



CPW

CANCER PREVENTION at WORK

Report on existing HPV prevention programs
Deliverable D4.2

05.2024

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10	Fundacion para la investigacion y la innovacion biosanitaria del Principado de Asturias	FINBA	B	ES	NGO
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19	Health Service of the Principality of Asturias	SESPA	AP	ES	PHI

***Legend** = Role in the Project: **C** – Coordinator // **B** – Beneficiary // **AP** – Associated Partner // Organization Type: **RTD** – Research and Technological Development// **PHI** – Public Health Institution // **Hosp** – Hospital // **SME** – Small and medium-sized enterprises. // **LC** – Large Company // **NGO** – Non-Governmental Org.

	Work Packages Name	WP Leader
1	WP1 Coordination and Management	UNIBO
2	WP2 Gastric Cancer Prevention Through Helicobacter Pylori Screening and Treatment	FINBA
3	WP3 Liver Cancer Prevention Through HCV Screening and Treatment	INSP
4	WP4 Prevention of Cancers Associated with HPV Infection	RAPH BB
5	WP5 Behavioural and Sociocultural Assessment	SDU
6	WP6 Cost Effectiveness Analysis	RPA Prague
7	WP7 Dissemination, Outreach and Exploitation	WEDO

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Report on existing HPV (Human papilloma virus) prevention programs with focus on HPV vaccination (CPW D4.2)

TABLE OF CONTENT

1	EXECUTIVE SUMMARY.....	7
2	SYNOPSIS.....	8
3	LIST OF ACRONYMS AND ABBREVIATIONS	8
4	LIST OF FIGURES	9
5	LIST OF TABLES	9
6	INTRODUCTION	10
6.1	PROJECT INTRODUCTION	10
6.2	OBJECTIVES OF WP4 AND TASKS	10
6.3	CONTENTS OF THE DELIVERABLE D 4.2.....	11
7	BACKGROUND	11
8	ELIMINATION GOALS AND RESOLUTIONS	12
9	RESEARCH METHODOLOGY	12
9.1	METHODOLOGY	12
9.2	HPV-RELATED STATISTICS.....	13
10	EXISTING IMMUNIZATION PROGRAMS	16
10.1	RECOMMENDATION ON HPV VACCINATION IN EUROPE:	16
10.2	EXISTING POLICIES ON HPV VACCINATION IN EU/EEA COUNTRIES.....	18
11	HUMAN PAPILLOMAVIRUS VACCINATION COVERAGE, POLICIES, AND PRACTICAL IMPLEMENTATION IN SLOVAKIA AND ITALY.....	22
11.1	SLOVAKIA.....	22
11.2	ITALY	27
	SUMMARY AND CROSS-CUTTING RECOMMENDATIONS	30
11.3	UNIVERSAL HPV VACCINATION	30
11.4	VACCINATION UPTAKE.....	31
11.5	FEASIBILITY OF INCORPORATING HPV VACCINATION INTO EXISTING OCCUPATIONAL SURVEILLANCE SYSTEMS – EXPECTED IMPACT	32

1 EXECUTIVE SUMMARY

This document is Deliverable 4.2 (“Report on existing HPV prevention programs”) of the CANCER PREVENTION AT WORK project. It is issued under the responsibility of the Regional Authority of Public Health, Banská Bystrica, Slovakia (RAPH BB) with the contribution of a working group comprising principal investigators and team members from the implementation centers in Slovakia, Italy, and principal investigators from partners in Denmark, Germany, Czech Republic and Spain.

HPV infection is associated with 5 % of all cancers worldwide. Cervical cancer is the fourth most common cancer among women globally, with an estimated 604 000 new cases and 342 000 deaths in 2020. The highest incidence and death rates are in developing countries with low income and socioeconomic level. In the EU, cervical cancer is the second most common cancer after breast cancer to affect women aged 15 – 44. Each year, there are around 33 000 cases of cervical cancer in the EU, and 15 000 deaths. Although the cervical cancer is the most common of these cancers, the virus is also implicated in cancers of the vagina, vulva, anus, penis, head and neck. A significant proportion of the cancers caused by HPV in Europe are in men¹.

The World Health Organization (WHO) has a global strategy for the elimination of cervical cancer. This has three main elements: vaccinating at least 90 % of girls, screening 70 % of women, and treating at least 90% of precancerous lesions and invasive cancers. Europe’s Beating Cancer Plan, published by the European Commission in 2021², is more ambitious. It contains a ‘flagship’ commitment to gender-neutral HPV vaccination in every WHO member state and aims to eliminate all the cancers caused by HPV.

Therefore, the D4.2 is a public report which aims to summarise, at country level and regional level, the status of HPV prevention in the member states of the European Union (EU) or the European Economic Area (EEA). This report includes a set of indicators on the burden of HPV infections and HPV-related cancers, and the introduction of the HPV vaccine, based on official WHO estimates and existing publicly available datasets. This mapping exercise has enabled us to identify EU/EEA countries that are already taking the necessary steps to tackle those cancers caused by HPV and, even more importantly, the countries that are falling behind. Several countries in Europe still have no HPV vaccination or effective cervical cancer screening programs. Many vaccination programs still do not take a gender-neutral approach. Moreover, a significant number of countries with vaccination and screening programs have sub-optimal levels of service uptake.

The protocol, which has been discussed and agreed with all the WP4 partners, will be submitted for local ethical evaluation. Each partner in its own country will undergo necessary procedures for obtaining the approval by local Ethics Committee.

The intended audience of this deliverable consists of members of the CPW consortium and the European Commission.

¹ Baker P, Kelly D, Medeiros R (2020). Viral Protection: Achieving the Possible. A Four Step Plan for Eliminating HPV Cancers in Europe. European Cancer Organisation; Brussels.

² European Commission: Europe’s Beating Cancer Plan. 2021. Available online: https://health.ec.europa.eu/system/files/2022-02/eu_cancer-plan_en_0.pdf

2 SYNOPSIS

WP4 Protocol working group	P. Boffetta, A. Cataneo, S. Mellone, D. Mates, E. Fabiánová, Z. Klöslová, J. Oravec Bérešová, Z. Klócová Adamčáková, D. Mašlejová, J. Beláková, A. Schneider-Kamp, T. Rageliene, A. Honrado, R. Vilček, M. Jendrušáková, E. Púchyová, V. Pohančániková, L. Mojžišová, Z. Bečková, V. Ďurajová, E. Gorra, Ma. Venturini, E. Stocco, A. Godono, V. De Pasquale, M. Wensing, D. Vencovsky, E. Murínová, E. Kapustíková, M. Kočtúchová Blažinová, Ľ. Latináková, Ľ. Kamenská, B. Korbelová, R. Gili.
Project Coordinator	Paolo Boffetta, UNIBO
Study rationale	Pilot intervention, targeted to the prevention of HPV infection-related cancers, which will be conducted within the framework of existing occupational health surveillance program in three centres, on four different workers groups. The intervention will follow the World health Organisation (WHO) guidelines focusing mainly on HPV vaccination. After 6 months, a follow-up will be conducted to record attitudes and decisions of the respondents and their family members (FMs) towards HPV vaccination.
Study design	Multicentre, prospective, interventional (HPV vaccination recommendation and follow-up of the decisions towards HPV vaccination.)
Study population	Health care workers (HCW), metal workers, finance institution workers and their FMs.
Inclusion criteria	All workers participating in the preventive medical examination at work providing informed consent to participate as respondents. For HPV vaccination: all workers participating in the preventive medical check-up under the age of 45 and their FMs suitable for vaccination.
Exclusion criteria	Unable to consent. For HPV vaccination: pregnancy.
Contraindicated or Not Recommended	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component
Precautions	Moderate or severe acute illness with or without fever
Timeline	24 months enrollment, 12 months follow-up
Partners involved	UNIBO, RAPH BB, SDU, FDRH, ISP, UNITO, UKHD, ZP, ASL TO

3 LIST OF ACRONYMS AND ABBREVIATIONS

Abbreviation	Description
CPW	Cancer Prevention at Work project
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medical Agency
EU	European Union
HPV	Human Papilloma Virus
OH	Occupational Health
OHS	Occupational Health Services
WHO	World Health Organization (WHO)
WP	Work Package

4 LIST OF FIGURES

Figure 1 Demographic and socioeconomic factors - Population pyramid of Europe for 2022 ¹³	13
Figure 2 Demographic and socioeconomic factors - Population trends in four selected age groups in Europe ¹³	14
Figure 3 Comparison of HPV related cancers incidence to other cancers in men and women of all ages in Europe (estimates for 2020) ¹³	14
Figure 4 Comparison of HPV related cancers incidence to other cancers among men and women 15-44 years of age in Europe (estimates for 2020) ¹³	15
Figure 5 Comparison of HPV related cancers mortality to other cancers in men and women of all ages in Europe (estimates for 2020) ¹³	15
Figure 6 Human papillomavirus vaccination coverage, policies, and practical implementation across Europe	16
Figure 7 Comparison of HPV vaccination with at least one dose in girls born in 2009 by regions of the Slovak Republic	24
Figure 8 Comparison of HPV vaccination with at least one dose in boys born in 2009 by regions of the Slovak Republic ²¹	24
Figure 9 Age-specific prevalence of genital HPV infection in Europe: prevalence of any HPV, HR-HPV, and HPV-16 by age group.....	27
Figure 10 Promotional image for the HPV vaccination.....	29
Figure 11 HPV vaccination coverage as of 31 December 2021, in Italy ³³	29

5 LIST OF TABLES

Table 1 Existing policies on HPV vaccination in EU/EEA countries. Adapted	18
Table 2 WP4 intervention - Study partners and workers' populations.....	22
Table 3 Data about imported and reimbursed number of HPV vaccines in Slovakia.....	25

6 INTRODUCTION

6.1 Project introduction

Chronic infections represent a major cause of human cancer: on a global scale, they are responsible for an estimated 13 % of human cancers. *Helicobacter pylori* (Hp), Hepatitis C virus (HCV), and Human Papilloma Virus (HPV) are responsible together for 75 % of these cases, or 10 % of total cancer burden³. Occupational health surveillance is mandatory in all European countries: although the mechanisms of its implementation vary between the countries, these programs are in general aimed at diagnosing and preventing work-related diseases. Prevention of occupational cancers has therefore been a component of Occupational health (OH) surveillance. In recent years, however, there has been a movement towards including in occupational health surveillance aspects of health promotion which are not occupational in a strict sense.

This approach stems from several considerations:

- I. the contact between the worker and the health professional in charge of the surveillance can be seen as a privileged opportunity for health promotion in general;
- II. through the worker, the health promotion initiative may reach other groups of the population;
- III. because of the periodic nature of the visits entailed by the occupational health surveillance, it is possible to efficiently implement follow-up mechanisms.

The conceptual framework of the proposed research is based on the incorporation into preventive medical check-ups at work of primary prevention programs against Hp, HCV and HPV infections. The overarching objectives of the proposed research are:

- to conduct a series of pilot projects aimed at assessing the effectiveness (including cost-effectiveness) of incorporating primary prevention interventions against Hp, HCV and HPV into existing occupational surveillance systems in high-risk populations, including its impact beyond the workers directly involved in the pilot projects;
- to identify barriers and bottlenecks for the implementation of such interventions.
- This action is part of the Cancer Mission cluster of projects on 'Prevention and early detection'.

6.2 Objectives of WP4 and tasks

The overarching objective of WP4 is the implementation of HPV Vaccination as primary prevention of HPV infection and its complications including cervical, anal, vulvar, vaginal, penile, and oropharyngeal cancer within occupational health surveillance programs. Comprehensive cervical cancer control includes as primary prevention vaccination against HPV. Three vaccines are currently licensed in the EU. They are safe and effective in preventing infections with HPV infections, high grade precancerous lesions and invasive cancer. HPV vaccines work best if administered prior to exposure to HPV.

The Specific Objectives of WP4 include:

- 04.1** To design the protocol for HPV vaccination of workers involved in occupational health surveillance, including follow-up and promotion of HPV vaccination of eligible family members (FMs) of workers.
- 04.2** To implement the pilot project on HPV vaccination in participating centers.
- 04.3** To analyse the data collected within the pilot projects on determinants of vaccination.
- 04.4** Based on the results of the pilot projects, to develop plans for large-scale implementation of HPV prevention within occupational health surveillance systems.
- 04.5** To engage the national stakeholders in the implementation and/or adaptation of country tailored preventive interventions for HPV infection within existing occupational health surveillance programs.

³ de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health*. 2020;8: e180-e190.

The objectives of WP4 will be reached by completing the following tasks:

Task 4.1. Identification and evaluation of current national/regional programs for prevention of HPV-related cancers.

Task 4.2. Design of a protocol for a pilot study on implementation of HPV vaccination of eligible workers involved in occupational health surveillance, and their household members.

Task 4.3. Implementation and coordination of the pilot project on HPV vaccination in selected centers participating in CPW.

Task 4.4. Analysis of data collected within the pilot projects on HPV prevention on determinants of effectiveness of intervention.

Task 4.5. Development of plans for large-scale implementation of prevention of HPV-related cancers within occupational health surveillance systems.

Task 4.6. Identification of the best strategies to increase the adherence of European populations to the program of vaccination against HPV.

6.3 Contents of the deliverable D 4.2

Deliverable 4.2 is a public report which aims to summarize, at country level and regional level, the status of HPV prevention in the member states of the European Union (EU) or the European Economic Area (EEA). This report includes a set of indicators on the burden of HPV infections and HPV-related cancers, and the introduction of the HPV vaccine based on official WHO estimates and existing datasets publicly available. The protocol is designed in accordance with the specifications of task 4.2.

7 BACKGROUND

Europe has a population of 327.91 million women aged 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year 58,169 women are diagnosed with **cervical cancer** and 25,989 die from the disease. Cervical cancer ranks as the 9th most frequent cancer among women in Europe. HPV causes virtually 100 cervical cancers. Worldwide, HPV 16 and 18, the two vaccine-preventable types, contribute to over 32% of low-grade cervical lesions. After HPV 16, 18, the six most common HPV types are the same in all world regions, namely 31, 33, 35, 45, 52 and 58; these account for an additional 20 cancers worldwide⁴.

Anal cancer is similar to cervical cancer with respect to overall HPV DNA positivity, with approximately 100% of anal squamous cell carcinoma cases associated with HPV infection worldwide³. HPV 16 is the most common type detected, representing 73 % of all HPV-positive tumours. HPV 18 is the second most common type detected and is found in approximately 5 % of cases⁵.

The last evaluation of the International Agency for Research in Cancer (IARC) on the carcinogenicity of HPV in humans concluded that

- (a) there is enough evidence for the carcinogenicity of HPV 16 in the oral cavity, oropharynx (including tonsil cancer, base of tongue cancer and other oropharyngeal cancer sites), and
- (b) limited evidence for laryngeal cancer⁶.

Some studies indicate that the most likely explanation for the origin of this distinct form of head and neck cancers associated with HPV is a sexually acquired oral HPV infection that is not cleared, persists

⁴ Clifford G, Franceschi S, Diaz M, Muñoz N, Villa LL. Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases. *Vaccine*. 2006 Aug 31;24 Suppl 3:S3/26-34. doi: 10.1016/j.vaccine.2006.05.026. Epub 2006 Jun 2. PMID: 16950015.

⁵ De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer*. 2009 Apr 1;124(7):1626-36. doi: 10.1002/ijc.24116. PMID: 19115209.

⁶ IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological Agents. Lyon (FR): International Agency for Research on Cancer; 2012. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 100B.) Human Papillomaviruses. <https://www.ncbi.nlm.nih.gov/books/NBK304347/>

and evolves into a neoplastic lesion. Around 30 % of oropharyngeal cancers (which mainly comprises the tonsils and base of tongue sites) are caused by HPV with HPV 16 being the most frequent type⁷.

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"⁸.

8 ELIMINATION GOALS AND RESOLUTIONS

Globally, by 2020, about half of all countries have introduced HPV vaccination, covering about one third of the eligible population of girls. Low- and middle-income countries have the lowest rates of introduction of HPV vaccination and some are struggling with its introduction while experiencing a high burden of cervical cancer and HPV-associated illness⁹. A recent update of the International Agency for Research on Cancer's GLOBOCAN data showed that 84 % of cervical cancer cases still occur in low-resource settings¹⁰.

A call for elimination of cervical cancer was issued by the World Health Organization (WHO) in May 2018¹¹. In September 2019, the European Cancer Organisation passed a resolution for the elimination of all HPV-associated cancers, thus setting the bar even higher⁸.

The WHO considers vaccination fundamental for equity in healthcare and beyond. It is one of the key elements of primary healthcare and universal healthcare coverage. All vaccinations should thus be offered in an equitable way to all those that could benefit from the vaccines.

On January 31, 2024 the European Commission presented new recommendations on vaccine-preventable cancers, setting targets for member states to boost human papillomaviruses (HPV) vaccination. The new recommendations, initially expected by the end of 2023, aim to achieve the objectives already set by Europe's Beating Cancer Plan and the World Health Organisation (WHO)¹².

Europe's Beating Cancer Plan set a goal to fully vaccinate for HPV 90 % of the target population of girls and to increase the vaccination rate in boys by 2030. Despite these goals being already in place, the Commission communication warned that "there is still a long way to go in reaching these objectives" as many member states are still below 50 % HPV vaccination coverage for girls with limited data available for boys and young adults. Thus, the Commission calls on member states to strengthen HPV vaccination by integrating them into their national programmes and to improve the monitoring of vaccination coverage rates through electronic vaccination registries².

9 RESEARCH METHODOLOGY

9.1 Methodology

In the WP4, the feasibility of **incorporating primary prevention interventions for HPV into existing occupational surveillance systems**, in occupational groups with various risk level, needs to be explored. So, barriers and facilitators, acceptance and compliance, beyond the group of workers directly involved has to be evaluated in comparison with other community based preventive interventions. The report provides the overview of national primary prevention programs aimed to prevent HPV-related diseases

⁷ de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. 2017 Aug 15;141(4):664-670. doi: 10.1002/ijc.30716. Epub 2017 Jun 8. PMID: 28369882; PMCID: PMC5520228.

⁸ European Cancer Organisation: A Four Step Plan for Eliminating HPV Cancers in Europe. 2020. Available online: <https://www.europeancancer.org/component/attachments/?task=download&id=260>

⁹ Colzani Edoardo, Johansen Kari, Johnson Helen, Pastore Celentano Lucia. Human papillomavirus vaccination in the European Union/European Economic Area and globally: a moral dilemma. *Euro Surveill*. 2021;26(50): pii=2001659. <https://doi.org/10.2807/1560-7917.ES.2021.26.50.2001659>.

¹⁰ Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, Bray F. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health*. 2020 Feb;8(2): e191-e203. doi: 10.1016/S2214-109X(19)30482-6. Epub 2019 Dec 4. Erratum in: *Lancet Glob Health*. 2022 Jan;10(1): e41. PMID: 31812369; PMCID: PMC7025157.

¹¹ Cahill GL, Stankey MC, McClain CD, Park KB. World Health Assembly 73: A Step Forward for Global Surgery. *Ann Glob Health*. 2021 Feb 15;87(1):17. doi: 10.5334/aogh.3237. PMID: 33633928; PMCID: PMC7894378.

¹² European Commission: Commission recommends new measures on vaccine-preventable cancers under Europe's Beating Cancer Plan. 2024. Available online: https://ec.europa.eu/commission/presscorner/detail/en/ip_24_519

through HPV vaccination in the following EU/EEA member states: Belgium, Bulgaria, Cyprus, Denmark, Germany, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Croatia, Latvia, Liechtenstein (EEA), Lithuania, Luxembourg, Malta, The Netherlands, Norway (EEA), Austria, Poland, Portugal, Romania, Slovenia, Slovakia, Spain, Czech Republic, Iceland (EEA), Sweden. Switzerland is not an EU/EEA member state and therefore not included in the report.

9.2 HPV-related statistics

The HPV-related statistics used in this document is based on the 2023 Summary Report “Human Papillomavirus and Related Diseases in Europe” published by the ICO/IARC Information Centre on HPV and Cervical Cancer¹³.

The statistics shown in this D4.2 report focuses on cervical cancer and other HPV-related cancers (anus, vulva, vagina, and penis) and head and neck cancers (oral cavity, oropharyngeal, and larynx). Data include relevant cancer statistic estimates, epidemiological determinants of cervical cancer such as demographics, socioeconomic factors, and burden of HPV infection in women and men.

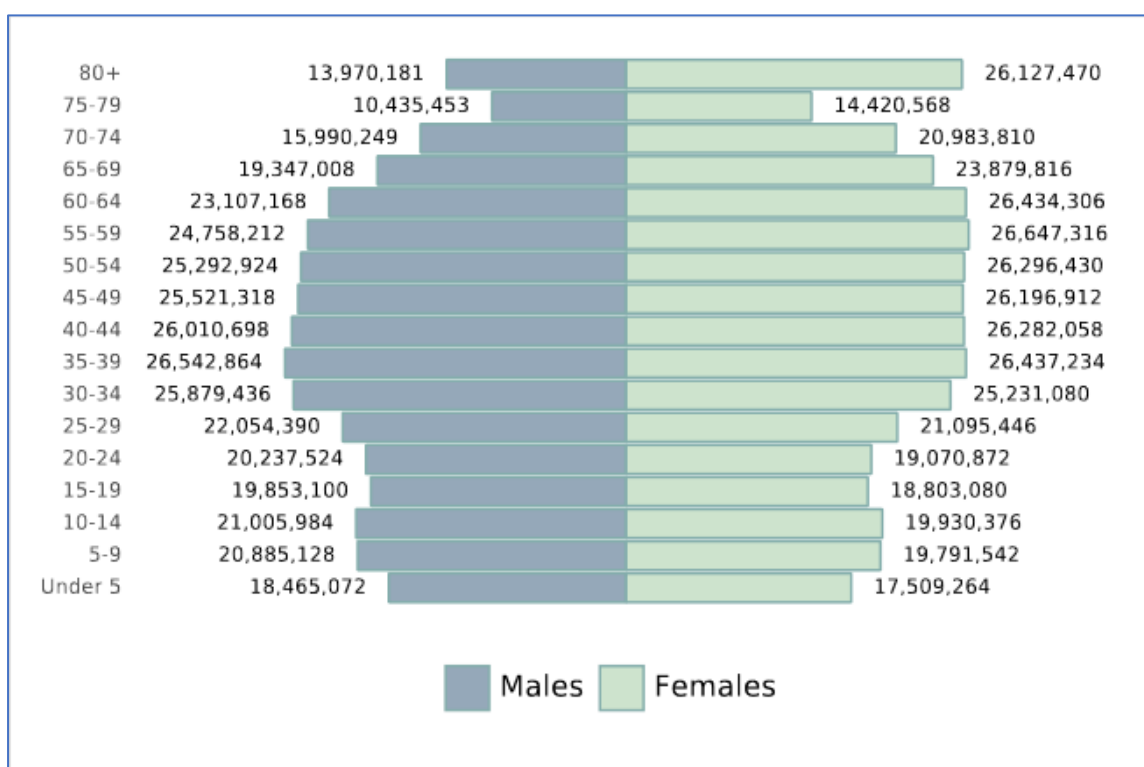


Figure 1 Demographic and socioeconomic factors- Population pyramid of Europe for 2022¹³

¹³ Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Europe. Summary Report 10 March 2023. [Accessed on March 19, 2024]

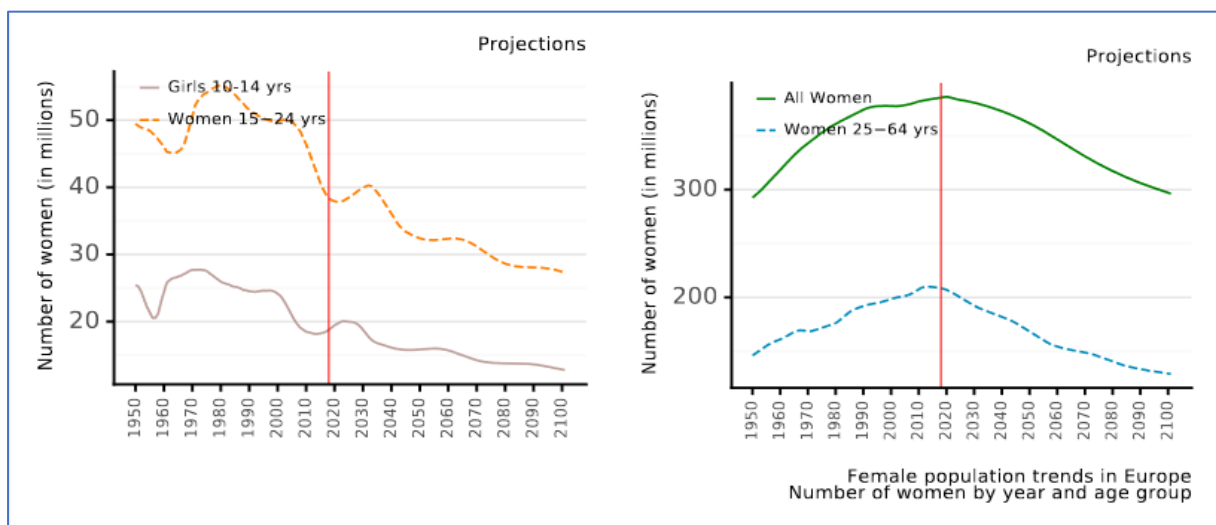


Figure 2 Demographic and socioeconomic factors- Population trends in four selected age groups in Europe¹³

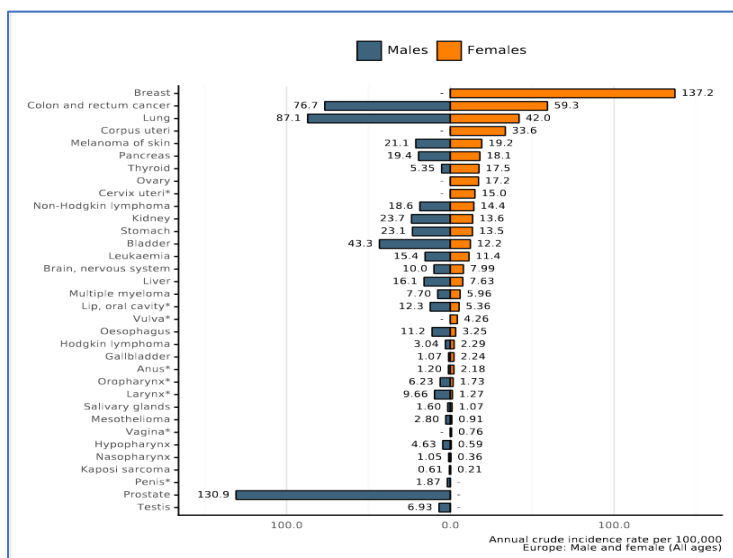


Figure 3 Comparison of HPV related cancers incidence to other cancers in men and women of all ages in Europe (estimates for 2020)¹³

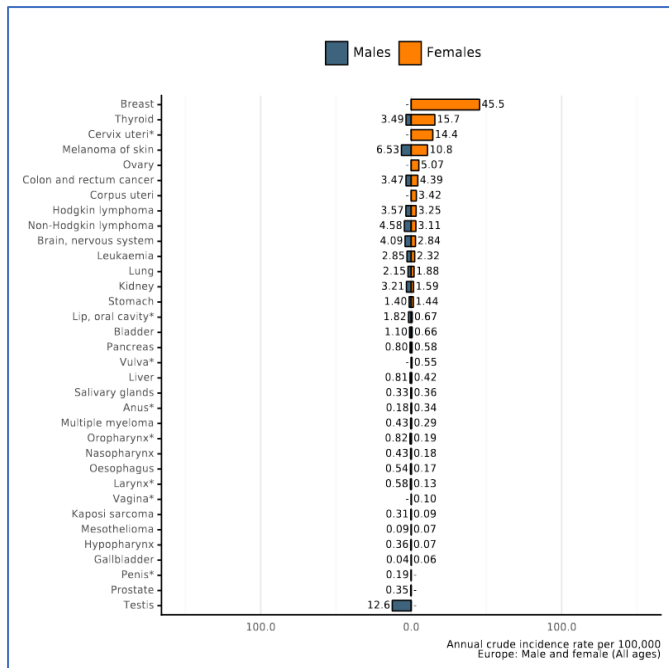


Figure 4 Comparison of HPV related cancers incidence to other cancers among men and women 15-44 years of age in Europe (estimates for 2020)¹³

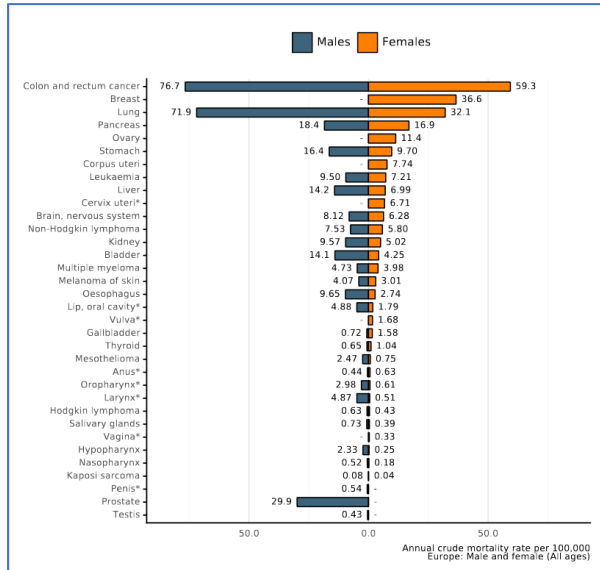


Figure 5 Comparison of HPV related cancers mortality to other cancers in men and women of all ages in Europe (estimates for 2020)¹³

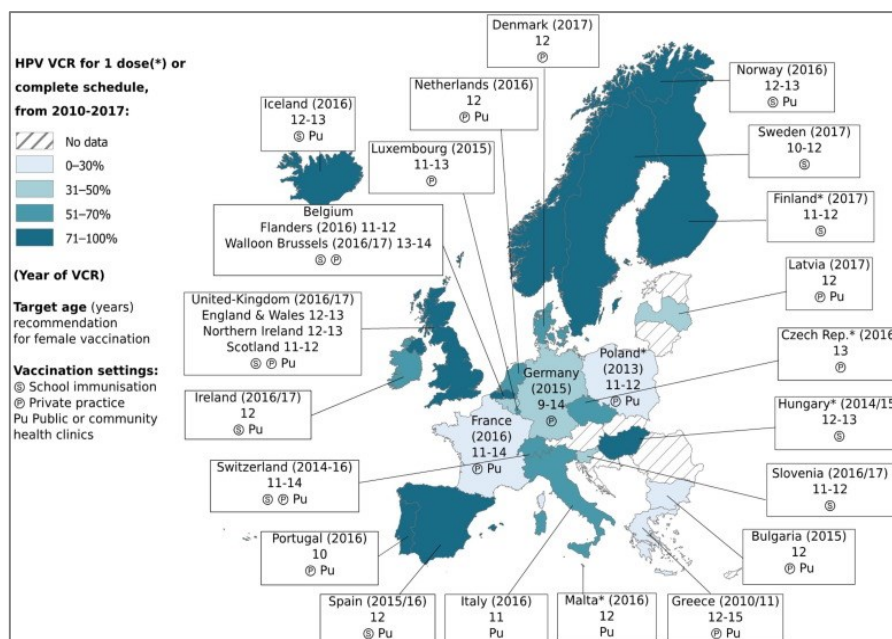


Figure 6 Human papillomavirus vaccination coverage, policies, and practical implementation across Europe¹⁴

10 EXISTING IMMUNIZATION PROGRAMS

10.1 Recommendation on HPV vaccination in Europe:

Since 2006, vaccines have been available to prevent HPV infection and HPV-associated illness. Three products are currently licensed in the European Union (EU) :

- **Cervarix** - Bivalent vaccine against two types of HPV 16 and 18 (GlaxoSmithKline Biologicals, Rixensart, Belgium;
- **Gardasil** - Quadrivalent vaccine against four types of HPV 6, 11, 16, 18 (MSD VACCINS, Lyon, France).
- **Gardasil 9** - Nine-valent vaccine against nine types of HPV: 6, 11, 16, 18, 31, 33, 45, 52 and 58 (MSD VACCINS).

These vaccines can be administered to both males and females. All three vaccines include highly purified virus-like particles (VLPs) of the major HPV L1 protein and provide protection from HPV 16 and 18 genotypes associated with more than 90 % of pre-cancerous lesions diagnosed in Europe. HPV vaccines are formulated to induce humoral immune responses, are effective, well tolerate and safe (VLPs are unable to infect cells, reproduce or cause disease in vaccinated subjects)¹⁵.

According to the age, the vaccination schedule provides for the administration of two doses at 0 and 6 months for subjects up to 13 or 14 years or the administration of three doses at the time 0, 1–2 and 6 months for subjects >14 years of age. The three-dose schedule is recommended even if the interval between the first two doses was less than five months or if the subject is suffering from immunosuppression.

All three licensed vaccines have proven their safety in clinical trials submitted at the time of their approval and are currently undergoing post-marketing monitoring by the EMA and other European national drug agencies confirming their safety.

¹⁴ Ngoc-Ha Nguyen-Huu, Nathalie Thilly, Tarik Derrouh, Emmanouela Sdona, Frédérique Claudot, Céline Pulcini, Nelly Agrinier, Human papillomavirus vaccination coverage, policies, and practical implementation across Europe, Vaccine, Volume 38, Issue 6, 2020, Pages 1315-1331, ISSN 0264-410X, <https://doi.org/10.1016/j.vaccine.2019.11.081>.

¹⁵ European Medical Agency. Human papillomavirus vaccines - Cervarix, Gardasil, Gardasil 9, Silgard – referral, <https://www.ema.europa.eu/en/medicines/human/referrals/human-papillomavirus-vaccines-cervarix-gardasil-gardasil-9-silgard>

Human papillomavirus vaccination by Gardasil 9:

Gardasil 9 helps protect individuals ages 9 to 45 against the following diseases caused by 9 types of HPV: cervical, vaginal, and vulvar cancers in females, anal cancer, certain head and neck cancers, such as throat and back of mouth cancers and genital warts in both males and females.

Gardasil 9 may not fully protect everyone, nor will it protect against diseases caused by other HPV types or against diseases not caused by HPV. Gardasil 9 does not prevent all types of cervical, vulvar, vaginal, anal or head and neck cancers. Vaccination does not remove the need for recommended screenings for these cancers, and it is important for girls to get routine cervical cancer screenings later in life and for women to continue routine cervical cancer screenings. Gardasil 9 does not treat cancer or genital warts.

Gardasil 9 is a shot that is usually given in the arm muscle. Gardasil 9 may be given as 2 or 3 shots.

For persons **9 through 14 years of age**, Gardasil 9 can be given using a 2-dose or 3-dose schedule. For the 2-dose schedule, the second shot should be given 6–12 months after the first shot. If the second shot is given less than 5 months after the first shot, a third shot should be given at least 4 months after the second shot. For the 3-dose schedule, the second shot should be given 2 months after the first shot and the third shot should be given 6 months after the first shot.

For persons **15 through 45 years of age**, Gardasil 9 is given using a 3-dose schedule; the second shot should be given 2 months after the first shot and the third shot should be given 6 months after the first shot.

Side effects of HPV vaccination

The safety and efficacy of vaccines have been demonstrated at a very high level. As with all drugs, side effects can occur. Most commonly, however, redness, itching and swelling at the site of administration. Headache, muscle pain and fatigue may occur. Transient discomfort of the digestive system such as nausea, vomiting, diarrhoea or abdominal pain has also been described. Very rarely, severe (anaphylactic) allergic reactions might occur after vaccination. People with severe allergies to any component of a vaccine should not receive that vaccine.

In 2008, the European Centre for Disease Prevention and Control (ECDC) produced its first guidance on HPV vaccination in EU/EEA countries following the introduction of the first two vaccines against human papillomavirus. The guidance was updated in 2012 following the collection of evidence of efficacy of HPV vaccination in males. In 2020, ECDC published its first evidence-based guidance on HPV vaccination, applying the methodological guidelines of the grading of recommendations, assessment, development and evaluation (GRADE) to complement and update the information included in the previous two guidance documents.

This document focused on four separate topics:

- (i) the efficacy of the 9-valent HPV vaccine licensed by the European Medicines Agency in 2015 for males and females;
- (ii) the efficacy and effectiveness of any licensed HPV vaccine for males;
- (iii) the cost-effectiveness of extending routine HPV vaccination to males and;
- (iv) the efficacy and effectiveness of any licensed HPV vaccine for people living with HIV. The guidance concluded that HPV vaccination is effective in males against persistent HPV infections, anal pre-cancerous lesions and anogenital warts based on direct evidence from a pivotal 4-valent recombinant HPV vaccine trial and on data from immuno-bridging studies for the other licensed vaccines¹⁶.

¹⁶ Colzani Edoardo, Johansen Kari, Johnson Helen, Pastore Celentano Lucia. Human papillomavirus vaccination in the European Union/European Economic Area and globally: a moral dilemma. *Euro Surveill.* 2021;26(50):pii=2001659. <https://doi.org/10.2807/1560-7917.ES.2021.26.50.2001659>

10.2 Existing policies on HPV vaccination in EU/EEA countries

The overview of existing policies on HPV vaccination policies in EU/EEA is provided in the table below:

Table 1 Existing policies on HPV vaccination in EU/EEA countries. Adapted⁹

Country or territory	Year of introduction	Current age targets for primary and catch-up vaccination for females and males				Delivery
		Primary vaccination (years)		Catch-up vaccination (years)		
		Female	Male	Female	Male	
Austria	2014	9	9	10–11 12–15 (PF)	10–11 12–15 (PF)	School: Grade 4 Health centre (catch-up)
The HPV vaccine has been available since February 2014 for all children in Grade 4, aged 9 years, free of charge. Before 2014, the vaccine was recommended but not publicly funded. The HPV vaccine is offered free of charge to children aged 9–12 years in public vaccination centres. Federal provinces also provide catch-up vaccinations at a reduced price for children up to the age of 15 years.						
Belgium						
Flanders	2010	13–14	13–14	12–18 (PF)	12–18 (PF)	Secondary school: Grade 1 Health centre (catch-up)
Wallonia and Brussels ^b	2011	13–14	13–14	12–18 (PF)	12–18 (PF)	Secondary school: Grade 2 Health centre (catch-up)
For girls in Flanders who do not qualify for the free vaccination or opt for a vaccine that is different from the free vaccine offered, a partial reimbursement is provided through health insurance. From September 2019, HPV vaccination is offered free of charge to all boys and girls aged 13–14 years in Flanders, Wallonia and Brussels.						
Bulgaria	2012	12–13	NA	14–26		Health centre
In 2007, an expert advisory body, including members from the Ministry of Health and the National Centre for Infectious and Parasitic Disease Control, issued official recommendations for the use of HPV vaccines for girls aged 12–18 years, before first sexual contact. In June 2009, the Ministry of Health included the HPV vaccine in the recommended vaccination list. In 2012, the National Programme for Primary Prevention of Cervical Cancer was approved. Vaccination and reimbursement of the vaccination cost by the National Health Insurance Fund for girls aged 12 years started at the beginning of 2013.						
Croatia	2016	13	13	NA		School: Grade 8
Voluntary HPV immunisation is available free of charge to all girls and boys in schools.						
Cyprus	2016	12–13		NA		School
HPV vaccination offered to girls only in schools and governmental immunisation centres since 2016.						
Czech Republic	2012	13–14	13–14	NA		Health centre
As for girls, HPV vaccination has been reimbursed since the 1 April 2012. The vaccination programme was extended in August 2017 to cover boys as well (by Draft Amendment to Act No. 290/2017 Coll.). The above-mentioned age interval applies to both sexes, effective from 1 January 2018. Large differences between the regions. Low numbers of boys vaccinated against HPV in 2016 or in 2017 can be explained by the fact that HPV vaccination was not reimbursed from the public health insurance in that period.						
Denmark	2009	12	NA	<18	NA	Health centre
Vaccination against human papilloma virus (HPV) was implemented in the Danish childhood vaccination programme in 2009. The vaccine provides protection in up to 70% of all cervical cancer cases. Combined with the cervical screening programme, the vaccination programme can prevent the majority of cervical cancer cases over time. The Danish Health Authority recommends that all girls are vaccinated against HPV at the age of 12.. Since 2019, HPV vaccination is offered to both boys and girls.						
Estonia	2018	12–14		NA		School
From January 2020 all girls aged 12–14 years are offered the HPV vaccination within the immunisation programme.						
Finland	2013	11–12	11–12	NA		School: Grade 6–7
During the first 2 years of the programme, HPV vaccination was administered to girls aged 13–15 years while currently it is administered to girls aged 11–12 years. Boys have been offered HPV vaccination since 2020.						
France	2007	11–14 (PF)	11–14 (PF)	<20 (PF)	<20 (PF)	Health centre

Country or territory	Year of introduction	Current age targets for primary and catch-up vaccination for females and males				Delivery
		Primary vaccination (years)		Catch-up vaccination (years)		
		Female	Male	Female	Male	
Until September 2012, French guidelines recommended the three-dose vaccine regimen to be administered routinely to all girls aged 14 years and catch-up vaccination to women aged 15–23 years without sexual activity or with a sexual debut during the year before vaccination. In 2012, the recommendation expanded to girls aged 11–14 years with catch-up vaccination until the age of 20 years. The reimbursement rate for these vaccines is 65% of the price. Boys aged 11–14 years have been offered HPV vaccination since January 2021.						
Germany	2007	9–14	9–14	<18	<18	Health centre
In June 2018, the Standing Committee on Vaccination (STIKO) recommended vaccination of boys in Germany. The STIKO recommendation is needed for statutory health insurance companies to cover the costs of vaccination. Thereafter, the federal joint committee Gemeinsame Bundesausschuss decided to include HPV vaccination to all girls and boys 9–14-year-olds in the catalogue of statutory health insurance in September 2018. Since November 2018, HPV vaccination for all 9–14-year-olds, and catch-up HPV vaccination for girls and boys 15–17-year-olds, is included in the catalogue of mandatory benefits of statutory health insurance.						
Greece	2008	11–14	NA	15–18	NA	Health centre
The HPV vaccination is currently offered only to girls. Until December 2016, catch-up vaccination was offered free of charge to girls 18–26-year-olds. From January 2017 it is offered only to 15–18-year-olds. The vaccination is also recommended for 18–26-year-old men who have sex with men.						
Hungary	2014	12	12	NA		School: Grade 7
Several local governments have decided to extend the vaccine offer to those who are not eligible for the national vaccination programme because of their age. Since October 2020 HPV vaccination is also available for boys.						
Iceland	2011	12	NA			School: Grade 7
Females older than 12 years can obtain the HPV vaccine against prescription using out-of-pocket payment.						
Ireland	2010	12–13	12–13	NA		Secondary school: Grade 1
In September 2011, a catch-up programme that targeted all girls aged 17–18 years from 2011 to 2014 was introduced. Boys have been offered the vaccination since September 2019.						
Italy	2008	11	11	Variable by region	NA	Health centre
The HPV vaccination is actively offered free of charge to girls up to 12 years of age in all Italian regions. Some regions have extended the offer of vaccination to girls in other age groups. Some regions also offer free of charge HPV vaccination to people living with HIV. Most regions also consider a facilitated payment for ages not included in the primary target group.						
Latvia	2010	12	NA			School Health centre
The vaccination is currently offered only to girls.						
Liechtenstein	2008	11–14	11–14	15–26	15–26	NA
Liechtenstein follows the recommendations of Switzerland. Vaccination is free of charge for girls and those aged 11–16 years within the framework of the cantonal vaccination programmes. This has been extended to males aged 11–26 years since July 2016.						
Lithuania	2016	11	NA			
The HPV vaccination is currently offered only to girls.						
Luxembourg	2008	9–13	9–13	NA		Health centre
The HPV vaccination programme was introduced in 2008, targeting 12–17-year-old girls, offering bivalent or 4-valent recombinant vaccines free of charge. In 2015, the programme was changed, offering the bivalent vaccine only to 11–13-year-old girls. Since January 2019, the programme has been expanded free of charge to all boys and girls aged 9–13 years.						
Malta	2012	12	NA			Health centre
Vaccination is offered to all girls aged 12 years since 2012. One of the actions included in the national cancer plan for the Maltese islands 2017–2021 is the consolidation of the HPV vaccination programme. An evaluation of the programme will be performed at the completion of the first 5 years. This will include an exploration of the impact of expanding the programme to boys of the same age cohort of the girls already being invited.						
Netherlands	2009	12–13	12–13	NA		Health centre
In 2009, a HPV vaccination catch-up campaign was organised for girls born between 1993 and 1996 (aged 13–16 years at the time). Since 2010, girls aged 12 years are invited to receive the HPV vaccination within the National Immunisation Programme. This includes girls who were born in 1997 or later. All girls receive an invitation when turning 13 years old. Boys have been offered HPV vaccination since 2021. The vaccination is free of charge and not mandatory.						

Country or territory	Year of introduction	Current age targets for primary and catch-up vaccination for females and males				Delivery
		Primary vaccination (years)		Catch-up vaccination (years)		
		Female	Male	Female	Male	
Norway	2009	12	12	NA		School: Grade 7
In 2016–2018, women born in 1991 or later were offered catch-up HPV vaccination free of charge. Since the school year 2018/19, the government offers the HPV vaccination to all boys in Grade 7 as part of the childhood immunisation programme.						
Poland	NA					
Since 2008, HPV vaccination has been recommended in the national immunisation programme for girls aged 11–12 years. The expert committee, appointed on the initiative of the Polish Paediatric Society in 2010, recommended HPV vaccines also for girls aged 13–18 years who had not been vaccinated previously. However, Poland did not introduce this vaccination into the mandatory immunisation programme. Prophylactic vaccination against HPV is charged at an extra cost in primary healthcare centres and the coverage of Polish teenagers vaccinated against HPV is estimated to be between 7.5%– 10%. Some districts have decided to introduce and finance programmes of prophylactic HPV vaccination. Currently, HPV vaccination is not part of the mandatory vaccination programme, but it is recommended for boys and girls.						
Portugal	2008	10	10	NA		Health centre
In October 2008, HPV vaccination was introduced in the national immunisation programme for girls aged 13 years born in 1995 and after. From 2009 to 2011, a catch-up vaccination campaign was run for girls aged 17 years and older born between 1992 and 1994. From 2014 to 2016, girls aged 10–13 years were covered. Since 2017, only 10-year-old girls are being vaccinated. In October 2020, the HPV vaccination was expanded to all 10-year-old children independent of sex.						
Romania	2008	11–18	11–18	19–45	NA	Health centre
In Romania, first HPV vaccination campaign was launched in 2008, the Romanian Ministry of Health rolling out a school-based immunisation campaign providing free HPV vaccination for girls aged 10–11 years. Coverage statistics revealed that only 2.6% of the girls received vaccination. Other attempts of strengthening the HPV vaccination in Romania were recorded in 2009, 2011 and 2013, but the uptake remained low. In 2020, the HPV vaccination within the National Vaccination Programme was started, initially for girls aged 11 to 14 years old. In September 2021, the HPV vaccination was extended for girls aged 15 to 18 years old (up to 19). The vaccination within the National Vaccination Programme was carried out with vaccine purchased by the Ministry of Health based on the submitted request of parents, in the family doctors’ offices (GPs). In order to increase the access to vaccination, starting by 1st December 2023, the HPV vaccine is totally reimbursed for girls and boys aged 11 to 18 years old (up to 19) and partially reimbursed (50%) for women aged 19 to 45, based on a medical receipt issued by any physician, no matter the specialty having a valid contract with the National Insurance House. The vaccination is carried out in the family doctors’ offices (GPs) or in the offices of any physician having a certificate in vaccinology. Summarising, in Romania the HPV vaccine is currently provided for at-risk groups through the National Vaccination Programme (according to the existing stockpile) or with vaccine reimbursed. In addition, the vaccine is available for being purchased.						
Slovakia	2016	13 (PF)	13 (PF)	NA		
Since April 2007 a four-valent vaccine with 10% reimbursement has been offered to 11 years old girls. Since January 2019, a bivalent vaccine against HPV has been fully reimbursed and nonvalent vaccine partially reimbursed for 12 years old girls and boys. Since 2020, gender-neutral (boys and girls) HPV vaccination has been offered free of charge. As of May 1, 2022, the Slovak Republic has joined other EU countries with full reimbursement of the nonvalent vaccine. A bivalent vaccine and a nonvalent vaccine have been available free of charge between the 12th and 13th birthday of the child. From December 1, 2023, the vaccine has been fully reimbursed also for 13–14 years old. HPV vaccination in other age groups (14+ years) is not fully reimbursed from public health insurance and these groups have to pay for it in pharmacies. Health insurance companies, however, provide some level of payback within their benefit programs for age groups 14+ – 17.						
Slovenia	2009	11–12	11–12	NA		School: Grade 6
The vaccination is offered to all girls and boys in Grade 6 within the compulsory national health insurance scheme. Boys are offered the HPV vaccination from the school year 2021/22.						
Spain	2007–2008	12	12	13–18	NA	School Health centre (depending on the region)
The Inter-territorial Council of the National Health System, the coordination body for the different Health services from the autonomous communities of Spain, approved a general recommendation to initiate routine HPV vaccination in Spain in 2007. The recommendation was for girls between 11 and 14 years of age, with a preference for those aged 14 years. The deadline for implementation of this recommendation was 2010. Afterwards, each autonomous community designed its own implementation programme. Three autonomous communities started in 2007 and the rest followed in 2008. Since 2015, as agreed by the Inter-territorial Council, HPV is recommended for girls aged 12 years in every region. Since 2018, HPV has also been recommended for the following risk groups/conditions: anogenital warts; hypogammaglobulinaemia; immunodeficiency and Myelokathexis (WHIM) syndrome (a primary immunodeficiency); women with solid organ and haematopoietic transplant up to 26 years of age; people living with HIV (male and female, with a three-dose schedule and up to age of 26 years); commercial sex workers up to the age of 26 years						

Country or territory	Year of introduction	Current age targets for primary and catch-up vaccination for females and males				Delivery
		Primary vaccination (years)		Catch-up vaccination (years)		
		Female	Male	Female	Male	
(three-dose schedule); and women with excisional treatment of the cervix. Since 2019, catch-up vaccination in girls is performed until the age of 18 years. Since 2021, HPV vaccination is offered to all girls and boys aged 12 years.						
Sweden	2012	10–12	10–12	<18	NA	School: Grades 5–6
In 2010, the HPV vaccine was included in the free of charge national vaccination programme targeting all girls born in 1999 or later and attending Grade 5–6 in school. However, vaccinations did not start until 2012 because of delays in the procurement process. Concurrently, all counties additionally introduced free of charge catch-up vaccinations targeting girls born between 1993 and 1998. According to an update of the regulation of child vaccinations (HSLF-FS 2016:51), all girls should now be offered HPV vaccinations up to the age of 18 years. From August 2020, the vaccination is offered to all girls and boys attending school Grade 5, starting from those born in 2009.						

Notes: HIV: human immunodeficiency virus; HPV: human papillomavirus; NA: not available; PF: partially funded; a Funded vaccination programmes unless otherwise stated; b The regions of Brussels and Wallonia undergo the same decisions on vaccination policies.

11 HUMAN PAPILLOMAVIRUS VACCINATION COVERAGE, POLICIES, AND PRACTICAL IMPLEMENTATION IN SLOVAKIA AND ITALY

The WP4 intervention will be conducted in seven centers located in 2 EU member states (eg. Slovakia and Italy) at high risk of the HPV infection. All the project partners involved in this intervention are listed in Table 2. The aim of this chapter is to summarize the current situation in Slovakia and Italy and to discuss the strategies that have been implemented to increase overall vaccination coverage rates in both member states.

Table 2 WP4 intervention - Study partners and workers' populations

WP 4		
Partner	Worker's population	Characteristics

Notes: FP – female predominance; MP – male predominance; SES – socioeconomic status.

11.1 Slovakia

Cervical cancer incidence in Slovakia:

About 698 new cervical cancer cases are diagnosed annually in Slovakia (estimations for 2020). Cervical cancer ranks as the 5th leading cause of female cancer in Slovakia. Cervical cancer is the 2nd most common female cancer in women aged 15 to 44 years in Slovakia.

Ranking of cervical cancer incidence to other cancers among all women according to highest incidence rates (ranking 1st) excluding non-melanoma skin cancer. Ranking is based on crude incidence rates (actual number of cervical cancer cases). Ranking using age-standardized rate may differ¹⁷.

HPV vaccination policy

One of the priorities of the National Oncology Programme for 2021-2025 of the Slovak Republic is to increase vaccination rates of girls and boys against HPV. The first reimbursed vaccine against HPV was a four-valent vaccine with 10 % reimbursement for 11 years old girls from April 1st, 2007. A bivalent vaccine against HPV has been fully reimbursed and nonvalent vaccine partially reimbursed for 12 years old girls and boys since January 1st, 2019.¹⁸

The HPV immunization programme is part of a broader set of actions taken by the Ministry of Health towards cervical cancer elimination, together with raising awareness about HPV, increasing cervical cancer screening rates, implementation of a coordinated prevention and treatment strategy. As of May 1st, 2022, the Slovak Republic has joined other EU countries with full reimbursement of the nonavalent vaccine. This step was expected to rapidly increase vaccination coverage rates in this core cohort providing better protection for the youth. In May 2022, the Ministry of Health of the Slovak Republic also introduced a free HPV vaccination to children between the ages of 12 and 13. Since December

¹⁷ Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Slovakia. Summary Report 10 March 2023. [Accessed on March 19, 2024]

¹⁸ HPV vaccination is recommended for the vaccination of 12 years old boys and girls in the Slovak Republic based on Decree of the MoH No. 585/2008 Coll.6, <https://www.zakonypreludi.sk/zz/2008-585>.

2023, the HPV vaccine has been fully covered by health insurance for children aged 12-14 years (up until their 15th birthday). This coincides with the prevention components of the nation's National Oncology Programmes Action Plan.¹⁹

A 2-dose vaccination schedule is in effect for persons aged 9-14 years. The second dose should be given between 5 and 13 months after the first dose. If the first dose was given at the age of 12, the second dose is covered by public health insurance after the child reaches the age of 13.

Persons aged 15 years and older need 3 doses of the HPV vaccine and can take advantage of their health insurance company's benefit.

Benefits of health insurance companies

- **Všeobecná zdravotná poisťovňa:** As part of the group benefits through Health Wallet MAXI, the insured person can benefit from an optional HPV vaccination reimbursement (Cervarix or Gardasil 9 vaccine) at the age of 13 to 17 years of age of up to 50 % for each dose of the vaccine, up to a maximum of € 31.45 per dose of the vaccine²⁰.
- **Dôvera**²¹ grants a contribution if the following criteria are met: The insured person aged 13 to 14 years inclusive, at the time of the first dose (i.e. from the day after the insured person reaches the age of 13 until the insured person reaches the age of 15 years) has completed a complete two-dose vaccination schedule when vaccinated with Cervarix or Gardasil 9 (if the insured person completes a three-dose vaccination schedule at this age, the insured person is not eligible to receive a benefit). The insured person aged 15 years up to and including the age of 18 years at the time of the first dose (i.e. from the day after the fifteenth birthday until the eighteenth birthday) has completed the full three-dose vaccination schedule when vaccinated with the Cervarix or Gardasil 9 vaccine. The amount of the contribution for the Cervarix or Gardasil 9 vaccine is:
 - a) €43.40 for each one dose of vaccine for an insured person who has been continuously insured with Dôvera for more than ten years at the date of vaccine dispensing;
 - b) €31 for each single dose of vaccine for an insured person who has been continuously insured with Dôvera for more than five and less than ten years at the date of dispensing of the vaccine;
 - c) €18.60 for each single dose of vaccine for an insured person who has been continuously insured with Dôvera for less than five years at the date of dispensing of the vaccine.
- **UNION**²² to make this vaccination available to older children, provides a 50 % contribution for each dose of Cervarix or Gardasil 9 for children (girls and boys) aged 13 years and older until they reach the age of 18 years. This means from the day of the 13th birthday to the day before the 18th birthday.

Vaccination Uptake

Data on HPV vaccination rates for children born in 2006-2010 in the Slovak Republic are processed and analysed by the National Centre for Health Information (NCZI) on the basis of data from health insurers on the total consumption of vaccines paid for²³.

Already the introduction of the nine-valent vaccine into full coverage for 12-year-olds in 2022 has contributed to increased interest in vaccination. As of 31.12.2022, 22,8 % of girls born in 2009 were vaccinated with two or more doses. So far, children born in 2010 are the best vaccinated year group against HPV: 43 % of girls and 22 % of boys were vaccinated against HPV with at least one dose in 2022 and 2023. In the Banská Štiavnica district, more than 80 % of twelve-year-old girls have been vaccinated, and in the Žiar nad Hronom district, more than 67 % of twelve-year-old boys have been vaccinated -

¹⁹ Očkovanie proti HPV, <https://www.health.gov.sk/Clanok?ockovanie-hpv-rakovina>

²⁰ VŠZP: Príspevok na nepovinné očkovanie proti vírusu HPV. <https://www.vszp.sk/benefit/zoznam-benefitov/pre-poistencov/prispevok-nepovinne-ockovanie-proti-virusu-hpv.html>.

²¹ ZP Dôvera: Kritériá na poskytnutie príspevku na úhradu vakcíny proti vírusu HPV. <https://www.dovera.sk/poistenec/potrebujem-poradiť/vyhody-pre-poistencov/kriteria-na-poskytnutie-prispevku-na-uhradu-vakciny-proti-virusu-hpv>.

²² ZP UNION <https://www.union.sk/ockovanie-proti-infekcii-hpv/>

²³ Národné centrum zdravotníckych informácií publikuje dáta o očkovaní detí proti ľudskému papilomavírusu <https://www.nczisk.sk/AKTUALITY/Pages/Narodne-centrum-zdravotnickych-inform%C3%A1ci%C3%AD-publikuje-data-o-ockovani-deti-proti-ludskemu-papilomavirusu.aspx>

thanks to paediatricians, these districts are the leaders in HPV vaccination. As of 31.12.2022, 22,8 % of girls born in 2009 were vaccinated with two or more doses, see figures below for more detailed information.

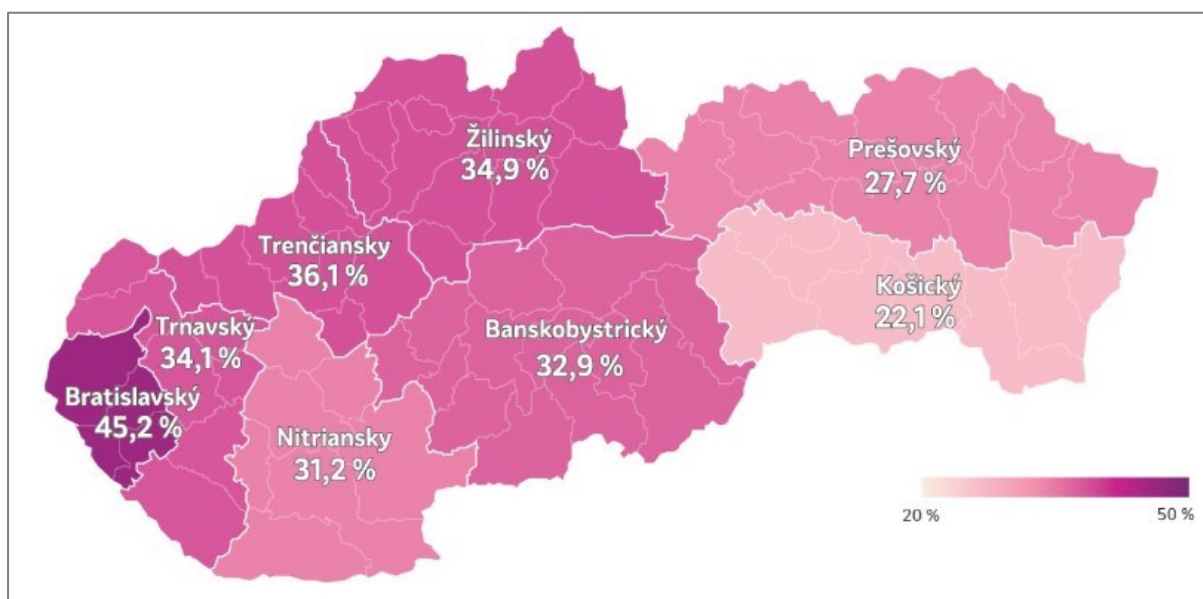


Figure 7 Comparison of HPV vaccination with at least one dose in girls born in 2009 by regions of the Slovak Republic²⁴

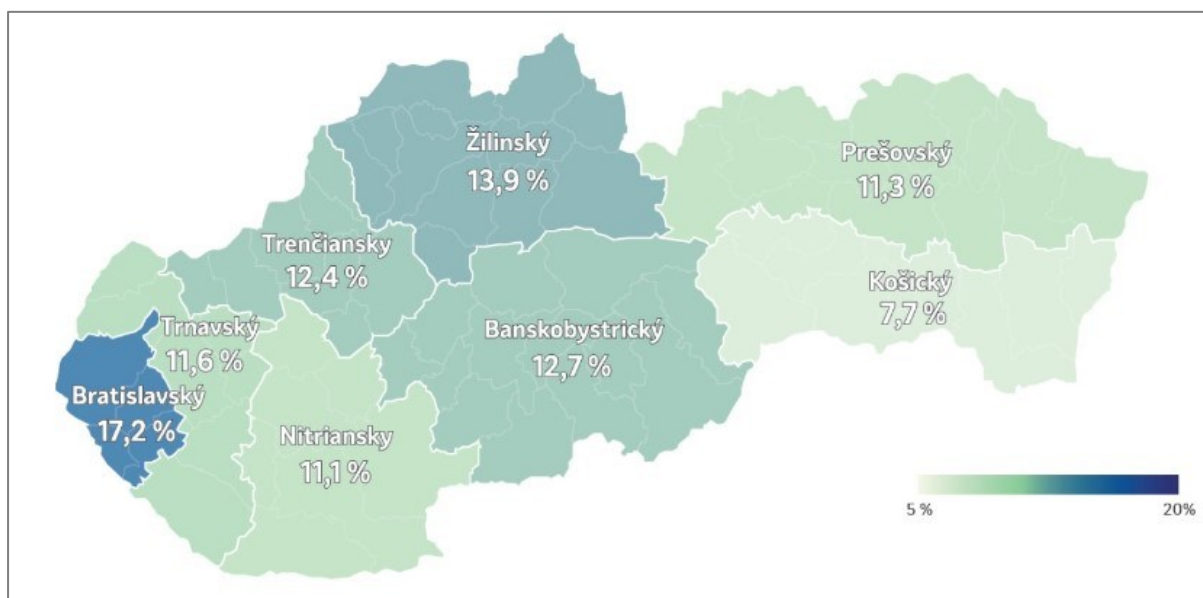


Figure 8 Comparison of HPV vaccination with at least one dose in boys born in 2009 by regions of the Slovak Republic²⁴

The data on the total consumption of HPV vaccines issued between 2021 and 2023 are presented in the table below:

²⁴ Human papillomavirus (HPV) vaccination coverage of children in Slovakia Petra Ištokovičová* Matej Mišík† Tomáš Szalay‡ February 16, 2023.
https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjut6i5_NyEAXWm_bslHQj3BS0QFnoECA4QAQ&url=https%3A%2F%2Fwww.health.gov.sk%2FZdroje%3F%2FSources%2Fdokumenty%2FIZA%2Fhpv-vaccination-coverage-of-children-in-slovakia.pdf&usg=AOvVaw30-Xe3v6Z5SA0hGnq0xya-&opi=89978449

Table 3 Data about imported and reimbursed number of HPV vaccines in Slovakia²²

Number of units	2021				2022			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Panel A. Imported number of units of HPV vaccines reported by distributors¹								
Nonavalent	1 136	8 951	820	7 052	6 804	22 409	11 074	6 180
Bivalent					2 888	3 184		375
Total	1 136	8 951	820	7 052	9 692	25 593	11 074	6 555
Panel B. Reimbursed number of units of HPV vaccines based on insurance claims²								
Nonavalent	1 696	2 247	1 859	2 412	2 207	9 088	5 220	0
Bivalent	2 617	2 978	1 315	223	1 107	1 508	264	0
Total	4 313	5 225	3 174	2 635	3 314	10 596	5 484	0

Notes: HICs data sent to NHIC according to Section 15 (6) of Act No. 581/2004 Coll. on Health Insurance Companies, Health Care Supervision and on the Amendment and Supplementing of Certain Laws, as amended and pursuant to Act No. 153/2013 Coll. on the National Health Information System and on the Amendment and Supplementing of Certain Laws, as amended.

¹ Reported by State Institute of Drug Control, not completed data.

² Reported by NHIC, not completed data.

However, coordinating and funding prevention is a constant challenge for Slovakia. With the decentralisation of the health system and the application of free market principles in healthcare, the coordination and financing of prevention from the position of the state are becoming more complex²⁵. Our goal, which is also in line with the European Cancer Plan, is to increase the HPV vaccination rate for girls to 90 % by 2030, as well as to significantly increase the vaccination rate for boys. In this context, it should be added that the HPV vaccination rate in Slovakia, which stands at 15 %, is significantly lower than in neighbouring countries. In the Czech Republic, for example, 60 % of girls and 30 % of boys are vaccinated. In Austria, the vaccination rate is also 60 % for girls and 40 % for boys. The highest proportion of vaccinated girls is in Hungary, up to 70 %.

The cervical cancer screening programme launched by the Ministry of Health of the Slovak Republic is an important step towards targeted improvement of cervical cancer prevention in Slovakia. In addition to screening programmes, i.e. secondary prevention, effective primary prevention of HPV-caused cancers is primarily based on vaccination. This is confirmed by the results of several studies by leading scientific institutes and professional societies.

Proposed solutions:

- Increasing vaccination coverage;
- Improving access to vaccination;
- Effective education and awareness building on the risks associated with HPV;
- Adequate funding;
- Quality data available.

Several corrective actions were implemented in 2022, which together contributed to a significant increase in interest in HPV vaccination:

- Improving access to the 9-valent HPV vaccine through full reimbursement of the HPV vaccine for the age group 12 to 15 years, for whom the two-dose schedule is designed, the vaccine is fully covered by public health insurance;
- Active involvement of health insurance companies in the HPV vaccination information campaign;
- Organisation of 2 HPV vaccination days in the Bratislava region and preparation of plans to continue the campaign at regular intervals;

²⁵ Increasing uptake: the impact of Slovakia's free HPV vaccination rollout, <https://eurohealthnet-magazine.eu/increasing-uptake-the-impact-of-slovakias-free-hpv-vaccination-rollout/>

- Launching a pilot project of cancer prevention education in secondary schools under the guidance of patient organisations (League Against Cancer and NO CANCER) and the Slovak Society of Primary Paediatric Care;
- Extension of health insurance benefits for HPV vaccination for children aged 13-17 years;
- Active participation in the following EU projects:

➤ **EU Joint Action PERCH:** Since 2022, the Ministry of Health has been involved in the EU Joint Action PERCH that contributes towards the implementation of Europe's Beating Cancer Plan. It supports Member States' efforts to scale up routine HPV vaccination of all children to reduce the incidence of cervical cancer and other HPV-associated cancers over the next 10 years. This 3-year Joint Action (running from 1 November 2022 to 30 April 2025) funded by the European Commission involves 18 European countries and 34 partner organisations. Through collaborative efforts, the aim is to increase HPV vaccination coverage, particularly in low-coverage regions, and optimise data collection for monitoring HPV vaccination coverage and impact.²⁶

The marginalised Roma community in Slovakia is one of those targeted groups. In addition to incorporating lessons learned to change the behaviour of healthcare professionals, this initiative will support the design and implementation of interventions to enable improved vaccine uptake in the five selected underserved communities.

➤ **The Prevention and Screening Innovation Project Toward Elimination of Cervical Cancer (PRESCRIP-TEC)**²⁷ is a three-year project (February 2021 – January 2024) that focuses its research on increasing the adoption of cervical cancer screening in resource-poor or hard-to-reach settings of Bangladesh, India, Uganda and Slovakia. PRESCRIP-TEC leads to effective and innovative cervical cancer screening, including direct treatment and follow-up for women in these four countries, improving availability, accessibility, acceptability and, quality of health care services. The PRESCRIP-TEC project is trying an innovative approach to cervical cancer screening, using HPV self-tests for at-home use. It incorporates artificial intelligence as a decision support system for cases requiring Visual Inspection with Acetic Acid (VIA) in the absence of a gynaecologist.

With the implementation of PRESCRIP-TEC project in Slovakia, we aim to achieve the following goals:

- Reaching over 1 000 000 people through targeted advertising campaigns in digital media;
- Sensitising over 70 000 men and women about cervical cancer prevention and screening;
- Interacting with over 15 000 women eligible for screening (especially from vulnerable groups, like minority groups, HIV-positive women, low health-literate women).

➤ **RIVER-EU (Reducing Inequalities in Vaccine uptake in the European Region – Engaging Underserved communities)**²⁸ aims to improve access to vaccination services for children and adolescents in selected underserved communities, specifically reducing inequity in measles, mumps, rubella (MMR) and human papillomavirus (HPV) vaccines. The target community within Slovakia where RIVER-EU aims to promote increased use of vaccines is the marginalized Roma community in Slovakia (focus on HPV).

To conclude, systematic and transparent dialogue between all stakeholders is key to achieving the set objectives. Planned, constructive and regular discussions are of key importance to identify, develop and promote possible solutions leading to a successful fight against HPV cancer in Slovakia.

The Ministry of Health of the Slovak Republic is taking the lead in establishing the HPV National Coalition of Partners as part of its ongoing PERCH initiatives. On October 24, 2023, the coalition was officially launched with a kick-off event attended by our Minister. This ambitious endeavour aims to: craft a comprehensive framework for HPV communication strategy, develop a centralised design for future

²⁶ PERCH - PartnERship to Contrast HPV, https://health.ec.europa.eu/non-communicable-diseases/cancer/europes-beating-cancer-plan-eu4health-financed-projects/projects/perch_en

²⁷ The Prevention and Screening Innovation Project Toward Elimination of Cervical Cancer (PRESCRIP-TEC), <https://prescriptec.org/>

²⁸ RIVER-EU (Reducing Inequalities in Vaccine uptake in the European Region – Engaging Underserved communities), <https://river-eu.org>

communication campaigns, implement a comprehensive plan for educational activities at schools, organise workshops for journalists to enhance public awareness about cancer prevention, HPV vaccination, and screening. Through collective efforts, Slovakia can make a substantial impact in the fight against HPV-related cancers and improve the well-being of all Slovak citizens.

11.2 Italy

Papillomavirus infections in Italy

With regards to the Italian population, it is estimated that up to 80% of sexually active women acquire an HPV infection during their lifetime, with more than 50% being infected with a potentially oncogenic genotype¹. In 2012, a systematic review revealed an 8% prevalence of oncogenic HPV genotypes in the general Italian population, with a peak among women under 25 years old. A second, though less pronounced, peak in prevalence is observed in post-menopausal age groups. Similarly, in Italy, HPV 16 stands as the predominant genotype, detected in 5% of the healthy population, followed by HPV 18 (approximately 1%).²⁹

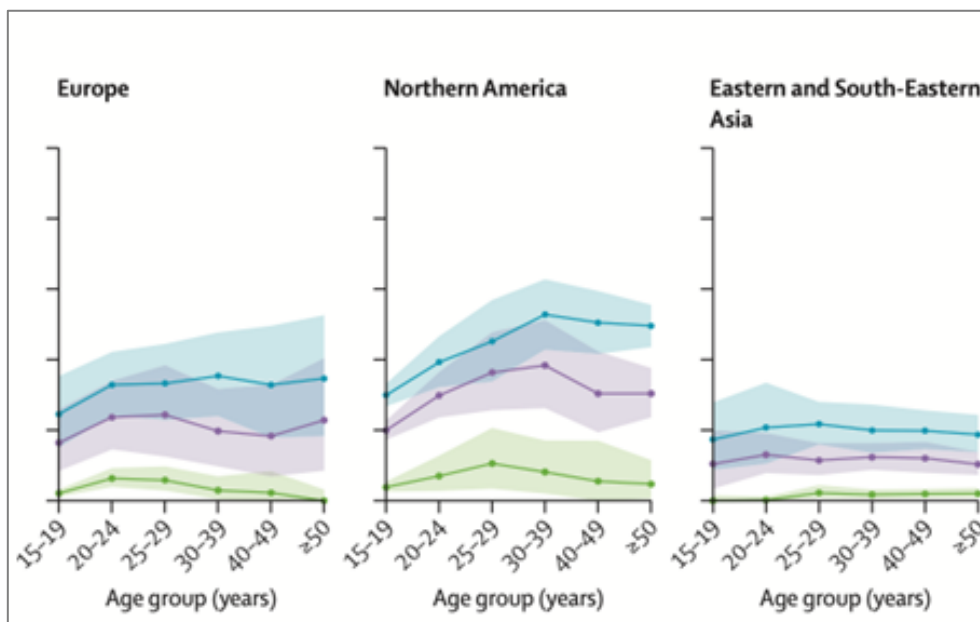


Figure 9 Age-specific prevalence of genital HPV infection in Europe: prevalence of any HPV, HR-HPV, and HPV-16 by age group.

The prevalence of HPV increases in women with abnormal cytology (34-68%), proportionally to the severity of the lesions, exceeding 90% in invasive cervical cancers. Specifically, a prevalence of 24-56% has been observed in cases of ASCUS (atypical squamous cells of undetermined significance), 42-72% in cases of LSIL (low-grade squamous intraepithelial lesions), and 73-95% in HSIL (high-grade squamous intraepithelial lesions) and beyond.³⁰ In a global context, the prevalence of HPV infections in men, as highlighted in a 2023 systematic review and meta-analysis by Bruni et al.³¹, stands at 31% in Europe overall, with a general prevalence of 22% for high-risk HPV strains. Notably, an Italian study included in the review reported a prevalence of 27% and a high-risk HPV prevalence of 11% among men.

Epidemiology of cervical cancer in Italy

²⁹ European Centre for Disease Prevention and Control Prevention and Control Measures for Human Papillomavirus.

³⁰ Agodi A, Barchitta M, La Rosa N et al. Human Papillomavirus infection. Low-risk and High Risk genotypes in women in Catania, Sicily. Int J Gynecol Cancer 2009; 19:1094-98.

³¹ Bruni L, et al. Global and regional estimates of genital human papillomavirus prevalence among men: a systematic review and meta-analysis. The Lancet Global Health, Volume 11, Issue 9, e1345 - e1362

In Italy, a total of 26.7 million women aged 15 and above are at risk of developing cervical cancer. Annually, approximately 3152 women receive a diagnosis of cervical cancer, resulting in 1011 deaths attributed to the disease. The age standardized incidence rate of cervical cancer in 2020 was 6.9 per 100,000 women.

Cervical cancer holds the 15th position among the most common cancers affecting women, and it ranks as the fourth most prevalent cancer in women aged 15 to 44 years old. Within the general population, around 4.1% of women carry cervical HPV 16/18 infection, being responsible for 72.2% of all invasive cervical cancers cases³². Despite the implementation of secondary preventive measures, such as free Pap tests and HPV tests for screening, mortality rates for all HPV-related cancers remain stubbornly high. Primary screening methods for cervical cancer include the Pap test and the Human Papillomavirus DNA (HPV-DNA) test. Traditionally, Pap tests have been conducted every three years for women aged 25 to 64³³. However, recent scientific evidence suggests that the HPV-DNA test, performed every five years, is more cost-effective for women over 30. Efforts are underway in all regions to adopt the HPV-DNA test model. Between ages 25 and 30, the recommended screening remains the Pap test, to be done every three years. The new screening test primarily targets high-risk HPV infections and is not recommended before age 30³³. Cervical cancer has a high mortality rate (24% within 5 years), as do oropharynx cancer (75% in both genders) and anal cancer (86% and 89% in women and men, respectively).

National Immunization Plans (NIP) in Italy

In Italy, HPV vaccination has been recommended since 2007, primarily targeting 12-year-old girls. Additionally, secondary target groups, such as 25-year-old women engaged in HPV screening services and a potential third cohort aged between 12 and 25, were proposed.³⁴ As for other European countries, the start of the vaccination campaign in Italy was not uniform in the various regions of the peninsula: the first to start were the Basilicata and Valle d'Aosta regions in 2007 and then Tuscany, the Autonomous Province of Trento, Liguria, Veneto, Emilia-Romagna, Molise, Calabria, Lazio and Campania which started the vaccination campaign in the first part of 2008. Only in the last months of the same year Lombardy, the Autonomous Province of Bolzano, Friuli-Venezia Giulia, Umbria, Abruzzo, Puglia, Marche, Sardinia and Piedmont have aligned themselves with the vaccination.

Subsequently, the National Immunization Program (NIP) for 2012–2014 aimed to achieve HPV vaccination coverage of at least 70% for three doses in 12-year-old girls from the 2001 cohort, 80% from the 2002 cohort, and ultimately 95% from the 2003 cohort³⁵.

In 2014, the Calendar for Life, endorsed by the Italian Society of Paediatrics, the Italian Federation of Paediatricians, the Italian Society of Hygiene, Preventive Medicine and Public Health, and the Italian Federation of Family Doctors, proposed including HPV vaccination for twelve-year-old males in the immunization schedule³⁶.

The 2017–2019 NIP expanded its focus to include both sexes as primary targets for HPV vaccination during adolescence, ideally before sexual debut. Consequently, the aim was to immunize the entire population (males and females), with the preferred age for offering free HPV vaccination set at 12 years old in Italy.

³² ICO/IARC Information Centre on HPV and Cancer. Italy. Human Papillomavirus and Related Cancers, Fact Sheet 2023.

³³ Gabutti G, Ogliastro M. History of Human Papilloma Virus Vaccination with a Focus on Italy. Women. 2024; 4(1):42-52. <https://doi.org/10.3390/women4010004>

³⁴ Ministry of Health. Consiglio Superiore di Sanità Sessione XLVI—Sezioni congiunte II e III—Seduta del 11 Gennaio 2007; Ministry of Health: Roma, Italy, 2007.

³⁵ Ministero della Salute Piano Nazionale Prevenzione Vaccinale 2012–2014. Available online: https://www.salute.gov.it/imgs/C_17_pubblicazioni_1721_allegato.pdf

³⁶ Board del Calendario per la Vita Razionale Calendario per la vita. 2 Edizione 2014. Available online: <http://www.igienistonline.it/docs/2019/21cvplv.pdf>

Additionally, vaccination was recommended (in a catch-up vaccination strategy) for women never vaccinated before at age 25 during their initial call for cervical cytology screening (Pap test). Furthermore, the 2017–2019 NIP introduced a recommendation for HPV vaccination among at-risk groups, including men who have sex with men³⁷.

In the new 2023–2025 NIP, one of the main objectives is to strengthen the prevention of cervical cancer and other HPV-related diseases. The NIP highlights the persistently low levels of HPV vaccine coverage, with only 32.22% coverage in females and 26.75% in males in 2009, significantly below the expected 95%³⁸ (Figure 9). The vaccination coverage trend shows a significant reduction compared to the pre-pandemic period. The full cycle coverage in the cohort of 15-year-olds (2005 cohort in 2021, who turn 16 in the year of the survey) used by the WHO as a reference in its statistics is 70.55%, up from the value for the same age group in the previous year (63.84%)³⁹.



Figure 10 Promotional image for the HPV vaccination

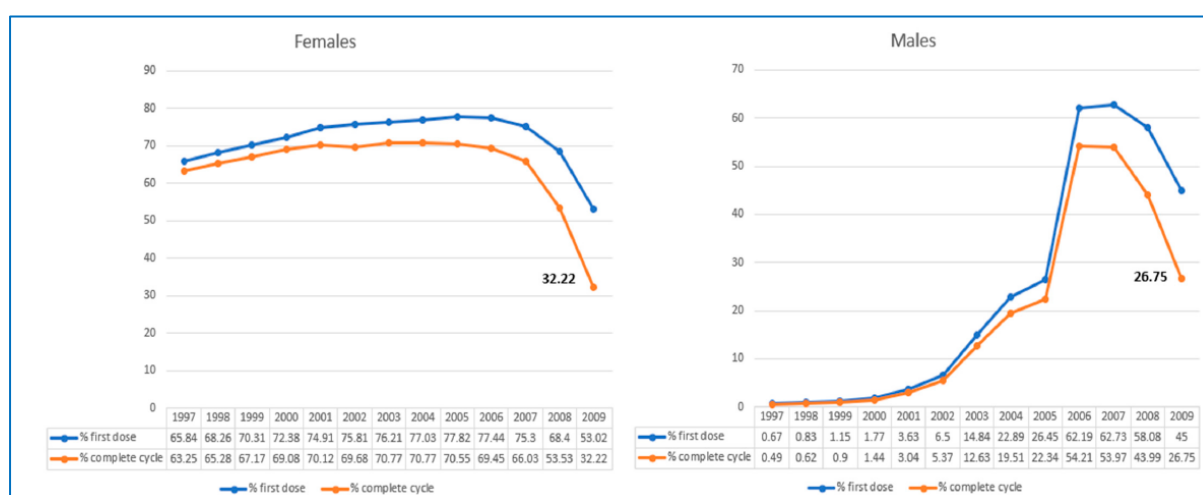


Figure 11 HPV vaccination coverage as of 31 December 2021, in Italy³³

The Italian NIP 2023–2025 recommends HPV vaccination for at risk groups, including HIV-individuals, men who have sex with men (MSM), women with high-grade cervical lesions, and people who travel for tourism, study, or work. Catch-up vaccination is recommended for women up to the age of 26, utilizing opportunities such as the first cervical cancer screening appointment for vaccination. For men, catch-up vaccination is advised up to and including the age of 18 if they haven't received prior vaccination or completed the vaccination cycle. Individuals with HPV-related diseases still face the risk of subsequent HPV infection and associated diseases even after treatment of specific lesions. Preventive HPV vaccines have demonstrated efficacy in preventing subsequent HPV-related diseases when administered before or shortly after treatment⁴⁰.

³⁷ Presidenza del Consiglio dei Ministri. Conferenza Permanente per i Rapporti tra lo Stato le Regioni e le Province Autonome. Piano Nazionale di Prevenzione Vaccinale (PNPV) 2023–2025 e Calendario Nazionale Vaccinale

³⁸ Ministero della Salute. Commento alle Coperture Vaccinali al 31 Dicembre 2021 per HPV. Available online: https://www.salute.vgov.it/imgs/C_17_tavole_27_1_6_file.pdf

³⁹ Gabutti, G.; D'Anchera, E.; De Motoli, F.; Savio, M.; Stefanati, A. Human Papilloma Virus Vaccination: Focus on the Italian Situation. *Vaccines* 2021, 9, 1374

⁴⁰ Reuschenbach, M.; Doorbar, J.; del Pino, M.; Joura, E.A.; Walker, C.; Drury, R.; Rauscher, A.; Saah, A.J. Prophylactic HPV vaccines in patients with HPV-associated diseases and cancer. *Vaccine* 2023, 41, 6194–6205.

Italian Strategies to Increase HPV Vaccination Coverage

Despite robust evidence supporting HPV vaccination, Italy experienced a decline in HPV vaccination coverage among eleven-year-old girls and boys in 2020 (birth cohort 2008). This decrease was exacerbated by the significant impact of the pandemic on activities and vaccinations, particularly affecting adolescents. Similar disruptions were observed in cervical cancer screening activities, underscoring the urgency to implement comprehensive measures in the coming years to effectively revitalize HPV vaccination efforts. The goal is to attain $\geq 95\%$ coverage in adolescents through HPV vaccination, leading to a gradual reduction in the incidence of cervical and uterine cancer⁴¹.

As outlined in the 2023–2025 NIP, key actions include:

- Reinforcing and revitalizing the national HPV vaccination campaign by actively engaging the local scientific community, specialists, and scientific and civil societies.
- Expanding access to vaccination services through initiatives such as organizing open days and catch-up activities. Additionally, extending the provision of free HPV vaccines to cohorts up to the age of initiation of cervical cancer screening, providing free vaccines for males up to and including 18 years old, maintaining free vaccination for beneficiary cohorts, and leveraging tools and technologies to facilitate active outreach and appointment management.
- Developing an effective communication campaign to address vaccine hesitancy.
- Integrating primary and secondary prevention efforts.

To address vaccination delays caused by the SARS-CoV-2 pandemic, certain regions have strengthened the recommendations for co-administering the HPV vaccine with other age-recommended vaccines¹⁷⁴².

SUMMARY AND CROSS-CUTTING RECOMMENDATIONS

11.3 Universal HPV Vaccination

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.

A few countries 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.⁸

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 the greatest risk for cervical cancer are least likely to have access, as only 13 low-income countries have so far introduced the vaccine.

The HPV vaccine shortage was expected to be resolved by 2023 (perhaps earlier if new vaccines manufactured in China become available), meaning that European countries had an opportunity to develop their plans over the next 2-3 years and had them ready for implementation in 2023 or soon

⁴¹ Ministero della Salute. Commento alle Coperture Vaccinali al 31 Dicembre 2021 per HPV. Available online: https://www.salute.gov.it/imgs/C_17_tavole_27_1_6_file.pdf

⁴² Regione Lazio. Trasmissione Documento: "Raccomandazioni Riguardanti la Co-Somministrazione dei Vaccini". Available online: <https://www.vaccinarsinlazio.org/assets/uploads/files/7/rf-documento-co-somministrazione-vaccini-384782-28apr2>

after. In the meantime, European countries, and the EU itself, could offer support to low-income countries developing HPV prevention programmes.⁸

11.4 Vaccination Uptake

HPV vaccination uptake in females varies significantly across EU countries – few meet the widely-accepted target of at least 80 % coverage.⁴³ 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. There is evidence of lower rates of uptake among ethnic minority communities and disadvantaged socio-economic groups in both Europe and the USA.¹¹

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. 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.

There is already significant support for the introduction of universal vaccination across Europe:

- The European Commission's new **Beating Cancer Plan**² provides a major new opportunity for the development of 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.
- The European Commission's **Roadmap for the Beating Cancer Plan** specifically mentions HPV as a potential area for action. The new EU Cancer Mission, as part of the Horizon Europe Framework Programme for Research and Innovation, creates an opportunity for complementary action.
- On January 31, 2024 the **European Commission** presented new **recommendation on vaccine-preventable cancers**, setting targets for member states to boost human papillomaviruses (HPV) vaccination.⁴⁴ Recommendation includes a series of measures that Member States could take to improve the uptake of these life-saving vaccines. These include:
 - Providing vaccination free of charge and/or fully reimbursed;
 - Ensuring that vaccination is easily accessible, particularly to the targeted groups and vulnerable or high-risk populations;
 - Integrating vaccine-preventable cancer immunisation into their national cancer plans;
 - Strengthening communication efforts, particularly by highlighting the benefits of vaccination to parents, young people and target groups and addressing mis- and disinformation;
 - Improving monitoring and reporting of vaccination coverage, to identify where gaps may need to be addressed;
 - Setting a concrete target for HPV vaccination for boys;
 - Putting strong electronic vaccination registries in place;
 - Exchanging best practices with other Member States to improve national efforts.

⁴³ Bruni L, Diaz M, Barrionuevo-Rosas L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *Lancet Global Health* 2016; 4: e453–63. doi: 10.1016/S2214-109X(16)30099-7.

⁴⁴ Commission recommends new measures on vaccine-preventable cancers under Europe's Beating Cancer Plan, https://ec.europa.eu/commission/presscorner/detail/en/IP_24_519

- Additionally, the new **EU4Health Programme** could support HPV cancer and disease elimination by developing tools such as a European Cancer Dashboard to monitor progress towards vaccination, screening and treatment goals.⁴⁵
- The **European Parliament**, in its resolution on vaccine hesitancy⁴⁶ 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.
- **WHO Europe's men's health strategy**⁴⁷, 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. Almost half of all the countries in the WHO European Region now provide HPV vaccination to both sexes or plan to do so.

11.5 Feasibility of incorporating HPV vaccination into existing occupational surveillance systems - expected impact

Available literature suggests that HPV interventions have the potential to be cost-effective. However, cost-effectiveness ratios in the literature vary and depend on a number of factors, such as the targeting of the intervention (high risk vs low risk group). There is thus a need to improve our understanding of the impact that the design of such interventions (especially in the European context) and structural conditions can have on cost-effectiveness. In addition, there is a significant need to improve the evidence base for public health interventions implemented within the framework of OH surveillance. Multiple studies suggest that health care workers treating human papillomavirus (HPV)-associated conditions may experience occupational exposure to the virus. Case reports describe the development of cancer and other disease in health care professionals at low risk for such conditions except for their work.⁴⁸ No data are available for other sectors and industries. Despite limited data, vaccination can be a safe and effective method to reduce this uncertain risk. If the results of the pilot studies will be successful and cost-effective, the research group, together with relevant stakeholders, will be able to provide guidance and recommendations for large-scale implementation of the intervention.

⁴⁵ New measures to prevent cancer through vaccination, https://commission.europa.eu/news/new-measures-prevent-cancer-through-vaccination-2024-02-02_en

⁴⁶ European Parliament resolution of 19 April 2018 on vaccine hesitancy and the drop-in vaccination rates in Europe, https://www.europarl.europa.eu/doceo/document/TA-8-2018-0188_EN.html

⁴⁷ Strategy on the health and well-being of men in the WHO European Region, <https://www.who.int/europe/publications/i/item/WHO-EURO-2018-4209-43968-61973>

⁴⁸ Harrison, Ross MD; Huh, Warner MD. Occupational Exposure to Human Papillomavirus and Vaccination for Health Care Workers. *Obstetrics & Gynecology* 136(4):p 663-665, October 2020. | DOI: 10.1097/AOG.0000000000004021