Chapter

The Importance of the Problem of HPV-Associated Diseases in KhMAO-Ugra: Vaccination of Adolescents against HPV - Problems and Prospects

Larisa Dmitrievna Belotserkovtseva and Yulia Igorevna Mayer

Abstract

In a survey of adolescents aged 14–17 years, we found that 25% already have experience of sexual contact and they do not know the methods of contraception and neglect condoms. About 77.6% of sexually active adolescent girls had genital infection, including HPV 52.7%, highly oncogenic types 37.9%, and mixed infections 51.4%. Adolescents are extremely vulnerable to HPV-related diseases. Cervical cancer takes the 2nd place in the structure of cancer in women in KHMAO-Ugra and the 1st place at the age of 30 years. Since 2009, girls have been vaccinated against HPV in Ugra. Over 10 years, there was a 39% decrease in the incidence of anogenital warts. We meet with parents, provide information about the risks of HPV infection, expose myths, and discuss the safety and effectiveness of HPV vaccines. Our goal is to win the trust of parents in vaccines, resist anti-vaccine propaganda, increase motivation, and reduce the number of refusal.

Keywords: papillomavirus, vaccination, cervical cancer, anogenital warts, adolescent reproductive behavior

1. The problem of HPV in Russia and in the Khanty-Mansiysk autonomous region-Ugra

Human papillomavirus (HPV) is the most frequent sexually transmitted infection. The prevalence of HPV in the world is about 10%.

HPV is the cause of a wide range of serious diseases in both men and women, including cancer and precancerous lesions of the cervix, vulva and vagina, anogenital area and anal canal, penis, and oropharynx, and also plays a crucial etiological role in the development of anogenital warts in both sexes [1–4]. Anogenital (venereal) warts are the most common clinical manifestation of HPV infection. More than 90% of all cases of anogenital warts are caused by 6 and 11 types of HPV. These types of HPV are also responsible for the development of recurrent respiratory papillomatosis [1–3, 5].

The problem of HPV infections during pregnancy can lead to complications such as intrauterine and intrapartum infections of the fetus, increased frequency of

cesarean sections, and the risk of developing laryngeal papillomatosis of the larynx of the newborn, increasing the risk of infant mortality and the number of surgical interventions on the cervix for severe dysplasia in young women with risk of complications for subsequent pregnancies—spontaneous abortions and premature births.

2. Epidemiology of HPV-associated pathology in Russia and KhMAO-Ugra

Every year, more than 600,000 new cases of HPV-associated cancer are registered in the world, approximately 90% of which is cervical cancer. According to the statistics of the Russian Center for Information Technology and Epidemiological Research in Oncology of the Herzen Institute (branch of the Federal State Institute "National Medical Research Center of Radiology" of the Ministry of Health of the Russian Federation), in the structure of the incidence of malignant neoplasms of the population of the Russian Federation in 2015, cancers associated with HPV infection accounted for about 10% of the total incidence of cancer, and their total number was about 32,000 cases [6].

In the structure of female cancer incidence, cancers of the anogenital region are presented in different ways. Thus, cervical cancer in the Russian Federation occupies the 5th place (5.2%); cancer of the rectum, rectosigmoid junction, and anus, 6th place (4.6%); vulvar cancer, 20th place (0.6%); pharyngeal cancer (0.2%) and vaginal cancer (0.2%), 25–26th place; and laryngeal cancer—28th place (0.1%) [6].

However, if we consider the structure of oncological diseases of the female reproductive system, cervical cancer takes the second place in prevalence among malignant neoplasms of women under 45 years and the first in the number of lost years of life (the life expectancy of sick women is reduced by 26 years on average). The incidence of cervical cancer is steadily increasing and has increased by 28% on average over the past 10 years [7].

Only in 10 years, the incidence of cervical cancer in Russia has increased by an order of magnitude: from 7.9 per 100,000 of the female population in 2002 to 17.2—in 2012 [7]. In 2018, 17,000 new cases of cervical cancer and 6.6 thousand deaths were registered in the Russian Federation. In 2018, the incidence rate fell slightly to 15.76. Important markers characterizing the neglect of cervical cancer and the quality of treatment are the proportion of patients with advanced tumor process (3–4 stages), as well as the mortality of patients within a year from the moment of diagnosis, which in the Russian Federation in 2018 remained at a fairly high level: 34.6 and 13.8%, respectively. In the structure of disability, 83% of cases in oncogynecology are cervical cancer [8]. The frequent incidence of cervical cancer, the tendency to rejuvenate this pathology, a high percentage of neglected cases, and, as a consequence, the growth of disability among women of working age are a world problem, involving the most active, socially significant part of the female population. The occurrence of cervical cancer in young women is a serious social problem, causing deterioration in health, disability, and reduced fertility.

As for cancers of other localizations, annually in the Russian Federation, about 4000 cases of laryngeal cancer and 3000 deaths, for this reason, are registered. Morbidity and mortality from cancer of the vulva, vagina, anus, and penis in the Russian Federation are not registered, which is obviously due to low diagnosis and underreporting of cases. There are about 100,000 new cases of cancer of these locations in the world every year, and two-thirds of the incidence falls on women [8].

Anogenital (venereal) warts are the most common clinical manifestation of HPV infection, more than 90% of which are caused by HPV types 6 and 11. In Russia, this pathology is among the five leaders among sexually transmitted infections. It should be emphasized that the level of official registration is significantly different from the true prevalence and the possible true figure of the prevalence of anogenital warts, according to ongoing studies to assess the prevalence, can be more than 1,000,000 cases, which will bring this nosology to the first place in frequency among all recorded genital infections. The lack of specific antiviral therapy, as well as frequent relapses after the use of destructive methods, complicates the treatment of the disease, significantly reducing the quality of life of these patients [9].

The average annual population of Khanty-Mansiysk Autonomous Region-Ugra is 1,659,436 people, of which 851,588 are women and 805,848 are men.

Cervical cancer in our region occupies the second place in the structure of tumors of the reproductive system of women and the first place in the age category up to 30 years. Precancerous lesions of the cervix are detected more than 6000 cases per year [10].

The clinical burden of cancer (cervical cancer, vulvar and vaginal cancer, anal cancer) among the female population in our region is up to 300 cases per year, which is relevant within the workload of cancer beds and rationalization of health-care costs. In KhMAO-Ugra, according to the state registration, the incidence of cervical cancer does not tend to decrease: in 2018, it was 14.7 per 100 thousand population and in Russia 15.76. The number of registered women diagnosed with cervical cancer is steadily increasing. Annually in Ugra, about 160–170 cases of cervical cancer are registered for the first time. Among the newly identified cases, every second patient (50.8%) is under the reproductive age of 45 years and every third woman (33.2%) had an advanced stage 3–4 of the disease. About 12–15% of patients with cervical cancer die in the first year of diagnosis. Mortality from this disease in Ugra in 2018 was 6.0 per 100,000 population; in 2018 54 women died [10].

The standard screening procedure in KhMAO-Ugra, as well as in the world, is the PAP test, the effectiveness of which does not exceed 30–40%. Despite the introduction of modern methods and some progress in diagnosis and treatment, cancer prevention is still crucial.

3. Study of the expression of oncoprotein E7 in the diagnosis of cervical diseases associated with human papillomavirus

Infection caused by human papillomavirus occurs in 50–80% of the population and in 99.7% of cases of confirmed cervical cancer and therefore is an important problem of modern health care. First of all, this applies to the pathology of the cervix, which is the most important organ of the reproductive system of a woman. Thus, recent data indicate a fourfold increase in cases of cervical cancer among women under 35 years. The incidence of papillomavirus infection in general has also increased, which occurs in 44% of women who have seen a gynecologist. Against the background of persistent HPV of the urogenital tract, most cervical intraepithelial neoplasms develop, which in 15–20% of cases can end in oncological pathology (carcinoma in situ and invasive cancer) [3, 6, 9].

Given the high prevalence of papillomavirus infection, the uncertainty of its outcome, it is important to determine the phase of interaction of HPV with the cell. During the reproduction of HPV in the body, there is a persistence of its genome in the episomal form with the production of viral particles. In this phase of reproduction, there is a high probability of spontaneous remission [2, 9].

The integrative phase is characterized by the embedding of HPV DNA sequences of the 16th and 18th serotypes into the chromosome of the infected cell, which is accompanied by the synthesis of oncoprotein E7. Viral particles are not produced. Expression of oncoprotein E7 is a factor that significantly increases the risk of oncogenic transformation of the cervical epithelium. Increased synthesis of oncoprotein E7, a product of the viral genome, indicates an integrative phase of HPV-cell interaction in which the probability of spontaneous remission is low. However, this pattern is not absolute, as some cases in malignant tumors identified episomal form of HPV DNA or a combination of episomal and integrated forms [11, 12].

The insufficient number of clinical studies on the content of oncoprotein E7 in HPV does not yet allow for widespread use of this indicator in practical health care.

The aim of the study was to study the level of expression of cancer protein E7 in patients with cervical pathology with positive and negative HPV tests [11, 12].

Materials and methods: We conducted a continuous randomized prospective study. According to the results of HPV testing by polymerase chain reaction (PCR), all patients with cervical pathology (95 women) were divided into two groups: the 1 group (control group) (HPV-negative, n = 57) and the 2 group (main group)(HPV-positive, n = 38). Group 1 (control group), consisting of 57 women with cervical pathology (HPV-negative test) was divided into two subgroups by analysis for the presence of oncoprotein E7 expression. In first subgroup, 13 women had a positive result which is 1 E7-positive subgroup, and 44 women had a negative result which is 1 E7-negative subgroup. Group 2 (main group) consisting of 38 women with cervical pathology, were infected with human papillomavirus of high carcinogenic risk. Group 2 (main group) was divided into two subgroups: subgroup of 11 women is 2 E7-positive subgroup, who tested positive for oncoprotein E7, and of 27 women, whose E7 was not detected—a negative result is 2 E7-negative subgroup.

Clinical observation and bacteriological, bacterioscopic, cytological, endoscopic (colposcopy), and histomorphological methods were used during the examination. All women were tested for papillomavirus infection. Verification of the diagnosis of papillomavirus infection was carried out by polymerase chain reaction. Quantitative determination of oncoprotein E7 in cervical samples was carried out using the enzyme immunoassay system NPF "Mirax-Pharma" (Moscow). Purified recombinant type 16 protein E7 was titrated as standard. The optical density, which is critical for each formulation, was determined. The test result of the sample was considered positive if the optical density was greater than or equal to the critical. The result of the sample study was considered negative if the optical density was less than the critical one. A survey card was filled in for each patient.

The comparison was carried out on the basis of sample averages (M), medians (Me), and standard deviation (Q25–Q75). Statistical analysis was performed using the nonparametric Mann–Whitney criterion (U) for independent groups. The reliability of the differences between the percentages of the two samples was estimated by the value of the Fisher angular distribution criterion (φ). The values at $p < 0.05$ were considered reliable.

4. Results and discussion

The average age of the patients, the onset of menstrual function, the duration of their residence in the North, and the onset of sexual life were comparable in all groups and had no statistical significance ($p > 0.05$). The number of sexual partners had statistical significance in 1 E7-negative subgroup of the control group compared with the main group—2.00 (2.00–3.00), 2.00 (1.00–3.00), 3.00 (2.00–7.00), and

3.00 (2.00–5.00), respectively (2–3,4*$p < 0.05$). In the study of obstetric history, the number of births and abortions in all groups had no statistical significance ($p > 0.05$).

In the study of somatic history in 2 E7-positive subgroup, kidney disease accounted for 27.3% and endocrine disease 27.3% and had statistical significance in comparison with 1 E7-negative subgroup (*$p < 0.05$), respectively.

In the study of hereditary oncological history, oncological diseases were found in relatives, 15.38, 40.91, 45.45, and 22.22% in subgroups, respectively (21–2, 3*$p < 0.05$; 2–4*$p < 0.05$), where in the 2 E7-positive subgroup, a burdened family oncological history was revealed in 45.45% of cases.

In the study of gynecological history, we paid attention to diseases that could serve as additional factors in the development of neoplasia and cervical cancer. Among gynecological pathology, inflammatory diseases of the female genital organs in the 2 E7-positive subgroup were significantly more common, such as endometritis (27.27%) (3–2*$p < 0.05$), vulvovaginitis (90.90%) (*$p < 0.05$), and salpingo-oophoritis (36.36%) (3–4*$p < 0.05$); inflammatory diseases can reduce immunity and stimulate the tumor process. Infection of the genitourinary organs by pathogens of sexually transmissible infections according to the anamnesis also prevailed in the 2 E7-positive subgroup, such as *Ureaplasma* (27.27%), *Mycoplasma* (18.18%), and *Chlamydia* infection (18.18%) (4–2*$p < 0.05$), which required an in-depth study of the anamnesis and examination of the sexual partner.

Attention is drawn to a large number of cervical pathology in history. Cervical diseases in the history of patients in subgroups had, respectively, 84.62, 88.64, 100.00, and 81.42%.

When cytological examination of patients for atypical cells is performed, signs of cervical intraepithelial neoplasia (CIN) were found in 45,5, 61,54, 77,3, 81,81, and 66.66% (1–3* * $p < 0.01$; 1–4. 5*$p < 0.05$) in subgroups, respectively (**Table 1**).

A HPV effect was observed in patients only in 1 E7-negative (in 4.5% of cases) and 2 E7-positive (in 18.2% of cases); the reliability was confirmed in comparison with the control group (3,4–1,2**$p < 0.01$).

In recent years, the impact of sexually transmitted infections on the likelihood of developing dysplasia and cervical cancer has been considered. The structure of chronic inflammatory diseases of the cervical canal and cervix is currently dominated by cervicitis caused by *Chlamydia trachomatis* in combination with human papillomavirus. In these conditions, CIN and possibly cervical cancer often develop. Many researchers note that *Chlamydia* infection is a cofactor in the occurrence of cervical intraepithelial neoplasia in the presence of HPV.

Chlamydia infection was found only in 2 E7-positive subgroup (9.1%); *Ureaplasma* infection also prevailed in this subgroup (27.3%) (3–2*$p < 0.05$). *Mycoplasma* infection prevailed in the 2 E7-positive subgroup (14.8%) (4–1**$p < 0.01$) (**Table 2**).

Group mark	Control group HPV (−)		Main group HPV (+)	
	1 E7-positive (n = 13)[1]	1 E7-negative (n = 44)[2]	2 E7-positive (n = 11)[3]	2 E7-negative (n = 27)[4]
NILM	38,46% (5)	25,00% (11)	18,18% (2)	33,33% (9)
LSIL	61,54% (8)	77,27% (34)	81,81% (9)	66,66% (18)
HSIL	7,69% (1)	4,54% (2)	18,18% (2)	14,81% (4)
HPV effect	0,00% (0)*3	2,27% (1)*[3]	18,18% (2)**[4]	0,00% (0)

*φ **$p < 0,01$; φ *$p < 0,05$.*

Table 1.
The results of the PAP test.

Infection with human papillomavirus in women with cervical pathology was confirmed in 40% of patients. In the main group, a positive test for HPV type 16 was detected in 68.4% (26 women) and HPV type 18 in 42.1% (16 women). The combination of HPV 16 and 18 genotypes was found in 10.5% (4 women). HPV type 16 infection in the main group was found in subgroups 54.54 and 74.07%, respectively, and HPV type 18 was found in subgroups 54.54 and 37.04%, respectively.

Thus, HPV infection alone is not enough to induce tumor growth and confirms the role of mixed infection as a cofactor in HPV-dependent carcinogenesis.

During colposcopy (**Table 3**), the condition of the cervix and vagina was assessed, the localization and boundaries of the lesion were determined, benign changes were differentiated from suspected malignancies, and cytological smears and biopsies were taken from suspicious areas of the cervix. Among the results of a colposcopic view, 2 E7-positive and 2 E7-negative subgroups prevailed of CIN (45.45%) (3-2* $p < 0.05$). Atypical vessels were determined in 63.63% (3–2** $p < 0.01$; 3–1*$p < 0.05$) and 59.26% (4–2**$p < 0.01$; 4–1*$p < 0.05$), respectively; the mosaic in the subgroups was 54.54% (3–2** $p < 0.01$; 3–1*$p < 0.05$) and 44.44% (4–2**$p < 0.01$; 4–1*$p < 0.05$), respectively.

In the group of HPV-positive women, abnormal colposcopic views (iodine-negative epithelium, punctuation, mosaic, aceto-white epithelium, atypical vessels) were much more common, which confirms the damaging effect of the human

Group mark	**Control group HPV (–)**		**Main group HPV (+)**	
	1 E7-positive (n = 13)[1]	**1 E7-negative (n = 44)[2]**	**2 E7-positive (n = 11)[3]**	**2 E7-negative (n = 27)[4]**
Chlamydia trachomatis	0,00% (0)	0,00% (0)*[3]	9,09% (1)*[4]	0,00% (0)
Ureaplasma spp.	15,38% (2)	6,82% (3)*[3]	27,27% (3)	11,11% (3)
Mycoplasma spp.	0,00% (0)*[2]**[4]	9,09% (4)	9,09% (1)	14,81% (4)
HPV 16	0,00% (0)**[3,4]	0,00% (0)**[3,4]	54,54% (6)	74,07% (20)
HPV 18	0,00% (0)**[3,4]	0,00% (0)**[3,4]	54,54% (6)	37,04% (10)

*φ **p < 0,01; *p < 0,05; φ *p < 0,05.*

Table 2.
Results of examination for sexually transmitted infections.

Group mark	**Control group HPV (–)**		**Main group HPV (+)**	
	1 E7-positive (n = 13)[1]	**1 E7-negative (n = 44)[2]**	**2 E7-positive (n = 11)[3]**	**2 E7-negative (n = 27)[4]**
Normal	0,00% (0)	0,00% (0)	0,00% (0)	0,00% (0)
Aceto-white epithelium	23,08% (3)*[4]	13,64% (6)*[3]**[4]	45,45% (5)	55,55% (15)
CIS	0,00% (0)	0,00% (0)*[3]	9,09% (1)	3,70% (1)
Atypical vessels	23,08% (3)*[3,4]	18,18% (8)**[3,4]	63,63% (7)	59,26% (16)
Mosaic	15,38% (2)*[3,4]	11,36% (5)**[3,4]	54,54% (6)	44,44% (12)
Punctuation	0,00% (0)	4,54% (2)	9,09% (1)	7,40% (2)

*φ **p < 0,01; *p < 0,05; φ *p < 0,05.*

Table 3.
Extended colposcopy results.

papillomavirus on the state of the cervical epithelium and complicates the course of pathological processes toward carcinogenesis. All abnormal colposcopic views were indications for biopsy. Tissue for biopsy was taken by radio-wave loop.

Histological examination revealed the following results (**Table 4**). Signs of chronic inflammatory process prevailed in the control group and amounted to 61.54% and 56.82%, respectively (2–1, 3–1* * $p < 0.01$). Signs of stationary endocervicosis were found in the control group (30.77 and 38.63%, respectively) and in the main group (18.18 and 33.33%, respectively). This had no statistical significance ($p > 0.05$). Epidermizing endocervicosis prevailed in 2 E7-positive, and its detection rate was 45.45% (4–1* * $p < 0.01$; 4–5*$p < 0.05$).

CIN I, II, and III prevailed in women with HPV (+) in the main group, and according to the results of histological conclusion, CIN I was found in subgroup 2 E7-positive in 36.36% of cases (4–1* * $p < 0.01$; 4–2*$p < 0.05$) and in subgroup 2 E7-negative in 40.74% of cases (5–1,2**$p < 0.01$).

CIN II was diagnosed in the main group in 27.27% (4-1**$p < 0.01$) and in 29.63% of cases (5-1**$p < 0.01$; 5-3*$p < 0.05$), respectively, subgroups. CIN III was observed in women with HPV (+) of the main group in 27.27% (4–1,3**$p < 0.01$) and in 22.22% of cases (4–1,3**$p < 0.01$), respectively. Cancer in situ was diagnosed in the main group in 9.09% (4-3*$p < 0.05$) and 7.40% of cases (5-1,3*$p < 0.05$), respectively, subgroups, indicating the role of HPV in the carcinogenesis of cervical cancer.

Signs of koilocytosis were determined in subgroups 0, 7,69, 2,27, 54,54, and 51.85%, respectively. In women with HPV (+) of the main group, these indicators were maximum and had statistical significance (4,5–1,2,3**$p < 0.01$). It should be noted that the maximum of abnormal colposcopic species were women in subgroups with increased expression of oncoprotein E7.

Thus, in the group of HPV-positive women, according to the results of histological examination, cervical intraepithelial neoplasia of medium and severe degree and cervical cancer were more common. Moreover, koilocytic transformation of the epithelium, CIN III, and cervical cancer was diagnosed more often in subgroup

Group mark	**Control group HPV (−)**		**Main group HPV (+)**	
	1 E7-positive (n = 13)[1]	**1 E7-negative (n = 44)[2]**	**2 E7-positive (n = 11)[3]**	**2 E7-negative (n = 27)[4]**
No evidence	0,00% (0)	0,00% (0)	0,00% (0)	0,00% (0)
Chronic cervicitis	61,54% (8)	56,82% (25)	45,45% (5)	55,55% (15)
Stationary endocervicosis	30,77% (4)	38,63% (17)	18,18% (2)	33,33% (9)
Epidermizing endocervicosis	38,46% (5)	38,63% (17)*[4]	45,45% (5)*[4]	18,52% (5)
Leukoplakia	23,08% (3)	9,09% (4)	18,18% (2)	18,52% (5)
CIN I	7,69% (1)*[3]**[4]	22,72% (10)	36,36%(4)	40,74%(11)
CIN II	15,38% (2)	9,09% (4)*[4]	27,27% (3)	29,63% (8)
CIN III	7,69% (1)*[2]	0,00% (0)**[3,4]	27,27% (3)	22,22% (6)
Cervical cancer	0,00% (0)	0,00% (0)*[4]	9,09% (1)	7,40% (2)
Koilocytes	7,69% (1)**[3,4]	2,27% (1)**[3,4]	54,54% (6)	51,85% (14)

***p < 0,01; *p < 0,05.*

Table 4.
Results of histological examination.

2 E7-positive than in subgroup 2 E7-negative, according to the conclusion of morphologists.

The results of the study of the level of expression of cancer protein E7 are presented in **Table 5**. Indicators were distributed according to subgroups: 0,087 (0,07–0,12); 0,190 (0,18–0,39); 0,074 (0,06–0,10); 0,200 (0,17–0,31); and 0.081 (0.07–0.10) (**p < 0.01). We found a significant increase in the indicator in the main group (2 E7-positive), compared with the control group 1 E7-negative and 2 E7-negative (**p < 0.01). In the main group (subgroup 1 E7-positive), this indicator also had statistical significance in comparison with subgroups 1 E7-negative and 2 E7-negative (**p < 0.01).

The increased expression of oncoprotein E7 in the main group (2 E7-positive) was maximal in comparison with subgroups 1 E7-negative and 2 E7-negative (**p < 0.01), which is an indicator of the aggressiveness of the incipient tumor process and a criterion for an unfavorable prognosis. In subgroup 1 E7-positive, increased expression of oncoprotein E7 was also detected in comparison with the control 1 E7-negative subgroup and the main 2 E7-negative subgroup (**p < 0.01).

As a result of studying the level of expression of oncoprotein E7 in HPV-positive and HPV-negative women, we made the following conclusions:

1. In the group of women with cervical pathology associated with human papillomavirus infection, an increased frequency of abnormal colposcopic views, mosaic (3.5 times higher, p <0.01), acetone-white epithelium (2.4 times higher, p < 0.05), atypical vessels (3.5 times higher, p <0.01), punctuation (2.3 times more often, p <0.05), as well as cytological examination, LSIL signs (2.4 times higher), HSIL was found only in the HPV group (p <0.01), and histological examination of CIN I found is 4.7 times higher (p < 0.05), CIN II is 3.2 times more likely (p < 0.05), CIN III is 22.3 times more often (p < 0.01), and cervical cancer is 7.89%. This confirms the damaging effect of the human papillomavirus on the cervical epithelium and complicates the course of pathological processes toward carcinogenesis.

2. The results of the study showed that in cervical pathology caused by HPV of high carcinogenic risk, the increased content of cancer protein E7 is detected 2.5 times (p < 0.01) more often than in women that are HPV (–). The level of E7 indicates an aggressive process of carcinogenesis and can be considered as an unfavorable prognostic sign.

Group mark	**Control group HPV (–)**		**Main group HPV (+)**		**Statistic parameters**
	1 E7-positive (n = 13)[1]	**1 E7-negative (n = 44)[2]**	**1 E7-positive (n = 13)[1]**	**1 E7-negative (n = 44)[2]**	**Kruskall-Wallis**
	Me (Q_{25}–Q_{75})	**Me (Q_{25}–Q_{75})**	**Me (Q_{25}–Q_{75})**	**Me (Q_{25}–Q_{75})**	**χ^2**
E7	0,190 (0,18–0,39) U**[2,4]	0,074 (0,06–0,10) U**[2,4]	0,200 (0,17–0,31) U**[4]	0,081 (0,07–0,10)	33,116 p < 0,001
ОП крит	0,145 (0,145–0,196)	0,145 (0,145–0,196)	0,145 (0,145–0,196)	0,145 (0,145–0,196)	

*Kruskall-Wallis: χ2; p (**p < 0,01; *p < 0,05); Mann–Whitney (U) U **p < 0.*

Table 5.
The results of the study of the level of expression of the oncoprotein E7.

3. Laboratory test evaluation of oncogenic transformation of the cervical epithelium requires further study, as it allows in conjunction with other diagnostic methods to determine the group of increased oncogenic risk among patients with gynecological diseases. The proven relationship between elevated levels of expression of oncoprotein E7 and the presence of CIN allows us to recommend the definition of oncoprotein E7 for inclusion in the diagnostic program for HPV-positive women with changes in the cervix and pathological cervical smears.

5. Teenagers are a risk group: reproductive behavior and adolescent reproductive health

Biological susceptibility to HPV and structural immaturity of the cervix in adolescence, high frequency of ectopia of the cylindrical epithelium, and activation of squamous metaplasia processes create optimal conditions for the introduction and replication of human papillomavirus, which makes the adolescent population extremely vulnerable to the development of CIN.

Features of reproductive behavior of adolescents determine the risks that contribute to the development of diseases of the reproductive system. These are the early beginning of sexual life, frequent change of sexual partners due to the absence of persistent lasting relations in paired unlike adults, who create families and in most adhere to monogamous relations. As a result of adolescents' neglect of barrier contraception, they have a high incidence of sexually transmitted infections. Early sexual life and especially sexual behavior of adolescents contribute to the spread of sexual infections among them, which often remain undiagnosed and not treated in time [13].

Physiological features of the anatomy of the cervix in adolescent girls' anatomy create prerequisites for the persistence of HPV in the epithelial cells of the cervix of the girl; long-term persistence of the virus can lead to the development of precancerous lesions and cervical cancer. *Chlamydia* and *Mycoplasma* infections associated with HPV are cofactors that exacerbate the situation. Age-related physiological ectopia of the cylindrical epithelium, characteristic of adolescence, and defective hormonal homeostasis lead to a violation of the physiological barriers of the genitals. The cylindrical epithelium is an ideal environment for papillomavirus invasion due to the availability of reserve cells and the large area of the transformation zone [14].

Promiscuity and unsettled partnerships are of primary importance in early HPV infection and increased risk of CIN against the background of high infection rates among adolescents with sexually transmitted infections.

In sexually active girls, genital inflammation is detected three times more often (45.2%) than in their peers who do not live a sexual life—in 15.1% of girls. Pathology of the cervix at the age of 18 is detected in 33.4% of girls. According to the results of the survey of sexually active adolescents for genital infections, sexually transmissible infections were detected in 77.8%, including *Mycoplasma genitalium*, 18.4%; *Chlamydia trachomatis*, 6.2%; and HPV, 52.7% (including highly oncogenic types—34.7%), and mixed infections in 51.4%. In KhMAO-Ugra, the HPV infection rate of girls aged 14–16 is 40%, and among girls aged 17–18, the infection rate increases to 60% [13].

We conducted an anonymous survey of schoolchildren in Surgut, which was attended by 389 high school students, including 201 girls and 188 boys aged from 14 to 18. The median age was 16.9 years. Among them, 24% have experience of sexual contact. About 50% of sexually active adolescents indicated that they had a sexual

debut at the age of 16 and younger. About 14.6% of them had the first sexual contact at the age of 15, 10.4% from 13 to 14 years old, 31.2% from 17 years old, and 16.7% from 18 years old. About 66.7% of them had 1 sexual partner; every third (33.3%) sexually active teenager under the age of 18 had 2 or more sexual partners. For contraception, 57% of respondents use a condom, 29%—combined oral contraceptives. Only 23.5% of adolescents are regularly protected from sexual infections, 27% never use barrier contraception.

6. Introduction of vaccination of adolescents against HPV infection in KhMAO-Ugra: problems and solutions

The strategic direction of the development of modern health care in the Russian Federation is prevention and early detection of diseases, which contributes to more effective treatment and improvement of demographic indicators of public health. One of the most important preventive measures is vaccination, and today more than 30 diseases that cause serious damage to human health can be prevented with its help. Immunization prevents 2.5 million deaths per year across all age groups.

These facts indicate that the issues of prevention and treatment of HPV-associated diseases require a multidisciplinary approach, as they affect such specialists as gynecologists, oncologists, epidemiologists, pediatricians, immunologists, dermatologists, etc.

The World Health Organization has been recommending the inclusion of HPV vaccination in vaccination calendars around the world since 2009 [15]. The WHO and the United Nations Children's Fund (UNICEF) consider HPV vaccination a priority for national immunization programs. More than 60 countries have already introduced universal mass vaccination of girls; in a number of countries (the USA, Australia, Canada, Austria, New Zealand, etc.), boys are vaccinated along with girls.

To date, the Russian Federation has two documents regulating measures for the prevention of HPV-associated diseases.

1. "Federal clinical guidelines for the management of patients with anogenital (venereal) warts," Russian society of dermatovenerologists and cosmetologists, (Moscow, 2015). For the prevention of diseases associated with HPV, two vaccines are registered in the Russian Federation: bivalent and quadrivalent. The bivalent HPV vaccine is used to prevent cancer and precancerous diseases of the cervix, vulva, and vagina in women aged 9 to 45 years. Quadrivalent HPV vaccine is used for the prevention of cancer and precancerous changes of the cervix; vulva cancer, vagina cancer, and anal cancer; and anogenital warts in women from 9 to 45 years, as well as anal cancer and anogenital warts in men from 9 to 26 years [16].

2. "Federal clinical guidelines for HPV vaccine prevention," Union of Pediatricians of Russia (Moscow, 2016). These clinical guidelines regulate two vaccination regimens. Standard scheme: girls/women from 14 to 45 years old and boys/men from 14 to 26 years old—three doses (0–2–6 months). Alternative scheme: girls and boys from 9 to 13 years old—it is possible to carry out two-dose immunization (0–6 months) [17].

Despite government HPV vaccination programs, female vaccination rates remain below targets in many countries [18, 19]. Models tend to demonstrate that vaccination of boys is most cost-effective if vaccination coverage of the female

population is at a suboptimal level (less than 50%) [20, 21]. The benefits of vaccinating adolescent boys are not only the prevention of HPV infection for the partner but also the prevention of cancer of the penis and anal canal and anogenital warts.

Vaccination is the most effective investment in health care. The cost of treatment of one case of cervical cancer in the Russian Federation on average is $3000 and the cost of vaccination with preventive vaccination Gardasil—$235. With mass immunization of adolescents aged 12 years old, the pharmacoeconomic efficacy of vaccine introduction was calculated on a national scale, which showed the amount of prevented costs to be $235,000,000, and in the first 5 years, only $16,000,000 will be prevented by reducing genital warts [22].

There are numerous publications confirming the pharmacoeconomic effectiveness of HPV vaccination not only in computational models but also in real life [22–28].

In 2013, the Research Institute of Childhood Infections of the FMBA conducted a pharmacoeconomical evaluation of the cost-effectiveness of vaccination of 12-year-old girls with a quadrivalent HPV vaccine in Russia. For the period of survival, taking into account both direct medical and indirect costs, the vaccine is characterized by a cost-effectiveness ratio equal to $5800/QALY. When the gross domestic product of the Russian Federation was $6000, vaccination of girls with a quadrivalent HPV vaccine in the Russian Federation is characterized by high cost efficiency and can be recommended for routine use in the Russian population.

According to the instructions, the vaccine is approved for use in women aged 9 to 45 years old and in men aged 9 to 26 years old and can protect against diseases such as cervical cancer, vulvar cancer, vaginal cancer, anal cancer, and anogenital warts. Due to the fact that the human papillomavirus causes serious diseases in men, and screening methods for HPV-associated lesions of the anal canal and penis do not exist today, universal vaccination of adolescents of both sexes with quadrivalent HPV vaccine, the only one approved for use in boys, will achieve significant results in reducing the level of HPV-associated diseases and the rapid spread of HPV infection in the world [29].

The primary target cohort for HPV vaccination is children and adolescents aged 9 to 13 years before sexual debut, as recommended by the World Health Organization. The WHO since 2009 recommends that vaccination against human papillomavirus be included in vaccination calendars of all countries of the world. The WHO and the United Nations Children's Fund consider HPV vaccination as a priority for national immunization programs. Sixty countries have already introduced universal mass vaccination of girls, and three countries (the USA, Australia, Canada) also vaccinate boys against HPV.

At the moment, two HPV vaccines are registered in the Russian Federation: bivalent vaccine (Cervarix, contains antigens to 16 and 18 types of HPV) and quadrivalent vaccine (Gardasil, contains antigens 6, 11, 16, and 18 types of HPV). Bivalent HPV vaccine is used to prevent cancer and precancerous lesions of the cervix, vulva, and vagina. Quadrivalent HPV vaccine can protect not only from cervical, vulvar, and vaginal cancer but also from cancer of the anal canal and anogenital warts in women and men. The primary target cohort for HPV vaccination is adolescents aged 9–13 years old prior to sexual debut, as recommended by the World Health Organization [1].

The monitoring of epidemiological effectiveness is an integral part of HPV vaccination programs. In the long term, HPV vaccination can reduce the incidence and mortality from a number of cancers (cervical cancer, anal cancer, etc.), the prevention of which is a public health priority. Evaluation of the effectiveness of vaccination programs in the medium term is possible to reduce precancerous dysplasia

and in the short term (2–4 years from the beginning of the program)—to reduce the prevalence of anogenital warts. Experience with national HPV vaccination programs has shown that maximum coverage can be achieved with school-based vaccination, as recommended by the WHO.

Since 2007, 27 regional programs of primary prevention of HPV-associated diseases have been implemented in Russia, which indicates the importance of protection against HPV infection.

A decrease in the incidence of anogenital warts in the general population has been recorded in the USA, Australia, New Zealand, Belgium, Sweden, and Germany. For example, in Australia, 4 years after the introduction of vaccination, there were the almost complete disappearance of anogenital warts in the population of young women and almost 40% reduction in precancerous lesions of the cervix in young women. The rate of decline was clearly correlated with vaccination coverage. The greatest effect was observed in countries with high coverage (70–85%) [26, 27, 30–33].

The experience of such regions as KhMAO, where the vaccination calendar is constantly being improved and the result is evaluated, can be an example for other regions and become one of the arguments for expanding the national calendar of preventive vaccinations.

The regional HPV vaccination program for adolescent girls in KHMAO was launched in 2009. In the process of introducing the vaccination program, we faced a number of difficulties and objections, which were mainly related to the lack of awareness of pediatricians and parents, and a lot of myths and negative reviews on the Internet and in the media.

We studied the opinions of parents and doctors on the vaccine prevention of HPV-associated diseases. Our goal was to raise awareness among parents and health-care providers and to assess the impact of anti-vaccine advocacy on the population in order to develop a program of further interventions to improve vaccination adherence.

The results of the opinion study of 358 people demonstrated that parents are extremely poorly aware of the problem of HPV infection, the associated risks, and the possibility of preventing diseases caused by HPV with vaccines. Only 21% of respondents know about the HPV problem and 31% have heard about vaccination. Only 49% of parents believe that it is necessary to vaccinate, but only 9% of respondents are ready to vaccinate their children. About 69% of parents doubt the need for vaccination, 22% categorically refused. Also, parents do not have exact knowledge at what age and who needs to be vaccinated, 63% believe that only girls need to be vaccinated, and 35% believe that adolescents of both sexes need to be vaccinated. For explanations about vaccination, 31% will turn to a pediatrician and 15% to a gynecologist; 39% prefer to study reviews on the Internet, and only 12% will receive information on official websites about vaccination.

The results of the opinion study of 254 doctors showed better awareness, and 83% gave a positive answer about the risks of HPV infection and the possibilities of vaccination; the most informed were obstetricians and gynecologists. The majority of doctors (98%) support vaccination, but only 50% are ready to vaccinate their child, 36% of them doubt the effectiveness, and 14% are not sure about the safety of vaccines, which also indicates a lack of knowledge. Obstetricians and gynecologists showed the highest adherence to HPV vaccination (86%). The majority of doctors are ready to receive additional information on vaccination of HPV-associated diseases from official sources: when contacting a polyclinic 59%; a skin and venereal

dispensary, 21%; a pediatrician, 11%; an obstetrician-gynecologist, 28%, a dermatologist, 9%; and on official websites about vaccination—47%.

To raise awareness of the population and the medical community in our region, we have developed lectures and presentations for medical professionals and parents; created a video about vaccination, which was demonstrated in children's polyclinics; and developed and published booklets, posters, and leaflets for the population. Meetings were held with parents and teachers and medical workers in schools of the city, which were organized with the assistance of the Department of Education of KhMAO-Ugra. The text of the voluntary informed consent for parents has been developed, which includes all necessary information about the risk of HPV-associated diseases, the vaccination program and the effectiveness of immunization, and contraindications and possible postvaccination reactions. The introduction of such voluntary informed consent has increased the commitment of health professionals and parents to vaccination and reduced the frequency of refusals.

A "School of Health" is organized, where meetings with parents and schoolchildren are held on a regular basis. The objectives of this school are the following:

- Advocate to motivate vaccination and provide information on the risks of HPV infection and associated diseases
- Expose myths in order to gain the trust of parents and counter anti-vaccine agitation
- Persuade doubters on the example of highlighting the effectiveness of the regions where vaccination is carried out and familiarization with their own experience of vaccination in previous years in the KhMAO
- Live stream on Instagram account "School of Health"

Monitoring the effectiveness and safety of vaccines is an integral part of any vaccination program, which should be carried out both at the vaccination implementation stage and in the future.

Evaluation of the effectiveness of vaccination in the short term is traditionally carried out according to the incidence of genital warts, as the earliest marker of HPV infection.

HPV vaccination in the long term aims to reduce the incidence and mortality from cervical cancer, anal cancer, and other HPV-associated cancers. However, the introduction of a monitoring system, or register of vaccinated, will allow assessing not only the indicators of early effectiveness but also monitoring adverse events associated or not associated with vaccination.

Indicators such as a decrease in cases of genital warts or genital intraepithelial neoplasia in the vaccinated population will be recorded earlier than results in a decrease in HPV-associated cancers and may indicate the effectiveness of HPV vaccination.

For monitoring it is necessary to have a register of vaccinated. The creation of the register of vaccinated will allow assessing the following parameters: indicators of early effectiveness and monitoring adverse events associated and not associated with vaccination. The introduction of the HPV register should be carried out at all levels, from doctors involved in vaccination to health administrators involved in evaluating strategies to improve the health of citizens.

The information contained in the register will assess the following criteria for the implementation of the HPV vaccination program:

1. Accounting of vaccine coverage, age, and sex of the vaccinated. The ability to call adolescents for missed doses of the vaccine

2. Efficacy in reducing precancerous, cancerous, and other HPV-associated diseases: HPV infection; cervical and other HPV-associated genital neoplasia (CIN, AIN, VIN, VaIN); cervical cancer, adenocarcinoma in situ (AIS), anal cancer, vulvar cancer, and vaginal cancer; and anogenital warts

3. Monitoring adverse events related to vaccination time and distant in time

4. Modeling or correcting existing cervical cancer prevention screening programs

7. First results and expected effect of vaccination

The average age of development of cervical cancer and other HPV-associated cancers is 45 years, but it should be understood that cancer of the cervix, vulva, vagina, and anal canal is preceded by precancerous lesions, namely, cervical intraepithelial neoplasia 1/2/3 degree (CIN), adenocarcinoma in situ, vulvar and vaginal intraepithelial neoplasia (VIN, VaIN), and anal intraepithelial neoplasia (AIN), which occur at a younger age. The time required to develop cervical, vulvar, vaginal, and anal cancer from CIN, VIN, VaIN, AIN can take 9–15 years [1, 2].

International experts, including experts from the World Health Organization, agree that the ethical and time frame necessitates the use of precancerous lesions rather than cancer as the endpoint of HPV vaccination effectiveness. The ability of vaccination to effectively reduce precancerous lesions of the anogenital region in men and women suggests the absence of anogenital cancers in the future. Thus, the reduction of precancerous lesions of the anogenital region and the development of genital warts in women and men is recognized as the main marker for assessing the short- and medium-term effectiveness of HPV vaccination.

The economic damage of HPV in the Khanty-Mansiysk Autonomous Region-Ugra is about $5,730,000 per year.

Predicted effect of HPV-associated disease vaccination in KhMAO-Ugra:

- will be prevented by infection with human papillomavirus 6, 11, 16, and 18 types, which is not less than 99% of vaccinated teenagers due to development of postvaccinal immunity; this will prevent about 70% of all cervical cancer cases, 80% of cases of anal cancer, 60% of oropharyngeal cancer cases, 55% of cases of vaginal cancer, 48% of vulvar cancer cases, and 48% of cases of penile cancer.

- The incidence of genital warts will be reduced by at least 90% in the cohort (compared with unvaccinated groups) in the future 3–5 years.

- HPV vaccination will prevent costs by reducing the incidence of HPV in the amount of $3,900,000.

- Positive economic effect will be provided for the period of 5 years in the amount of $2,300,000, provided 70% vaccination coverage for girls 12 years in the Khanty-Mansiysk Autonomous Region-Ugra

- HPV vaccination will save 11,015 bed occupancy per year and prevent 101 deaths from malignant neoplasms per year.

When analyzing the incidence of HPV-associated diseases in KhMAO-Ugra, it was found that since 2011, the incidence of anogenital warts in adolescent girls has decreased both by the results of preventive examinations and by the incidence in the offices of a gynecologist. The incidence of HPV-associated diseases was monitored in a group of young women 8 and 10 years after vaccination. We examined 871 girls aged 20–22 who received vaccination at the age of 12 years old, and we did not register clinical manifestations of HPV infection (anogenital warts, CIN).

In addition, we noted the general population effect. The rate of primary incidence of anogenital warts in the adult population in KhMAO-Ugra for the period 2009–2008 decreased by 39%.

8. Conclusion

The lack of national HPV vaccination programs is not due to the lack of relevance of HPV-associated disease prevention but to the lack of sufficient financial resources to implement it. We hope that in the coming years, HPV vaccination will also be included in the Russian national vaccination calendar.

Factors that prevent the formation of recognition of vaccination are ignorance about HPV and cancer, lack of awareness of the risks of cancer, fears of undesirable consequences, and uncertainty about long-term vaccine protection. The effectiveness of HPV vaccination programs depends on the level of vaccination coverage, which in turn depends on the recognition of the importance of HPV vaccination by the government, health authorities, doctors, vaccinees, and their parents.

During vaccination, we should:

- Consider the possibility of protection against the largest range of HPV-associated cancer and other diseases, that is, use at least quadrivalent HPV vaccine with inclusion in the vaccination program for boys aged 12–14.

- Achieve vaccination coverage for at least 70% of girls aged 12–13.

- Implement a system to monitor the effectiveness of the vaccination program, including short-, medium-, and long-term indicators.

It is necessary to work on the improvement of professional training of health workers in preventing communicable diseases—organization of thematic conferences and round tables and development of thematic improvement of doctors and nurses.

We see the need to continue to work to provide the public with reliable and objective information on vaccination.

In order to promote vaccination and improve its effectiveness, further activities should be undertaken with the involvement of the pediatric care service under the immunization program:

- Conduct field meetings with parents, representatives of schools, and children's clinics.

- Continue explanatory work in mass media in connection with high activity of anti-vaccine agitation on the Internet.

- Prepare booklets with questions on reproductive health, develop volunteer movement among students, and conduct surveys of young people.

Author details

Larisa Dmitrievna Belotserkovtseva* and Yulia Igorevna Mayer
Surgut Clinical Perinatal Center, Surgut State University, KhMAO-Ugra, Russia

*Address all correspondence to: mayerjul@gmail.com

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