CHAPTER 11:

General discussion
This thesis describes research on monitoring activities of the Dutch HPV vaccination program, concerning intermediate endpoints (HPV-infections) related to vaccine effectiveness and immunogenicity in the Netherlands and gives insight into several challenges encountered. In this discussion, I will elaborate on the most important findings from this thesis, in relation to the current Dutch vaccination program and future perspectives.

Current Dutch HPV vaccination program: bivalent vaccine in a two-dose schedule
As mentioned in Chapter 1 of this thesis, the Netherlands have implemented HPV vaccination in their National Immunization Program (NIP) in 2010 for girls aged 12 years. In 2009 a catch up campaign was offered to girls born between 1993 and 1996. Up to 2013 girls received three-doses (0, 1, 6 months) of the bivalent HPV vaccine. From 2014 onwards (birth cohort 2001) girls were vaccinated with a two-dose (0,6 months) schedule.[1] For any NIP disease monitoring of vaccination effects and impact in the population after implementation is considered of great importance. Monitoring the NIP provides the opportunity to explore the impact of routine vaccination in a real life setting. Ideally vaccine effectiveness for the HPV vaccine from a public health perspective is shown on the reduction in HPV-associated cancer cases. Given the long duration between HPV infection and the onset of HPV-associated cancers, several intermediate endpoints (persistent infections of at least six months or anal/cervical intraepithelial neoplasia) are considered by the World Health Organization (WHO) for the evaluation of HPV vaccines. Several factors are of influence on the ultimate impact of HPV vaccination programs, i.e. HPV vaccination coverage, the original prevalence distribution of HPV types, and characteristics of different HPV types, such as the ability to generate persisting infections and the transmission probability.[2]

In the Netherlands, several studies are in place to monitor the effects on effectiveness or immunogenicity of the HPV vaccination program. In a population-based effectiveness study, among girls eligible for the catch-up vaccination campaign we showed high vaccine effectiveness against incident and 12-month persistent infections with HPV16/18/31/33/45 up to six years post-vaccination.(Chapter 2) Findings of our study were in line with previous trials and other observational studies examining the bivalent vaccine. [3-6] Importantly during our follow-up up to six years post-vaccination we did not find indications for waning of
cross-protective effectiveness. Our findings are in line with recent results from Scotland [7] and a Dutch study among STI clinic visitors [8], but are in contrast to Malagon et al. where indications for waning after five years were found. [9] Differences might be explained by systematic differences, for example in duration of follow-up or inclusion criteria, between the included trials in the meta-analysis. Longer follow-up of our cohort should reveal whether cross-protective effectiveness will wane or not.

In several countries observational studies showing good vaccine effectiveness against cervical precursor lesions have become available.[4, 10-12] Most of these countries start their cervical cancer screening program at a younger age, for example two years after sexual debut or from the age of 21, than the Netherlands and therefore effects on prevalence of CIN are earlier available. In the Netherlands where screening starts from the age of 30 years onwards, the first vaccinated women will be eligible for cervical cancer screening in 2023.

Implementation of HPV vaccination raised the concern that a vaccine against an STI might lead to more and/or riskier sexual behavior by vaccinated adolescents. [13] Possible differences in behavior that exist or may develop over time between vaccinated and unvaccinated girls might influence the effectiveness of HPV vaccination.[14] In evaluation of sexual behavior over time, it should be considered that vaccinated and unvaccinated girls differ in their characteristics already by start of vaccination.[15, 16] In Chapter 3 we explored how possible differences in sexual behavior and HPV knowledge developed over time between HPV-vaccinated (3-doses) and unvaccinated girls eligible for catch-up vaccination. We did not find indications for a change in difference in condom use over time with casual and steady partner. However, in our study vaccinated girls were less likely to always use a condom with their steady partner. Although the HAVANA-study was not designed and powered for the evaluation of sexual (risk) behavior, questions with regard to sexual behavior were posed each round to the participants. We did not observe any significant difference in sexual behavior or in change over time between vaccinated and unvaccinated participants in the HAVANA study (Chapter 2). So our findings in Chapter 3 were mainly in line with Chapter 2.

In 2014, the Dutch Minister of Health, Welfare and Sports, based on approval by the EMA, decided to implement a two-dose schedule for HPV vaccination.[17]
At that time analyses so far mainly compared immunogenicity in girls (9-13/14 years of age) to immunogenicity in young adult women (15-25 years of age), the so called immuno-bridging comparison. Based on this comparison the approval for a two-dose schedule was given by regulatory authorities.[18, 19] At the time of implementation of the two-dose schedule in the Dutch National Immunization Program (NIP), we systematically reviewed (Chapter 4) available information with regard to antibody concentrations of two- and three-dose schedules in (young) women. Our review showed that the immuno-bridging results were non-inferior up to 36 months for the quadrivalent vaccine and up to 48 months for the bivalent vaccine. However non-inferiority could not be shown at all time points for both the bivalent (at 7 and 24 months for HPV16 and from 24 months for HPV18) and quadrivalent vaccine (from 18 months onwards for HPV18), when comparing girls within their own age group. These findings were confirmed in a cross-sectional observational study using immunogenicity data from girls (birth cohort 1997-2000) routinely eligible for three-doses, but having received two- or three-doses up to 4 ½ years ago (Chapter 5). We only found non-inferior antibody concentrations for the vaccine and cross-protective types, for HPV18/31/33/45 at 2-3 years post-vaccination. Independent of antibody concentrations we observed non-inferior antibody avidity for vaccine and cross-protective types comparing three versus two-doses up to 4 ½ years vaccination. We concluded that close monitoring of vaccinated cohorts with two-dose vaccination schedules was needed. Following-up the first birth cohort eligible for two-dose HPV vaccination (HPV2D), birth cohort 2001 eligible for vaccination in 2014, in the Netherlands showed high antibody levels, with high avidity against vaccine types, up to 24 months after vaccination. (Chapter 7)

The discussion with regard to reduced dosing schedules for HPV vaccination, is hampered by the lack of an immune correlate of protection, i.e. no threshold level of antibodies resulting in protection could be defined. Even with low antibody levels, protection sustained.[20, 21] Also other factors of the immune response are of influence on the success of HPV vaccination schedules.[22] In Chapter 6, a review up to the fall of 2015, we found comparable results with regard to antibody levels and avidity as in our previous review and cross-sectional study. Data with regard to T-cell formation after a two-dose schedule (0,6 months) was inconclusive. A study using the quadrivalent vaccine found for HPV11 comparable T-cell memory and a lower response for HPV6/16/18 when comparing girls (9-13
years) to young adults (immuno-bridging) or when comparing girls to girls of their own age.[23] Another study using the quadrivalent vaccine and comparing girls within their own age group (9-14 years) found comparable T-cell memory for HPV16/18.[24] B-cell memory seems to be mainly influenced by age and not by dose. Comparable B-cell responses were found in girls 9-14 years of age receiving either two- (0,6 months) or three-doses. For HPV18 a better B-cell response was observed among the younger recipients.[24] Data on cellular immunity against cross-protective types after vaccination with a two-dose schedule is currently not available.

Till date, data with regard to comparable immunogenicity between two- and three-dose schedules up to sixty months has become available and is reassuring.[25] Effectiveness studies on genital warts [26, 27], HPV infections [28-30] and cervical lesions [10, 31, 32] indicate in some cases a slightly lower effectiveness for a two-dose schedule. However, some methodological challenges arise when using these studies. Girls included in these studies received this schedule unintentionally, while being eligible for a 3D schedule, [33, 34]. It should be considered that girls who have completed their schedule appear to be different than those who do not.[35] In addition, girls who had received two-doses by accident, not always received the licensed dosing schedule, but could have received the second dose too early (within five months) after vaccination. Kavanagh et al. indicated that although a slightly higher infection rate was found after two-doses, no difference in cross-protective effectiveness against prevalent infections (HPV31/33/45) was observed between two- and three-dose recipients.[28] The study by Kreimer et al. indicate slightly lower cross-protective effectiveness (HPV31/33/45) against incident and persistent infections after two- compared with three-doses, however did not take into account timing of the second dose. [30] The timing of the second dose seems to be of large influence on the effectiveness estimates, an increasing interval between the doses diminished differences between the three- and two-dose schedules.[26] Although at implementation of the two-dose schedule uncertainties especially with regard to long-term protection existed [17, 36], by combining available data on immunogenicity and effectiveness of the two-dose schedule (with the recommended interval) so far, results of the two-dose schedule are reassuring for vaccine types HPV16/18 and cross-protective types HPV31/33/45, and for the quadrivalent vaccine also against genital warts.[7, 26-30]
No monitoring data on early intermediate endpoints like presented for the three-dose schedule (Chapter 2) is available yet in routinely vaccinated cohorts with two-doses. Currently these kinds of studies are being set-up and performed globally. Examples of long-term cohort studies evaluating the effectiveness of the two-dose HPV vaccination schedule are the Canadian QUadrivalent HPV vaccine Evaluation STudy (QUEST) and the Dutch HAVANA2 study [37]. QUEST examines non-inferiority of six-month persistent HPV infections by comparing two- with three-dose recipients. The HAVANA2 study is a longitudinal study following girls eligible for routine vaccination with two-doses of bivalent HPV vaccine including both vaccinated and unvaccinated girls. Primary objective is to show vaccine effectiveness against 12-month persistent vaccine-type HPV infections. On a longer time frame, also data on precursor lesions from cervical cancer screening is expected to become available, expected to give an even more stable estimate on the effects of a two-dose schedule against cervical disease.

Key points:
Monitoring of the Dutch HPV vaccination program has shown:
- High vaccine effectiveness of the three-dose schedule up to six years post-vaccination with the bivalent vaccine against vaccine types HPV16/18 and cross-protective types HPV31/45 was found, in a longitudinal cohort of routinely vaccinated girls.
- We did not observe indications for waning of cross-protection, in this same cohort study.
- No statistical significant different changes occurred over time for vaccinated versus unvaccinated girls in sexual behavior. Vaccinated and unvaccinated girls were equally likely to always use a condom with their casual partner, vaccinated girls were less likely to use condoms with their steady partner.
- Evaluation of immunogenicity and first international data on effectiveness of two-doses of HPV vaccination so far is reassuring
- No data on intermediate endpoints for two-dose HPV vaccination in routinely vaccinated cohorts is available yet, but a cohort study with this aim is in place.
Methodological challenges in monitoring the vaccination program

Several challenges exist when monitoring vaccination programs. A challenge which not only applies to HPV but also to other diseases is the non-inferiority margin. As described in Chapter 8, no clear guidelines are available for the use of non-inferiority margins in vaccine studies. We found that most studies used the implicitly recommended margins of a difference of 10%, or a geometric mean concentration/titer of 1.5/2.0. In most articles reporting on non-inferiority, explanation with regard to the margin was lacking. It is questionable whether vaccines for different pathogens, with different reactogenicity and immunogenicity profiles, should all use the same non-inferiority margin. Doing so, might lead to the use of margins that might be too strict or too loose, and therefore showing or rejecting non-inferiority unfairly. Therefore we suggested a framework to determine a margin. The proposed methodology indicates that a starting value for the non-inferiority margin should be adapted based on characteristics of the vaccine and trial. This suggested framework could further be adjusted by regulatory authorities, for example, using an expert panel.

In Chapter 2, we estimated the vaccine effectiveness against HPV16/18 persistent infections (of at least 12 months) up to six years post-vaccination at 97.6% (82.2-99.7%). Although precursor lesions represent a stage of disease closer to cervical cancer, persistent HPV infections of longer than six months are considered as a more convenient endpoint for the evaluation of HPV vaccines.[38] The use of persistent infections as an outcome itself comes with several challenges. There are some uncertainties at this point in the natural history of HPV, for example whether HPV infections are really cleared and reinfection occurs or that infections can become latent and later reactivated.[39] Measuring persistent infections requires longitudinal studies with standardized follow-up periods and participation in these kinds of studies, especially in adolescent populations can be challenging. In the Dutch cohort studies with annual follow-up we achieved participation rates of approximately 10-20%. Loss to follow-up in our observational cohort study HAVANA was approximately 40% over time, with the biggest drop observed in the first two years of the study. After this time the loss to follow-up became more stable with almost no loss in the latest years of follow-up.

Also, there are various statistical approaches available to analyze data from longitudinal studies evaluating effectiveness against persistent HPV infections. In
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Chapter 9, we have examined these different statistical methods, specifically to get insight into differences between available statistical methods and compared the impact on VE estimations by applying these methods to data of the HAVANA study. Although differences with regard to underlying assumptions between these methods exist we found quite comparable estimation for the effectiveness against HPV16/18/31/33/45 persistent infections in young women eligible for routine HPV vaccination. We suggest the Prentice Williams Peterson Total-Time approach as most valid approach, as the assumption of proportional hazard was not violated and an event-specific hazard was observed. Confirmation of these findings should come from longer follow-up in the HAVANA-study and from other populations.

Key points:
Intermediate endpoints are accepted for the evaluation for HPV vaccination programs. Given the short follow-up since introduction of the HPV vaccine in the Netherlands, we monitored incident and persistent infections and immunogenicity and encountered the following challenges:

- Currently no clear guidelines exist for the use of non-inferiority margins in vaccine studies. Most studies use the implicitly recommended margins. However, it is debatable whether non-inferiority margins should be the same for all vaccines.
- Using persistent infections as an outcome in HPV vaccine evaluation studies comes with several challenges, as unknowns in the natural history and compliance of participants in these long-term studies.
- We suggest the Prentice Williams Peterson Total-Time approach as most valid statistical approach for the evaluation of vaccine effectiveness in adolescent girls.

Future perspectives
Since the original introduction of the HPV vaccine new insights have been generated. For example the shown efficacy and increase in knowledge on other HPV-associated diseases, as well as growing evidence with regard to reduced dosing schedules. In addition, as vaccinated cohorts mature it should be considered if and how cervical cancer screening might be adapted. Given the extensive developments in the HPV field, from 2017 onwards the Dutch Health Council will start a new advisory trajectory with regard to HPV vaccination, considering both boys and
girls. Another important development with regard to HPV vaccination in the Netherlands at the moment, is the suboptimal (declined) vaccination coverage. Some suggestions for improvement are described below.

**Non-cervical HPV-associated diseases**

Originally in the Netherlands, as in other countries, HPV vaccination was implemented for its known efficacy in the prevention of cervical cancer.[40] However since its implementation and original registration knowledge on the role of HPV as etiological agent in other than cervical cancers, as anal, penile, vaginal, vulvar and oropharyngeal cancer has been increasing. In addition also effectiveness of the prophylactic HPV vaccines against anogenital diseases has been shown and registration indications have been expanded to other HPV-related cancers.[3, 41] In Chapter 10, we explore the role of including non-cervical HPV-associated diseases in cost-effectiveness analyses. Including these diseases in the Incremental Cost-Effectiveness Ratio (ICER) shows a decrease of almost three (girls only programs) or four (gender-neutral programs) times. These much lower ICERs make it more likely for programs to fall beneath the cost-effectiveness threshold, enlarging the possibilities for large scale (gender-neutral) vaccination programs. It has been estimated that with an uptake of 60% among females, 795 boys should be vaccinated to prevent one case of HPV-related cancer in males.[42]

**Gender-neutral vaccination**

As mentioned previously, since the introduction in routine vaccination programs for girls, new evidence with regard to efficacy of the vaccine against diseases in males has become available. The registration of vaccines for non-cervical HPV-associated diseases has been expanded and all three vaccines have been licensed for their use in males.[3, 41] Considerations regarding implementing male vaccination could be to reduce transmission of HPV thereby increasing herd immunity and cervical cancer prevention; on the other hand it could be used for the individual protection of males against HPV-associated diseases (such as genital warts and anal and oropharyngeal cancer). In several countries the HPV vaccine is now offered in gender-neutral (vaccinating both boys and girls) programs. Besides the shown efficacy of the HPV vaccine in males, also equity is used frequently as an argument to also give the vaccine to boys. Originally several studies have suggested that the HPV vaccine wouldn’t be cost-effective in boys. However, as shown in Chapter 10, including all HPV-associated diseases compared to only
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cervical cancer as endpoint in a gender-neutral program the ICERs became 3.89 times lower, and will more likely to be within the cost-effectiveness thresholds. Recent analyses have shown that for the Netherlands, vaccination of boys will be cost-effective.[43]

Currently the share of males with regard to burden of HPV-associated diseases is rapidly increasing compared to women.[44] However, vaccination of boys is likely to be less efficient on a population level than increasing the uptake among girls. It has been estimated that to obtain the same effect for each female, two males should be vaccinated.[43] On the other hand, it should be mentioned that increasing the coverage among females might be much more complicated than getting a sufficient uptake among boys. Possibly, introduction of vaccination to boys will also have a positive effect on the uptake by girls. Moreover vaccination of MSM at older age will be less efficient than vaccinating boys since the prevalence of HPV in MSM is high at the time of vaccination and possibly less effective. Also it is of importance to consider, that men who have sex with men, will not benefit from HPV vaccination in women. Collectively these data argue for gender neutral vaccination and a new evaluation whether gender neutral vaccination should be introduced in the Netherlands. In 2018 the health council will start evaluate these and other arguments in their advice about HPV Vaccination to the minister of Health, Welfare and Sports.

Room for improvement: suboptimal vaccination coverage

As described above effectiveness of the current vaccination schedule is likely to be high for the vaccine types, as well as for cross-protective types. Furthermore, indications have been found that in case of good coverage of HPV vaccine among women herd protection in unvaccinated boys as well as unvaccinated girls are present.[42, 43, 45-47] However at present the vaccination uptake of the HPV vaccine in the Netherlands is suboptimal (53.4% in 2015). At this time, HPV vaccination in the Netherlands is offered in local (group) sessions by municipal health services. The invitation for the HPV vaccination in the Netherlands concerns an introduction folder and a link to a website with more information. [48] Since its introduction in 2009, the coverage slightly increased from 52.3% for the catch-up cohorts till 61.0% for birth cohort 2001 (Chapter 1, Introduction, Table 6). Unfortunately the uptake of the HPV vaccine in the Netherlands has now for the first time declined (vaccination year 2016) according to the most recent
vaccination coverage measurements.[49] Also in other countries, like for example in Denmark and Ireland a decline was seen. In Denmark girls vaccinated with the first dose declined from >90% in 2013 to about 40% in 2017.[50] Negative media attention after reporting of adverse events after immunization that are perceived by the public as being caused by the vaccine can have a strong impact on acceptance of vaccination.[51] As experienced in the UK after a sudden death shortly after vaccination, a fast response might help to prevent a decrease in vaccine uptake. Within several days health authorities were able to communicate that this death was not related to vaccination (but due to a tumor). Although otherwise suggested by several media and on social media, till date in line with the randomized clinical trials, as well as in post-licensure surveillance HPV-vaccination was shown to be safe. Most vaccine recipients experience mild and transient adverse events such as pain at the injection site and headache. No causal relation was found between the HPV vaccine and more serious adverse events found.[52-56]

Although this problem will not be easy to solve, some points for consideration will be stated here. Recent experiences in Denmark and Ireland in response to the decline in uptake is that creating a broad collaboration with various organizations which bring the same message of full support of vaccination to the public seem to be helpful to increase the public confidence in the HPV vaccine. In addition tailored communication strategies to improve the public knowledge are of great importance. Recently a web-based tailored intervention was developed, which has shown to improve the informed decision making and to improve HPV vaccination uptake. [48] It is worthwhile to explore how this tool can be implemented in the current information process for HPV vaccination. It has been suggested that a school-based HPV vaccination program would be the most acceptable in achieving high vaccination coverage.[57] As all childhood vaccines in the Netherlands are offered through the municipal health services, changing to a school-based program would require large and structural changes in the NIP. At the moment the HPV vaccination is mostly given in a group in for example a gym. It might be worthwhile to consider alternative delivery strategies for the HPV vaccine for the Netherlands. A benefit from changing to a school-based program could be that logistics of the program become more easier, especially when girls miss a vaccination opportunity Also groups might be reached which are underrepresented in the current program through mass vaccination by the municipal health services, as people from non-Dutch origin, or lower educated.
It might also be worthwhile to consider a more individual-based approach, where during an individual consultation with a professional questions can be answered and the vaccine can be given. Parents view health care workers as an important and reliable source with regard to vaccination information. [58] Also possibly changing to a gender-neutral HPV vaccination program might increase uptake, as it might become more natural to vaccinate adolescents against HPV, making the vaccine a vaccine that saves lives instead of women's lives. [59] Also the age at which the HPV vaccination is under debate in some countries. Some say that lowering the age to 9 or 10 years might be beneficial.

**Protection against genital warts**

Although not considered in the original aim by the Dutch Health Council based on the seven criteria described previously [40], genital warts represent a high burden among HPV-associated diseases. As stated in the introduction of this thesis, genital warts incidence is increasing in the Netherlands. Genital warts also have a large influence on quality of life, as they impact on emotional well-being and sexual activity. [60] In addition, the costs of treatment for genital warts are high. Recurrence rates even after treatment are high, 30% or higher. Surgical therapies have a higher initial clearance rate, almost 100%, but recurrences remain. [61] Including the prevention of genital warts (by use of the quadrivalent vaccine) into to NIP, showed a more favorable ICER for HPV vaccination. [62] It might be worthwhile, although not life-threatening, to consider including genital warts in the advice of the Health Council based on the economic burden and quality of life. Several studies so far have shown a strong decline in the incidence of genital warts after implementation of the quadrivalent HPV vaccine to their vaccination program. [63]

**Reduced dosing schedules: could one-dose of HPV vaccine be enough?**

Recently post-hoc analyses of the original vaccine trials and population-based effectiveness studies among women who did not complete the full HPV vaccine dosing scheme have suggested efficacy after even one dose of the vaccine. [30, 64, 65] If only one dose of HPV vaccine would be sufficient to guarantee protection, this opens the great opportunity to vaccinate more individuals against HPV with the same resources, especially in low-resource settings. The structure of the HPV vaccine antigen attributes largely to the exceptional immunogenicity of the HPV vaccine. HPV virus like particles (VLP) forms a particulate structure, displaying
on their surface a repetitive array of epitopes. The alliance of these repetitive structures with receptors on naïve B-cells is thought to lead to a cascade ultimately leading to strong induction of memory B-cells and long lived plasma cells, which produce antibodies for long periods of time.[66]

So far some data on effectiveness has become available. Two population-based registry studies examining the efficacy of different doses against genital warts, have found efficacy of one-dose of quadrivalent vaccine compared to unvaccinated, however was not as effective as two- or three-doses.[26, 27] Studies with regard to HPV infections showed for the bivalent HPV vaccine that cross-protective vaccine effectiveness against HPV31/33/45 could only be observed after two- or three-doses and not after one-dose of vaccine.[4, 30] Against HPV16/18 prevalent, incident and twelve-month persisting infections comparable effectiveness was observed. [4, 29, 30] Also for the quadrivalent vaccine comparable efficacy was observed for one, two and three-doses of the vaccine against incident HPV16/18 infections, with a median follow-up of 4.7 years. In addition also no HPV 16/18 persistent infections were found for any of the dosing schedules.[65]

With regard to immunogenicity for both the bivalent and quadrivalent vaccine antibody levels were lower (inferior) after a one-dose schedule.[65, 67] However, for the bivalent vaccine it was also shown that antibody concentrations were higher than those observed after natural infection.[67] Available evidence and the public health imperatives are requiring further exploration. Given the inferior immunogenicity, virological or disease endpoints will be required for the evaluation of a one-dose schedule.[66] Currently a one-dose efficacy trial is under development with NIH.[68] In this trial non-inferiority against six month persistent HPV16/18 infections of one-dose of bivalent and nonavalent vaccine is explored in comparison to two-doses among approximately 20,000 girls between 13-16 years of age. From a public health perspective, with high vaccination coverage, a slightly lower effectiveness of one-dose might not be prejudicial, if the uptake is high enough to avert HPV transmission in the population.

Cervical cancer screening
As stated in the introduction of this thesis, in 2017 the Dutch Cervical Cancer Screening Program changed their primary screening tool from cytology to HPV testing.[69] This has led to significant changes in the communication for women
eligible for the screening program. At this point this might indirectly influence the knowledge with regard to HPV vaccination, as mothers who are eligible for cervical cancer screening, might have daughters who are eligible for HPV vaccination.

In the Netherlands, cervical cancer screening only starts from the age of thirty, meaning that the first vaccinated cohort (birth cohort 1993), will be eligible for screening in 2023. Meanwhile a possible decline in histological and cytological outcomes (and from 2017 also HPV positivity) could be detected among women eligible for HPV vaccination, who had a gynecologic examination based on anogenital complaints. All histological and cytological outcomes in the Netherlands are kept in the PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief) database. and by linking this database to Praeventis, vaccine effectiveness among these opportunistically screened women can be determined. This data-linkage is currently planned.

In extension, a linkage between the cervical cancer screening program - and the vaccination registry is not only valuable for the evaluation of HPV vaccination effectiveness. It will also be helpful, when vaccinated cohorts become eligible for cervical cancer screening. The currently available vaccines, are not protecting against all high-risk HPV types, it is unknown whether the vaccines provide lifelong protection. Therefore screening of vaccinated women will still be needed, but it should be explored whether the current algorithm would be still the most optimal. In the Netherlands uptake of the vaccine is at this time approximately 60%. This leads to a mixed population of vaccinated and unvaccinated women, becoming eligible for cervical cancer screening. When cytology-based screening is used, the positive predictive value is negatively influenced by the decrease in CIN2+ prevalence among vaccinated women, because its subjective nature. As the accuracy of the HPV test is not dependent on the prevalence of HPV in the population, this problem is less severe when using HPV-based screening. On the other hand given the effectiveness of the HPV vaccine, it might be worthwhile to consider alternative algorithms for vaccinated cohorts. In addition it should be considered that if herd effects occur and might increase over time, also the screening algorithm in unvaccinated cohorts could be optimized. Cost-effectiveness analyses have suggested that using HPV-testing as primary screening tool, optimally three life-time screens for vaccinated women should be performed.
Key points:
Several new developments are ongoing since the implementation of HPV vaccination programs:

- The past years registration of the HPV vaccines has been broadened to other HPV-associated diseases and males. The Dutch Health Council will start a new advisory trajectory on HPV vaccination from 2017 onwards.
- When the additional benefits of the vaccine, with regard to non-cervical diseases are translated into cost-effectiveness analyses, the ICERs become more favorable. This broadens the scope for HPV-vaccination, more specifically for gender-neutral vaccination.
- There is growing interest in the possible efficacy of one-dose of HPV vaccine, but further research at this point is required. Several studies on immunogenicity and effectiveness are currently under development.
- With vaccinated cohorts becoming eligible for cervical cancer screening, adjustment of screening algorithms in terms of frequency and intervals need to be considered.
- Linkage between vaccination and screening registries is required, to make different algorithms for vaccinated and unvaccinated possible, but also to evaluate the effectiveness of the vaccination program.

Uptake in the Netherlands is currently declining. Possibilities to be considered to study for the potential to increase/stabilize uptake could be:

- Provide quick and reliable responses in case of negative (media) attention for the vaccine.
- Try to generate a broad alliance of organizations underlining the importance of HPV vaccination, in order to enlarge the public confidence in the program.
- Consider alternative delivery strategies, as for example more individual based/school-based HPV and/or gender-neutral vaccination programs an/or vaccination at younger age.

Currently also another initiative for a complementary prevention of cervical cancer is in place, HPV-FASTER. This protocol suggests HPV vaccination up to the age of 45/50 years old, in combination with HPV-based screening from the age of 30...
onwards, mainly for low- and middle-income countries.\[72\] The advantage is that by this approach vaccinated and unvaccinated women are synchronized in time and therefore can have the same screening program with extended intervals. For high-income countries, vaccination at young age and comprehensive screening might be more effective, given the limited effectiveness of the vaccines in older women.

**CONCLUSION**

Monitoring the Dutch HPV vaccination program has shown a high effectiveness of the bivalent HPV vaccine in a three-dose schedule against twelve month HPV16/18 persistent infections. In addition we did not find indications for waning of cross-protection. When comparing girls who had accidentally received two-doses to girls of their own age group receiving three-doses, although antibody levels were not non-inferior, antibody avidity was found non-inferior. Also follow-up of the first cohort of two-dose vaccinated girls showed high antibody concentrations and avidity up to 24 months after the first dose. Observational studies on the effectiveness of the two-dose schedule in a population-based setting are currently ongoing and are of great importance, especially in showing the long-term protection of the two-dose schedule. From 2017, the Dutch Health Council will start a new advisory trajectory with regard to the HPV vaccination program to address evidence with regard to the prevention of other HPV-related disease in addition to cervical cancer and vaccination of males. In coming years important policy and research questions are the effectiveness of one-dose schedules, gender-neutral vaccination and the confluence of the HPV vaccination program and the cervical cancer screening program. Given the high immunogenicity and effectiveness in observational studies among girls eligible for the routine vaccination programme in The Netherlands, efforts to try to increase vaccination uptake are needed to try to generate higher health benefits as result of HPV vaccination.
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