Modeling the effects of cervical cancer prevention in the Netherlands

Vink, M.A.

2015

document version
Publisher's PDF, also known as Version of record

7 | Summarizing discussion

In this thesis we described newly developed mathematical models for evaluating the effects of public health measures for cervical cancer prevention. A detailed discussion regarding the research questions themselves has been provided at the end of each chapter. This section will briefly summarize the policy questions that we addressed and explain the added value of mathematical modeling to inform public health policy. We end with recommendations for future research and the role of mathematical modeling therein.

EFFECTS OF HRHPV SCREENING ON THE CERVICAL CANCER RISK

Randomized controlled trials (RCT's) have shown that adding hrHPV DNA testing to cytology in organized screening increases the sensitivity and the negative predictive value for CIN2+ detection[1-4] and hence has the potential to increase the effectiveness of cervical screening. As of 2016, the Netherlands will use the hrHPV test as a primary screening instrument and the screening interval will be extended from 5 to 10 years in women who are hrHPV screen -negative at age 40 or 50 years.[5] Although the population-based screening trials support the use of hrHPV testing based on its superior accuracy for detecting CIN2/3 and cancer, the effect of extending the screening interval has not been investigated in any of the trials. An interval extension seems recommendable as the hrHPV test has a slightly lower specificity than cytology and may therefore lead to an increase in redundant colposcopies.

New screening algorithms are preferentially evaluated with regard to the end-point cervical cancer. However, in Western countries with population based screening programs, the cervical cancer incidence is low. The trial size necessary to evaluate a new screening program on cervical cancer incidence would be very large and the study unmanageable. Therefore, the primary end-point in screening trials is CIN2/3. In a pooled analysis of four large RCT's, the effect of hrHPV screening on the cervical cancer incidence could be assessed but the effect of an interval extension was not an objective in any of these studies. We developed a simulation model for studying this. For this simulation model, knowledge about the duration from CIN2/3 to cancer is required. This information is hard to obtain as women with a detected CIN2/3 are treated and for that reason, follow-up is subject to informed censoring: the probability to detect CIN2/3 scales inversely with the rate of progression to cervical cancer. In **Chapter 2**, we developed a statistical model to estimate the duration from age-specific proportions of CIN2/3 versus cancer obtained from cancer registry data in the Netherlands. The statistical model takes the treatment-related censoring explicitly into account, distinguishes between progressive and non-progressive CIN2/3, and estimates the duration to cancer for progressive CIN2/3 by a gamma distribution. This distribution has a shape parameter to describe a change in cancer hazard since onset of CIN2/3. The median duration between CIN2/3 onset and preclinical cervical cancer was estimated at 23.5 years. The median duration was similar for HPV16-positive CIN2/3 and HPV16-negative CIN2/3, but within 10 years the proportion that progressed to cancer was larger for HPV16-positive CIN2/3.

The estimated distribution of the time to cancer allowed us to assess the effects of the new screening program in detail. In **Chapter 3** we developed a cohort simulation model for studying the change in lifetime cervical cancer risk under the new screening program for women without a hrHPV infection at age 30 to 50 years. We showed that the new screening program is expected to lead to a further reduction in the lifetime cancer risk for these age cohorts. The effects depend on the mean value of the time to cancer, and on the shape parameter of its probability distribution. We performed a sensitivity analysis varying both, and observed a reduction in lifetime cancer risk in most scenarios. An increase in cancer risk was only observed when CIN2/3 developed to cancer relatively fast (i.e., 30% progression within 10 years). In literature, there is lack of consensus on the duration from CIN2/3 to cervical cancer. We compared our estimated distribution of the time to cancer with the duration observed in a historic longitudinal analysis in New Zealand, one of the few studies available that presents empirical data on this topic.[6] The duration between CIN2/3 and cancer in the progressive cases in the New Zealand study could accurately be estimated by a gamma distribution with mean 10 years (and shape parameter 1) which is markedly shorter than our estimated duration. An important difference is that our estimate represents the time between CIN2/3 *onset* to cancer, while the estimate from the New Zealand study represents the time between CIN2/3 *detection* to cancer. The time between CIN2/3 *onset* and CIN2/3 *detection* was in our model approximately 5 years, and it is likely to be even larger in the opportunistic screening setting in which the New Zealand study was conducted.

- *The safety of the new screening program strongly depends on the time to cancer distribution*
- *The duration from onset CIN2/3 to preclinical cervical cancer is long; the median duration is 23.5 years*
- *The proportion CIN2/3 that progresses to cancer fast (within 10 years) is larger for HPV16-positive CIN2/3 compared with HPV16-negative CIN2/3*
- *The new screening program is expected to further reduce the lifetime cervical cancer risk for women without an hrHPV infection at age 30 to 50 years*

EFFECTS OF HPV VACCINATION ON MARKERS OF HPV16 INFECTION

The introduction of HPV vaccination will lead to a change in infection risk in the unvaccinated population. These indirect effects of vaccination are called herd effects and are expected to be relevant for unvaccinated women and men.[7, 8] It will take decades before the clinical impact of HPV vaccination on cancer can be detected. Studies on the prevalence of type-specific HPV DNA (a marker of current HPV infection) or on the prevalence of type-specific IgG antibodies in serum

(a marker of past infection) might provide an early insight into the herd effects of the current girls-only vaccination program.

For monitoring the herd effects of prophylactic HPV16/18 L1 VLP vaccination by means of serosurveillance, knowledge of the pre-vaccination natural antibody response to HPV16 and HPV18 in the general population is essential. This will serve as a benchmark for future serological surveys. In **Chapter 4** we analyzed natural HPV16 IgG serum antibodies against HPV16 L1 virus-like-particles (VLP) from data collected prior to the introduction of vaccination.[9] The serological measurements were obtained with a VLP-based multiplex immunoassay that was designed for detecting antibody responses evoked after prophylactic HPV16/18 L1 VLP vaccination. This immunoassay provides weak signals when used for the detection of natural HPV16 and HPV18 antibodies; the levels of naturally occurring HPV antibodies are low and sometimes difficult to contrast from the background noise of the multiplex assay.[10] We developed a two-component mixture model with age-specific mixing proportions to estimate the HPV16 seroprevalence in the general Dutch population prior to introduction of prophylactic HPV16/18 vaccination. We provided prior knowledge to the statistical model: because the chance that young children have had an HPV infection is very low, we assumed that the antibody concentrations of 0-10 year olds contributed to the seronegative mixture component only. We estimated sex-specific HPV16 seroprevalence figures and showed that men have a weaker seropositive response compared with women, while the seronegative response is independent of sex. Using a cut-off value for classifying a person as seropositive will underestimate the true seroprevalence because of the poor sensitivity combined with high specificity. The sensitivity is lower for men compared with women and therefore the underestimation will be stronger in men. Individual classification by means of a cut-off value is not necessary if the objective is to estimate the HPV seroprevalence in the population. As our aim is to use serological data for surveillance purposes, it is sufficient to give persons a probability of being seronegative or seropositive as in our mixture model approach.

To further understand the serological response after a natural HPV infection, we performed a joint analysis on HPV16 and HPV18 antibody concentrations in women by a four-component bivariate mixture model (**Chapter 5**). This bivariate model was better able to classify individuals in the correct out of 4 components (i.e., seropositive or seronegative for HPV16 and/or HPV18) compared with a univariate analysis. Moreover, it enabled quantification of the association between naturally occurring HPV16 and HPV18 seropositivity and of their association in antibody concentrations in the multiplex assay. The estimated marginal HPV16 seroprevalence from the bivariate model was larger than the HPV16 seroprevalence of the univariate analysis in **Chapter 4**. In **Chapter 6**, we linked incident HPV16 infection to a subsequent serological response in order to match the pre-vaccine HPV16 seroprevalence as estimated in **Chapter 4** to transmission model estimates. Using a two-component mixture model, we estimated that approximately 76% of women seroconverted. In order to match the HPV16 seroprevalence figures of **Chapter 5**, the seroconversion rate would probably be near 100%. It should be further investigated if and

how these differences in marginal seroprevalences affect the interpretation of future serological surveys for the herd effects of HPV vaccination.

From the bivariate analysis, we could also assess dependencies between HPV16 and HPV18 antibody detection. We found a strong correlation between the natural antibody concentrations in the mixture components that represent individuals that are double seronegative or double seropositive to HPV16 and HPV18. This correlation might be caused by the multiplex assay itself. It might be that these natural HPV16 and HPV18 antibodies as found in non-vaccinated women show high cross-reactivity in this assay, or that the read-out of type-specific signals is, despite its high reproducibility,[9] affected by systematic assay variation. However, the strong correlation in the seropositive antibody concentrations could also reflect the immunologic profile of a host's response to HPV infection. Alternatively, the immunological response might be directed to common epitopes of types 16 and 18 upon repeated encounters with HPV. We also found that association in HPV16 and HPV18 seropositivity was stronger than expected by chance, particularly for the age group 10-20 years. This might indicate that the double seropositive persons between age 10 and 20 years are people with high-risk sexual behavior.

In **Chapter 6** we used an HPV transmission model, published before,[11] to study how vaccination changes the infection risk in the unvaccinated population. We assessed the herd effects of HPV vaccination on the HPV16 infection prevalence and HPV16 seroprevalence. Large reductions in both the HPV infection prevalence as well as the seroprevalence are expected within 10 years after the introduction of HPV vaccination. Because the vaccinated women will shield their sexual partners from infection, the reductions will be larger for unvaccinated men (reduction of 74%) compared with unvaccinated women (reduction of 58%). For unvaccinated women, the reductions are mainly limited to the vaccinated age cohorts while a spillover to older age groups for unvaccinated men is expected. We showed that after the introduction of female vaccination, a small increase in the HPV16 incidence for unvaccinated women around age 30 years is expected. Our predicted prevalence and seroprevalence figures will aid in organizing monitoring studies and can be used for validating model outcomes when post-vaccine cross-sectional data become available.

- *The use of a cut-off value to denote seropositivity will underestimate the prevalence of naturally occurring HPV16 antibodies (HPV seroprevalence).*
- *The HPV16 seroprevalence in women as estimated by a bivariate analysis with HPV18, is larger than the HPV16 seroprevalence estimated in univariate analysis.*
- *HV16 and HPV18 seropositivity co-occurs more frequently than expected by chance, in particular for the age groups 10-20 years.*
- *At the vaccine coverage of 60% large reductions in the HPV16 infection prevalence and HPV16 seroprevalence are expected in the unvaccinated population within 10 years after the introduction of prophylactic HPV16/18 vaccination. These reductions will be larger for unvaccinated men compared with unvaccinated women.*

FUTURE PERSPECTIVES

Monitoring the effects of HPV vaccination

The ultimate goal of HPV vaccination is to reduce the cervical cancer incidence. Until the clinical effects become apparent, surrogate endpoints (e.g., incident or prevalent HPV infection, seroprevalence or CIN2/3 lesions) may be employed to obtain a measure of vaccination effectiveness at an earlier instance. In this thesis, we studied the expected changes in markers of HPV infection: the HPV DNA status (representative for current HPV infection) or the presence of HPV antibodies (representative for past HPV infection). The first effects of HPV vaccination will appear in studies targeting these surrogate endpoints. However, more advanced surrogate endpoints in terms of disease progression will better reflect the effectiveness of vaccination on the end-point cervical cancer. Over time, the effects of HPV vaccination on more advanced disease stages, in particular the CIN2/3 prevalence, will become apparent. Organized screening programs will inform on the change in CIN2/3 detection and will replace the monitoring studies targeting HPV infection markers.

The effects of bivalent HPV vaccination should be monitored carefully in both the vaccinated and the unvaccinated population. Next to studies in the teenage population that target type-specific HPV DNA prevalence and HPV seroprevalence (the HAVANA study that follows a partly vaccinated cohort of young girls over time,[12] and the PASSYON study that performs cross-sectional surveys amongst visitors of STI clinics[13]), two other data sources are available that enable monitoring the population-based effects of vaccination: the Dutch nationwide pathology registry of histological and cytological specimen (PALGA) and the population-based serological surveys PIENTER. In the next section, we will highlight some of the possibilities that these frameworks offer for monitoring vaccination effects on surrogate endpoints.

Monitoring by means of HPV DNA prevalence figures

The hrHPV test will be used in organized screening starting in 2016.[5] This provides a framework for monitoring the effects of vaccination on a change in the hrHPV prevalence in women from 2023 onwards (when the vaccinated cohorts reach screen eligible age). The high participation rate of organized screening of around 70% of the Dutch female population is a big advantage for monitoring the effects of vaccination by means of this framework. Since vaccination effects are mainly limited to the vaccinated age cohorts (see **Chapter 6**), the hrHPV DNA prevalence figures from the cohorts that participate in screening in 2016 can serve as a benchmark of the pre-vaccine population. From 2023 onwards, a substantial reduction in the hrHPV prevalence in the vaccinated but only a small reduction in the unvaccinated female population is expected (**Chapter 6**). For monitoring purposes it would be valuable to use a clinically validated HPV test for cervical screening that gives at least information about HPV16 and HPV18 genotypes for studying type-specific changes in the HPV DNA prevalence. For further evaluation of the effect of bivalent vaccine on the prevalence of other HPV types it is advised that cervical material of women who are HPV screen-positive, is further genotyped for at least the hrHPV types.

Monitoring by means of HPV antibodies from cross-sectional serological surveys

The next PIENTER survey (scheduled for 2016/2017) will enable a first population-based assessment of the effects of bivalent HPV vaccination in the Netherlands. The use of serological surveys is twofold. First, the vaccine-induced antibody levels in the vaccinated population can be assessed. A strong serological response after vaccination is considered a measure of vaccine protection, although the exact correlate of protection (i.e., the level of antibodies that implies protection against future HPV infection) is unknown. A decay in HPV16/18 antibody levels over time may indicate a loss of vaccine-induced protection against infection with HPV and thus point to imperfect protection against cervical cancer. In addition, this survey might be used for assessing whether there is a difference in antibody levels or in the decrease in these levels between the cohorts that received the HPV vaccine at a 3-dose schedule compared with those that received the vaccine at a 2-dose schedule. If the antibody levels in the 2-dose cohorts are indeed lower, this might indicate imperfect protection. However, as the 2-dose vaccine schedule is only in place since 2014, the next PIENTER survey might come too soon for differences to become apparent.

Second, serological surveys will give insight into the indirect effects of vaccination. A large reduced seroprevalence of HPV16 and HPV18 is expected in the unvaccinated population already within 10 years or even earlier post vaccination (see **Chapter 6**). Despite the large potential, it should be assessed whether the expected reduction in HPV seroprevalence can indeed be observed by 2017. The natural HPV16/18 antibody response as measured by the serological assay is weak and therefore we estimated the HPV16 seroprevalence with wide 95% credible intervals. In addition, as the vaccine coverage is currently around 60%, only 40% of the female population of the vaccinated ages can be used for evaluating the change in seroprevalence in women. Although a large reduction is expected, it might not be discernible due to a lack of statistical power. Note that the serological surveys have the big advantage that they can inform on the change in HPV infection dynamics in the male population. As we expect stronger herd effects in men than in unvaccinated women, and all males can be used for assessing these effects, the next PIENTER survey holds promise for showing a reduced HPV16 transmission in the general male population.

Implications if the duration of vaccine-induced protection is not lifelong

So far, the bivalent vaccine has proven efficacious against incident and persistent HPV infections and incident CIN2/3 up to 9.4 years of follow-up.[14] However vaccines rarely provide lifelong protection[15] and therefore the duration of vaccine-induced protection should be monitored carefully. The duration of protection will obviously impact the direct effects of vaccination but also the indirect effects as discussed in **Chapter 6** will be affected. If protection is not lifelong, vaccinated individuals that have lost their vaccine-induced immunity might benefit from the reduced force of infection. The impact of a vaccine that does not provide lifelong protection should be further investigated. A transmission model as used in this thesis is necessary for integrating disease natural history and the complex structure of disease transmission.

Monitoring by means of CIN2/3 prevalence figures

All cytological and histological excerpts that are made inside or outside the national screening program are registered by the nationwide network and registry of histo- and cytopathology reports in the Netherlands (PALGA). After the introduction of HPV16/18 vaccination, a change in the prevalence of CIN2/3 is expected. Although most CIN2/3 lesions are diagnosed in women of screen-eligible age, yearly around 500 CIN2/3 cases are detected in women below age 29 years through opportunistic screening (PALGA data from the years 2000-2005, see **Appendix 1**). Hence, early empirical evidence on the effectiveness of HPV16/18 vaccination may already be discernible in the PALGA database in the next couple of years.

From 2023 onwards, when the vaccinated cohorts reach screen-eligible age, also a large reduction in CIN2/3 lesions is expected in both vaccinated and unvaccinated women. In the Netherlands, around 1800 CIN2/3 cases are yearly diagnosed in women aged 29-30 years.[16] If it is assumed that the vaccine coverage remains 60% and that 60% of the CIN2/3 lesions are caused by HPV16 (see appendix of **Chapter 2**), a reduction of at least 650 CIN2/3 is expected. In addition, protection against HPV18 related CIN2/3, cross-protection offered by the bivalent vaccine, and the indirect benefit in the unvaccinated women will further contribute to a reduction in the number of CIN2/3 lesions.

Currently, screening and vaccination registries in the Netherlands are not linked. In addition, hrHPV typing of high-grade lesions or the referral smear is not standard practice. This will complicate estimation of the vaccination effects. Linkage of the vaccination and screening registries is necessary for comparing the effects of HPV vaccination in vaccinated women (direct effects) and unvaccinated women (indirect effects). Partial hrHPV genotyping, as present in most clinically validated HPV screening tests, of cervical smears and CIN2/3 lesions will further aid in determining the effects of HPV16/18 vaccination, and in assessing the amount of cross-protection to non-vaccine HPV types or the occurrence of type replacement.

Optimization of the screening program for partly vaccinated age cohorts

Cervical cancer screening will continue after vaccination. The current vaccine does not provide protection against all oncogenic types, although cross-protection has been demonstrated and a new nonavalent vaccine has recently been approved by the Food and Drug Administration. However, lifelong protection has not yet been proven, and the vaccine uptake is far from 100%. However, the introduction of HPV vaccination to the national immunization program will likely affect the efficiency of the organized screening program for cervical cancer. The examination of the Pap-smear is subjective and a decrease in the CIN2+ prevalence will influence the positive predictive value of cytology-based screening.[17, 18] It is expected that this problem is less severe when using the hrHPV test as primary screening instrument; the hrHPV test result is objective and does not depend on the prevalence of hrHPV infections in the population. Nevertheless, compared with the pre-vaccine era the expected gain of screening for an individual in the post-vaccine era will decrease. Therefore, the screening program in the post-vaccine era should be

modified in order to redress the balance between the screening burden and gains. A natural way of reducing the screening burden is by revising the invitation scheme and inviting women less frequently (e.g., longer intervals in between screening rounds). Note that the new Dutch screening program that will start in 2016 involves a screening interval extension up to 10 years for HPV screen-negative women aged 40 and 50 years, but this has not specifically been designed for the vaccinated cohorts. Reconsidering the screening interval for the vaccinated age cohorts is further supported by the fact that vaccination strongly reduces the prevalence of the most oncogenic hrHPV type: HPV16. Further research on the optimal screening interval and whether the screening algorithm should depend on vaccination status is necessary. Mathematical modeling will prove useful for answering these questions as one has to account for herd effects, and one has to project the change in cancer risk for a variety of screening algorithms.

In conclusion, the introduction of HPV vaccination and of hrHPV-based cervical screening are expected to further reduce the lifetime cervical cancer risk for both vaccinated and unvaccinated women. In the years to come, the effects of vaccination still have to be monitored, and primary and secondary prevention programs should be integrated in order to optimally protect women from developing cervical cancer. Modeling studies will help to find out how this integration can be optimally implemented.

REFERENCES

1. Naucler P, Ryd W, Tornberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med.* 2007;357(16): 1589-1597.
2. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol.* 2010;11(3): 249-257.
3. Rijkaart DC, Berkhof J, Rozendaal L, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. *Lancet Oncol.* 2012;13(1): 78-88.
4. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet.* 2014;383(9916): 524-532.
5. National Institute for Public Health and the Environment (RIVM). Feasibility study for improvements to the population screening for cervical cancer [in Dutch]. 2013.
6. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol.* 2008;9(5): 425-434.
7. Bogaards JA, Coupe VM, Xiridou M, et al. Long-term impact of human papillomavirus vaccination on infection rates, cervical abnormalities, and cancer incidence. *Epidemiology.* 2011;22(4): 505-515.
8. Brisson M, van de Velde N, Franco EL, et al. Incremental impact of adding boys to current human papillomavirus vaccination programs: role of herd immunity. *J Infect Dis.* 2011;204(3): 372-376.
9. Scherpenisse M, Mollers M, Schepp RM, et al. Seroprevalence of seven high-risk HPV types in The Netherlands. *Vaccine.* 2012;30(47): 6686-6693.
10. Stanley M, Gissmann L and Nardelli-Haefliger D. Immunobiology of human papillomavirus infection and vaccination - implications for second generation vaccines. *Vaccine.* 2008;26 Suppl 10: K62-67.
11. Bogaards JA, Xiridou M, Coupe VM, et al. Model-based estimation of viral transmissibility and infection-induced resistance from the age-dependent prevalence of infection for 14 high-risk types of human papillomavirus. *Am J Epidemiol.* 2010;171(7): 817-825.
12. Mollers M, Scherpenisse M, van der Klis FR, et al. Prevalence of genital HPV infections and HPV serology in adolescent girls, prior to vaccination. *Cancer Epidemiol.* 2012;36(6): 519-524.
13. Vriend HJ, Boot HJ, van der Sande MA, et al. Type-specific human papillomavirus infections among young heterosexual male and female STI clinic attendees. *Sex Transm Dis.* 2012;39(1): 72-78.
14. Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine. *Hum Vaccin Immunother.* 2014;10(8): 2147-2162.
15. Moxon ER and Siegrist C-A. The next decade of vaccines: societal and scientific challenges. *The Lancet.* 2011;378(9788): 348-359.
16. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol.* 2007;29(1): 19-24.
17. Franco EL, Cuzick J, Hildesheim A, et al. Chapter 20: Issues in planning cervical cancer screening in the era of HPV vaccination. *Vaccine.* 2006;24 Suppl 3: S3/171-177.
18. Franco EL and Ferenczy A. Cervical cancer screening following the implementation of prophylactic human papillomavirus vaccination. *Future Oncol.* 2007;3(3): 319-327.