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Human Papilloma Virus. Prevention of HPV-Associated Diseases

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High prevalence of sexually transmitted diseases among the population attracts attention of specialists in all countries due to frequent development of complications resulting in reproductive dysfunction. The article presents one of the urgent issues of modern medicine – papillomavirus infection, which is the most common sexually transmitted disease. 70-80% of the sexually active persons contract human papilloma virus at one point. HPV induces a broad range of oncological reproductive diseases, including cervical, vulvar, vaginal and anal cancer and anogenital condylomae, which are observed both in men and women. The only reliable method of preventing papillomavirus infection is vaccination. The authors present new data on the use of the quadrivalent vaccine, including a new immunization pattern for 9-14-years-old girls.
Keywords: *papillomavirus infection, human papilloma virus, cervical cancer, anogenital region, prevention, vaccination, quadrivalent vaccine, girls, adolescents.*

INTRODUCTION

Human Papilloma Virus, or HPV, is a group of extremely prevalent and genetically heterogeneous DNA-containing viruses that affect skin epithelium and mucous membranes.
HPV has been infecting people for a long time. Warts on hands and feet as well as anogenital warts have been known since antiquity. A polymerase chain reaction helped identify HPV 18 DNA in the XVI century mummy of Maria of Aragon (1503 to 1568 AD) [1].
Humanity obtained means to decrease the prevalence of HPV only at the beginning of the XXI century. In 2008, Harald zur Hausen, a famous German scientist, was awarded the Nobel Prize for his discovery of the relation between human papilloma virus and the development of oncological diseases, which allowed focusing at the development of vaccines capable of preventing HPV-associated diseases.
As of now, 57 countries have introduced HPV vaccination into their National Immunization Calendars and adolescent vaccination programs. In 6 countries, both girls and boys undergo vaccination [2].
In Russia, free vaccination as a part of healthcare development program is available in Saint Petersburg, Moscow, the Moscow Region, Surgut, Novosibirsk, Orenburg, and several other cities. In other cities and towns, immunoprophylaxis of HPV is available only at for-profit vaccination centers.

HUMAN PAPILLOMA VIRUS

Human papilloma viruses that infect the epithelial cells of the skin and mucous membranes are etiologically related to the development of pathological alterations of the cervix uteri and cervical cancer as well as anogenital warts and recurrent respiratory papillomatosis. Besides, HPV is associated with other malignant neoplasms, e.g. dermoid anal cancer, vaginal cancer, trema cancer, penis cancer, and head and neck cancer.

130 different HPV types have been well-studied and described so far. An even greater number of viruses have been studied partially and may be later classified as new HPV types. Ca. 30 to 40 types of the causative agents infect the anogenital site. 15 to 20 of these types are associated with cancer and belong to the high risk group; 10 to 15 are associated with genital warts and other benign tumors and thus belong to the low risk group.

It has been proved that up to 70% of cervical cancer and anal cancer cases are caused by highly oncogenic HPV types 16 and 18; more than 90% of anogenital warts are caused by HPV types 6 and 11 (Fig. 1).

The mechanism of oncological disease development is related to HPV E7 and E6 protein expression. These proteins deactivate the retinoblastoma protein and destroy protein p53, which leads to an uncontrollable cell division and accumulation of mutations in the cellular DNA [5].

Low seroconversion rate and reduced production of HPV antibodies are observed after a natural HPV infection. As a rule, the antibodies produced after the body is infected with one type of the causative agents cannot prevent infection with other HPV types. [6].

CLINICAL MANIFESTATIONS OF HPV INFECTION

Papilloma virus infection may be clinically intense, or latent, or its course may be subclinical. The incubation period fluctuates for up to 3 months on the average. In infected cells, the virus exists in two forms: the episomal form (outside of the cell chromosomes), which is thought to be benign, or intrasomal form (integrated into the cell genome), which is malignant. The clinical manifestations of HPV in the epithelium vary significantly (Fig. 2) due to several possible serotypes of this infection [16].

Cervical Cancer (CC)

CC is the most frequent malignant tumor affecting young women, second only to breast cancer (and the most frequent one in some countries) [17].

500,000 new cervical cancer cases are registered worldwide per annum. Every 2 minutes, a woman dies of cervical cancer. In Russia, 20 women die of this disease per annum [18]. Both in Russia and worldwide, more than 70% of cervical cancer cases are caused by HPV types 16 and 18 [19]. The gravity of other HPV types is 0.5% to 5%, according to the World Health Organization (WHO) [20].

Vaginal and trema cancer

More than 20,000 vaginal and trema cancer cases are registered worldwide per annum. In Russia, these diseases account for up to 5% of all anogenital site cancers. However, no data on the morbidity and mortality of those have been presented. HPV types 16 and 18 cause more than a third of all trema cancer cases (36%) and more than a half of all vaginal cancer cases (58%). Almost every tenth vaginal cancer case, or 9.3%, is caused by HPV types 6 and 11 that are considered low oncogenic [21].

Anal cancer

Some 100,000 anal cancer cases are registered worldwide per annum. This disease is 1.5 times more frequent in women than in men. As of the latter, it is mostly identified in gay men, yet may

sometimes be registered in heterosexuals. Studies have shown that anal HPV infection is mostly related to anal sex, yet there are other ways of transmission (manual, contact) [12-15].
HPV types 16 and 18 cause almost 75% of all anal cancer cases. The gravity of other HPV types is 0.1 to 3.5% [22].

Penis cancer
In many countries including Russia, penis cancer is badly identified. According to the WHO evaluations, penis cancer accounts for 0.5% of oncological diseases in men. The areal correlation between the cases of penis cancer and cervical cancer as well as the correspondence of these neoplasms in married couples have given rise to a suggestion on their common etiology [23]. HPV types 16 and 18 cause 38% of all penis cancer cases, HPV types 6 and 11 cause 5%; the role of other HPV types is insignificant [22].

Anogenital warts
HPV types 6 and 11 cause more than 90% of all cases of anogenital warts [24]. According to the WHO, more than 30 million cases of anogenital warts are registered worldwide per annum.
A study has been conducted in Russia in 2012 to evaluate the prevalence of this pathology in 18-60-year-old men and women. The study was carried out in different areas of Russia from Far East to North-West. A similar study was carried out in some other countries at the same time. In Russia, the study involved more than 100 doctors including obstetrician-gynecologists, dermatovenerologists, and urologists. Those experts were asked to keep account of all the visiting patients for 2 weeks and to determine the percentage of patients with anogenital warts. It was found out that in Russia, 9.2% of all visits were due to this disease. The maximum prevalence in 18-24-year-old women was 14.5% [25].

DIAGNOSIS
HPV infection is diagnosed based on clinical manifestations, histological tests, colposcopy, and determination of viral DNA by means of polymerase chain reaction.

TREATMENT OF HPV-ASSOCIATED INFECTIONS
Comprehensive and combined therapy, which involves local removal of the affected tissue in the setting of systemic treatment, is believed to be the most effective and promising way to treat HPV-associated infection. There is no specific antiviral therapy, which is why the undergone treatment cannot prevent recurrence of the disease and may thus be considered symptomatic.

PREVENTION
Nowadays, two vaccines against HPV-associated diseases are registered and used in Russia.
Use of antiviral HPV vaccines is crucial for primary prevention of HPV infections.
Due to the fact that the first 5 years of sexual life represent the highest risk of HPV infection development, the best time for vaccination is before the first sexual intercourse and probable exposure to HPV.
There are now two HPV vaccines. One is a quadrivalent vaccine capable of protecting from the most prevalent types (6, 11, 16, 18), and the other one is a bivalent vaccine capable of protecting from types 16 and 18 (tb.).

Bivalent Vaccine Cervarix by the GlaxoSmithKline Biologicals, Belgium.
Clinical effectiveness:
- 94.7% in terms of infection prevention;
- 96% in terms of cervical infection persistent for at least 6 months;

- 100% in terms of cervical infection persistent for at least a year;
- 95.7% in terms of HPV infection at the stage of cervix uteri cytological disorders;
- 100% protection from HPV infection at stages CIN1+ and CIN2+.

Indications: the vaccine is used to prevent cervical cancer, vaginal and trema cancer in 10-45-year-old women. It helps to prevent acute and chronic infections caused by HPV types 16 and 18.
Cervarix is administered intramuscularly into the area of the deltoid muscle in doses of 0.5 ml according to a 0-1-6 month pattern. A two-dose vaccination pattern (0-6 months) has also been registered.
Contraindications: increased sensitivity to any vaccine component, and increased sensitivity response to previous Cervarix administrations [27].
There are data on cross-protection of the bivalent vaccine from HPV types 31, 33, and 35; however, the titer of antibodies to non-vaccinal strains reduces gradually and practically subsides in 8 years [28].

Quadrivalent vaccine Gardasil by Merck Sharp & Dohme**,** the Netherlands
Clinical effectiveness
Effectiveness of this vaccine has been confirmed by large-scale international studies involving Russian centers and is close to 100% with regard to the diseases caused by HPV types 6, 11, 16 and 18, i.e. cancer and pre-malignant changes of cervix uteri, vagina, trema, anal canal, and genital warts. Based on results of the conducted studies, duration of the protection is close to 10 years; however, evidence has been acquired on the immunological memory and allows to rely upon a life-long protection [27].
The clinical studies on the quadrivalent vaccine have involved 24,358 9-45-year-old girls and women from Europe, the Americas, Asia, and Africa. Protection of the vaccinated people from cervical cancer and precancer amounted to 98%; protection from premalignant lesions and cancer of trema and vagina was 100%, protection from the development of anogenital warts – 99% [29, 30].
The third-phase studies involved 5,300 16-26-year-old boys and men vaccinated with the quadrivalent HPV vaccine or a placebo. It has been proved that the vaccine is very effective against HPV types 6, 11, 16, 18. The effectiveness reached 90% to 100% in terms of anogenital warts, premalignant diseases of the penis, lesions of external genitalia. The effectiveness was 78% in terms of premalignant diseases of the anal canal [27].
Vaccination with the quadrivalent vaccine was carried out according to a 0-2-6 month three-dose pattern.
Contraindications include hypersensitivity to the vaccine components. In Russia, the two-dose vaccination pattern for adolescents is being registered.
According to the WHO guidelines on HPV prevention, the two-dose pattern for both vaccines is recomended when administered to 9-14-year-old adolescents, the three-dose pattern – for over-15 adolescents, immunocompromised patients, and HIV patients. The two-dose pattern of HPV vaccination was approved after publication of the data on the comparable immune response in adolescents to two-dose and three-dose HPV vaccination. It should be noted, however, that the data on clinical effectiveness of HPV vaccines were acquired after using only the three-dose vaccination pattern for the patients of all other age groups.

PREVENTIVE VACCINATION PROGRAMS

Since 2006, many countries have been carrying out programs of preventive vaccination against HPV, and the effect of those programs is increasing in scale, yet it is possible that the full impact of the implementation of such programs on genital cancer prevalence will take several decades to

achieve. The decreased prevalence of HPV types included into the vaccine, as well as the frequency of condylomata acuminate, are the first indicators of quadrivalent HPV vaccine effectiveness. The decreased frequency of severe dysplastic lesions and cancers is considered to be the mid-term and long-term effectiveness indicator, which can be evaluated only in a decade or two.

There are data on the results of cohort immunization of adolescents in countries with large vaccination coverage. For instance, in Australia where more than 70% of girls have been receiving three-dose vaccination since April 2007, a more than 90% reduction of genital wart prevalence in the vaccinated cohort and a significant reduction of the cervical pathology have been observed within the past 5 years (Fig. 3). These indicators are the earliest markers of HPV vaccination effectiveness and are valuable for healthcare system in terms of HPV vaccination evaluation. The acquired data on the significant reduction of anogenital warts prevalence in the female population have urged Australia to make a decision in 2013 to introduce HPV vaccination of 12-13-year-old boys into the program [35].

CONCLUSION

HPV causes a broad range of oncological diseases of the reproduction system, including cervical cancer, vaginal and trema cancer, anal canal cancer, and anogenital warts. When it comes to the protection against HPV-associated diseases, it is reasonable to vaccinate 12-13-year-old boys and girls before the first sexual intercourse and possible exposure to HPV.

To obtain relevant results, the coverage of vaccination should be at least 70%; this can be achieved by implementing regional healthcare development programs. HPV vaccination may have an indirect impact on such aspects of these programs as:

- prevention of HPV-associated diseases;
- enhancement of specialized and high-technology healthcare;
- development and implementation of innovative prevention techniques;
- mother and child healthcare.

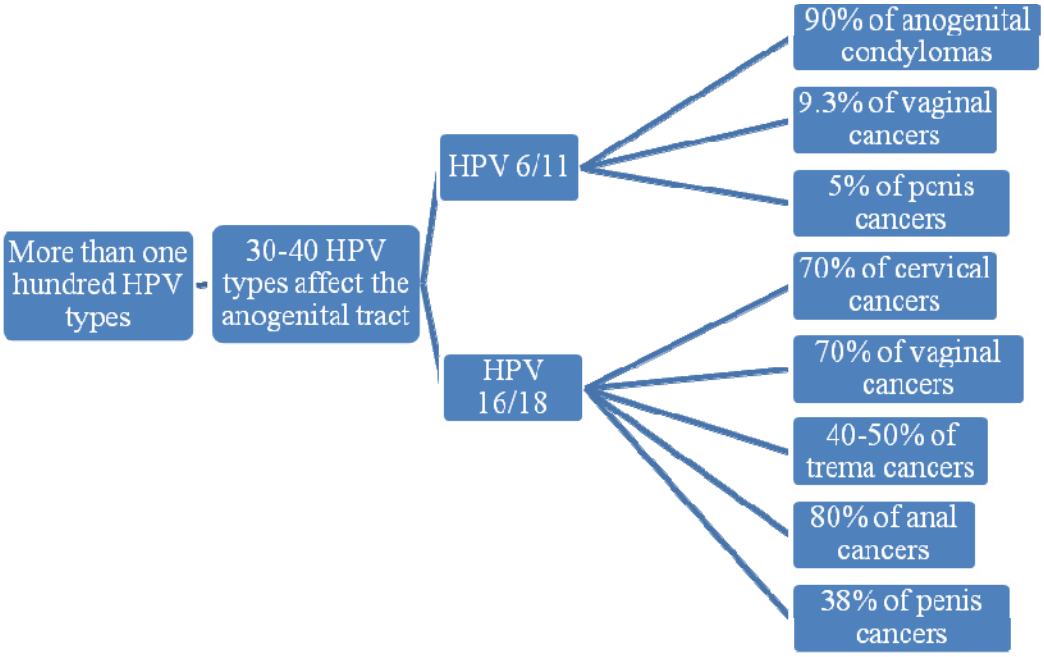
Given the extreme prevalence of HPV and its contribution to the structure of oncological morbidity and mortality among women, it is clear why the problem must be solved at the national level. Vaccines may significantly reduce the global burden of HPV-associated diseases.

In those areas and cities where no national immunization program is in effect, pediatricians have to inform patients and their parents on the availability of paid vaccination at specialized centers for the sake of protection against severe HPV sequelae.

Conflict of interest

The article was supported by MCD Co.

Fig. 1. Percentage of HPV 6, 11, 16, and 18 in the development of HPV-associated diseases [3, 4]



Note. HPV stands for human papilloma virus.

Fig. 2. Prevalence of HPV-associated diseases in the world [7-15]

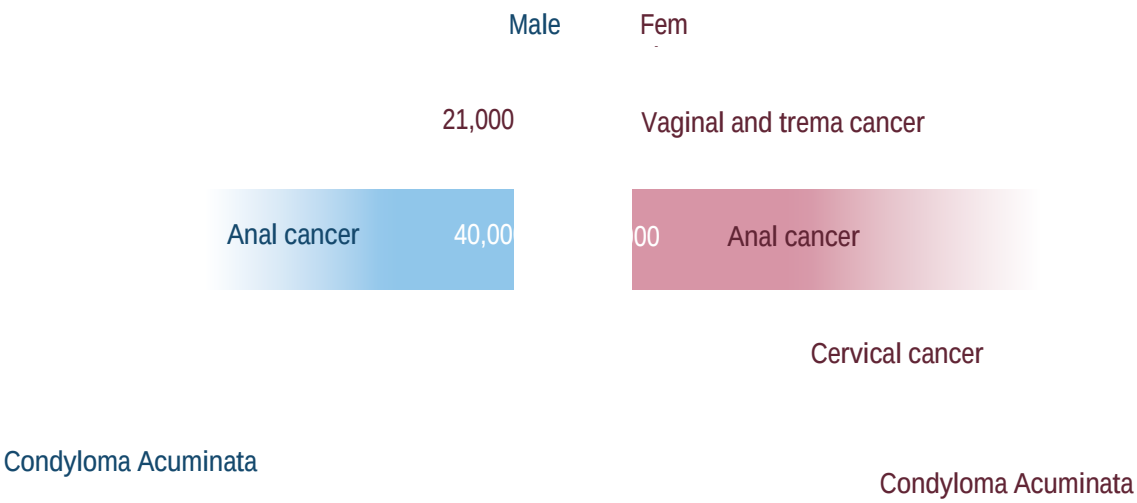
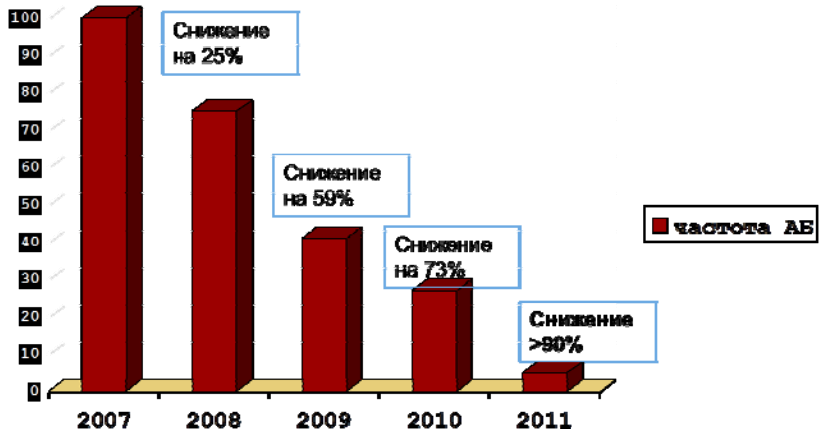


Fig. 3 Reduction in the number of anogenital warts forming in under-30 girls and women in Australia [31-34]



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ENGLISH
Reduction by
AW frequency

Table. Comparison of the bivalent vaccine and the quadrivalent vaccine [21, 26]

Vaccine	Quadrivalent	Bivalent
Tradename	Gardasil	Cervarix
HPV types	6, 11, 16, 18	16, 18
Indication	9-45-year-old girls and women 9-26-year-old boys and men	9-45-year-old girls and women
Prevention	Cervical cancer Vaginal and trema cancer Anal canal cancer Anogenital warts	Cervical cancer Vaginal and trema cancer

Note. HPV stands for human papilloma virus.