Review of HPV vaccination in the Netherlands

Review and Response to Review of "HPV-vaccination in the Netherlands: clinical efficacy, immunogenicity, safety and estimated impact of the HPV-vaccines licensed for use in pre-adolescent girls"

Center for Infectious Disease Control – 15 June 2016
Reviewer 1

In general, the data presented in the document represent the knowledge currently available in the scientific literature, and taken together with the advisory document from 2008, and the relatively straightforward modelling approach presented (including the type-specific vaccine efficacy estimates for the three vaccines), can provide a solid basis for the tendering process.

My suggestions are relative to obtaining the best possible estimates of the attributable fractions for HPV in certain non-cervical cancers. Indeed, [...], we have an ongoing research theme on the fraction of cancers around the world that are attributable to oncogenic infections. This was last published in de Martel, Lancet Oncol 2012, but methodology is being continuously improved as new data become available. Based on our experience, I would suggest the following evidence-based improvements to AFs for HPV in non-cervical cancers:

**OROPHARYNX CANCER**

- There has been a clear choice to consider the AF for HPV in oropharynx cancer to be zero, but no clear explanation why (as was done for genital warts).
- The causal link between HPV16 and oropharyngeal cancer has been established by an international expert working group (IARC monograph 100b) and is well accepted. Indeed evidence for the link between HPV16 and oropharynx cancer at that time was considered stronger than that for many non-HPV16 types with vulva, vagina and anal cancer.
- Whilst the HPV AF in oropharynx cancer is known to vary around the world, and by gender within the same country (Combes, CEBP, 2014), I do not believe that the assumptions involved for the causality of HPV16 in oropharynx cancer are any less evidence-based than those for non-HPV16 types in anal, vulva or vagina cancer.
In the latest update of our AF work, that is soon to be released, the following approach was taken: "the prevalence of high-risk HPV in OPC was estimated from case series where HPV diagnosis in tumour samples was ascertained using PCR methodology (studies extracted and updated from Kreimer et al, and Ndiaye et al). Then a "corrected" PCR-based HPV positivity was applied by multiplying the regional prevalence by 87% (Combes et al, CEBP 2014). The corrected prevalences were assumed to represent the attributable fractions.". The resulting AF for North-West Europe was calculated as 42% for example.

Data have even been summarised in recent meta-analyses specifically for women (15%, n=350) in the Netherlands (Combes, CEBP, 2014).

Given the strong importance of HPV16 in oropharynx cancer (an estimate of which can be obtained from other meta-analyses or big case series), and the fact that the number of cases are higher than for vulva or anal cancer in the Netherlands, it would likely have the effect to slightly reduce the difference between the estimated impact of 2v and 9v overall.

I do not know if differential survival of HPV-positive and HPV-negative OPC poses additional problems for the modelling of Life-years gained.

Response: we acknowledge that the choice to omit oropharynx cancer from our analysis was not clearly motivated. We concur with the reviewer that there is strong evidence for a causal association of HPV-16 with oropharynx cancer, but vaccine efficacy against (precursors of) oropharynx cancer has not yet been demonstrated. For this reason, none of the three HPV vaccines is registered for the prevention of (precursors of) oropharynx cancer. As we based our analysis on EPAR registration documents, we decided not to include oropharynx cancer. The reviewer points out that inclusion of oropharynx cancer would slightly reduce the difference in estimated impact between the HPV vaccines. This is true in a relative sense, but the absolute differences between the vaccines would remain the same; almost all cases of HPV-positive oropharynx cancer are due to HPV-16, which is included in each vaccine.
VULVA CANCER

- Another improvement in attributable fractions that are being used in our ongoing work is to apply an age-specific AF for HPV in VULVA cancer, given that age is a well-established and strong determinant of HPV positivity (de Sanjosé et al., Eur J Cancer 2013; de Vuyst, IJC, 2009). Based on the same data used in the current analysis (de Sanjose Eur J Cancer 2013), we apply the following age-specific AFs for vulva cancer: Age 15–54 years=48%; Age 55–64 years=28%; Age 65+=15%. These AFs could easily be applied to the age-specific national vulva cancer statistics for the Netherlands. However, it may not affect the relative impact of 2v, 4v and 9v very much.

Response: we did not consider age-specificity in etiologic fractions, and thank the reviewer for sharing this insight. We may have underestimated the impact of HPV vaccination, as more life-years are to be gained from the prevention of cancers occurring at a relatively young age, where HPV is more likely to be the causal factor in case of vulva cancer. We assumed that 14.5% of HPV-positive vulva cancer cases are due to HPV9v-specific types, i.e. HPV-31/33/45/52/58. Therefore, the extent of underestimation would tend to be somewhat larger for HPV9v than the other vaccines.

We used an overall etiologic fraction for vulva cancer of 18%, which is close to the 15% figure for 65+ women. In the Netherlands, 75% of vulva cancer diagnoses over the period 2013-2015 occurred in women older than 60 years, and only 18% occurred in women below the age of 55 years. Hence, application of age-specific etiologic fractions to the vulva cancer incidence would only have a limited effect on the estimated impact of HPV vaccination. Likewise, the difference in estimated impact between the vaccines would only be slightly affected.
CIN2/3

- Type-specific AFs for CIN2/3 are more difficult to estimate due to the high prevalence of multiple infections for HR types in meta-analytical data of these lesions. Hence some algorithm for causal attribution has to be applied, and I do not have a strong opinion of one over any other. In any case, it would seem that CIN2/3 does not contribute to the main outcomes for prevention of cancer nor Years gained.

- The type-specific prevalences for CIN2 and CIN3 shown in Table 3 are taken straight from our meta-analysis by Guan et al, and add up to more than 100%. It would be important to show those obtained AFTER the weighted re-distribution of multiple infections, i.e. those applied in the impact estimate, which would also clarify the effect of the redistribution algorithm.

- Of note, the type-specific proportions taken from Guan et al are based on HPV-positive cases only, so the estimates include an implicit assumption that all CIN2 and CIN3 are HPV-positive. This may be acceptable.

- Furthermore, estimates are from the worldwide pooled estimate. We can provide the estimates from Guan et al for the CIN2 and CIN3 cases from Europe only, which are far less related to HPV52 (~7% and 6% for CIN2 and 3 respectively) and 58 (~6% and 4%) (which are particularly prevalent in Asia) compared to the world picture. I believe this would reduce the difference in estimated impact on CIN2/3 between 2v and 9v.

- There is a section reporting vaccine protection against CIN 2 and 3 of any type. However, I am assuming that these estimates did not feed into impact models (because they cannot be extrapolated from CIN 2 and 3 to cancer, which is due to a different balance of HPV types).

- I believe the 97.1% vaccine efficacy for Gardasil 9 against HPV31/33/45/52/58 CIN2+ presented in Table 3 is calculated versus Gardasil 4 not placebo, and so though it can make only a small difference, this is maybe worth a footnote.
Response: the reviewer correctly asserts that we assumed all CIN2/3 cases to be caused by HPV. Perhaps our statement that “HPV is presumed to be the causative agent of all cervical disease” was a bit cryptic, but this is what we meant to imply. The reviewer is also correct in assuming that the estimated impact of HPV vaccination on CIN2/3 occurrence does not feed into the estimated impact on cancer incidence or life-years gained. The reviewer points out that attribution of high-grade lesions to HPV types is complicated by the fact that some lesions test positive for multiple HPV types. We did not so much alter HPV-type distribution of CIN2/3 cases, but used a weighted vaccine efficacy for those CIN2/3 cases testing positive for multiple HPV types. To elaborate, we applied the following algorithm:

\[ V_{E_w} = \frac{1}{n}(V_{E_1} + \ldots + V_{E_n}) \]

Here, \( V_{E_i} \) denotes the vaccine efficacy against the \( i \)-th type detected in the lesion, and \( V_{E_w} \) denotes the weighted vaccine efficacy. If multiple types are detected in a lesion, we simply take the average of the type-specific efficacies. This effectively conforms to assigning equal probabilities of causality to either type detected in a multiple lesion. One could also consider assigning probabilities on the basis of HPV-type distribution in cervical cancer (leading to preferential attribution to HPV-16 whenever this is detected in a multiple lesion) but this might lead to an overestimation of the impact of vaccination on CIN2/3 occurrence.

We did not correct for geographic variation in HPV-type distribution in CIN2/3. If HPV-52 and HPV-58 are detected less frequently in the Dutch screening programme than we assumed on the basis of worldwide estimates, than we may have overestimated the impact of HPV9v on CIN2/3 occurrence and likewise the difference with HPV2v or HPV4v. However, this will not feed into the number of cancer cases prevented or the number of life-years gained per cohort of vaccinated girls.

Vaccine efficacy of HPV9v was indeed calculated versus HPV4v and not placebo. This could have been added as a footnote to Table 3.
Reviewer 2

On the whole this constitutes a well-written and scientifically robust summary of the evidence around the three current HPV vaccines licensed for use in adolescent girls. I will comment mainly on the section on estimated impact since that is my field of expertise.

It is not clear to me exactly how the information in the document will be used in the vaccine tendering process. The information in the document is accurate and adequate, but I think that there are a number of issues that are also relevant to the value of the three available vaccines:

**Other outcomes**
The document discusses HPV vaccine protection against cervical, anal, vulvar and vaginal cancer, as well as mentioning protection against warts. However, there are a number of other endpoints for which there is fairly strong support that the vaccines are likely to prevent. An example is oropharyngeal cancer. A proportion of oropharyngeal cancers are related to HPV infection (IARC says “there is strong epidemiological evidence for the causal role of HPV 16 in the etiology of cancers of the oropharynx and tonsil”), and studies in Costa Rica have found that HPV vaccination reduces oral HPV infection. Hence it is extremely likely that HPV vaccination will prevent some oropharyngeal cancers. There are also other outcomes which may be relevant eg. laryngeal and tonsillar cancers, and recurrent respiratory papillomatosis.

*Response:* we do believe that the eventual impact of HPV vaccination may extend to other outcomes than those considered in our analysis, but the current analysis was based on EPAR registration documents. None of the three HPV vaccines is registered for the prevention of cancers (or precursors thereof) related to the tonsils, oropharynx, or larynx. We concur with the reviewer that there is strong evidence for a causal association of HPV with cancers of the tonsils and oropharynx, but vaccine efficacy has only been demonstrated against oral HPV infection and not against disease precursors, which is a prerequisite for registration. Recurrent respiratory papillomatosises (RRP) were not considered because we restricted our analysis to the direct benefits of vaccination, i.e. disease outcomes prevented in a cohort of vaccinated girls. Clinical symptoms of RRP are commonly found in babies or small children, but they seldom occur in preadolescents and adults.
Clinical efficacy

The direct impact of vaccines is estimated based on clinical efficacy against CIN2+ as shown in Table 3 of the document. However, it needs to be acknowledged that there are considerable uncertainties around these figures because of multiple HPV types often being found in cervical lesions. There are a number of different ways of attributing lesions to HPV types, and the figures here only represent one way. Efficacy against persistent infection is less susceptible to these differences in interpretation, although further away from the main endpoint that we want to prevent (i.e. cervical cancer).

Response: the reviewer points out that type-specific efficacy against CIN2+ is less certain than efficacy against type-specific persistent infection. This is true to some extent; the proportion of CIN2 cases testing positive for multiple HPV-types makes it difficult to assess causality. However, this is less of a problem with CIN3 cases and even less for cervical (or other) cancers. Moreover, we deliberately aimed to quantify the impact of HPV vaccination on disease outcomes. If we would have started from efficacy against type-specific infections, we would be faced with many more uncertainties than in the current analysis. For example, we would have had to making assumptions about the natural history of infection for all the relevant HPV-types, about progression to the various disease endpoints, the intervening effect of cervical screening, et cetera. Thus, while the use of type-specific clinical efficacy certainly has its shortcomings, it enables a relatively straightforward approach to assess the impact of HPV vaccination in terms of cancers prevented and life-years gained in a cohort of vaccinated girls.

Indirect effects

It is not clear to me why the document does not discuss herd protection, which is a major component of the benefit of all three vaccines, and for which there is strong supportive evidence from both mathematical models and post-vaccination surveillance. In particular, the considerable burden of HPV related diseases in males will likely be partly prevented through herd protection from a female-only programme such as the current one in the Netherlands.

Response: the choice to ignore herd protection was motivated by the advisory document from 2008 and the cost-effectiveness calculations that were made at the time. Inclusion of herd effects would likely lead to considerably higher estimates of the HPV vaccination impact in the total population, but would only marginally alter the number of cancers prevented or life-years gained in the cohort of vaccinated girls. Moreover, there is no reason to suspect that herd protection would be much different between the three HPV vaccines (apart from their differential impact on genital warts, which are not considered in the document). Nonetheless, the current analysis should be seen as a very conservative approach to estimating the population impact of HPV vaccination, irrespective which vaccine is used.
Duration of protection

The document assumes no difference in the duration of protection between the vaccines (page 14). In fact, what it assumes in the impact calculations is that the vaccines all give lifelong protection. Both of these are strong assumptions, although admittedly any other assumption will be equally contentious. Normally I would expect to see sensitivity analyses around such major sources of uncertainty such as this. It should be noted that assuming lifelong protection, even if the same assumptions is made across all three vaccines, will affect the three vaccines differently and hence may be seen as favourable to particular vaccines. This is because different HPV types have different rates of acquisition and progression to cancer.

Response: a full assessment of the population impact of HPV vaccination should consider sensitivity analysis around some key parameters. Duration of vaccine protection is one of those, and our assumption of lifelong efficacy is perhaps optimistic. However, there is no indication of waning efficacy from long-term follow-up of girls or adults vaccinated with HPV2v or HPV4v. For HPV9v, our assumption of lifelong efficacy is more uncertain, as there really is no information on this parameter at the moment. We could have performed calculations on the basis of a number of scenarios, but this was outside the scope of the current analysis. We fully acknowledge that the duration of protection is a major source of uncertainty, especially regarding HPV9v. This could have been stressed at several instances, but it is mentioned prominently in the Conclusion.