Risk-benefit analysis of 9-valent HPV vaccination for adolescent boys from an individual perspective.

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The author meets the ICMJE authorship criteria

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Summary

Japan recently approved quadrivalent human papillomavirus (HPV) vaccine for males, but 9-valent vaccine is only approved for females. Given the low female vaccination rate due to a concern of adverse events in Japan, quantifying the risk and benefit of the HPV vaccination for male may help the decision making to vaccinate adolescent boys in Japan. Using quality-adjusted life years, the risk-benefit ratio for an adolescent boy to get the 9-valent HPV vaccination was calculated. The male HPV vaccination reduced the QALY gain due to head and neck cancer, anal cancer, penile cancer, genital warts and recurrent respiratory papillomatosis by 401.63, 20.38, 9.40, 28.79 and 69.13/100,000 vaccinated persons, respectively. The total risk of the vaccination was 11.85. The risk-benefit ratio for a 12-year old boy to receive the HPV vaccination series is calculated as 0.022 (the benefit-risk ratio 44.67). In the sensitivity analysis the risk-benefit ratio ranged from 0.0001 to 0.11. for all scenarios. The much larger benefit compared with the risk for the male HPV vaccination was observed from an individual perspective. The result supports the inclusion of sex-neutral HPV vaccination into the national immunization program as well as the decision making for adolescent boys to get the vaccination.
Introduction

The human papilloma virus (HPV) is primarily transmitted by sexual intercourses, and some HPV genotypes are carcinogenic to cause oropharyngeal, cervical and anogenital cancers (1). The HPV vaccine is effective to prevent the infection of HPV virus. Currently, the 9-valent vaccine against HPV genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58 is available in many countries. While the HPV vaccine is safe, some countries suffer from the low vaccine coverage rates (2). The HPV infection causes one of the highest burdens in Japan among vaccine-preventable diseases (3). Although the HPV vaccination for girls has been included into national immunization programs in many countries, only a small number of countries have started the HPV vaccination for boys (4). Japan has recently approved a quadrivalent HPV vaccine for males aged 9 years or older. However, the 9-valent vaccine is only approved for females at this moment. The male HPV vaccination has not widely been implemented yet, and the government has not actively recommended the HPV vaccine yet due to the safety concern in Japan (5).

Quantification of the risk and benefit of the vaccination has been conducted to help children, their family and their health care providers make a decision on the vaccination by comparing the risk and benefit of the vaccination using quality adjusted life year (QALY) or disability-adjusted life year (6). While it is apparent that the beneficial impact
of HPV vaccination for adolescent girls outweighs the risk of the vaccination (6), the risk-
benefit analysis data regarding the HPV vaccination for boys are limited (7). Because the
evaluation of risk and benefit of universal HPV vaccination for adolescent boys from an
individual perspective may support their decision making as well as the governmental
active recommendation, our objective of this study was to quantify the risk and the benefit
of universal male HPV vaccination in Japan.

Methods

With a decision tree model (Fig. 1), the risk and benefit of the 9-valent HPV vaccination
for a 12-year-old adolescent boy was calculated using QALY. The lifetime QALY gain
and loss due to the benefit and risk of the vaccination were calculated from a vaccinated
individual perspective. The outcome of the study is the risk/benefit ratio for a 12-year boy
to get the HPV vaccination. The 12 years old is the age that adolescent girls are included
into the Japanese national immunization program for the HPV vaccination. QALY is a
measure to value health outcome calculated by multiplying health utility and years of life
(8). The health utility is presented by a numerical value between 0 and 1 (1 is a perfect
health and 0 is death). The Japanese population and life expectancy data in 2019 were
obtained from Ministry of Health, Labour and Welfare (9). Regarding the data sources to
calculate the outcome, the Japanese data were selected wherever possible. In case of the lack of Japanese data, international data were obtained. Based on the previous studies of the health value of the HPV-related diseases, discount rate was 3% for both health and economic outcomes in the base case analysis with the exploration of the effect of discount rate (0-6%) (6,10). The calculations were conducted by Microsoft Excel 2016 (Redmond, WA, USA). Because the study only used publicly available data, the study did not require a review of human research subject.

The vaccine benefits

The benefits of the male HPV vaccination include the prevention of head and neck cancer, anal cancer, penile cancer, genital warts and adult-onset recurrent respiratory papillomatosis caused by the HPV genotypes covered by the 9-valent vaccine. The age-specific incidence of head and neck cancer and the age-specific mortality for all HPV-related cancers evaluated in this study were obtained from the National Cancer Center (11), while the incidences of anal and penile cancers were collected from Globocan (Table 1) (12). The stage of cancer was divided into local, regional and distant stages. The incidence of genital warts was obtained from a previous study which estimated the annual incidence of genital warts stratified by age and sex (13). The incidence of adult-onset
recurrent respiratory papillomatosis was obtained from the US study (1.8/100,000 person-years) given the lack of Japanese data (14). Based on the previous studies, the rates of vaccine-covered HPV types related with these HPV-related diseases are 25.7% for head and neck cancer, 77.9% for anal cancer, 32.3% for penile cancer, 91.4% for genital warts and 93.7% for recurrent respiratory papillomatosis, respectively (Table 2) (15-20). While the rates of vaccine-covered HPV types were obtained from Japanese studies in head and neck cancer, penile cancer and genital warts (15,16,18,19), the rates for anal cancer and recurrent respiratory papillomatosis were from international studies (17,20). Although there have been immunogenicity and safety data for male 9-valent HPV vaccination, the vaccine efficacy to prevent HPV related diseases were obtained from female studies given the lack of male-specific efficacy data. The vaccine efficacy was assumed to be 96.7% for HPV-related diseases related with genotypes covered by the 9-valent vaccine (21). In this study, the protective effect of the vaccine was assumed to start from the age of 15 with a lifetime protection. The duration of protection was explored in the sensitivity analysis.

The age-specific health utility for men as well as the QALY loss and the duration for each disease condition are presented in Table 2 (22-27). For cancers, based on a previous study, the relative reduction of health utility was 27.0%, 37.0%, 45.0%, 11.7% and 22.3% for
head and neck cancer, anal cancer, penile cancer, genital warts and recurrent respiratory papillomatosis, respectively (23,24,26).

The vaccine risks

The risk of vaccination was quantified by QALY loss per 100,000 vaccinated persons. There is a large amount of data to negate the causality between chronic symptoms and the HPV vaccination, and many previous studies about the HPV vaccination assumed no negative impact of adverse events by the vaccination to calculate QALY (2,10,23). However, this study evaluated the impact of the acute and chronic symptoms after the vaccinations as if the HPV vaccinated had been related with acute and chronic adverse reactions. This is because the concern of adverse reactions is the primary driver for the current hesitation of the HPV vaccination in Japan, and the evaluation of the risk and benefit with a consideration of this concern may help the decision making about the vaccination (5,6). Give the relative scarcity of safety data regarding the HPV vaccine for Japanese boys, the previously published data regarding the QALY loss due to acute and chronic symptoms after the HPV vaccination in Japanese adolescent girls were used to quantify the negative impact as if the HPV vaccination had been related with these symptoms (6). This previous study for girls used the adverse event data from Ministry of
Health, Labour and Welfare as well as the QALY loss data for each adverse reaction (28-33). The causality between chronic symptoms and the HPV vaccination was assumed by the difference of chronic symptoms between the vaccinated and the unvaccinated populations based on the retrospective study (27.8 and 20.4/100,000 vaccinated and unvaccinated persons experienced chronic symptoms, respectively, which indicated that 26.6% cases with chronic symptoms after the vaccination may have been related with the vaccination) (30). However, the study showed no statistical significance in the incidence of the chronic symptoms between the vaccinated and the unvaccinated populations, and the difference (if any) may have been because of the biases indicated in this study. Therefore, the assumed causality between chronic symptoms and the vaccination in our calculation is to maximize the possibility of the negative impact of the vaccination. This uncertainty was also explored in the sensitivity analysis (the rate of causality between chronic symptoms and the HPV vaccination 0-100%). The detailed indicators and method to calculate the QALY by the potential adverse reactions of the HPV vaccination are described in Table 2 and in the previous study for Japanese girls (6).

**Incremental cost-effectiveness ratio**

While the main objective of this study is to evaluate the risk and benefit of the HPV
vaccination for males from a QALY perspective without economic consideration, the incremental cost-effectiveness ratio (ICER) was estimated. ICER was calculated incremental cost per one incremental QALY. The cost of each event was obtained from a recent Japanese modeling study (34).

**Sensitivity analysis**

The one-way sensitivity analysis was conducted with the parameters of vaccine efficacy (90.4% to 100%) (35), the duration of protection (until 30 years old to lifelong) (36,37), the HPV infection rate in the population (-80% to +10%) (38,39), the chronic adverse reactions after the HPV vaccination (0% to 100% of causality rate between chronic symptoms and the HPV vaccination) and discount rate (0% to 6%) (6,10).

Some study estimated a lifelong protection as the base case and a 20-year protection as a sensitivity analysis (36). In the sensitivity analysis for the duration of protection, the protection was assumed to only sustain until 30 years old. For those older than 30 years, the incidence and mortality of cancer were assumed to be prevented by 50% of that in the lifetime protection scenario. Although a modeling study estimated that 75% of HPV infections causing cancer were acquired by the age of 31 (37), the value of 50% was selected to maximize the impact of this uncertainty. The protective effect of the vaccine
on genital warts and recurrent respiratory papillomatosis for those older than 30 years were assumed to be none in this sensitivity analysis.

The range of the HPV infection rate in the population was selected based on the annual fluctuation of the incidence of HPV-related diseases and the expected reduction of HPV infection in a highly vaccinated population (38,39). The HPV infection rate in the population was assumed to be proportional to the chance for an individual to develop any HPV-related diseases.

Results

The HPV vaccination for boys reduced the QALY loss due to head and neck cancer, anal cancer, penile cancer, genital warts and recurrent respiratory papillomatosis by 401.63, 20.38, 9.40, 28.79 and 69.13/100,000 vaccinated persons, respectively (Table 3). The total benefit of the vaccination was 529.32 QALY/100,000 vaccinated persons. The QALY loss by adverse event lasting <1 week, lasting ≥1 week with assistance requirement and lasting ≥1 week without assistance requirement 0.07, 5.89 and 5.89/100,000 vaccinated persons, respectively. The total risk of the vaccination was 11.85 QALY/100,000 vaccinated persons. Therefore, the risk-benefit ratio for a 12-year old boy to receive the HPV vaccination series is calculated as 0.022 (the benefit-risk ratio 44.67). The ICER for the
3-dose and 2-dose programs are 12,660,298 and 8,179,493 JPY, respectively. Without discount, the ICER were 10,045,252 and 5,564,447 JPY for the 3-dose and 2-dose programs.

The sensitivity analysis is presented in the Fig. 2. The risk-benefit ratio ranged from 0.0001 in the scenario with 0% causality between chronic symptoms and the vaccination to 0.11 in the scenario with 80% reduction of the HPV infection in the population. The vaccine efficacy was the least sensitive among the investigated parameters. The benefit was much larger compared with the risks for all scenarios.

**Discussion**

The study showed that the benefit of the male HPV vaccination was much larger compared with the risk despite the assumption that chronic symptoms had been associated with the vaccination from the individual perspective. This was consistent with all scenarios in the sensitivity analysis. The results support the universal and sex-neutral HPV vaccination in Japan even though the current vaccine coverage rate for girls is still low.

The previous study for Japanese girls in 2019 showed that even if there had been the causality between the HPV vaccination and the chronic symptoms, the benefit-risk ratio
of the female HPV vaccination was 64 (6). The previous study for girls investigated the quadrivalent HPV vaccine and only included the prevention of cervical cancer and genital warts as the beneficial impacts of the female vaccination. Therefore, the direct comparison between the risk-benefit ratios of the previous study for girls and this study for boys should only be performed with cautions.

This study focused on the risk and benefit of the male vaccination from the individual perspective. There are numerous studies which revealed the beneficial impact of male vaccination from a population perspective (10,37). These study results emphasize that the HPV vaccination for boys should be beneficial both from an individual and population perspective, irrespective of the relationship of the HPV vaccination and chronic symptoms reported from Japan. Of note, this analysis was based on the current disease burden in Japan. If the epidemiology of HPV-related diseases significantly changes over time, then the risk and benefit as well as the cost-effectiveness may need to be re-evaluated. However, given the stagnant vaccination rate in Japanese girls and the fact that the incidence of HPV-related diseases has not decreased at all, the result of this study to guide the recommendation of the HPV vaccination for Japanese boys may also be applied in the future. In addition, our result showed that the beneficial impact of male HPV vaccination was consistent even with the reduction of the HPV infection in a population
level, which advocates the initiation of national HPV vaccination program for boys as well as the catch-up program for girls in Japan. There is a concern for the supply of HPV vaccines worldwide (40). Given the beneficial impact of universal HPV vaccinations for both girls and boys, strengthening the global supply chain to cover sex-neutral vaccination should be in a high prioritization.

This study suggests that the male HPV vaccination may not be very cost-effective compared with the female vaccination (23,34). While this study also showed that the 2-dose program may be more cost-effective that the 3-dose program, whether the fewer dose programs are equally effective to the 3-dose program in the long run needs to be further investigated given the lack of long-term efficacy data for the fewer dose vaccination.

The study is limited by the lack of long-term data regarding vaccine efficacy for males and the lack of Japanese data for some other indicators used in this study. In addition, the actual incidence of chronic adverse events after the HPV vaccination among Japanese boys is unknown at the time of this study was conducted. Some reports revealed that males were less likely to develop adverse events compared with females with the HPV vaccination, and the multiple studies, including Japanese studies, showed that the HPV vaccine did not cause any serious adverse reactions (2). Therefore, our assumption as if
there had been causal relationship between the vaccination and the chronic symptoms likely overestimates the risk of the male HPV vaccination. Given the nature of this study design, this study could not evaluate some beneficial impacts of the HPV vaccination, including herd immunity.

In conclusion, the benefit of the male HPV vaccination is much larger compared with the risk through the quantification of the risk and the benefit from an individual perspective. The result supports the inclusion of sex-neutral HPV vaccination into the national immunization program and the approval of the 9-valent HPV vaccine for males as well as the decision making for adolescent boys to get the vaccination.

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The author received no financial support.

Conflict of interest

The author reports no conflicts of interest. The author alone is responsible for the content in and writing of the paper.
References


34. Cody P, Tobe K, Abe M, Elbasha EH. Public health impact and cost effectiveness


will a nonavalent vaccine prevent? Euro Surveill. 2018;23:1700737.

Figure Legends

Figure 1. Decision tree model
HPV; human papillomavirus, RRP; recurrent respiratory papillomatosis

Figure 2. Sensitivity analysis
Vaccine efficacy (90.4%–100%); Duration of protection (until 30 years old to lifelong);
Burden of HPV infection (-10%–+80% of HPV infection in the population level): Chronic
adverse reactions (0%–100% of causality rate between chronic symptoms and the HPV
vaccination); Discount rate (0%–6%)
### Table 1 Age specific incidence (/1000,000 person-years) of each disease in males

<table>
<thead>
<tr>
<th>Age 15-19</th>
<th>Head and neck cancer</th>
<th>Anal cancer</th>
<th>Penile cancer</th>
<th>Genital warts</th>
<th>Recurrent respiratory papillomatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 20-24</td>
<td>1.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>183.5</td>
</tr>
<tr>
<td>Age 25-29</td>
<td>2.1</td>
<td>0.0</td>
<td>0.1</td>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td>Age 30-34</td>
<td>3.4</td>
<td>0.2</td>
<td>0.0</td>
<td>219.9</td>
<td></td>
</tr>
<tr>
<td>Age 35-39</td>
<td>4.2</td>
<td>0.2</td>
<td>0.0</td>
<td>147.9</td>
<td></td>
</tr>
<tr>
<td>Age 40-44</td>
<td>7.8</td>
<td>0.2</td>
<td>0.2</td>
<td>126.2</td>
<td></td>
</tr>
<tr>
<td>Age 45-49</td>
<td>11.9</td>
<td>0.2</td>
<td>0.2</td>
<td>79.1</td>
<td>1.8 for all age groups</td>
</tr>
<tr>
<td>Age 50-54</td>
<td>20.4</td>
<td>0.7</td>
<td>0.0</td>
<td>67.0</td>
<td></td>
</tr>
<tr>
<td>Age 55-59</td>
<td>37.7</td>
<td>0.5</td>
<td>0.5</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>Age 60-64</td>
<td>63.0</td>
<td>1.3</td>
<td>0.8</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>Age 65-69</td>
<td>91.0</td>
<td>1.8</td>
<td>1.3</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>Age 70-74</td>
<td>87.9</td>
<td>2.4</td>
<td>3.4</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>Age 75-79</td>
<td>94.7</td>
<td>2.4</td>
<td>3.4</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>Age 80-84</td>
<td>97.1</td>
<td>2.4</td>
<td>3.4</td>
<td>19.7</td>
<td></td>
</tr>
</tbody>
</table>

The reference years were 2017 for head and neck cancer (11), 2020 for anal and penile cancer (12) and 2015 for genital warts (13). The incidence of recurrent respiratory papillomatosis was from the US data (14).
Table 2. Model parameters

<table>
<thead>
<tr>
<th>Disease with HPV genotypes covered by 9-valent vaccine</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck cancer</td>
<td>25.7% (15.16)</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>77.9% (17)</td>
</tr>
<tr>
<td>Penile cancer</td>
<td>32.3% (18)</td>
</tr>
<tr>
<td>Genital warts</td>
<td>91.4% (19)</td>
</tr>
<tr>
<td>Recurrent respiratory papillomatosis</td>
<td>93.7% (20)</td>
</tr>
</tbody>
</table>

Vaccine efficacy: 96.7% (21)
Discount rate: 3% (6,10)

**QALY parameters**

**Healthy male**

<table>
<thead>
<tr>
<th>Age</th>
<th>Health Utility (0–1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 12-19</td>
<td>0.9305 (22)</td>
</tr>
<tr>
<td>Age 20-29</td>
<td>0.9225 (22)</td>
</tr>
<tr>
<td>Age 30-39</td>
<td>0.8965 (22)</td>
</tr>
<tr>
<td>Age 40-49</td>
<td>0.8545 (22)</td>
</tr>
<tr>
<td>Age 50-59</td>
<td>0.8155 (22)</td>
</tr>
<tr>
<td>Age 60-69</td>
<td>0.7915 (22)</td>
</tr>
<tr>
<td>Age 70-79</td>
<td>0.7405 (22)</td>
</tr>
<tr>
<td>Age 80-</td>
<td>0.6745 (22)</td>
</tr>
</tbody>
</table>

**Disease Condition**

<table>
<thead>
<tr>
<th>Disease Condition</th>
<th>Relative health utility loss</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer local stage</td>
<td>-27.0% (23)</td>
<td>4 months (23)</td>
</tr>
<tr>
<td>Cancer regional stage</td>
<td>-37.0% (23)</td>
<td>3 years (23)</td>
</tr>
<tr>
<td>Cancer distant stage</td>
<td>-45.0% (23)</td>
<td>3 years (23)</td>
</tr>
<tr>
<td>Genital warts</td>
<td>-11.7% (24)</td>
<td>36 days (25)</td>
</tr>
<tr>
<td>Recurrent respiratory papillomatosis</td>
<td>-22.3% (26)</td>
<td>8 years (27)</td>
</tr>
</tbody>
</table>

**Adverse events parameters**

<table>
<thead>
<tr>
<th>Incidence of adverse events</th>
<th>Incidence/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 week</td>
<td>67.69 (28-30)</td>
</tr>
<tr>
<td>1 week–3 months</td>
<td>2.07 (28-30)</td>
</tr>
<tr>
<td>3–6 months</td>
<td>0.33 (28-30)</td>
</tr>
<tr>
<td>6–12 months</td>
<td>0.33 (28-30)</td>
</tr>
<tr>
<td>1–3 years</td>
<td>0.71 (28-30)</td>
</tr>
<tr>
<td>3–5 years</td>
<td>0.47 (28-30)</td>
</tr>
<tr>
<td>Permanent</td>
<td>2.19 (28-30)</td>
</tr>
</tbody>
</table>

**Severity of adverse events**
Requiring assistance | 33.9% (29)  
Not requiring assistance | 66.1% (29)  

**QALY loss**  
Adverse event (lasting <1 week) | 0.001/event (31)  
Adverse event (lasting ≥1 week)  
   - Requiring assistance | 0.28/year (32)  
   - Not requiring assistance | 0.14/year (33)  

**Cost parameters**  
Vaccination cost per dose | 23,718 (34)  
Penile cancer, local disease | 647,000 (34)  
Penile cancer, regional disease | 1,165,000 (34)  
Penile cancer, distant disease | 1,249,600 (34)  
Anal cancer, local disease | 1,183,000 (34)  
Anal cancer, regional disease | 1,809,200 (34)  
Anal cancer, distant disease | 2,659,300 (34)  
Head and neck cancer, local disease | 1,169,110 (34)  
Head and neck cancer, regional disease | 3,695,570 (34)  
Head and neck cancer, distant disease | 5,794,276 (34)  
Genital warts | 11,356 (34)  
Recurrent respiratory papillomatosis | 1,144,296 (34)  

**Abbreviation:** QALY; quality-adjusted life year.  
Health utility for healthy male was calculated from the age-specific health utility for both sexes and the average difference of healthy utility between males and females (22).  
The incidence of adverse events for each duration is calculated as follows.  
- The incidence of any adverse events (90.6/100,000 vaccinated persons) was multiplied by the proportion of each duration among cases with adverse events (28,29).  
- For adverse events lasting ≥1 week, the difference in incidence of these chronic symptoms between vaccinated and unvaccinated population was used to assume the causality (26.6% cases with chronic symptoms after the vaccination were assumed to be related with the vaccination compared with the unvaccinated population). However, the study showed no statistical significance of the incidence of the chronic symptoms and the difference (if any) may have been simply because of biases of the study (ie, recall bias). Therefore, the assumed causality between chronic symptoms and the vaccination is to maximize the possibility of the negative impact of the vaccination (30).  
Adverse events lasting ≥1 week were divided into two severities based on assistance requirement (29). The adverse events lasting 5 years or more were assumed to be lifelong in this study.  
The cost for each event was obtained from a Japanese modeling study by Cody P et al (34).
Table 3. Base case results

<table>
<thead>
<tr>
<th>Benefit</th>
<th>QALY gain/100,000 vaccinated persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck cancer</td>
<td>401.63</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>20.38</td>
</tr>
<tr>
<td>Penile cancer</td>
<td>9.40</td>
</tr>
<tr>
<td>Genital warts</td>
<td>28.79</td>
</tr>
<tr>
<td>Recurrent respiratory papillomatosis</td>
<td>69.13</td>
</tr>
<tr>
<td>Total benefit</td>
<td>529.32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>QALY loss/100,000 vaccinated persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event (lasting &lt;1 week)</td>
<td>0.07</td>
</tr>
<tr>
<td>Adverse event (lasting ≥1 week)</td>
<td></td>
</tr>
<tr>
<td>Requiring assistance</td>
<td>5.89</td>
</tr>
<tr>
<td>Not requiring assistance</td>
<td>5.89</td>
</tr>
<tr>
<td>Total risk</td>
<td>11.85</td>
</tr>
</tbody>
</table>

The risk/benefit ratio in QALY change 0.022

QALY; quality-adjusted life year