

HPV VACCINATION PROGRAMMES: HOW EFFICIENT AND SAFE?

Călina MAIER¹
Elvira BRĂȚILĂ²
Ovidiu Gabriel BRATU³
Claudia MEHEDINȚU⁴
Mădălina CRIVEANU⁵

ABSTRACT:

THE PURPOSE OF THIS PAPER IS TO ASSESS THE DATA CURRENTLY AVAILABLE IN LITERATURE REGARDING THE EFFECTIVENESS AND HARMS OF HPV VACCINATION PROGRAMMES. THERE ARE NOW MORE THAN FIFTEEN COUNTRIES WHICH HAVE DATA REGARDING VACCINE EFFECTIVENESS AND SHOW FALLS IN TARGETED TYPES FOLLOWING VACCINATION. THERE ARE CURRENTLY THREE FDA-APPROVED MULTIVALENT PROHYLACTIC HUMAN PAPILLOMAVIRUS VACCINES AND ALTHOUGH THERE IS RIGUROUS PROOF OF THE NEED FOR IMPLEMENTING VACCINATION NATIONAL SCHEDULES, CONCERNS REGARDING THEIR SAFETY CONTINUE TO EMERGE.

KEY WORDS: HPV VACCINATION, EFFECTIVENESS, SAFETY

INTRODUCTION

It has been clearly proven that persistent infection with human papillomavirus oncogenic types is a necessary cause of cervical cancer and other types of neoplasia⁶. Case-control studies,

¹ MD, Obstetrics and Gynecology Department, Panait Sarbu Hospital, Bucharest, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

² MD, Obstetrics and Gynecology Department, Panait Sarbu Hospital, Bucharest, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

³ MD, Urology Department, University Emergency Central Military Hospital, Bucharest, University of Medicine and Pharmacy Carol Davila, Bucharest, Academy of Romanian Scientists, Bucharest

⁴ MD, Obstetrics and Gynecology Department, Malaxa Hospital, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

⁵ MD, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

⁶ Walboomers, JM; Jacobs, MV; Manos, MM; et al. *Human papilloma virus is a necessary cause of invasive cervical cancer worldwide.* J Pathol 1999; 189 (1):12-9; Mehedintu, C; Plotogea, M; Antonovici, M; Todea, C. *The human papillomavirus infection.* Dermato Venerol 2013;58:277-86; Tataru, AL; Furau, G; Afilon, J; Ionescu, C; Dimitriu,

case series and prevalence surveys have unequivocally shown that HPV DNA can be detected in adequate specimens of cervical cancer in 90-100% cases in comparison with a prevalence of 5-20% in cervical specimens from women identified as suitable epidemiological controls⁷. In consequence, in public health terms this finding is equally important as the discovery of the association between cigarette smoking and lung cancer or between chronic infections with hepatitis B virus or hepatitis C virus and the risk of liver cancer.

As a consequence of these findings, three FDA- approved multivalent prophylactic vaccines composed of virus-like particles (VLPs) have been developed.

HPV VACCINE DEVELOPMENT

The public health impact of cervical cancer was the aspect that practically obliged for a vaccine to be created. Most licensed vaccines against infectious agents are preventive, as it has proven easier to use the immune system to prevent a new infection or the disease rather than to treat the established infection or disease⁸. Drugs that are used in HPV infection act as immunomodulators, thus trying to help the host fight against the viral strain and prevent the occurrence of cervical dysplasia⁹.

The latest figures from the International Agency for Research on Cancer (IARC) show that an estimated 570.000 new cases of cervical cancer were diagnosed worldwide in 2018, making it the fourth most common cancer in women globally. Moreover, every year more than 310.000 women die from this preventable disease. IARC'S projections show that unless preventive measures are implemented promptly, the burden of cervical cancer is expected to increase to almost

M; Bratu, OG; Tit, DM; Bungau, S; Furau, C. *The situation of cervical cancers in the context of female genital cancer clustering and burden of disease in Arad County, Romania. J. Clin. Med.* 2019, 8(1), E96; Sinescu, RD; Niculae, A; Peride, I; Vasilescu, F; Bratu, OG; Mischianu, DL; Jinga, M; Checheriță, IA. *Uterus neuroendocrine tumor - a severe prognostic factor in a female patient with alcoholic cirrhosis undergoing chronic hemodialysis. Rom J Morphol Embryol.* 2015; 56(2):601-605; Cozma, CN; Raducu, L; Avino, A; Scaunasu, RV; Bratu, O; Marcu, DR; Jecan, CR. *A rare case of vulvar squamous cell carcinoma; case presentation. Journal of Clinical and Investigative Surgery,* 2018, 3(1): 32-36; Dimitriu, MCT; Ionescu, CA; Gheorghiu, DC; Socea, LI; Bratu, OG; Constantin, VD; Ples, L; Neacsu, A; Bobic, S; Socea, B. *Mepivacaine hydrochloride - an efficient local anesthetic solution for the electroresection of the benign and preneoplastic lesions of the cervix and uterus. Rev Chim (Bucharest),* 2018, 69(9): 2391-2395; Stanescu, AMA; Grajdeanu, IV; Iancu, MA; Stefani, C; Serban, B; Bratu, OG; Socea, B; Diaconu, CC. *Condylomata acuminata and Candida vulvovaginitis during pregnancy – current facts and therapeutic possibilities. Romanian Medical Journal,* 2019, LXVI(2): 119; Spinu, D; Radulescu, A; Iatagan, C; Popescu, R; Madan, V; Bratu, O; Ranetti, AE; Mischianu, D. *Bilateral inguinoscrotal Buschke-Lowenstein disease-a case report. Revista Română de Urologie,* 2013, 12(1): 41-43; Spinu, D; Mischianu, D; Bratu, O; Aungurenci, A; Manache, S; Ciuca, A. *HPV implications in benign prostatic impairments-a literature review. Modern Medicine,* 2014, 21(4): 298-303; Spinu, D; Radulescu, A; Bratu, O; Checherita, IA; Ranetti, AE; Mischianu, D. *Giant condyloma acuminatum - Buschke-Lowenstein disease - a literature review. Chirurgia,* 2014, 109(4): 445-450; Spinu, D; Bratu, O; Oprea, I; Marcu, D; Mischianu, D. *Human papilloma virus infection in men-topographical and procedural aspects-a systematic review. Revista Română de Urologie,* 2016, 15(4): 23-27; Spinu, D; Bratu, O; Marcu, D; Niculae, A; Geavlete, B; Diaconu, C; Mischianu, D. *HPV and bladder cancer-is there a connection?. Modern Medicine,* 2017, 24(1): 1-4.

⁷ Bosch, FX; Lorincz, A; Munoz, N; Meijer, CJLM; Shah, KVS. *The causal relation between human papilloma virus and cervical cancer. J Clin Pathol* 2002;55(4): 244-65.

⁸ Lowy, DR. *HPV vaccination top revert cervical cancer and other HPV- associated disease: from basic science to effective interventions. J Clin Invest* 2016;126(1): 5-11.

⁹ Mehedintu, C; Bratila, E; Cirstoiu, M; et al. *A fixed herbal combination- a new approach in HPV cervical infection treatment. Farmacia* 2018;66(3):502-6.

460.000 deaths per year in 2040, an increase of nearly 50% over the estimated number of deaths in 2018¹⁰.

Cervarix[®] and Gardasil[®] were the first vaccines for the prevention of cervical cancer. Cervarix[®] targets types 16 and 18 HPV, which are responsible for 70% of all cervical cancer¹¹, while Gardasil[®] adds also activity against typed 6 and 11 HPV, which cause 90% of anogenital warts¹². The nonavalent HPV vaccine contains additionally types 31, 33, 45, 52 and 58 antigens. Interesting enough, as of May 2017 Gardasil 9 is the only HPV vaccine available for use in the United States (while Cervarix and Gardasil are still used in other countries).

The current CDC recommendations for Gardasil 9 vaccination in the USA are:

- All children aged 11 or 12 years should get two HPV vaccine shots 6 to 12 months apart. If the two shots are given less than 5 months apart, a third shot will be needed.
- HPV vaccine is recommended for young women through age 26 and young men through age 21.
- Adolescents who get their first dose at age 15 or older need three doses given over 6 months
- Persons who have completed a valid series with any HPV vaccine do not need any additional doses¹³.

According to the health care system's organisation the coverage rate and the programmes of vaccination differ: some of them are offered through schools (Australia, UK) while others are provided in private clinics or public primary care (United States)¹⁴. In Romania, despite the implementation of two HPV vaccination programmes, the uptake remained extremely low and the programmes were discontinued. A content analysis of mass media reports regarding HPV vaccination showed that while 23.6% of the materials were positive towards the vaccine, 28% were negative or extremely negative and 31.4% were neutral; side effects and insufficient testing were the main vaccine-related concerns¹⁵.

HOW EFFICIENT?

The initial controlled clinical trials observed that VLPs were highly immunogenic, even without adjuvant, and well tolerated¹⁶. The bivalent vaccine was evaluated in a phase III trial of

¹⁰ Global Cancer Observatory, *Cancer Tomorrow*: <https://gco.iarc.fr/tomorrow/home>; https://www.iarc.fr/wp-content/uploads/2019/02/pr264_E.pdf

¹¹ Wang, CJ; Palefsky, JM. *Human papillomavirus (HPV) infections and the importance of HPV vaccination*. *Curr Epidemiol Rep* 2015;2(2): 101-9.

¹² Kessels, SJM; et al. *Factors associated with HPV vaccine uptake in teenage girls: a systematic review*. *Vaccine* 2012;30(24):3546-56.

¹³ <https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet>

¹⁴ Skinner, SR; Cooper Robbins, SC. *Voluntary school-based human papillomavirus vaccination: an efficient and acceptable model for achieving high vaccine coverage in adolescents*. *J Adolesc Health* 2010;47(3):215-8.

¹⁵ Penta, MA; Baban, A. *Mass media coverage of HPV vaccination in Romania: a content analysis*. *Health Educ Res* 2014;29(6):977-92.

¹⁶ Harro, CD; Pang, YY; Roden, RB; et al. *Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine*. *J Natl Cancer Inst* 2011;93(4):284-92.

girls and women aged 15-25 years and its efficacy against CIN2+ was 94.9%¹⁷. The efficacy against 6-month and 12-month persistent HPV 16 or 18 cervical infections in the per-protocol cohort was 94.3% (96.1% CI=91.5-96.3) and 91.4% (96.1% CI=86.1-95.0), respectively¹⁸. The bivalent vaccine was also highly efficient (90%) for prevention of CIN 2/3 among participants who were DNA-positive to one vaccine HPV type¹⁹.

The quadrivalent vaccine also proved high efficacy (> 98%) for prevention of HPV 6-, 11-, 16-, and 18-related CIN 2/3 or AIS, grade 2 or 3 vulvar intraepithelial neoplasia (VIN 2/3) and grade 2 or 3 vaginal intraepithelial neoplasia (VaIN 2/3)²⁰. The qHPV vaccine also provided effective and durable protection against low-grade CIN, VIN and VaIN²¹.

In a phase III efficacy trial among men, qHPV also showed great results in preventing genital warts among 4,055 males aged 16 through 26 years; there was no clear evidence of protection from disease caused by HPV typed for which boys and men were DNA-positive regardless of serostatus at baseline²². In a sub-study of the phase III efficacy trial the authors randomly assigned 602 healthy men who have sex with men (MSM), 16 to 26 years of age, to receive either qHPV or placebo. The primary efficacy objective was prevention of anal intraepithelial neoplasia (AIN) or anal cancer related to infection with HPV-6, 11, 16 or 18. The rate of grade 2 or 3 AIN was reduced by 54.2% in the intention-to-treat population and by 74.9% in the per-protocol efficacy population. No vaccine-related serious adverse events were reported²³.

The nonavalent HPV vaccine was studied in 6 clinical trials including more than 13,000 individuals aged 9-26 years and it was proved to be safe, with a 93% efficacy against anogenital lesions/ cancers caused by the included HPV types²⁴. A randomised, double-blind, efficacy, immunogenicity, and safety study of the 9vHPV vaccine was undertaken at 105 study sites in 18 countries. The results showed that the 9vHPV vaccine prevents infection, cytological abnormalities, high-grade lesions and cervical procedures related to HPV 31, 33, 45, 52 and 58. In comparison to qHPV vaccine, both of them had a similar immunogenicity profile with respect to HPV 6, 11, 16 and 18. Vaccine efficacy was sustained for up to 6 years. Moreover, the 9vHPV

¹⁷ Lehtinen, M; Paavonen, J; Wheeler, CM; et al. *Overall efficacy of HPV- 16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial.* Lancet Oncol 2012;13(1):88-9.

¹⁸ Paavonen, J; Naud, P; Salmeron, J; et al. *Efficacy of human papillomavirus (HPV)- 16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women.* Lancet 2009;374:301-14.

¹⁹ Hildesheim, A; Herrero, R; Wacholder, S; et al. *Effect of human papillomavirus 16/18 LI viruslike particle vaccine among young women with preexisting infection: a randomized trial.* JAMA 2007;298:743-53.

²⁰ Kjaer, SK; Sigurdsson, K; Iversen, OE; et al. *A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions.* Cancer Prev Res (Phila) 2009;2:868-78.

²¹ Group, FIIS; Dillner, J; Kjaer, SK; et al. *Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial.* BMJ 2010;341:c3493.

²² Spinu, D; Radulescu, A; Iatagan, C; Popescu, R; Madan, V; Bratu, O; Ranetti, AE; Mischianu, D. *Bilateral inguinoscrotal Buschke-Lowenstein disease-a case report.* Revista Română de Urologie, 2013, 12(1): 41-43.

²³ Palefsky, JM; Giuliano, AR; Goldstone, S; et al. *HPV vaccine against anal HPV infection and anal intraepithelial neoplasia.* N Engl J Med 2011;365(17):1576-85.

²⁴ https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf Accessed on 17th June.

vaccine could potentially provide broader coverage and prevent 90% of cervical cancer cases worldwide²⁵.

Regarding the long-term effectiveness of the vaccines, a recent study assessed the combined incidence of CIN 2,3, AIS and cervical cancer related to HPV 16 and 18. Statistical power was sufficient to conclude that qHPV vaccine effectiveness remains above 90% for at least 10 years, with a trend for continued protection through 12 years of follow-up²⁶.

Three studies reported immunogenicity data comparing 9vHPV to qHPV in females aged 16-26 years²⁷, in females aged 9-15 years²⁸ and in males aged 16-26 years. The 9vHPV vaccine prevented infection and disease related HPV-31, 33, 45, 52 and 58 in a susceptible population and generated an antibody response to HPV-6, 11, 16 and 18 that was noninferior to that generated by the qHPV vaccine.³³ Same results were obtained for the group of girls aged 9-15 years, with a similar safety profile between the two vaccines²⁹.

A recent Cochrane Database review evaluated the harms and protection of prophylactic HPV vaccines against cervical precancer and HPV 16/18 infection in adolescent girls and women³⁰. The authors included 26 randomised controlled trials (73,428 participants) and the primary outcomes were: histologically- confirmed high-grade cervical intraepithelial neoplasia (CIN 2, CIN 3 and AIS) or worse associated with the HPV types included in the vaccine or any lesions irrespective of HPV type, invasive cervical cancer and safety/ occurrence of adverse effects. The latter include local adverse effects (redness, swelling, pain, itching at the injection site), mild and serious systemic effects, mortality and pregnancy outcomes observed during the trials, in particular occurrence of congenital anomalies.

The results showed that there is clear evidence that HPV vaccines protect against cervical precancer in adolescents and young women aged 15 to 26 and the effect is higher for lesions associated with HPV 16/18 than for lesions irrespective of HPV type.

In addition, a pivotal efficacy study was conducted to analyse the level of HPV types 6/11 antibodies in peripartum maternal blood and in cord blood of infants born to women who received 9vHPV or qHPV vaccine. The results indicate that antibodies induced by the 9vHPV vaccine cross the placenta which could potentially be beneficial against HPV 6/11 infection and related disease such as recurrent respiratory papillomatosis³¹. In addition, vaccination has the potential to

²⁵ Huh, WK; Joura, EA; Giuliano, AR; et al. *Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial*. Lancet 2017;390(10108):2143-59.

²⁶ Kjaer, SK; Nygard, M; Dillner, J; et al. *A 12-year follow-up on the long-term effectiveness of the quadrivalent human papillomavirus vaccine in 4 nordic countries*. Clin Infect Dis 2018;66(3):339-45.

²⁷ Joura, EA; Giuliano, AR; Iversen, OE; et al. *A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women*. N Engl J Med 2015;372(8):711-23.

²⁸ Vesikari, T; Brodzski, N; van Damme, P; et al. *A randomized, double-blind, phase III study of the immunogenicity and safety of a 9-valent human papillomavirus L1 virus-like particle vaccine (V503) versus Gardasil in 9-15-year-old girls*. Pediatr Infect Dis J 2015;34(9):992-8.

²⁹ Vesikari, T; Brodzski, N; van Damme, P; et al. *A randomized, double-blind, phase III study of the immunogenicity and safety of a 9-valent human papillomavirus L1 virus-like particle vaccine (V503) versus Gardasil in 9-15-year-old girls*. Pediatr Infect Dis J 2015;34(9):992-8.

³⁰ Xu, L; Simoens, C; Martin-Hirsch, P; Arbyn, M. *Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors*. Cochrane Database Syst Rev 2018;2018(5):CD009069.

³¹ Guevara, AM; Suarez, E; Victoria, A; et al. *Maternal transfer of anti HPV 6 and 11 antibodies upon immunization with the 9-valent HPV vaccine*. Hum Vaccin Immunother 2019;15(1):141-5.

massively reduce the burden that cervical dysplasia has during pregnancy regarding both diagnostic means and treatment³².

Most post-licensure studies report highest effectiveness with a three-dose regimen; some of them found no statistically significant difference between two and three doses and almost half found some effectiveness with one dose³³. This is especially important for many sub-Saharan African countries where the HIV burden is high but where the high cost of HPV vaccine programmes has to date proved a deterrent to introduction. A study revealed that at 90% coverage of females age 9 years with 80% lifelong vaccine efficacy, single dose HPV vaccination was projected to reduce cervical cancer incidence by 74% and mortality by 71% in the general female population at 70 years after the start of the vaccination program³⁴.

HOW SAFE?

In a statement issued in February the current year, IARC fully endorsed the position of the World Health Organization (WHO) on HPV vaccination and confirmed that the vaccine is safe, efficacious and critical in the fight against cervical cancer. Unfounded rumours about HPV vaccines continue to unnecessarily delay or impede the scaling up of vaccination, which is so urgently needed to prevent cervical cancer³⁵.

A safety review by the FDA and Centers for Disease Control and Prevention (CDC) considered adverse side effects related to Gardasil immunization. The rates of adverse side effects were consistent with what was seen in safety studies carried out before the vaccine was approved and were similar to those seen with other vaccines.²⁰ Still, a higher proportion of syncope and venous embolic events were observed with Gardasil than are usually seen with other vaccines. On the other hand, a large cohort study performed in Denmark and Sweden found no evidence to support the association between exposure to qHPV vaccine and autoimmune, neurological, and venous thrombembolic adverse events³⁶.

Regarding the 9-valent HPV vaccine, efficacy, immunogenicity and safety outcomes were assessed in Latin American participants enrolled in 2 international studies. The results showed that the most common adverse effects of vaccination were injection-site related, mostly of mild and moderate intensity³⁷. In studies assessing concomitant vaccines administration, injection-site adverse effects of swelling after 9vHPV and Tdap-IPV were more frequent in concomitant arms as compared with non-concomitant ones (after 9vHPV 14.4% vs. 9.4%, after Tdap-IPV was 21.7%

³² Berceanu, C; Bratila, E; Cirstoiu, M; et al. *Colposcopic assessment and management of HPV infection in pregnancy*. Ginecologia. Ro 2016;14(4):6-12.

³³ Markowitz, LE; Drolet, M; Perez, N; Jit, M; Brisson, M. *Human papillomavirus vaccine effectiveness by number of doses: systematic review of data from national immunization programs*. Vaccine 2018;32:4806-15.

³⁴ Tan, N; Monisha, S; Winer, R; et al. *Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa*. Vaccine 2018;36(32 Pt A):4830-6.

³⁵ https://www.iarc.fr/wp-content/uploads/2019/02/pr264_E.pdf

³⁶ Arnheim-Dahlstrom, L; Pasternak, B; Svanstrom, H; Sparen, P; Hviid, A. *Autoimmune, neurological, and venous thrombembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study*. BMJ 2013;347:f5906.

³⁷ Ruiz-Sternberg, AM; Moreira, ED Jr; Restrepo, JA; et al. *Efficacy, immunogenicity, and safety of 9-valent human papillomavirus in Latin American girls, boys and young women*. Papillomavirus Res 2018;5:63-74.

vs. 31.3%), the risk difference between the groups being statistically significant. This strategy would minimize the number of visits required to deliver each vaccine individually³⁸.

CONCLUSIONS

We now know that the combination of HPV vaccination and cervical screening provide the best protection against cervical cancer. Various markers have been developed in order to detect cervical lesion which benefit of prompt treatment³⁹. Also, vaccination is the approved public health intervention for reducing the risk of developing HPV-associated cancers at sites other than the cervix⁴⁰. Widespread vaccination has the potential to reduce cervical cancer incidence around the world by as much as 90%⁴¹.

The 9-valent HPV vaccine appears to be non-inferior to other HPV vaccines in terms of safety, short-term immunogenicity and efficacy against common HPV types. However, the impact on reducing cervical cancer burden depends greatly on vaccine uptake and coverage, availability and affordability. It is therefore extremely important that international and national health authorities engage in planning and implementing immunization programmes to increase the level of knowledge and awareness of HPV prevention among providers, parents and people receiving the vaccine⁴².

ACKNOWLEDGEMENTS

All authors equally contributed in the research and drafting of this paper.
All authors report no potential conflict of interest.

³⁸ Schilling, A; Parra, MM; Gutierrez, M; et al. *Coadministration of a 9-valent human papillomavirus vaccine with meningococcal and Tdap vaccines*. Pediatrics 2015;136(3):e563-72.

³⁹ Stanculescu, R; Ceausu, M; Ceausu, Z; Bausic, V. *Immunofluorescence expression of Ki-67, p53, and cyclin inhibitors (p16^{ink4a}, p21 and p27) in low-grade cervical lesions versus high-grade cervical lesions. Research study on cell cultures*. Rom J Morphol Embryol 2013;54(3 Suppl):725-34; Stanculescu, R; Bratila, E; Bausic, V; Vladescu, T. *The triage of low-grade cytological abnormalities by the immunocytological expression of cyclin-dependent kinase inhibitor p16^{INK4a} versus human papillomavirus test: a real possibility to predict cervical intraepithelial neoplasia CIN2 or CIN2+*. Rom J Morphol Embryol 2013;54(4):1061-5; Berceanu, C; Paitici, S; Berceanu, S; Bratila, E; et al. *Colposcopic, histologic and immunohistochemical assessment in cervical intraepithelial lesions*. Rev Chim 2018; 69(8):2245-50.

⁴⁰ Kessels, SJM; et al. *Factors associated with HPV vaccine uptake in teenage girls: a systematic review*. Vaccine 2012;30(24):3546-56.

⁴¹ Signorelli, C; Odone, A; Ciorba, A; et al. *Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence*. Epidemiol Infect 2017;145(10):1962-82.

⁴² Kavanagh, K; Pollock, KG; Cuschieri, K; et al. *Changes in the prevalence of human papillomaviruses following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study*. Lancet Infect Dis 2017;17(12):1293-1302.

REFERENCES

1. **Walboomers, JM; Jacobs, MV; Manos, MM; et al.** *Human papilloma virus is a necessary cause of invasive cervical cancer worldwide.* J Pathol 1999; 189 (1):12-9.
2. **Mehedintu, C; Plotogea, M; Antonovici, M; Todea, C.** *The human papillomavirus infection.* Dermato Venerol 2013;58:277-86.
3. **Tataru, AL; Furau, G; Afilon, J; Ionescu, C; Dimitriu, M; Bratu, OG; Tit, DM; Bungau, S; Furau, C.** *The situation of cervical cancers in the context of female genital cancer clustering and burden of disease in Arad County, Romania.* J. Clin. Med. 2019, 8(1), E96.
4. **Sinescu, RD; Niculae, A; Peride, I; Vasilescu, F; Bratu, OG; Mischianu, DL; Jinga, M; Checheriță, IA.** *Uterus neuroendocrine tumor - a severe prognostic factor in a female patient with alcoholic cirrhosis undergoing chronic hemodialysis.* Rom J Morphol Embryol. 2015; 56(2):601-605.
5. **Cozma, CN; Raducu, L; Avino, A; Scaunasu, RV; Bratu, O; Marcu, DR; Jecan, CR.** *A rare case of vulvar squamous cell carcinoma; case presentation.* Journal of Clinical and Investigative Surgery, 2018, 3(1): 32-36.
6. **Dimitriu, MCT; Ionescu, CA; Gheorghiu, DC; Socea, LI; Bratu, OG; Constantin, VD; Ples, L; Neacsu, A; Bobic, S; Socea, B.** *Mepivacaine hydrochloride - an efficient local anesthetic solution for the electroresection of the benign and preneoplastic lesions of the cervix and uterus.* Rev Chim (Bucharest), 2018, 69(9): 2391-2395.
7. **Stanescu, AMA; Grajdeanu, IV; Iancu, MA; Stefani, C; Serban, B; Bratu, OG; Socea, B; Diaconu, CC.** *Condylomata acuminata and Candida vulvovaginitis during pregnancy – current facts and therapeutic possibilities.* Romanian Medical Journal, 2019, LXVI(2): 119
8. **Spinu, D; Radulescu, A; Iatagan, C; Popescu, R; Madan, V; Bratu, O; Ranetti, AE; Mischianu, D.** *Bilateral inguinoscrotal Buschke-Lowenstein disease-a case report.* Revista Română de Urologie, 2013, 12(1): 41-43.
9. **Spinu, D; Mischianu, D; Bratu, O; Aungurenci, A; Manache, S; Ciuca, A.** *HPV implications in benign prostatic impairments-a literature review.* Modern Medicine, 2014, 21(4): 298-303
10. **Spinu, D; Radulescu, A; Bratu, O; Checherita, IA; Ranetti, AE; Mischianu, D.** *Giant condyloma acuminatum - Buschke-Lowenstein disease - a literature review.* Chirurgia, 2014, 109(4): 445-450.
11. **Spinu, D; Bratu, O; Oprea, I; Marcu, D; Mischianu, D.** *Human papilloma virus infection in men-topographical and procedural aspects-a systematic review.* Revista Română de Urologie, 2016, 15(4): 23-27.
12. **Spinu, D; Bratu, O; Marcu, D; Niculae, A; Geavlete, B; Diaconu, C; Mischianu, D.** *HPV and bladder cancer-is there a connection?.* Modern Medicine, 2017, 24(1): 1-4.
13. **Bosch, FX; Lorincz, A; Munoz, N; Meijer, CJLM; Shah, KVS.** *The causal relation between human papilloma virus and cervical cancer.* J Clin Pathol 2002;55(4): 244-65.
14. **Lowy, DR.** *HPV vaccination top revert cervical cancer and other HPV- associated disease: from basic science to effective interventions.* J Clin Invest 2016;126(1): 5-11.
15. **Mehedintu, C; Bratila, E; Cirstoiu, M; et al.** *A fixed herbal combination- a new approach in HPV cervical infection treatment.* Farmacia 2018;66(3):502-6.
16. **Global Cancer Observatory, Cancer Tomorrow:** <https://gco.iarc.fr/tomorrow/home>.
17. https://www.iarc.fr/wp-content/uploads/2019/02/pr264_E.pdf
18. **Wang, CJ; Palefsky, JM.** *Human papillomavirus (HPV) infections and the importance of HPV vaccination.* Curr Epidemiol Rep 2015;2(2): 101-9.
19. **Kessels, SJM; et al.** *Factors associated with HPV vaccine uptake in teenage girls: a systematic review.* Vaccine 2012;30(24):3546-56.
20. <https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet>
21. **Skinner, SR; Cooper Robbins, SC.** *Voluntary school-based human papillomavirus vaccination: an efficient and acceptable model for achieving high vaccine coverage in adolescents.* J Adolesc Health 2010;47(3):215-8.
22. **Penta, MA; Baban, A.** *Mass media coverage of HPV vaccination in Romania: a content analysis.* Health Educ Res 2014;29(6):977-92.

23. Harro, CD; Pang, YY; Roden, RB; et al. *Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine*. J Natl Cancer Inst 2011;93(4):284-92.
24. Lehtinen, M; Paavonen, J; Wheeler, CM; et al. *Overall efficacy of HPV- 16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial*. Lancet Oncol 2012;13(1):88-9.
25. Paavonen, J; Naud, P; Salmeron, J; et al. *Efficacy of human papillomavirus (HPV)- 16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women*. Lancet 2009;374:301-14.
26. Hildesheim, A; Herrero, R; Wacholder, S; et al. *Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial*. JAMA 2007;298:743-53.
27. Kjaer, SK; Sigurdsson, K; Iversen, OE; et al. *A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions*. Cancer Prev Res (Phila) 2009;2:868-78.
28. Group, FIIS; Dillner, J; Kjaer, SK; et al. *Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial*. BMJ 2010;341:c3493.
29. Palefsky, JM; Giuliano, AR; Goldstone, S; et al. *HPV vaccine against anal HPV infection and anal intraepithelial neoplasia*. N Engl J Med 2011;365(17):1576-85.
30. https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf Accessed on 17th June.
31. Huh, WK; Joura, EA; Giuliano, AR; et al. *Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial*. Lancet 2017;390(10108):2143-59.
32. Kjaer, SK; Nygard, M; Dillner, J; et al. *A 12-year follow-up on the long-term effectiveness of the quadrivalent human papillomavirus vaccine in 4 nordic countries*. Clin Infect Dis 2018;66(3):339-45.
33. Joura, EA; Giuliano, AR; Iversen, OE; et al. *A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women*. N Engl J Med 2015;372(8):711-23.
34. Vesikari, T; Brodzski, N; van Damme, P; et al. *A randomized, double-blind, phase III study of the immunogenicity and safety of a 9-valent human papillomavirus L1 virus-like particle vaccine (V503) versus Gardasil in 9-15-year-old girls*. Pediatr Infect Dis J 2015;34(9):992-8.
35. Xu, L; Simoens, C; Martin-Hirsch, P; Arbyn, M. *Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors*. Cochrane Database Syst Rev 2018;2018(5):CD009069.
36. Guevara, AM; Suarez, E; Victoria, A; et al. *Maternal transfer of anti HPV 6 and 11 antibodies upon immunization with the 9-valent HPV vaccine*. Hum Vaccin Immunother 2019;15(1):141-5.
37. Berceanu, C; Bratila, E; Cirstoiu, M; et al. *Colposcopic assessment and management of HPV infection in pregnancy*. Ginecologia. Ro 2016;14(4):6-12.
38. Markowitz, LE; Drolet, M; Perez, N; Jit, M; Brisson, M. *Human papillomavirus vaccine effectiveness by number of doses: systematic review of data from national immunization programs*. Vaccine 2018;32:4806-15.
39. Tan, N; Monisha, S; Winer, R; et al. *Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa*. Vaccine 2018;36(32 Pt A):4830-6.
40. Arnheim-Dahlstrom, L; Pasternak, B; Svanstrom, H; Sparen, P; Hviid, A. *Autoimmune, neurological, and venous thrombotic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study*. BMJ 2013;347:f5906.
41. Ruiz-Sternberg, AM; Moreira, ED Jr; Restrepo, JA; et al. *Efficacy, immunogenicity, and safety of 9-valent human papillomavirus in Latin American girls, boys and young women*. Papillomavirus Res 2018;5:63-74.
42. Schilling, A; Parra, MM; Gutierrez, M; et al. *Coadministration of a 9-valent human papillomavirus vaccine with meningococcal and Tdap vaccines*. Pediatrics 2015;136(3):e563-72.
43. Stanculescu, R; Ceausu, M; Ceausu, Z; Bausic, V. *Immunofluorescence expression of Ki-67, p53, and cyclin inhibitors (p16^{ink4a}, p21 and p27) in low-grade cervical lesions versus high-grade cervical lesions. Research study on cell cultures*. Rom J Morphol Embryol 2013;54(3 Suppl):725-34.

44. **Stanculescu, R; Bratila, E; Bausic, V; Vladescu, T.** *The triage of low-grade cytological abnormalities by the immunocytological expression of cyclin-dependent kinase inhibitor p16^{INK4a} versus human papillomavirus test: a real possibility to predict cervical intraepithelial neoplasia CIN2 or CIN2+.* Rom J Morphol Embryol 2013;54(4):1061-5.
45. **Berceanu, C; Paitici, S; Berceanu, S; Bratila, E; et al.** *Colposcopic, histologic and immunohistochemical assessment in cervical intraepithelial lesions.* Rev Chim 2018; 69(8):2245-50.
46. **Signorelli, C; Odone, A; Ciorba, A; et al.** *Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence.* Epidemiol Infect 2017;145(10):1962-82.
47. **Kavanagh, K; Pollock, KG; Cuschieri, K; et al.** *Changes in the prevalence of human papillomavir following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study.* Lancet Infect Dis 2017;17(12):1293-1302.