sharing

The statistical code and datasets are available from the corresponding author upon request.

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