Anti–HPV vaccination: A review of recent economic data for Italy

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Abstract

The total cost of HPV-related diseases accounts for €200–250 million of which €210 million is absorbed by the prevention and treatment of precancerous lesions and cervical cancer. Although both available HPV vaccines are below the threshold value for economic convenience (€9,569 and €26,361 per QALY-gained for the quadrivalent and bivalent vaccines, respectively), at this point in time long-term economic models developed for Italy seem to indicate the quadrivalent vaccine as the most cost-effective option.

Recent publications by official bodies, including the World Health Organization and the Supervisory Authority for Public Contracts in Italy, recommend that the decision-making process be based on both the quality of goods and services as well as the best achievable price.

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Keywords:
HPV vaccine
Cost-effectiveness analysis
Economic evaluation
Italy

1. Introduction

During the past few years new vaccines have been made available, and others shall be introduced in the near future. Therefore, it is necessary to define a process for the identification of priorities in this area of prevention. This is a very complex technical-scientific process. The current system is characterized by limited resources, and in order to maximize the net benefit in terms of public health, it is essential to allocate resources in the best possible way considering the various available options, while respecting the principles of equity and solidarity [1]. The decisional process should take place through a comparative evaluation of different vaccination strategies, taking into account both structural resources and economic sustainability.

Economic theory provides us with specific methods for economic evaluation such as cost-effectiveness analysis and bound optimization models. Through the use of such techniques it is possible to identify the best choice among several alternatives, and also how the entire system sustains the related financial burden.

As far as the level of expenditure for human prevention is concerned, Italy substantially differentiates itself from the main industrialized countries as it is one of the countries that invests the least in this area. Although prevention is increasingly considered as one of the cornerstones for healthcare outcomes, many other OECD countries do not allocate significant funds for health prevention (Fig. 1) [2].

With regard to vaccines, it is important to mention the latest National Vaccine Plan (Piano Nazionale Vaccini – PNV) from the Italian Ministry of Health to comprehend how this fundamental prevention tool is perceived from an economic point of view: «… although the overall expenditure for the implementation of vaccine prevention campaigns is a very limited part of healthcare expenditure (approx. 1% of 1000), in LHAs with a budget of hundreds of millions of Euro the lack of resources to purchase vaccines is frequently complained about, while there is absolutely no problem in purchasing the latest high technology equipment.».

As also defined in the PNV, once vaccination strategies have been selected, it is then decided which vaccinations should be included in the Levels of Essential Assistance (Livelli Essenziali di Assistenza – LEA), based on the available economic and organizational resources.

The constant growth of healthcare demand requires that the decision-making process be based on the comparison of alternative...
options, because the economic context is characterized by limited resources.

Although it is still particularly complex to measure the actual expenditure for the early diagnosis and treatment of diseases induced by the Human Papillomavirus (HPV), current data are sufficiently reliable. It has been estimated that in Italy the total annual cost for HPV-related diseases is between €200 and €250 million [3,4] of which €210 million [5] is absorbed by the prevention and treatment of precancerous cervical lesions and cervical cancer. The implementation of vaccination programmes should make it possible to considerably reduce the costs generated by cervical cancer and HPV-related diseases.

Findings from recent economic evaluations are certainly encouraging with evident cost-reductions associated with the most appropriate vaccination strategies. This review focused on economic assessments of HPV vaccination strategies developed for Italy. Such economic evaluations are crucial to allow policy-makers to make appropriate decisions considering the current healthcare budget constraints.

Finally, based on the indications of the World Health Organization (WHO) [6] and the main regulatory agencies of EU countries [7,8], there is an increasing need in Italy to base the decision-making process in healthcare not exclusively on price, but through a quality-price ratio instead. This approach should allow a more efficient delivery of healthcare interventions.

2. Methods

A systematic literature review using Medline and Embase (from January 2006 to June 2008) was conducted to search for studies containing the following keywords “HPV vaccination”; “cost-effectiveness analysis”; “Italy”; and “economic evaluation”. We selected studies that were original research articles published in Italian or in English. To ensure that all relevant studies were found, web sites supported by either Italian scientific societies (such as the Italian Society of Hygiene, and the Italian Society of Health Technology Assessment) or sites dedicated to the rapid worldwide dissemination of social science research such as the Social Science Research Network (SSRN) were also regularly consulted. Peer-reviewed journals, conferences, congresses, and Internet resources were monitored up to July 2008 for presentations of additional data or publications related to studies included in the review. Since only a few Italian papers have been published, the economic evaluation performed by the Canadian Agency for Drugs and Technologies in Health [9] was considered based on two selection criteria: the Canadian Agency used the same methodology in the evaluation of both vaccines and more significantly Canada and Italy have very similar National Health Services (NHS) at an organizational level. Other economic evaluations that did not match these inclusion criteria were not taken into account. Economic models considered in this review are shown in Appendix A.

3. Economic impact and cost-effectiveness analysis (CEA)

In a study recently carried out in Italy, the cost-effectiveness of an anti-HPV vaccination programme with the quadrivalent vaccine for a cohort of 12-year-old girls has been assessed considering the current cervical cancer screening programme [10].

<table>
<thead>
<tr>
<th>CC\ number of cases</th>
<th>Deaths from CC</th>
<th>CIN(^a) 1</th>
<th>CIN 2</th>
<th>CIN 3</th>
<th>Genital warts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual cases</td>
<td>2,262</td>
<td>809</td>
<td>21,888</td>
<td>9,582</td>
<td>10,976</td>
</tr>
<tr>
<td>Estimated cases (vaccination and screening)</td>
<td>830</td>
<td>296</td>
<td>17,633</td>
<td>5,150</td>
<td>5,771</td>
</tr>
<tr>
<td>Avoided events</td>
<td>1,432</td>
<td>513</td>
<td>4,255</td>
<td>4,432</td>
<td>5,205</td>
</tr>
</tbody>
</table>

\(^a\) CC – cervical cancer.

\(^b\) CIN – cervical intraepithelial neoplasia.
Italian epidemiological data were entered in this Markov model simulating the natural history of HPV infection and cervical cancer as well as estimating the expenses induced by HPV-related diseases. A comparative analysis was performed in relation to the present screening and management of HPV-related diseases (Table 1).

The implementation of a quadrivalent HPV vaccination with an 80% coverage rate would avert, in the same birth cohort followed until death, 1432 cervical cancer cases (−63.3%), 513 deaths from cervical cancer (−83.4%), 5205 diagnosed CIN 3 (−47.4%), 4432 diagnosed CIN 2 (−46.3%), 4225 diagnosed CIN 1 (−19.4%), 19,801 abnormal pap smears (−13.4%) and 14,810 cases of genital warts (−70.6%). The vaccination programme with the quadrivalent HPV vaccine alongside current cervical cancer screening in Italy would produce an incremental cost-effectiveness ratio (ICER) of €9569 per quality-adjusted life year (QALY) gained [10].

In another assessment carried out in Italy to estimate the efficiency of an anti-HPV vaccination plan with the bivalent vaccine, a value per QALY gained of €26,361 was obtained [11], confirming that vaccination is significantly below the threshold value (€30,000–45,000) used to estimate the economic gain of a health-care intervention [12,13].

An analysis recently carried out by the Canadian Agency for Drugs and Technologies in Health, evaluated the medium and long-term effects of anti-HPV vaccination programmes and compared the cost-effectiveness of the bivalent and quadrivalent vaccines [9]. As the perspective of the National Health Service (NHS) was considered, only direct costs (in 2005 Canadian dollars – CANS) were included. For the quadrivalent and bivalent vaccines a cost per QALY-gained of 20,512 CANS (€14,224) and 31,060 CANS (€21,539) was estimated respectively [9]. The results of this economic assessment are reported in Table 2.

The differences between the bivalent and quadrivalent vaccines resulted mainly from the prevention of genital warts and low-grade cervical lesions. Using a threshold of CANS40,000 (€27,740) per QALY-gained as strong evidence for cost-effectiveness, HPV vaccination was estimated to be cost-effective under a wide range of assumptions and vaccination scenarios [14] (Fig. 2).

Even more encouraging results in terms of cost-effectiveness were reported in a recent study [4] showing how a multi-cohort vaccination strategy (3 cohorts: 12, 18 and 25-years-old) should make it possible to cover a wide portion of the female population in 6–7 years. Subsequently the reduction of costs associated with the treatment of high and low-grade cervical lesions, of invasive cervical cancer and genital warts should progressively compensate for the cost of the vaccination programme. At the end of the period separating the three cohorts, vaccination would be restricted to a single cohort (12-years-old), resulting in a reduction of expenses for the Italian NHS [4]. Furthermore, this study also confirmed the economic advantages originating from the combination of the quadrivalent vaccine in combination with current screening which was associated with an incremental reduction in the incidence of cervical cancer (Fig. 3).

Despite the specific value of HPV vaccination it is essential that vaccinated women continue with the recommended screening programme. Otherwise, the effectiveness and cost-effectiveness of the entire intervention may be seriously compromised [15].

3.1. Low-grade cervical lesions and genital warts

Favato et al. developed a partially dynamic computer-based model reproducing the possibility of progressing or regressing from one disease state to another [4]. The resulting Markov model was based on a set of defined transition probabilities, which were a function of Italian population demographics and time-dependent characteristics of HPV infection [4]. Subsequently, by entering the results reported in several clinical studies [16–20] into this model, it was possible to estimate the effect of the quadrivalent vaccine in terms of low-grade cervical lesions and genital warts avoided, as well as the related potential expenditure reduction in Italy [3]. As outcomes, the expected reductions of abnormal pap smears, colposcopies, low-grade cervical lesions, ASCUS (atypical squamous cells of undetermined significance) and genital warts were taken into consideration.5

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5 CIN – Cervical Intraepithelial Neoplasia.
6 The threshold value considered in the UK is £20,000–30,000 [12,13] which corresponds to approximately €29,513–44,270 (€1 = £0.677663 according to the official exchange rate published by BankItalia in 2007). The threshold value per QALY gained is a common method used in evaluating the cost-effectiveness of health interventions. An intervention with an ICER that falls below the threshold value might be deemed cost-effective by decision-makers as good value for money.
7 The threshold value used in Canada as strong evidence of cost-effectiveness is 40,000 CAD$ per QALY gained. This corresponds to €27,740 (€1 = 1.44203 Canadian Dollars, according to the official exchange rate published by BankItalia in 2007). This value does not differ significantly from the lower value of the range considered in the UK.
8 A detailed description of the UK model developed by Favato et al. has been reported in Appendix B.
9 The higher estimated number of cases was evaluated.
Table 3
Annual expenditure decrease obtainable as a consequence of maximum theoretical reduction of low-grade lesions [3].

<table>
<thead>
<tr>
<th>Process</th>
<th>Events induced by HPV 6–11</th>
<th>Avoided events for HPV 6–11</th>
<th>Expenditure reduction (€ × 10^6)</th>
<th>Events induced by HPV 16–18</th>
<th>Avoided events for HPV 16–18</th>
<th>Expenditure reduction (€ × 10^6)</th>
<th>Expenditure reduction (€ × 10^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal pap smears</td>
<td>83,000</td>
<td>47,643</td>
<td>0.71</td>
<td>332,000</td>
<td>190,573</td>
<td>2.86</td>
<td>3.57</td>
</tr>
<tr>
<td>Colposcopies</td>
<td>17,400</td>
<td>10,433</td>
<td>2.6</td>
<td>98,600</td>
<td>59,121</td>
<td>14.8</td>
<td>17.4</td>
</tr>
<tr>
<td>LSIL(^a) and ASCUS(^b)</td>
<td>13,923</td>
<td>8,354</td>
<td>3.3</td>
<td>77,077</td>
<td>46,246</td>
<td>18.5</td>
<td>21.8</td>
</tr>
<tr>
<td>Total</td>
<td>114,323</td>
<td>66,430</td>
<td>6.6</td>
<td>507,677</td>
<td>295,940</td>
<td>36.2</td>
<td>42.8</td>
</tr>
<tr>
<td>Genital warts</td>
<td>125,000</td>
<td>112,500</td>
<td>27.0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>239,323</td>
<td>178,930</td>
<td>33.61</td>
<td>507,677</td>
<td>295,940</td>
<td>36.2</td>
<td>69.8</td>
</tr>
</tbody>
</table>

The reduction of expenses for low-grade lesions and genital warts of 16 million Euro is calculated as follows: € 6.6 million + (€ 27 million × 0.35) = € 16.05 million.

\(^a\) LSIL – low-grade squamous intraepithelial lesions.
\(^b\) ASCUS – atypical squamous cells of undetermined significance.

Low-grade lesions related to HPV-6 and -11 accounted for 18.4 ± 0.2% (range: 18.2–18.6%) of the total number of lesions averted (LSIL, ASCUS and genital warts) induced by HPV-6, -11, -16 and -18 (Table 3). When genital warts were included, the contribution of HPV-6 and -11 was even more relevant. In this case, the reduction increased to 43.2 ± 6.5% (range: 34.8–53.1%) of total low-grade lesions and genital warts avoided.

As a result of the reduction of abnormal pap smears, colposcopies, low-grade precancerous cervical lesions and ASCUS depending on HPV 6–11, it is possible to generate expenditure reductions of € 6.6 million. If 35%\(^{10}\) of the total direct costs for treating genital warts is added to this reduction, the quadrivalent vaccine determines a decrease in expenses of more than € 16 million for the Italian NHS (Table 3). The total potential cost-reduction for HPV-6 and -11 related low-grade cervical lesions and genital warts reached almost € 34 million.

Finally, by establishing a correlation between the total cost-reduction (approx. € 70 million) and the expenditure currently borne for the management of low-grade cervical lesions and genital warts (approx. € 102 million) [3], the quadrivalent vaccine should determine a net cost-reduction of 68.6%. This is a considerable economic reserve that could be channelled toward other public health priorities.

The UK model not only assessed the efficiency of a multi-cohort vaccination strategy, but also gave the opportunity to identify clinical and economic indicators (e.g. breakeven point and economic advantage of vaccination) through which it was possible to calculate the level of investment compatible with the available resources. It was also possible to estimate the reduction of low-grade lesions over time (Fig. 4). The multi-cohort vaccination strategy appeared as one of the most cost-effective options in healthcare policy.

\(^{10}\) The reported percentage is conservative. In fact, it is possible that up to 70% of costs related to the treatment of genital warts is borne by the Italian NHS [21].
Table 4
Outcomes avoided with the quadrivalent vaccine and related reductions in expenditure [3].

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Outcomes without vaccination</th>
<th>Outcomes avoided with quadrivalent vaccine</th>
<th>Expenditure reduction (€ × 10^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal pap smears</td>
<td>415,000</td>
<td>258,337</td>
<td>3.8</td>
</tr>
<tr>
<td>Colposcopies</td>
<td>116,000</td>
<td>76,909</td>
<td>19.2</td>
</tr>
<tr>
<td>LSIL&lt;sup&gt;a&lt;/sup&gt; and ASCUS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>91,000</td>
<td>56,648</td>
<td>22.7</td>
</tr>
<tr>
<td>HSIL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13,700</td>
<td>9,097</td>
<td>8.2</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>4,000</td>
<td>2,988</td>
<td>49.9</td>
</tr>
<tr>
<td>Genital warts</td>
<td>125,000</td>
<td>115,625</td>
<td>27.8</td>
</tr>
<tr>
<td>Total</td>
<td>764,700</td>
<td>519,604</td>
<td>131.6</td>
</tr>
</tbody>
</table>

In the analysis the following outcomes were evaluated: abnormal pap smears, colposcopies and follow-up to colposcopies, low and high grade precancerous cervical lesions, carcinoma in situ, invasive cervical cancer, vulvar dysplastic lesions, vaginal dysplastic lesions, and genital warts. A 3-cohort vaccination strategy was considered (12, 18 and 25 years old) with a vaccination coverage rate of 80%. Reductions were calculated at peak efficiency (35 years) of the vaccination programme. The effect of cross-protection was also considered.

<sup>a</sup> LSIL – low-grade squamous intraepithelial lesions.

<sup>b</sup> ASCUS – atypical squamous cells of undetermined significance.

<sup>c</sup> HSIL – high-grade squamous intraepithelial lesions.

Table 5
Estimation of outcomes avoided with the two vaccines and consequent failed expenditure reduction [22].

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Outcomes avoided with quadrivalent vaccine</th>
<th>Outcomes avoided with bivalent vaccine</th>
<th>Differential</th>
<th>Failed expenditure reduction (€ × 10^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal pap smears</td>
<td>258,337</td>
<td>206,336</td>
<td>52,001</td>
<td>0.8</td>
</tr>
<tr>
<td>Colposcopies</td>
<td>76,909</td>
<td>59,932</td>
<td>16,977</td>
<td>4.2</td>
</tr>
<tr>
<td>LSIL&lt;sup&gt;a&lt;/sup&gt; and ASCUS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>56,648</td>
<td>48,045</td>
<td>8,603</td>
<td>3.4</td>
</tr>
<tr>
<td>HSIL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9,097</td>
<td>7,666</td>
<td>1,431</td>
<td>1.3</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>2,988</td>
<td>2,346</td>
<td>642</td>
<td>10.7</td>
</tr>
<tr>
<td>Genital warts</td>
<td>115,625</td>
<td>115,625</td>
<td></td>
<td>27.8</td>
</tr>
<tr>
<td>Total</td>
<td>519,604</td>
<td>324,325</td>
<td>195,279</td>
<td>48.2</td>
</tr>
</tbody>
</table>

<sup>a</sup> LSIL – low-grade squamous intraepithelial lesions.

<sup>b</sup> ASCUS – atypical squamous cells of undetermined significance.

<sup>c</sup> HSIL – high-grade squamous intraepithelial lesions.

3.2. Comparative results of economic modelling

When a multi-cohort vaccination strategy was assumed, the combined reduction of events was dependent on HPV-6 and -11, and HPV-16 and -18. The reduction of low-grade cervical lesions and genital warts related to HPV-6 and -11 was clearly detectable in an early phase of the vaccination programme [3,4]. In the subsequent steady-state phase the prevalent effect of the quadrivalent vaccine was due to the prevention of HPV-16 and -18 related events and, to a lower extent, HPV-6 and -11 related events [3].

The overall reduction of HPV-6, -11, -16, and -18 related events over time was associated with a total decrease in costs of approximately €132 million (Table 4).

The economic value of the differential protective effect of the two vaccines is depicted in Table 5. Independently of the type of vaccination strategy implemented (individual cohort of 12-year-old girls, multi-cohort, catch-up), the overall comparison of variables significant for decision-making and economic analyses (indications, clinical endpoints cross-protection) is in favour of the quadrivalent vaccine. The analysis of data from published studies [4,23] shows that a price differential of €5–8 per dose (in favour of the bivalent vaccine) does not compensate for the increased expenditure expected with the bivalent vaccine and caused by the failure to prevent the following HPV-related outcomes: low-grade precancerous cervical lesions induced by HPV-6 and -11, vulvar dysplastic lesions, vagi-
rial dysplastic lesions and genital warts. Since a lower reduction of combined events (−38%) was predicted with the bivalent compared with the quadrivalent vaccine, a 10% price difference between vaccines was in any case associated with a failed reduction of expenditure with the bivalent vaccine corresponding to $247 per event [22] (Fig. 5).

If both vaccines had the same level of effectiveness, a cost-minimization analysis [24] would be the most appropriate evaluation to assess the impact of anti-HPV vaccination.

In a cost-effectiveness analysis which compared the bivalent and quadrivalent vaccines base case results predicted that the cost per cycle for the bivalent vaccine would have to be CANS 105 (±73) less than that of the quadrivalent vaccine [assuming a cycle cost of CANS 400 (±277)] to produce equivalent cost per QALY-gained ratios [14]. With the currently available data, no economic, mathematical, or probabilistic model would support a price difference between the quadrivalent and bivalent vaccines if this difference was not of at least 20–44 Euro.11

4. Discussion

The solution to the problem of efficient healthcare resource allocation cannot only be based on a search for the minimum price for goods or services. To ensure the introduction of new innovative products (medications, diagnostic equipment and vaccines) it is mandatory to perform an appropriate spending review in order to make cost-effective choices. As far as vaccines are concerned the World Health Organization recommends that the decision-making process be based on quality as well as price, emphasizing that making choices based on price alone may be hazardous and uneconomic [6].

As shown in recent studies [26,27], health systems including the Italian NHS must assess the level of innovation [28], expressed by the “value” of medications and their cost-effectiveness, which provides a solid base for price negotiation. Both anti-HPV vaccines have been clearly demonstrated to have values per QALY-gained below the current threshold value to evaluate the cost-effectiveness of healthcare interventions.

The objective of the Italian NHS should be to provide the most effective drug or vaccine at the lowest price. In order to do this it will also be important to set an appropriate ICER [29,30]. The cost-effectiveness threshold adopted by NICE (National Institute for Clinical Excellence) of around £30,000 per QALY-gained represents an informed estimate based on the evidence available regarding the productivity of other NHS activities [12]. Since large differences in healthcare organization models exist, the results of economic evaluations are not entirely applicable between different countries. Therefore, each country, Italy included, should try to estimate its own threshold value to make appropriate healthcare evaluations and decisions.

The alternative to this method may be to negotiate on the basis of value-based pricing (VPB), in relation to the number of patients or subjects interested in a specific health intervention (Fig. 6) [26].

For VPB implementation, it is important to consider a number of essential elements. A key role is certainly played by cost-effectiveness. A second important element is drug effectiveness. Since the effectiveness of a drug cannot be assessed before its price has been set, it would be useful to connect the price with the uncertainty of the value of innovativeness (the expected net health benefits).

Effectiveness data from clinical practice should be of real interest to the Italian NHS. By definition these data are not available ex-ante, but they could be collected (e.g. through ad-hoc studies) a few years after product introduction. It is subsequently necessary to perform an ex-post economic evaluation and renegotiate the price on the basis of drug utilisation and effectiveness data. Prices could increase or decrease depending on the achievement of pre-defined effectiveness outcomes. This methodology could create important opportunities for a healthcare system. If all critical issues are considered, this new approach would allow the healthcare system to redistribute pharmaceutical expenditure toward other healthcare priorities (e.g. new innovative drugs, preventive procedures or medical devices).

The Italian Supervisory Authority for Public Contracts (Autorità Garante per la Vigilanza sui Contratti Pubblici di Lavori, Servizi e Forniture) [31] expressed an opinion regarding tender procedures for HPV vaccines. The Italian Supervisory Authority said “Considering that the drug market is controlled, the price cannot be the only criterion to compare products because it is set by the regulatory authority from the beginning”. In addition The Italian Supervisory Authority stated that “the assignment of a contract must be operated through the implementation of objective criteria that respect the principles of transparency, non-discrimination and equality, ensuring the evaluation of offers in a competitive contest”.

Therefore, the Supervisory Authority recommended that the decision-making process be based on both quality and price (cost-effectiveness), since basing decisions exclusively on price does not allow the identification of the truly best offer. “The fact that only one of the two vaccines has, from the beginning, an additional level of quality related to the two viral genotypes (HPV-6 and -11) for the prevention of genital warts, an analysis of cost-effectiveness (quality and price) could allow the assessment of the level of performance of each offer” [31].

Finally, as medical technology evolves, understanding how and when to adopt or invest in it is critically important. Move too early and the infrastructures needed to support the innovation may not yet be in place; wait too long, and the time to gain economic advantages may have passed. It is important to bear in mind that competition exists not only within each technology (i.e. among vaccines or drugs aimed at a disease category) but also across different technologies. The polio vaccine eliminated the need for drugs, devices, and services that had been used to treat the disease, just as kidney transplants have reduced the need for dialysis. Conversely, the discovery of an effective molecular diagnostic method for a disease would greatly enhance the demand for therapeutic drugs and devices.

11 Similar findings have recently been reported by Jit et al. [25].
Health care delivery is convoluted, expensive, and from time to time dissatisfying to patients. It should be acknowledged that a way out of this impasse now finally opens.

5. Conclusions

Although both vaccines have been shown to be below the threshold value for economic convenience, at this point in time long-term economic models developed for Italy seem to indicate the quadrivalent vaccine as the most cost-effective option, as a result of a more favourable cost-effectiveness ratio which is dependant on a wider prevention profile.

Even though some important variables generally used for modelling still need to be verified over time (e.g. vaccination coverage rate, duration of protection and discount rates adopted), the expected economic superiority of the quadrivalent vaccine should also be confirmed in the clinical practice setting.

It is also necessary to consider the issue of proper resource allocation. Recent publications by official bodies recommend that the decision-making process be based on both the quality of goods and services as well as the best achievable price.

The optimization of vaccination activities (implementation plan and economic sustainability) should take into consideration an appropriate evaluation of the available resources.

Appendix A. Main parameters used in the economic models considered

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Markov</td>
<td>Quadrivalent</td>
<td>Markov</td>
<td>Markov</td>
</tr>
<tr>
<td>Type of vaccine</td>
<td>Quadrivalent</td>
<td>Quadrivalent</td>
<td>Bivalent</td>
<td>Quadrivalent and bivalent</td>
</tr>
<tr>
<td>Number of cohorts</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age of cohorts (years)</td>
<td>11, 12, 18, 25</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Coverage rate (%)</td>
<td>80</td>
<td>80</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>Efficacy (%)</td>
<td>90</td>
<td>100</td>
<td>95.9</td>
<td>100</td>
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<tr>
<td>Endpoint</td>
<td>Clinical endpoints</td>
<td>Clinical endpoints</td>
<td>Persistent infection</td>
<td>Clinical endpoints</td>
</tr>
<tr>
<td>Current screening duration of protection (years)</td>
<td>Considered</td>
<td>Considered</td>
<td>Considered</td>
<td>Considered</td>
</tr>
<tr>
<td>Time horizon (years)</td>
<td>Lifetime</td>
<td>Considered</td>
<td>Lifetime</td>
<td>95</td>
</tr>
<tr>
<td>Booster</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>318</td>
</tr>
<tr>
<td>Cost of full vaccination cycle (€)</td>
<td>312</td>
<td>318</td>
<td>318</td>
<td>277.40 b</td>
</tr>
<tr>
<td>Discount rate (%)</td>
<td>3 – 3</td>
<td>3 – 15</td>
<td>Not reported</td>
<td>3 – 3</td>
</tr>
<tr>
<td>Cost (utility)</td>
<td>3 – 3</td>
<td>3 – 20</td>
<td>16 – 60</td>
<td></td>
</tr>
<tr>
<td>Timeframe for expected cost-reductions (min–max in years)</td>
<td>8 – 40</td>
<td>20 – 90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: premalignant genital lesions, cervical cancer, genital warts.


Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2009.02.052.

References


[31] Autorità per la vigilanza sui contratti pubblici di lavori, servizi e forniture. Parere n. 78 del 20.03.2008. PREC 55/08/F.