QUANTIFYING THE BROADER ECONOMIC CONSEQUENCES OF QUADRIVALENT HPV IMMUNIZATION IN GERMANY USING A GOVERNMENT PERSPECTIVE QUANTITATIVE ANALYTIC FRAMEWORK

Nikolaos Kotsopoulos

Awarded poster, published as: Kotsopoulos N, Connolly M, Remy V, Assessing the Fiscal Consequences of Immunizing the Female and Male Population Against Human Papillomavirus (HPV) in Germany. Value in Health 16 (7): A363 November 2013

Submitted to the Journal of medical economics

Summary

HPV infections cause a substantial burden in females and males as it is associated with several genital cancers and a subset of head and neck cancers as well as with genital warts. The aim of this study was to estimate both the fiscal consequences associated with HPV immunization in males and females and to conduct a cost-benefit analysis of investing in universal immunization in Germany. Methodologies from generational accounting, human capital and health economics were combined to estimate the broader economic impact with emphasis on the lifetime tax revenues and transfers between the government and cohorts of 12-year-old immunized and non-immunized boys and girls. To estimate the economic benefits attributed to immunization-related changes in morbidity and mortality, direct and indirect tax rates were linked to differences in age- and gender-specific earnings. Over the lifetime of the combined male/female cohorts, the analysis demonstrated that immunization against HPV (with a coverage rate of 55%) could prevent 1,188 HPV-related cancer deaths. Based on costs of HPV immunization we demonstrate that investing €1 in universal HPV vaccination yields €1.2 in gross tax revenues for the German government for the combined cohort. Moreover, universal HPV immunization in Germany may result in positive incremental net tax (i.e tax revenue-transfers) for the German government. The vaccination of males and females with the quadrivalent HPV vaccine is likely to have positive effects on public finances and economic growth over subsequent generations.
Introduction
The acquisition of vaccines for national immunization programs are unique among health care purchases in that stakeholders often include Treasury and other federal ministries necessary for procurement decisions\(^1,\,2\). To inform stakeholders of the broader economic consequences of immunization, there is some potential value to interpret the broader benefits of vaccine investments in terms of future economic growth and fiscal benefits\(^3\).

It is increasingly recognized that diseases resulting in individuals withdrawing from the work force, working inefficiently (i.e. presenteeism), retiring or dying prematurely can impact economic conditions and influence governments’ finances\(^4\). The importance of investing in population health is seen as a key component that reinforces employment opportunities, and is an important consideration in light of ageing populations and shrinking number of working aged adults relative to retired persons required for maintaining economic living standards\(^5\). Recent studies have also highlighted the burden that ill-health in working aged populations can pose for governments\(^6\). Estimates from the United Kingdom suggest that ill-health in working age persons represents £29 billion in workless benefits and £28-36 billion annually in lost taxes, with health costs representing only 11% (£5-11 billion) of government costs. The magnitude of government costs suggests a cross-sectorial negative impact of disease extends beyond the health service; consequently investments in health care are likely to influence government finances.

The human papillomavirus (HPV), in particular subtypes 6, 11, 16 and 18, is responsible for a number of conditions in both males and female including genital warts (GW) and a subset of head and neck cancers as well as vaginal, vulvar, cervical and anal cancers in females and penile and anal cancers in males\(^7\). A broad range of short and long-term direct and indirect medical costs are attributed to HPV encompassing costs for treating genital warts, cervical cancer other HPV-related cancers in both males and females\(^8\)-\(^10\).

In Germany, since 2007, HPV vaccination has been recommended and funded for all girls aged 12 to 17 in combination to a yearly cervical cancer screening starting from age 20. Several cost-effectiveness analyses suggested that vaccinating girls against HPV is a cost-effective strategy both in Germany and elsewhere\(^8,\,11\). Preventing the long-term mortality and morbidity of HPV infections will result not only in public health benefits, but also it is expected to result in considerable economic benefits in terms of medical cost-savings, increased productivity, increased earnings and increased tax revenue for the governments. Consequently, investing in vaccination can be viewed as a public investment that stimulates economic growth and influences government finances\(^12\)-\(^15\).
To estimate the broader economic consequences of HPV vaccination in boys and girls we estimated how resulting changes in HPV related morbidity and mortality may influence government fiscal accounts based on the efficacy profile for the quadrivalent HPV vaccine under a fixed economic scenario (“ceteris paribus”).

**Methods and Data**

The aim of this study was to estimate both the broader economic consequences associated with HPV immunization in males and females in Germany and to conduct a cost-benefit analysis (CBA) of investing in immunization from a societal and a government’s or fiscal perspective. The emphasis was put on the immediate economic benefits that the government derives from decreased mortality and morbidity i.e tax revenue from the higher quantity of survival and reduced health care costs stemming from decreased morbidity.

**Epidemiological modelling**

A single-cohort prospective model was developed to simulate the lifetime of 12 year old boys and girls with and without immunization against HPV. Lifetime survival was projected based on the current life expectancy in Germany, age-specific incidence and age-specific mortality of HPV-related diseases. The cohort model projected the lifetime survival of equally-sized male and female birth cohorts with and without immunization against HPV. The following HPV-related diseases were analyzed: genital warts (GW); cervical intraepithelial Neoplasia (CIN) I, II and III; cervical cancer; anal cancer; head and neck cancer; vulvar cancer; vaginal cancer. To calculate the morbidity and mortality of the immunized male and female cohorts, age- and gender-specific incidence and mortality was adjusted for the efficacy of the quadrivalent vaccine against each of the scope HPV-related cancers and pre-cancer states. The age-specific incident cases of GW, CIN and HPV-related cancers were multiplied by the, per case, medical costs. The age and disease specific deaths were multiplied by the projected loss of earnings and tax revenue for the remaining statistical life. The above two were summed to estimate the burden of disease (BOD) with and without immunization for the society and the government (i.e societal BOD and fiscal BOD models). A mathematical illustration of the epidemiological calculations is presented in the technical appendix. The reduction of the BOD following immunization was deemed as the benefit of immunization.

**Economic modelling and appraisals**

An Excel model was developed to estimate the incremental benefits of immunization from different perspectives. Firstly, a societal CBA was conducted based on the societal Burden of Disease (BOD) difference for
the immunized and the non-immunized cohorts. The societal analysis took into account the foregone consumers surplus as a result of premature mortality. Foregone surplus refers to the productivity loss, in terms of lost earnings, for the remaining statistical life of individuals that die as a result of HPV infection. Thus, in the societal analysis in order to calculate the societal BOD, HPV-related deaths were multiplied by the present value of the remaining lifetime earnings lost due to premature deaths. Moreover, the societal analysis included the health care costs associated with HPV-related diseases. The societal BOD for the immunized and non-immunized cohort of males and females was quantified. The societal BOD included the HPV-related medical costs as a result of the disease and the productivity loss as a result of premature deaths. The incremental BOD between the immunized and non-immunized cohort of males and females was considered as the benefit of immunization which was subsequently compared with the cost of immunizations to establish the net benefit [i.e Benefits of vaccination – immunization investment] and benefit cost ratio.

Secondly a fiscal CBA was conducted following a “government perspective” or fiscal approach. The gross lifetime tax revenue loss, as a result of HPV-related deaths, of the immunized and non-immunized cohorts of males and females was projected. The projected lifetime tax revenue loss as a result of HPV-related deaths and the HPV-related health care costs were considered a measure of the fiscal BOD. The fiscal BOD was subsequently compared between the immunized and non-immunized cohorts. The reduction of the fiscal BOD was considered the benefit from investing in HPV immunization. The aforementioned benefit of immunization was then compared with the cost of immunization.

Thirdly, a government perspective analysis was conducted applying the “generational accounting” methodology to assess the net discounted tax of immunized and non-immunized cohorts. In the net discounted tax analysis, cohorts, the immunized cohorts were expected to have increased health costs compared to non-immunized cohorts at the beginning of life due to immunization costs; lower lifetime health care costs due to prevention of HPV-related medical and indirect costs; higher life years lived and productive life year lived, thus more tax revenue paid to government; higher transfer costs as more people will survive to receive pensions and other allowances. Because increasing survival can have both negative and positive fiscal effects for government (i.e government pays more pensions and allowances when survival of a population increases while receiving more tax) an appraisal based on the net tax, i.e based on lifetime gross tax minus the lifetime transfers from the government to the citizens was considered as relevant. The objective
of such an analysis is to calculate the incremental net discounted tax (Tax revenue minus government transfers). This analysis helps quantify the net effect or the net fiscal benefit for the government after taking into account the above opposing fiscal forces (i.e. impact on tax revenue and impact of government transfers as a result of the immunization’s effects).

The net discounted tax analysis uses a longitudinal timeframe that constructs the average life course for immunized and non-immunized cohorts. The model simulates how the cohorts influence fiscal accounts both in terms of lifetime taxes and government transfers received based on changes in morbidity and mortality attributed to HPV vaccination. The modified “generational accounting” framework applied here combines three modelling approaches to capture the influence of HPV vaccination on discounted net tax. Firstly, all health costs related to HPV and the HPV-related cancers were derived. Secondly, applying human capital economics, the future productivity of 12 year old immunized and non-immunized male and female cohorts was projected to determine how changes in HPV related morbidity and mortality affect lifetime earnings. Direct and indirect tax rates were then applied to earnings to determine the expected fiscal revenues in terms of gross tax. Lastly, applying the principles of “generational accounting” the average lifetime transfer costs and tax revenues attributed to changes in morbidity and mortality resulting from HPV immunization were estimated. To avoid double calculations of health care costs, non-HPV related health expenditure was not included. In addition, educational costs were not considered in this analysis since the level of mortality and morbidity during the first years of life for both immunized and non-immunized cohorts were considered as similar.

For the three modelling approaches, only those factors that have direct influence on government fiscal accounts were assessed. The mathematical details of the aforementioned economic appraisals are illustrated in the technical appendix.

This analysis produced results for the societal and fiscal CBA and the “government perspective” net discounted tax analysis. In the first two analyses, the metrics were quantified in terms of the difference between, and the ratio of the discounted benefits of vaccination minus the discounted costs of vaccination. In the societal and fiscal CBA the benefits of immunization were quantified as the reduction of the corresponding BOD and were compared with the costs of immunization. In the above CBAs, a positive benefit minus cost difference and a benefit: cost ratio greater than 1 signifies a positive economic effect for immunization. The net discounted tax analyses quantified the incremental cumulative discounted net tax for immunized versus non-immunized combined cohort of boys and girls. A positive
incremental net discounted tax signifies that the government has a positive return from immunization after taking into account the additional transfer costs associated with increased survival.

**Data inputs**
The cohort size (n=400,000) was set equal to the size used in previous economic analyses of HPV immunization in Germany\(^\text{10}\). Evidence from the literature was obtained in order to simulate the age- and gender-specific mortality associated with each of the HPV-related cancers. Age-specific incidences were obtained from the literature\(^\text{16-18}\). In the absence of age-specific mortality data for all HPV-related cancers, except for cervical cancer, age-specific mortality was modeled as a percentage of the annual incident cases dying. The percentage of annual incidence cases dying by disease was obtained from the IARC data for Germany\(^\text{17}\). A detailed illustration of the epidemiological inputs used in the model is described in the technical appendix.

Vaccine efficacy was obtained from the clinical trials of the quadrivalent HPV vaccine\(^\text{19}\). The efficacy of the vaccine was weighted for the mortality and morbidity attributable to the HPV serotypes included in the vaccine i.e HPV6/11/16/18. The cost for the three doses of the quadrivalent HPV vaccination was modeled at €453 (3 doses x €135.75 + €15.10 administration cost) with a coverage rate of 55% consistent with published economic analysis in Germany\(^\text{8}\). Cost per case estimates for GW, CIN and HPV-related cancers were also obtained from the literature\(^\text{8}\). Vaccine efficacy and cost data are illustrated in Table 1.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine efficacy</th>
<th>Proportion attributable to HPV 6/11/16/18</th>
<th>Model’s efficacy</th>
<th>Cost per case</th>
</tr>
</thead>
<tbody>
<tr>
<td>GW females 99%; 89% for males</td>
<td>90%</td>
<td>Females 89%; males 81%</td>
<td>€550</td>
<td></td>
</tr>
<tr>
<td>CIN I 98%</td>
<td>35%</td>
<td>34.3%</td>
<td>€336</td>
<td></td>
</tr>
<tr>
<td>CIN II 98%</td>
<td>55%</td>
<td>53.9%</td>
<td>€336</td>
<td></td>
</tr>
<tr>
<td>CIN III 97%</td>
<td>55%</td>
<td>53.3%</td>
<td>€1,498</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer 100%</td>
<td>76%</td>
<td>76%</td>
<td>€12,499</td>
<td></td>
</tr>
<tr>
<td>H&amp;N cancer 78-96% on persistent infection</td>
<td>19%</td>
<td>18.2%</td>
<td>Females €16,990; males €18,188</td>
<td></td>
</tr>
<tr>
<td>Anal cancer 87%</td>
<td>79%</td>
<td>68.7%</td>
<td>Females €25,097; males €29,473</td>
<td></td>
</tr>
<tr>
<td>Vulvar cancer 100%</td>
<td>37%</td>
<td>37%</td>
<td>€12,499</td>
<td></td>
</tr>
<tr>
<td>Vaginal cancer 100%</td>
<td>61%</td>
<td>61%</td>
<td>€12,499</td>
<td></td>
</tr>
</tbody>
</table>

**Sources:** Efficacy: \(^\text{19, 27, 28, 29, 30, 31, 32, 33, 7}\) Costs: \(^\text{8, 9}\)
To conduct the aforementioned economic analyses, labor market lifetime outcomes based on expected norms were obtained. Age-specific wages and age and gender specific unemployment rates for the German male and female population were quantified annually in the model based on published sources. In order to account for gender differences, an estimate of the gender wage gap in Germany (23%) was applied across all age-groups. Retirement age was set at 67 years of age. Consistent with the generational accounting methodology wages were adjusted for future labor productivity.

Similarly, age-specific transfers, tax burden and health care costs originated from the national statistics. In the absence of gender-specific data, the same figures were used for both males and females. An average tax burden rate of 55% was modeled to quantify direct income tax, indirect tax and social insurance contributions for the average German individual. Taxes included in the analyses encompassed the tax burden of the average German citizen. Governmental transfers included benefits, allowances and subsidies received by the average German citizen from the government.

Health costs were inflated at an annual historical average rate of 2.4%. To reflect changes in productivity the average annual increase of the labor unit cost equal to 0.6% was used. In the base-case analysis a 1.4% discount rate was used following the ten-year long-term bond rates. The latter was deemed as a reasonable assumption for the opportunity costs of money, since other public investments are very likely assessed under the same assumption.

**Results**

In the base-case analysis, over the lifetime of the male and female cohorts, the analysis demonstrated that immunization against HPV (with a coverage rate of 55%) may prevent 1,188 HPV-related cancer deaths in Germany. Of the preventable deaths 599 were cervical cancer deaths. Immunization prevented 1,584 cervical cancer cases, 1,036 head and neck cancer cases, 352 anal cancer cases, 228 vaginal cancer cases and 116 vulvar cancer cases. In addition, immunization resulted in 45,808 less cases of genital warts and 127,462 cases of CIN I-III for the lifetime of the cohort.

**Societal and Fiscal CBA**

For the combined population of females and males the results showed that HPV immunization resulted in reducing both the societal BOD in terms of the present value of lifetime earnings or productivity loss due to premature mortality and the fiscal BOD in terms of the present value of lifetime gross tax loss due to premature mortality. In addition, immunization resulted in the reduction of HPV-related medical costs (Table 2). When comparing the investment costs and the benefits of immunization from a societal
perspective, the CBA suggested that for every euro spent on immunization the society gets back €1.3 euros in terms of averted lifetime productivity loss and prevented HPV-related medical costs. The disaggregated results of the societal CBA suggested that female vaccination results in a positive rate of return for the society almost by two fold the investment costs, whereas for males the cost-offsets are sufficient to return 60% of the initial investment (Table 3). The results suggest that there are societal gains associated with vaccinating females which counterbalance the cost of immunizing males.

<table>
<thead>
<tr>
<th>Table 2 Estimated discounted lifetime societal, fiscal and medical cost burden for immunized and non-immunized cohorts of males and females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome/Type</strong></td>
</tr>
<tr>
<td>BOD-societal in terms of discounted lifetime productivity loss due to premature mortality</td>
</tr>
<tr>
<td>BOD-fiscal in terms of discounted lifetime gross tax</td>
</tr>
<tr>
<td>Discounted lifetime HPV-related medical costs</td>
</tr>
<tr>
<td>Immunization investment cost</td>
</tr>
</tbody>
</table>

In the fiscal CBA it was estimated that for every €1 invested in immunization the government would gain €1.2 in terms of averted tax revenue loss and prevented HPV-related medical costs. Female immunization yielded as expected higher returns compared to male immunization. Thus, for every €1 spent on immunization of male the government would get back almost half of the investment cost whereas, for females the government would have a gain of €1.8 euros per euro spent on immunization. The combined immunization of males and females resulted in a benefit cost ratio of 1.2.

Figure 1 provides a time series for the incremental net discounted tax (tax minus transfers) between immunized and non-immunized cohorts, respectively. Combined female and male immunization resulted in higher net discounted tax compared to the strategy of not immunizing the combined population. The results of the combined net discounted tax analysis suggest that even after deducting transfers, the German government has a fiscal benefit from immunizing the female and male population.
One-way sensitivity analysis

The model performed a Min-Max (±20%) sensitivity analysis to all the parameters modeled. We hereby present the tornado diagrams (Figure 2) for the ten most sensitive parameters, for the gross tax based CBA (benefit: cost ratio, B/C ratio). The results of the sensitivity analysis suggested that a number of economic variables were associated with high sensitivity however; the B/C ratios consistently remained above 1 except in one scenario. One noteworthy finding was the influence of the incidence of GW which highlights the economic importance of this outcome. The reason for the high sensitivity may related to the high incidence of GW as well as the accumulation of most GW cases in early years of life.

The sensitivity analysis results showed that a variation of +/- 20% in the vaccine cost (vaccine price plus administration cost) both resulted in positive fiscal B/C ratio (>1). Moreover, if two doses of vaccine were administered the benefit/cost ratio would considerably increase to 1.8. An additional scenario included the indirect costs of HPV related diseases in terms of sick days lost. As expected the results are more favorable for the vaccination compared to the basic scenario. Finally, the scenario which assumed no vaccine efficacy against head and neck cancer resulted in a marginally positive B/C ratio. The latter influence of the results can be explained from the reduction of male mortality and the relatively higher lifetime earnings of males.

Discussion

Decision-making regarding funding of vaccines is a complex process involving numerous government stakeholders and health service officers. In some countries Ministers of Finance are considered central to the decision-making process due to their control over finances\(^2\). Even when vaccines have been approved by national advisory groups it is acknowledged that funding must be independently sought from finance ministries\(^3\). Underpinning the importance of finance in the decision-making process some have advocated that finance ministries should be involved earlier in the consultation process to ensure more rapid uptake of vaccines\(^4\). To this end it is important to provide financiers with important economic metrics which they are familiar with to demonstrate the relationship between immunization, health and growth. This includes fiscal modelling and generational accounting models which serve as the basis of the research methodology described here.

In 2009 the World Health Organization\(^4\) developed the WHO Guide to Identify the Economic Consequences of Disease and Injury in which the impact of poor health on government fiscal accounts was recognized. Providing data on the fiscal consequences of immunization informs stakeholders of the broader benefits of immunization that is not addressed by conventional cost-
effectiveness analysis; namely in defining how government and society in general will benefit from investing in vaccines. In recent years, preventative health care budgets vital for funding immunization programs have been decreasing which suggests a need to highlight to stakeholders the economic and health importance of prevention. When positioned within the broader consequences of ageing populations, the benefits of preventative health care for influencing working-aged populations is likely to gain increasing attention. Ironically funding decisions in health care are seldom made based on economic growth where cost-effectiveness is the dominant tool for determining allocation decisions. Considering the budgeting challenges posed by increasing demands of ageing populations, increasing health expenditure, and austerity measures introduced due to current economic conditions, the need to demonstrate the benefits of preventative health interventions as found with vaccination is imperative.

To achieve operational efficiency cost-effectiveness is often employed to ensure efficient use of health care resources. This can be important for informing the choice between effective interventions; however cost-effectiveness usually focuses on a health care payer perspective and does not inform stakeholders of the broader consequences of investments in health care. The distinction in the analysis described here is that we consider tax financed health systems to be within the government sphere, hence these can be considered as government transfers. Considering the broader economic consequences of vaccine preventable conditions suggests that changing population health through immunization can offer economic advantages for government in the form of future tax revenues and potential savings attributed to social care. In this respect health acts like unemployment on governments causing a fiscal drain in relation to lost taxes and spending on unemployment benefits. When taking into consideration the fact that many health technology appraisal agencies do not consider indirect costs, and the resulting effects on productivity, poses additional challenges for vaccine technologies which prevent morbid events and early mortality over many generations.

The broader societal perspective CBA suggests that surplus societal benefits (in terms of additional earnings) are achieved by vaccinating boys and girls against HPV. The fiscal CBA that took into account only the gross tax shows that that investing €1 in universal HPV vaccination yields €1.2 in gross taxes for the German government. As expected, individually the CBA ratio is greater for girls at 1.8 compared to 0.5 for boys (Table 3). The government perspective analysis described here estimates both positive and negative consequences linked to changes in morbidity and mortality of HPV-related diseases on fiscal budgets in Germany. The analysis described here applies a long-term horizon to estimate fiscal consequences associated with HPV vaccination and suggests that in the long-term the vaccination of boys and girls offers positive fiscal benefits.
Table 3  CBA of male, female and combined cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Discounted benefits minus Investment Costs</th>
<th>Discounted benefits: Investment Costs ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Societal CBA</td>
<td>Male cohort  € (43,264,436)</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Female cohort  € 95,983,847</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Total cohort   € 52,719,411</td>
<td>1.3</td>
</tr>
<tr>
<td>Fiscal CBA</td>
<td>Male cohort  € (50,245,290)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Female cohort  € 81,712,141</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Total cohort   € 31,466,852</td>
<td>1.2</td>
</tr>
</tbody>
</table>

There are many inherent weaknesses in making long-term projections based on current macroeconomic parameters due to uncertainty regarding the future. In this respect the results described here should not be seen as a precise forecast of the future. Rather, the fiscal analysis reflect a potential scenario based on current economic and epidemiological conditions, and that future changes in unemployment, growth rates, tax burden, government transfers or inflation could either positively or negatively influence the conclusions described here. This is particularly important to consider in relation to the static incidence rates applied in our analysis and failure to account for herd immunity which could influence incidence rates and the likely benefits attributed to vaccination. Consistent with the generational accounting framework on which our analysis is based we have held parameters constant over time. We acknowledge this weakness but in the absence of knowledge of the future, the approach is useful for making policy decisions today, and in this respect is no different than any other funding or policy decisions made by governments.

The framework described here estimates how saving lives and influencing HPV infections in boys and girls can have fiscal benefits for government. This raises questions about how to apply a fiscal accounting framework in health care decision-making when health care resources are often influenced by unmet need, burden of illness, affordability, equity and sometimes politics. Therefore, it is reasonable to ask how this framework should be applied in decision-making, in particularly considering the differences in the benefit: cost ratios observed between boys and girls. While it is tempting to invest in only those strategies that yield benefits for government, it is questionable whether it is justifiable to exclude treatment from some groups on the basis of having a low fiscal return for government. Clearly this is not the case as resources are allocated for many interventions in terminal conditions that generate no fiscal benefits for government. On this basis we do not expect decision-makers to abandon the core principles of decision-making which include unmet need, equity and fairness. However, this approach can be supplementary to existing analytic frameworks used by decision-makers to consider a broader range of benefits from the perspective of government. This
can be particularly important for tax financed pay as you go health systems that rely on younger, healthy generations to continue paying for the health care needs of older generations.

**Figure 1** Cumulative incremental net discounted tax of the combined cohort over time

![Cumulative incremental net discounted tax of the combined cohort over time](image)

**Figure 2** One way sensitivity analyses for the fiscal B/C ratio

![One way sensitivity analyses for the fiscal B/C ratio](image)
**Technical appendix**

**Epidemiological calculations: Mortality**
Equations 1 and 2 illustrate the mortality calculations included in the model for Cervical Cancer. For all other cancers, mortality was linked to the incidence as indicatively shown for head and neck cancer in equations 3.

\[
DCC_t = S_t \times mCC_t \quad (1)
\]

\[
DCC_{\text{lifetime}} = \sum_{13}^{100} S_t \times mCC_t \quad (2)
\]

\[
DDHN_{\text{lifetime}} = \sum_{13}^{100} S_t \times pt \times HN_t \times IncHN_t \quad (3)
\]

Where \( S_t \): number of survivors at the beginning of year (t); \( mCC_t \): mortality attributed to cervical cancer in year t; \( DCC_{\text{lifetime}} \): deaths attributable to cervical cancer for the lifetime of the cohort; \( pt \): proportion of incident cases dying in year t; \( DDHN_{\text{lifetime}} \): Deaths attributable to head and neck cancer for the lifetime of the cohort; \( IncHN_t \): Incidence of head and neck cancer in year (t).

For the non-immunized cohorts the age – and gender – specific mortality at each year was multiplied with the number of survivors at the beginning of each year (t). The resulting deaths at each year were summed to produce the total HPV attributable mortality.

**Epidemiological calculations: Morbidity**
Equation 4 illustrates the incidence calculation for cervical cancer for the immunized cohorts. Similar calculations were conducted for each of the scope HPV-related diseases. Thus, following immunization against HPV with the quadrivalent HPV vaccine:

\[
CC_{\text{lifetime}} = \sum_{13}^{100} S_t \times IncCC_t \times \left(1 - effCC\right) \times Cov \quad (4)
\]

Where \( effCC\): Efficacy of the quadrivalent HPV vaccine against cervical cancer incidence, adjusted for the proportion of cervical cancers attributed to the vaccine HPV serotypes; \( Cov \): Vaccination coverage.
Economic appraisals
The fiscal CBA was conducted as illustrated in equation 5 and equation 6. Furthermore, a cost: benefit ratio was calculated as a proxy measure of return on investment.

\[
BOD_{\text{fiscal}} = \sum_{t}^{\infty} \frac{\text{expected annual gross tax}}{(1+r)^t} + \sum_{t}^{\infty} \frac{\text{annual direct costs+ indirect costs to the government}}{(1+r)^t}
\]  (5)

Net Benefit fiscal = (\text{BOD}_{\text{non-immunized}} - \text{BOD}_{\text{immunized}}) - \text{Immunization cost}  \hspace{1cm} (6)

The societal analysis was conducted following a similar approach however, instead of the expected annual gross tax, the expected annual earnings was factored into the calculations.

The generational accounting assessment of net discounted tax was assesses using equations 7-9.

\[
NPV_{\text{lifetime}} = \sum_{t}^{\infty} \frac{\text{Tax}_t - \text{Cost}_t}{(1+r)^t}
\]  (7)

Where in year t:

\[
\text{Tax}_t = \text{Direct tax}_t + \text{Indirect tax}_t + \text{National insurance}_t
\]  \hspace{1cm} (8)

\[
\text{Cost}_t = \text{Health}_t + \text{Transfers}_t + \text{Pension}_t
\]  \hspace{1cm} (9)

References
19. SPMSD. SmPC Gardasil 2009.


