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ORIGINAL RESEARCH

An estimate of the public health impact and cost-effectiveness of universal vaccination with a 9-valent HPV vaccine in Germany

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ABSTRACT

Introduction: Since 2007, the German Standing Vaccination Committee recommends HPV vaccination for girls aged 12–17 with a 2- (Cervarix®) or 4-valent (Gardasil®) vaccine. A 9-valent vaccine (Gardasil 9®) recently received a European market authorization in 2015.

Methods: A dynamic transmission model was calibrated to the German setting and used to estimate costs and QALYs associated with vaccination strategies.

Results: Compared to the current vaccination program, the 9-valent vaccine extended to boys shows further reductions of 24% in the incidence of cervical cancer, 30% and 14% in anal cancer for males and females, as well as over a million cases of genital warts avoided after 100 years. The new strategy is associated with an ICER of 22,987€ per QALY gained, decreasing to 329€ when considering the vaccine switch for girls-only.

Conclusion: Universal vaccination with the 9-valent vaccine can yield significant health benefits when compared to the current program.

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Cost-effectiveness; Germany; HPV; cervical cancer; vaccination

1. Introduction

Human papilloma virus (HPV) infections are responsible for nearly all cases of cervical cancers (4647 per year in Germany), 19% of vulvar cancers (605 per year), 71% of vaginal cancers (360 per year), 88% of anal cancers (1627 per year), and 90% genital warts (113,039 per year) [1,2]. HPV is a family of viruses that infect epithelial tissues including skin and moist membranes [3]. For this reason, HPV is one of the most common sexually transmitted infections [3]. Among the over 100 different types of HPV identified, some are referred as high-risk because they increase the probability of developing anogenital cancers. This group includes types 16, 18, 31, 33, 45, 52, and 58. High-risk types 16 and 18 alone contribute for 70% of invasive cervical cancers and high-grade cervical intraepithelial neoplasia (CIN) [4]. Low-risk types 6 and 11 account for 85% of genital warts cases [5,6].

The economic burden that HPV infections and related diseases cause in Germany is heavy on health-care system and society [7,8]. Screening and vaccination strategies against HPV represent the primary method to prevent HPV-related precancers and cancers.

Early detection of cervical cancer was introduced in Germany is 1971. Currently, all woman aged 20 or older are entitled to an annual free-of-charge Pap smear, with no age limit for cessation. The German screening program is a self-referring screening policy without an invitation and regulation system. Insurance data shows that around 15 million smears are currently taken every year, which implies a compliance with annual screening of around 50% of the target population [9,10]. In 2015, the national health institution *Gemeinsamer Bndesausschuss* (G-BA) decided to change the screening policy to include HPV testing every five years for woman older than 30 years. However for an interim period, these woman will be allowed to choose annual Pap smear screening instead. Since there is a lot of uncertainty around the impact of this policy in the cost of screening in Germany, the base case analysis is based on the current screening practice [11].

Currently two vaccines are commercially available: Gardasil® (Sanofi Pasteur MSD) which is a recombinant vaccine with protection against HPV types 6, 11, 16, and 18, and Cervarix® (GlaxoSmithKline) that offers protection against the HPV types 16 and 18 [12–14]. While Cervarix® is indicated for the prevention of cervical pre-cancerous lesions and cervical cancer caused by HPV types 16 and 18, the 4-valent vaccine indication also includes vulvar, vaginal, and anal cancers, and respective precancerous dysplastic diseases (vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), and anal intraepithelial neoplasia (AIN)) as well as genital warts [13,14]. In 2007, the German Standing Vaccination Committee (STIKO) recommended vaccination with either Gardasil® or Cervarix® in a three-dose schedule for girls aged 12–17. The vaccines are free of charge in the target age group, although reimbursement is also available for women aged 18–26 [15–17]. Although both vaccines are equally reimbursed, Gardasil® holds the majority of the market share (up to 90%) [9]. A recent update shifted the target age group to 9–14, and limited the recommended number of doses to two. A third dose is scheduled for girls 14 or older or for catch-up vaccinations [18]. Official figures for

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vaccination coverage rates (VCR) in light of the new recommended age-classes are not yet available. The latest figures from Robert Koch Institute (RKI) show compliance rate of 55.6% among the target population (12–17-year-old girls) [19].

Gardasil 9® is a new vaccine that offers protection against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Gardasil 9® is expected to prevent infection from the majority of the HPV types with carcinogenic properties, since types 16, 18, 31, 33, 45, 52, and 58 are among the most commonly detected [20]. Hartwig et al. estimate that 89% of the HPV-positive cervical, vaginal vulvar, and anal cancers are attributable to the 7 oncogenic HPV types for which Gardasil 9® offers protection, whereas the high-risk types 16 and 18 included in the previous vaccines (Gardasil® and Cervarix®) account for 75% of HPV-related cancers. Therefore, the new vaccine significantly broadens the protection offered by the first generation of HPV vaccines [1].

In the United States, Gardasil 9® has been approved by the US FDA in December 2014, for females aged 9–26 and males aged 9–15 [21]. The Committee for Medicinal Products for Human Use of the European Medicine Agency recommended the marketing authorization of Gardasil 9® that received approval from the European Commission on June 2015 [22]. The indication is for individuals of at least nine years of age and the dosing schedule is fully aligned with the national recommendations on HPV vaccination, with 2 doses below 15 years of age and 3 doses above.

While HPV vaccination was originally focused on the prevention of cervical cancer and targeted girls only, more and more countries recommended the HPV vaccination for girls and boys. Indeed, the burden of HPV-related diseases is heavy on the male population. In Germany, about 800, 740, and 12,000 new cases of penile, anal, and head & neck (H&N) cancers, respectively, are reported each year [2]. The economic burden is important as well. It was shown in Europe that non-cervical cancers accounted for a substantial proportion of the economic burden of HPV-related cancers, and that this burden was mainly driven by men (about 70%) [7]. Although female vaccination can indirectly protect males, it does not reach the homosexual population. In addition, evidence shows that a reasonable protection in the male population is only achievable when the VCR is high on females [9]. However, to increase the coverage in females may be challenging especially in countries like Germany where the vaccination is done by self-referral. Furthermore, some experts argue that universal (boys and girls) vaccination can greatly contribute to contain the virus propagation and that it is the only way to ultimately eradicate it [23]. Accordingly, universal vaccination is being recommended and introduced in several European countries (Austria, Norway, Switzerland, and 9 regions in Italy).

Cost-effectiveness studies of the 9-valent vaccine in the United States showed that universal vaccination is likely to be cost saving when compared to the current strategy [24–26]. In Canada, the HPV-ADVISE-CAN model showed that the 9-valent vaccine is cost-effective with respect to the 4-valent vaccine if the price increment does not exceed $24 [27]. A recently published paper concluded that universal vaccination with the 9-valent vaccine in Austria could reduce the cervical cancer incidence by an additional 17%, compared to vaccination with the 4-valent vaccine and be a cost-effective or cost-saving strategy, depending on the price per dose [28].

In Germany, cost-effectiveness studies of the new vaccine are not available in the literature; however, studies regarding HPV vaccination have been published. Hillemanns et al. used an empirically calibrated Markov model of the natural history of HPV to assess the cost-effectiveness of the 4-valent vaccine administered to 12-year-old girls alongside existing cervical screening programs in Germany [29]. The authors estimated that 2835 cervical cancer cases and 679 deaths could be prevented in a cohort of 400,000, at an incremental cost-effectiveness ratio (ICER) of 10,530€ per quality-adjusted life-years (QALY) gained [29]. Schobert et al. used an HPV dynamic transmission model in the German context [30]. They found that vaccination with the 4-valent vaccine of girls aged 12–17 was cost-effective (ICER 5525€/QALY) and that the ICER would increase substantially (10,293€/QALY) when the vaccine effects on HPV6/11 diseases were excluded [30]. Horn et al. developed a dynamic mathematical model for the natural history and transmission of HPV infections. They found that over 100 years, a 4-valent HPV vaccination program could prevent around 37% of cervical cancer cases assuming a 50% VCR in the 12-year-old girls [9].

Although cost-effectiveness evidence for a new technology is not mandatory in Germany, the STIKO might consider available studies in their recommendations. In accordance, the scope of the current study is to provide an epidemiological and cost-effectiveness analysis of the implementation of the 9-valent vaccine in Germany in comparison of the current practice. As the 4-valent vaccine holds the vast majority of the German HPV vaccine market, the current practice is represented in our model by a 4-valent vaccination program targeted to girls aged from 9 to 17 years old.

2. Methods

2.1. Mathematical model

Elbasha et al. developed a deterministic SIRS (Susceptible-Infected-Recovered-Susceptible) model to assess the cost-effectiveness of HPV vaccination [31]. The first version of the model simulated the epidemiology of HPV 6/11/16/18 infections and related diseases (CIN, cervical cancer, and genital warts). A German adaptation of this model was performed by Schobert et al. [30]. The model structure was first updated in 2010 to take into account all HPV-related diseases, adding to the original model the indication on vaginal, vulvar, anal, H&N, and penile cancers as well as respiratory papillomatosis and more recent data on the natural history of the infections [32,33]. In 2014, the effect of HPV types 31, 33, 45, 52, and 58 were added to the original four (types 6, 11, 16, and 18) in order to be suitable for the 9-valent vaccine. However, the model uses a conservative assumption considering that the types 33/33/45/52/58 are only responsible for cervical diseases and anal cancer. The contribution of the five additional types to the burden of other diseases (vaginal, vulvar, penile, H&N cancers, genital warts, and recurrent respiratory papillomatosis [RRP]) is not modeled currently.

The current model features a high level of detail, involving hundreds of inputs and several thousand ordinary differential equations (ODEs). Sub-models are evaluated successively: an initialization *demographic and epidemiologic model* informs an *economic model* that can compare vaccination strategies and evaluates the epidemiological impact and cost-effectiveness of the implementation of a new vaccination program.

The demographic model defines the characteristics of the population being simulated and describes how persons enter, age, and exit various categories. The population is divided into 17 age groups, classified into three levels of sexual activity. Persons then move between successive age groups and exit the model upon death. Cancer patients have an additional age and stage-dependent death rate. Patients with CIN or genital warts do not face an additional risk for death.

The epidemiologic model simulates HPV transmission and the occurrence of consequential diseases. The acquisition of infection and progression of persons from infection to disease follow a natural history structure that remains similar across the versions. The population was divided into distinct epidemiologic categories, according to the person's status with respect to infection, disease, screening, and treatment over time. The epidemiologic module includes one HPV6-specific model (RRP, genital warts, and CIN1), one HPV11-specific model (RPP and genital warts), one separate model for each disease related to HPV16 or HPV18 (cervical precancerous lesion and cancer, vulvar precancerous lesion and cancer, vagina precancerous lesions and cancer, anal precancerous lesion and cancer, penile precancerous lesions and cancer, and H&N cancer). The 5 additional types (HPV31, 33, 45, 52, and 58) have been merged together and one separate model has been created for them: one for cervical diseases and another one for anal diseases [28].

Finally the economic model considers the implementation of screening and vaccination strategies that will impact the infection transmission among the population and the development of the diseases. By assigning costs and utilities to each health state (defined by the person's status), the model will generate cost-effectiveness results along with the epidemiological results.

The adaptation to the German setting was carried out by informing the model with German-specific inputs. This study evaluates two strategies using a two-dose schedule of the 9-valent vaccine: a universal vaccination program covering equally boys and girls in the recommended age group, and a girls-only vaccination scenario. Both are compared to the current practice of a two-dose vaccination with the 4-valent vaccine covering girls aged between 9 and 17 years.

2.2. Epidemiological model inputs

The parameters are divided in five distinct sections: demographics, sexual behavior, disease and treatment patterns, screening, and natural history of disease. The parameter groups are summarized in Table 1 along with the references.

2.2.1. Demographics

Age-stratified population figures and all-cause mortality rates were retrieved from the German Federal Statistical Office (Statistisches Bundesamt) [48,49].

Table 1. Summary table on the epidemiological input groups with some of the references used.

Parameter	References
Demographics	
Annual all-cause mortality rate	[34]
Female and male population	
Female and male population >12yo	
Sexual behavior	
Percent of population in low/medium/high sexual activity category	[35]
Mean number of sexual partners by activity category	
Mean number of sexual partners by age group	
Sexual mixing among activity categories	
Sexual mixing among age groups	
Disease and treatment patterns	
Female population receiving hysterectomy each year	[36]
Age- and stage-specific mortality rates	[2]
Population recognizing their symptoms and seeking treatment by disease	Calibration
Percent of cases treated	
Screening	
Percent of females receiving a follow-up screening test after abnormal Pap smear	[37]
Percent of females screened every 3 years	[38]
Age-specific percent of females screened in the past year	[39]
Diagnostic performance of PAP test and colposcopy	[40–42]
Natural history of disease	
Probability of transmitting genital, anal, penile, and head and neck HPV infection per sexual partnership, by sex and HPV genotype	[43]
Recurrence rate of treated CIN, by stage	
Rate of cancer progression, by stage	[44,45]
Fraction of persistent cervical HPV infections, by type 16 or 18	[32,33]
Clearance rate of cervical HPV infections, by type 16 or 18	[43]
Fraction of people who seroconvert following a cervical HPV infection, by type 16 or 18	[46,47]
Degree of protection against cervical HPV infections provided by natural immunity following seroconversion, by type 16 or 18	[32,33]
Fraction of females transiently infected who progress to CIN over the course of one year, by type 16 or 18	[43]

2.2.2. Sexual behavior

German-specific sexual behavioral data is not available in the literature. Previous German and Austrian cost-effectiveness models relied on the second UK National Survey of Sexual Attitudes and Lifestyle (NATSAL-2) [9,30,50], as sexual behavior patterns are similar in Germany and the UK [51]. As a new version of this study (NATSAL-3) was published in 2014, we used the updated figures in the model. Since results were not reported per model requirements, NATSAL authors were contacted [35]. The amount of sexual mixing among members of different age cohorts (a value between 0 and 1 with 0 representing no mixing) and the amount of sexual mixing among members of different sexual activity groups requested in the model were extracted from Elbasha and Dasbach [32,33]. The sexual behavior parameters are displayed in Table 2.

2.2.3. Natural history of disease

We assume that the natural history of the disease in Germany follows the same patterns as in the US, as the Wolfsburg HPV Epidemiological Study (WOLVES) shows comparable data between California and Lower Saxony [52–54]. Therefore, we relied on the extensively calibrated parameters previously described and reported by Elbasha and Dasbach [32]. For the transmission rates, calibration techniques were used to obtain

Table 2. Summary table on sexual behavior.

Definition of sexual activity categories					Mean number of sexual partners per year		
Low	mean number of sexual partners/year: ≤1				Age group	Male	Female
Medium	mean number of sexual partners/year: 2–4				13–14	0.0001	0.0001
High	mean number of sexual partners/year: 5+				15–29	1.7	1.4
Size of categories and mean number of partners					30–34	2.0	1.6
	Percent of population		Mean number of partners		35–44	1.7	1.3
	Male	Female	Males	Females	45–49	1.5	1.2
Low	85.10%	90.70%	0.79	0.75	50–54	1.5	1.0
Medium	11.90%	7.60%	2.54	2.52	55–59	1.1	1.5
High	3.00%	1.70%	9.8	9.66	60–64	1.1	1.0
Sexual mixing					65–69	1.1	0.9
Among members of different age cohort					70–74	1.0	0.7
	Between debut and cessation			0.4	75–79	0.9	0.6
	After cessation			0.1	80–84	0.8	0.5
Among members of different sexual activity groups				0.5	85+	0.5	0.3

the best set of parameters for Germany. The model parameters on the natural history of disease can be found in Appendix.

2.2.4. Disease and treatment patterns

Calibration was used to estimate the parameters related to the percent of treated CIN, VaIN, VIN, and Carcinoma *in Situ* (CIS), as well as the percentage of females with cancer recognizing their symptoms and seeking treatment.

The hysterectomy rates were derived from a 2013 publication by the German Federal Statistical Office (DRG-related hospital statistics – Fallpauschalenbezogene Krankenhausstatistik) reporting the total number of hysterectomies performed. We calculated the hysterectomy rates using population numbers by age class from 2013 [36,49].

2.2.5. Cancer mortality

The model requires HPV-related cancer-associated mortality (i.e. the fraction of individuals with cancer who are expected to die over the course of 1 year) stratified by age and stage (local, regional, and distant). Since survival data was only available by age class, an extrapolation to estimate the stage-stratified data as required by the model was performed. UK data from Cancer Research UK was used to calculate the relative risk of each stage and applied to the German-specific survival statistics (assumed to be representative of regional stage) in order to calculate survival rates for local and distant cancers [55].

To estimate HPV-related cancer-associated mortality, we used survival data from the European Cancer Registry (EUROCARE-5) and the German Centre for Cancer Registry Data (ZfKD) [2,56]. The ZfKD was preferred where possible because data were more recent and more representative of the German population [2]. EUROCARE-5 data were used for H&N and penile cancers. Assumptions were necessary to conform to the model inputs: mortality for vaginal cancer was assumed equal to vulvar cancer, mortality for anal cancer was assumed equal to colon and rectum pooled. The five-year mortality rates were then converted to one-year death probabilities (Table 3).

Table 3. Summary table on cancer mortality.

	Age group	Annual probability of death		
Cancer type	(years)	Local cancer	Regional cancer	Distant cancer
Cervical cancer	15–44	0.010	0.032	0.081
	45–54	0.022	0.069	0.173
	55–64	0.031	0.097	0.224
	65–74	0.039	0.123	0.309
	75+	0.069	0.219	0.552
Vaginal cancer	15–44	0.013	0.023	0.041
	45–54	0.017	0.030	0.053
	55–64	0.035	0.061	0.109
	65–74	0.053	0.091	0.162
	75+	0.095	0.163	0.291
Vulvar cancer	15–44	0.011	0.023	0.050
	45–54	0.014	0.030	0.064
	55–64	0.028	0.061	0.132
	65–74	0.042	0.091	0.197
	75+	0.075	0.163	0.353
Anal cancer (Females)	15–44	0.030	0.066	0.114
	45–54	0.032	0.072	0.123
	55–64	0.032	0.072	0.123
	65–74	0.041	0.091	0.157
	75+	0.077	0.172	0.295
Anal cancer (Males)	15–44	0.032	0.072	0.123
	45–54	0.038	0.085	0.147
	55–64	0.040	0.088	0.152
	65–74	0.049	0.109	0.188
	75+	0.081	0.180	0.310
Penile cancer	15–44	0.008	0.037	0.080
	45–54	0.015	0.072	0.159
	55–64	0.017	0.083	0.183
	65–74	0.027	0.130	0.286
	75+	0.038	0.181	0.398
Head & Neck cancer (Females)	15–44	0.052	0.075	0.094
	45–54	0.071	0.104	0.130
	55–64	0.080	0.116	0.145
	65–74	0.088	0.128	0.160
	75+	0.149	0.216	0.271
Head & Neck cancer (Males)	15–44	0.093	0.134	0.168
	45–54	0.107	0.155	0.194
	55–64	0.121	0.176	0.220
	65–74	0.141	0.204	0.255
	75+	0.176	0.255	0.319

2.2.6. Screening

Age-specific screening adherence was calculated from a report from the Central Institute for ambulatory health care in the Federal Republic of Germany [39]. Those values were used to inform the percent of females screened for cervical cancer in the model (Table 4). From the same source, we retrieved the percentage of females receiving a follow-up screening test after abnormal Pap smear diagnostics. The percentage of woman screened at least once every three years was found in a retrospective cohort study from Rückinger et al. [38].

Table 4. Cervical cancer screening rates.

Age group	Percentage of females screened in the past year (%)	Reference
0–19	0.00	[39]
20–24	54.62	
25–29	55.93	
30–34	53.90	
35–39	52.09	
40–44	50.29	
45–49	49.51	
50–54	48.80	
55–59	46.94	
60–64	43.76	
65–69	37.63	
70–74	27.50	
75–79	19.26	
>80	9.02	

2.3. Economic model inputs

Inputs of the economic model include the vaccination strategy, vaccine properties, costs, and utilities.

2.3.1. Vaccination strategy

The most recent report on the German Health Interview and Examination Survey for Children and Adolescents (KiGGS Wave 1) of the Robert Koch institute was used to inform the vaccination strategy section [19]. As the recommendation regarding HPV vaccination shifted recently, (from the age group 12–17 to 9–14, with catch-up vaccination until the age of 17) coverage rates in light of the new vaccination schedules are not yet available. Thus, we adapted the figures from the KiGGS Wave 1 to fit the new recommended age classes as shown in the Table 5.

A compliance rate of 90% was assumed for the second dose.

2.3.2. Vaccine properties

Clinical trial data provide values for the prophylactic efficacy of the vaccine [57–62]. The duration of protection was assumed to be lifelong in the base case, the relative effectiveness of the vaccine was assumed as zero if less than the full regimen of two doses is received, and no herd immunity was considered. Table 6 summarizes the vaccine efficacy parameters related to the protection against transient and persistent infections.

2.3.3. Costs

All costs collected from the literature were inflated to 2014€, using the German Consumer Price Index (CPI) [64]. A discount rate of 3% is considered for costs as per indication of the Institute for Quality and Efficiency in Health Care (IQWiG). All costs used in the model are listed in Table 7.

The cost of vaccination in Germany varies across federal states according to the availability of office supply. For the purpose of this analysis, a cost of 140€ for a dose was considered for the 4-valent vaccine [72]. This corresponds to a tenth of the price of a 10-dose pack (1400€). A cost of 146.5€ was used for the 9-valent vaccine corresponding to a tenth of the price of a 10-dose pack [73]. Vaccination administration costs also differ across federal states. An average administration cost of 9€ per dose was considered for both vaccines.

No publications reporting German-specific costs per episode of care of cervical cancer were identified. Siebert et al. reported 5-year treatment costs for cervical cancer stratified by stage [68]. Schobert et al. used these figures to inform cost per episode of care parameters; therefore, we applied the same assumption [30]. Cost of CIN 1, 2, 3, VaIN, and CIS were collected from two German studies [65,69].

Costs per episode of care for non-cervical cancers could not be found as literature on the economic burden of non-cervical

Table 5. Vaccination coverage rates.

Age group	Vaccination coverage rate (%)	Reference
9–10	16.3	[19]
11–12	37.7	
13–14	45.6	
15–17	55.6	

Table 6. Summary table on vaccine assumptions.

Vaccine assumptions	HPV 16	HPV 18	HPV 31, 33, 45, 52, and 58
Cervical cancer			
Vaccine efficacy for preventing cervical HPV16/18/31/33/45/52/58 infections:			
- Male*	0.411	0.621	0.411
- Female**	0.760	0.963	0.760
Degree of protection of the vaccine against cervical HPV16/18 infections becoming persistent	0.988	0.984	0.988
Degree of protection of the vaccine against HPV16/18-related CIN	0.979	1.000	0.979
Vaginal and vulvar cancers			
Vaccine efficacy for preventing vaginal/vulvar HPV16/18 infections:			
- Male*	0.411	0.621	
- Female**	0.760	0.963	
Degree of protection of the vaccine against vaginal/vulvar HPV16/18 infections becoming persistent	0.988	0.984	
Degree of protection of the vaccine against HPV16/18-related /VaIN/VIN	1.000	1.000	
Anal cancers***			
Vaccine efficacy for preventing anal infections			
- Male*	0.411	0.621	0.621
- Female**	0.760	0.963	0.963
Degree of protection of the vaccine against anal infections becoming persistent			
- Male*	0.787	0.960	0.960
- Female**	0.988	0.984	0.984
Degree of protection of the vaccine against HPV16/18-related AIN neoplasia	0.000	0.000	0.000
Penile and H&N cancers***			
Vaccine efficacy for preventing penile and H&N infections			
- Male*	0.411	0.621	
- Female**	0.760	0.963	
Degree of protection of the vaccine against penile and H&N infections becoming persistent			
- Male*	0.787	0.960	
- Female**	0.988	0.984	
Degree of protection of the vaccine against HPV16/18-related PIN and H&N neoplasia	0.000	0.000	

* Preventing male genital infections through male vaccination is assumed to prevent transmission of genital infections to females;

** Preventing female genital infections through vaccination is assumed to prevent transmission of genital infections to males;

***The efficacy against anal, Head and Neck, Penile, and RRP diseases is conferred through protection against infection only.

Source:

Females: Future II study group [63] and Joura [61] for disease endpoints, Internal data file (protocol 007 and 012 combined per protocol) and Elbasha and Dasbach [32] for transient and persistent infections.

Table 7. Costs and utilities.

	Costs (€)			Utilities		
HPV-related disease	Females	Males	References	Females	Males	References
CIN 1	363.30		[65]	0.822		[32,66,67]
CIN 2				0.822		
CIN 3, CIS	1619.50			0.822		
Cervical cancer, local disease	8812.70		[68]	0.822		
Cervical cancer, regional disease	18,331.70			0.732		
Cervical cancer, distant disease	20,092.30			0.542		
Cervical cancer, cancer survivor				0.822		
VaIN 2	1117.40		[69]	0.822		
VaIN 3, CIS				0.822		
Vaginal cancer, local disease	7667.00		[68,70]	0.822		
Vaginal cancer, regional disease	15,948.60			0.732		
Vaginal cancer, distant disease	17,480.30			0.542		
Vaginal cancer, cancer survivor				0.822		
Vulvar cancer, local disease	7667.00			0.822		
Vulvar cancer, regional disease	15,948.60			0.732		
Vulvar cancer, distant disease	17,480.30			0.542		
Vulvar cancer, cancer survivor				0.822		
Penile cancer, local disease		6168.90			0.751	
Penile cancer, regional disease		12.832.20			0.661	
Penile cancer, distant disease		14,064.60			0.471	
Penile cancer, cancer survivor					0.751	
Anal cancer, local disease	8988.90			0.645		
Anal cancer, regional disease	18,698.30			0.555		
Anal cancer, distant disease	20,494.20			0.365		
Anal cancer, cancer survivor				0.645		
Head & Neck cancer, local disease	10,575.20			0.756		
Head & Neck cancer, regional disease	21,998.00			0.666		
Head & Neck cancer, distant disease	24,110.80			0.476		
Head & Neck cancer, cancer survivor				0.756		
Genital warts	633.80		[71]	0.900		

cancers in Germany is scarce. In a cost-effectiveness study from Brisson et al. [70], the authors calculated the ratio between costs of each non-cervical cancer and cervical cancer using published literature. They applied these ratios to Canadian cervical cancer cost data to get estimates for vaginal, penile, and oropharyngeal cancers. We retrieved the ratios calculated in this publication and applied them to the German cervical cancer costs to estimate the costs of the remaining HPV-related cancers.

Unit costs of screening and diagnostic tests were retrieved from a cost-effectiveness model from Hillemans et al. [29].

2.3.4. Health-related quality of life

Hinz et al. used the EQ-5D questionnaire in a large cohort (N = 2022) between 16 and 93 years old, which informed the utilities for the general population [74]. No German-specific utilities for health states were found; hence, the health utility values for cancer patients were derived from several sources. In the absence of UK-specific stage-stratified data in the population with HPV-related diseases, a combination of best available UK and US data were used to calculate the required utilities. (Table 7)

2.3.5. Model calibration and validation

The ZfKD provided most of the calibration targets required to validate the inputs. Annual numbers of incident cases and deaths as well as incidence and mortality rates for all cancers were retrieved from this source [2]. The registry did not report data for H&N cancers; therefore, a cluster of sites was used as a proxy (HPV-related oral cancers, oropharynx cancers, and larynx cancers) [75]. Genital warts' values were retrieved from Klussmann et al. [75] and Kraut et al. [76]. The proportions of diseases attributable to HPV infection were collected from two publications [1,77]. Regarding the incidence of CIN, we chose to use incidence rates observed in the UK, as Germany does not have a systematic screening registry and the existing literature shows that the epidemiology of these lesions are similar across both countries [53,54]. These incidence rates were calculated using the most recent statistics for the Cervical Screening Programme and population figures in the UK [78,79].

The epidemiological model produces the incidence rates of the diseases related to the 4 HPV types included in the 4-valent vaccine and to the 9 types included in the 9-valent vaccine. As a consequence, the overall incidences collected in the literature were adjusted using the HPV-attribution reported by Hartwig et al., as shown in Table 8 [1].

In the calibration process, the model inputs were iteratively modified in order to get model outcomes closer to the validation targets. The targets with greatest impact on overall cost-effectiveness and the targets with best quality data were prioritized. Since the natural history parameters used in the model followed an extensive calibration process in the original US model, they were not modified. We focused on other parameters such as transmission rates. To fine-tune the results to match each target, local variables such as mortality rates and proportion of individuals of seeking treatment were adjusted.

2.4. Model analyses

With the set of inputs previously described, we estimated the total number of events, incidence, and mortality of HPV-

Table 8. HPV attribution rates.

	Females		Males		
	HVP4	HVP9	HVP4	HVP9	References
Cervical cancer	72.8%	89.0%	NA	NA	[1]
CIN 1	24.0%	48.5%	NA	NA	
CIN 2+	45.5%	82.3%	NA	NA	
Vaginal cancer	50.7%	60.6%	NA	NA	
Vulvar cancer	14.2%	16.2%	NA	NA	
Anal cancer	76.3%	78.7%	76.3%	78.7%	
Head & Neck cancers	17.8%	17.8%	18.5%	18.5%	
Penile cancer	NA	NA	34.4%	34.4%	
Genital warts	90.0%	90.0%	90.0%	90.0%	

related diseases (cervical cancer, CIN, anal cancer, and genital warts) as well as costs and QALYs per person over a time horizon of 100 years. Incremental ICERs were then calculated with the quotient: Incremental costs/Incremental QALYs.

In Germany, HPV vaccination is delivered through the statutory health insurance (SHI) plans, and purchase is done through several sickness funds. All analyses were performed from the SHI perspective.

A deterministic sensitivity analysis (DSA) was conducted in order to access the robustness of the results. The parameters modified in the DSA were: vaccine price, VCR, duration of protection, utilities, and discount rates, inclusion of cross protection and inclusion of H&N and penile indication. Sensitivity analyses were performed deterministically, modifying the value of one base case parameter at a time and recording the corresponding ICER.

Additional exploratory analyses were performed in order to evaluate the cost-effectiveness of the 9-valent vaccine against the 2-valent vaccine.

3. Results

3.1. Model calibration

The summary of the incidence targets collected from the literature and the model outcomes are summarized in Table 9. After calibration, the model shows a good fit on the estimated incidence of cervical, anal, and penile cancers, as well as genital warts. The main obstacle of the calibration relates to the incidence of CIN, which is significantly underestimated by our model.

Table 9. Overview of the calibration incidence targets.

	Incidence rates (per 100,000)			
	HPV 16,18, 6, 11 related		HPV-9 related (adding 31, 33, 45, 52, and 58)	
	Target	Calibration	Target	Calibration
Female				
Cervical cancer	7.21	7.14	8.81	8.82
CIN 1	72.61	30.20	146.74	39.23
CIN 2+	71.22	61.97	128.82	77.68
Vaginal	0.30	0.19	0.36	0.19
Vulvar	0.45	0.26	0.52	0.26
Anal	1.14	1.14	1.18	1.17
Genital warts	171.99	169.76	171.99	169.76
Male				
Penile cancer	0.45	0.44	0.45	0.44
Anal cancer	0.84	0.85	0.87	0.86
Genital warts	132.89	133.26	132.89	133.26

In addition, the incremental proportion of CIN cases attributable to the 5 additional genotypes included in the 9-valent vaccine is also underestimated. Hartwig et al. showed that the HPV6/11/16/18 are responsible for about 24% of CIN1 and 45% of CIN2 cases whereas HPV6/11/16/18/31/33/45/52/58 targeted by the 9-valent vaccine account for 48% and 82% of CIN 1 and CIN 2+, respectively [1]. This means that the 9-valent HPV infections were responsible for twice as much of CIN1 and 1.8 times more for CIN2+ compared to the 4-valent. Our calibrated model estimates that the 9-valent HPV accounts for 1.3 times more for CIN1 and 1.25 times more for CIN2+ the 4-valent HPV.

3.2. Epidemiological results

Figures 1 and 2 show the epidemiological impact of the different scenarios over a time horizon of 100 years. The curves show that the incidence and mortality rates of HPV-related diseases stabilize before the end of the analyzed time horizon (100 years).

These results show the added benefits of the 9-valent vaccine. Considering the scenarios with vaccination coverage only for girls, 9-valent vaccine is associated with a reduction of 31,500 additional cases and 7408 additional deaths of cervical cancer over 100 years. Furthermore, when compared to the current vaccination program, the new vaccine shows an additional reduction of 21% and 19% on CIN 1 and CIN 2+ incidence, respectively. This represents a reduction of 234,899 cases of CIN 1 and 399,410 cases of CIN 2+ over 100 years, as reported in Table 10.

Adopting a vaccination program with universal coverage is associated with further epidemiological benefits. This reflects the indirect benefits, through herd immunity effects, of vaccinating boys. Over 100 years, the universal coverage scenario is associated with a reduction of 14,954 cases of cervical cancer, 90,330 cases of CIN 1, and 171,603 cases of CIN 2+ when compared to a girl-only coverage with the same vaccine. When compared to the current vaccination program, universal coverage with the 9-valent vaccine can avoid up to 46,454 cases of cervical cancer, 325,229 cases of CIN 1, and 571,013 cases of CIN 2+, as shown in Table 11. The universal coverage also shows added benefit in the incidence of genital warts and anal cancer; the model estimates that anal cancer incidence can be reduced by 12% and 29% in females and males, respectively. In addition, we observe a reduction of 20% and 22% in the incidence of genital warts for males and females, respectively, when comparing 9-valent universal vaccination with the current practice. This corresponds to 1.5 million cases of genital warts and 8456 cases of anal cancer avoided over 100 years.

3.3. Cost-effectiveness results

The model estimates showed that switching for the 9-valent vaccine in Germany is highly cost-effective with an ICER of 329€/QALY (Table 12). The ICER increased to 22,987€/QALY when universal vaccination with the 9-valent vaccine was considered.

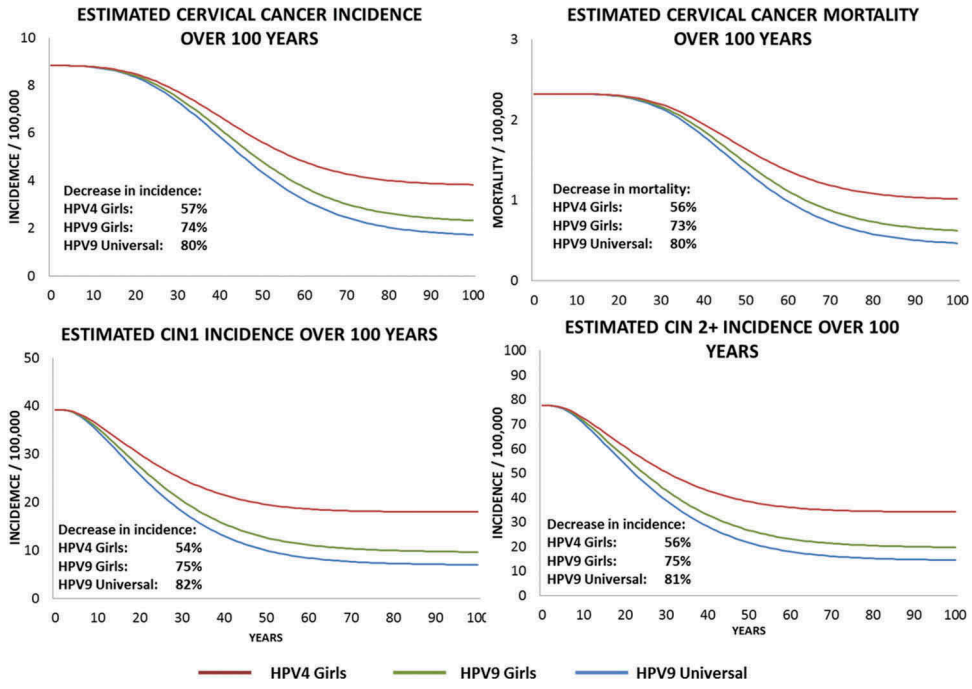

Figure 1. Epidemiological impact of three vaccination strategies on the incidence and mortality of cervical diseases.

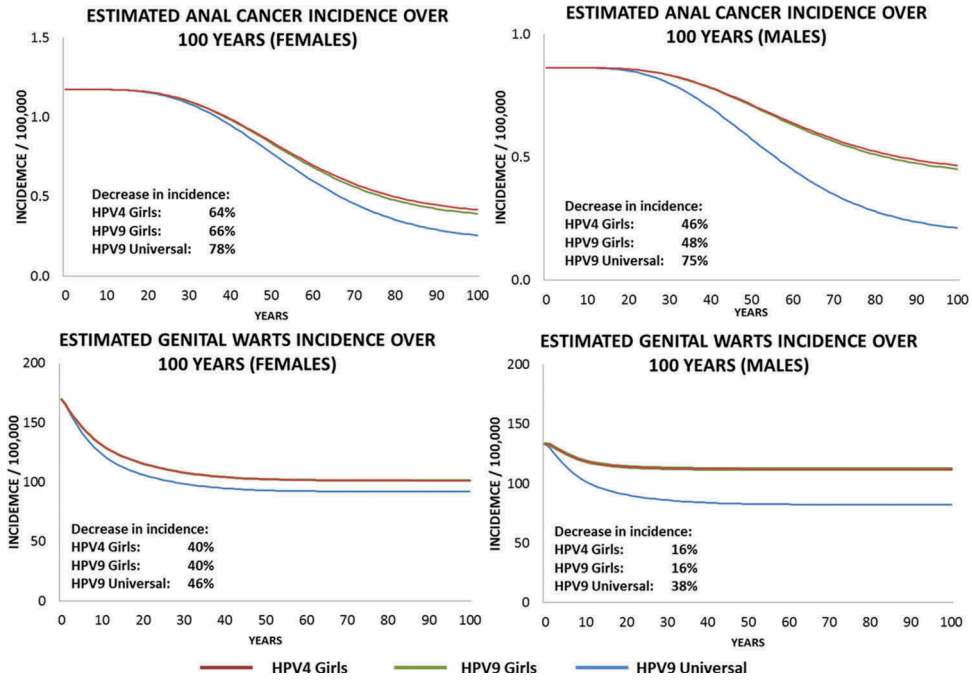

Figure 2. Epidemiological impact of three vaccination strategies on the incidence of genital warts and anal cancer.

Both strategies show an estimated ICER below the threshold commonly used by the National Institute for Health and Clinical excellence (NICE) in the UK (£30,000/QALY or 40,000 €/QALY).[1] We use this value as a reference since there is not a fixed threshold for the ICER in Germany.

When considering universal coverage with the 9-valent vaccine, there are considerable health benefits and cost savings in all diseases considered in the model. CIN and anal cancer are associated with the most significant cost savings and additional health benefits. In the instance of girls-only coverage, the benefits can only be seen in cervical diseases and anal cancer.

The effect of the new vaccine price on its cost-effectiveness is graphically represented in Figure 3. All threshold analyses were performed considering the base case price of the 4-valent vaccine (140€). The results show that changing the

Table 10. Disease events prevented with HPV9 girls in comparison with the current strategy (HPV4 girls).

		Years since start of vaccination program		
Disease event		25	50	100
Females				
	Cervical cancer	378	5210	31,500
	CIN 1	14,894	72,335	234,899
	CIN 2/3	23,364	119,048	399,410
	Anal cancer	2	47	438
Males				
	Anal cancer	1	22	240

Table 11. Disease events prevented with HPV9 universal in comparison with the current strategy (HPV4 girls).

		Years since start of vaccination program		
Disease event		25	50	100
Females				
	Cervical cancer	692	8546	46,454
	CIN 1	38,882	141,381	398,993
	CIN 2/3	40,312	183,373	571,013
	Vaginal cancer	2	45	315
	Vulvar cancer	3	65	429
	Genital warts	75,189	172,001	364,313
	Anal cancer	16	381	3036
Males				
	Genital warts	182,712	470,841	1,084,422
	Anal cancer	37	804	5420

vaccination strategy to the 9-valent vaccine when targeting girls only remains under the NICE cost-effectiveness threshold if incremental price of the new vaccine does not exceed 126€. The same strategy can be cost-saving if the price increment per dose of the new vaccine does not exceed 5€. As for universal vaccination the threshold analysis shows that this strategy can be cost-effective if the price increment per dose of the new vaccine does not exceed 60€.

3.4. Sensitivity analyses

The results of the DSA are summarized in the tornado diagrams represented in Figure 4. The ICER of the switch to a 9-valent HPV vaccine remained below the NICE cost-effectiveness threshold of 40,000€/QALY in all the sensitivity analyses.

Decreasing the duration of protection of the vaccines (assumed lifelong in the base case) to 20 years improves the ICER in both comparisons. For the scenarios with girl-only vaccination (HPV9 Girls vs. HPV4 Girls), the 9-valent vaccine becomes a cost-saving strategy while the same alteration causes a reduction in the ICER from 22,987€/QALY in the base case to 14,827€/QALY in the scenario with 9-valent universal vaccination. This alteration produces higher costs and lower QALYs per person for the three scenarios.

Assuming a lower discount rate for outcomes (1.5% in spite of 3% in the base case), causes an overall decrease of the ICER

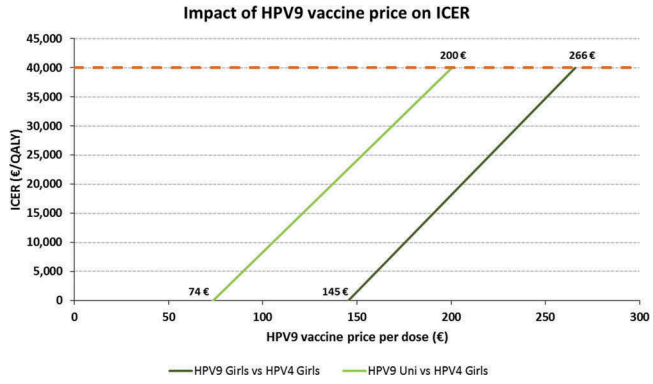

Figure 3. Price threshold analysis of HPV9 vaccination vs HPV4 girls vaccination with the 4-valent vaccine priced at €140.

for both comparisons. The lower discount rate translates in higher QALYs per person while the costs remain unchanged, thus resulting in a lower ICER. A lower discount rate for outcomes has greater impact on universal vaccination compared to the current practice, where the ICER drops to 8748€/QALY.

Boosting the VCR to 70% increases the ICER in both comparisons. HPV 9 girl-only vaccination vs. current practice increases to 707€/QALY whereas universal vaccination with the 9-valent vaccine vs. current practice increases to 27,986 €/QALY. The increment in the costs due to the additional number of vaccines administered is higher than the QALY benefits, regardless of the target population of the vaccine.

Using utilities from Elbasha and Dasbach [32] causes a small increase in the ICER for both comparisons. The utilities associated with the different health states are lower than the ones used in the base case. Therefore the QALYs per person are lower.

Including all diseases simulated by the model (base case only includes the diseases disclosed in the vaccine label), accounts for the costs and QALYs associated with H&N and penile cancers as well as RRP. The benefits of a universal program with the 9-valent vaccine are greatly enhanced if the analysis includes the additional diseases, as the ICER decreases to 14,286€/QALY. If the vaccination is targeted only to girls, the inclusion of the additional diseases has a negligible impact on the ICER.

3.5. Scenario analysis

The additional scenario analysis results show that the 9-valent vaccine is a dominant strategy against the 2-valent vaccine when only girls are covered in the vaccination program. Similarly to the base case, the ICER increases to 11,596 €/QALY for a universal vaccination program with the 9-valent

Table 12. Cost-effectiveness results in the base case analysis.

Scenarios	Strategies	Costs/person (€)	QALYs/person	Incremental costs (€)	Incremental QALYs	Cost per QALY gained (€/QALY)
Scenario 1	HPV9 Girls	336.41	28.36934	0.24	0.00073	328.77
	HPV4 Girls	336.17	28.36861	-	0.00157	-
Scenario 2	HPV9 Universal	372.26	28.37018	36.09	0.00073	22,987.26
	HPV4 Girls	336.17	28.36861	-	0.00157	-

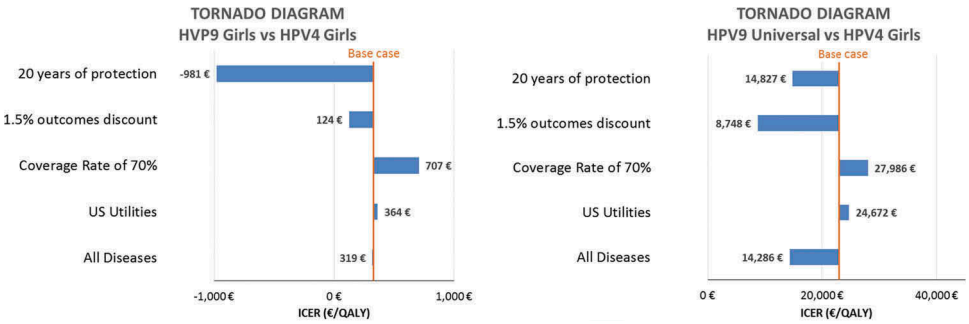

Figure 4. Tornado diagrams.

vaccine, compared to girls-only coverage with the 2-valent vaccine.

4. Discussion

We present the first cost-effectiveness analysis of the implementation of a vaccination program with the new 9-valent HPV vaccine extended to boys in Germany. All analyses were performed in a model originally designed for the US. The adaptation for the German context was achieved through an extensive data collection and calibration. After the calibration process, the model accurately estimated indicators such as incidence and mortality of HPV-related diseases in Germany. The impact on health outcomes and costs were estimated through various scenarios allowing testing of different vaccination strategies and assumptions.

The results from this analysis show that, in the current German setting, replacing the current 4-valent vaccine with the new 9-valent technology in the vaccination program is highly cost-effective with an ICER of 329€/QALY. The very low ICER (329€/QALY), along with the assumption that the coverage rate would remain the same (i.e. same number of vaccine doses administered) and the very similar price of both vaccines, suggests that the net budget impact of the switch to the 9-valent vaccine would be low. If the vaccination program is extended to boys (in the same age groups recommended for girls), the ICER remains cost-effective with a ratio equal to 22,987€/QALY. It is noteworthy the ICER reported in the base case considers the indicated diseases only. The inclusion of all diseases in the analysis decreases the ICER between universal vaccination with the 9-valent vaccine and the current practice to 14,286€/QALY.

These results are in line with the conclusions reported in three US studies presented during the ACIP (Advisory Committee on Immunization Practices) meeting. All studies estimated that a universal vaccination program with the 9-valent vaccine was likely to fall within an acceptable range of cost-effectiveness or even become cost saving compared to the current universal vaccination program with the 4-valent vaccine [24–26]. In Canada, the new vaccine was shown to be cost-effective for a price increment lower than +CAN$24 [27].

Our model predicts that replacing the current vaccine recommendation with the 9-valent vaccine could lead to further reductions of 17%, 21%, and 19% in the incidence of cervical cancer, CIN 1, and CIN 2+, respectively. Universal vaccination would allow to further reduce the incidence in 24% for cervical cancer, 21% for CIN 1, and 24% for CIN 2+. Several studies regarding the effects of the 9-valent vaccine report the same trend, although they do not concern the German population [24,25].

The effect of universal vaccination in Germany was discussed by Horn et al. [9]. Vaccination of girls-only was generally more effective than vaccination both genders. They estimated that 83,567 cases of cervical cancer were prevented assuming a VCR of 40% among girls, while vaccinating 20% of both boys and girls resulted in 75,152 cases avoided [9]. These results are consistent with our model, which predicts additional health benefits in the scenario where a higher coverage rate (70%) is assumed for girls-only, compared to the base case scenario with universal vaccination (cumulative VCR of 55.6% at the age of 17 years for each gender). However, increasing the vaccination coverage in girls may be very difficult to achieve since the majority of vaccines in Germany are administered by private physicians, rather than school delivery programs as it happens in other European countries. Furthermore, universal vaccination would provide additional benefits by protecting men exposed to male partners and unvaccinated females. On the other hand, a universal vaccination schedule against HPV would allow for a more efficient way to stop the virus transmission and ultimately achieve the virus eradication [23]. Lastly, universal vaccination may contribute to raise awareness to the prevention of HPV-related diseases. Overall, universal vaccination is justified by epidemiological, equity, and vaccination-efficiency factors. With this study we demonstrate that it is also economically viable.

Regarding screening strategies, the HPV-DNA test was not considered in the model as it was only recently recommended; the Pap smear test remains the current practice and data on the implementation of the HPV-DNA test are still scarce; moreover, the model does not allow for flexibility in the use of mixed screening strategies.

It must be noted that the base case estimates account only for the diseases mentioned in the vaccine SPC (Summary of Product Characteristics). As shown in the sensitivity analysis, the health and economic benefits of a universal vaccination program with the 9-valent vaccine are substantially increased if H&N and penile cancers are considered in the analysis. Besides, the results presented underestimate the additional benefits of 9-valent vaccination on

CIN. The estimates from the calibrated model show a significant underestimation on the incidence of both grades of CIN. Furthermore, due to lack of German-specific data, our model was calibrated toward CIN incidence rates observed in the UK. Since this country has an organized screening program and higher VCR, CIN incidence rates may be higher in Germany. In turn, our calibrated model underestimates the CIN attribution to the 5 additional types included in the 9-valent vaccine. In addition, we do not account for neonatal morbidity and mortality due to cervical lesions. It is widely accepted that women who undergo excisional treatments are at increased risk of preterm delivery and low birth weight [80,81]. A German study showed that HPV vaccination could be cost-effective considering only the decrease in neonatal morbidity and mortality due to the lower number of conisations [82]. Finally, the indirect costs related to productivity losses were not considered in this study. However, HPV-related cancers affect productivity. Lerner et al. showed that women with HPV-related cervical lesions had higher absence rates and productivity loss compared with healthy woman [83].

In conclusion, a 9-valent vaccination program can yield significant incremental public health benefits and was shown to be cost-effective when compared to the current 4-valent vaccination program. Inclusion of boys in the 9-valent vaccination program would constitute an efficient and cost-effective strategy to further reduce HPV-related cancers and diseases in the German population.

Key issues

- The 9-valent vaccine yields significant incremental public health benefits and is shown to be cost-effective when compared to the current 4-valent vaccination program.
- Inclusion of boys in the 9-valent vaccination program would constitute an efficient strategy to further reduce HPV-related cancers and diseases in both sexes in Germany.
- Some potential benefits are concealed by the underestimation on the CIN incidence and the attribution of HPV diseases related to the new genotypes included in the vaccine.
- All vaccination strategies evaluated remained within an acceptable range of cost-effectiveness and the sensitivity analyses show robustness of the results across various assumptions on the vaccine duration of protection and the VCR.
- Including all the HPV-related diseases without limiting to the ones indicated in the SPC, improves the cost-effectiveness of the 9-valent vaccine, especially when considering the universal vaccination strategy.
- This study accounts only for the direct medical costs. A wider societal perspective may yield additional advantages of the new vaccine, as HPV-related diseases are associated with long-term maternal consequences and productivity losses.

Note

1. Converted to Euros. Rate: 1.35869. Reference: http://www.xe.com/ date: 06/01/2016 17:00 UTC and rounded to 40,000.

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Appendix

Table A1. Natural history of disease-related parameters.

Probability of transmitting genital HPV infection					
Transmission	HPV 16	HPV 18	HPV 6	HPV 11	HPV 31, 33, 45, 52, or 58
To males	0.1109	0.1109	0.415*	0.415*	0.076
To females	0.1109	0.1109	0.415*	0.415*	0.076

Stage	Recurrence rate	Reference	Cancer progression		Reference
CIN 1	0.05	Assumption	Direction	Rate	
CIN 2	0.05	Assumption	Local -> regional	0.1	
CIN 3	0.05	Assumption	Regional -> distant	0.3	[44,45]

Parameters	HPV 16	HPV 18
Fraction of persistent cervical HPV infections (Elbasha [31])	0.25	0.075
Clearance rate of cervical HPV infections (Insinga [43])		
Male	0.3955	0.37755
Female	0.354	0.348
Fraction of people seroconvert following a cervical HPV infection (Ho [46] and Onda [47])		
Male	0.6	0.6
Female	0.6	0.6
Degree of protection against cervical HPV infections provided by natural immunity following seroconversion (Elbasha [31])		
Male	0.5	0.5
Female	0.8	0.8
Fraction of females transiently infected with HPV16 progress to CIN over the course of one year (Insinga [43])		
CIN 1	0.105	0.068
CIN 2	0.045	0.055
CIN 3	0.024	0.009
Probability of transmitting anal HPV infection (Calibration)		
To males	0.16	0.16
To females	0.173	0.173
Probability of transmitting penile HPV infection (Calibration)		
To males	0.123	0.123
To females	0.123	0.123
Probability of transmitting head and neck HPV infection (Calibration)		
To males	0.14118	0.13228
To females	0.14118	0.13228

*Adjusted during the calibration process.