



## Review of HPV vaccination in The Netherlands

January 2020

Review and response to review of  
PROJECTED DIRECT BENEFIT OF VACCINATION AGAINST HPV-RELATED  
CANCER IN THE NETHERLANDS

REVIEWER 1

I reviewed the report – it strongly draws from evidence based data and is appropriate. I have 2 mains comments:

1) The WHO SAGE recently recommended that all new country introductions of gender-neutral vaccination be temporarily postponed until the vaccine shortage is important. See attached. Given the limited number of vaccine-preventable cases in males in your country, I think this is relevant.

**Response:** This report has the specific aim to inform on the differential health gains for vaccinated individuals that are to be expected from using either one of the available HPV vaccines and was prepared in response to the ministerial decision to introduce sex-neutral vaccination in the Netherlands from 2021 onward. As such, we did incorporate health gains for vaccinated boys in our calculations of the projected benefit of vaccination against HPV-related cancer in the Netherlands. The recommendation to introduce sex-neutral vaccination predates this report and was made by the Ministry of Health Welfare and Sport (VWS) taking into account the Dutch Health Council report, based on considerations (amongst others) of disease burden in men as well as women. Ultimately, vaccine choice will be based on multiple criteria, of which continued supply (or global shortage) could be one.

2) At the end of your document, you state 'Thus, HPV9v is projected to gain 4.3% more life-years than HPV2v, which is in turn projected to gain 10.7% more life-years than HPV4v.' You need to indicate the variability in these estimates using confidence intervals. I suspect they overlap, at least for HPV9v and HPV2v, thus making those 2 vaccines indiscernible in terms of life years saved.

**Response:** The calculations of the projected benefit of vaccination against HPV-related cancer were based on a Bayesian evidence synthesis framework that was previously used to assess the cost-effectiveness of sex-neutral HPV vaccination in the Netherlands. While this framework allows for a quantification of uncertainty in life-years gained that derives from uncertainty in model parameters, the uncertainty in long-term outcomes of vaccination is also strongly dependent on model structure several qualitative factors, such as duration of vaccine-type protection, level of cross-protection, and the still unresolved possibility of type-

CIb

A. van Leeuwenhoeklaan 9  
3721 MA Bilthoven  
Postbus 1  
3720 BA Bilthoven  
www.rivm.nl

T 030 274 91 11  
info@rivm.nl

replacement. To elaborate, our calculations assume that the overall benefit of vaccination can be quantified as a sum of type-specific benefits across multiple disease outcomes. This approach assumes independent natural histories of infection by HPV type and HPV-related cancer, as well as independent modes of protection by HPV type and HPV-related cancer. While these assumptions provide a plausible paradigm for describing HPV epidemiology, it is difficult to fully quantify our uncertainty around the long-term outcomes of vaccination. Even so, we do not concur with the supposition of the reviewer that the difference between HPV9v and HPV2v in life-years gained could become indiscernible, at least not within the framework used for calculations. Assuming that HPV9v provides stronger protection than HPV2v against types other than HPV16/18, as suggested by the EMA EPAR documentation, their difference in terms of life-years to be gained is real and 4.3% is currently our best estimate.

## REVIEWER 2

It is with pleasure that I offer Prof van Dissel and colleagues my comments to your report 'Projected direct benefit of vaccination against HPV-related cancer in the Netherlands', which I understand will serve the basis of the tendering procedure for gender-neutral HPV vaccination program in the Netherlands.

I first note that the purpose of this report is not to inform the decision of whether to advise gender-neutral vaccination or not. This separate, but related, issue requires more attention to the incremental benefit of gender-neutral vaccination above that of indirect protection from girls-only vaccination, which is not addressed here. To this end, I would also highlight the recent recommendations made by WHO SAGE given global HPV vaccine shortages and coverage inequality (see attached). Most notably "that all countries should temporarily postpone implementation of HPV vaccination strategies that are gender-neutral".

Response: The WHO SAGE recommendation was also brought up by the previous reviewer. The advice on sex-neutral vaccination was not based on this report; for that, it would be erroneous to disregard herd effects, as pointed out by the reviewer. To reiterate, the recommendation to introduce sex-neutral vaccination predates this report and was made by the Dutch Health Council, based on considerations (amongst others) of disease burden in men as well as women, and of (economic) efficiency, including an assessment of indirect protection from girls-only and sex-neutral vaccination.

I also note my support for the approach taken to focus on life years gained (i.e. prevention of cancer mortality) of HPV vaccines, rather than issues of genital warts.

Response: This report was prepared in response to the ministerial decision to extend HPV vaccination in the Netherlands with inclusion boys next to girls from 2021 onward. However, the objective of the HPV vaccination remains the prevention of HPV-related cancer, as specified in the ministerial decision. For this reason (apart from the fact that their

prevention does not alter the health gains in terms of life-years to be gained), anogenital warts are not considered in the document.

Given these premises, my subsequent advice concerns only the estimation of the direct effect of male vaccination on male cancers, (and of female vaccination on female cancers), as outlined in the report.

The overall approach based on a combination of 1) Dutch cancer incidence (and survival), 2) HPV type-specific prevalence in cancer cases, and 3) type-specific vaccine efficacy data against cervical disease, is a strong and appropriate one. I address these components one by one below. I do not expect the overall conclusions to be changed according to my comments, which mainly serve to highlight how, given the limitations of the available data, how projected life-years gained in men are expected to be highly similar for the different vaccines.

#### Cancer incidence

- Given that data are based on a national cancer registry with longstanding and comprehensive coverage, data on the number of male cancer cases and survival are robust and relevant. Even if there were some small changes to incidence, e.g. future increases because of changing exposure to HPV, this would not expect to greatly effect relative impact of the different vaccines. Nor would any improvements in survival.

**Response: We thank the reviewer for this endorsement.**

#### Type-specific HPV prevalence in cancer

- Based on the evidence from cervical cancer, an IARC expert group classified 14 high-risk HPV types as human carcinogens. Although the DNA of many other HPV types can also be found in cervical cancer series (e.g. 0.5% for HPV6), there was not significant evidence to show that these prevalences were elevated above that which would be expected in the cervix of women without cancer, and so there was not considered to be sufficient evidence of causality for additional types.
- For HPV-related cancers outside the cervix, however, only HPV16 has been recognised as showing sufficient evidence for causality (see summary of IARC monograph 100B attached). Indeed, as can be seen in the table 2B of the present report, HPV16 is found in the large majority of male HPV-related cancer.
- Thus, given that all vaccines are expected to protect against HPV16 approximately equally, any eventual difference in vaccine impact is largely driven by decisions about causality for non-HPV16 types. The decision has been made to include HPV18, HPV39, HPV45, HPV31, HPV33, HPV52, HPV58 and HPV51 as causal types, with fractions based largely on detection of DNA from large case series. I suspect this list is based on those 14 cervical carcinogens which have been shown to be significantly protected in some way at the cervix by existing vaccines (i.e. those types that could potentially change the differential between vaccines), rather than an a priori decision of causality at non-cervical sites.

- That being said, etiological fractions for these types remain small, so these decisions have relatively little impact on an eventual difference between vaccines on male-cancers, which is expected to be small.

Response: We agree with the reviewer that differences in vaccine impact between the available HPV vaccines are driven by prevention of non-HPV16 (and -18) types, and that etiological fractions for these types are much smaller than for HPV16 (and, to a lesser extent, -18). We also agree that differences are predominantly due to projected impact on female cancers, much less than male cancers. Consequently, the projected differences in terms of life-years gained are small but not negligible, as non-HPV16/18 attribution to cervical cancer is still substantial. After all, HPV is presumed to be the causative agent of all cervical disease, constituting a very high disease burden, and almost 30% of cervical cancers are due to non-HPV16/18 types. We based our calculations on the 14 high-risk HPV types that have been classified as human carcinogens, but omitted those types that are not prevented by the available HPV vaccines from calculation, as these other types are immaterial for eventual differences in vaccine impact.

#### Type-specific vaccine efficacy

- These estimates are based on evidence of efficacy on type-specific CIN2+ (i.e. in the cervix). Given that these are the best and only data that are readily available, it is a reasonable assumption to extrapolate such data to type-specific protection at other sites. Indeed, at a population-level in the Netherlands, type-specific effectiveness on HPV prevalence at the anus (Woestenberget al, J Infect Dis, 2019), has recently been shown to mirror that seen against HPV types at the cervix (Woestenberget al, J Infect Dis, 2018).

Response: The reviewer is correct in pointing out that all our estimates are based on vaccine efficacy (VE) as demonstrated against cervical disease. This is because VE against non-cervical disease has been studied less extensively, especially with regard to type-specific efficacy for non-HPV16/18 types (i.e. those driving eventual differences in vaccine impact between the available HPV vaccines). However, there is no evidence to suggest that VE is dependent on site of HPV infection, and we thank the reviewer for mentioning this. Note that the study providing type-specific VE estimates against anal HPV infections was already included in the list of references, although we did not make explicit that this concerned anal (as opposed to genital) outcomes. We also note that VE against prevalent oral HPV 16/18 infections four years after vaccination has been estimated at 0.93 (95% confidence interval 0.63 to 1.00), which is not significantly different from protection against persistent cervical infections (Herrero et al, PLoS One 2013; e68329.).

- Some of the absence of cross-protection knowledge is more due to lack of data than evidence of lack of effect. Particularly for HPV4v for which the publication of cross-protection data from clinical trials has not been pursued with as much energy as for HPV9v. Nevertheless, data of HPV4v cross-protection are now arising from population-level studies of effectiveness against HPV infection, e.g. 60% against HPV31, 33, and 45

in Australia (Tabrizi SN, lancet Infect Dis 2014). Furthermore, we have recently observed 47% (95% CI 23 to 64%) effectiveness against all non-HPV16 alpha-9 types in the HPV4v program in Rwanda (Baussano, submitted). This is not so relevant for the difference between HPV2v and HPV9v, however.

Response: We based our analysis on EPAR registration documents, that report a lower cross-protective efficacy from HPV4v than HPV2v. While lack of evidence is indeed not equal to evidence for lack of effect, we do not concur with the reviewer that this would be due to a paucity of data. In fact, most post-vaccine surveillance studies concern HPV4v and not HPV2v, as the four-valent vaccine has been the preferred choice in most Western countries (e.g. Australia, USA, UK nowadays) since vaccine implementation. A systematic review comparing the cross-protective efficacy of HPV2v and HPV4v already concluded that cross-protective vaccine efficacy estimates against infections and lesions associated with non-HPV16/18 types were higher for the bivalent vaccine than the quadrivalent vaccine (Malagón et al, Lancet Infect Dis 2012). This finding has recently been reiterated in a post-vaccine surveillance study in Luxembourg, where both HPV2v and HPV4v have been used by (pre)adolescent girls since 2008 (Latsuzbaia et al, Cancer Epidemiol 2019). For HPV4v, significant cross-protection on a type-specific level in post-vaccine surveillance has only been reported for HPV-31 in Norway (Feiring et al, J Infect Dis 2018). In Australia, where HPV4v has been used from the onset, post-vaccination studies have indeed reported a significantly lower prevalence of HPV-31/33/45 combined in vaccinated versus unvaccinated women (see also Chow et al., Lancet Infect Dis 2015), but with HPV-45 still predominating among these types (Garland et al, Vaccine 2018). In the USA, the prevalence of HPV  $\alpha$ -9 types, genetically related to HPV-16, decreased significantly among women who received only HPV4v, but the prevalence of HPV  $\alpha$ -7 types, genetically related to HPV-18, did not (Covert et al, Hum Vaccin Immunother 2019). Finally, the reviewer points to (as yet unpublished) data from Rwanda, but as far as we know, estimates of cross-protective VE in this study were derived from HPV tested on urine samples, but cross-protection could not be replicated when using DNA extracted from cervical smears.

To provide more information on the cross-protection from HPV4v in the report, we have added the following paragraph (with references as mentioned above) to Section 1, preceding Table 4 on type-specific efficacy estimates:

*"For HPV4v, significant cross-protection on a type-specific level in post-vaccine surveillance has been reported for HPV-31 in Norway [19]. In Australia, where HPV4v has been used from the onset, post-vaccination studies have reported a significantly lower prevalence of HPV-31/33/45 combined in vaccinated versus unvaccinated women [20,21], but with HPV-45 still predominating among these types [22]. In the USA, the prevalence of HPV  $\alpha$ -9 types, genetically related to HPV-16, decreased significantly among women who received only HPV4v, but the prevalence of HPV  $\alpha$ -7 types, genetically related to HPV-18, did not [23]. Luxembourg has offered either HPV2v or HPV4v to (pre)adolescent girls since 2008,*

*and observed significant protection against HPV-31/33/45/52/58 in girls who received HPV2v, but not for girls who received HPV4v [24].”*