COURSE: Evidence-Based Approaches to HPV Screening implementation

Module 6. Impact of HPV vaccination on screening

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CONTENTS

INTRODUCTION AND LEARNING OBJECTIVES

Following the licensure of the first generation of HPV vaccines in 2006-2007, many countries have incorporated these vaccines into their national immunization schedules. This has led to what are known as 'vaccinated cohorts', i.e birth cohorts that were eligible for routine vaccination and got the vaccine at the target ages. Each cohort includes both vaccinated and unvaccinated individuals, with the proportions among women and men reflecting the vaccination strategy implemented and coverage achieved. These new populations of women, characterized by a distinct HPV epidemiology due to vaccination impact, are now reaching the age of screening initiation at 25 years and represent most younger women undergoing screening in the countries that started systematic HPV vaccination programs more than 10 years ago.

Quantifying the impact of the HPV vaccination program is essential for decision makers, not only to examine whether to introduce or modify HPV vaccination programmes but to evaluate those cervical cancer screening programmes already implemented.

This module reviews the impact of HPV vaccination on cervical cancer epidemiology and the potential impact of HPV vaccination on cervical cancer screening performance.

At the conclusion of this module, participants will be able to:

- Assess the impact of HPV vaccination programs on the epidemiology of HPV infection and HPV-related lesions and cancers in the cervix and other anatomical sites.
- Interpret the direct and indirect effect of HPV vaccination by vaccination strategy (girls-only versus gender-neutral vaccination)
- Describe the rationale and needs for adapting cervical cancer screening in the post-vaccination era, including the selection of screening tests, appropriate screening age and frequency, as well as triage and lesion management.

UNIT 1. IMPACT OF HPV VACCINATION ON HPV-RELATED BURDEN

It is estimated that by 2094, 11.6 million cervical cancer cases worldwide will occur in birth cohorts born between 2005 and 2014 if unvaccinated. Global vaccination of these cohorts could prevent 8.3 million cases (Bonjour et al., 2021 **RISCC**).

More than 18 years have passed since the first HPV vaccine was licensed as a 3-doses schedule and HPV vaccination became a reality. As of January 2025, 147 countries worldwide (76%) have introduced HPV in their national immunisation programmes albeit not equally across the board (**Figure 1**). In high income countries, 98% have introduced the vaccine, with 90% of them offering it to both girls and boys. In contrast, in low-income countries, only 46% have introduced HPV vaccination, only offered to girls, and therefore the vaccine uptake is much lower (Bruni et al., 2016).

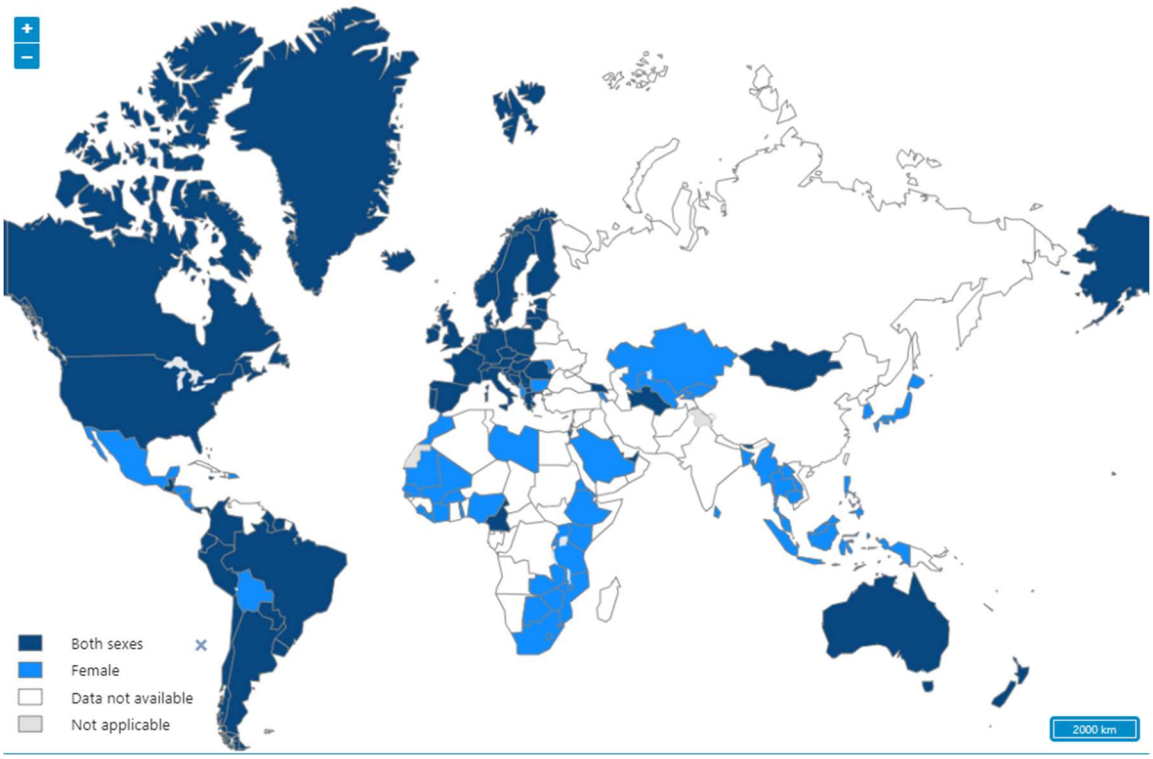


Figure 1. HPV vaccine introduced in national immunization programmes by targeted sex (World Health Organization, 2023)

Data from national immunisation programmes confirm the high efficacy against cervical precancerous lesions and cancer (90-100%) observed in randomised trials.

The huge population-level impact and effectiveness of HPV vaccination has been widely proven with respect to reducing cervical infection with the vaccine types, cervical precancerous lesions and, more recently, early-onset cervical cancer.

To record progress towards this objective and inform public health decision-making, it is important to be able to quantify the impact of the HPV vaccination programs. Measuring the impact is essential both to consider whether to introduce or modify existing HPV vaccination programmes and to assess the need for adjusting existing cervical cancer screening programmes.

How do we measure the effects of a vaccine?

The performance of a vaccine (i.e, the reduction in disease attributed to the vaccine) is described differently depending on the population analysed (Hanquet et al., 2013):

- **Efficacy** – It is measured in individuals randomly assigned to vaccination that have received the vaccine as intended (i.e, ideal conditions in clinical trials). Therefore, reflects the maximum effect that the vaccine can achieve.
- **Effectiveness** – It is measured under real-world conditions through observational studies and therefore is influenced by the population characteristics and/or factors related to vaccination such as problems with vaccine storage or modified vaccination schedules (interval between or number of doses).

Generally, the effect is estimated in vaccinated versus unvaccinated individuals, which is known as the **direct effect** of vaccination. However, In populations with sufficiently high vaccination coverage, unvaccinated individuals also benefit of a certain level of protection due to a reduced transmission of the infectious agent that leads to a lower probability of exposure. This is known as the **indirect effect** of vaccination, also known as **herd protection or herd effect**. To estimate both the direct or the indirect effect, the individual vaccination status of the subjects under study must be known.

- **Impact** – It is measured under real-world conditions through observational studies, that compare a population exposed to the vaccine to an unvaccinated one or a population before and after the HPV vaccine programme introduction. Consequently, the comparison groups are not necessarily 100% vaccinated or unvaccinated. The measured effect reflects both the direct and the indirect effect of the vaccine rather than the sum of both.

These effects are graphically depicted in **Error! Reference source not found.**.

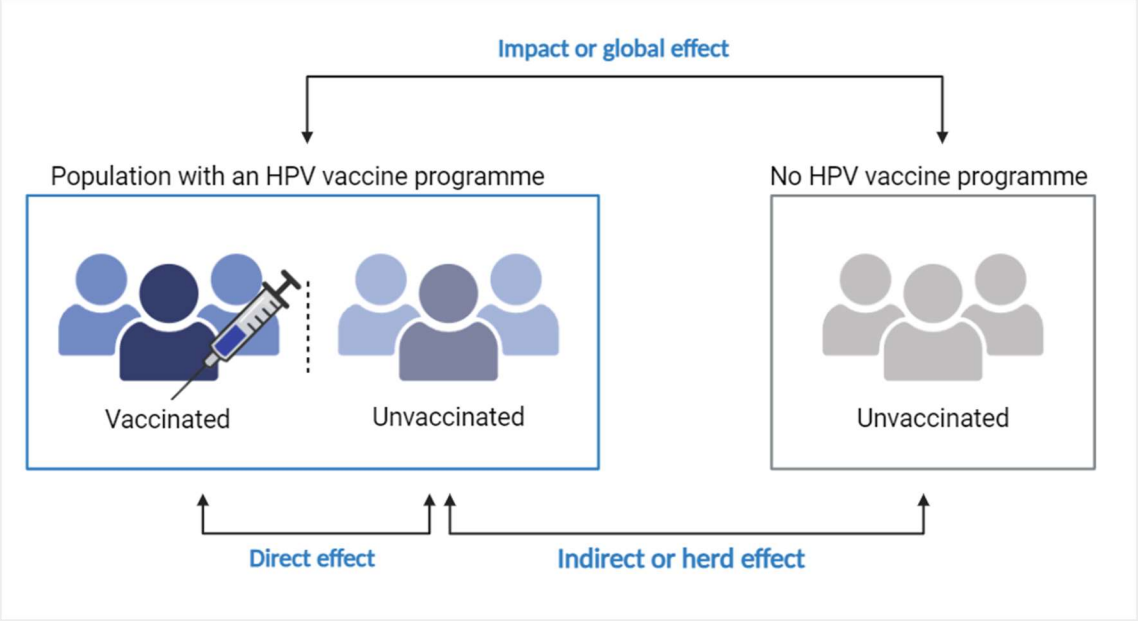


Figure 2. The effects of vaccination programmes. Adapted from Halloran et al., 2010 and Rosenblum et al., 2022.

Assessing the effect of HPV vaccination can be challenging for several reasons:

- Long latency from HPV infection to cancer. Fortunately, the natural history of cervical cancer provides us with multiple intermediate biological endpoints that can be measured (such as HPV infection, precancerous lesions and cancer), though this also increases the complexity of the assessment.
- Quality of information sources
- Coexistence of HPV vaccination programmes with cervical cancer screening activities that also contribute to reducing cervical cancer incidence and mortality.

The currently licensed HPV vaccines are prophylactic; they prevent HPV infection and HPV-related disease but have no therapeutic effect on existing infections and lesions.

1.1 The effect of HPV vaccination programs on cervical HPV infection, precancerous lesions and cervical cancer.

NOTE: *As of November 2024, there are 6 commercialised HPV vaccines. This module focuses on the three HPV vaccines distributed in Europe, which differ on the HPV types they include:*
- Cervarix or bivalent vaccine: HPV16/18
- Gardasil or quadrivalent vaccine: HPV16/18/6/11
- Gardasil 9 or nonavalent vaccine: HPV16/18/31/33/45/52/58/6/11.

Effect of HPV vaccination programs on cervical HPV infection by girls-only vaccination

This section examines the impact of the introduction of HPV vaccination programs using the results of a systematic review and meta-analysis of 65 studies published up to 2019 (Drolet et al., 2019). The meta-analysis includes data on more than 60 million individuals from 14 high-income countries that incorporated the bivalent or quadrivalent vaccines into their national immunisation programmes. The study compared the frequency of various HPV-related outcomes during the pre-vaccination periods (before a programme was introduced) and post-vaccination periods (after the programme was introduced) and included follow-up of up to 8 years after vaccination.

NOTE: *This study provides the impact of HPV vaccines when only girls with the initial schedule of 3 doses were vaccinated but larger effects in boys and girls are obtained when gender-neutral vaccination is implemented, as described in Unit 1.3.*

As expected, the first observed impact following the implementation of the HPV vaccine was a reduction in the prevalence of HPV infections and a reduction in the incidence of anogenital warts (**Figure 3**).

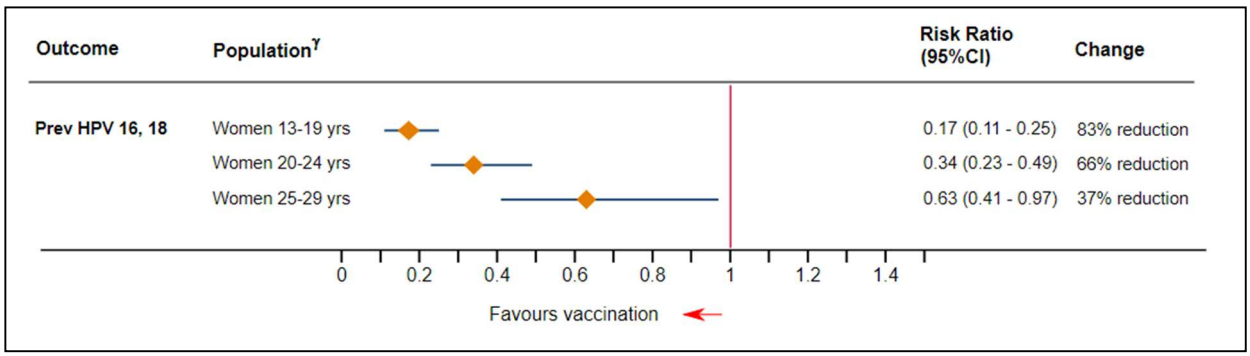


Figure 3. Pre- vs post-vaccination changes in HPV16/18 infection prevalence at 5-8 years following vaccination. Adapted from Drolet et al. 2019

***NOTE**: The figure above is a forest plot, commonly used in meta-analyses. The diamond represents the estimated effect while the horizonal lines indicate the 95% confidence interval (95%CI). In this figure, the vertical line at 1 represents no vaccine effect – if a 95%CI crosses it, the estimated effect is not statistically significant. Estimated effects below 1 indicate HPV prevalence reduction.*

HPV16 and HPV18 prevalence was reduced in girls and women aged 13-29 in comparison with the pre-vaccination period, with a more pronounced reduction in younger age groups (83% reduction among girls and women aged 13-19). Women aged 25-29, most of which unvaccinated, showed a 37% reduction in HPV16 and HPV18 prevalence, pointing to herd protection.

HPV vaccines reduce cervical disease in women of all ages, providing individual benefits that vary by age of vaccination. Therefore, to maximize the overall reduction in cervical disease, vaccination programs should begin at an early age and aim for high coverage.

There was also a 54% reduction in the prevalence of some HPV genotypes not targeted by the vaccine (HPV31, 33 and 45) among girls and women aged 13-19 (**Figure 4**). This effect is called ***cross-protection***. However, it should be noted that cross-protection with Cervarix® has been observed for HPV types 31/33/45 and 52 whereas cross-protection with the quadrivalent vaccine is only observed for HPV31 due to their different adjuvant composition.

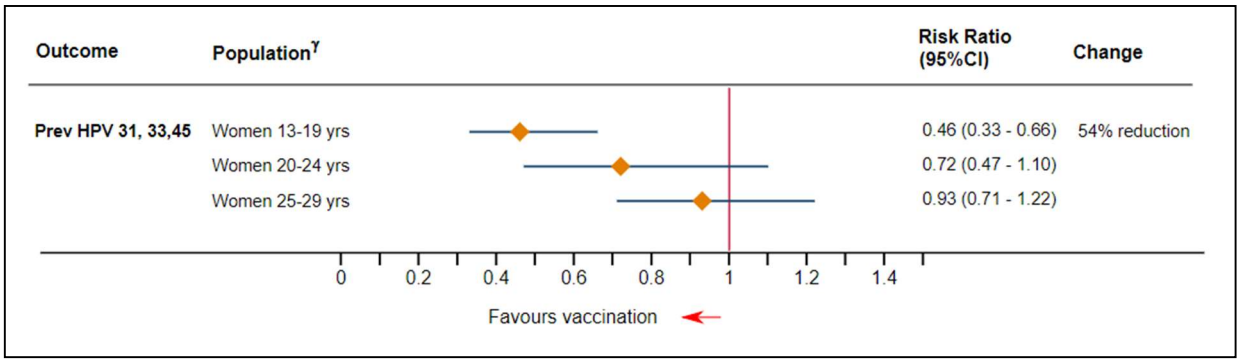


Figure 4. Pre- vs post-vaccination changes in HPV31, 33 and 45 infection prevalence at 5-8 years following vaccination. Adapted from Drolet et al. 2019

The impact of the HPV vaccine has also been observed in resource-limited countries. Bhutan and Rwanda introduced the quadrivalent vaccine into their vaccination programs in 2010 and 2011, respectively. In these countries, where high coverage rates have been achieved, the HPV vaccination programs have resulted in an 88% and 78% reduction in the prevalence of infections caused by vaccine-included types, respectively (Baussano et al., 2021).

The antibody response for HPV types not included in the vaccine (cross-protection) is not comparable to the specific response obtained when those HPV types are included in the vaccine.

Even though the immune response differs between vaccines, both the nonavalent vaccine and Cervarix® are expected to provide similar protection against cervical cancer—as long as Cervarix® continues to offer cross-protection over time, which has been shown to last at least 12 years so far (Mariz et al., 2021).

Did you know?

Since the introduction of HPV vaccines, a potential *type replacement effect* is being investigated. This biological phenomenon is suspected to occur when the prevalence of high-risk HPV types targeted by HPV vaccine decreases, potentially allowing other non-vaccine HPV types to increase and fill the ecological niche left behind (i.e, changes in non-vaccine HPV types prevalences).

Some studies on girls-only HPV vaccine programs have shown some slight increases in the prevalence of non-vaccine types that could be explained by factors other than type replacement (Mesher et al., 2016).

Effect of HPV vaccination on cervical precancerous lesions by girls-only vaccination

There is also evidence (**Figure 5**) showing the impact of HPV vaccination programmes on high-grade cervical precancerous lesions (CIN2+).

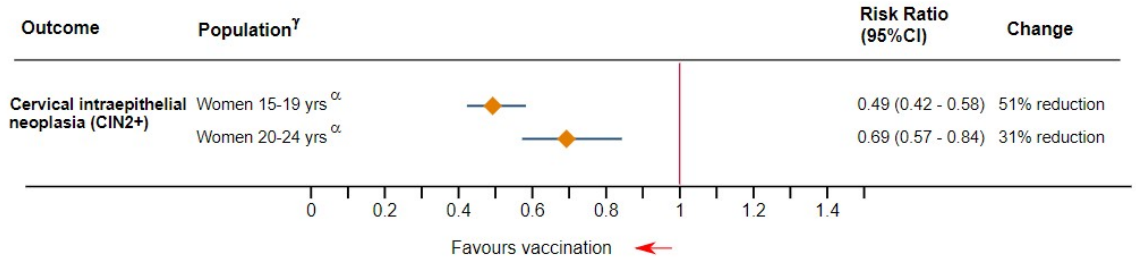


Figure 5. I Adapted from Drolet et al. 2019.

In women who attend screening, including vaccinated and unvaccinated ones, the occurrence of CIN2+ decreased by 51% in women aged 15-19 and by 31% in women aged 20-24.

Cervical precancerous lesions are diagnosed through cervical cancer screening programmes. Therefore, any change in the screening programme recommendations, the screening test or participation can directly impact the prevalence of these lesions.

Did you know?

Besides type replacement, another potential phenomenon is clinical unmasking. HPV vaccination reduces the number of excisional treatments due to the lower prevalence of lesions caused by HPV16 or HPV18. As a result, other HPV types that progress more slowly to malignancy - HPV types that would have been removed in the event of lesions caused by HPV16/18 - may now have the needed time to progress to lesions.

Slight increases in the prevalence of lesions caused by non-vaccine types have been observed at 7-11 years of follow-up (Shing et al., 2022). However, these lesions are a very small fraction of those prevented by the vaccine and further follow-up and research are necessary.

More recently published studies have shown that the reduction in the prevalence of high-grade cervical precancerous lesions is even greater:

- In Scotland, routine vaccination of girls with the bivalent vaccine has led to a reduction in the diagnosis of pre-invasive cervical cancer at age 20 (89%, 88%, and 79% reduction in CIN3+, CIN2+, and CIN1, respectively), compared to unvaccinated cohorts (Palmer et al., 2019). The vaccine showed higher reductions at younger ages (86% and 51% reduction in CIN3+ in women vaccinated at age 12-13 and age 17, respectively).
- In England, a reduction in the incidence of CIN3 cases in cohorts of girls vaccinated with the bivalent vaccine was higher in girls vaccinated at younger ages, compared to reference unvaccinated cohorts (97%, 75%, and 39% reduction in women vaccinated at 12–13 years, 14–16 years, and 16–18 years, respectively) (Falcaro et al., 2021).

Did you know?

Recent data has shown that one, two and three dose schedules of HPV vaccine are similarly effective against high-grade cervical lesions if vaccination occurs before age 17 (Wu et al., 2025).

The increasing evidence on the effect of a single dose of HPV vaccine (WHO, Strategic Advisory Group of Experts on Immunization (SAGE), 2022; World Health Organization, 2022b) instead of the initial schedule of 3 doses is leading to an increasing adoption (over 50 countries worldwide by December 2024) of a one dose vaccine schedule (World Health Organization, 2023).

Effect of HPV vaccination on cervical cancer by girls-only vaccination

The first evidence of the efficacy of both the bivalent and quadrivalent HPV vaccines in women vaccinated at age 16-17 was reported in Finland in 2018. During the 8-years follow up of two vaccination trials, only 10 cases of HPV-related cancers were detected (eight cervical cancers, one oropharyngeal cancer and one vulvar cancer), all of them among unvaccinated women (Lehtinen et al., 2021; Luostarinen et al., 2018).

Since then, further population-based evidence to support the effectiveness and impact of HPV vaccines in the incidence of cervical cancer has been published (**Table 1**). All studies estimated vaccine effectiveness through registry linkage except England, that evaluated the impact of the vaccine comparing vaccinated versus unvaccinated cohorts.

Table 1. Real-world evidence on the effect of HPV vaccines in cervical cancer incidence. Adapted from Arbyn et al., 2024 (RISCC).

Study	Vaccine	Age at vaccination (years)	Effect (95%CI)	Effect measure
Sweden (Lei et al., 2020a)	Quadrivalent	<17 17-30	81% (35 - 95%) 36% (0 - 61%)	Effectiveness
Denmark (Kjaer et al., 2021)	Quadrivalent	<16 17-19 20-30	87% (59 - 96%) 69% (-7 – 91%) N. S.	Effectiveness
England (Falcaro et al., 2021)	Bivalent	12-13 14-16 16-18	87% (72 - 94%) 62% (52 - 71%) 34% (25 - 41%)	Impact
Scotland (Palmer et al., 2024)	Bivalent	12-13 14-18	100% (67 - 100%) 69% (54 - 79%)	Effectiveness

N.S. - Reduction not statistically significant.

NOTE: *When comparing vaccinated cohorts versus unvaccinated cohorts (impact) instead of vaccinated versus unvaccinated individuals (effectiveness), it is crucial to consider vaccination coverage rates. In the previous study from England, between 2008 and 2012 the coverage with at least one dose was 86%–91% in the routine vaccination cohort and 56%–82% in the catch-up cohort.*

All the studies above have measured an important reduction in cervical cancer incidence after 11 -13 years after vaccination. However, this effect largely varies by age (34%-100%), showing that the effect of HPV vaccines is greater in women vaccinated at younger ages as depicted in **Figure 6**.

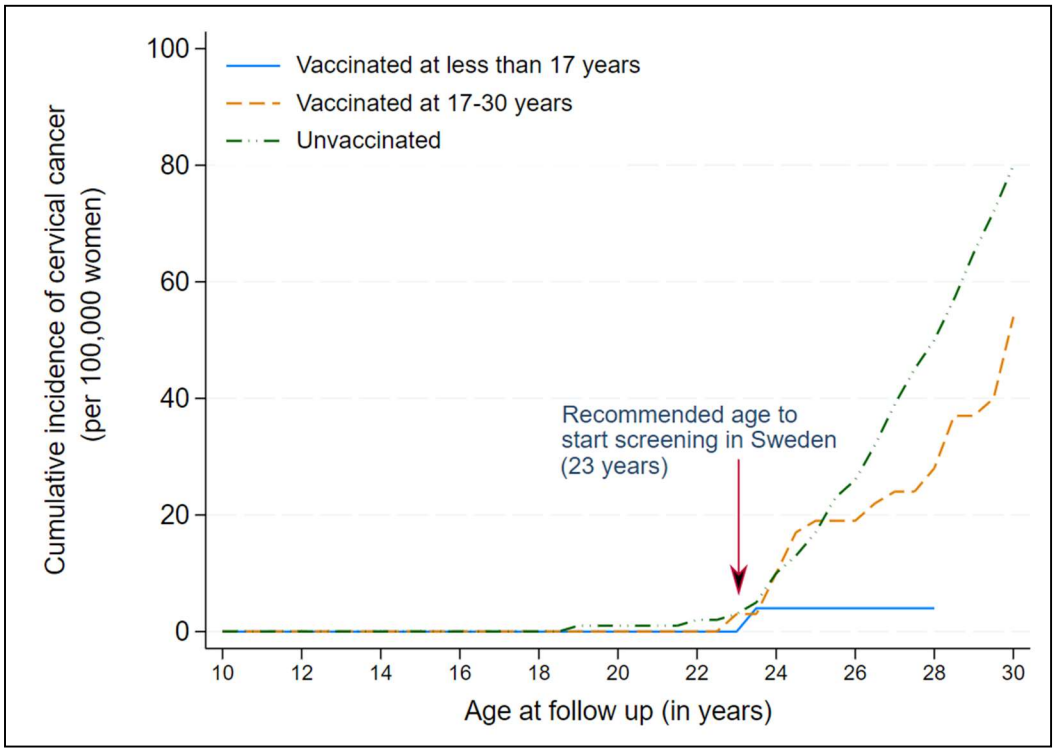


Figure 6. Cumulative incidence of cervical cancer based on vaccination status. Adapted from Lei et al., 2020a.

In the figure above, cervical cancer incidence started to rise at the start age of cervical cancer screening. Incidence remained low for those women vaccinated before age 17 (**blue line**). For those vaccinated at age 17-30, cervical cancer incidence continued to increase (**orange line**) although not as much as the unvaccinated ones (**green line**).

Did you know?

In the Danish study, women were followed-up until age 30. Therefore, while no vaccine effect was observed in women vaccinated at 20-30 years, a potential reduction in cancer incidence could be observed in these women after a longer follow-up until age 40.

The studies above emphasize the crucial role of linking vaccination records with screening or cancer registries.

Linkage of screening data with vaccination records or integration into one comprehensive program can estimate the effectiveness of HPV vaccines against cervical disease, improve the screening quality and efficiency of screening programs, fine-tuning of screening policies adjusted by vaccination status and address scientific questions that otherwise would remain unanswered (Arbyn et al., 2024 RISCC).

1.2 The effect of HPV vaccination programs on HPV diseases other than cervical.

As observed with cervical precancerous lesions and cervical cancer, the introduction of HPV vaccination programs has led to a significant reduction on the incidence of other HPV-related diseases.

Effect of HPV vaccine in anogenital warts

Over 90% of **anogenital warts** are associated to HPV 6 and 11, which are included in the quadrivalent and nonavalent vaccine. Although they are not severe as cancer, warts affect a large proportion of the population.

These were the first disease endpoint in which the population impact of HPV vaccination programs and herd-effects was demonstrated, and many countries that introduced the quadrivalent HPV vaccine have documented a dramatic reduction on its incidence.

Effect of HPV vaccine in anogenital lesions other than cervix

For other anogenital precancerous lesions, data on HPV vaccine effectiveness and impact are more limited. This is because the incidence of lesions and cancer at these sites is much lower than at the cervix. Nevertheless, these outcomes make a significant contribution to the overall HPV-attributable disease burden.

In Denmark, after more than a decade of follow-up, a 78% and 84% reduction in the incidence of **high-grade lesions in the vulva and vagina**, respectively, has been observed in girls vaccinated up to the age of 16 (Dehlendorff et al., 2021). In the U.S., a

decrease in the incidence of **high-grade precancerous lesions in the vulva (VIN3)** has been observed in women up to 29 years old and **in the vagina (VaIN3)** in women up to 39 years old, with this decline being more pronounced at younger ages (Mix et al., 2022).

In the U.S., stabilization in the incidence of **high-grade precancerous anal lesions (AIN3)** has also been observed in women aged 15 to 29. In men, although the incidence of AIN3 continues to rise, the growth has slowed within the same age range (Mix et al., 2022). Also in the U.S., since 2008, a reduction in the incidence of **squamous anal cancer (both in situ and invasive)** has been observed in women and men aged 20-44 years (Berenson et al., 2022).

Finally, in the U.S., an 85% reduction in **HPV infections in the penis** has been observed in men who have sex with men aged 18 to 26, vaccinated with the quadrivalent vaccine before the age of 18 (Winer et al., 2022). In Australia, a reduction in the **prevalence of infection by HPV genotypes included in the quadrivalent vaccine in the penis** has also been observed in heterosexual men up to 35 years old (Chow et al., 2019; Machalek et al., 2018).

Effect of HPV vaccine on oral and oropharyngeal HPV infection

A systematic review found that, despite the heterogeneity among the included studies, a reduction in the **prevalence of oral and oropharyngeal infections by HPV genotypes included in the vaccines** was confirmed, with an estimated relative prevention rate exceeding 80% in all studies except one (Nielsen et al., 2021).

Did you know?

HPV vaccination has been associated with a reduction of adverse pregnancy outcomes such as preterm births or low weight at birth. For a review on the available evidence, please refer to Kalliala et al. (2021) and Yuill et al. (2021).

1.3 Effect of HPV vaccination by gender-neutral vaccination

The effects of an HPV vaccination program within a population differ based on several factors, including:

- *Program characteristics* – The achieved coverage and the targeted population, i.e girls-only vs gender-neural vaccination, age at vaccination or the number of cohorts vaccinated.
- *Other prevention efforts* – The existence of additional preventive measures such as cervical cancer screening activity
- *Sexual behaviour* – Factors like the average age of sexual debut or the age difference between sexual partners
- *HPV prevalence and disease cofactors* – For example, the HIV prevalence.

The present unit focuses on the differences observed between girls-only and gender-neutral vaccination.

Unvaccinated women are protected from cervical cancer through screening - which they are less likely to participate compared to vaccinated ones (Lei et al., 2020b) - and the herd effect of the HPV vaccine, which differs by vaccination strategy. In a girls-only vaccination approach, the herd effect in unvaccinated women is a second order (weaker) effect indirectly resulting from the protection of unvaccinated boys. In a gender-neutral vaccination strategy, the first order herd effect is observed from the beginning in both groups (**Figure 7**).

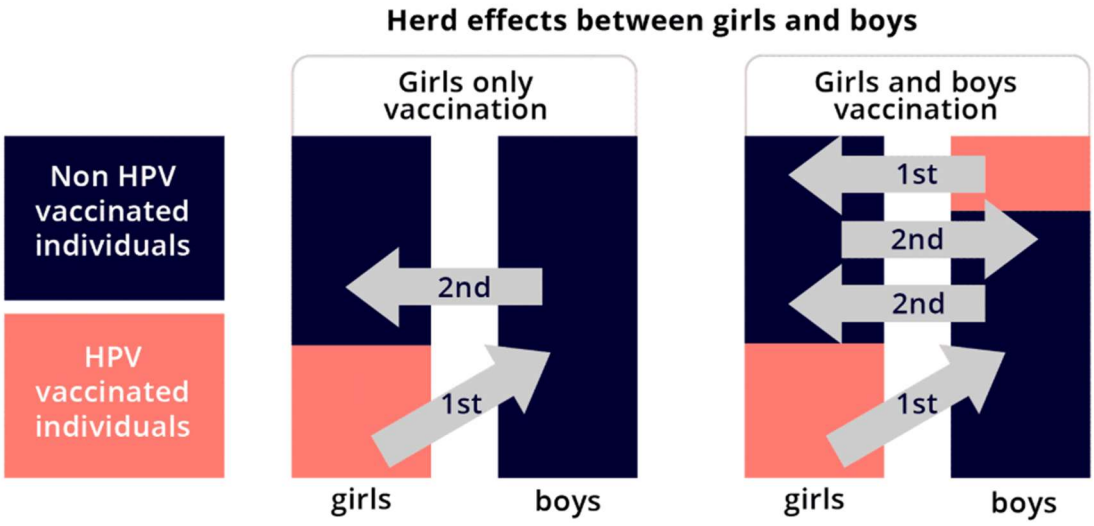


Figure 7. Herd effects of HPV vaccination. Adapted from Vänskä et al., 2020.

On the other hand, modelling analyses have determined that Finland needs a coverage of 95% with girls-only vaccination to eradicate HPV16, the most carcinogenic virus (Vänskä et al., 2020). Yet, this coverage level is only achieved by a few countries (Bruni et al., 2021). A gender-neutral strategy will decrease the required coverage level to 74%, a reasonable target that has been reached.

Did you know?

Sweden is nationally offering concomitant HPV vaccination and screening of cervical cancer to unvaccinated women aged 23 to 29. Modelled data based on the baseline results on screening and acceptance rates predict that this strategy can reduce the incidence of hrHPV infections in the targeted women by 62-64% in 3 years, leading to a faster elimination of cervical cancer (Arroyo Mühr et al., 2024 **RISCC**).

A large community-randomised trial was set up to examine the effect of the bivalent HPV vaccine when offered through a gender-neutral vaccination strategy (Lehtinen et al., 2015). The study randomised 33 communities in Finland to three arms: no vaccination, vaccination of only preadolescent (12-15 years) girls or vaccination of preadolescent girls and boys between 2007 and 2009. At a later stage, the trial was re-randomised to infrequent vs frequent screening to assess the screening needs of vaccinated cohorts.

Despite moderate coverage levels (approximately 45% in girls in both arms and 20% in boys), relevant results have been observed:

- Four years after vaccination, unvaccinated women from the gender-neutral vaccination communities showed a statistically significant 59% reduction in HPV 18, 31 and 33 prevalence (Vänskä et al., 2020) which is 150% stronger than in communities with girls-only vaccination.
- Four years after vaccination, a herd effect for HPV16 was only observed in the gender-neutral vaccination communities (Gray et al., 2021).
- Eight years after vaccination, HPV 16, 18 and 31 prevalence was lower in both vaccinated communities (girls-only or gender-neutral vaccination) but HPV45 was only lower in gender-neutral vaccinated communities (Pimenoff et al., 2023 **RISCC**).

Using a gender-neutral vaccination strategy shows signs of ecological niche occupation (type replacement); 8 years after vaccination, HPV 33/35/51/52/56/66 (non-vaccine types) prevalence was higher than in unvaccinated communities. In fact, a 12.6-20% change in non-vaccine targeted HPV types distribution was observed in these communities (Pimenoff et al., 2023 **RISCC**). However, this increase in prevalence may not lead to increased cervical disease due to lack of progression potential in HSIL associated with HPV types 51/52/58/59 (Louvanto et al., 2024 **RISCC**).

Furthermore, a gender-neutral vaccination strategy can make an HPV vaccination program more resilient to sudden and prolonged vaccination interruptions than a girls-only vaccination strategy (Elfström et al., 2016).

Did you know?

Excluding males from HPV vaccination negatively impacts both males and females such as lower awareness of HPV and associated diseases among males or absence of protection for some groups.

For more information on the ethical and legal aspects of gender-neutral vaccination, please refer to Logel et al. (2022).

ACTIVITY

Read the following statements about the HPV vaccine effect and decide if they are TRUE or FALSE.

1. There are significant differences in HPV vaccine uptake across the world.
2. Vaccines only offer protection against the HPV types included in the vaccine among vaccinated individuals.
3. HPV vaccines differ by the number of HPV types included in each of them.
4. HPV vaccine protection against cervical cancer is not yet conclusive.
5. HPV vaccines protect also against anogenital warts, precancerous lesions in vulva, vagina and anus and penile, oral and oropharyngeal infections.
6. Gender-neutral vaccination offers a higher cross-protection in unvaccinated women than that achieved with a girls-only vaccination strategy.

The correct answers are:

1 True, 2 False, 3 True, 4 False, 5 True, 6 True

UNIT 2. CERVICAL CANCER SCREENING IN THE ERA OF VACCINATION

The impact of the vaccine in the prevalence and HPV type distribution raises the following issues affecting ongoing cervical cancer screening programs:

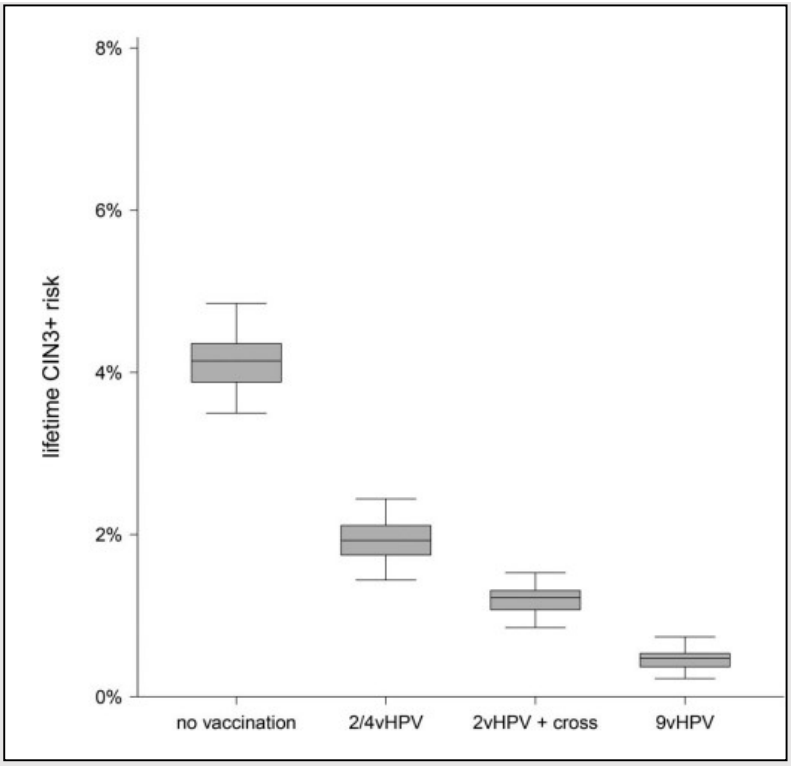
- Should screening be continued in vaccinated women?
- Which primary screening test should be used?
- Should screening intensity (screening interval and start/end age) change?
- Should clinical management algorithms be adapted in vaccinated women?
- Should vaccinated and unvaccinated women follow the same screening protocol?

Should screening be continued in vaccinated women?

Women vaccinated in pre-adolescence have a lower risk of developing high-grade cervical precancerous lesions and cervical cancer. Therefore, continuing with current screening recommendations, originally tailored for unvaccinated populations, may lead to over-screening in vaccinated cohorts, thereby increasing screening-related harms (see **MODULE 2**).

EXAMPLE

Using the follow-up screening data from over 20,000 Dutch women (Inturrisi et al., 2021 RISCC), it was estimated that the lifetime risk of CIN3+ to be detected by a five-yearly primary HPV screening programme in vaccinated women between age 30-60 is very low, particularly when protection is life-long and beyond genotypes 16 and 18 (lifetime CIN3+ risk of 4.1% in unvaccinated women vs 0.5% in women with the nonavalent vaccine).



However, cervical cancer screening in vaccinated women may remain beneficial as:

- Current vaccines do not protect against all oncogenic HPVs, leaving approximately 10% of cervical cancer cases still not vaccine preventable (de Sanjosé et al., 2018).
- Women already infected with an oncogenic HPV type are not protected by the vaccine for that type (Hildesheim et al., 2007).
- Although there is no evidence of waning efficacy, the HPV vaccines are relatively new and there is no data on whether girls vaccinated at young ages will still be protected from infection 15-25 years later.

Did you know?

All vaccines achieve seroconversion rates close to 100% and induce antibody titres much higher and with longer protection than those achieved after natural infection. There is no evidence of waning efficacy up to 10 years after vaccination. The presence of immunological memory by these vaccines, suggests that the immune protection conferred may be lifelong (World Health Organization, 2022a).

There is generally consensus among countries with well-established and well-resourced screening programmes on the need to maintain screening in women vaccinated during pre-adolescence, although there is also consensus that their screening needs will be much lower and the screening strategy needs to be adapted.

In populations with high vaccination coverage across all age cohorts, along with cross-protection and herd immunity, HPV transmission will be significantly reduced. This decline in transmission will result in low HPV prevalence of the vaccine types, which, in turn, will decrease the positive predictive value (PPV) of HPV molecular tests.

In the foreseeable future, in settings with high vaccination coverage, cross-protection and herd-immunity, screening may likely need to stop or be reduced to a minimum, since the harm caused by potential overdiagnosis and overtreatment could outweigh the benefits of screening depending on the screening strategy followed.

Which primary screening test should be used?

Since the introduction of HPV vaccines, experts have debated the impact of vaccination on the performance of screening tests (Brenner & Gefeller, 1997; Franco et al., 2009). As described in previous modules, the PPV, the sensitivity and specificity of primary screening tests is expected to decrease in vaccinated women as it depends on the HPV prevalence (both for vaccine and non-vaccine HPV types), the risk of progression of HPV type-specific infections to high-grade lesions, and the subsequent prevalence of high-grade lesions.

Furthermore, in unvaccinated women, high hrHPV positivity correlates with a high prevalence of CIN2+. However, in vaccinated women, a positive hrHPV result is more likely to be associated with non-vaccine HPV types with lower oncogenic potential (non-HPV16/18) and therefore a lower prevalence of CIN2+ is expected (Giorgi-Rossi et al., 2012).

Irrespective of the HPV vaccination status, HPV molecular testing is considered more appropriate than cytology for cervical screening (IARC, 2022).

The decrease in the PPV of cytology as primary screening test in vaccinated women has already been confirmed in several countries with high HPV vaccine coverage levels (Munro et al., 2017; Palmer et al., 2016; Sultana et al., 2019) and even moderate ones (Irzaldy et al., 2025).

EXAMPLE

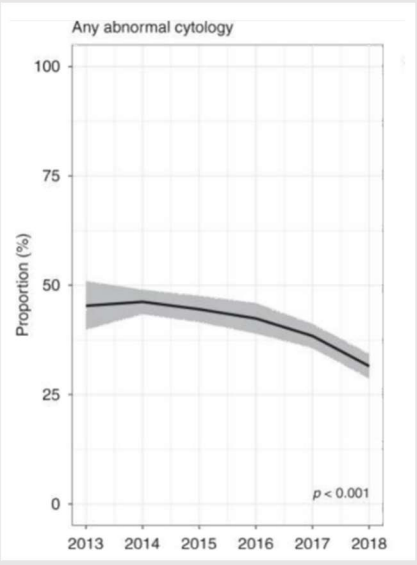
In Sweden, the PPV for high-grade cytology decreased from 70% to 57%, representing a 17% reduction in those vaccinated before the age of 17 years compared to those unvaccinated (Lei et al., 2020).

This decrease on the PPV has been observed in both conventional and liquid-based cytology samples and is more pronounced the earlier the age of vaccination (Munro et al., 2017; Palmer et al., 2016; Sultana et al., 2019; Teoh et al., 2022).

Although the evidence is more limited than that for cytology, some declines in PPV have also been observed for hrHPV testing without genotyping for primary screening in vaccinated women (Bhatia & Cuschieri, 2019; Rebolj et al., 2022).

EXAMPLE

In England (Rebolj et al., 2022), a decreasing trend in the PPV of the referral of those women with a positive HPV result and an abnormal cytology triage has been observed overtime.



Did you know?

A rapid increase in the false positive rate after HPV testing has been predicted at a critical threshold of 0.2% in the prevalence of precancerous cervical lesions (Franco, 2017).

Despite a slight reduction in HPV testing performance, an increased detection of precancerous lesions has been observed in vaccinated women screened with HPV testing compared to those with cytology (Canfell et al., 2017).

EXAMPLE

In the COMPASS trial (Australia), women eligible for vaccination (aged 33 or under) were screened with HPV testing every 5 years or cytology every 2.5 years (Canfell et al., 2017). A higher detection rate of CIN3+ was observed in the HPV testing arm (2.2% and 2.0%, when triaged with cytology or dual staining, respectively) when compared to the cytology arm (0.5%).

Furthermore, HPV tests are not influenced by the subjectivity present in cytology. Their performance depends on its analytical ability (i.e ability to detect infection by the included HPVs, the target of the test) combined with the ability of these HPV infections to predict CIN2+ (i.e PPV) (Giorgi-Rossi et al., 2012).

Given its superior performance, HPV testing remains the primary test of choice for cervical cancer screening in vaccinated women, leaving tests with high specificity for triage of HPV-positive women.

The use of HPV testing with extended genotyping would allow for better risk-based management of detected infections, identifying those with a higher probability of progression regardless of the vaccination status (Lei et al., 2020).

Cost-effectiveness studies indicate that most strategies with partial genotyping as the primary screening test are more effective and less costly than strategies with cytology or HPV testing without genotyping (Lew et al., 2016, 2017). Studies that have

evaluated extended genotyping show that it is often more cost-effective than partial genotyping strategies (Asti et al., 2021). Extended genotyping would also allow better risk stratification and optimize referral to colposcopy by concentrating cases to maintain disease prevalence and thus ensure the performance of colposcopic evaluation whose PPV may be affected by a lower prevalence of lesions and risk of disease.

Did you know?

Data from Scotland showed a decrease from 79% to 67% in the PPV of colposcopic impression for detecting HSIL/CIN2+ over 5 years as vaccinated cohorts entered the screening population (Cruickshank et al., 2017). Although in Sweden, another more recent evaluation found no impact yet (Sahlgren et al., 2022).

Should screening intensity (screening interval and start/end age) change?

Screening interval

The very low absolute risk of lifetime CIN3+ observed before (Inturrisi et al., 2021 **RISCC**) points to a de-intensification of screening programs in settings with high vaccination coverage. Additionally, mathematical modelling and cost-effectiveness studies point to the need to de-intensify screening to remain cost-effective in HPV-vaccinated women (Lehtinen et al., 2024; Naber et al., 2016; Pedersen et al., 2018; Portnoy et al., 2022). In addition to using appropriate screening tests, this implies reducing the frequency and extending the intervals between screenings. Analyses agree that more cost-effective screening implies fewer rounds or lower frequency of screening in vaccinated cohorts compared to unvaccinated cohorts.

There is no clear consensus and evidence is insufficient to define the optimal interval or total number of screenings over a lifetime but available data suggests that in vaccinated women the interval between screening visits could be extended to ≥10 years (two to five screens in a lifetime) (Baussano, 2010; Ortega Llobet et al., 2025 **RISCC**).

EXAMPLE

In the Finnish vaccination community-randomised trial, participants were individually randomised to screening once at age 28 or every three years at ages 22/25/28. Unpublished data found a similar risk of developing CIN2+ at ages 25 and 28 (hazard ratio: 1.03% (0.54-1.99) and 0.97% (0.50-1.88), respectively) in the infrequently versus the frequently screened arms (Lehtinen et al., 2025 RISCC; Ortega Llobet et al., 2025 RISCC). The widely confidence intervals around the null value (1) support the safety of extended intervals in vaccinated women.

A de-intensification of the current cervical screening programs could be perceived as negative by the targeted population, reluctant to be screened less than usual. However, in the Finnish randomized trial (Taavela et al., 2024 **RISCC**), no differences were observed on the satisfaction with cytology screening with a frequent (at age 22/25/28) or infrequent intensity (at age 28). This finding suggests that vaccinated women feel safe with a less intensive cervical cancer screening.

Vaccination with the nonavalent vaccine or Cervarix® and its cross-protection may further reduce the need for screening.

Start age

There is general agreement that the optimal age to initiate screening in vaccinated cohorts is higher than in unvaccinated cohorts, recommending starting screening at 30-35 years.

Should clinical management algorithms be adapted for vaccinated women?

Among vaccinated women, the prevalence of significant disease detected at colposcopy is expected to decline. Consequently, the number of women needed to refer to detect one case of CIN2+ will increase significantly if management algorithms remain unchanged (Palmer et al., 2016).

On the other hand, as observed for HPV prevalence, a different distribution of HPV types in high-grade lesions has been observed by vaccination status, with a predominance of vaccine types in unvaccinated women and other hrHPV types in vaccinated women (Hu et al., 2022; Louvanto et al., 2024). The lower risk of progression of non-vaccine types further suggests the use of progression biomarkers, such as methylation tests, to determine the most appropriate clinical management of women with high-grade lesions caused by other hrHPV types; active surveillance vs immediate treatment.

EXAMPLE

The methylation levels and HPV genotype of cervical samples of 403 vaccinated women at age 25 prior to detection of LSIL or HSIL in 15 and 17 women, respectively, were measured (Louvanto et al., 2024).

- In HSIL cases, the predominant HPV genotypes were HPV52 (29.4%), HPV59/HPV51/HPV58 (each 23.5%), and HPV33 (17.7%). No HSIL cases were HPV16/18 positives.
- Among vaccinated women, methylation levels of viral and host genes did not differ between women with HSIL, LSIL or women with normal tissue.
- The host gene EPB42L3 methylation levels from vaccinated women with LSIL or HSIL were lower than those from unvaccinated women with HSIL.

There are no consensus guidelines for the management of cervical cancer screening abnormalities in HPV-vaccinated women. However, updated recommendations for triaging HPV-positive vaccinated women, will be needed. Triaging strategies must better balance benefits and harms, ensuring women with infections or lesions unlikely to progress are not unnecessarily referred for colposcopy or treated.

NOTE: *For more information on risk-based screening and potential triage strategies, please refer to* ***MODULE 4A****.*

Should vaccinated and unvaccinated women follow the same screening protocol?

The need to adjust screening strategies for vaccinated women has been previously recognized. However, when these women reach screening ages, not all women in the birth cohort might have received vaccination.

When transitioning to a de-intensified screening strategy for vaccinated women, it is recommended that screening protocols initially be based on vaccination status. Yet, for women vaccinated at ages 15 years or older, it is suggested to maintain a similar protocol as for unvaccinated cohorts.

To be able to identify the vaccination status of women, it is crucial to have proper vaccination records, ideally integrated into the screening programme.

Eventually, these screening protocols, differentiated by vaccination status, should transition to universal screening protocols for predominantly vaccinated populations (i.e, unvaccinated women will be treated as vaccinated). This shift can occur once vaccination coverage and herd effects have made the prevalence and transmission of HPV vaccine-type infections negligible in both vaccinated and unvaccinated women (Giorgi Rossi et al., 2017).

Designing an optimal screening protocol for cohorts of vaccinated women requires considering multiple factors beyond the screening techniques themselves. These factors include cervical cancer incidence, prevalence of oncogenic HPV types, vaccination coverage and age, available resources (both material and human), and the benefit-risk balance of screening. Recommendations should be continuously reviewed and adapted to each context, using cost-effectiveness studies and establishing robust information systems that link vaccination, screening, and cancer registries at the individual level. This approach would enable the implementation of personalized screening protocols based on vaccination status, monitor the prevalence of different HPV genotypes and the incidence of precancerous lesions, and jointly evaluate the impact of prevention programs (screening and vaccination) while assessing the benefit-risk balance of screening in vaccinated women.

ACTIVITY

Read the following statements about screening in vaccinated cohorts and decide if they are TRUE or FALSE.

1. Screening in vaccinated cohorts should stop now.
2. Screening in vaccinated cohorts should be as intensive as in unvaccinated cohorts.
3. HPV testing, especially with genotyping, is considered more appropriate than cytology for screening.

The correct answers are:

1 False, 2 False, 3 True

SUMMARY

- Since the introduction of HPV vaccines in 2006, compelling evidence has been gathered on the substantial impact of HPV vaccination programmes in reducing persistent infection, precancerous cervical lesions and, cervical cancer.
- The impact of vaccination (direct and indirect effects) is predicted to be stronger and faster if boys are also included in the vaccination campaigns (gender-neutral vaccination), specially in unvaccinated women.
- HPV vaccination programmes directly impact vaccinated cohorts but will also impact unvaccinated cohorts if a gender-neutral vaccination strategy and high coverage are attained.
- An efficient linkage between vaccination and screening records is necessary for effective screening implementation, among others.
- In the near future, screening will still be required in countries with vaccination programmes although adapted:
    a. HPV testing is recommended. Its performance is less affected by the decrease in disease prevalence. Additionally, if HPV genotyping information, it allows for better risk-based management of the detected infections.
    b. Screening programmes needs to be de-intensified in terms of screening start age (30-35 years) and the screening interval or number of lifetime screening events.
    c. Lesion management guidelines will need to be re-assessed to optimally balance benefits and harms
- At some point, in setting with high vaccination coverage, screening may likely need to stop or be reduced to a minimum.

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