ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Immunisation Advisory Committee

UPDATED RECOMMENDATIONS FOR HPV VACCINATION

NIAC | 14.04.2022

About NIAC

NIAC membership includes nominees from the RCPI, its Faculties and Institutes, the RCSI, the ICGP, the National Immunisation Office, the Nursing and Midwifery Board of Ireland, the Infectious Diseases Society of Ireland, the Travel Medicine Society, the National Virus Reference Laboratory and lay members. Meetings are attended by representatives from the Department of Health and the HSE. Representatives of the Health Products Regulatory Agency attend to provide regulatory advice in relation to vaccines.

NIAC meets to consider new evidence about vaccines and provide advice to the Chief Medical Officer and the Department of Health. The Department and the Minister for Health make policy decisions on vaccines which are implemented by the HSE.

RECOMMENDATIONS

1. Priority must be given to re-establishing the high uptake of national immunisation programmes including the school-based human papillomavirus (HPV) vaccination programme.

2. HPV catch-up vaccination is recommended for unvaccinated females and males under the age of 25 years. Second level students and females under the age of 25 years should be prioritised.

3. HPV vaccination is recommended for unvaccinated females under the age of 45 years within 48 months following treatment of cervical intraepithelial neoplasia grade 1 (CIN1) or higher.

These recommendations reflect a dynamic vaccination programme strategy. Scientific evidence about HPV vaccines is evolving and being refined. Recommendations may be updated when more information becomes available.

1. EXECUTIVE SUMMARY

- All immunisation programmes, including the HPV vaccination programme, have been disrupted due to the COVID-19 pandemic so national immunisation programmes must be prioritised.
- HPV vaccines have excellent safety, efficacy and immunogenicity. They are effective in preventing cervical cancer. They are recognised as a critical intervention in the cervical cancer elimination strategy.
- The benefits of HPV vaccines are greatest when given before exposure to HPV infection. This underpinned the current recommendation for vaccination of boys and girls in their first year of second level school.
- HPV vaccines have been shown to be effective in preventing pre-cancer and cancer of the cervix in those aged under 31 years and have excellent durability of antibody response when administered to those aged under 46 years.
- There is evidence that HPV vaccines are safe and effective in preventing pre-cancer and cancer of the cervix when administered to older adolescent girls and young women.
- Quadrivalent HPV vaccine (HPV4) was introduced for girls aged 12 to 13 years in the first year of second level school in 2010. A catch-up programme for those still attending school took

place between 2011-2014. Because of the dramatic decline in vaccine uptake in 2015, a further catch-up programme was available until 2019.

- In 2019, nonavalent HPV vaccine (HPV9) was offered to boys and girls in first year of second level school, and the catch-up programme for girls was discontinued.
- Since 2019, the only way for older males and females to receive HPV vaccine is to source it privately. This leads to a significant barrier for some and creates inequity in terms of access to the vaccine.
- Vaccinating males benefits females indirectly and contributes to the elimination of cervical cancer.
- Vaccinated males also benefit directly by gaining protection against persistent infection and disease; there is evidence that to suggest that this will protect them from developing HPV related cancers, including oropharyngeal, genital and anal cancers.
- Gender neutral vaccination contributes to herd immunity and helps to improve vaccine resilience in the face of variable vaccine uptake at local, national, and international level.
- NIAC previously recommended HPV vaccine for females aged under 45 years within 48 months following treatment of 2 (CIN2) and higher. There is accumulating evidence that HPV vaccination reduces recurrence of infection in unvaccinated females aged under 45 years following treatment of CIN1 and higher.
- NIAC previously recommended HPV vaccine for other groups at higher risk for HPV disease. Access to vaccination for these groups should be facilitated.
- Reductions in the HPV vaccine dosing schedule have just been recommended by WHO and the UK in April 2022 and are undergoing stakeholder consultation. NIAC is reviewing the vaccine schedule for routine and catch-up cohorts and expects to publish recommendations in the coming months.

These recommendations reflect a dynamic vaccination programme strategy. Scientific evidence about HPV vaccines is evolving and being refined. Recommendations may be updated when more information becomes available.

2. DOH REQUEST FOR ADVICE

On 6 October 2021 NIAC received a request from the Department of Health (DOH) for advice regarding the evidence of clinical effectiveness and population wide benefit to providing human papillomavirus (HPV) vaccine to:

- girls and boys still in secondary school who were eligible to receive HPV vaccine in first year but who did not receive it
- the current cohort of girls up to the age of 25 years (when they become eligible for CervicalCheck) who have left secondary school and who did not receive the vaccine when they were eligible.

While addressing these issues, NIAC reviewed evidence on HPV vaccination in preventing HPV related cancers.

3. BACKGROUND

Almost all cervical cancers (99%) are linked to (HPV infection, an extremely common virus transmitted mainly through sexual contact. It is estimated that globally there were over 600,000 new cervical cancer cases and over 300,000 related deaths in 2020.[1] In the same year WHO published the "Global strategy to accelerate the elimination of cervical cancer as a public health problem".[2]

HPV vaccines have excellent safety, efficacy, immunogenicity and effectiveness. They are effective in preventing HPV infection and related cancers. HPV vaccination is recognised as a critical component of the cervical cancer elimination strategy.

4. HPV INFECTION AND HPV RELATED CANCERS

Between 50% and 80% of sexually active males and females will acquire genital HPV infection in their lifetime. Most infections are transient, resolving completely within two years without causing disease. Some infections persist and lead to precancerous lesions or cancer. Cervical cancer remains the most widely known HPV associated cancer. HPV is also associated with vulvar, vaginal, penile, anal and oropharyngeal cancer, anogenital warts and recurrent respiratory papillomatosis.

Munoz et al found that up to two-thirds of women aged 24 to 45 years remain susceptible to all serotypes in the HPV4 vaccine.[3] Joura et al reported low baseline HPV seropositivity in healthy

women with no history of genital warts, abnormal smear or cervical biopsy results aged 16 to 45 years, suggesting low prior exposure to HPV.[4]

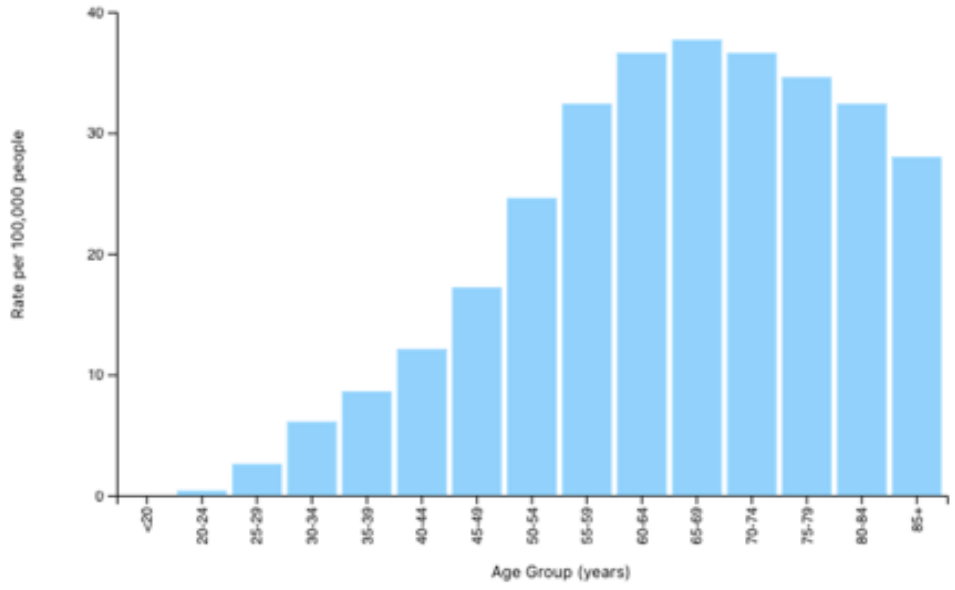
The age-distribution of HPV infection differs by gender. In females, the prevalence peak of infection occurs typically within the first decade after onset of sexual activity, between ages of 15 and 25 years. Males have a constant HPV prevalence over age. Their cumulative probability of infection increases progressively with age and is overall higher than in females. In males, a lower immune response to HPV infection has been reported, with low seroconversion rates . Long term persistence of oral HPV 16 infection is also reported for males. More efficient HPV heterosexual transmission from females to males than from males to females has been reported.[5]

It takes 10 to 30 years from infection to the development of HPV related cancer. In the US, the median age at diagnosis of HPV related cancers is (Figure 1).

- 49 years for cervical cancer
- 68 years for vaginal cancer
- 66 years for vulvar cancer
- 69 years for penile cancer
- 62 years among females and 59 years among males for anal cancer
- 63 years among females and 61 years among males for oropharyngeal cancer.[6,7]

These vaccine preventable cancers contribute to significant economic loss, morbidity and mortality.

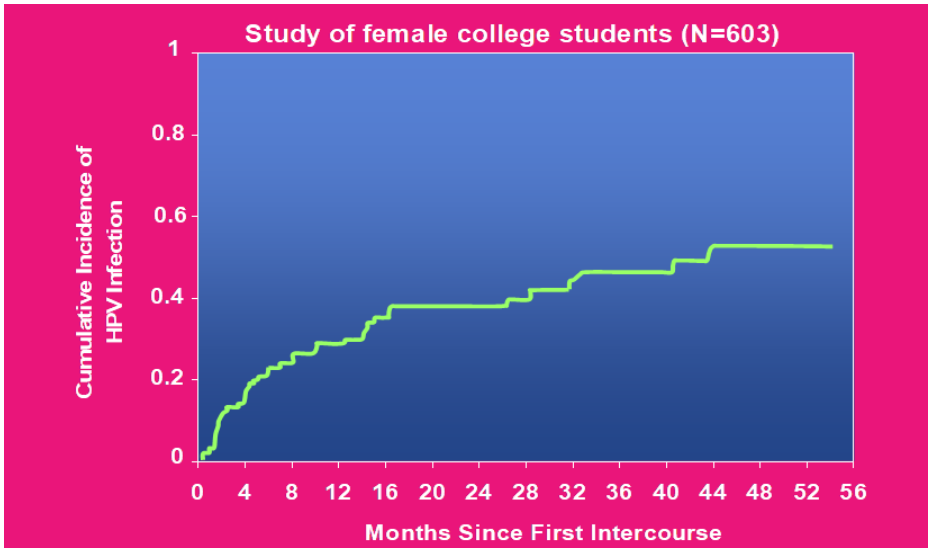
Figure 1. Rate of new HPV associated cancers (males and females) by age group, United States 1999-2018. Source: US Cancer Statistics Working Group.[6,7]



Cervical Cancer

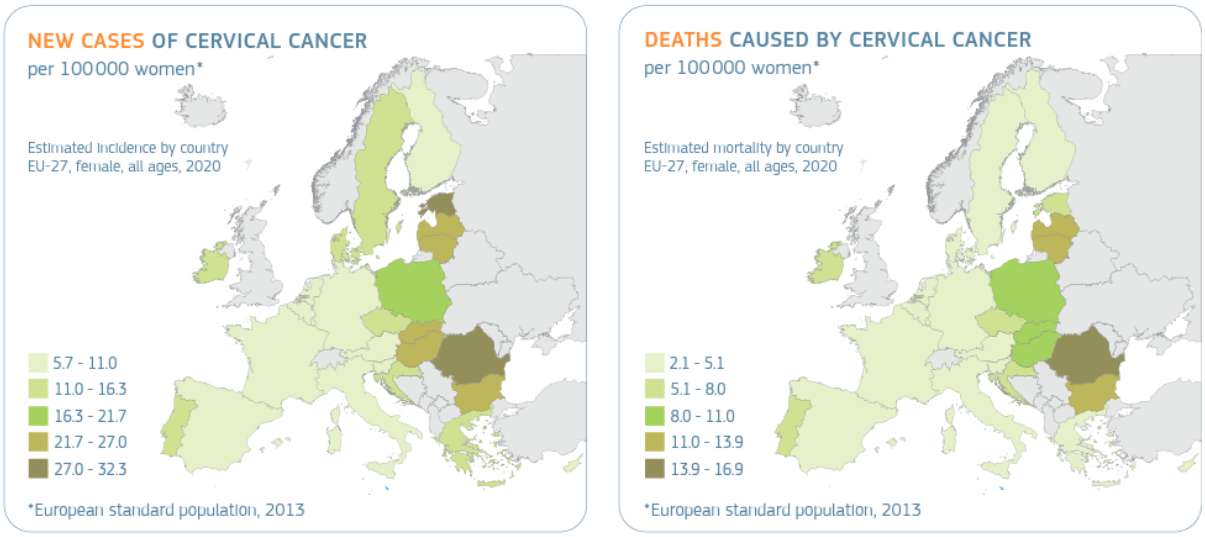
HPV infects up to 80% of sexually active adults. Of new infections in those aged 15 to 24 years, about 40% occur within two years of becoming sexually active.[8] (Figure 2)

Figure 2: Acquisition of HPV in females following sexual debut. Source: Winer RL.



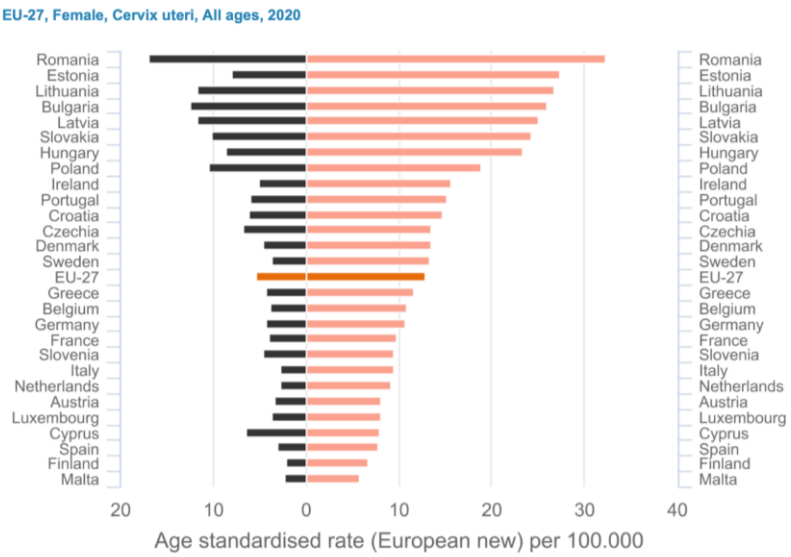
In Ireland, cervical screening and HPV vaccination have resulted in a decline in cervical cancer incidence from 2009-2019, although due to the long lead time mortality rates are not yet affected. Notwithstanding the decrease in incidence, Ireland compares unfavourably with many other European countries, with 292 cases per year and an age standardised incidence rate of 11.3/100,000. (Figure 3)

Figure 3: Cervical cancer incidence and mortality by country. Source: ECIS–European Cancer Information System, accessed 11 April 2022.



Ireland ranks ninth in the EU for the incidence of, and twelfth for the death rate for cervical cancer. (Figure 4)

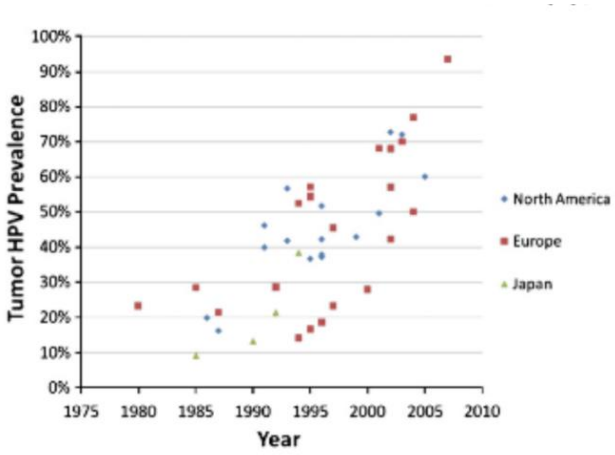
Figure 4: Estimated cervical cancer incidence and mortality by country. Source: ECIS–European Cancer Information System, Accessed 11 April 2022.



Oropharyngeal cancer (OPC)

Oropharyngeal cancer includes cancer of the tonsils, soft palate, and base of the tongue. The incidence of OPC is rising in the Western world, despite a decline in smoking, a known risk factor.[9] In the US, between 2014 and 2018, OPC was the most commonly diagnosed HPV associated cancer. (Figure 5) The majority of these cancers are linked to HPV16.

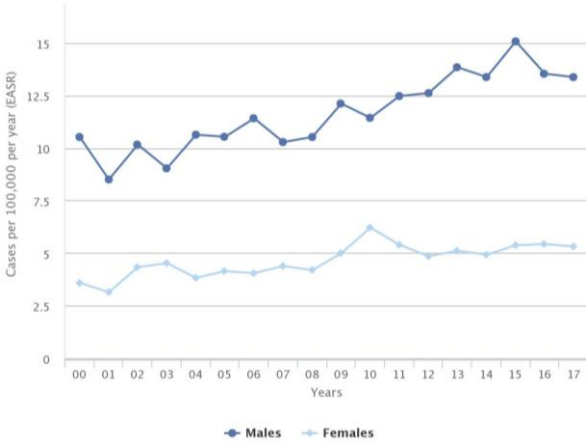
Figure 5: Summary of the prevalence of HPV in oropharyngeal cancer cases reported by calendar time of case diagnosis and geographic region. Source: D'Souza G et al.[10]



CDC attributes 70% of OPC to HPV.[11] These cancers are more common in males than females. They tend to present at a younger age and a more advanced stage than other head and neck cancers.[9]

Mouth and oropharyngeal cancer rates increased in Ireland between 2000 and 2017. (Figure 6)

Figure 6: Mouth and Oropharyngeal cancers (C01-C14) in Ireland 2000-2017 (all ages). Source: National Cancer Registry.



In Ireland (2017-2019) an annual average of 517 HPV and non-HPV related OPCs were reported, with an incidence of 14/100,000 in males and 5/100,000 in females. The 2021 Annual National Cancer Registry Report highlighted the importance of HPV vaccination not only in the context of cervical cancer prevention but also that of OPC.

Other HPV related cancers

In Ireland, HPV is an important cause of cancer of the anus, vulva, penis and vagina, with annual average case numbers of 78, 65, 46 and 11 respectively.[12] In the US, HPV accounts for 91% of anal, 69% vulvar, 63% penile and 75% vaginal cancers. These cancers are associated with considerable morbidity, mortality and burden on the health care system. [13]In Ireland it is estimated that 38% of OPCs are attributable to HPV strains targeted by HPV9 vaccine; this figure is 51% in the UK and 70% in the US; 75% of these cancers occur in males.

There are no screening programmes in Ireland for HPV related cancers other than cervical cancer.

5. HPV VACCINES

Three HPV vaccines are authorised for use in Ireland:

- HPV2 targets HPV types 16, 18
- HPV4 targets HPV types 6, 11, 16, 18
- HPV9 targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58.

The vaccines are authorised for the prevention of premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by the constituent HPV types, and genital warts (Condyloma acuminata) causally related to specific HPV types. Almost 90% of cervical and anal cancers are caused by HPV strains targeted by HPV9 vaccine. HPV4 and HPV9 vaccines target HPV types associated with over 90% of anogenital warts.

HPV9 vaccine was authorised in 2015 and is the vaccine recommended for use in the school vaccination programme in Ireland.

In June 2020, the FDA expanded the licence for HPV9 vaccine for all aged 9 years through 45 years to include the prevention of oropharyngeal and other head and neck cancers on the basis that the potential benefits outweigh the potential risks.[14] This was based on epidemiology, pharmacological evidence and biological plausibility that persistent HPV infection causes oropharyngeal cancer. There is evidence to show that prevention of persistent oral infection with high risk HPV types can be used as a surrogate for the prevention of HPV related cancer. The EMA has not amended the licence indications.

A 2017 safety review by the WHO Global Advisory Committee on Vaccine Safety, at which time more than 270 million doses had been distributed, concluded that HPV vaccines are very safe. The risk of anaphylaxis was 1.7/million doses.

Vaccine effectiveness in females aged up to 25 years

Because of the long lag time between HPV infection and development of invasive disease (10 to 30 years), initial reports of vaccine efficacy and effectiveness concentrated on prevention of HPV infection and of genital warts.[15-17] These early indicators of success were followed by reports of the positive impact on low and high grade cellular changes and precancerous lesions.[16]

Reductions in the prevalence of HPV vaccine types have been reported in vaccinated females in many countries. A 2019 meta-analysis documented an 83% reduction in the prevalence of HPV types 16 and 18 in females aged 13 to 19 years when vaccine uptake was at least 50%.[18]

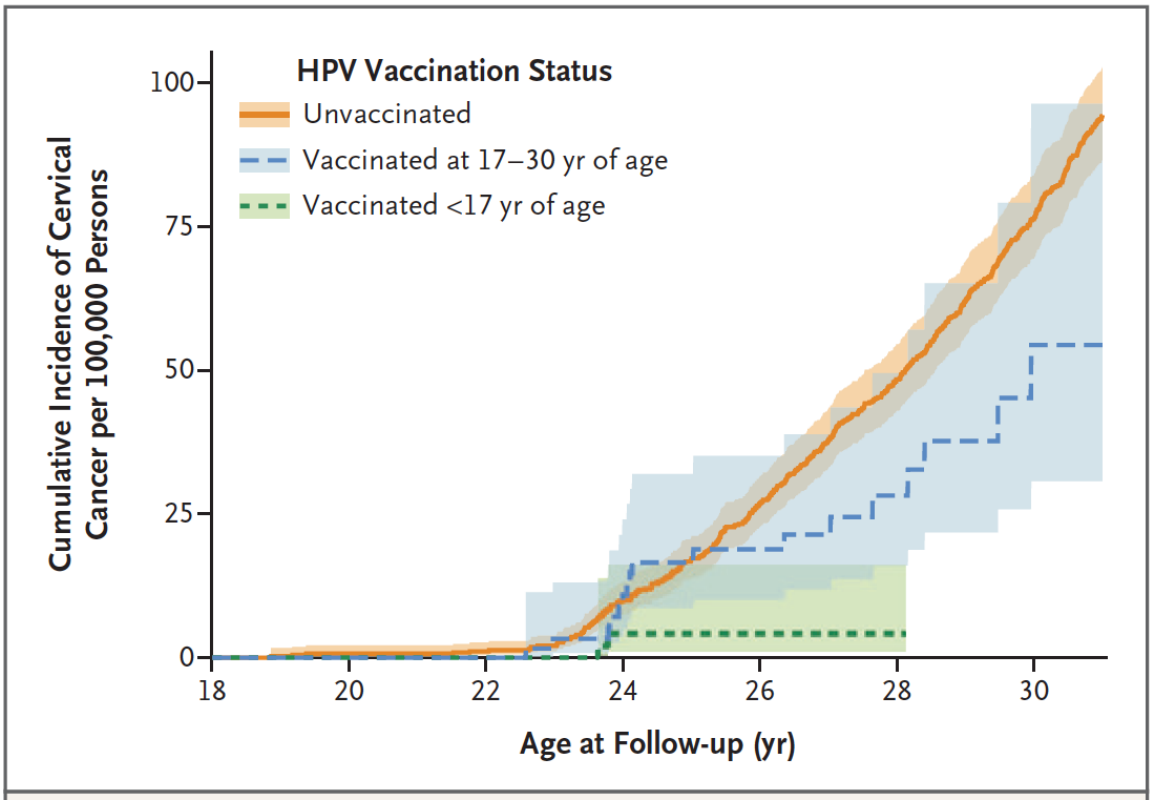
A reduction in high-grade cervical precancerous lesions has also been seen in vaccinated populations in several countries, and Australia has reported reductions in high-grade precancerous lesions in females up to 30 years of age.

Indications of herd immunity with benefits extending to the unvaccinated are also reported, e.g., with reductions in HPV prevalence in vaccinated females and males in the US, in unvaccinated females in the UK and in unvaccinated males in Australia.

In 2018, Finland reported the first evidence that vaccination protects against HPV-associated invasive cancers noted in their population based cancer registry data.[19]

In 2020, a Swedish population based cohort study, which included over 1.6 million females aged 10 to 30 years, reported that HPV4 vaccination was associated with a substantially reduced risk of invasive cervical cancer. While the greatest benefit was in those vaccinated aged under 17 years, with risk reduction of 88% (95% CI 66-100%), benefits were also accrued by those vaccinated aged 17 to 30 years, with greater risk reduction for those vaccinated before age 20 years. (Figure 7)

Figure 7: Cumulative incidence of invasive cervical cancer according to HPV vaccination status. Age at follow up is truncated as no cases of cervical cancer were observed in girls younger than 18 years of age. Source: Lei J et al.[20]



In a UK observational study of cancer registry data, the estimated relative reductions in cervical cancer rates by age at HPV2 vaccine offer were 34% for those aged 16 to 18 years, 62% for those aged 14 to 16 years, and 87% for those aged 12 to 13 years compared with the reference unvaccinated cohort. The corresponding risk reductions for CIN3 were 39% for those offered the vaccine at age 16 to 18 years, 75% for those aged 14 to 16 years, and 97% for those aged 12 to 13 years.[21] Of note, vaccine uptake rates were highest in the youngest cohort.

In a US randomised double blind trial of HPV4 vaccine in females aged between 16 and 26 years who were seronegative and HPV PCR negative at enrolment, the vaccine was highly effective in preventing CIN2 or 3 and anal intraepithelial neoplasia. Efficacy was reduced to 44% for the whole population which included those with infection at enrolment.[22]

In Australia, a study of HPV4 vaccine in adolescent females aged 16 and 24 years, including those with prevalent infection or disease caused by HPV, found that vaccination reduced the rate of any vulvar or vaginal perianal lesions regardless of HPV type by 34%. The rate of cervical lesions regardless of HPV type was reduced by 20%.[23,24]

A trial in 13 countries enrolled females aged 15 to 26 years who reported zero to four sexual partners without clinically evident genital HPV disease. While 27% had evidence of HPV infection, the majority remained uninfected at time of vaccination. Vaccination was 100% effective against CIN2/3 and cervical adenocarcinoma in situ caused by the HPV types in those negative at enrolment. Efficacy for preventing vulvar or vaginal HPV related lesions was 94%.[25]

An international immunogenicity and safety study of HPV9 vaccine in healthy women aged 16 to 45 years, with no history of abnormal cervical smear or cervical biopsy results, genital warts or a positive HPV test, found that more than 99% of participants seroconverted to the seven high risk HPV serotypes.[4]

HPV9 vaccine includes a greater number of high risk serotypes than HPV2 or HPV4 (the vaccines used in most trials to date), thus broadening the protection against more high risk serotypes.

There is robust evidence on the safety and effectiveness of the HPV vaccines in preventing cancer even when administered to older adolescents and young women.

Vaccine effectiveness in males

HPV4 vaccine is highly effective in preventing persistent HPV infections, genital warts and high grade anal intraepithelial lesions caused by HPV types 6, 11, 16 and 18 in males aged 16 to 26 years.[26] By extrapolation, HPV9 vaccine is very likely to provide similar or greater protection; direct evidence is not yet available because of the long time lag between infection and disease. Men who have sex with men (MSM) have the highest rates of HPV related anal infection.[26] Unlike heterosexual men, MSM are very unlikely to benefit from the herd protection provided by the vaccination of females and thus require direct protection.

HPV4 vaccine has shown high efficacy against anal intraepithelial neoplasia grade two and three.[27]

Vaccine effectiveness in those with HIV infection

People with HIV have a higher risk of developing HPV infection and HPV-associated cancers due to a lower immune response and viral interaction. A systematic review of RCTs to assess HPV vaccine efficacy in HIV-infected people showed a seroconversion rate close to 100% for all HPV vaccines.[28]

Vaccine effectiveness in women treated for CIN 1 or higher

Women treated for CIN3 have an increased risk of death from invasive cervical or vaginal cancer compared with the general female population.[29] In studies reported between 2013 to 2020, variable benefit for those vaccinated following treatment for cervical dysplasia was shown.[30-34]

A 2021 meta-analysis explored the role of adjuvant HPV vaccination to prevent recurrent cervical dysplasia after surgical treatment and showed risk reductions for CIN 1+ (OR 0.51; P 0.006), and CIN 2+ (OR 0.35; $p < 0.0001$) for those vaccinated compared with the unvaccinated.

6. THE HPV VACCINATION PROGRAMME IN IRELAND

In May 2010, HPV4 was introduced for girls aged 12 to 13 years in first year of second level school, following NIAC's recommendations and a 2008 health technology assessment (HTA) by the Health Information and Quality Authority (HIQA). The HTA findings were based on the assumptions that the HPV4 vaccine could prevent 70% of cases of cervical cancer related to HPV16 and HPV18 in individuals that did not have HPV infection at the time of vaccination, that the cost of administering a three dose course as part of a school based programme would be €390, that it would provide life-long protection, and, assuming an uptake of 80%, would result in an incremental cost-effectiveness ratio of approximately €17,400/life year gained.

At that time, it was considered that the additional benefit of vaccinating females aged 15 to 26 years might be very small compared to the associated increase in vaccine costs. It was however noted that *"The results of this evaluation are considered conservative as the benefits of including improvements in quality of life, potential cross-protection of the vaccine against other HPV types, as well as the efficacy of the vaccine against HPV types 6 and 11 which cause anogenital warts were not included".*[35]

Since then there have been a number of changes to the HPV vaccination programme. A catch-up programme for those still attending school took place between 2011-2014. Following a dramatic decline in uptake in 2015 a further catch-up programme was available until 2019.

In 2018 HIQA published a "Health technology assessment (HTA) of extending the national immunisation schedule to include HPV vaccination of boys". While recommending the adoption of HPV9 vaccine, the substantial uncertainty in the costs and benefits associated with the programme were acknowledged. HIQA determined that a gender-neutral programme would likely be considered cost-effective. Gender-neutral vaccination could also improve vaccine resilience in the context of variable vaccine uptake at a local, national, and international level. The population would be provided with protection against significant movements of individuals into and out of the country and ensure the national programme would be resilient to future changes in the vaccine uptake rate. However, at that time a catch-up programme for older boys was not thought to be cost effective.

The recommendation for a school based gender neutral programme, initiated in 2019/2020 was based on direct benefits to girls and boys, the indirect benefits through the population effect and

herd immunity, and the potential to improve the resilience of the immunisation programme to fluctuations in vaccine uptake and to the movement of individuals into and out of the country.

In 2019, HPV9 vaccine was offered to boys and girls in first year of second level school. At the same time the catch-up programme for girls was discontinued. Since 2019, the only way for unvaccinated older girls and boys to receive the vaccine is to source it privately. This is a significant barrier for those in age cohorts previously eligible for vaccination who missed their initial opportunities for vaccination but wish to access it now because of the compelling evidence of benefit to both females and males.

7. CURRENT HPV VACCINE RECOMMENDATIONS BY NIAC

Routine programme

All children at 12 to 13 years of age should receive HPV9 vaccine as part of the national HPV vaccination programme.

Older children and adults

Ideally, the vaccine should be administered before potential exposure to HPV through sexual contact. Those who are sexually active should be advised that the vaccine has not been shown to have a therapeutic effect on existing HPV infection or cervical lesions.

Dosage (Table 1)

Table 1: HPV vaccine dosage and schedule by age. Source: Chapter 10, Immunisation Guidelines for Ireland

Age	Doses and Schedule
Under 15 years	Two doses six months apart
15 years and older and those who are immunocompromised	Three doses at 0, 2, and 6 months. All three doses should preferably be given within 12 months.

Men who have sex with men (MSM)

HPV9 vaccine is recommended for MSM aged ≤45 years.

Immunocompromised persons

HPV9 vaccine is recommended for:

• HIV infected men and women aged ≤26 years

• HIV infected MSM aged ≤45 years

• haematopoietic stem cell or solid organ transplant recipients aged ≤45 years.

Fanconi Anaemia

Patients with Fanconi Anaemia aged over 12 months should be offered HPV vaccine as soon as the diagnosis is made, due to their significantly increased risk of oropharyngeal and anogenital squamous cell carcinomas.

Vaccination within 48 months of treatment of CIN2+ lesions

HPV4 or HPV9 vaccine should be offered to women under 45 years of age in this cohort. There is evidence that giving HPV vaccination within 48 months prior to or after primary surgical excision of CIN 2 or greater in females aged between 15 and 45 years is associated with a decreased risk of recurrent disease on the order of 66%.

8. INTERNATIONAL RECOMMENDATIONS

EU

The following EU countries have a gender-neutral HPV vaccine catch up programme: Austria (to 30 years of age), the Czech Republic (to 26 years), Italy (to 49 years), Liechtenstein (to 19 years) and Luxembourg (to 18 years).

The following countries have a female-only catchup programme: Denmark (to 18 years), France (to 19 years), Germany (to 17 years), Greece (to 26 years) and Spain (to 18 years).

UK

HPV vaccination is routinely recommended for girls and boys at 11 to 14 years of age as part of the national programme. Males and females in cohorts eligible for vaccination in the national programme remain so until their 25th birthday.

The Joint Committee on Vaccination and Immunisation (JCVI) has considered data on a one dose schedule of HPV2 or HPV4 vaccine and reviewed HPV9 vaccine efficacy data and sustained and consistent immunogenicity data that allows immunobridging from HPV4 to HPV9 vaccine. In

February 2022, JCVI agreed there was enough evidence to support a one dose schedule of HPV9 vaccine for those under 15 years of age. This advice is interim pending stakeholder consultation.

JCVI also reviewed immunogenicity and effectiveness data from two and three dose vaccine schedules for those aged 15 years and older and concluded there was no compelling reason to continue with a three dose schedule. On 1 April 2022, the UK HPV vaccine dosage recommendations changed to a two dose schedule for all ages except those who are immuncompromised.[36]

US

Gender neutral HPV vaccination is recommended at age 11 or 12 years; vaccination can be given from age 9 years. Gender neutral catch-up HPV vaccination is recommended for all persons through age 26 years who are not adequately vaccinated.[37]

In June 2020, the FDA expanded the licence for HPV9 vaccine for all aged 9 through 45 years to include the prevention of oropharyngeal and other head and neck cancers.

Canada

Gender neutral HPV2, HPV4 or HPV9 vaccine is recommended for those aged nine to less than 27 years of age.[38]

Australia

Females and males aged up to 19 can receive two doses of the HPV vaccine as part of the National HPV Vaccination Programme. Vaccination is routinely given in school-based programs at age 12 to 13, with catch up of older children supported by general practice and primary health care clinics.[39]

New Zealand

Gender neutral HPV immunisation is free for those aged 9 to 26 years, including non-residents under the age of 18 years.[23]

World Health Organization

Vaccination of secondary target populations, e.g., females aged 15 years and older or males, is recommended only if feasible, affordable, cost-effective and does not divert resources from vaccinating primary target population or from effective cervical cancer screening programmes.[2]

On 11 April 2022, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) published the outcome of their review of the evidence for the HPV vaccine schedules in routine and catch-up cohorts.[40]

“SAGE recommends updating dose schedules for HPV as follows:

- one or two-dose schedule for the primary target of girls aged 9-14 years
- one or two-dose schedule for young women aged 15-20 years
- two doses with a six month interval for women older than 21 years.

Immunocompromised individuals, including those with HIV, should receive three doses if feasible, and if not at least two doses. There is limited evidence regarding the efficacy of a single dose in this group".

These recommendations will be updated following further consultation with stakeholders.

9. DISCUSSION

There is a large body of evidence to show that HPV vaccines are very safe and effective. The maximum benefit is achieved with administration prior to HPV exposure. Thus, the first year of secondary school is chosen for the school-based programme. By the later teens a significant minority have acquired infection with at least one, but often only one, HPV serotype. Once infected, the risk of acquiring infection with additional serotypes is increased. A large majority, decreasing by age, remain uninfected and will benefit fully from HPV vaccination. Those who have acquired infection can achieve protection against the remaining vaccine serotypes through vaccination.

In May 2018 the WHO announced a global call for action to eliminate cervical cancer. In August 2020 the World Health Assembly adopted the Global Strategy for cervical cancer elimination.[2] Vaccination is a critical component of the strategy. To progress the goal to eliminate cervical cancer within the next century as called for by the WHO, HPV vaccine uptake needs to reach 90% of girls by the age of 15 years.

The initial rollout of the vaccination programme in Ireland was warmly welcomed. Initial vaccine uptake rates surged. Subsequently, parental concerns regarding the safety of the vaccines, fuelled by misinformation campaigns, resulted in a dramatic decline in vaccine uptake. Thorough evaluation of vaccine safety and dissemination of trustworthy information gradually restored vaccine confidence.

The global COVID-19 pandemic has increased awareness of the importance of vaccination and together with vaccine advocacy this may reduce vaccine hesitancy. There are those who declined HPV vaccination who now wish to be vaccinated.

There is a considerable number of young women who are unvaccinated. Offering the vaccine to those who did not receive it will benefit them. For those uninfected the full benefits can be anticipated. For those already infected, protection against additional serotypes will be given.

There is evidence to support safety and effectiveness of HPV vaccines in protecting against cervical cancer if they are given up to 30 years of age. In Ireland, the cervical screening programme commences when women reach 25 years of age and plays an important role in cervical cancer elimination.

The effectiveness of HPV vaccines is not gender specific. The case for vaccinating boys against HPV is reinforced by the fact that men have a poorer immune response to HPV infection than women. Men are less likely to seroconvert following infection, leaving them more vulnerable to re-infection. HPV infection rates appear to stay constant in men, independent of age, whereas HPV prevalence in women is highest between 18 and 24 years of age and then decreases until middle age.[41]

Providing catch-up vaccination to unvaccinated males up to 25 years of age will protect them against anal warts and HPV related cancers. For those uninfected the full benefits can be anticipated. For those already infected, protection against additional vaccine serotypes will be given.

Catch-up vaccination of males will also increase the resilience of the HPV vaccination programme and its overall impact on cervical cancer and enable an effective and faster approach to preventing and reducing the incidence of cancers and other HPV-related diseases. This would significantly contribute to Ireland's attainment of targets to achieve cervical cancer elimination[2] and reductions in other HPV related cancers including oropharyngeal cancer, which in the US has surpassed cervical cancer as that most commonly associated with HPV.

Since the previous two HTAs, there has been an accumulation of evidence of benefit that may affect the risk-benefit ratio in a cost-effectiveness analysis. Reductions in the HPV vaccine dosing schedule have just been recommended by WHO and the UK in April 2022 and are undergoing stakeholder consultation. NIAC is reviewing the vaccine schedule for routine and catch-up cohorts and expects to publish recommendations in the coming months.

10. RECOMMENDATIONS

RECOMMENDATIONS
1. Priority must be given to re-establishing the high uptake of national immunisation programmes including the school-based human papillomavirus (HPV) vaccination programme. 2. HPV catch-up vaccination is recommended for unvaccinated females and males under the age of 25 years. Second level students and females under the age of 25 years should be prioritised. 3. HPV vaccination is recommended for unvaccinated females under the age of 45 years and within 48 months following treatment of CIN1 or higher. These recommendations reflect a dynamic vaccination programme strategy. Scientific evidence about HPV vaccines is evolving and being refined. Recommendations may be updated when more information becomes available.

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References

1. Sung H, Ferlay J, Siegel RL, et al (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*. 71(3): 209-49. https://doi.org/10.3322/caac.21660

2. World Health Organization (2020). Global strategy to accelerate the elimination of cervical cancer as a public health problem. https://www.who.int/publications/i/item/9789240014107

3. Muñoz N, Manalastas R, Jr., Pitisuttithum P, et al (2009). Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. *Lancet.* 373(9679): 1949-57. doi: 10.1016/S0140-6736(09)60691-7.

4. Joura EA, Giuliano AR, Iversen O-E, et al (2015). A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. *New England Journal of Medicine*. 372(8): 711-23. DOI: 10.1056/NEJMoa1405044

5. European Centre for Disease Prevention and Control (2020). Guidance on HPV vaccination in EU countries: focus on boys, people living with HIV and 9-valent HPV vaccine introduction Stockholm. https://www.ecdc.europa.eu/sites/default/files/documents/Guidance-on-HPV-vaccination-in-EU-countries2020-03-30.pdf

6. Viens L, Henley S, Watson M, et al (2016). Human Papillomavirus–Associated Cancers — United States, 2008–2012. *MMWR Morb Mortal Wkly Rep*. 65: 661-6. https://www.cdc.gov/mmwr/volumes/65/wr/mm6526a1.htm#:~:text=An%20average%20of%2038%2C793%20HPV,15%2C793%20(9.7)%20among%20males.

7. Centers for Disease Control and Prevention. HPV Associated Cancer, Diagnosis by Age. https://www.cdc.gov/cancer/hpv/statistics/age.htm.

8. Winer RL, Lee S-K, Hughes JP, et al (2003). Genital Human Papillomavirus Infection: Incidence and Risk Factors in a Cohort of Female University Students. *American Journal of Epidemiology*. 157(3): 218-26. DOI: 10.1093/aje/kwf180

9. Marklund L, Hammarstedt L (2011). Impact of HPV in Oropharyngeal Cancer. *Journal of Oncology*. 2011: 509036. DOI: 10.1155/2011/509036

10. D'Souza G, Dempsey A (2011). The role of HPV in head and neck cancer and review of the HPV vaccine. Preventive Medicine (accessed Suppl 1 53 Suppl 1). https://doi.org/10.1016/j.ypmed.2011.08.001

11. Centers for Disease Control and Prevention (2020). Head and Neck Cancers. https://www.cdc.gov/cancer/headneck/index.htm

12. Ireland National Cancer Registry. National Cancer Registry Ireland (2019) Cancer in Ireland 1994-2017 with estimates for 2017-2019: Annual report of the National Cancer Registry. https://www.drugsandalcohol.ie/32500/1/NCRI_Annual%20Report2019.pdf

13. Centers for Disease Control and Prevention (2021). HPV and Cancer. https://www.cdc.gov/cancer/hpv/statistics/cases.htm (accessed 06 April 2022).

14. Food and Drug Administration (2020). Gardasil 9. https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil-9.

15. Ali H, Donovan B, Wand H, et al (2013). Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. BMJ. DOI: https://doi.org/10.1136/bmj.f2032

16. Brotherton JML (2019). Impact of HPV vaccination: Achievements and future challenges. DOI: 10.1016/j.pvr.2019.04.004

17. Kahn JA, Widdice LE, Ding L, et al (2016). Substantial Decline in Vaccine-Type Human Papillomavirus (HPV) Among Vaccinated Young Women During the First 8 Years After HPV Vaccine Introduction in a Community. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 63(10): 1281-7. DOI: 10.1093/cid/ciw533

18. Drolet M, Bénard É, Pérez N, Brisson M (2019). Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet*. 394(10197): 497-509. DOI: 10.1016/S0140-6736(19)30298-3

19. Luostarinen T, Apter D, Dillner J, et al (2018). Vaccination protects against invasive HPV-associated cancers. *Int J Cancer*. 142(10): 2186-7. DOI: 10.1002/ijc.31231

20. Lei J, Ploner A, Elfström KM, et al (2020). HPV Vaccination and the Risk of Invasive Cervical Cancer. *New England Journal of Medicine*. 383(14): 1340-8. DOI: 10.1056/NEJMoa1917338

21. Falcaro M, Castañon A, Ndlela B, et al (2021). The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. *Lancet*. 398(10316): 2084-92. DOI:https://doi.org/10.1016/S0140-6736(21)02178-4

22. Future II Study Group (2007). Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 356(19): 1915-27. DOI: 10.1056/NEJMoa061741.

23. New Zealand Ministry of Health (2021). HPV immunisation programme. https://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/hpv-immunisation-programme.

24. Garland SM, Kjaer SK, Muñoz N, et al (2016). Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. *Clin Infect Dis*. 63(4): 519-27. DOI: 10.1093/cid/ciw354

25. The Future II Study Group (2007). Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. *J Infect Dis*. 196(10): 1438-46. DOI: 10.1086/522864

26. European Center for Disease Control (2020). Guidance on HPV vaccination in EU countries: focus on boys, people living with HIV and 9-valent HPV vaccine introduction. https://www.ecdc.europa.eu/sites/default/files/documents/Guidance-on-HPV-vaccination-in-EU-countries2020-03-30.pdf

27. Food and Drug Administration (2020). sBLA CLinical review Memoramdum. https://www.fda.gov/media/139433/download.

28. Zizza A, Banchelli F, Guido M, et al (2021). Efficacy and safety of human papillomavirus vaccination in HIV-infected patients: a systematic review and meta-analysis. *Sci Rep*. 11(1): 4954. DOI: 10.1038/s41598-021-83727-7

29. Strander B, Hällgren J, Sparén P (2014). Effect of ageing on cervical or vaginal cancer in Swedish women previously treated for cervical intraepithelial neoplasia grade 3: population based cohort study of long term incidence and mortality. *Bmj*. 348: f7361. DOI: 10.1136/bmj.f7361

30. Ghelardi A, Parazzini F, Martella F, et al (2018). SPERANZA project: HPV vaccination after treatment for CIN2. *Gynecol Oncol*. 151(2): 229-34. DOI: 10.1016/j.ygyno.2018.08.033

31. Kang WD, Choi HS, Kim SM (2013). Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)? *Gynecol Oncol*. 130(2): 264-8. DOI: 10.1016/j.ygyno.2013.04.050

32. Petrillo M, Dessole M, Tinacci E, et al (2020). Efficacy of HPV Vaccination in Women Receiving LEEP for Cervical Dysplasia: A Single Institution's Experience. *Vaccines*. 8(1): 45. DOI: 10.3390/vaccines8010045

33. del Pino M, Martí C, Torras I, et al (2020). HPV Vaccination as Adjuvant to Conization in Women with Cervical Intraepithelial Neoplasia: A Study under Real-Life Conditions. *Vaccines.* https://www.mdpi.com/2076-393X/8/2/245.

34. Sand FL, Kjaer SK, Frederiksen K, Dehlendorff C (2020). Risk of cervical intraepithelial neoplasia grade 2 or worse after conization in relation to HPV vaccination status. *International Journal of Cancer*. 147(3): 641-7. DOI: 10.1002/ijc.32752

35. Health Information and Quality Authority (2008). The role of human papillomavirus vaccines in reducing the risk of cervical cancer in Ireland. A health Technology Assessment. https://www.hiqa.ie/sites/default/files/2017-02/HTA_HPV_Full_report.pdf

36. UK Health Security Agency (2022). Human papillomavirus (HPV): the green book, Chapter 18a. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1065283/HPV-greenbook-chapter-18a.pdf

37. Meites E, Szilagyi PG, Chesson HW, et al (2019). Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. *Morbidity and Mortality Weekly Report*. 68: 698 -702. https://www.cdc.gov/mmwr/volumes/68/wr/mm6832a3.htm

38. Canadian Immunisation Guide (2017). Human papillomavirus vaccine. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-9-human-papillomavirus-vaccine.html#p4c8a5_d2022).

39. Australia Immunisation Handbook. National Immunisation Programme 2020. https://www.health.gov.au/health-topics/immunisation/when-to-get-vaccinated/national-immunisation-program-schedule#catch-up-immunisations.

40. World Health Organization (2022). One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer. https://www.who.int/news/item/11-04-2022-one-dose-human-papillomavirus-(hpv)-vaccine-offers-solid-protection-against-cervical-cancer#:~:text=%E2%80%9CSAGE%20urges%20all%20countries%20to,the%20course%20of%20their%20lifetimes.%E2%80%9D.

41. European Cancer Organisation. ACTION AREA 1: HPV Prevention Via Gender Neutral Vaccination Programmes. https://www.europeancancer.org/2-standard/107-hpv-action-area-1-hpv-prevention-via-gender-neutral-vaccination-programmes#:~:text=About-,ACTION%20AREA%201%3A%20HPV%20Prevention%20Via%20Gender%20Neutral%20Vaccination%20Programmes,the%20virus%20through%20sexual%20activity.