Viral Protection: Achieving the Possible

A Four Step Plan for Eliminating HPV Cancers in Europe
The HPV Action Network is one of the European Cancer Organisation’s Focused Topic Networks, established as part of our Strategy for 2020-2023. The HPV Action Network was launched in December 2019, following the resolution passed at the 2019 European Cancer Summit in September: ‘By 2030, effective strategies to eliminate cancers caused by HPV as a public health problem should be implemented in all European countries.’

The HPV Action Network urges Europe to make HPV cancer elimination a formal European shared goal. Europe’s Beating Cancer Plan and other Regional/EU/National initiatives present significant opportunities for progress to be made.

Co-chaired by Professor Daniel Kelly, European Oncology Nursing Society (EONS), and Professor Rui Medeiros, Association of European Cancer Leagues (ECL), the HPV Action Network convenes Member Societies and Patient Advocacy Groups of the European Cancer Organisation, as well as our Community 365 and other interested stakeholders. The up-to-date list of the Network participants is available on the Network website and acknowledged on the inside back cover of this report.

More information is available on our website: www.europeancancer.org/topic-networks/1:hpv-action

If you would like to find out more about the HPV Action Network, please contact us at: info@europeancancer.org.
FOREWORD

Now is the time for ambition. Now is the time for inspiration. Now is the time for decisive action to create an HPV-cancer-free future for men and women across Europe.

This report has been written with the input and endorsement of a wide range of organisations and individual experts with an interest in cancer and HPV. It is a multi-disciplinary and inter-professional initiative that constitutes a public appeal to decision-makers across Europe to seize the moment.

The new World Health Organization (WHO) strategy for the global elimination of cervical cancer as a public health problem, together with the forthcoming Europe’s Beating Cancer Plan, the EU Cancer Mission and the EU4Health Programme, create a unique opportunity for Europe to be an international regional leader in replicating what has already been achieved for another once-endemic virus, smallpox – the elimination of all the cancers and diseases caused by HPV.

This goal is achievable through evidence-based steps in four key areas: vaccination, screening, treatment, and public awareness.

OUR CENTRAL RECOMMENDATION

The European Union and the wider WHO European region should commit to the core goal of matching and exceeding the WHO Global Strategy for Cervical Cancer Elimination and implement policies and strategies for the elimination of all the cancers and diseases caused by HPV.

This report sets out how this goal can be realised through realistic investment and by building on good practice already in place in many but not all European countries.
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Acknowledgements

This report has been produced by the European Cancer Organisation’s HPV Action Network and approved according to its policy decision-making process. The Network comprises representatives drawn from the European Cancer Organisation’s Member Societies, Patient Advisory Committee members, Community 365\textsuperscript{a} and other invited stakeholders.

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\textsuperscript{a} Community 365 is a group of charity, philanthropy and industry contributors to the Focused Topic Networks of the European Cancer Organisation. Community 365 provide ideas, guidance, practical support and resources for our work in convening stakeholders and building consensus in the European cancer community. Community 365 contributors do not have a decision-making role in our policy work. Rather, policies of the European Cancer Organisation, such as those represented in this document, are agreed by our Board after consultation with our Member Societies and Patient Advisory Committee, via our Policy Pathway process. More information here: www.europeancancer.org/community-365

\textsuperscript{b} The content of this report does not necessarily reflect the views of these individuals and organisations.
Executive Summary

- HPV (human papillomavirus) is a very common sexually transmitted infection that causes almost 5% of all cancers in women and men worldwide. These include cervical, anal, penile, vaginal, vulval and oropharyngeal cancers.

- HPV also causes genital warts and recurrent respiratory papillomatosis (RRP).

- Diseases caused by HPV can be prevented through vaccination. Ideally, this should be done in adolescence, before exposure to the virus.

- HPV vaccination is most effective if provided to both sexes. However, most countries in Europe do not currently vaccinate boys. HPV vaccination uptake also remains low in some countries.

- Cervical cancer screening is available in most European countries but only a minority of programmes can be described as adequate. Moreover, most countries do not yet offer HPV testing, now recognised to be the most effective screening method. The uptake of cervical cancer screening also varies widely within and between countries. Self-sampling HPV testing could play an important role in increasing uptake.

- Treatment outcomes vary widely across European countries, with five-year survival rates for cervical cancer ranging from 54-80%.

- There are very concerning gaps in public and professional awareness of HPV issues and a significant risk that vaccination programmes in particular will be affected by safety fears fuelled by ‘fake news’.

- The COVID-19 pandemic has had a serious adverse impact on vaccination and screening programmes. This problem must be addressed as soon as possible.

The European Cancer Organisation is calling for urgent evidence-based policy and practical action by the EU and all governments throughout the WHO European region to eliminate cancers and diseases caused by HPV. The goals must include:

1. Universal (or ‘gender-neutral’) HPV vaccination for adolescents and optimal levels of uptake.

2. National organised population-based cervical cancer screening programmes using HPV testing systems and with higher levels of uptake.

3. Cancer treatments consistently and equitably offered in line with best practice guidelines and care and support that maximises patients’ quality of life.

4. Action to improve public and professional awareness and education about HPV in order to improve vaccination and screening uptake.
Introduction

At the European Cancer Organisation’s annual European Cancer Summit held in Brussels in September 2019, a consensus resolution was passed by over 300 cancer stakeholders. It stated that: ‘By 2030, effective strategies to eliminate cancers caused by HPV as a public health problem should be implemented in all European countries.’

In December 2019, at a meeting in the European Parliament in Brussels, the European Cancer Organisation launched the HPV Action Network. This involves the widest possible range of professional, patient and civil society organisations at both the Europe-wide and national levels. It aims to influence the policy, practice and research agendas by engaging with clinicians and academics, politicians, government officials and those working for European or international agencies, professional associations, civil society organisations and the general public. The HPV Action Network’s area of activity extends beyond the European Union and covers the 53 countries in the wider WHO European region.

The European Commission’s new Beating Cancer Plan, currently under development and due to be published in late-2020, provides a major new opportunity for the development of a comprehensive set of recommendations to, and support for, Member States that aim to reduce the cancer burden caused by HPV and address inequalities between EU countries. Encouragingly, the European Commission’s Roadmap for the Beating Cancer Plan specifically mentions HPV as a potential area for action.¹

There is already significant support for the introduction of universal vaccination across Europe. The European Parliament, in its resolution on vaccine hesitancy adopted in 2018, welcomed ‘the encouraging progress made in the fight against HPV diseases and cancers thanks to vaccination programmes against the HPV virus’ and called on Member States ‘to further develop these programmes and explore ways to increase coverage rates and prevent other forms of cancer, for example by including boys in vaccination programmes.’²

WHO Europe’s men’s health strategy, adopted in 2018, contains a recommendation that its Member States should consider a wide range of measures to improve the health and well-being of men and boys including ‘promoting the role of adolescent boys and men in policies, programmes and services related to […] sexually transmitted infections.’³ Almost half of all the countries in the WHO European Region now provide HPV vaccination to both sexes or plan to do so.

The WHO has a global strategy to accelerate cervical cancer elimination, with clear goals and targets for the 2020–2030 period. The strategy calls for global targets of 90% of girls to be vaccinated by the age of 15, 70% of women to be screened with a high-precision test at 35 and 45 years of age, and 90% of women with cervical disease to receive treatment and care.⁴ The WHO strategy provides a target for Europe and also the basis for a more ambitious programme to tackle all the cancers caused by HPV.

Europe can act as a beacon to other global regions to show what can be achieved when countries work together to achieve a major public health goal. Action across the European region to eliminate the cancers and diseases caused by HPV has the potential to save hundreds of thousands of lives and improve the quality of life of many more.

VIRAL PROTECTION: ACHIEVING THE POSSIBLE A FOUR STEP PLAN FOR ELIMINATING HPV CANCERS IN EUROPE
The Impact of HPV

HPV (human papillomavirus) is a very common sexually transmitted infection that causes 4.5% of all cancers in women and men worldwide.\(^5\) In the European continent, about 2.5% of cancers are attributable to HPV. The virus causes more than cervical cancer; it is also responsible for a high proportion of anal, penile, vaginal, vulval and oropharyngeal cancers. The virus is also responsible for genital warts and recurrent respiratory papillomatosis (RRP).

Almost all (85–90%) sexually active women and men will acquire HPV at some point in their lives.\(^6\) There are around 200 different types of HPV. 12 of these HPV types are associated with a high risk of cancer,\(^7,8\) the most significant being types 16 and 18. HPV types 6 and 11 are not carcinogenic but can cause warts on or around the genital area. They are also implicated in recurrent respiratory papillomatosis (RRP), a relatively rare but very disabling condition that adversely affects breathing in children and adults of both sexes.

In some European countries, the prevalence of high-risk HPV infection exceeds 15% in women.\(^8\) One study of oncogenic HPV types in men found a prevalence rate of 12%.\(^9\) In men who have sex with men specifically, the prevalence rate of HPV types 16 or 18 could be as high as 20%.\(^10\) High-risk oral HPV infection specifically has been found to be much more prevalent in men than women.\(^11\)

Most people exposed to HPV suffer no ill-effects. But some, particularly those who are repeatedly exposed to high-risk HPV types or who are already immunocompromised (e.g. because they are HIV+), may go on to be diagnosed with a cancer caused by HPV.

HPV is implicated in virtually all cases of cervical cancer and around 90% of anal cancers. Estimates vary concerning the role of HPV in other cancers but one global analysis suggested that it causes 12%–63% of oropharyngeal cancers, 36%–40% of penile cancers, 40%–64% of vaginal cancers, and 40%–51% of vulvar cancers.\(^12\) There is some greater uncertainty about the proportion of oropharyngeal cancers caused by HPV. A 2018 global study concluded that HPV was responsible for 30% of oropharyngeal cancers while the CDC (Centers for Disease Control and Prevention) in the USA suggests 70%.\(^13\)

If 2.5% of cancers in Europe are HPV-related, this suggests that about 67,500 cancer cases out of a total of 2.7 million across the 27 EU states will be caused by HPV in 2020.

For the other cancers, the CDC estimates that 91% of anal cancers are caused by HPV, 63% of penile, 75% of vaginal and 69% of vulvar. For all the cancers that can be caused by HPV combined, including cervical cancer, the CDC considers that HPV is implicated in 79% of cases. The CDC estimate does not include a small proportion of other head and neck cancers, affecting the sino-nasal tract, the oral cavity and the larynx, that can also be caused by HPV.

If 2.5% of cancers in Europe are HPV-related, this suggests that about 67,500 cancer cases out of a total of 2.7 million across the 27 EU states will be caused by HPV in 2020. More specific studies have estimated that HPV is responsible for about 53,000 new cases of cancer annually across 31 European countries,\(^16\) and 87,000 across the wider WHO European region.\(^17\) About 20% of cases occur in men, although one study suggests the proportion could be closer to 30%.\(^18\) In recent years, there has been a marked increase in the incidence of oropharyngeal cancers, mainly caused by HPV type 16, particularly in men.\(^19\) In the USA, HPV-positive oropharyngeal cancer has overtaken cervical cancer as the most common HPV-associated cancer type.\(^20\)
HPV-related cancers and genital warts can be prevented by HPV vaccination. This is most effective when administered in adolescence, before exposure to the virus through sexual activity. There is, however, value in vaccinating older teenagers and young adults, at least up to the age of 26 because it can protect against a new infection or re-infection and block transmission to a new partner. In the USA, HPV vaccination is now recommended for all men and women up to the age of 26. There is also some evidence supporting the vaccination of all women up to the age of 30 (or older) at the same time as a cervical screen; this approach is currently being considered in Sweden.

When HPV vaccination programmes were first introduced, three separate doses were recommended to ensure optimal immunity. It has since been recognised that two doses are sufficient and research is currently underway in Costa Rica and elsewhere to determine the efficacy of a single dose regime. This follows evidence that women in current programmes who did not receive the recommended number of vaccinations nevertheless appear to be well-protected. If a single dose proves to be effective, this would have a major impact worldwide, making it easier and cheaper to deliver vaccination programmes. The public health benefits in low-income countries would be particularly significant.

The impact of HPV vaccination on cancer incidence is clear and significant. A large-scale study in Scotland found that, compared with unvaccinated women born in 1988, vaccinated women born in 1995 and 1996 had an almost 90% reduction in the highest-risk cervical pre-cancers (Cervical Intraepithelial Neoplasia [CIN], i.e. cervical pre-cancer, grade 3 or worse), an almost equivalent reduction in CIN grade 2 or worse and a near-80% reduction in CIN grade 1.

100% vaccine effectiveness was demonstrated over 12 years in four Nordic countries: no cases of high-grade cervical dysplasia linked to HPV types 16 or 18 were found in a large sample of vaccinated women.

No data is available on the total number of cancer deaths in Europe caused specifically by HPV. However, data is available for cervical cancer specifically. In Europe, in 2018, there were almost 26,000 deaths attributable to cervical cancer, of which about 16,000 were in Central-Eastern Europe, 2,100 in Northern Europe, 3,500 in Southern Europe, and 4,250 in Western Europe. The cervical cancer mortality rate was significantly higher, almost threefold, in Central-Eastern Europe.

Every case of genital warts is caused by HPV. There are between 379,000 and 510,000 new cases of genital warts in women and between 377,000 and 428,000 new cases in men annually across 31 European countries. There is no Europe-wide data on RRP but the prevalence in the United Kingdom has been estimated at about 1.5 per 100,000. Both genital warts and RRP can have a significant impact on quality of life and treatments are costly.

The US Food and Drug Administration (FDA) has recently approved vaccination as a means of preventing head and neck cancers caused by HPV. The almost unique potential of HPV vaccination for improving public health is clear. Compared to many other cancer prevention interventions – such as tobacco control, reducing risky alcohol consumption, increasing physical activity or tackling obesity – it is easy-to-deliver, has an immediate impact and is highly effective.
The Case for Universal HPV Vaccination

The vaccination of females alone will not provide effective protection for men against HPV infection. Unvaccinated females – such as those too old to have been offered routine vaccination or women who, although eligible, did not receive it – remain at risk of infection and can pass the virus on. In Europe as a whole, only about 4% of all women are estimated to have been vaccinated; in Northern Europe, the best-performing region, the figure rises to only 8%. Although these statistics are expected to improve over time as more women receive the vaccine, they do indicate the extent of the HPV infection ‘reservoir’.

Heterosexual men living in countries with relatively high female HPV vaccination rates remain at risk of infection from unvaccinated women locally, as well as from women from countries with low-uptake, or no, vaccination programmes. Men who have sex with men are at particular risk as they are completely unprotected by female-only HPV vaccination programmes, even in countries with very high levels of uptake by girls. It should be noted that HPV can also be transmitted between unvaccinated female sex partners.

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 during 18–24 years of age and then decreases until middle age.

Vaccinating both sexes against HPV (known as ‘universal’ or ‘gender-neutral’ vaccination) provides much greater levels of protection for everyone. Its efficacy lies in preventing the transmission of HPV between the sexes and in same-sex couples, reducing the circulation of the virus overall and creating what is termed ‘herd protection’. Universal HPV vaccination is an especially important public health strategy in countries where vaccination uptake in girls is relatively low.

Universal HPV vaccination is consistent with the fundamental human right to the highest attainable standard of health. Excluding men is unfair, and in some jurisdictions possibly unlawful on grounds of sex discrimination, as it makes a potentially life-saving intervention unavailable solely on the grounds of sex. Universal vaccination would also lead to greater equity between the sexes, between countries, and between income groups (in the absence of national programmes, wealthier families are choosing to purchase vaccines for their sons or daughters).

Universal HPV vaccination programmes also remove from females the sole responsibility for preventing HPV infection and help to overcome stigma about female vaccination based on unfounded concerns that it might encourage ‘promiscuity’. Universal programmes are also more resilient to unexpected falls in uptake, for example as a result of unfounded scares spread by ‘fake news’.

Vaccinating both sexes against HPV provides an effective and faster approach to preventing or reducing the incidence of cancers and other HPV-related diseases. A universal approach could make the elimination of HPV-caused diseases possible even with moderate levels of vaccination uptake (50–75%).

The European Centre for Disease Prevention and Control (ECDC) has suggested that if the objective of HPV vaccination is to prevent all HPV-caused disease, rather than cervical cancer alone, then universal vaccination may be a cost-effective option. In 2018, the highly-influential Joint Committee on Vaccination and Immunisation (JCVI), the UK government’s vaccination advisory committee, concluded that vaccinating both boys and girls is cost-effective, even when over 80% of girls are vaccinated, if the impact of HPV-related diseases in the long-term is taken into account. It should be noted, however, that cost-effectiveness modelling is contingent on highly variable
assumptions (e.g. vaccine price, the proportion of cancer cases attributable to HPV and the costs of treatments) and, in any event, should not be the sole factor in decision-making about access to vaccines. Issues of equity, ethics and patient experience must also be taken into account.41

25 EU countries now provide national HPV vaccination programmes for girls. (The exceptions are Romania and Poland, although Poland plans to introduce a girls’ programme in 2021.) 40 out of 54 countries across the WHO European region as a whole42 have national HPV vaccination programmes for girls.

Boys are currently included in national HPV vaccination programmes in ten out of 27 EU countries and in eight other countries in the rest of the WHO European region. Finland, France, Hungary, the Netherlands, Poland, Portugal, Slovenia and Sweden have made a commitment to introduce HPV vaccination for boys. A total of 26 countries are therefore currently, or will be, including boys in their national HPV vaccination programmes; this represents almost half (48%) of all countries in the region.

Figure 1. Countries in WHO European region with national HPV vaccination programmes

- GIRLS ONLY (*where planned to include girls)
- UNIVERSAL (*where planned to include boys)
- Countries in WHO European region with no national vaccination programme for girls or boys (*where girls’ vaccination is recommended)

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a Includes Liechtenstein, which is not a WHO Europe member.

b Information about vaccination policies in specific countries may not be complete as up-to-date information for every state in the WHO European Region is not readily available. The same caveat applies to the section below on cancer screening.
Generally, countries in Northern, Western and some parts of Southern Europe are more likely to have an HPV vaccination programme, as compared to Eastern European countries. With some exceptions, the HPV vaccination programmes that include boys are located in Northern and Western Europe.

Universal HPV vaccination programmes are also becoming more common outside Europe. It is thought that 42 countries worldwide are currently vaccinating both boys and girls against HPV, including Argentina, Australia, Barbados, Bermuda, Brazil, Canada, Guyana, New Zealand, Trinidad and Tobago and the United States.

A few countries, including France and the UK, have introduced HPV vaccination programmes targeted specifically at men who have sex with men and other high-risk groups, such as sex workers. Such programmes have relatively low levels of uptake and their users are generally of an age where they are highly likely to have already been exposed to HPV infection. While they cannot be seen as a substitute for universal vaccination, these programmes can play an important role if properly resourced, especially since it will take many years before HPV vaccination programmes currently delivered to adolescents protect adults at higher risk. Migrants are another high-risk group which could benefit from targeted vaccination (as well as cervical cancer screening) programmes.

There is currently a short-term global shortage of HPV vaccine and the WHO has recommended that countries ‘should temporarily pause implementation of boy, older age group (>15 years) and multi-age cohort (MAC) HPV vaccination strategies until vaccine supply allows equitable access to HPV vaccine by all countries’. This is intended to support cervical cancer prevention programmes in mainly low-income countries. Fewer than one in three girls lives in a country in which HPV vaccine is in the national immunization schedule, and those at greatest risk for cervical cancer are least likely to have access, as only 13 low-income countries have so far introduced the vaccine.

The COVID-19 pandemic has significantly disrupted HPV vaccination programmes across Europe and will undoubtedly cause a dip in uptake, at least in the short-term. The European Federation for Colposcopy (EFC) and the European Society for Gynaecological Oncology (ESGO) suggest that HPV vaccination can continue in countries with no cases or sporadic cases of COVID-19 but should be delayed in countries with clusters of cases and/or community transmission and where the mobility of vaccine recipients and healthcare staff must be restricted to restrict transmission of the SARS-CoV-2 virus.

Vaccination Uptake

HPV vaccination uptake in females varies significantly across EU countries – few meet the widely-accepted target of at least 80% coverage. In some countries, such as Bulgaria, France and Greece, vaccination rates are particularly low.

In Western and Southern Europe, about one-third of females in the targeted populations is estimated to have completed the full course of HPV vaccination. In Eastern Europe, the proportion is only one-fifth. However, in Northern Europe, the best-performing region, about two-thirds of eligible females have been vaccinated.

HPV vaccination rates can also vary widely within countries themselves. The UK, for example, has a high overall vaccination rate (just over 80%) but, at the local level, uptake varies between 50% and 95%. There is evidence of lower rates of uptake among ethnic minority communities and disadvantaged socio-economic groups in both Europe and the USA.

Low vaccination uptake has a range of causes, including cost, restricted access to health services, concerns about vaccine safety and lack of service co-ordination, which need to be better understood for each country. But action is needed to improve HPV vaccine delivery systems (school-based systems generally have higher levels of uptake and are usually considered to represent best practice but other models, such as Portugal’s use of community health clinics, can also be very effective) and to reassure the public, using robust scientific evidence about vaccine safety. Guidance about best practice would be very helpful, especially for those countries wishing to launch, develop or expand their vaccination programmes.

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The JCVI has advised that, for the UK, the priority is for all eligible children to receive at least the first dose of the HPV vaccine. The committee considers that the interval between the first and second dose can be extended by a number of years without compromising protection or the boosting effect of the second dose.

EFC and ESGO consider that careful planning is needed to handle the backlogs accumulated due to COVID-19 to minimise drops in mid- and long-term HPV vaccination coverage. Measures should be taken to complete vaccination schedules for those who have already started HPV vaccination, assuring an interval less than 12–15 months from the first dose. Some local vaccination teams have developed innovative ‘drive through’ HPV vaccination schemes to reach children who would normally have been vaccinated at school. There may also be a potential role during the pandemic for community pharmacists.

CASE-STUDY

Drive-Through HPV Vaccination Clinics

COVID-19 meant that the school nursing service in the Isle of Wight in Southern England was unable to complete scheduled range of childhood immunisations in schools prior to their enforced closure. Recognising the vital need to vaccinate as many children as possible, the service worked with partner organisations to reconfigure the delivery system. Drive-Through immunisation clinics were quickly developed and launched.

‘Pods’ with power and hot water were established in local council car parks. Parents were contacted, the process was explained and they were given an appointment time. The programme at first focused on the routine child health immunisation programme but it worked so well that the model was extended to HPV vaccinations.

This approach has been extremely well received by families. Comments received included: ‘Thank you so much for today; it was an absolute breeze, no fuss, clear instruction and quick and efficient service.’ ‘... was super anxious beforehand but the school nurses were all so kind and welcoming and they put him completely at ease. Fabulous team.’ In the context of the Coronavirus, being able to offer the service in the open air gave parents more confidence than a traditional clinic setting.

It is too soon for data analysis but the school nursing service is confident that immunisation uptake and coverage is much better than it would have been due to restrictions of the Coronavirus. This approach has now gone ‘viral’ with numerous UK-wide children and young people immunisation providers adopting this model of practice as well as other health services such as asthma check-ups for children.

– Sharon White, CEO, School and Public Health Nurses Association (UK)
Recommendations on Vaccination

- As part of an overall EU ambition for eliminating HPV cancers and diseases, Europe’s Beating Cancer Plan should encourage all EU member states to implement gender-neutral vaccination programmes. Progress towards this goal should be monitored via a European Cancer Dashboard.

- By 2025, all European country cancer plans should include actions towards achieving population-based and gender-neutral HPV vaccination, if not already in place.

- By 2030, gender-neutral vaccination programmes against HPV infection should be in place in all European countries.

- The target vaccination rate by 2030 in all European countries should be at least 90% of adolescents of both genders completing the full course with particular attention paid to ensuring equitable access for all demographic groups.

- Supplementary to gender-neutral vaccination programmes, consideration should be given to the needs of high-risk groups, including men who have sex with men, migrants and sex workers, that may otherwise fall outside of the age parameters of the universal vaccination programme.

- Consideration should be given to extending routine vaccination programmes to older age groups on a gender-neutral basis.

- Best practice guidance should be developed and published by the WHO and/or EU on how HPV vaccination programmes can be delivered to ensure optimal uptake.

- In support of vaccination goals, global cooperation should be fostered, through WHO or other organisations, to resolve vaccine supply issues to ensure no country’s HPV vaccination programmes are impacted because of shortages. The EU should work with vaccine manufacturers to ensure that the supply of vaccines is sufficient in future to meet the growth in demand. Current global supply issues need not impact adversely on the timescales proposed in these recommendations.

- Action must be taken to ensure minimum disruption to HPV vaccination programmes by COVID-19.
ACTION AREA 2: 
Early Detection by HPV Testing

Late diagnosis of cancer increases the risk of serious disease and death. Cervical cancer screening can reduce cervical cancer mortality by up to about 90%, according to a study of its impact in Europe.54 Screening programmes will remain an essential element of the management of cervical cancer for the foreseeable future. This is because vaccination only began in Europe in 2008 and there are no countries that have achieved 100% vaccination uptake. Moreover, vaccination does not protect from all the oncogenic HPV types and some cases of cervical cancer are not caused by HPV. Many millions of women therefore remain at risk of HPV infection and cervical cancer. As the vaccinated cohort expands, however, screening will become a more straightforward process for women and clinicians.

Currently there are no screening programmes available for any of the other HPV-caused cancers, including those affecting men. Currently available screening tests for oropharyngeal cancer are insufficiently accurate and the benefits and potential harms (such as overdiagnosis or unnecessary treatment of patients with false-positive results) are unknown.55 Screening for anal pre-cancers is technically possible and has been suggested for high-risk groups, such as men who have sex with men, people with HIV/AIDS, and women with a history of HPV-caused cervical, vaginal or vulval cancers. However, the evidence of benefit has not yet been clearly established.56

More research is needed into potential screening programmes for the non-cervical HPV-caused cancers; in the meantime, the best way of achieving early diagnosis is through public education about the symptoms and training the medical workforce, including dentists, to detect the early signs of all cancers. It has been suggested that dentists and dental hygienists may have a potentially important role in the opportunistic detection of oral lesions but robust evidence for this approach is currently lacking, particularly in the case of oropharyngeal cancer.

A recent analysis of cervical cancer screening across 46 European countries found that, with the exception of one country (Azerbaijan), all had a screening programme of some sort.59 17 had population-based organised programmes described as ‘mature’ and 11 had ‘nascent’ organised population-based programmes. Organised population-based screening refers to an approach in which invitations to screening are systematically issued by public authorities to a defined target population, within the framework of a documented public policy specifying key modalities for screening examinations. This approach is recommended in the European Guidelines for Quality Assurance in Cervical Cancer Screening.60

Another 16 countries had opportunistic programmes, meaning that their success depends on the initiative of individual women and their doctors. This approach to screening often results in high coverage only in certain parts of the population, while other groups, usually with a lower socioeconomic status, have more limited uptake. Opportunistic programmes result in not only uneven coverage but also less consistent quality assurance, limited impact, and reduced cost-effectiveness.61

Also, while cervical cancer screening and cancer treatment is free of charge in most Eastern European and central Asian countries in the WHO European region, few cover the cost of following up a positive screening test or the treatment of precancerous lesions.62 The value of free cervical cancer screening at no cost is limited unless the treatment of precancerous disease is also provided free of charge.

Uptake of screening is highly variable between and within countries. Rates vary from over 70% in some EU member states to around 30% in others.64 The highest recorded rate is in Sweden (83% in 2017) and the lowest in Romania (1%). In countries with historically high screening rates, uptake has been falling in recent years. Overall, in 2014, about 14% of EU women aged 20–60 had never had a Pap smear.
In every country, women with lower educational attainment are least likely to have been screened.

HPV testing is the most effective, and accurate, method of cervical cancer screening. It is supported by the European Guidelines for Quality Assurance in Cervical Cancer Screening and is now being adopted by an increasing number of countries in place of cytology-based screening. However, it is not yet universal. Finland, France, Germany, Italy, The Netherlands, Spain and Sweden, as well as Norway, Turkey and the United Kingdom outside of the EU, have either started to implement HPV testing on a regional or national level or plan to do so. It has also been piloted in several other countries, including Poland and Portugal.

Uptake of screening is highly variable between and within countries. Rates vary from over 70% in some EU member states to around 30% in others.
As part of the process of introducing HPV testing, women need to be fully informed about the nature of the test (for example, they need to know that being HPV positive is not on its own evidence of a pre-cancerous lesion) and to understand the nature of HPV infection in order to avoid potential relationship difficulties and stigma. In the absence of this understanding, some may believe they have acquired the virus from an unfaithful partner or their partner may assume that she has become HPV+ as the result of sexual activity outside of their relationship. There is also a need for clinical consensus about how best to follow-up positive tests.

HPV testing does not have to be clinic-based. HPV self-sampling is now an option. Women use a kit, either provided at a clinic, sent to their homes or delivered there by a health worker. Greater use of this tool could undoubtedly help to improve access to screening programmes and improve uptake. It may be particularly suitable for women who are unable to access standard screening facilities, perhaps because they live in countries with less provision or in remote areas or have a disability, or where there are cultural barriers or previous traumatic experiences. It is essential, however, that self-sampling programmes address the potential risks of lower rates of follow-up by patients or increased patient anxiety following a positive result.

Self-sampling has already been incorporated into the cervical cancer screening in the Netherlands and in the Capital Region of Denmark and should be considered for wider roll-out across Europe. Self-sampling could also help mitigate the disruption caused to cervical cancer screening programmes by COVID-19 although it is essential that ‘mainstream’ screening resumes, where it is safe to do so, as soon as possible following the guidance developed by EFC and ESGO.

CASE-STUDY

HPV Testing in Turkey

A cytology-based cervical cancer screening programme was introduced in Turkey in 2004 but only reached 3% of the target population by 2012. Key barriers included a lack of coloscopists and cytopathologists and poor quality assurance for the testing process.

HPV testing was introduced in 2014 in an attempt to increase screening uptake, to provide a more accurate test, and to eliminate the human resource bottleneck. Women aged 30–60 were now invited for screening every five years, a well-defined protocol for screening intervals and referrals was introduced, and a single nationwide centralised diagnostic laboratory was established. The testing service was delivered by family physicians and nurses.

Two samples are taken from each woman which enables cytology testing for those found to be HPV-positive without women having to return for a separate test to provide an additional sample. Because only HPV-positive tests have to proceed to cytology, larger numbers of women can be screened without an excessive burden being placed on the coloscopy and cytopathology workforce.

HPV testing enabled a ten-fold increase in screening coverage to be achieved by 2017, by that time reaching 35% of the target population. The uptake among 30–45 year olds specifically reached 64%. The success of the programme suggests that HPV testing could be a feasible option for other upper-middle-income and socially conservative states in the European region.


VIRAL PROTECTION: ACHIEVING THE POSSIBLE A FOUR STEP PLAN FOR ELIMINATING HPV CANCERS IN EUROPE

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CASE-STUDY

HPV Self-Sampling

Women who are underscreened for cervical cancer are more likely to participate when offered HPV self-sampling kits, according to a trial in Belgium.

The women, aged 25-64, were recruited from attendees at a GP practice in a Flemish municipality near Brussels who had not been screened for cervical cancer for at least three years. The GPs invited 50% of the women to use a self-sampling kit. This could be used at home and then sent by post to a laboratory or returned to the GP practice. The other 50% of the women were asked to make an appointment for a Pap smear test at the practice or with a gynaecologist.

78% of the self-samplers completed the test compared to 51% of those offered a Pap test. Women in the self-sampling group were 1.5 times more likely to participate in testing. The trial suggests that direct GP involvement leads to higher rates of self-sampling than other systems, such as sending kits to women by post. Other studies have also shown that the involvement of community health workers can lead to an increased uptake of self-sampling.

—Peeters E, Cornet K, Devroey et al.72
Recommendations on Screening

- By 2025, all European country cancer plans should include actions towards achieving a minimum 70% screening target, if not already achieved.

- By 2030, at least 70% of women in Europe should have been screened for cervical cancer with an appropriate high-precision HPV test within the last five years. This coverage should be reached, at minimum, at 35 and 45 years of age, as part of an organised population-based programme. HPV screening programmes should take into consideration innovations such as self-sampling in respect to their potential for achieving higher rates of screening, particularly during the COVID-19 pandemic.

- In support of screening goals, EU guidelines on integrated HPV vaccination and cervical cancer screening should be regularly updated. A third edition of evidence-based guidelines should be developed by 2021/2022 to take account of recent developments in HPV testing technologies (which are now capable of identifying high-risk infections that are present and active with both high accuracy and high specificity) and to maximise the benefits for women and health professionals.

- More research is needed into improving the early detection of non-cervical cancers caused by HPV. This effort should be supported under the aegis of the EU Cancer Mission and Horizon Europe research programme.

- Progress on improving and widening access to HPV testing should be monitored by a European Cancer Dashboard.
There are wide variations in survival from the various cancers caused by HPV. A study of patient outcomes in the USA found that the 5-year age-standardised relative survival rate was 66% for vulval and anal cancers, 64% for cervical cancers, 53% for vaginal cancers, 51% for oropharyngeal cancers and 47% for penile cancers.74

There are also wide variations in survival from specific HPV-related cancers across Europe. Among women diagnosed with cervical cancer between 2010 and 2014, age-standardised five-year survival ranged from 80% in Iceland and 73% in Norway and Cyprus to 56% in Latvia and 55% in Poland and Bulgaria. The average among EU countries was 63%.75,76 Similar inequalities have been identified concerning other HPV-caused cancer types: age-standardised five-year survival among individuals diagnosed between 2000 and 2007 ranged from 47% to 81% for HPV-caused anal cancer,77 from 40% to 65% for vaginal and vulval cancer, from 30% to 60% for penile cancer and from 30% to 65% for oropharyngeal cancer,78 across European countries. Survival rates are significantly lower in many Central and Eastern European countries, in part reflecting variations in access to high-quality cancer treatment and care.

There are now consensus guidelines for the clinical treatment of the cancers caused by HPV which, if followed by practitioners, would help to achieve improved and more equitable outcomes across Europe. ESGO, the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Pathology (ESP) have developed guidelines for the management of patients with cervical cancer across Europe.79

A consensus statement on colposcopy, developed by ESGO and EFC will soon be published. It will recommend that women detected at risk of cervical disease in a cervical cancer screening programme be referred to a trained colposcopist and provided with written information prior to their colposcopy. Furthermore, local treatment of CIN (cervical pre-cancer) should be performed under colposcopic guidance and whenever possible as an out-patient procedure under local anaesthetic.

Guidelines for the diagnosis, treatment and follow-up of anal cancer have been drawn up by the European Society for Medical Oncology (ESMO), the European Society for Surgical Oncology (ESSO) and ESTRO.80 Clinical practice in the field of head and neck cancers caused by HPV should follow best practice guidelines such as those developed by the National Cancer Institute in the USA81 or by a multi-disciplinary group in the UK.82 For penile cancer, clinical practice guidelines have been published by ESMO.83

There are, clearly, resource implications for the successful implementation of clinical guidelines in terms of timely patient access to appropriate secondary care facilities (such as multi-disciplinary specialist cancer treatment centres), the availability of medicines, clinical staff training and other factors including public awareness of symptoms. These will be easier to achieve in some countries than others. Medical audits on cancer cases in each country could help to identify gaps in prevention strategies and be a catalyst for action.

Attention must also be paid to quality of life issues for people undergoing treatment and in its aftermath. Cervical cancer survivors commonly experience bladder and bowel dysfunction, sexual problems, lymphedema (swelling in the limbs) and psychosocial issues.84 Survivors of oropharyngeal cancer frequently face particular problems with dry mouth, swallowing, chewing and concerns about speech and appearance.85 Anal cancer survivors also suffer serious long-term impacts on their quality of life, including bowel, urinary and sexual problems.86

ACTION AREA 3: Getting Better on HPV Cancer Treatment
Recommendations on Treatment

- By 2030, across all European countries, a minimum of 90% of women with Grade 3 cervical pre-cancer should be treated within three months; and a minimum of 90% of all invasive cervical cancer cases should have been detected and managed.

- By 2025, all European country cancer plans should include actions to achieve these cervical cancer treatment goals, if not already achieved. They should also contain actions to implement best practice guidelines for non-cervical cancers caused by HPV.

- All country cancer plans should ensure that quality of life issues are fully addressed.

- A European Cancer Dashboard, operating as part of the monitoring and implementation element of Europe's Beating Cancer Plan, should provide regular publicly available updates on the progress being made towards these goals.

ACTION AREA 4: Raising Awareness and Education

The WHO has identified vaccine hesitancy as one of the top ten health threats in the world. Efforts to eliminate the diseases caused by HPV risk being undermined by a lack of public awareness about HPV, the diseases it can cause and the importance of vaccination. ‘Fake news’ about vaccination safety generally and HPV vaccination specifically is often relayed by mainstream media reports and amplified by social media. This has recently been associated with rapid falls in uptake in Denmark, Ireland and Japan. In Denmark specifically, the uptake of the first HPV vaccine dose was around 90% for girls born in the period 1998 to 2000 but dropped to 54% for girls born in 2003.87

Recent research suggests that only 73% of people in Northern Europe believe that vaccines, in a general sense, are safe. In Western Europe, this figure is even lower, at 59%; and in Eastern Europe this stands at 40%.
Recent research suggests that only 73% of people in Northern Europe believe that vaccines, in a general sense, are safe. In Western Europe, this figure is even lower, at 59%; and in Eastern Europe this stands at 40%. Across Europe, the main causes of HPV ‘vaccine hesitancy’ specifically are related to: insufficient and inadequate information about HPV vaccination; misinformation about the potential side effects of the vaccine; issues around trust in health authorities, doctors and in new vaccines; and a perception of low vaccine effectiveness. There are differences between countries: in Italy, for example, there are greater concerns about the vaccine impacting negatively on sexual activity in younger women.

Many people currently lack basic knowledge about HPV and the associated risks. One study of men and women in the United Kingdom, where HPV vaccination for girls began in 2008 and systematic cervical cancer screening in 1988, found that just over one third (37%) had even heard of HPV. Of these, 70% were aware that HPV could be transmitted during sex, and about 40% recognised that HPV could cause oropharyngeal cancer but only two thirds (64%) knew that a preventive vaccine existed. A study of some 17,000 Europeans across 10 countries found that a quarter (24%) of people believed HPV to be ‘quite rare’ or ‘extremely rare’ and that over two thirds (70%) were not aware that HPV could cause cancer in males. There is also evidence that some women are deterred from screening because of a fear that it is a test for cancer rather than primarily a means of preventing cancer.

Online information provided about HPV, vaccination, cervical cancer and screening varies widely in terms of type and quality, according to a recent study conducted across 46 European countries. In 37 countries, information is provided through a government website and in only 19 countries was the quality of the information judged to be ‘excellent’ or ‘good’ across four domains (information on HPV; information on cervical cancer and screening; information on ways to access vaccines; and online discoverability). In 10 countries, the quality of information was deemed ‘insufficient’ across the four domains, suggesting that there is considerable room for improvement.

It is not yet possible to be certain of the impact of COVID-19 on vaccine confidence and uptake. It is possible that the pandemic will serve to increase public understanding of viruses in general and the potential role of vaccines in disease prevention and generate greater faith in and respect for science and scientists. The pandemic has certainly been a stark reminder of the impact of a serious disease in the absence of a vaccine and any effective treatment.

If a safe COVID-19 vaccine is successfully developed and delivered to millions of people worldwide, this could have a positive impact on vaccine confidence generally. But it is also apparent that COVID-19 has re-invigorated the anti-vaccination movement and sparked the proliferation of many patently absurd conspiracy theories. Vaccine scepticism may also be fuelled if participants in the COVID-19 vaccine trials suffer serious side-effects, if the vaccine (or vaccines) that are eventually deployed prove to be less effective than hoped, or if the governments that recommend them are not credible to their citizens because of their overall management of the pandemic.

There is a clear need to improve public knowledge about HPV-related health risks, to raise awareness of HPV in general, including the value of HPV screening and the safety of vaccination. The utilisation of a Precaution Adoption Process Model (PAPM), which describes the psychological stages individuals go through when making decisions about behaviour change, might be helpful. In Ireland, a sharp decline in HPV vaccination uptake was successfully reversed in part by the dissemination of emotive stories of patient advocates; such stories can be more impactful than science-based communications. Celebrities may also have a role to play.
Messages should be tailored to particular population sub-groups, differentiated by gender, sexuality, age, race and other identities. Action must be taken on a sustained basis but the annual HPV Awareness Day in March (run by the International Papilloma Virus Society), the European Immunisation Awareness Week in April and the European Cervical Cancer Prevention Week in January present particular opportunities, as do cervical cancer awareness weeks held at different times in individual countries.

The education of health professionals, especially in primary care, is also of critical importance. Consistent and well-informed information and advice to patients from GPs, nurses, pharmacists and dentists can make a significant difference to the decisions individuals make about vaccination and screening. There is evidence of doubts about vaccine safety generally among healthcare workers in several countries and of a need for additional training in HPV vaccination and screening in particular.

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**CASE STUDY**

**Tackling ‘Fake News’ on HPV Vaccination in Ireland**

After an emotive political debate, Ireland introduced a free school-based HPV vaccination programme for 1st year secondary school girls in 2010. The programme enjoyed high levels of uptake until a targeted media campaign by a small group of anti-vaccination activists led to a national TV ‘shockumentary’ catalysing a freefall in vaccine confidence. This campaign was professionally executed at local and national levels to the extent that the viability of the programme came under threat.

Over the next few years, The HPV Vaccination Alliance, a coalition of NGOs, health agencies, professionals and those impacted by HPV cancer, developed and implemented a recovery strategy which has restored levels of vaccine uptake close to those needed to ensure maximum health benefit in the community.

First and foremost, this initiative focused on collaborative communication, collegiately uniting various stakeholders under the one banner of communicating the facts about the opportunity that HPV vaccination gives to eliminate a number of dreadful diseases. Clear concise, easy to understand public communication tools, including social media, were employed to target parents as well as those being vaccinated.

Educational initiatives were developed and provided to ensure that key and trusted public gatekeepers, such as nurses, doctors and pharmacists, had access to robust information and could reinforce positive public health messages about the vaccine. Time was also spent to ensure that politicians and media had easy and ready access to factual information.

Public cancer advocates lent their voice and considerable insight to illustrate why the vaccine is important to young people. Leading international agencies, including the WHO, engaged with and endorsed the campaign and this was further reinforced by strong and unambiguous political support at the very top level from the health and prime ministers.

—Dr Robert O’Connor, Director of Research, Irish Cancer Society

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CASE STUDY

HPV e-Learning for Health Professionals

Distance learning has developed significantly in recent years. It has become an increasingly important part of the global mandate of the Education for All movement led by UNESCO and the COVID-19 pandemic has hugely reinforced its importance, not least for the training of health professionals.

The Cancer Epidemiology Research Programme at the Catalan Institute of Oncology (ICO) along with the ICO e-learning programme e-oncología, (www.e-oncologia.org), have been developing an extensive virtual training programme on HPV and associated diseases for over eight years.

The following courses are now available:

1. Cervical cancer prevention (launched 2011 and now available in seven languages); 18,500 students, to date.
2. Strategies in the primary and secondary prevention of cervical cancer (2017); 4,000 students.
3. HPV Epidemiology and Prevention to Paediatrics and Primary Care (2018); 1,000 students.
4. HPV Vaccine Safety (2018); 6,000 students.
5. HPV-associated Head and Neck cancers: epidemiology, prevention and clinical management (2020); 500 students.

The digital content of all the courses has been developed using interactive elements and multimedia to facilitate learning. The modular structure of the courses allows for the addition of specific modules including the prevention and screening protocols for the country or region of interest.

The course is intended for a wide range of professionals, including health professionals involved in the prevention of cervical cancer, gynaecologists, paediatricians, oncologists, microbiologists, primary care physicians, nurses, midwives, public health professionals, health managers and planners, researchers and educators.

-Xavier Bosch, Director, e-oncologia and Assumpta Company Serrat, Academic Director, e-oncologia
Recommendations on Public and Professional Awareness of HPV

- By 2025 all European country cancer plans should include actions to increase public, patient and healthcare professional understanding and awareness about HPV. This awareness should include the range of related cancers and diseases, their symptoms and forms of prevention. Furthermore, this communication effort should elaborate to the public, patients and healthcare professionals the potential and need for HPV elimination, the strategies being pursued to achieve that goal, and the role of the public, patients and healthcare professionals. Awareness levels of the public, patients and healthcare professionals on HPV should be thereafter be monitored and reported on.

- These awareness raising actions should encompass the dental workforce, the schooling system, community pharmacists and nurses as well as physicians in primary and secondary care.

- By 2021, cancer societies, patient and healthcare professional associations, and other stakeholders, should publish a core list of consensus recommendations for European member states to implement in order to combat the impacts on HPV vaccination uptake posed by fake news.

- By 2021, all major social media platforms operating in Europe should have developed and implemented effective strategies that build on already-implemented measures to reduce significantly further the spread of fake news on vaccination.

- By the end of 2022, all national cancer plans in Europe should include actions to combat the deterrence effects of fake news upon HPV vaccination rates, as part of a broader campaign to reduce the negative impact of fake news on all vaccination programmes.
Cross-Cutting Recommendations

- By 2025, all European countries should have accountable population-based registries in place to track and report on HPV vaccination, HPV screening and HPV related (and other) cancer incidence, survival and mortality data.

- ECDC should be given the authority to oversee the implementation of an EU goal to eliminate cancers caused by HPV.

- By 2021, the EU Cancer Mission should have clear elements within its programme that support the WHO global strategy for the elimination of cervical cancer as a public health problem and the European Cancer Organisation 2019 European Cancer Summit resolution on the elimination of cancers caused by HPV. This should include supporting research priorities such as new vaccine and screening technologies as well as care and treatment modalities. Research is also needed into the vaccination of women found to be HPV-positive at cervical cancer screening as a way of interrupting the transmission of the virus into the community.

- EU Cancer Mission goals, such as on HPV, should be complemented by an EU Cancer Masterplan that supports achievement in respect to non-research-related matters. This might include facilitating greater use of EU structural funds to achieve EU- and WHO Europe-wide HPV vaccination, cervical cancer screening, and treatment goals for HPV-related cancers.

- As part of the coordination role that the EU should play in assisting member states to combat cancer by 2025, a public monitoring and reporting exercise should be established in respect of EU Member State cancer plans, similar to ‘the State of Health in the EU’ exercise. This should include the monitoring of actions towards goals on HPV-related cancer elimination. Such a mechanism could be developed within the context of the European Cancer Dashboard suggested within the European Parliament Research Service Report ‘Strengthening Europe in the Fight Against Cancer’.
REFERENCES


## HPV Action Network Participants

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<th>Member Organisations Part of this Network</th>
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To view the latest list of the HPV Action Network participants, visit: www.europeancancer.org/topic-networks/1:hpv-action

If you would like to find out more about the HPV Action Network, please contact us at: info@europeancancer.org.
As the not-for-profit federation of member organisations working in cancer at a European level, the European Cancer Organisation convenes oncology professionals and patients to agree policy, advocate for positive change and speak up for the European cancer community.