COST-EFFECTIVENESS OF GENDER-NEUTRAL NINE-VALENT HPV VACCINATION IN DENMARK

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OBJECTIVES

Human papilloma virus (HPV) is one of the most common sexually transmitted infections. HPV infections are mostly time transient and cleared up within a few months after acquisition. However, some infections do not clear up, and persistent HPV infections may lead to cancer as it is estimated that HPV types 16, 18, 31, 33, 45, 52 and 58 are associated with almost all cervical cancers, 90% of anal cancers, 65% of vaginal cancers, 50% of vulvar cancers and 35% of penile cancers. In addition, HPV type 6 and 11 causes 90% of genital warts cases.
In 2009, a publicly financed HPV vaccination program for 12-year old females was initiated in Denmark. Vaccination among males has been financed via 100% self-payment. However, from 2019 it is expected that a publicly financed gender-neutral vaccination program of 12-year olds will be initiated.

From 2009 to 2013, female vaccination rates were high (>70%), but in 2014, 2015 and 2016 the vaccination rates were low (34%-57%). Since 2009, the vaccination rate in males has been approx. 3%.
In addition, the nine-valent (HPV9) vaccine is now available. This causes the need for updated cost-effectiveness analyses, which take the reduced vaccination rates and the improved protection from the HPV9 vaccine into account.
It is the objective of this study to compare the potential public health impact and economic impact of a gender-neutral vaccination program with a HPV9 vaccine using different assumptions in terms of vaccination rates in Denmark.

METHODS

The analysis was performed by adapting an existing dynamic transmission model to a Danish setting. The model includes the HPV9 vaccine in order to evaluate the cost-effectiveness of vaccination providing protection against HPV types 6, 11, 16 and 18 and the new types: 31, 33, 45, 52 and 58. In total, the model accounts for the transmission dynamics of all nine HPV types covered by the HPV9 vaccine and takes herd immunity into account.
The structure of the model is formulated as a system of ordinary differential equations and consists of three connected components: a demographic model, an epidemiological model and an economic model.

The model has a high level of detail, and many input parameters are required. The model parameters include the following categories:

- Demographics
- Sexual behavioural data
- Screening parameters
- Natural history of disease
- Treatment patterns
- Cancer mortality
- Vaccine properties
- Vaccination coverage by strategy
- Costs
- Health-related quality of life

Comparing HPV9 2-dose vaccination to cervical cancer screening only and given the described input variables and assumptions, the total number of events, incidence and mortality of HPV-related diseases as well as costs and QALYs per person over a time horizon of 100 years were estimated. Incremental cost-effectiveness ratios (ICERs) were then calculated as incremental costs/incremental QALYs.

Analyses of both vaccination of females only and gender-neutral vaccination (i.e. vaccination of males and females) were performed. Actual vaccination rates for females have been applied and vaccination of males via a publicly financed program (i.e. vaccination rates higher than 5%) is only included from year 10 and onwards.
Different scenarios were analysed (table 1). In table 1, the vaccination rates for year 1-8 reflect the actual rates for the first 8 years of the program (i.e. 2009-2016). This implies that these rates are the same for all scenarios. The 3% vaccination rate for males in year 1-8 reflects the percentage of males who paid for the vaccination themselves.
In scenario 1a, it is assumed that the female vaccination rate will return to the same high level as in the first 5 years. This is displayed as an increase to 60% in year 9. A vaccination rate of 65% in year 10 and of 70% from year 11 and onwards is assumed. That is, scenario 1a is a "female only" vaccination program.
Contrary to 1a, scenario 1b is a gender-neutral vaccination program since it is assumed that vaccination of males is included in the program from year 10 and onwards, which is reflected by a vaccination rate of 55% in year 10 and of 65% from year 11 onwards.
In scenario 2a and 2b, it is assumed that the low vaccination rate observed in year 8 is maintained. Scenario 2b is the gender-neutral vaccination program but with a low participation for both females and males.

Table 1. Vaccination rates for different scenarios

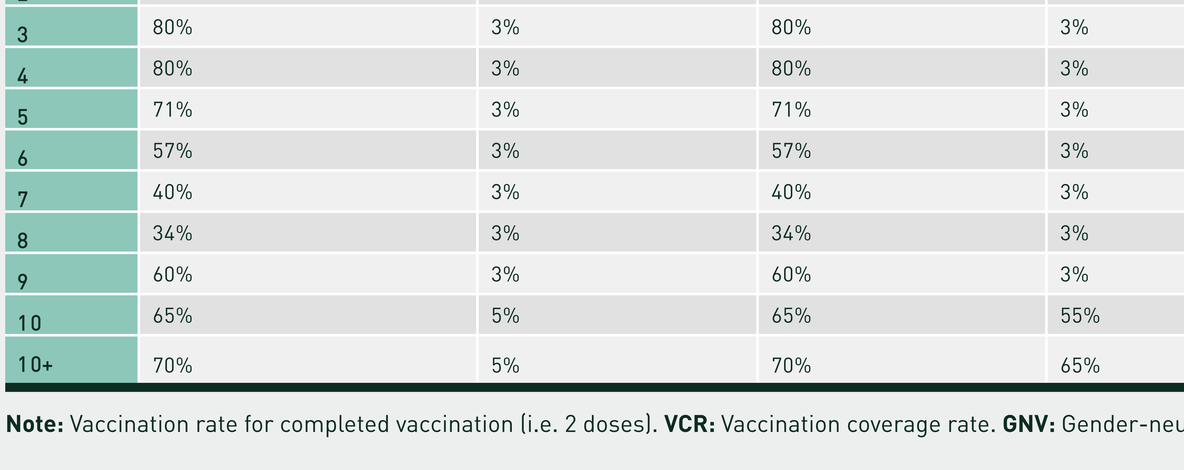
	Scenario 1a (female only vaccination, high VCR)		Scenario 1b (GNV, high VCR)		Scenario 2a (female only vaccination, low VCR)		Scenario 2b (GNV, low VCR)	
Year	Vaccination rate, females	Vaccination rate, males	Vaccination rate, females	Vaccination rate, males	Vaccination rate, females	Vaccination rate, males	Vaccination rate, females	Vaccination rate, males
1	71%	3%	71%	3%	71%	3%	71%	3%
2	79%	3%	79%	3%	79%	3%	79%	3%
3	80%	3%	80%	3%	80%	3%	80%	3%
4	80%	3%	80%	3%	80%	3%	80%	3%
5	71%	3%	71%	3%	71%	3%	71%	3%
6	57%	3%	57%	3%	57%	3%	57%	3%
7	40%	3%	40%	3%	40%	3%	40%	3%
8	34%	3%	34%	3%	34%	3%	34%	3%
9	60%	3%	60%	3%	34%	3%	34%	3%
10	65%	5%	65%	55%	34%	5%	34%	34%
10+	70%	5%	70%	65%	34%	5%	34%	34%

Note: Vaccination rate for completed vaccination (i.e. 2 doses). **VCR:** Vaccination coverage rate. **GNV:** Gender-neutral vaccination.

RESULTS

By applying the market price for the HPV9 vaccine (pharmacy purchasing price), the ICER is estimated to 3,455 Euros/QALY for female vaccination only compared to screening only and 5,890 Euros/QALY for gender-neutral vaccination compared to screening only (scenario 1a and 1b).
In scenario 2a and 2b, the ICER is estimated to 2,923 Euros/QALY for female vaccination only compared to screening only and 4,260 Euros/QALY for gender-neutral vaccination compared to screening only (figure 1).

Figure 1. ICER (incremental cost-effectiveness ratios), HPV9 vaccination compared to no vaccination (€/QALY)



If the low female vaccination rate of 34% is maintained (scenario 2a), the number of avoided HPV-related cancers will overall decrease with 33% compared to scenario 1a, where the future vaccination rate is higher.
In scenario 2a with maintained low vaccination rates (34%), inclusion of boys in the vaccination program (scenario 2b) will increase the number of avoided HPV-related cancers with almost 17%. In scenarios 1a and 1b with high future vaccination rates, gender-neutral vaccination (scenario 1b) will increase the number of avoided HPV-related cancers with 12%.
Table 2 shows the specific reduction rates in the HPV-related cancers for the four scenarios.

Table 2. Incidence reduction HPV9-vaccination vs. screening only

	Scenario 1a (female only vaccination, high VCR)	Scenario 1b (GNV, high VCR)	Scenario 2a (female only vaccination, low VCR)	Scenario 2b (GNV, low VCR)
Cervical cancer	-44.8%	-46.5%	-30.4%	-32.8%
Vaginal cancer	-39.4%	-41.1%	-26.8%	-29.1%
Vulvar cancer	-39.3%	-40.9%	-26.5%	-28.7%
Anal cancer				
females	-34.0%	-36.2%	-23.0%	-25.7%
males	-24.5%	-33.2%	-16.3%	-23.2%
Penile Cancer	-8.3%	-23.8%	-5.6%	-14.4%
Head and neck cancer				
females	-34.8%	-37.2%	-22.3%	-25.0%
males	-23.4%	-34.4%	-14.5%	-22.5%
Genital warts				
females	-65.5%	-70.8%	-39.1%	-44.6%
males	-48.4%	-64.2%	-26.2%	-38,9%

The gender-neutral vaccination program will improve the protection in females and males since the number of avoided HPV-related cancers and deaths increase, especially for anal, penile, and head and neck cancer.

CONCLUSIONS

The HPV9 vaccine's additional protection against HPV-related pre-cancers and cancers leads to improved cost-effectiveness. This implies that gender-neutral HPV vaccination is cost-effective in a Danish setting (ICER 5,890 Euros/QALY). Given the reduced female vaccination rates as well as the cost-effectiveness and the increased number of avoided HPV-related cancers and deaths offered by a gender-neutral vaccination program, the latter will be beneficial from a public health perspective.