ORIGINAL ARTICLES AND REVIEWS

# Vaccination against human papilloma virus in a Northeastern Italian area

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#### **Abstract**

**Objectives.** Vaccination against human papilloma virus (HPV) in adolescents and persons at increased risk of infection and related consequences is an effective strategy to prevent genital cancers. The objective of this study was to assess vaccination activity and coverages in a Northeastern Italian area.

**Methods.** Anonymous data from various health administrative databases of the Italian 530,000-inhabitant Health Authority "Azienda Sanitaria Universitaria Friuli Centrale" were deterministically linked at the individual level through an anonymous stochastic key. Doses of HPV vaccine administered by year and coverages in different birth cohorts were calculated. Vaccinations of women treated for a CIN2+ lesion were also identified. **Results.** The number of doses administered by year followed the evolution of national and regional laws. A steep drop was observed in 2020 and 2021 in both males and females (from 6,907 in 2019 to 5,027 in 2020 in males and from 6,989 in 2019 to 4,348 in 2020 in females). Coverages in adolescents were variable across Vaccination Services located in different sub-areas (complete cycle coverage in the 2008 cohort ranged from <40% in some Districts to >70% in others). Vaccination doses administered in adult women have increased almost steadily since 2018. One third of women treated for a CIN2+ were vaccinated.

**Conclusions.** In this area, efforts must be done to catch-up with doses missed during the pandemic and to overcome differences among different sub-areas.

### Key words

- human papilloma virus
- vaccination
- Udine, Italy

#### **INTRODUCTION**

Human papilloma virus (HPV) is the most common sexually transmitted disease. Transmission may occur through either genital or skin contact. This infection is considered responsible for almost all cervical cancers and for a part of cancers of the vagina, vulva, penis, anus, rectus and oropharynx [1, 2].

More than 200 HPV strains exist. Of those that are sexually transmitted, some do not usually cause any disease and are defined as low risk; others, at high risk, have an effect on cancer incidence (for example, types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). In particular, HPV16 e HPV18 are responsible for 66% of cervical cancers [3].

Since 2006, various vaccines against HPV have been approved in the European Union: a 2-valent vaccine (effective against types 16 and 18), a 4-valent one (types 6, 11, 16, 18), and, in 2015, a 9-valent one (types 6, 11, 16, 18, 31, 33, 45, 52, 58).

The Italian National Vaccine Prevention Plan (Piano Nazionale Prevenzione Vaccinale, PNPV) which is currently in force (PNPV 2017-19) sets a 95% coverage goal for HPV vaccination among boys and girls in their twelfth year of age [4], i.e., before there are expected to encounter the virus through sexual activity. HPV vac-

cination is effective in reducing the incidence of genital warts, pre-cancer lesions, malignant cervical cancer and related deaths [3]. All types of HPV vaccine (2-valent, 4-valent, and 9-valent) were shown to be cost-effective in Italy when used in adolescents [5, 6].

PNPV 2017-19 also recommends the HPV vaccination in all women (in co-payment, and according to regional guidelines) and suggests taking advantage of the first invitation to the cervical cancer screening program to catch the 25-year-olds. Finally, the vaccination is recommended in men having sex with men (MSM) as a specific risk group [4].

The US CDC also recommend vaccination in unvaccinated persons up to 26 years of age but not in those between 27 and 45, unless a careful medical assessment is carried out. In fact, in such age group the efficacy of the vaccine may be reduced because most people have already encountered the virus [7]. In persons >45, the vaccine is not considered cost-effective in the USA and is not covered by health insurance. Cost-effectiveness is actually dubious starting from 30 year of age [8]. In the UK, HPV vaccination is offered free of charge to MSM, trans women and men up to age 45 [9].

In accordance with the Italian PNPV, the Italian Friuli Venezia Giulia (FVG) Region, approximately

1,200,000 inhabitants, HPV vaccination is offered free of charge to adolescents (boys and girls) and to several risk groups: HIV subjects, patients undergoing immunomodulating or immunosuppressive therapy that may increase the risk of HPV infection (e.g., chronic inflammatory bowel disease, multiple sclerosis, etc.), MSM and, since 2018, women previously treated for CIN2+ lesions [10, 11]. The vaccine offered at the beginning of the HPV vaccination campaign, in 2008, was the 2-valent one; in 2011, the 4-valent vaccine became the mostly used one, whereas the 9-valent one was used almost universally in FVG≥ from 2018. The FVG Region started to recommend and offer the HPV vaccine free of charge to boys as early as 2015, from the birth cohort of 2004 [12], before the national recommendation was issued in 2017 [4].

Regarding women treated for CIN 2+, an Italian health technology assessment (HTA) was published in 2019 [13]. Such HTA was mostly based on the results of the SPERANZA project [14] and concluded that the HPV vaccine could decrease the risk of relapses in women undergoing surgery for HPV-related lesions. Thus, its use should be increased, although it is less cost-effective than if administered in pre-adolescence.

However, the efficacy or cost-effectiveness of the vaccination in some risk groups was questioned by recently published studies [15, 16].

The Vaccination Service of the Local Health Authority of Udine (Azienda Sanitaria Universitaria Friuli Centrale, ASUFC), FVG, Italy, provides all the vaccinations recommended in the PNPV and in the regional documents, for a catchment area of approximately 530,000 inhabitants, corresponding to the former province of Udine. The health emergency due to the COVID-19 pandemic, which lasted more than 2 years and officially ended in Italy on March 31st, 2022, caused interruptions or delays of normal preventive activities because of the restrictions imposed by the national and local health authorities on one side [17] and of the diversion of healthcare resources to COVID-19 responses on the other (e.g., contact tracing and COVID mass vaccination).

The objective of this study was to quantify the doses of HPV vaccine administered by the Vaccination Service of the ASUFC from the vaccine approval by the European Medical Agency to the end of 2022 (i.e., to examine the HPV-vaccine-related workload from the Vaccination Service perspective) and to describe the persons vaccinated against HPV and the vaccination coverage in target populations (i.e., to examine the public health performance, the temporal and the geographical variability from a population perspective). In addition, we aimed to assess the impact of the CO-VID pandemic on the HPV vaccination activity and to evaluate any differences in the coverage of adolescents across different subareas or pediatricians.

#### **METHODS**

This population-based retrospective cohort study used the Regional Health Information System (RHIS) of FVG as the source of information. The RHIS is a data warehouse including many anonymized health-related administrative databases which can be determin-

istically linked to one another through a stochastic key that is univocal at the person level in all databases. In detail, in this study, we used the list of all the potential healthcare beneficiaries, the residence database, the vaccination database, and the cervical cancer screening and cervical histology databases.

The study was focused on the subset of the FVG Region corresponding to the former administrative province of Udine.

Two different analyses were conducted. In the first, we extracted data on all the HPV vaccination doses administered from 2008 (when it started being offered in FVG) to 2022 (the most recent complete year with available data) and stratified them by calendar year, age, and sex of the vaccinated person. The purpose of this analysis was to describe the HPV vaccination-related activity in the ASUFC Vaccination Services, to highlight modifications and peculiarities in the age at administration, to show differences by sex, and to identify temporal fluctuations in the number of administered doses (Vaccination Service perspective).

The second analysis aimed to show HPV vaccination coverage among the population born between 1998 and 2009 and living in the ASUFC area as of December 31st, 2022. Only vaccinations administered to persons in the cohort were included in the analysis (population perspective). HPV vaccination cycles were considered complete if two doses were administered to adolescents <15 years of age or if three doses were administered to older young persons (i.e., 15-24 years of age). We calculated the coverage with complete cycles as well as coverage with at least one HPV vaccine dose (incomplete cycle). Coverages were expressed as percentages of the population as of December 31st, 2022 and were calculated by birth cohort, sex, District and primary care paediatrician. Although the HPV vaccination is a Vaccination Service's responsibility, we were interested to assess the variability across primary care paediatricians because they can influence coverages, either recommending or discouraging vaccination.

We also quantified women who started a vaccination cycle after receiving a diagnosis of CIN2+ lesion through the screening program and assessed whether their number changed in time.

All analyses were conducted using SAS Enterprise Guide v 7.15 (SAS Institute Inc., Cary, NC, USA).

The study was approved by the Ethics Committee of the Friuli Venezia Giulia Region on March 14th, 2023 (Parere CEUR-2023-Os-40). All the data in the data warehouse used in the analysis were anonymous, thus subjects could not be identified and no informed consent could be sent.

## RESULTS

The Vaccination Services of the ASUFC administered 82,279 HPV vaccine doses to females ≥10 years of age from 2008 to 2022 and 25,724 doses to males ≥10 years of age from 2015 to 2022 (*Tables 1* and 2). Approximately 1.5% of the overall doses administered to females and 3.3% of those administered to males regarded persons >45 years of age; the maximum age of persons being vaccinated was 78 in women and 84

**Table 1**Human papilloma virus (HPV) vaccination doses administered by the Vaccination Services of ASUFC in the former Italian province of Udine, females

							Caler	ndar ye	ar							
Age	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total
10	73	1,386	672	442	589	425	186	168	41	13	18	20	2	2	12	4,049
11	1,011	3,655	2,378	2,721	3,037	3,022	2,677	1,991	1,856	992	990	1,027	384	141	163	26,045
12	37	975	711	805	1,073	798	813	598	540	1,164	1,902	1,515	801	435	1,554	13,721
13	17	109	173	160	273	170	176	133	93	258	191	500	350	643	1,922	5,168
14	396	2,220	1,900	1,343	285	186	220	109	103	238	163	113	47	221	903	8,447
15	2,287	2,916	2,234	2,611	941	157	175	106	81	282	188	102	54	38	113	12,285
16	90	686	350	275	332	111	80	73	44	249	210	140	64	43	83	2,830
17	76	214	103	81	98	108	46	39	41	180	148	89	61	41	53	1,378
18	34	74	42	46	72	61	16	22	19	61	91	34	33	27	36	668
19	16	27	22	13	31	29	10	6	6	32	52	41	27	18	30	360
20	8	14	12	16	14	15	16	6	15	17	28	42	25	21	33	282
21	8	9	10	9	26	19	12	7	5	23	31	49	13	19	20	260
22	7	5	6	10	13	10	13	5	8	7	41	57	28	15	45	270
23	3	7	7	7	13	11	21	17	10	14	46	57	32	17	38	300
24	8	5	4	5	13	5	11	9	9	34	46	69	57	48	45	368
25	3	10	2	11	10	19	20	37	19	44	71	48	46	33	60	433
26	6	2	2	3	5	9	15	29	32	33	51	50	33	37	26	333
27	1	0	0	3	4	13	11	18	23	14	36	62	34	23	21	263
28	0	0	1	1	3	3	9	18	18	21	40	75	62	32	29	312
29	0	3	0	3	2	1	8	16	9	11	31	58	66	43	40	291
30	0	4	1	2	1	4	3	9	9	10	23	33	47	45	64	255
31	0	1	1	0	5	1	7	4	15	10	29	35	49	33	52	242
32	0	0	0	0	3	1	3	10	1	6	21	41	29	38	60	213
33	0	0	0	0	1	5	5	5	10	10	25	36	40	26	38	201
34	0	0	0	2	5	5	2	15	10	7	31	42	36	22	45	222
35	2	1	0	0	4	1	0	7	11	7	33	35	40	27	35	203
36	0	0	0	0	2	2	1	7	9	6	27	19	35	33	34	175
37	0	1	0	0	2	3	2	4	4	14	33	39	26	32	41	201
38	0	0	0	0	0	0	1	4	11	10	11	37	36	33	39	182
39	0	0	0	2	2	0	0	2	6	12	27	36	36	18	52	193
40	0	0	0	0	1	1	3	6	9	8	20	36	36	21	29	170
41	0	0	0	0	2	0	0	0	3	4	18	37	24	36	26	150
42	0	0	0	0	1	0	2	5	5	8	14	32	31	14	41	153
43	0	0	0	0	0	6	5	10	6	9	14	24	26	13	25	138
44	0	0	0	0	2	1	1	2	2	9	16	16	28	24	32	133
45	0	0	0	1	0	5	1	3	0	4	15	33	29	23	35	149
>45	0	0	0	1	0	0	1	12	18	40	119	206	240	235	364	1,236
Total	6,091	14,333	10,641	10,584	8,877	7,220	6,586	5,527	5,117	5,878	6,868	6,904	5,027	4,591	8,260	82,279

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in men. In the first years, the maximum number of doses were administered to 11-year-olds; however, progressively more and more doses were administered to 12-year-olds, and since 2017 the maximum number of doses have been administered at age 12.

In 2020 and 2021 there was a sharp decrease in HPV vaccination activity, as shown by the number of admin-

istered doses in females (from 6,904 in 2019 to 5,027 in 2020 and 4,591 in 2021), and even more in males (from 6,989 in 2019 to 4,384 in 2020 and 3,812 in 2021). Surprisingly, vaccinations in women >45 were not reduced during the pandemic.

From 2015 to 2022, 651 women started their HPV vaccination cycle after a diagnosis of CIN2, CIN3 or

**Table 2**Human papilloma virus (HPV) vaccination doses administered by the Vaccination Services of ASUFC in the former Italian province of Udine, males

				Calend	ar year				
Age	2015	2016	2017	2018	2019	2020	2021	2022	Total
10	54	39	10	19	19	2	1	12	156
11	578	1,423	922	991	960	350	128	150	5,502
12	7	666	1,227	1,865	1,526	681	398	1,477	7,852
13	13	58	357	226	510	364	596	1,777	3,903
14	5	41	197	179	84	41	221	893	1,665
15	5	39	146	304	246	39	21	99	899
16	5	23	130	306	409	118	37	79	1,107
17	1	21	68	196	198	117	39	60	700
18	0	5	42	111	110	44	43	30	385
19	0	3	14	53	74	34	21	33	232
20	1	4	5	41	49	31	19	15	165
21	0	2	16	47	41	39	18	41	204
22	2	0	13	38	60	29	16	23	182
23	0	1	7	31	70	44	18	22	197
24	2	3	21	47	65	39	27	23	227
25	3	7	13	35	43	42	21	27	192
26	0	10	9	21	25	16	18	16	118
27	2	1	4	19	19	9	10	10	74
28	3	6	1	17	14	20	4	15	82
29	1	3	2	6	17	12	7	14	63
30	0	2	6	15	10	8	5	12	58
31	0	3	7	17	13	11	5	11	67
32	2	1	6	18	13	13	2	28	83
33	3	5	6	21	17	6	5	19	82
34	0	2	3	16	15	4	7	7	54
35	0	1	13	12	12	10	9	4	61
36	0	5	7	21	7	7	2	12	61
37	0	2	4	12	13	3	7	7	48
38	2	1	6	7	19	10	8	8	64
39	0	4	1	16	15	3	2	7	48
40	2	3	4	8	21	5	1	3	48
41	2	1	14	17	10	18	5	7	74
42	1	2	6	18	12	13	9	2	65
43	1	2	3	17	14	7	4	12	60
44	0	3	12	10	21	18	5	8	77
45	0	0	6	18	15	8	5	6	58
>45	3	35	112	226	204	113	47	100	842
Total	2,713	4,443	5,437	7,039	6,989	4,348	3,812	7,091	25,755

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infiltrating cancer and their median age at administration of the first dose of vaccine was 40 years (25<sup>th</sup> percentile: 33; 75<sup>th</sup> percentile: 48). Median time from diagnosis to administration of the first vaccine dose was 199 days (25<sup>th</sup> percentile: 83; 75<sup>th</sup> percentile: 595). Of 304 women with a diagnosis of CIN2+ in 2022, 102 started a vaccination cycle after being treated (33.5%):

28 out of 75 women with a CIN2 diagnosis (37.3%), 73 out of 196 with a CIN3 diagnosis (37.2%), and 1 out of 33 with infiltrating cancer (3.0%).

Figure 1 shows the increase in time in the number of cycles started in women >45, among whom the cost-effective of the vaccine has not been proved. The number increased steeply from 2018, when the vaccine was

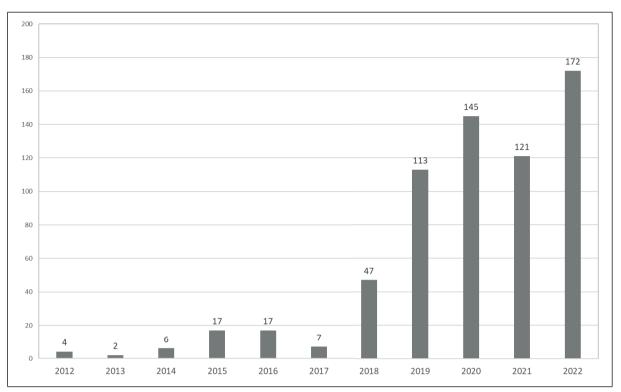


Figure 1

Number of human papilloma virus (HPV) vaccination cycles started among women >45 years of age by year, former province of Udine, Italy.

offered free of charge in the FVG Region, and only slightly decreased in 2021 during the COVID pandemic (on the other hand, the number of CIN2+ diagnoses did not show an increasing pattern: 280 in 2018, 278 in 2019, 270 in 2020, 271 in 2021, and 304 in 2022). Of 479 HPV vaccine cycles started before 2022 in women >45, which were expected to be complete at the end of 2022, only 56 (11.7%) were not.

Table 3 shows vaccination coverage among young females and males born between 1988 and 2009 and living in the ASUFC catchment area as of December 31st, 2022. Relatively good coverages with complete vaccination cycles were obtained starting with the birth cohort of 1993 (≥60% up to the cohort of 2007, with a peak of 72% in the cohorts of 2005 and 2006). Among males, coverages started to increase very slowly up to the cohort of 2004, in which 56% of males were vaccinated with complete cycle, and reached a peak of 67% in the cohort of 2006. The coverage with incomplete cycles was always higher, indicating that, in every cohort, a part of the persons interrupted the cycle. Coverages were slightly decreased in boys and girls from the cohorts of 2008, who were expected to be fully vaccinated during the pandemic, and 2009, who missed the second dose and were planned to be caught up in 2023 for cycle completion.

Figure 2 shows the differences across sub-areas (Health Districts A-I) in the coverage with complete cycles for the 2006 cohort, registering the highest values ever in the ASUFC area, the cohort 2007, which should have started the cycle before the pandemic and con-

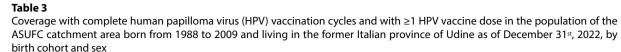
cluded it before or during the pandemic, and the 2008 cohort, which should have received the complete cycle during the pandemic. In the 2006 cohort, the differences among Districts were slight, although becoming much more evident in the two younger cohorts, indicating a differential capacity of maintaining or recovering the activities during and after the pandemic. If we consider coverage with ≥1 dose, however, differences among Districts are smaller (2006 cohort: 64.6%-89.2%; 2007 cohort: 63.4%-82.4%; 2008 cohort: 44.8%-82.0%).

High variability was also observed in coverage across paediatricians; the full-cycle coverage for the 2008 cohort, for example, ranges between 30.0% and 81.6% (data not shown).

#### **DISCUSSION**

This analysis shows that in a few years after the approval of the HPV vaccine by EMA, vaccination activity increased dramatically in this Northeastern Italian area, with coverages among adolescents and young adults reaching higher and higher values from the oldest cohorts, vaccinated in the initial period, and the younger ones. In this area, complete cycle coverages were similar to those reported for the larger FVG Region at the end of 2021, and for most cohorts higher than Italian values [18]. Our coverages are also consistent with those reported in a US survey [19], and even higher in some female cohorts.

Our data show very clearly that vaccination in boys started with a delay of several years after girls started to be vaccinated, consistently with the evolution of the im-



		Females		Males					
Birth cohort	Population Dec 31, 2022	Coverage complete cycle	Coverage at least 1 dose	Population Dec 31, 2022	Coverage complete cycle	Coverage at least 1 dose			
1988	2,607	3.2%	4.0%	2,643	0.3%	0.4%			
1989	2,555	3.1%	3.9%	2,584	0.3%	0.7%			
1990	2,474	5.1%	6.7%	2,583	0.9%	1.2%			
1991	2,460	6.0%	7.1%	2,536	0.4%	0.7%			
1992	2,466	8.6%	9.9%	2,568	0.9%	1.4%			
1993	2,152	60.2%	62.6%	2,445	0.9%	1.5%			
1994	2,226	61.1%	62.8%	2,424	1.4%	1.9%			
1995	2,287	61.7%	64.0%	2,479	1.9%	2.4%			
1996	2,210	63.8%	65.9%	2,512	2.1%	2.9%			
1997	2,231	68.1%	70.5%	2,479	1.5%	2.5%			
1998	2,247	70.1%	72.4%	2,544	2.1%	3.1%			
1999	2,195	69.7%	71.6%	2,449	2.7%	3.9%			
2000	2,314	71.3%	73.9%	2,549	4.6%	6.6%			
2001	2,222	70.7%	72.5%	2,428	7.7%	9.8%			
2002	2,270	70.0%	72.7%	2,423	10.9%	14.0%			
2003	2,224	70.5%	74.2%	2,601	13.0%	19.5%			
2004	2,278	71.2%	75.9%	2,435	55.9%	59.9%			
2005	2,241	72.2%	76.8%	2,411	65.1%	69.1%			
2006	2,255	72.4%	77.6%	2,394	67.3%	71.9%			
2007	2,267	67.1%	75.6%	2,322	63.0%	72.8%			
2008	2,221	59.3%	71.6%	2,276	53.0%	64.8%			
2009	2,304	43.4%	67.2%	2,312	39.4%	61.9%			

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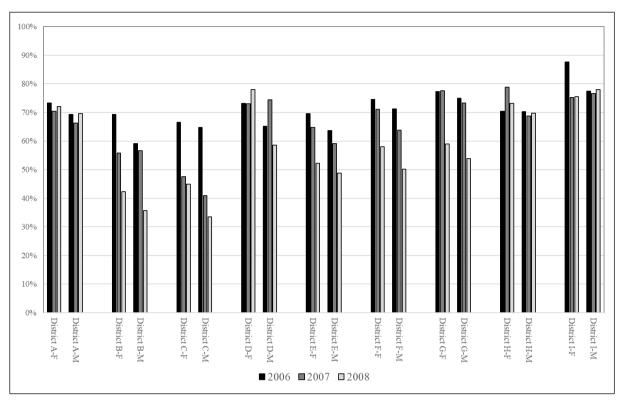
munization schedules of the FVG Region [12], which anticipated the national schedule extending to boys the recommendation of HPV vaccination [3]. However, soon since 2015, coverages approached those obtained among girls. In 2019, the number of HPV doses administered was virtually identical among males and females. but the impact of the COVID pandemic on HPV vaccination was much more evident among males (from almost 7,000 doses in 2019 to less than 4,500 in 2020 and less than 4,000 in 2021) than among females (from almost 7,000 in 2019 to 5,000 in 2020 and approximately 4,600 in 2021). The impact of the COVID pandemic on HPV vaccination in boys, as well as the need to catch up on adolescents that missed doses during the pandemic, were also highlighted in Germany [20]. In 2022 the activity returned to pre-pandemic levels in males (7,000 doses) and even higher in females (more than 8,000 doses), indicating the catch-up implementation in the ASUFC area was effective.

Interestingly, more than 3% of all doses administered in 2022 regarded persons >45 years of age.

Vaccinations in persons >45 decreased during the

COVID pandemic among men, but not among women. In fact, adult women who were vaccinated likely belonged to the group that was diagnosed and treated for a CIN2+ cervical lesion (more than 600 were diagnosed thanks to the organized regional screening program as well as in other circumstances): although screening activity was also reduced during the pandemic [21], the program was completely interrupted in Friuli Venezia Giulia only for few months, so CIN2+ lesions continued to be detected. On the other hand, adult men requesting HPV vaccination were more likely to be MSM or other groups with high-risk behaviours, among whom the need for vaccination could have been reduced during the pandemic because of the restriction imposed by Governments regarding travelling and social events [22].

Our data also show that even within a relatively small study area (approximately 530,000 inhabitants on 5,000 km<sup>2</sup>), high variability may exist in vaccination coverage and in the ability to catch up on boys and girls with missed doses. Baseline coverage differences may depend on organizational differences in the local



**Figure 2**Coverage with complete human papilloma virus (HPV) vaccination cycles among female and male adolescents born in 2006, 2007, and 2009 as of December 31st, 2022 in 9 Health Districts of the Italian former province of Udine.

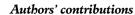
Vaccination Services, the size of their target population, the persuasive ability of paediatricians and general practitioners, and cultural differences, including the population's attitude towards vaccination. The local Vaccination Services of the different sub-area also showed different abilities to catch up on boys and girls with missed vaccine doses. Organizational issues may explain this difference (target population, number of available vaccinal ambulatories, human resources). As an alternative, the staff of the different Services may have been differently involved in the COVID-related activities management. Such activities regarded virtually all the healthcare professionals of all sub-areas in the first months of the pandemic but, during the last months, were gradually centralized in specific areas, where the return to normality was postponed. Finally, during the COVID pandemic, a different resource allocation characterized the various Services, with only some of them having to interrupt adult vaccinations.

Regardless of the reasons for the delay in HPV vaccinations, in the Health Districts with the lowest coverages, we must actively call on the telephone the boys and girls of the 2009 cohort with missed doses and invite them to special massive catch-up vaccination sessions. In doing so, we must pay attention to timing since we ideally want to administer second doses to teens before they turn 15. Afterwards, 3 doses are needed to complete the cycle, despite the most recent World Health Organization recommendations including a two-dose schedule, and even an off-label one-dose schedule, for girls and women from 9 to 20 years [23]. In fact, accord-

ing to current evidence, a single dose shows comparable efficacy and duration of protection as two doses. As a matter of fact, coverages with ≥1 dose were very high in all adolescent cohorts and differences across Health Districts were less evident, suggesting that single-dose coverage is easier to obtain and allows for equity. Thus, the Italian Ministry of Health and Regions should consider the tradeoff of switching to the single-dose schedule in adolescents and to the two-dose schedule in the age group 15-20. Furthermore, a two-dose schedule in women >21 may also increase vaccine take-up in adulthood, especially among persons to whom the vaccine is not offered free of charge.

Vaccination after treatment for cervical lesions only occurs in one-third of women. Thus, efforts are needed to inform women with a CIN2+ diagnosis of the potential benefits of being vaccinated and to schedule an appointment to start the cycle. For this aim, a close collaboration with gynaecologists is crucial.

The pandemic slowed down most of our routine schedules. Nonetheless, it also taught us to be quicker and more flexible, manage larger vaccination sessions, and pay more attention to communication than before. Thus, we are confident we will successfully catch up on most missed doses and return to pre-pandemic HPV vaccine coverage during 2023. For the most effective prevention of cervical cancer, we will also work to strengthen complementary and synergic public health programs such as educational interventions and cervical screening, as recommended by the World Health Organization [23].



FV designed the study, analyzed the data and wrote the manuscript; LD contributed to the study design and critically revised the manuscript; GD contributed to the study design and critically revised the manuscript.

## Conflict of interest statement

The Authors have no conflicts of interest.

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#### **REFERENCES**

- Centers of Disease Control and Prevention. HPV and cancer. Available from: https://www.cdc.gov/cancer/hpv/ statistics/cases.htm.
- IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. A review of human carcinogens. Part B: Biological agents. Lyon: IARC; 2009.
- 3. Centers for Disease Control and Prevention; Hall E., Wodi AP, Hamborsky J, et al. (Eds). Epidemiology and prevention of vaccine-preventable diseases. 14th ed. Washington, DC: Public Health Foundation; 2021.
- Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2017-19. Available from: https://www.salute. gov.it/imgs/C\_17\_pubblicazioni\_2571\_allegato.pdf.
- La Torre G, de Waure C, Chiaradia G, Mannocci A, Capri S, Ricciardi W. The health technology assessment of bivalent HPV vaccine cervarix in Italy. Vaccine. 2010;28(19):3379-84. doi: 10.1016/j.vaccine.2010.02.080
- Mennini FS, Bonanni P, Bianic F, de Waure C, Baio G, Plazzotta G, Uhart M, Rinaldi A, Largeron N. Costeffectiveness analysis of the nine-valent HPV vaccine in Italy. Cost Eff Resour Alloc. 2017;15:11. doi: 10.1186/ s12962-017-0073-8
- Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human Papillomavirus Vaccination for Adults: Updated recommendations of the Advisory Committee on Immunization Practices MMWR. 2019;68(32);698-702.
- Kim JJ, Simms KT, Killen J, Smith MA, Burger EA, Sy S, Regan C, Canfell K. Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A costeffectiveness analysis. PLoS Med. 2021;18(3):e1003534. doi: 10.1371/journal.pmed.1003534
- NHS. HPV vaccine overview. Available from: https:// www.nhs.uk/conditions/vaccinations/hpv-human-papillomavirus-vaccine/.
- Regione Autonoma Friuli Venezia Giulia. Aggiornamento dell'offerta vaccinale per adulti, anziani e soggetti a rischio nella Regione Friuli Venezia Giulia 2019. Allegato alla Delibera della Giunta Regionale n. 2425 del 21 dicembre 2018. Available from: https://www.regione.fvg.it/rafvg/export/sites/default/RAFVG/salute-sociale/promozione-salute-prevenzione/FOGLIA5/allegati/Allegato\_2\_alla\_Delibera\_2425-2018.pdf.
- 11. Regione Autonoma Friuli Venezia Giulia. Aggiornamento dell'offerta vaccinale per infanzia e adolescenza nella Regione Friuli Venezia Giulia. Allegato alla Delibera n. 1919 del 16 dicembre 2022. Available from: http://mtom.regione.fvg.it/storage//2022\_1919/Allegato%201%20 alla%20Delibera%201919-2022.pdf.
- 12. Regione Autonoma Friuli Venezia Giulia. Offerta vaccinale regionale: Infanzia e adolescenza. Allegato alla Delibera n. 2535 del 18 dicembre 2014. Available from: http://mtom.regione.fvg.it/storage//2014\_2535/Allegato%201%20alla%20Delibera%202535-2014.pdf.
- Basile M, Bonanni P, Calabrò GE, Carini E, Cicchetti A, Conversano M, De Vincenzo R, Favaretti C, Ghelardi A,

- Tafuri S. Report di approfondimento e valutazione, con metodologia HTA (Health Technology Assessment), della vaccinazione anti-HPV nelle donne trattate per lesioni HPV-correlate. QIJPH. 2019;8(7):1-76. Available from: https://www.ijph.it/hta-vaccinazione-antiHPV.
- Ghelardi A, Parazzini F, Martella F, Pieralli A, Bay P, Tonetti A, Svelato A, Bertacca G, Lombardi S, Joura EA. SPERANZA project: HPV vaccination after treatment for CIN2. Gynecol Oncol. 2018;151(2):229-34. doi: 10.1016/j.ygyno.2018.08.033
- 15. Eriksen DO, Jensen PT, Schroll JB, Hammer A. Human papillomavirus vaccination in women undergoing excisional treatment for cervical intraepithelial neoplasia and subsequent risk of recurrence: A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2022;101(6):597-607. doi: 10.1111/aogs.14359
- Vargas Parada C, Lennert Veerman J. Cost-effectiveness study of HPV vaccination as a primary prevention strategy for anal cancer in HIV-positive men in Chile. Value Health Reg Issues. 2016;11:17-23. doi: 10.1016/j. vhri.2015.12.002
- Ministero della Salute. Covid-19: Norme, circolari e ordinanze. Available from: https://www.salute.gov.it/portale/ nuovocoronavirus/archivioNormativaNuovoCoronavirus. isp.
- Ministero della Salute. Direzione generale della prevenzione sanitaria. Ufficio 5 Prevenzione delle malattie trasmissibili e profilassi internazionale. Coperture vaccinali al 31.12.2021 per HPV (aggiornamento ottobre 2022). Available from: https://www.salute.gov.it/ imgs/C\_17\_tavole\_27\_1\_7\_file.pdf.
- Pingali C, Yankey D, Elam-Evans LD, Markowitz LE, Valier MR, Fredua B, Crowe SJ, Stokley S, Singleton JA. National Vaccination Coverage Among Adolescents Aged 13-17 years - National Immunization Survey-Teen, United States, 2021. MMWR Morb Mortal Wkly Rep. 2022;71(35):1101-8. doi: 10.15585/mmwr.mm7135a1
- Wähner C, Hübner J, Meisel D, Schelling J, Zingel R, Mihm S, Wölle R, Reuschenbach M. Uptake of HPV vaccination among boys after the introduction of genderneutral HPV vaccination in Germany before and during the COVID-19 pandemic. Infection. 2023;10:1-12. doi: 10.1007/s15010-023-01978-0
- Osservatorio Nazionale Screening. Rapporto sui ritardi accumulati dai programmi di screening italiani in seguito alla pandemia da Covid 19. Terzo rapporto aggiornato al 31 Dicembre 2020. Available from: https://www.osservatorionazionalescreening.it/sites/default/files/allegati/Rapporto%20ripartenza-12\_20.pdf.
- Ministero della Salute. Covid-19 Situazione in Italia. Available from: https://www.salute.gov.it/portale/nuovocoronavirus/dettaglioContenutiNuovoCoronavirus.jsp?a rea=nuovoCoronavirus&id=5351&lingua=italiano&men u=vuoto.
- World Health Organization. Human papillomavirus vaccines: WHO position paper (2022 update). Weekly epidemiological record. 2022;50:645-72.