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Cost-effectiveness of sex-neutral HPV-vaccination in Sweden, accounting for herd-immunity and sexual behaviour

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ABSTRACT

Introduction: The aim was to assess cost-effectiveness of expanding the Swedish HPV-vaccination program to include preadolescent boys, by comparing health-effects and costs of HPV-related disease, with a sex-neutral vaccination program versus only vaccinating girls.
Methods: We used a dynamic compartmental model to simulate the burden of HPV16/18-related disease in Sweden, accounting for indirect effects of vaccination through herd-immunity. The model accounted for sexual behaviour, such as age preferences and men who have sex with men. The main outcome was number of individuals with HPV-related cancers (cervical, genital, anal and oropharyngeal cancer) and cervical intraepithelial neoplasia (CIN). Costs included in the analysis were those incurred when treating HPV-related cancer and CIN, production losses during sick-leave, and acquisition and administration of vaccine. Health effects were measured as quality-adjusted life years (QALY). The time horizon was set to 100 years, and both effects and costs were discounted by 3% annually. Health effects and costs were accumulated over the time horizon and used to create an incremental cost-effectiveness ratio.
Results: A sex-neutral vaccination program would reduce HPV-related cancer and CIN, both due to direct effects among vaccinated as well as through herd-immunity, further decreasing HPV-related cancer burden annually by around 60 cases among men and women respectively in steady-state. The cost per gained QALY was estimated to 40,000 euro. Applying the procurement price of 2017, sex-neutral vaccination was dominant.
Conclusion: Introducing a sex-neutral HPV-vaccination program would be good value for money also in Sweden where there this 80% coverage in the current HPV-vaccination program for preadolescent girls. The cost-effectiveness of a sex-neutral program is highly dependent on the price of the vaccine, the lower the price the more favourable it is to also vaccinate boys.

1. Introduction

Since vaccination against human papilloma virus (HPV) in Swedish schools started for girls in 2012, the mean national coverage has been around 80% for one dose [1]. It has been argued that increasing the uptake among girls could have a greater impact on the burden of HPV-related disease than also introducing vaccination for boys [2,3]. However, increasing the coverage among girls in settings where the coverage is already high may be more difficult to achieve than to vaccinate a moderate proportion of boys.

HPV is considered to be the most prevalent sexually transmitted infection in both men and women. Over 200 types of HPV have been identified, of which 40 types are known to be sexually transmitted [4]. Around 90% of HPV infections are transient and cleared within 1–2 years, but some infections persist and may cause a range of clinical states, including anogenital warts, precancerous lesions, and cancer [5]. The thirteen HPV-types known to cause cervical cancer, also contribute to cancer in the anogenital region, such as cancer of the vagina, vulva, anus, and penis as well as in the oropharynx, mainly tonsillar and base of tongue cancer [6,7]. HPV

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16 is the dominating cause of non-cervical HPV-related cancer [6,8]. All three of the available vaccines specifically target HPV 16 and 18.

Oropharyngeal cancer mainly occur among men, and have increased rapidly in incidence in western countries over the last few years [9–13], and is today the second most common head and neck cancer in Sweden with 384 new cases diagnosed in 2015, 71% among men [14,15]. Around 100 men are diagnosed with invasive penile cancer annually [16]. Around 150 individuals are diagnosed with anal cancer annually in Sweden, 30% among men [17].

The introduction of HPV vaccination for girls in Sweden has led to a reduction in HPV infections [18], cervical intraepithelial neoplasia (CIN) [19] and genital warts [20] among women. Clear herd immunity effects among both women and men have been demonstrated in other countries with vaccination programmes for girls, [21] and recently also shown for sex-neutral vaccination programmes [22,23]. The follow-up time within national HPV vaccination programmes is still too short to evaluate the effect on cancer, although this has recently been demonstrated in one of the major HPV vaccine trials [24]. Only a few countries have implemented sex-neutral vaccination programmes against HPV. Some countries have instead implemented risk-group vaccination programmes offering HPV vaccination to men who have sex with men (MSM). The effect of introducing HPV vaccination for boys thus has to be modelled in order to estimate the effect on HPV-related cancer, using current cancer incidence data and estimates of the contribution of vaccine-preventable HPV-infection.

We modelled the effect of girls-only versus sex-neutral HPV vaccination programmes on health outcomes in both sexes, mainly HPV-related cancer and CIN incidence. Adding further to previously conducted modelling work, our model accounts for herd immunity and MSM. A cost-effectiveness evaluation was performed to evaluate sex-neutral HPV vaccination.

2. Method

2.1. Model overview

HPV-related cancer was modelled using a Markov multi-state model that accounted for herd immunity. The model was formulated as a system of differential equations that described the rate of change in the number of people in each health state in the population over time. The rate at which individuals were diagnosed with cancer or CIN and at what severity-state, was determined by the average incidence in Sweden between 2010 and 2014 (Table 2). The model was calibrated to fit historical data on HPV-related cancers and CIN [25,26].

The inflow in the model was based on a 2015 birth cohort and the outflow was either through cancer-related death or natural mortality. The individuals entered the model in the health state of "susceptible", and depending on the vaccination coverage, a proportion moved on to the health state "vaccinated". Those who were vaccinated received protection corresponding to the effectiveness of the vaccine. The health state of "HPV-related disease" in Fig. 1 represents CIN and the HPV-related cancer types: cervical, vaginal, vulvar, anal, and oropharyngeal (tonsillar and base of tongue) cancer for women and penile, anal and oropharyngeal cancer for men. Each of the diseases was modelled separately, with separate effects of vaccination and burden of disease. If an individual developed cancer he or she was assumed to stay in that health state for 5 years, before moving on to "recovered".

Boys and girls were modelled separately and affected each other through herd immunity that was accounted for using a previously developed method [27], where an adjustment term related to the proportion of vaccinated of the opposite sex was applied to the risk of HPV-related disease. In terms of age mixing, it was assumed that 90% of the individuals in the population had sexual contacts within 10 years of their own age. MSM were assumed not to be protected through herd immunity when only girls were vaccinated. MSM were estimated to be 2.5% of the male population [28]. The two sub-models (boys/girls) were in turn divided into eight sub-sub-models, each one corresponding to one age-group (10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–84, 85+ years). Movements between sub-sub-models occurred annually and was determined by the age structure of the age-group.

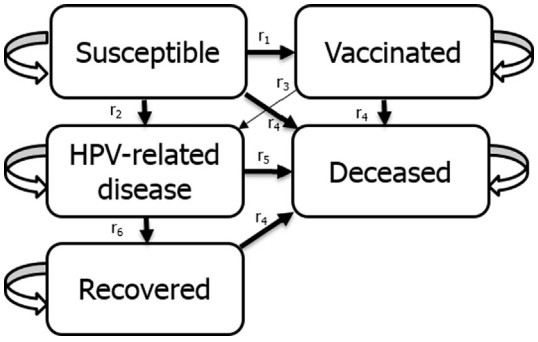

Fig. 1. Stylized compartmental model for HPV-related disease. r_1 = vaccination coverage. R2 = incidence rates for HPV-related cancer and CIN, by sex and age. R3 = incidence rated among vaccinated ("non-responders") for HPV-related cancer and CIN, by sex and age. R4 = rates of all-cause mortality from population lifetables by sex and age. R5 = excess mortality rates of death due to HPV-related cancer, by sex and age. R6 = rates of recovered from HPV-related cancer and CIN, by sex and age.

The national HPV vaccination programme aims to decrease HPV-related cancer in the population, and the model therefore focused on cancer and CIN. The key outputs of the model include: (1) number of incident cases of cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancer averted, (2) number of CIN averted and, as a sensitivity analysis, and (3) number of cases with anogenital warts averted.

2.2. Model input parameters

To calculate the risk of HPV-related cancer and CIN, first the average incidence of cervical, vaginal, vulvar, penile, anal and oropharyngeal cancer and CIN, by age-group and sex, for the years 2010–2014 were extracted and then the proportion of cases that could be attributed to HPV, and thus be affected by vaccination, were calculated (Table 2).

The different diseases were divided into two or three severity-states. The definition of these severity-states, denoted as A, B and C, is presented in Table 1. The 5-year relative survival was dependent on cancer type, age at diagnosis, and severity-state.

A vaccination coverage of 80% was assumed among boys, corresponding to the coverage achieved among girls in the current vaccination programme in Sweden for one dose [1]. As stated by the Global Advisory Committee on Vaccine Safety (GACVS) [29] the HPV vaccine is very safe, and adverse events are mainly mild local site reactions. Adverse events were therefore not considered in the model. The vaccine effectiveness in the model was HPV-type specific, and vaccination was assumed to provide life-long protection. The vaccine was assumed to be 100% effective against HPV-types 16/18, and the vaccine effectiveness against each HPV-related cancer or CIN was therefore dependent on the estimated proportion caused by HPV 16/18.

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Table 1
Severity-states for HPV attributable cancer, as modelled for Sweden, 2017, where A is the least severe state and C the most severe state.

	Severity-state		
	A	B	C
CIN*	I	II	III
Cervical cancer	1A + 1B**	2**	3+**
Vaginal cancer	1A + 1B**	2	3+
Vulvar cancer	1A + 1B**	2	3+
Penile cancer	Non-invasive, without lymph node metastasis	Invasive, without lymph node metastasis	With lymph node metastasis
Anal cancer	–	T1-T2 (<4 cm) N + M0***	T2(>4 cm)-T4N0/ N + M0***
Oropharyngeal cancer	–	I + II	III + IV

* Cervical intraepithelial neoplasia.
** Based on Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging.
*** Based on (Classification of Malignant Tumours) TNM staging, 7th Edition. Source; Expert opinion and Ref. [29].

2.3. Scenario investigated

The impact on HPV-related cancer and CIN of two different vaccination strategies was investigated: (1) a continuation of the current vaccination programme for girls 10–12 years old, with a vaccination coverage of 80%, (2) a sex-neutral vaccination programme for children 10–12 years old with a vaccination coverage of 80% in both sexes.

2.4. Cost-effectiveness evaluation

A cost-effectiveness evaluation, conducted from a health care perspective, added quality adjusted life years (QALY)-weights and costs to each health state that were accumulated over time to create an incremental cost-effectiveness ratio (ICER). The time-horizon was 100 years to capture all relevant costs and effects of vaccination, in accordance to Swedish guidelines for health economic evaluations [30]. The cycle length was one year. Both cost and health effects were discounted with 3% annually. All costs were measured in Swedish krona and converted to euro (exchange rate 100 SEK = 9.81 euro [2018-01-10, Swedish Central Bank]).

The resource use was based on national guidelines and expert opinion, and dependent on cancer type and severity-state. Costs were taken from the cost per patient database, and the average cost of 2014 and 2015 were used. The average cost of inpatient care varies between EUR 3892 and 7747. The corresponding figure for outpatient care varies between EUR 268 and 423. The vaccination programme assumed a 2-dose schedule at EUR 87 per dose. QALY-weights were assigned to each health state, and was based on relevant literature [31–33].

2.5. Sensitivity analyses

Deterministic sensitivity analyses were performed to investigate how varying the input parameters affected the results. All modelling and sensitivity analyses were performed in the computer software Vensim, with data extracted to Excel for the health economic calculations. The parameters varied were (1) price of the vaccine, (2) vaccination coverage, (3) risk of infection, (4) time-horizon, (5) effect of the vaccine, (6) discount rate, (7) administration cost of the vaccine, (8) inclusion of anogenital warts, and (9) exclusion of the effect on CIN. Costs due to productivity losses for people of working age were included in a sensitivity analysis, and based on the average monthly salary and the statutory employers' fee.

3. Results

3.1. Epidemiological model

Over the modelled time-horizon, continued vaccination of girls would lead to a decrease in HPV-related cancer among girls of 86%, and among boys of 69%. In comparison, sex-neutral vaccination would lead to a greater decrease in HPV-related cancer of 93% and 84% for girls and boys respectively (Fig. 2).

3.2. Cost-effectiveness evaluation

In the base-case analysis, sex-neutral vaccination led to accumulated costs of about EUR 200 million during the time-horizon, and to about 5600 gained QALY. This resulted in an ICER of about EUR 40,000 (Table 3).

If the effect on genital warts was included, the accumulated net costs decreased to EUR 178 million and the QALY gained increased to 6010.

To take into account the potential rebates that can be negotiated between county councils and vaccine producers during procurement, a sensitivity analysis was conducted to demonstrate the effect of the vaccine price on the ICER, given the assumptions made in the model. The ICER decreased by about EUR 5,000 for each 10% increase in the rebate. If the procurement price of 2017 was used, which had a rebate of about 85% [34], sex-neutral vaccination would dominate girl-only vaccination, i.e. lead to better health effects at a lower cost over time.

In another sensitivity analysis (Fig. 3), results were not greatly affected by a decrease in vaccination coverage (to 50%) among boys. However, if the vaccination coverage among girls were to decrease, the herd immunity from sex-neutral vaccination would make vaccination of boys more efficacious. On the contrary, if the vaccination coverage among girls was higher (90%) that would make sex-neutral vaccination less efficacious. The chosen discount rate also had a significant impact on the results as a consequence of the long time-horizon.

4. Discussion

The base-case analysis suggests that the cost per QALY gained by introducing sex-neutral HPV vaccination would be about EUR 40,000. The results are mostly affected by assumptions regarding the diseases included in the model, the discount rate, and the price of the vaccine. Vaccinating preadolescent boys in addition to girls within the Swedish national vaccination programme is likely to be cost-effective, especially considering current procurement

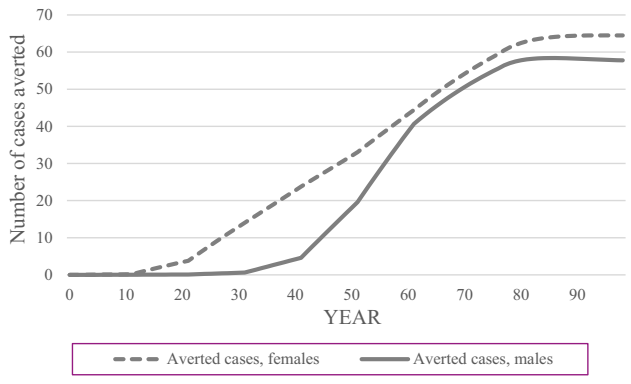

Fig. 2. Number of added averted cases of HPV-related cancer with sex-neutral vaccination compared to girls-only vaccination, modelled over a time-horizon of 100 years, for boys and girls, Sweden.

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Table 2
Average incidence of HPV-related cancer in boys and girls, identified via ICD-10 code, and estimated proportion that was HPV- and HPV 16/18-attributable in Sweden (2010–2014).

Cancer site	Cases (Sweden, average 2010–2014)				Proportion of HPV attributed that is attributed to HPV16/18 (%)	Estimated cases attributable to HPV 16/18		References
	ICD-10 code	Boys	Girls	Attributable to HPV (%)		Boys	Girls	
Anus	C21	46	108	88	84	34	80	[25]
Penis	C60	91	NA*	51	48	22	NA*	[25]
Oropharynx (tongue base, tonsil)	C01,C09	244	94	74	60	108	42	[25]
Cervix	C53	NA*	424	100	70	NA*	297	[25]
Vagina	C52	NA*	31	78	55	NA*	13	[25]
Vulva	C51.9	NA*	146	48, 28, 15	54	NA*	16	[25]
CIN** 1	NA*	NA*	8356	71	26	NA*	1545	[26]
CIN** 2	NA*	NA*	6357	87	43	NA*	2375	[26]
CIN** 3	NA*	NA*	6657	79	61	NA*	3208	[26]

* Not applicable.
** Cervical intraepithelial neoplasia.

Table 3
Incremental cost-effectiveness ratio (ICER), quality-adjusted life years (QALY) gained, and total cost of sex-neutral vaccination, comparing girls-only vaccination with sex-neutral vaccination.

Results	Girls-only vaccination	Sex-neutral vaccination	Difference
Added cost of vaccine		287,230,655€	287,230,655€
Treatment costs	113,613,375€	55,143,985€	−58,469,389€
Cost of production loss	28,458,113€	13,979,438€	−14,478,676€
Total costs	**142,071,488€**	**356,354,078€**	**214,282,590€**
QALY	62,399,875	62,405,479	5,604
ICER, societal perspective			**38,237€**
ICER, healthcare perspective*			**40,821€**

* Does not include gains from decreased production losses.

prices. Girls gain more QALY than boys from sex-neutral vaccination through herd immunity effects, due to their higher burden of HPV-related disease, where prevention of treatment costs of CIN-lesions was the key driver of the ICER.

Previous studies have shown that increasing the HPV vaccination coverage among girls is more beneficial than having a sex-neutral programme in reducing the overall burden of disease [2,3,27,35,36]. However, so far most countries with girls-only programmes have had difficulties reaching a high coverage. In Sweden the coverage has been stable around 80% for one dose since the implementation of the national vaccination programme 2012. It is not known what effect introducing sex-neutral vaccination might have on vaccination coverage in Sweden. Introducing a sex-neutral programme could lead to an increase in coverage also for girls by decreasing stigmatization concerning the connection between the vaccine and sexual behaviour. Countries that have introduced sex-neutral HPV vaccination have reached similar or slightly lower coverage among boys than among girls, without lowering the coverage among girls [37].

Mathematical modelling has previously been used to estimate the impact of vaccination on HPV-incidence in other countries [38–40]. The models have mainly focused on the effect of vaccination on HPV-transmission, and on indirect effects on HPV-related

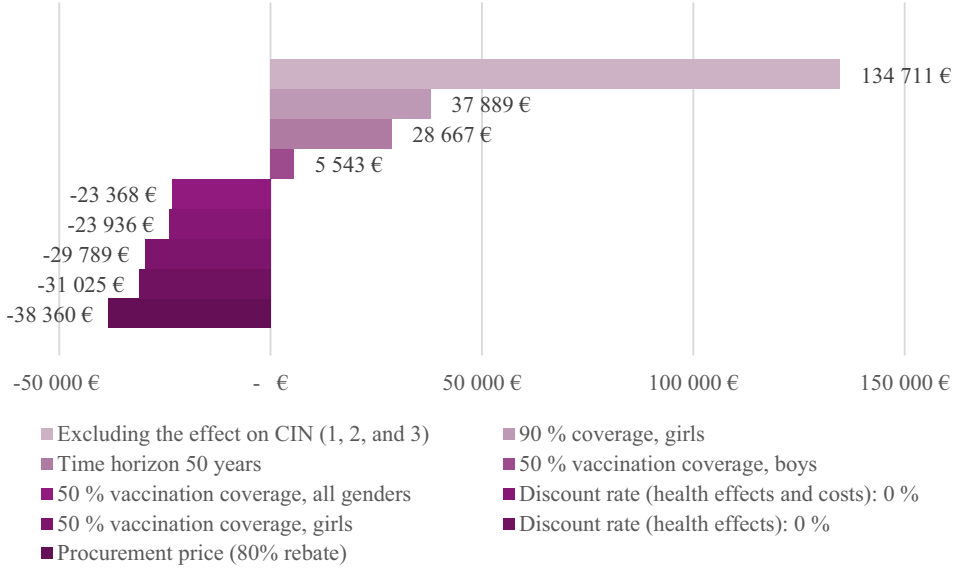

Fig. 3. Diagram presenting the impact of different assumptions on the incremental cost-effectiveness ratio (ICER) of a sex-neutral vaccination programme in comparison to a girls-only programme as presented through deviation from base-case results of about EUR 40,000.

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disease. Few models have taken same-sex transmission into account [41]. Modelling work from Australia including only heterosexual transmission shows that girl-only vaccination can provide three quarters of the maximum benefit that vaccination of both sexes could confer [42]. Models from high-income countries on heterosexual transmission also show that raising vaccination coverage to 80% in a girl-only vaccination programme effectively prevents infection with HPV-types 16/18 among boys, after which increasing coverage further had marginal effects [43]. This is important because there might be a point of diminishing returns in attempting to increase vaccination coverage among girls in settings where coverage is already high. It could thus be more effective to focus on achieving moderate coverage among boys.

Dynamic population systems are often modelled through deterministic difference equations, in order to obtain average estimates over the population [44]. A strength of our study was the use of such a model that, in contrast to static models, allows for indirect effects of herd immunity depending on the vaccination coverage in the populations. Previous studies have used the same concept as ours, with herd immunity being accounted for through a reduced incidence over time [36,45,46].

Our evaluation accounted for MSM, which few other studies have done. In a review from 2016, only two out of 18 studies explicitly reported the transmission of HPV-infection among MSM as in our study, i.e. taking into consideration that MSM do not benefit from herd immunity through girls-only vaccination [41]. It is important to consider that MSM do not benefit to the same extent from conferred herd immunity from girls, and that the effect of just vaccinating girls will thereby be overestimated leading to an underestimation of the effect of sex-neutral vaccination.

Our study relies on estimates of the proportions of the different cancer types that are attributable to HPV-infection rather than building a dynamic HPV-infection model based on HPV-infection data. This may be considered a limitation of the study since the model assumes that the vaccination effect is proportional to the effect on HPV-related cancer incidence. However, since it is the effect on HPV-related cancer that is of interest in this health economic evaluation, it is reasonable that an assumption has to be made about the proportions that are attributable to HPV-infection rather than to model HPV-infection.

A limitation of the study is that the model did not take into account cross-protection of the vaccines to non-vaccine-HPV-subtypes, nor did it estimate the added effect from using the nonavalent HPV vaccine, as this vaccine was not introduced in Sweden at the time of the study. However, both effects would serve to further increase the cost-effectiveness of the different vaccinations. A decreased type-specific vaccine efficacy would work in the other direction, decreasing the cost-effectiveness of the vaccines. To estimate and further quantify the possible implications these effects in the Swedish setting warrants further study.

Our model does not take into account differences in vaccination coverage or transmission patterns in other countries when calculating the effects of herd immunity, since such data is scarce. However, assuming that people who have sex with people in other countries have the same risk for HPV as when having sex with people in Sweden may overestimate the effect of herd immunity, considering the relatively high HPV vaccination coverage.

Our economic evaluation was conducted from a health care perspective, in line with several other studies [47–49]. Previous studies have evaluated the same vaccination strategies as our study, i.e. sex-neutral vaccination compared to girls-only vaccination [3,27,48,50]. In a review from 2016, the results from the different analyses varied due to assumptions in the models. As expected, analyses that included more HPV-related diseases had lower ICER than analyses including only cervical cancer. The ICER of the analyses that included all HPV-related diseases ranged between EUR 13,700 and EUR 261,866, with an average of approximately EUR 50,000, which is in line with the results from our evaluation. The single parameter that had the greatest influence on the results in all of the above mentioned analyses, including ours, was the expected price of the vaccine [41].

Our study fills a gap in the knowledge base for Swedish decision makers who are considering whether or not to implement a sex-neutral vaccination programme. It also adds to the studies that have investigated cost-effectiveness of vaccinating boys in addition to girls. Many of the previous studies that have assessed cost-effectiveness of sex-neutral programmes have only focused on cervical cancer, which may underestimate the impact of vaccinating boys [41]. Our study included various HPV-related cancer types and CIN, demonstrating the potential of improved cost-effectiveness. A big part of the reductions in treatment costs in our study was due to a reduction of CIN through herd immunity. Even though treating CIN-lesions is much less costly than treating HPV-related cancer, the incidence of CIN is higher than that of cancer. In addition, the effect of vaccination on CIN-lesions occur much sooner than the effect on HPV-related cancer, indicating a higher value due to discounting.

This is the first health economic evaluation of a sex-neutral HPV vaccination programme in the Swedish setting. Similar models to ours that concurrently have been developed in the Netherlands and Germany [38,39] also concluded that the cost-effectiveness of additional vaccination of boys is dependent upon the coverage among girls, and that a sex-neutral vaccination programme is likely to be cost-effective under current procurement prices. It is, however, also evident that results from cost-effectiveness analyses are highly dependent upon the vaccine price as well as how the vaccination programme and health care system are constructed. This motivates conducting national health economic evaluations, as compared to assuming that results from one country are transferable to another. In conclusion, the findings in this study demonstrate that sex-neutral HPV vaccination in the Swedish setting is cost-effective, i.e. good value for money, given a cost-effectiveness threshold of 50,000 Euro.

5. Conflict of interest

None.

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