Comparative Effectiveness Research/Health Technology Assessment (HTA)

Estimating the Effectiveness of HPV Vaccination in the Open Population: A Bayesian Approach

Willem Woertman, PhD*, Gert Jan van der Wilt, PhD
Department for Health Evidence, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

A B S T R A C T

Objectives: Estimation of the effectiveness of human papillomavirus (HPV) vaccination in the open population on the basis of published data from various sources. Methods: A Bayesian approach was used to reanalyze the data underlying a guidance by the Dutch National Health Insurance Board about the quadrivalent HPV vaccine Gardasil. Several studies document the vaccine’s effectiveness in preventing cases in different subpopulations. None of these subpopulations, however, is representative of the actual target population that the vaccination program will be applied to. We used a Bayesian approach for restructing the data by means of reweighting the subpopulations by using HPV prevalence data, to estimate the effectiveness that can be expected in the actual target population. Results: The original data show an effectiveness of 44% in the entire population and an effectiveness of 98% for women who were compliant and were HPV-free at the start of the study. In the study population, the HPV prevalence was below 4%. In the relevant target population, however, the actual prevalence could be very different. In fact, some publications find an HPV prevalence of around 10%. We used Bayesian techniques to estimate the effectiveness in the actual target population. We found a mean effectiveness of 25%, and the probability that the effectiveness in the target population exceeds 50% is virtually zero. The results are very sensitive to the HPV prevalence that is used. Conclusions: A supplementary analysis can put together the bits and pieces of information to arrive at more relevant answers. A Bayesian approach allows for integrating all the evidence into one model in a straightforward way and results in very intuitive probability statements.

Keywords: Bayesian analysis, decision support techniques, evidence-based medicine, Gardasil, health insurance reimbursement.

Conclusions: A supplementary analysis can put together the bits and pieces of information to arrive at more relevant answers. A Bayesian approach allows for integrating all the evidence into one model in a straightforward way and results in very intuitive probability statements.

Copyright © 2013, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc.

Introduction

Policy decisions concerning reimbursement of drugs have crucially important implications for access to medical treatments for patients. Therefore, the available evidence on clinical effectiveness and cost-effectiveness of drugs should be carefully considered and synthesized when reimbursement decisions are made. This task is frequently hampered because the available evidence is incomplete or inconsistent. Also, the evidence may originate from multiple, heterogeneous sources, including randomized controlled trials, cohort studies, record reviews, registries, laboratory studies, and clinical and patients’ experiences. It is rarely the case that there exists evidence that directly answers the questions that are most relevant for decision makers. Instead, there are usually bits and pieces of information available that answer subquestions that are relevant to the policy decision under consideration. Therefore, it often seems that there is a mismatch between the questions that policymakers are grappling with and the answers that science typically offers. Here, we argue that a supplementary analysis that combines all the relevant pieces of information (in the sense of a multiparameter evidence synthesis [1] or as in the confidence profile method [2]) might come closer to actually answering the main questions that decision makers are dealing with, and could therefore be very helpful in the policymaking process. Furthermore, we argue that Bayesian methods are well suited for such a supplementary analysis. Most of the literature on multiparameter evidence synthesis or the confidence profile method works within a Bayesian framework [1]. Moreover, it has often been suggested that a Bayesian approach to data analysis may be better suited than the standard frequentist methods for answering policy questions (e.g., [3–11]). There are two main reasons for this. First, a Bayesian approach offers a natural way for combining evidence from different sources in a systematic and transparent way, even when dealing with heterogeneous sources of evidence. In Bayesian statistics, unlike in frequentist statistics, it is very common to consider the new information that is gathered from an experiment together with the information that was available before the experiment. The Bayesian approach offers a formal
model for combining prior information with newly available information, so that previously held judgments are updated. Second, Bayesian statistics has important conceptual advantages over frequentist statistics, making the outcomes easier to interpret and understand for relative laypersons (i.e., members of appraisal committees). For instance, the frequentist concept of the P-value gives an estimate of the probability of obtaining an outcome equal to or more extreme than the observed outcome, under the null hypothesis of no effect. This P-value, however, does not provide a direct statement about how unlikely the null hypothesis in fact is, nor how likely any alternative hypothesis. Arguably, however, this is precisely the sort of statement that the various stakeholders would like to be able to make: what is the probability that intervention x will produce an effect of y (or larger), given the observed results? Bayesian analyses do produce such probabilities. Therefore, when used as a supplement to the standard frequentist results, perhaps Bayesian statistics could aid policymakers in comprehending and assessing what the data have to say about the questions that are most relevant to the problems they face.

In spite of these potential advantages, the Bayesian approach is relatively unfamiliar and relatively little used in the context of supporting policy decisions.

To put the alleged advantages of Bayesian methods for policymaking to the test, we performed a Bayesian reanalysis of an actual reimbursement advice that was drafted in 2009 by the National Health Insurance Board of The Netherlands (College voor Zorgverzekeringen [CVZ]), and compared the outcomes with the original results.

The Case of Gardasil

Gardasil is a prophylactic quadrivalent vaccine that prevents anogenital diseases associated with human papillomavirus (HPV) types 6, 11, 16, and 18. Infection with HPV is sexually transferable and can cause genital warts, intraepithelial neoplasia, and invasive cancers [12]. Of these diseases, cervical cancer is particularly important as it is the second most common cancer in women [13]. HPVs cause virtually all cervical cancers, and HPV types 16 and 18 cause approximately 70% of all HPV-related cervical cancers worldwide [13]. HPV types 6 and 11 cause most genital warts [12].

In 2007 and 2008, CVZ issued two advises to the Dutch Minister of Health about the reimbursement of Gardasil [14,15]. In 2007, CVZ recommended that Gardasil should not be reimbursed for 13- to 26-year-old women and girls [14]. CVZ acknowledged the therapeutic added value of Gardasil, but was not convinced of its cost-effectiveness. Shortly thereafter, the Dutch Health Council recommended including HPV vaccination in the national vaccination program for 12-year-old girls and that girls who were then 13 to 16 years old would also be eligible for vaccination [16]. After that, in 2008, the manufacturer of Gardasil asked for a reassessment, with the request to reimburse the vaccine for 17- and 18-year-old girls as well. For the same reasons as in 2007, CVZ advised not to reimburse Gardasil [15]. In both advices, one of CVZ’s main points of critique regarding the cost-effectiveness model supplied by the manufacturer was the effectiveness of the vaccine that was used in the model. In the first advice, the cost-effectiveness model used the per-protocol susceptible effectiveness from one of the phase 3 trials. CVZ considered this assumption to be unrealistic and overly optimistic. In the second advice, in the new cost-effectiveness model supplied by the manufacturer, attempts were made to correct for existing HPV-16/18 prevalence, but CVZ maintained that the assumptions were not sufficiently supported by data.

In both advices, the evidence came from a variety of sources and was analyzed with standard frequentist methods. The main articles that the advice refers to were a small phase 2 trial [17] and two large placebo controlled phase 3 trials (FUTURE I AND II [12,13]). The largest of these studies, the FUTURE II study, uses (the surrogate outcome measure of) HPV-16/18-related cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer as the primary end point [13]. In the FUTURE II study, both the placebo arm and the vaccine arm participants received injections at day 1, month 3, and month 6 of the follow-up period. The main measure of effectiveness that was used is the proportion of events that are prevented through vaccination, given by one minus the vaccine event rate divided by the placebo event rate. The FUTURE II study contained three main analyses, corresponding to three different populations: 1) the per-protocol susceptible population of women and girls, who were uninfected with HPV-16/18 until 1 month after the third and final injection, who received all the injections at approximately the right moment, and who had no other protocol violations; 2) an unrestricted susceptible population of women who were uninfected with HPV-16/18 at the day of the first injection; and 3) an intention-to-treat population of all participating women in the study. All participants who belong to the first population also belong to the second population, and all participants who belong to the second population also belong to the third. Women were eligible to participate in these studies if they were not pregnant, if they did not report abnormal results on a Pap smear, and if they had a lifetime number of no more than four sex partners. Moreover, subjects were asked to use effective contraception during the vaccination period (day 1 through month 7).

Clearly, not all women and girls were eligible to participate in these studies. Considering the exclusion criteria, it seems likely that among the women who were excluded the HPV prevalence would be higher than among the women who were included in the study. Indeed, a higher number of lifetime sex partners is strongly associated with HPV prevalence [18]. Also, it is known that HPV vaccination has no therapeutic benefit for women who are already infected with HPV before vaccination. In contrast, for women who were uninfected at the time of vaccination, Gardasil is highly effective in preventing events with effectiveness near 100% [13]. Therefore, the HPV-16/18 prevalence before vaccination in the population that is to be vaccinated will be a major determinant of the effectiveness that will eventually be found. Because even in the intention-to-treat populations the HPV-16/18 prevalence prior to vaccination will probably be lower than the HPV-16/18 prevalence in the open population, the intention-to-treat effectiveness is also likely to be an overestimate of the effectiveness in the actual target population.

Therefore, if we could estimate the effectiveness that can be expected in the target population, based on the above-mentioned effectiveness estimates and on information about the HPV prevalence, we would be much closer to a satisfactory answer to the most relevant question: “What will be the effectiveness—and therefore cost-effectiveness—among all girls who would be eligible for vaccination?”

Methods

Our supplementary analysis is mainly based on the data from the FUTURE II study [13], which provides estimates for the vaccine’s effectiveness in preventing cases in three different populations. This article also reports the numbers of subjects and the number of cases (having at least one primary end point event) underlying the effectiveness estimates in each of these three populations.

We started our supplementary analysis by restructuring the three populations that the FUTURE II study considers (populations 1, 2, and 3 from the previous section) into three other, newly formed groups of participants, which we will denominate groups A, B, and C. Group A exactly equals population 1 (the per-protocol susceptible population) from the FUTURE II study. Group B consists of subjects who were included in population 2 (the unrestricted susceptible population), but who were not included
in population 1. This group consists of participants who were
uninfected with HPV-16/18 at the day of the first vaccination, but
who had protocol violations, who did not receive all three
injections (or not at the appropriate times), or who became
HPV-16/18 infected during the vaccination period. Thus, this
group consists of susceptible noncompliers. The last group of
participants that we distinguish, group C, consists of those who
were included in population 3 (the intention-to-treat population),
but who were not included in population 2. This group consists of
those who were eligible to enter the study but who were HPV-16/
18 infected on day 1 of follow-up. Thus, this group is an HPV-16/
18 prevalent group.

Then, from the numbers of subjects and cases in populations
1, 2, and 3 from the FUTURE II study, we can determine the
numbers of subjects and cases in groups A, B, and C. We denote
the number of subjects in population 1 who were randomized to
get the vaccine by \( n_A \) and the number of cases in this group by \( m_A \).
The number of subjects in population 1 who got placebo injections
by \( n_B \), and the number of cases in this population by \( m_B \). And we
denote the corresponding numbers of subjects and cases in
populations 2 and 3, and in groups A, B, and C, by changing the
subscripts accordingly. Thus, we get that \( n_A - n_B \), \( n_B - n_C \),
and that \( n_C = n_A - n_B \). The same relations between groups A, B, C,
and populations 1, 2, and 3 hold for the cases \( m \) in the vaccine
group, and the same goes for all the placebo numbers \( n \) and \( m \).
Thus, we were able to calculate the vaccine’s effectiveness in each
of our three groups of participants, which can be considered as
the HPV-16/18-naive per-protocol effectiveness, an HPV-16/
18-naive noncomplier effectiveness, and an HPV-16/18-infected
effectiveness. By reweighting these effectiveness measures, we
estimated the effectiveness in our target population.

Age-dependent data on the HPV prevalence in The Nether-
lands were obtained from the literature [19]. Although this study
does not provide data on exactly our target group, this study
probably provides the best available approximation of that
number (see the “Discussion” section).

For the proportion of noncompliers (those susceptible subjects
not getting all three injections or not at the appropriate times, or
those who get an HPV-16/18 infection during the vaccination
period), the only direct data we could find were from the FUTURE
studies, which showed noncompliance rates of around 10%.
Hence, we assumed a 95% interval for the noncompliance rate
studied, which showed noncompliance rates of around 10%.

Analyzes were carried out by using Winbugs, a statistical
software package designed for Bayesian analysis. The WinBUGS
code for our Bayesian supplementary analysis is printed in
Figure 1.

We first estimated \( \hat{\theta}_A \), the probability of a case in the vaccine
arm for group A, by using a binomial likelihood function, and the
number of subjects and cases found in that group (line 1 of the
WinBUGS code), and a noninformative \((\text{beta}(1, 1))\) prior distribution
(line 8). We similarly estimated \( \hat{\theta}_B \), \( \hat{\theta}_C \), \( \hat{\theta}_D \), \( \hat{\theta}_E \), and \( \hat{\theta}_F \) (lines 2–6
and 9–13). Thus, we arrived at a posterior distribution for each of
these six probabilities of a random subject being a case. We
similarly estimated the HPV prevalence by using a binomial
likelihood function, the number of HPV-16/18–infected women
and the sample size from Coupé et al. [19], and a noninformative
prior (lines 7 and 14). The three posterior distributions for the
vaccine arm \( \hat{\theta}_V \), \( \hat{\theta}_N \), and \( \hat{\theta}_L \) were combined into a posterior
distribution for the probability of being a case for the entire
vaccine arm \( \hat{\theta} \) by reweighting them by using the estimated HPV
prevalence and the proportion of compliers [line 15]. The above
95% interval for the proportion of compliers was expressed by
means of a beta distribution (line 17). We did the same for the
placebo arm of the study, also arriving at a posterior distribution
for the probability of being a case in the entire arm \( \hat{\theta} \) (line 16).

Having thus calculated the posterior distributions for the
probabilities of being a case in both the vaccine arm and the
placebo arm in our target population, we could determine a
posterior distribution for the vaccine’s estimated effectiveness
for preventing cases in our target population (line 18). It is
important to note that the alternative (and perhaps seemingly
more straightforward and simple) strategy of first calculating the
effectiveness in each of our three groups, and then simply
determining a weighted average of these three effectiveness
measures, is in fact incorrect.

The information contained in the posterior distribution for the
effectiveness in the target population was summarized by providing
a mean and a Bayesian (equal-tail) 95% credible interval. We
also calculated the probabilities that the effectiveness in the target
population exceeds 50% or 25% (lines 19 and 20).

As the vaccine’s effectiveness for both groups of HPV-naive
participants (groups A and B) is high and the effectiveness in the
group of HPV-infected participants (group C) is dramatically lower,
the HPV prevalence is a crucial piece of information in our
combined analysis. Because we could not find prevalence informa-
tion for exactly the right group of women, we performed a
sensitivity analysis investigating the impact of the HPV prevalence
on the posterior distribution. Thus, we repeated our supplementary
analysis making four other assumptions regarding the HPV-16/18
prevalence: we replaced lines 7 and 14 of the WinBUGS code by a
line similar to line 17, thereby simply assuming 95% confidence
intervals \((\text{CIs})\) of \((1, 3), (5, 10), (5, 15),\) and \((10, 15)\). For each of these
CIs, we have tried to choose the parameters of the corresponding
beta distributions in such a way that the mean of the distribution
would be halfway between the lower bound and the upper bound,
so that the precise upper and lower bounds would be as close as
possible to the above rounded values.

For the Markov Chain Monte Carlo procedures that WinBUGS
performs for the Bayesian analyses, we took 50,000 iterations with

```{r}
model{  
1 mAv ~dbin(thetaAv, nAv)  
2 mBv ~dbin(thetaBv, nBv)  
3 mCv ~dbin(thetaCv, nCv)  
4 mBp ~dbin(thetaBp, nBp)  
5 mCp ~dbin(thetaCp, nCp)  
6 inf ~dbin(prev, n)  
7 thetaAv~dbeta(1,1)  
8 thetaBv~dbeta(1,1)  
9 thetaCv~dbeta(1,1)  
10 thetaAp~dbeta(1,1)  
11 thetaBp~dbeta(1,1)  
12 thetaCp~dbeta(1,1)  
13 prev~dbeta(1,1)  
14 theta_y<-prev*thetaAv+  
15 theta_y<-prev*thetaBv+  
16 theta_y<-prev*thetaCp+  
17 theta_y<-prev*thetaBp+  
18 theta_y<-prev*thetaAp+  
19 p25<-step(effect-25)  
20 p50<-step(effect-50)  
}  
list(mAv=1,nAv=5305,mBv=2,nBv=560,  
Cv=80,nCv=222,mAp=42,nAp=5260,  
mBp=20,nBp=603,mCp=86,nCp=217,  
inf=47,n=482)  
}
```

Fig. 1 – The WinBUGS code.
results show any problems, and there was no need for thinning.

Discussion

This article tries to illustrate that supplementary analyses, putting together the bits and pieces of (partially) relevant information, can help policymakers to better assess what the data have to say about the problems they are dealing with. In this article, we have performed such a supplementary analysis by using a Bayesian approach. By doing this analysis, we were indeed able to provide an answer to the question "What will be the effectiveness in our target population?" that is much more relevant than the answers to questions such as "What is the effectiveness in a per-protocol population?" and "What is the effectiveness in a constrained intention-to-treat population?" Moreover, our Bayesian outcomes allow for making statements such as "The probability that the effectiveness in our target population will exceed 50% is virtually zero," which is arguably more relevant and easier to interpret than the frequentist statement "The probability of observing an effectiveness as large or larger than observed, if the real effectiveness equals zero, is virtually zero." Using Bayesian methods it is straightforward to link together different subanalyses into one comprehensive analysis as we have done here. Most of this could also have been approximated by using non-Bayesian methods, for instance, by using formulas to determine the mean and variance of the resulting effectiveness variable from the means and variances of the constituent parts (the six subgroups for the probability of a case, the HPV prevalence, and the proportion of compliers). This would, however, involve normal approximations, and these approximations might not be very good because some of the constituent parts are much skewed.

Table 1 shows the posterior probability distribution for the effectiveness as well as a cumulative distribution plot for the posterior distribution.

Table 1 – The original FUTURE II data and the reorganized data.

<table>
<thead>
<tr>
<th>Population</th>
<th>Vaccine arm</th>
<th>Placebo arm</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>No. of subjects</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Original data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPS</td>
<td>1</td>
<td>5305</td>
<td>42</td>
</tr>
<tr>
<td>US</td>
<td>3</td>
<td>5865</td>
<td>62</td>
</tr>
<tr>
<td>ITT</td>
<td>83</td>
<td>6087</td>
<td>148</td>
</tr>
<tr>
<td>Reorganized data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1</td>
<td>5305</td>
<td>42</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>560</td>
<td>20</td>
</tr>
<tr>
<td>C</td>
<td>80</td>
<td>222</td>
<td>86</td>
</tr>
</tbody>
</table>

Note. Number of cases, number of subjects, and effectiveness for the per-protocol susceptible (PPS), unrestricted susceptible (US), and intention-to-treat (ITT) populations, as taken from the FUTURE II study [13] (original data). The same quantities are shown for our newly derived groups of participants (reorganized data).
women, where we needed data on 17- and 18-year-old girls). Lenselink et al. [18] also provide recent Dutch HPV prevalence data, which does not exactly match the information we are looking for either. Their data, however, seems to suggest that the HPV-16/18 prevalence for 18-year-old girls would lie somewhere around 2% (a figure that is rather different from that found by Coupe et al. [19]) and the first sensitivity analysis roughly corresponds to these figures. We do choose to use the data from Coupe et al. [19] in our base-case analysis for a number of reasons. First, these data were available at the time the CVZ advice was drafted (because we are doing a reanalysis). And second, the estimates from Coupe et al. more or less seem to be corroborated by Jacobs et al. [20] (although their sample is very small) and Bogaards et al. [21, 22]. Because the data on the HPV prevalence are not unequivocal, however, we performed sensitivity analyses making other assumptions on the HPV prevalence than used in our base case. This showed that outcomes are quite sensitive to varying the HPV prevalence. Therefore, acquiring new information about the appropriate age group could make our estimates more reliable.

Second, once the vaccination program would be operational, the HPV prevalence in the population would start to reduce over time. Moreover, as the (prevaccine) prevalence decreases, the efficacy of the vaccine across the population will increase. Therefore, our effectiveness estimates do not apply to longer time horizons after implementation of the vaccination program.

Third, the proportion of noncompliers was based on an assumption, which was made by taking an interval of values around the noncompliance rates from the FUTURE trials (which were approximately 10%). We based our assumptions on the FUTURE trials because data on noncompliance in the current sense (not getting all three injections or not at the appropriate times, or getting an HPV-16/18 infection during the vaccination period) can most probably be observed only in a trial situation. It is possible or even likely, however, that when a vaccination program is in fact offered, the noncompliance rate would be higher than that found in a controlled trial situation. Moreover, we could wonder whether it is reasonable to assume equal noncompliance rates for both the placebo and the vaccine arms as we have done. We also investigated the sensitivity of outcomes to alternate noncompliance rates, but the effectiveness measure proved not to be very sensitive to the noncompliance rate (certainly when compared with the HPV prevalence) (data not shown).

Fourth, in our analysis we have not made a distinction between HPV type 16 or HPV type 18 infections. In reality, the two types may be associated with different risk profiles, and we could want to take this into account by dividing up our group of HPV-16/18-infected subjects and by using separate HPV-16 and HPV-18 prevalences. In our case, however, the data from the FUTURE II study did not allow for making these distinctions. In a similar vein, if we had sufficient data we could in principle refine our analysis by distinguishing more groups. For instance, the second group from Table 2 was treated here as noncompliers, but if we look at the criteria that were used to distinguish the first two populations from the FUTURE II study (and thus the first two of our reorganized groups from Table 1), not all these subjects are in fact noncompliers, and even those who are noncompliers may be so because of different reasons. The methodology for the supplementary analysis that is used in this article could certainly be extended to allow for refinements of the cases and groups of patients, provided that such data are available from the literature or other sources.

We already noted that, based on numbers such as the per-protocol effectiveness of 98% and the intention-to-treat effectiveness of 44% from the FUTURE II study, CVZ concluded that the effectiveness of Gardasil was sufficient. On the basis of our

Table 2 – Bayesian results.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Prevalence 95% CI</th>
<th>Mean</th>
<th>95% credible interval</th>
<th>$P(\text{eff}) &gt; 0.5$ (%)</th>
<th>$P(\text{eff}) &gt; 0.25$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main analysis</td>
<td>7–13</td>
<td>25</td>
<td>7–41</td>
<td>0.0</td>
<td>53</td>
</tr>
<tr>
<td>SA1</td>
<td>1–3</td>
<td>63</td>
<td>30–91</td>
<td>76</td>
<td>99</td>
</tr>
<tr>
<td>SA2</td>
<td>5–10</td>
<td>30</td>
<td>12–46</td>
<td>0.5</td>
<td>73</td>
</tr>
<tr>
<td>SA3</td>
<td>5–15</td>
<td>27</td>
<td>7–44</td>
<td>0.0</td>
<td>58</td>
</tr>
<tr>
<td>SA4</td>
<td>10–15</td>
<td>22</td>
<td>3–38</td>
<td>0.0</td>
<td>38</td>
</tr>
</tbody>
</table>

Notes. Results from our main analysis (assuming a 95% interval for the HPV-16/18 prevalence ranging from 7% to 13%) and from four sensitivity analyses (making alternative prevalence assumptions). Shown are summary data for the posterior distributions on the final effectiveness: the mean, (Bayesian) 95% credible interval, and the probabilities that the effectiveness will exceed 50% and 25%.

Fig. 2 – Posterior distributions. The posterior probability distribution for the effectiveness (the proportion of HPV-16/18-related events that can be prevented because of vaccination) in the target population is shown in panel (A). A cumulative probability function for the posterior distribution is shown in panel (B). The vertical lines show that the probability that the effectiveness in the target population is smaller than 25% and 50% (the cumulative probability) is 0.47 and approximately 1, respectively.
supplementary analysis, we can see that an effectiveness of 25% is more likely in the actual target population and that the probability that the vaccine’s effectiveness in the target population exceeds 50% is virtually zero. Conceivably, having the outcomes from our supplementary analysis would have changed CVZ’s opinion about the prophylactic effectiveness of Gardasil.

Acknowledgments

We thank the Dutch National Health Insurance Board for giving the opportunity to perform this project by providing a case to reanalyze and their participation in the presentation of the results.

Source of financial support: This study is part of a larger project (Title: Potential and limitations of Bayesian analyses in synthesis of evidence from multiple sources. Project number 80-82500-98-8201. Coordinator: Professor. Dr. G.J. van der Wilt) funded by the Council for Health and Health Services Research from The Netherlands, ZonMw. The funding organization had no role in the conceptualization of the study, the collection and analysis of the data, or in the reporting of the results. There are no conflicts of interest.

REFERENCES