

Gender difference in human papillomavirus vaccine coverage in Italy and Europe

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Summary. The World Health Organization (WHO) recognizes cervical cancer and other diseases caused by HPV as a global public health issue. The maximum effectiveness of the vaccine in preventing cervical and anal cancer occurs when the vaccine is administered before the start of sexual activity. The WHO called for a joint action by scientific societies and cancer organizations aimed at achieving the goal of eliminating cervical cancer as a public health issue, also in Europe. All European Countries should, by 2030, achieve at least 90% human papillomavirus (HPV) vaccination coverage among both the girls and boys who fall within the recommended age group.

The goal of our study is to evaluate the differences in vaccination coverage between males and females in the different Italian regions, as well as in Europe.

The data published by the Italian Ministry of Health relating to the national coverage was analyzed, while for Europe data reference was made to that published on the websites of the European Center for Disease Prevention and Control (ECDC) and the WHO.

In Italy HPV vaccination has been offered for free since 2007/2008 by the National Health Service to all girls once they reach age 12. Starting from 2015, three Italian regions (Sicily, Puglia, Molise) also introduced the anti-HPV vaccination for males at the same age. This choice originated from a better understanding of HPV infection, its clinical manifestations in both sexes and the subsequent approval of the quadrivalent vaccine also for males.

Once introduced in national immunization programs, HPV vaccination has proven very successful; however, there are still many Countries that have not introduced vaccination at national level.

Despite the great promise offered by HPV vaccines in reducing the disease burden and promoting socioeconomic and gender equality, their implementation in national programs has been slow. In fact, despite the free vaccination and screening programs for females, coverage was not extended to males in all Countries.

The active offer of vaccination against HPV in males and females could drastically change the epidemiology of HPV-related diseases and their consequences.

The WHO recognizes cervical cancer and other diseases caused by HPV as a global public health issue. The maximum effectiveness in preventing cervical and anal cancer occurs when the vaccine is administered before the start of the sexual activity. All European Countries should, by 2030,

achieve at least a 90% HPV vaccination coverage among both the girls and boys who fall within the recommended age group.

Keywords. HPV, cervical cancer, coverage, vaccination.

Differenze di genere nella copertura vaccinale contro il papillomavirus in Italia e in Europa.

Riassunto. L'Organizzazione Mondiale della Sanità (OMS) riconosce il cancro al collo dell'utero e le altre malattie causate dallo Human Papillomavirus (HPV) come un problema di salute pubblica globale. La massima efficacia del vaccino anti-HPV (utilizzato nella prevenzione del cancro al collo dell'utero e cancro anale) si ottiene quando il vaccino viene somministrato prima dell'inizio dell'attività sessuale. L'OMS ha chiesto un'azione congiunta da parte delle società scientifiche e delle organizzazioni internazionali contro il cancro per raggiungere l'obiettivo di eliminarlo. Il cancro provocato dall'HPV è un problema di salute globale e coinvolge quindi anche l'Europa. L'Europa dovrebbe, entro il 2030, raggiungere almeno il 90% di copertura vaccinale (anti-HPV) tra ragazze e ragazzi che rientrano nella fascia di età raccomandata. L'obiettivo del nostro studio è stato quello di valutare le differenze nella copertura vaccinale tra maschi e femmine nelle diverse regioni italiane e in Europa.

Sono stati analizzati i dati pubblicati dal Ministero della Salute italiano relativi alla copertura nazionale, mentre per i dati europei si fa riferimento ai dati pubblicati dall'European Center for Disease Prevention and Control (ECDC) e dall'OMS. La vaccinazione anti-HPV in Italia è offerta gratuitamente dal 2007/2008 tramite il Servizio Sanitario Nazionale alle bambine nel dodicesimo anno di vita. A partire dal 2015, tre regioni italiane (Sicilia, Puglia, Molise) hanno introdotto la vaccinazione anti-HPV per i maschi a partire dal dodicesimo anno di vita. Questa scelta è il risultato di una migliore conoscenza sia dell'infezione sia delle manifestazioni cliniche che l'HPV sviluppa in entrambi i sessi, ma soprattutto dell'approvazione del vaccino quadrivalente anche per i maschi.

Anche se l'introduzione della vaccinazione HPV nei programmi di immunizzazione nazionali ha avuto molto successo, la sua attuazione è stata comunque lenta e sono ancora molti i Paesi che non la hanno introdotta a livello nazionale. Le numerose campagne di promozione della vaccinazione anti-HPV per ridurre le complicità della malattia e promuovere l'uguaglianza di genere non sempre hanno raggiunto l'obiettivo. Nonostante la vaccinazione sia gratuita e siano

stati proposti numerosi programmi di screening per le donne, la copertura vaccinale non è ancora stata estesa ai maschi in tutti i Paesi.

L'offerta attiva di vaccinazioni contro l'HPV nei maschi e nelle femmine potrebbe cambiare drasticamente l'epidemiologia delle malattie correlate all'HPV e le loro conseguenze.

Parole chiave. HPV, cancro cervicale, copertura vaccinale, vaccinazione.

Introduction and objectives of the study

Human papillomavirus (HPV) is among the most common sexually transmitted viruses, and is the cause of many conditions in men and women, including precancerous lesions and cancer. The peak in its incidence occurs between 20 and 25 years of age, followed by a decline that reaches a plateau around age 35. The second peak of incidence occurs around age 45-50. Each year, the virus is responsible for approximately 630,000 new cases of cancer in the anogenital region and in the upper airways. Of these, cervical cancer is the most common, accounting for nearly 85% of all HPV-associated cancers.¹

There are over 130 types of HPV viruses: types 16 and 18 are responsible for over 70% of all cervical cancers, while types 6 and 11 cause over 90% of anogenital warts, therefore vaccines are formulated against these four strains.² In fact, more than 80% of sexually active women and men are expected to be infected with at least one HPV serotype by age 45.³ Three different vaccines against HPV infection have been available in Italy since 2006:

- bivalent vaccine: contains serotypes 16 and 18;
- tetravalent vaccine: in addition to serotypes 16 and 18, it also contains serotypes 6 and 11;
- 9-valent vaccine: contains serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58.

In June 2015, the 9-valent vaccine was authorized in Europe and has been available in Italy since January 2018.⁴

HPV vaccination in Italy has been offered free of charge since 2007/2008 by the National Health Service to girls in their twelfth year of life. Until a few years ago, the main goal of vaccination against HPV was the prevention of cervical cancer, so vaccination was directed only to girls. However, in recent years – thanks to a better understanding of the HPV infection, its clinical manifestations in both sexes and the subsequent approval of the quadrivalent vaccine for males as well – vaccination has also been recommended for males.

Starting in 2015, three Italian regions (Sicily, Puglia, Molise) introduced the anti-HPV vaccination also for males in their twelfth year of life as well. In 2016, four regions (Calabria, Liguria, Friuli Venezia Giulia and Veneto) also extended the free offering for the 2004

cohort. The Emilia-Romagna and Friuli Venezia Giulia regions also offer the vaccine to HIV-positive males and females.

The new National Vaccine Prevention Plan 2017-2019 and the new Essential Levels of Assistance (LEAs)⁵ provide for the free vaccination of males as well, starting from the 2006 birth cohort. But the programs only reached full operation in 2018.^{6,7}

Since 2014, the HPV vaccine has been administered in 2 or 3 doses, depending on the type of vaccine used and the age at the time of first dose. The interval between doses is 6 months in the case of a 2-dose administration, while the intervals for a 3-dose regimen are fixed at 1 or 2 and 6 months after the first dose.⁸

However, available HPV vaccines do not protect against all high-risk HPV infections, which is why vaccination should not replace prevention, through cervical screening. According to the Italian Ministerial guidelines, women aged 25-30 should have a Pap test every 3 years, or the HPV test (HPV-DNA test) should be offered every 5 years to women between 30 and 64 years of age.⁹

The goal of our study is to evaluate the differences in vaccination coverage between males and females in the various Italian regions, as well as in Europe.

Material and methods

The study analyzed the data published by the Italian Ministry of Health on the national and regional coverage for HPV vaccination in the female and male populations for the 1994-2006 birth cohorts. Each year, the Ministry of Health receives the data collected through the vaccination coverage surveys performed by the various regions, and publishes them on their official website.¹⁰

With regard to European vaccination strategies in the various member States, reference is made to the data published on the European Center for Disease Prevention and Control (ECDC) website, while vaccination coverage data is taken from the WHO website.^{11,12}

Data is presented in the form of calculations and percentages by birth cohort and gender. Vaccination coverage was calculated for the 1997-2006 birth cohorts in the female population, and for the 1994-2006 birth cohorts in the male population. Differences in vaccination coverage were tested with the Chi-square test.

Results obtained

Vaccination coverage in Italy

In Italy, on 31/12/2018, vaccination coverage data relating to the 2006 female cohort shows a 61.7% coverage for the first dose and a 40.3% for the complete cycle. In

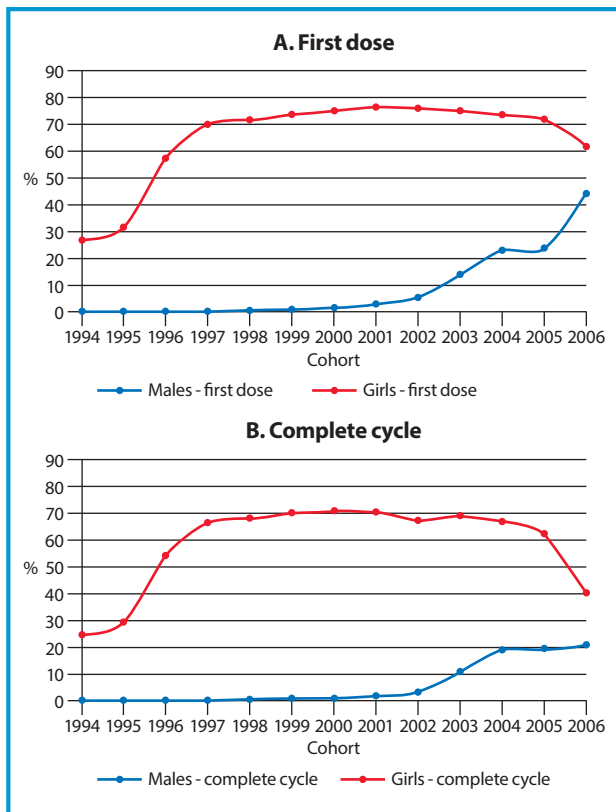


Figure 1. HPV vaccination coverage in Italy.

2017, for the 2005 female birth cohort, values were 64.4% and 49.9%, respectively; in 2016, the 2004 cohort had values of 65.0% for the first dose and 53.1% for the complete cycle, confirming the negative trend of the measurements for the last cohort on active call. In the 2006 male cohort, a coverage of 24.1% for the first dose and of 19.3% for the complete cycle was found. Figure 1 shows the increase over time in the administration of the first vaccination dose, which in girls reaches 76.52% in the 2001 cohort, while in boys reaches 44.05% in the 2006 cohort. For the administration of the second dose, there is a progressive decrease in vaccinations in girls starting from the 2001 cohort (70.45%); contrarily, the trend for boys has improved starting from the 2006 cohort (20.82%). The difference between males and females is therefore statistically significant for both the first and the second dose ($p < 0.001$).

Figure 2 shows vaccination coverage by region and sex.

Vaccination coverage in Europe

In Europe, a great heterogeneity was found regarding vaccination strategies, even though most of the EU (European Union) and EEA Countries had already committed to introducing vaccination against HPV within their own immunization programs by 2019 (Table 1).

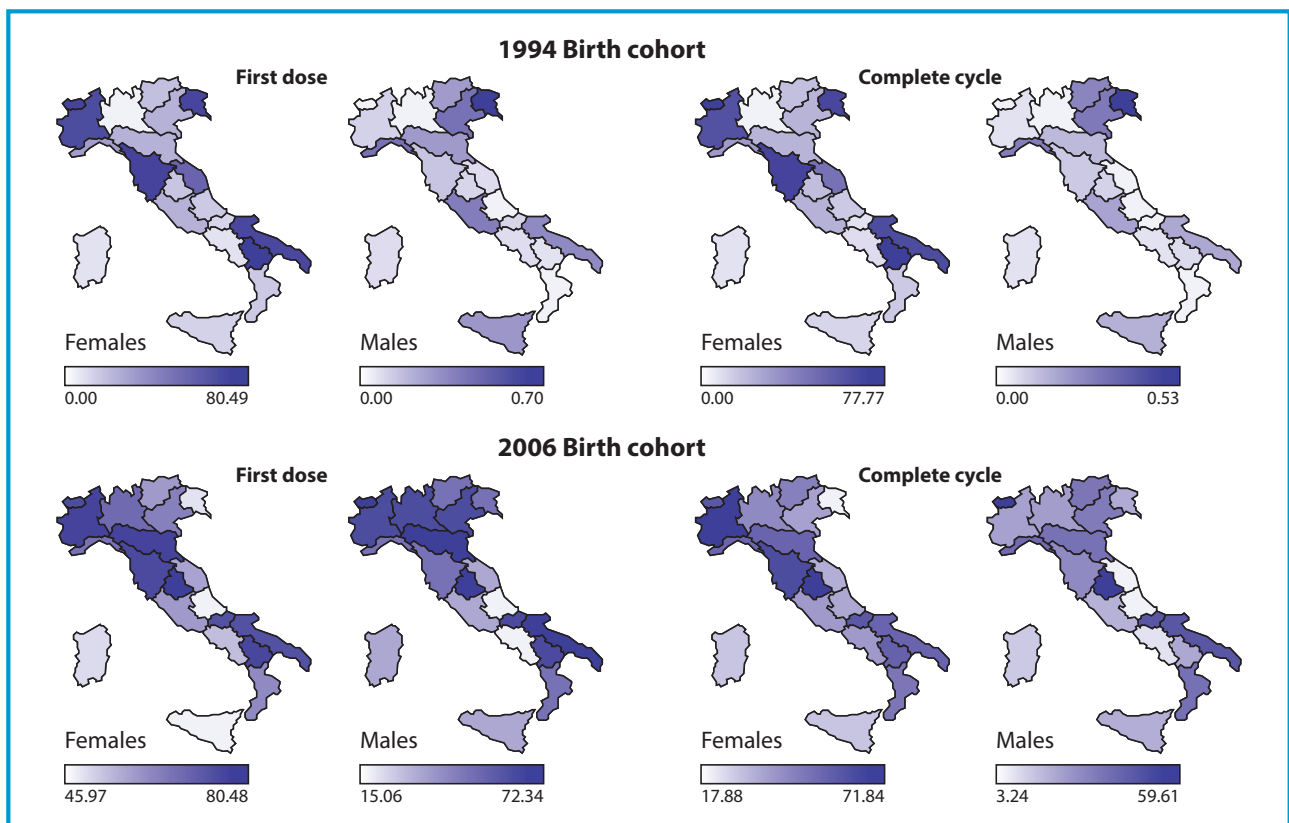


Figure 2. HPV vaccination coverage by region and sex.

Table 1. Status of the HPV national immunization programs in the EU/EEA Countries, 2018

Country or territory	Year of introduction	Current age targets for vaccination, in years (females, males ^a)				Delivery
		Primary (female, male)		Catch-up (female, male)		
Austria*	2014	9	9	10-11 12-15 (PF)	10-11 12-15 (PF)	S (4 th grade) HCS (catch-up)
Belgium						
Brussels	2007	13-14	-	12-18 (PF)	-	S (2nd year 2ry school) HCS (catch-up)
Flanders*	2007	12-13	-	12-18 (PF)	-	S (1st year 2ry school) HCS (catch-up)
Wallonia	2007	13-14	-	12-18 (PF)	-	S (2nd year 2ry school) HCS (catch-up)
Bulgaria*	2012	12-13				HCS
Croatia*	2016	13	13	-	-	S (8 th grade)
Cyprus	2016	12-13	-	-	-	S
Czech Republic	2012	13-14	13-14 (since 2018)	-	-	HCS
Denmark*	2009	12		<18		HCS
Estonia*	2018	12-14	-	-	-	S
Finland*	2013	11-12	-	-	-	S (6 th grade)
France*	2007	11-14 (PF)	-	<20 (PF)	-	HCS
Germany*	2007	9-14	9-14	<18	<18	HC
Greece	2008	11-14	-	15-18 18-26 (until December 2016)	-	HCS
Hungary*	2014	12	-	-	-	S (7 th grade)
Iceland*	2011	12	-	-	-	S (7 th grade)
Ireland*	2010	12-13	-	-	-	S (1st year 2ry school)
Italy*	2008	11	11 (since 2015 in certain regions)	Variable by region	-	HCS
Latvia	2010	12	-	-	-	S and HCS
Liechtenstein*	2008	11-14	11-14 (since 2016)	15-26	15-26 (since 2016)	
Lithuania	2016	11	-	-	-	
Luxembourg*	2008	11-13	-	-	-	HCS
Malta*	2012	12	-	-	-	HCS
Netherlands*	2009	12-13	-	-	-	HCS
Norway*	2009	12	12 (from 2018/2019)	≤25 (2016-2018)	-	S (7 th grade)
Poland*	2008					
Portugal*	2008	10	-	-	-	HCS
Romania*	2013	11-14	-	-	-	HCS
Slovakia*	2016	13 (PF)	-	-	-	
Slovenia	2009	11-12	-	-	-	S (6 th grade)

Table 1. Continued

Country or territory	Year of introduction	Current age targets for vaccination, in years (females, males ^a)			Delivery
		Primary (female, male)	Catch-up (female, male)		
Spain*	2007-8	12	-	-	S and/or HCS (depending on the region)
Sweden*	2012	10-12	-	<18	S (5-6 th grades)
United Kingdom*	2008-12	11-13	-	<18	S (8-10 th grades) HCS (catch-up)

a: funded vaccination programs, unless otherwise stated. PF: partially funded. S: school. HCS: Health Care System.

***Austria.** The HPV vaccine has been available since February 2014 for all children living in Austria in the fourth grade (consummate 9 year of age) free of charge. Before 2014, the vaccine was recommended but not publicly funded. The children are vaccinated at school and, in some Länders, also in public vaccination centers and by established pediatricians. In addition, the HPV vaccine is offered free of charge from the age of 9-12 in the public vaccination centers. Länders also provide catch-up vaccinations at a reduced cost for children up to the age of 15. **Flanders.** For girls who do not qualify for the free vaccination or opt for a different vaccine than the free vaccine offered, a partial reimbursement is provided through health insurance. **Bulgaria.** In 2007, an expert advisory body, including members from the Ministry of Health and National Center for Infectious and Parasitic Disease Control, issued official recommendations for the use of HPV vaccines in Bulgaria for girls aged 12-18 before first sexual contact, with catch-up vaccinations up to the age of 26. 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 by the Council of Ministers. Reimbursement of the cost of vaccination by the National Health Insurance Fund, for the cohort of girls aged 12 in Bulgaria and vaccination of this cohort, started in the beginning of 2013. **Croatia.** Voluntary HPV immunization with HPV vaccine was available free of charge to all females and males from the age of 9 until the end of 2016. **Denmark.** Starting from 1 February 2018, boys who felt attracted to boys could receive HPV vaccination free of charge if they are between 15 and 20 years old. The offer ended on 31 December 2018. From 1 January 2014 to 21 December 2015, HPV vaccination was offered to any girl or woman born between 1993 and 1997. Denmark is offering HPV vaccination to boys and girls as of 2019. **Estonia.** Starting from January 2020, all 12-year-old girls will be vaccinated within the immunization program. **Finland.** During the first two years of the program, the vaccination was also administered to girls aged 13-15 years (7th-9th grade). **France.** Until September 2012, French guidelines recommended the 3-dose vaccine regimen to be administered routinely to all girls aged 14 and catch-up vaccination to women aged 15-23 without sexual activity or with a sexual debut during the year before vaccination. In 2012, the recommendation expanded to girls aged 11-14, with a catch-up vaccination until the age of 20 years. The reimbursement rate for these vaccines is 65% of the price. **Germany.** On 8 June 2018, the Standing Committee on Vaccination (STIKO) recommended vaccination of boys in Germany. The STIKO recommendation is the basis for the fact that statutory health insurance companies have taken over the costs of vaccination. STIKO published its recommendation in the epidemiological bulletin of the Robert Koch-Institut. Thereafter, in September 2018, the federal joint committee Gemeinsame Bundesausschuss decided to include the vaccination against HPV to all 9-14-year-old girls and boys in the catalog of statutory health insurance. The decision has been submitted to the federal Ministry of Health for review and entry into force after publication in the federal gazette. **Hungary.** Several local governments have decided to pursue their own early initiative, thus providing the vaccine to those who are not eligible to the national vaccination program due to their age. **Iceland.** Older girls are given the opportunity to receive the vaccine, against prescription and paying for it. **Ireland.** In September 2011, a catch-up program was introduced, targeting all girls of 6 years of age or equivalent from 2011 to 2014. **Italy.** 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, males and females. Most regions also consider a facilitated payment for ages not included in the primary target. In 2015, male vaccination started free of charge in six regions. **Liechtenstein.** Liechtenstein follows the recommendations of Switzerland. Vaccination is free of charge for girls and women aged 11-16 within the framework of the cantonal vaccination programs. This has been extended to boys and young men aged 11-26 since 1 July 2016. **Luxembourg.** In Luxembourg, the HPV vaccination program was introduced in 2008, targeting 12-17-year-old girls and offering a choice of free bivalent or quadrivalent vaccine. In 2015, the program was changed, offering the bivalent vaccine only to 11-13-year-old girls. Since January 2019, the program has been expanded free of charge to all 9-14-year-old boys and girls. **Malta.** One of the actions included in the 2017-2021 national cancer plan for the Maltese islands is the consolidation of the HPV vaccination program. An evaluation of the program will be performed at the completion of the first five years. This will include an exploration of the impact of expanding the program to include male children of the same age cohort of the girls already being invited. **Netherlands.** In 2009, an HPV vaccination catch-up campaign was organized for girls born between 1993 and 1996 (13-16 years of age at the time). Since 2010, 12-year-old girls are invited to receive the HPV vaccination within the National Immunization Program, which includes girls who were born in 1997 or thereafter. All girls receive an invitation when turning 13. Vaccination is free and non-mandatory. **Norway.** From 1 November 2016, and for two years, women born in 1991 or later were offered HPV vaccination free of charge. The Government will offer HPV vaccine to all 7th grade boys as part of the childhood immunization program. The offer has been introduced from the school year 2018-2019. **Poland.** Since 2008, HPV vaccination has been recommended in the national immunization program for girls aged 11-12. The expert committee, appointed on the initiative of the Polish Pediatric Society in 2010, recommended HPV vaccines also for girls aged 13-18 who had not been vaccinated previously. However, Poland did not introduce this vaccination into the compulsory programs. Prophylactic vaccination against HPV is charged extra in primary healthcare centers, therefore the coverage of Polish teenagers vaccinated against HPV is estimated to be between 7.5% and 10%. Certain districts decided to introduce programs of prophylactic HPV vaccination, and to finance them. **Portugal.** In October 2008, the HPV vaccination was introduced in the national immunization program for 13-year-old girls born from 1995. From 2009 to 2011, a catch-up vaccination campaign was conducted for girls ≤17 (born between 1992 and 1994). From 2014 to 2016, girls from 10 to 13 years of age were covered. Since 2017, only 10-year-old girls are vaccinated. **Romania.** In 2008, the Romanian Ministry of Health rolled out a school-based immunization campaign providing free vaccines for 10-11-year-old girls. Coverage statistics revealed that only 2.57% of the girls received vaccination and the program was suspended. In 2009 an information campaign was launched, followed by a second vaccination program, targeting 12-14 year-old girls. A catch-up program was also launched, where adult women were given the opportunity to get the vaccine free of charge through their health provider. Despite the accessibility of the vaccine, initiation remained low and the school-based program was discontinued at the end of 2011. The program was launched for the third time in April 2013. HPV vaccination is included in the National Vaccination Program in the category 'Vaccination of Population at Risk' and is addressed to girls aged 11-14. **Slovakia.** The recommendation was implemented into legislation, and it says that if a doctor considers that there is a need for the vaccination against infections caused by oncogenic HPV, then the vaccination should be given to girls from the target age group. The recommendation is also targeting other age groups, but these have to pay the total cost of the vaccines. Neither routine HPV vaccination nor catch-up programs have been started in Slovakia. HPV vaccines are partially reimbursed by the national healthcare system: the bivalent HPV vaccine at 11% and the quadrivalent vaccine 7.5% subsidized. **Spain.** Vaccination programs vary by 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 general recommendation to initiate routine HPV vaccination in Spain in 2007, with a cohort of girls to choose between 11 and 14 years of age, but with a preference for age 14, and a deadline for implementation until 2010. Afterwards, each autonomous community designed its own implementation program, which in 3 of them started in 2007, while in the rest in 2008. **Sweden.** In 2010, the HPV vaccine was included in the free-of-charge national vaccination program targeting all girls born in 1999 or later and attending the 5th or 6th grade in school. However, the vaccinations did not start until 2012, due to delays in the procurement process. At the same time, all counties additionally introduced free-of-charge catch-up vaccinations targeting girls born from 1993 to 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. **United Kingdom.** Vaccination programs and start year of the program vary slightly by region. Girls who missed HPV vaccination first time around, can receive a catch-up HPV vaccination up to the age of 18. At the start of the program, there was a catch-up for girls born between 1991 and 1995. As of 2019, UK offers HPV vaccination to boys and girls.

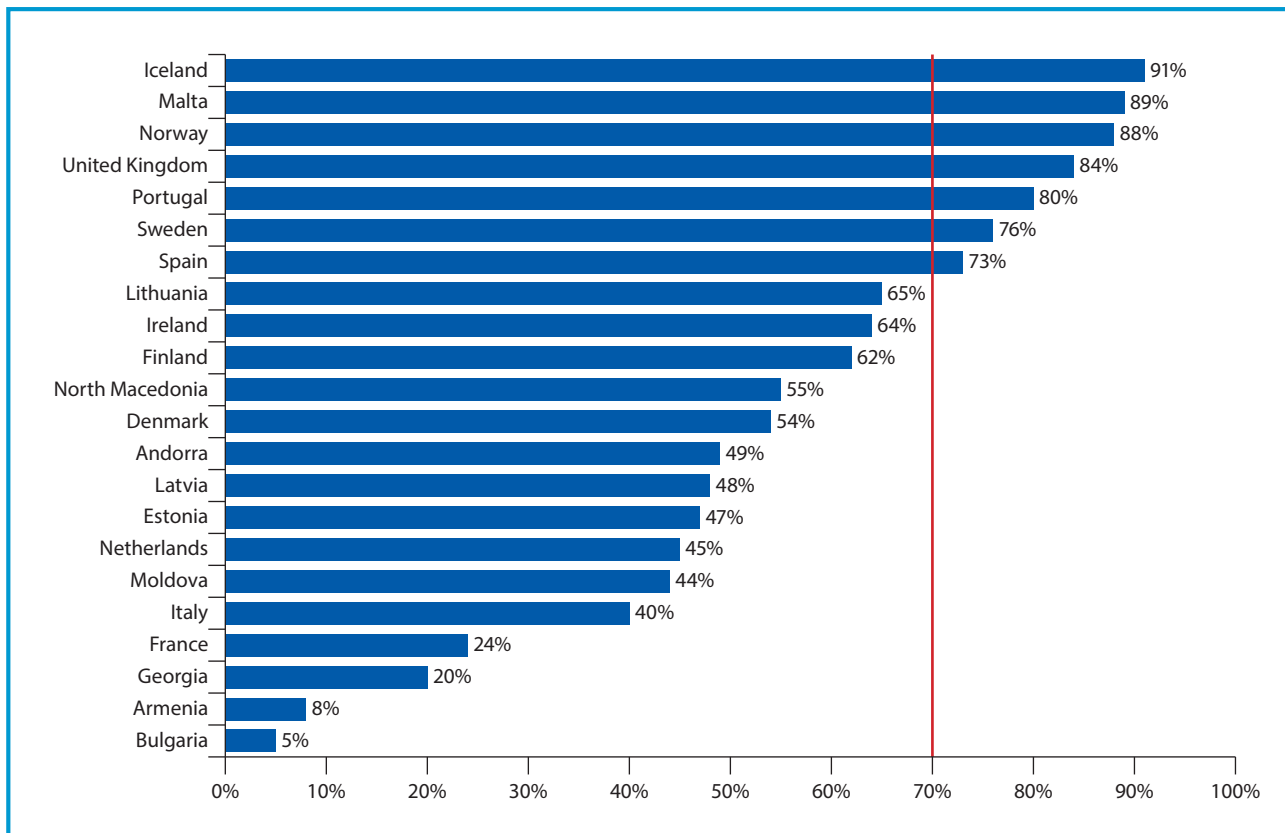


Figure 3. HPV vaccination coverage in Europe.

Belgium, France, Germany and Spain introduced vaccination against HPV in 2007, followed in 2008 by the United Kingdom, Portugal, Luxembourg, Liechtenstein, Greece and Poland, as well as Italy. Northern European Countries (Netherlands, Norway, Slovenia), then Latvia and Ireland, and finally Iceland followed suit, in 2009, 2010 and 2011, respectively. In the following years, Sweden, Malta, the Czech Republic and Bulgaria (2012), Finland and Romania (2013), Hungary and Austria (2014), and finally Croatia, Lithuania and Slovakia (2016) also implemented vaccination against HPV.

Hungary, Iceland, Malta, Norway, Portugal, Spain, Sweden and the United Kingdom reported a national coverage of over 70%. In some Countries, including France and Germany, coverage remained consistently below 50%, while others, such as Denmark and the Republic of Ireland, initially faced a drastic drop in vaccinations, including HPV (Figure 3).

Remarks and analytical discussion of the results

Italian data shows a wide variability of vaccination coverage (complete cycle) between the different regions, in both male and female cohorts. In females, the mean vaccination coverage for the HPV vaccine appears to be

higher than that found in males. However, no Italian region reaches a 95% vaccination coverage in any of the cohorts examined. Programs aimed at improving adherence to the national vaccination program would be useful, even if the HPV vaccine is not among the mandatory vaccinations in Italy. Compared with European data, it is evident that the average vaccination coverage for HPV in girls, despite being fairly good, still remains below the optimal threshold set by the 2017-2019 PNPV ($\geq 95\%$), while that of boys is even lower ($\geq 75\%$ for 2018).

In males, the low coverage found in the 2006 cohort is affected by some local differences in the start of the vaccination program in males (some regions implemented the program starting from the next cohort, that of 2007). In addition, for organizational reasons, similarly to what happened in previous years, in some regions part of the girls in the targeted cohort started or completed the vaccination cycle in the subsequent year; this explains the increase in vaccine coverage in the 2005 cohort (+7.3% for the first dose and +12.3% for the complete cycle).¹⁰

Globally, the HPV vaccination introduced in national immunization programs has been very successful; however, many Countries still have not introduced vaccination at national level, including most Countries in

Africa and Asia.^{13,14} Several factors affect the implementation of a national screening program, including a lack of healthcare funds, inadequate medical infrastructures, an insufficient political will, high costs of vaccine procurement and delivery nationwide, as well as inadequate involvement of healthcare professionals in recommending the vaccine.^{13,15} A major obstacle to vaccine adoption and screening in both females and males is the lack of a reliable source providing scientific information to improve HPV vaccination coverage.

In Europe, in August 2014, 58 Countries had introduced vaccination against HPV in girls into their National Immunization Programs, while some also vaccinated boys. Again, in mid-2015, in Europe 26 out of 31 States (28 Countries of the European Union, plus Norway, Iceland and Liechtenstein) officially recommended the vaccination. Of these, only Austria and Liechtenstein included vaccination against HPV in males.^{13,14,16} In recent years, several Countries – such as Belgium, Croatia, the Czech Republic, Denmark, Finland, Germany, the Republic of Ireland, Italy, the Netherlands, Norway, Sweden and the UK – have extended or are about to extend vaccinations also to males of the same age. Many Countries initially introduced HPV vaccination in multiple age cohorts, and implemented a catch-up program for cohorts that had already passed the recommended age for vaccination.¹⁵

It is evident that the services offered by vaccination programs in the EU/EEA vary not only between Countries, but also within them, at regional levels, such as in Italy. In any case, most of the vaccination programs currently in place in Europe also target pre-adolescent girls between 9 and 14 years of age, through vaccination programs organized in schools or provided by primary care services, such as family doctors, nurses, gynecologists, or through vaccination services.¹⁵

The WHO recognizes cervical cancer and other diseases caused by HPV as a global public health issue.¹⁷ The maximum effectiveness of the vaccine in the prevention of cervical and anal cancers occurs when the vaccine is administered before the start of sexual activity. However, a very high effectiveness has also been demonstrated in adulthood (up to age 45-50), or after the onset of sexual activity for both the vaccines currently available (HPV-2 and HPV-4).¹⁸ In fact, studies indicate that about 70% of women over 25 can be negative for any type of HPV, a benefit of vaccination. Vaccination is also recommended if women have contracted an HPV infection in the past, since it protects from other strains of the virus.¹⁹

HPV vaccines should be included in national immunization programs.

All 3 licensed HPV vaccines (bivalent, quadrivalent and 9-valent) have excellent safety and efficacy profiles.¹⁷

Despite the great promise offered by human papillomavirus vaccines in reducing the disease burden and

promoting socioeconomic and gender equality, their implementation in national programs has been slow. In fact, despite the free vaccination and screening programs for females, coverage was not extended to males in all Countries.

The WHO has therefore called for the joint action of scientific societies and cancer organizations to achieve the goal of eliminating cervical cancer as a global public health issue, also in Europe. All European nations should, by 2030, achieve at least a 90% HPV vaccination coverage among both the girls and boys who fall within the recommended age group, in addition to a screening program that continually reaches a 70% coverage in the target age group.^{13,14}

Conclusions

National vaccination coverage data for 2019 are still awaiting publication by the Ministry of Health; however, the COVID-19 pandemic may have negatively impacted vaccination coverage in the first half of 2020.^{20,21} Furthermore, it should be considered that the anti-HPV vaccination is not among the mandatory ones, according to Law 119/2017.^{15,10} The increased prevalence of HPV vaccination in males and females could drastically change the epidemiology of HPV-related diseases and their consequences. It would also be necessary to study outreach models capable of involving adolescents in a more participatory way.^{13,14} Currently, European guidelines recommend population-based screening organized along with primary HPV testing. However, this paradigm shift requires the reform of the current organization of cytology-based programs, or the implementation of new programs for the Countries that still rely on opportunistic screening, which primarily use cytology as a screening tool.^{22,23}

Key messages

- Improve HPV vaccination coverage.
- Standardize vaccination protocols in Europe.
- Raise awareness about HPV vaccination in males.
- Make adolescents aware of the risks associated with sexually transmitted diseases.

References

- de Oliveira CM, Fregnani JHTG, Villa LL. HPV vaccine: updates and highlights. *Acta Citol.* 2019;63(2):159-68.
- Human papillomavirus (HPV) [Internet]. Available from: <https://www.who.int/teams/maternal-newborn-child-adolescent-health-and-ageing/maternal-health/about/immunization-vaccines-and-biologicals>. NON c'è
- Chesson HW, Dunne EF, Hariri S, Markowitz LE. The estimated lifetime probability of acquiring human papillomavirus in the United States. *Sex Transm Dis.* 2014;41(11):660-4.
- EpiCentro. Vaccini disponibili contro l'HpV [Internet]. Available from: <https://www.epicentro.iss.it/hpv/Vaccini-Disponibili>.
- Torbica A, Fattore G. The "essential levels of care" in Italy: when being explicit serves the devolution of powers. *Eur J Health Econ* [Internet]. 2005;6(Suppl 1):46-52. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1388084/>.
- Ministero della Salute. I dati nazionali al 2017 sulle coperture vaccinali per papillomavirus (HPV) [Internet]. 2018. Available from: http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalmistero&id=3429.
- EpiCentro. Coperture vaccinali anti-Hpv: i dati al 31 dicembre 2018 [Internet]. 2018. Available from: <https://www.epicentro.iss.it/hpv/coperture-vaccinali-anti-hpv-dati-2018>.
- Mascaro V, Pileggi C, Currà A, Bianco A, Pavia M. HPV vaccination coverage and willingness to be vaccinated among 18-30 year-old students in Italy. *Vaccine.* 2019;37(25):3310-6.
- Ministero della Salute. Salute della donna. Screening oncologici [Internet]. 2021. Available from: <http://www.salute.gov.it/portale/donna/dettaglioContenutiDonna.jsp?lingua=italiano&id=4511&area=Salute+donna&menu=prevenzione>.
- Ministero della Salute. Coperture vaccinali al 31.12.2018 per HPV [Internet]. 2020. Available from: http://www.salute.gov.it/imgs/C_17_tavole_27_1_0_file.pdf.
- European Centre for Disease Prevention and Control. Public consultation on draft guidance for introduction of HPC vaccines in EU countries [Internet]. 2019. Available from: <https://www.ecdc.europa.eu/sites/portal/files/documents/hpv-public-consultation-3-April.pdf>.
- WHO. Monitoring and surveillance of HPV vaccination programmes [Internet]. 2020. Available from: <http://www.who.int/immunization/hpv/monitor/en/>.
- Sundaram N, Voo TC, Tam CC. Adolescent HPV vaccination: empowerment, equity and ethics. *Hum Vaccin Immunother.* 2020;16(8):1835-40.
- López N, Garcés-Sánchez M, Panizo MB et al. HPV knowledge and vaccine acceptance among European adolescents and their parents: a systematic literature review. *Public Health Rev.* 2020;41:10.
- Wentzensen N, Arbyn M. Hpv-based cervical cancer screening-facts, fiction, and misperceptions. *Prev Med.* 2017;98:33-5.
- EpiCentro. Strategie vaccinali per Hpv [Internet]. 2015. Available from: <https://www.epicentro.iss.it/hpv/Strategie-Vaccini>.
- WHO. Human papillomavirus vaccines: WHO position paper, *Vaccine.* 2017;35(43):5753-5.
- WHO. 24 October 2014, vol. 89, 43 (pp. 465-92) [Internet]. 2014. Available from: <https://www.who.int/wer/2014/wer8943/en/>.
- Zuccotti GV, Mameli C. I vaccini contro HPV: evoluzione e prospettive. *RIAP.* 2015;4:32-41.
- Bruni L, Saura-Lázaro A, Montoliu A, Brotons M, Alemany L, Diallo MS, et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010-2019. *Prev Med.* 2020;144:106399.
- Ciavattini A, Delli Carpini G, Giannella L, Arbyn M, Kyrgiou M, Joura EA et al. European Federation for Colposcopy (EFC) and European Society of Gynaecological Oncology (ESGO) joint considerations about human papillomavirus (HPV) vaccination, screening programs, colposcopy, and surgery during and after the COVID-19 pandemic. *Int J Gynecol Cancer.* 2020;30(8):1097-100.
- Arbyn M, Gultekin M, Morice P, Nieminen P, Cruickshank M, Poortmans P, et al. The European response to the WHO call to eliminate cervical cancer as a public health problem. *Int J Cancer.* 2021;148(2):277-84.
- Chrysostomou AC, Stylianou DC, Constantinidou A, Kostrikis LG. Cervical cancer screening programs in Europe: the transition towards HPV vaccination and population-based HPV testing. *Viruses.* 2018;10(12):729.

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