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# The Economic Evaluation of the Vaccination program implemented to prevent infection from the Human Papillomavirus (HPV) in males

UNIVERSITY OF ALGARVE
FACULTY OF ECONOMICS

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# THE ECONOMIC EVALUATION OF THE VACCINATION PROGRAM IMPLEMENTED TO PREVENT INFECTION FROM THE HUMAN PAPILLOMAVIRUS (HPV) IN MALES

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Dissertation work
made under the supervision of:
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Authorship and copyright declaration

# THE ECONOMIC EVALUATION OF THE VACCINATION PROGRAM IMPLEMENTED TO PREVENT INFECTION FROM THE HUMAN PAPILLOMAVIRUS (HPV) IN MALES

Work Authorship Declaration

I declare to be the author of this work, which is unique and unprecedented. Authors and works consulted are properly cited in the text and are included in the listing of references.

Filip Takáč

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# Dedication and Acknowledgements

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# I. Abstract in English

***Resumo em inglês***

Human papillomavirus (HPV) is a DNA virus. This virus causes both benign and malignant diseases in men and women such as laryngeal papillomatosis, genital warts, or pharyngeal carcinoma, cervical cancer, penile cancer and anus cancer. HPV can be prevented by appropriate precautionary measures. The main preventative method is vaccination against HPV. Besides vaccination, regular screening is necessary to detect premalignant changes on time.

The main aim of my dissertation is to analyze the effectiveness of the cost of male vaccination against human papillomavirus in the Slovakia. Besides the main aim the thesis also focuses on analysis of the current state of male vaccination against human papillomavirus in the Slovakia and abroad, selection of endangered group of men based on analysis of given issue and also calculation of vaccination cost from chosen perspective. Furthermore, the determination of clinical outcomes of vaccination and the calculation of the cost effectiveness of vaccination of an endangered group of men based on collected data. To achieve the objectives after accomplishing the given aims, the appropriate methods are applied in the practical part of the dissertation. The core of the thesis is formed by a literary research of the current state of the subject and an analysis of the costs of vaccination and treatment of anal cancer. The collected information is summed in Markov's model and the cost effectiveness together with the sensitivity analysis is calculated. To quantify the direct costs of treatment of anal cancer a data from healthcare payers was used. The cost of vaccination is determined in accordance with to the valid legislation. Costs and results for vaccinated and non-vaccinated individuals are compared in cost-effectiveness analysis. The dependence of the cost analysis parameters and the impact on its results are examined in the sensitivity analysis. At the conclusion of my dissertation, the results are discussed and eventual measures are suggested.

**Keywords: human papillomavirus, vaccination, prevention, cervical cancer, informedness, knowledge, attitudes, anal cancer, Markov model.**

# II. Summary in Portuguese

## *Resumo em português*

O virus do Papiloma Humano (HPV) é um vírus ADN. Este agente infecioso causa doenças, quer benignas quer malignas, em homens e em mulheres, tais como papilomatose laríngea, verrugas genitais, carcinoma faríngeo, cancro cervical, cancro do pénis e cancro anal. A infeção por HPV poderá ser prevenida através de medidas preventivas adequadas. O método preventivo de referência é o da vacinação anti HPV. Para além da vacinação, o rastreio regular é útil para detetar alterações pré-malignas de forma atempada.

O objetivo principal da presente dissertação é o de analisar o custo-efetividade da vacinação masculina contra o HPV na Eslováquia. Adicionalmente, é igualmente propósito da dissertação o de analisar a situação atual do processo de vacinação anti HPV na Eslováquia e em outros países, refletir acerca dos métodos e processos de seleção de grupos de homens em risco, e ainda proceder ao cálculo dos custos de vacinação sob diferentes perspetivas. São igualmente objeto de tratamento a verificação dos resultados clínicos da vacinação e o cálculo dos níveis de custo-efetividade da vacinação incidente em grupos de homens em risco com base em informação recolhida para tal efeito. De modo a fazer cumprir tais objetivos, métodos analíticos adequados são aplicados e apresentados nas secções práticas da dissertação. A parte nuclear da dissertação é composta pela revisão da literatura associada ao atual estado-de-arte do tema em apreço, bem como pela análise dos custos da vacinação e do tratamento do cancro anal. A informação recolhida é usada para operacionalizar o modelo de Markov. Os valores de custo-efetividade são calculados e uma análise de sensibilidade é levada a cabo. A quantificação dos custos diretos do tratamento do cancro anal baseou-se na perspetiva dos responsáveis pelo pagamento dos serviços de cuidados de saúde. O custo da vacinação é determinado em conformidade com a legislação em vigor. O custo-efetividade é calculado com base nos valores de custo e nos resultados apurados para os grupos de homens vacinados e não vacinados. A robustez dos valores dos parâmetros de custo e o seu impacto nos resultados obtidos são testados a partir de uma análise de sensibilidade. Na secção dedicada às conclusões os resultados são discutidos e algumas medidas de intervenção são objeto de recomendação.

**Palavras-chave: vírus do papiloma humano; vacinação; prevenção; cancro cervical; informação; conhecimento; atitudes; cancro anal; modelo de markov.**

# III. ABBREVIATIONS LIST

HPV- Human Papilloma Virus

FIGO - International Federation of Gynaecology and Obstetrics

IMRT - Intensity Modulated Radiation Therapy

VAERS - Vaccine Adverse Event Reporting System

MSD - Merck Sharp & Dohme Corporation

FDA - Food and Drug Administration

EMA - European Medicines Agency

GSK - GlaxoSmithKline Biological

VLP - virus-like particles

DRG - Diagnosis-Related Group

CEA – cost – effectiveness Analysis

DSA – Deterministic Sensitivity Analysis

HES - Hospital Episode Statistics

HGAIN - High-grade anal intraepithelial neoplasia

HTA - Health Technology Assessment

ICER - Incremental Cost-Effectiveness Ratio

LGAIN - Low – grade anal intraepithelial neoplasia

NHS - National Health Service UK

PCR - Polymerase Chain Reaction

CA – Carcinoma

SPZP – social insurance

MSM – men who have sexual intercourse with men

VoZP - Military Health Insurance Company of the Slovak Republic

VZP – Generl Health insurance (Všeobecná)

UZP - Union Health insurance (Union)

DPS – Dôvera Health insurance (Dôvera)

SI – Social Insurance

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# 1 INTRODUCTION

## 1.1 Introduction of the topic

Human papillomavirus (HPV) causes serious cancer in both women and men. Human papillomavirus infection is currently one of the most common sexually transmitted infections. It most often occurs in people aged 20-25 years. More than 80% of people living a sexually active lifestyle will experience this infection at least once. In most cases, due to the immune system, the infection resolves without it appearing in a spontaneous way.

One of the serious cancers caused by HPV is cervical cancer. It is currently the second most common cancer in women. About half a million cases of this disease are diagnosed worldwide each year. In men, HPV causes penile cancer. This cancer occurs predominantly in men over the age of 60. Although the disease is rare, it is very important that, like women, men are informed about the infection caused by the human papillomavirus.

Vaccination against HPV is the basic preventive measure against these diseases. It is best to get vaccinated before the first sexual intercourse, but not before the age of 9. There are currently three vaccines available, Cervix, Silgard and Gardasil 9. However, women should not forget about preventive check-ups with a gynecologist who cannot replace the vaccine. It is also important to follow other preventive methods, namely safe sexual intercourse, to limit smoking and a promiscuous lifestyle.

I wanted to find out what it's like among young people, whether they've heard of HPV or even been vaccinated against it themselves. Last but not least, because this topic is very current today and discussed either among experts or common people.

The dissertation is divided into two parts: theoretical and practical. The aim of the theoretical part is to provide descriptive information about the HPV virus, about the diseases that this virus causes, about the possibilities of prevention of these diseases and about the vaccination itself.

The infection itself is not directly life-threatening for humans. Today, however, there is no doubt that it can provoke the emergence of malignancies in specific areas of the human body. The treatment of these tumors is costly, often with satisfactory results, and in a small number of cases it ends fatally. One way to prevent it is to vaccinate against the most dangerous types of papillomaviruses. This vaccination undoubtedly has a positive effect when protecting a person against infection or tumorigenesis. Despite this fact, the incidence of malignancies caused by

papillomaviruses does not decrease significantly. Conversely, for some types of canisters or groups of people, it rises. This is undoubtedly influenced by human morality and behavior, poor education and the price and poor availability of vaccines in the most affected regions, namely in Third world countries. This work aims to analyze the cost-effectiveness of human papillomavirus vaccination in a at-risk group of men who have sex with men. The result of the work can serve as a basis for deciding whether it is appropriate to cover this group of vaccinations from public health insurance, or under what circumstances.

# 2 CURRENT SITUATION

## 2.1 Human papillomavirus

Human papillomavirus (HPV) is currently present Papillomaviridae, after being transferred from the family Papovaviridae, due to changes in genetic information. [1] HPV is one of the DNA viruses. [2] This virus affects men and women. [3] Its icosahedral capsid contains 72 capsomeres with a total size of 50-55 nm. [4] Based on the HPV genotype, human papillomaviruses are divided into low-risk genotypes and high-risk genotypes. The low-risk group includes HPV 6, 11, 40, 42, 43, 44, 54, 61, 72 and 81, which mainly affect the skin and mucous membranes. HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82 belong to the group with a high risk of malignancy in the genital tract. [5] The cause of many malignant and benign diseases, which affect the female and male sex in various places, but especially in the area of the transition of the squamous and cylindrical epithelium. [6] HPV infects humans in places where cells are present, which form the mucous membranes of mainly the genitals, rectum, but also the pharynx. [7]

HPV infection is one of the most common sexually transmitted infections today. More than 80% of the population living in a sexually active way will experience this infection at least once in their lifetime. [8]

Women under the age of 25 are the most infected. In 90% of cases, women can cope with the infection without knowing the presence of the infection. Thanks to the immune system, it is possible in most cases to destroy the virus within a year, thus preventing the emergence of serious diseases. [7]

### 2.1.1 Transmission

Today, more than 200 genotypes of this virus are known, but about 30 of them are transmitted in the genital area. In most cases, the virus is transmitted through sexual contact, directly with infected genitals. There

have even been cases in which the infection is not preceded by sexual intercourse and skin contact with the infected genitals is sufficient. By the age of 50, up to 80 percent of women and 50 percent of men have reported HPV. [5]

### 2.1.2 Risk factors

Today, HPV infection is widespread worldwide. The main risk factor is the presence of an immunosuppressive condition, due to which HPV can act in human tissue and cause serious diseases. People who start sex at a young age have the highest risk of developing an infection. Other risk factors for the development of HPV infection are promiscuous lifestyle, immunodeficiency, oral hormonal contraception used before the age of 15, frequent unprotected sexual intercourse, non-participation in preventive procedures. Smoking also increases the risk of HPV infection. [9]

### 2.1.3 Prevention

Diseases caused by HPV infection can be prevented by appropriate preventive measures. The basic measure of primary prevention (prevents the onset of the disease) is preventive vaccination against HPV. To achieve the desired effect of the vaccine, the patient must be vaccinated before the first contact with the infection. Primary prevention also includes reducing risk factors for HPV infection. Is an important to avoid a promiscuous lifestyle, to have safe sexual intercourse, to use a condom, to limit smoking. Adherence to these measures reduces the risk of many diseases. [10]

Secondary prevention measures (involved in the early detection of the disease) include screening, which is part of a preventive examination by a gynecologist. This makes it possible to detect abnormal changes in human tissue in time and to diagnose cancer. Men aged 23 to 64 participate in screening tests as well. The basic method of screening is cytological examination. The cytological finding can be verified by a more accurate histological examination, using colposcopy. [7, 11] There are two types of screening. The first type is opportunistic screening, in which men participate individually and undergo urologist examinations for personal reasons at their own request. The second type is systematic screening. It is a preventive examination involving a large group of women. [12]

## 2.2 Diseases

### 2.2.1 Genital warts

They are benign warty formations, which are most often found in the area of the external genitalia in both women and men. They can occur

around the rectum, groin, but also inside the vagina or urethra. [13] In most cases, they are caused by low-risk HPVs, genotypes 6 and 11. HPV infection is transmitted through sexual, oral or anal intercourse with an infected person. [14]

According to the shape, we distinguish four basic types of genital warts, namely:

1. Small, small pimples 1-2 mm

2. Cauliflower, acuminate lesions

3. Keratotic manifestations

4. Flat pimples and plaques most often located on the cervix [15]

#### 2.2.1.1 Risk Factors

The development of urogenital warts is unconditionally linked to the overall sexual life of a person. This disease affects most significantly women when HPV infection is present in her sexual partner. Promiscuous lifestyle, unprotected sexual intercourse, immunosuppressive condition, smoking, all these elements represent risk factors for HPV infection. [15]

#### 2.2.1.2 Manifestation

Growths can occur individually or cover areas of the external genitalia. In most cases, their symptoms do not appear, so the disease is asymptomatic and painless. However, the manifestation may be itching, burning of the genitals, a feeling of discomfort or pain during sexual intercourse. The incidence of this disease in the population is increasing every year, especially in young women and men, with the highest prevalence between 18 and 28 years of age. [16]

#### 2.2.1.3 Prevention

The primary method of prevention is vaccination with Silgard or Gardasil 9. These vaccines are in most cases effective in preventing the disease, which is caused by HPV genotypes 6 and 11. [17] Genital warts are transmitted through contact with the skin or mucous membranes. Their absolute primary prevention is sexual abstinence. As warts are also found in places that are not protected by a condom, its use is not an absolute protection. [18]

#### 2.2.1.4 Diagnostics

Most often, genital warts are diagnosed by physical examination. Visually, the doctor can diagnose different shapes of warts, as well as their color, which may differ from the color of the skin. Direct light or a

colposcopy is used for the examination, which enlarges the observed lesions. Biopsy is not the recommended diagnostic method for this disease, but in the case of genital warts with a tendency to pre-tumor changes, it is advisable to verify this by taking a tissue sample. The presence of genital warts is a reason to look for lesions on the cervix and urethra. [19]

### 2.2.1.5 Treatment

The main goal of treatment is to remove warts, prevent complications and cancer. Treatment can alleviate but not completely eliminate HPV infection. The patient can choose whether he wants to apply the treatment method himself or a doctor. The methods that the patient applies himself at home include the application of an antiviral - mitosis inhibitor podophyllotoxin 0.15% cream and immunomodulators imiquimod 5% cream, polyphone in the form of ointment. Techniques used by the doctor include cryotherapy, application of podophylline resin 10–25%, trichloroacetic acid 80–90%, surgical removal, curettage, laser or electrosurgical ablation. [16] Surgery is used in patients whose lesions are at higher risk of developing malignancy. Electrosurgical ablation removes warts based on the properties of the electric current. The laser removes warts in hard-to-reach places in the body. For well-defined lesions, curettage is the treatment method used. [20] In addition to choosing the right treatment method for the patient, it is very important that his sexual partners also undergo treatment. [15] It is very important that patients are informed about HPV infection, about the possible consequences, to improve their self-care after diagnosing the disease. [18]

### 2.2.2 Papillomatosis of the larynx

It is a benign form of laryngeal tumor, which is most often found in the vocal cords and supraglottic part of the larynx in the form of granular pink tufts. It occurs in both boys and girls. [21] This disease is caused by HPV infection, mainly by HPV genotypes 6,11, but also by HPV 16,18, 31, 33, 51. If the organism is infected with HPV 16, 18, i.e. high-risk genotypes, then laryngeal papillomatosis has a significantly increased risk of malignant tumor. In the case of laryngeal dysplasia, it is a pre-tumor condition from which in some cases a malignant tumor can develop. [22] Laryngeal papillomatosis occurs in children and adults. If the disease is present in childhood, it usually disappears during puberty and returns in adulthood. In adults, the infection manifests itself in one, but also in several places in the body. Papillomatosis, which has spread to multiple sites in the body, tends to recur over time. [23] HPV infection, which causes papillomatosis in childhood, is transmitted vertically, from mother to fetus. HPV infection, which is present in adulthood, is transmitted through sexual intercourse with an infected person. [24]

#### 2.2.2.1 Manifestations

As the vocal cords are mainly affected by this disease, it is manifested by hoarseness or a change in voice. They can also be manifested by coughing, shortness of breath, a feeling of the presence of a foreign body in the throat, narrowing of the airways, and a feeling of suffocation. This infection manifests itself clinically in the form of skin warts, epithelial hyperplasia of the skin or mucous membranes. [21]

#### 2.2.2.2 Risk factors

Risk factors for laryngeal papillomatosis vary in childhood and adulthood. Risk factors in children include young age at birth, long childbirth, and the presence of genital warts in the mother. The first-born child has a higher risk of developing laryngeal papillomatosis. [25] The risk factor in adulthood is a turbulent sex life, which includes a large number of sexual partners, frequent rotation of sexual partners, first sexual intercourse at a younger age, oral sex. Smoking, especially in combination with alcohol, also increases the risk of laryngeal papillomatosis. [24]

#### 2.2.2.3 Prevention

The most important way to prevent this disease is to vaccinate against HPV with Silgard or Gardasil 9. It is important to educate and inform the public about the use of the vaccine as a basic prevention procedure against HPV. As this disease occurs in childhood mainly due to the transmission of HPV from mother to fetus, cesarean delivery could reduce the risk of vertical transmission of HPV. [26]

#### 2.2.2.4 Diagnostics

The most common diagnostic examination is indirect laryngoscopy, which is used when the papillomas are not sufficiently visible. In laryngostroboscopy, in addition to the larynx, the movement of the vocal cords is also observed. With the help of micro laryngoscopy, it is possible to get into hard-to-reach parts of the larynx. [25] Flexible laryngoscopy diagnoses anatomical as well as functional disorders. [27] NBI (Narrow Band Imaging) is a diagnostic imaging method that uses light of two wavelengths to detect the presence of lesions on the laryngeal mucosa. It is a frequently used method in the diagnosis of new diseases, but it is also used to capture the recurrence of an already overcome malignancy. [28]

#### 2.2.2.5 Treatment

The main goals of treatment include alleviation of airway obstruction, improvement of voice quality, alleviation of symptoms of the

disease. The choice of treatment method depends on the spread and location of the lesion and on the side, effects associated with the type of treatment. The most commonly used treatment method for removing laryngeal papillomatosis is surgical treatment, either by mechanical removal of the lesion or by laser ablation. A laser, microsurgical instruments or a rotating knife with a suction device are used for removal. An effective antiviral treatment is to inject cidofovir (a DNA polymerase inhibitor), which is usually given to patients during surgery, after performing microsurgery using a micro laser. One dose of the drug ranges from 1-12 ml. Due to the high toxicity of cidofovir, it is necessary for the patient to undergo a laboratory examination after administration of this substance. The ideal treatment would be to remove papillomatous lesions by a single injection of cidofovir. In reality, however, the dose of cidofovir needs to be repeated for the treatment to be effective. [29]

### 2.2.3 Oropharyngeal carcinoma

It is a malignant disease (cancer C10), which most often occurs in the area of the posterior pharynx, but also in the area of the soft climate, tonsils or the root of the tongue. [30] Oropharyngeal carcinoma is divided into two types. The first types are HPV-positive, the cause of which HPV, HIGH-RISK, and are mainly HPV genotypes 16 and 33. Most infected people are able to cope with the infection within 1-2 years due to their immunity, but in some cases HPV related disease occurs. The second type is HPV-negative, which is caused by cigarette smoking, chewing tobacco, alcohol consumption or their combination. [31, 32] This type of cancer most often affects people aged 50-60, more often men than women. [33] In 2019, the incidence of this cancer in the Czech Republic was 11.2 / 100,000 in men and 2.4 / 100,000 in women. [8] In Slovakia, in 2019, the incidence of this cancer was 0.5 / 100,000 in women and 4.7 / 100,000 in men. [77]

The system that determines the extent of cancer is TNM (tumor, nodule, metastasis).

TNM classification of oropharyngeal carcinoma: T - primary tumor.

#### 2.2.3.1 Manifestations

In the initial stage, this cancer manifests itself only in rare symptoms such as difficulty swallowing (dysphagia), painful swallowing (odynophagia), and impaired speech intelligibility. Often, the first visible symptom is an enlargement of regional lymph nodes that are affected by metastases. At a more advanced stage, the disease may be bad breath, blood in saliva, chewing muscle cramps, weight loss. [32]

### 2.2.3.2 Risk factors

Risk factors that cause this type of cancer include the presence of HPV infection, which is transmitted through sexual intercourse with an infected person. This is associated with risk factors, such as promiscuous lifestyle, high number of sexual partners, oral sex, urogenital sexual practices, mucosal contact with an infected penis, vagina or anus, limited use of a condom. Young people who started sex before the age of 18 are more likely to become infected. Other important factors that increase the risk of cancer are smoking, frequent use of alcohol or marijuana. Insufficient oral hygiene can also make a very significant contribution to its development. [31, 35]

### 2.2.3.3 Prevention

Oral cancer is very difficult to diagnose prematurely. This cancer does not cause precancerous lesions, which means that a doctor very rarely can diagnose preventive examinations. The only effective prevention in this case is vaccination against HPV. [31] A vaccine that acts against genital infection caused by HPV 16, 18 and reduces its incidence, it also acts against oropharyngeal infection caused by the same genotypes of HPV 16, 18. [36]

### 2.2.3.4 Diagnostics

The basic diagnostic examination is the observation of the pharynx using a laryngoscope or rhino scope. In addition to visual examination, emphasis is also placed on palpation examination. Since one of the primary manifestations of oropharyngeal carcinoma is an enlargement of the lymph nodes in the neck, it is possible to diagnose this finding by touch. An important part of cancer diagnosis is tissue sampling (biopsy), which is usually performed under general anesthesia. The imaging diagnostic method is ultrasonography, which shows the area of the lymph nodes. However, its disadvantage is that it does not show the area where the prim is located. [33]

### 2.2.4 Penile cancer

It is a malignant tumor of the C60, which in more than 95% of cases originates from epithelial tissue, in this case from the skin of the penis. This type of cancer is called squamous cell carcinoma. [64, 65] A less common type is mesenchyme carcinoma. The disease is rare in Europe and North America, accounting for approximately 0.1-2% of the total number of malignancies. More often, this cancer affects people in Asia, Africa and South America, and represents 10-20% of the total number of malignant tumors. [65] In 2018, the incidence of this disease in the Czech Republic was 2 / 100,000 men. [66] In the same year, its incidence in Slovakia was

1.6 / 100,000 men. [77] Penile cancer is most common in patients aged 60-80 years. Adolescents rarely encounter this disease. [67]

### 2.2.4.1 Risk factors

One of the most important causes of penile cancer is non-compliance with hygiene habits in the genital area. As a result, smegma accumulates under the foreskin of the penis. It is a white product produced by the foreskin glands, which by its presence irritates the skin. Over time, it can lead to the development of pre-tumor conditions, which often tend to culminate in the development of a very serious disease, penile cancer. Another significant risk factor is phimosis. It is a condition where it is not possible to pass the foreskin over the acorn because it is abnormally narrow. [65] As a result, smegma is retained under the foreskin and cannot be removed. The degradation products of this white matter are carcinogenic substances causing cancer. [64] A less common but significant cause of penile cancer is HPV virus infection. As with other diseases caused by this virus, a promiscuous lifestyle is a risk factor. Smoking is a risk factor for many diseases and also this. [68]

### 2.2.4.2 Symptoms

Penile cancer initially manifests as a small pre-tumor reddish lesion called Queyrat's erythroplasia. This deposit gradually expands and affects the glans penis, tunica albuginea and the cavernous bodies of the penis. Later, the lesion enters the internal structures of the penis. Ulcer lesions may also be present, but delayed initiation of treatment may lead to complete disintegration of the male genitalia and infiltration of the groin. In addition to morphological changes, the secretion of foul-smelling secretions is also a common manifestation. At an advanced stage, the cancer spreads through the lymphatic system to the regional inguinal and pelvic lymph nodes. After the development of metastases in the lymph nodes, they enlarge, followed by the breakdown of ingvin and bleeding from blood vessels. The occurrence of metastases at distant sites in the body is not a very common phenomenon in this type of cancer. [66, 67] If distant metastases occur, it is in the lungs, brain, liver or bones. [64]

### 2.2.4.3 Diagnostics

The diagnostic method that detects the presence of penile cancer based on the symptoms is a physical examination. Another diagnostic method is biopsy. Several types of this method are known. In an aspiration biopsy, a tissue or fluid sample is taken with fine needles and then cytological examined. The basis of the incisional biopsy is the removal of a part of the abnormal tissue by excision. Excisional biopsy removes all abnormal tissue. If the diagnosis confirms the presence of cancer, staging follows to determine the extent and stage of the disease. The diagnostic

imaging methods used include computed tomography, which uses X-rays, magnetic resonance imaging and ultrasound to image the interior of the body. [69] In the early stages of the disease, when the nodes are not palpable, a sentinel lymph node biopsy is used as a diagnostic method, in which a radioactive colloid is applied to the tumor environment and the nodule is subsequently monitored with a gamma camera. If the disease is at a stage when the nodes are palpable, one of the types of biopsy can be used to examine them. [70] When the presence of a certain abnormality in the nodes is confirmed, metastases in distant organs are examined. Computed tomography of the pelvis, chest X-ray and skeletal scintigraphy are used to diagnose them. [64] There are certain reasons why penile cancer is diagnosed later than it should. One of the reasons is the irregular examination of a urologist. Men are afraid of seeing a doctor and the consequences of treatment. Another reason is the already mentioned phimosis, due to which it is not possible to examine the acorn and thus detect the presence of certain abnormalities. [67]

#### 2.2.4.4 Prevention

The basic preventive measure for this cancer is to maintain regular hygiene, especially in the area under the foreskin. Prevention also includes a controversial method, which is circumcision-male circumcision. It involves surgery to remove the foreskin that covers the acorn of the penis. The sooner the circumcision of the penis is performed, the more likely it is that cancer will never occur. Men who suffer from phimosis, i.e. their foreskin is abnormally narrow, are advised to have circumcision. The most reliable preventive method is vaccination against human papillomavirus, which is one of the causes of this disease. Although HPV vaccination is more widespread among women, it is also possible to prevent men 's vaccinations as a precaution. [65, 68] The main precaution is to avoid contact with the virus. The use of a condom may partially prevent the onset of infection, but it is not absolute protection. [71]

#### 2.2.4.5 Treatment

The choice of appropriate treatment for a patient is influenced by the stage of the cancer and the overall condition of the patient. It also depends on the size of the cancer, the location of the cancer, and whether the tumor is first diagnosed or recurrent. [69] The goal of penile cancer treatment is to remove the tumor from the tissue, while maintaining the functionality of the penis. The treatment of precancerous lesions and early-stage cancer is based on laser therapy. Brachyradiotherapy is a treatment method used in cancers up to 4 cm in size. The method is based on the use of a high dose of radiation that is applied to or directly into the cancer without irradiating the tissues around the cancer. The only disadvantage for the patient is that before

brachyradiotherapy, it is necessary to undergo circumcision (removal of the foreskin) in order to determine the extent of the cancer and to prevent complications such as edema or skin reaction. In advanced stages, the cancer is removed by a surgical method, which is penile amputation. Surgical treatment may be supplemented by radiotherapy or chemotherapy. In some cases, instead of the traumatic procedure of penile amputation, it is possible to use medical radiotherapy, which, however, has a number of permanent consequences, such as skin atrophy, damage to the bone marrow or digestive organs. Another method of treatment is chemotherapy, in which tumor cells are destroyed by the administration of cytostatic. If lymph nodes are affected, it is recommended to remove them surgically or by radiotherapy. In very advanced stages of cancer, combination chemo radiotherapy can be used. [72, 73]

### 2.2.5 Carcinoma of the anus and anal canal

This C21 malignancy is one of the less common cancers, but its incidence is increasing every year. In 2016, its incidence in the Czech Republic was 2.02/100,000 inhabitants for women and 1.08/100,000 inhabitants for men. [8] In Slovakia, in 2016, its incidence was 1.0/100,000 for women and 0.8/100,000 for men. [77] It can have a different character, because the tumor can develop on its outer or inner part. In most cases, it is squamous cell carcinoma. Uncommon types are adenocarcinoma, small cell carcinoma, sarcoma, lymphoma or carcinoid. [74, 75]

#### 2.2.5.1 Risk factors

The main risk factors for the development of cancer of the anus and anal canal are infection with human papillomavirus and smoking. The most common type of HPV that causes anus cancer is HPV 16; less common are HPV 18, 31, 33 and 35. HPV is more common in women as a risk factor for this cancer than in men. Homosexually oriented people and people who often change sexual partners are at increased risk of developing this cancer. The presence of immunosuppressive conditions in patients also increases the risk of HPV infection. Benign changes in the area of the anal orifice do not affect the development of anal cancer. [76]

#### 2.2.5.2 Symptoms

Anus cancer is most often manifested in the early stages by mild rectal bleeding. Other common manifestations of this disease are itching in the anus, pain during defecation, and a change in the frequency of defecations. The patient often associates these symptoms with the presence of benign diseases such as hemorrhoids, anal fissures or warts.

If the disease progresses to a more advanced stage, it manifests itself in the formation of ulcers in the rectum. If the anal sphincter is also damaged, the patient is often unable to hold the stool, leading to incontinence. [74]

### 2.2.5.3 Diagnostics

Anal cancer can be diagnosed on the basis of a physical examination, in particular by looking at the area of the anal opening or by examining with a finger. If the doctor suspects a tumor, he or she talks to the patient to find out the patient's personal and family history. Another diagnostic method used is endoscopy, in which the anal orifice and the adjacent part of the rectum are examined using a short-tube device. In the case of rectoscopy, it is possible to examine and examine the entire rectum using a long tubular device. The extent of the tumor can be determined by trans rectal ultrasound examination, in which an ultrasound probe is inserted into the rectum. Diagnostic methods that detect the presence of distant metastases include ultrasound or computed tomography of the abdomen and pelvis, X-rays of the lungs, as these areas are the risk areas for metastases. The results of the examination determine the extent of the primary tumor and the presence or absence of metastases. The TNM classification determines the stage of the disease at which the patient is. [74]

### 2.2.5.4 Prevention

The most important primary prevention of anal cancer is HPV vaccination. However, in addition to vaccination, it is important to undergo anorectic cytology, in which epithelial cells are removed from the mucosa of the anal canal and subsequently evaluated. This method is complemented by a more accurate endoscopic examination with tissue sampling. As this cancer, mainly in homosexual men, is transmitted by anal intercourse, the use of a condom is also an effective prevention. As smoking is a risk factor for anal cancer in addition to human papillomavirus infection, prevention methods include smoking cessation. [8]

### 2.2.5.5 Treatment

The standard treatment method for anus cancer is concomitant chemo radiotherapy, i.e the simultaneous action of radiation and cytostatics such as mitomycin or porphyromycin. Although this treatment method is the first choice for cancer, it has achieved a disease relief in patients of up to 90%, survival of patients without recurrence of symptoms of the disease up to 70%, and also brings with it a number of side effects. Acute side effects that often disrupt chemo radiotherapy include

inflammation around the rectum, groin, rectal mucosa, hematopoietic disorders, and gastrointestinal problems. Side effects that occur later include anal ulceration, fistulation, vaginal or rectal stenosis, and anal sphincter dysfunction and afecal incontinence. To reduce these side effects, a newer technique of radiation application is used, namely IMRT (intensity modulated radiation therapy), in which the radiation not only adapts to the shape of the target volume, but its intensity is also modulated, so the radiation saves healthy surrounding tissues. There is also a risk of recurrence of anus cancer with chemo radiotherapy. In this case, surgical treatment is used, namely abdominoperineal resection. Surgical treatment is used as the first-line treatment method for anus cancer only in the T1 or Tis stage without affecting the anal sphincter. In the presence of distant metastases, the first-line treatment is chemotherapy in combination with cisplatin and fluorouracil. [76]

## 2.3 HPV vaccination

### 2.3.1 Vaccination of men

Human papillomavirus causes the already mentioned penile carcinoma in men, but also genital warts. The HPV virus is also the cause of head and neck cancer. It has even been shown that the disease is more common in men than in women. Especially in homosexual men who practice anal intercourse, HPV is a cause of anal cancer. HPV vaccines have been developed as a primary prevention procedure against precancerous and cervical cancer. Later studies have shown that cancers of the vulva, vagina and anal canal are also indications for HPV vaccines. Despite controversial views on the vaccination of men with HPV vaccine, studies have shown that vaccines are sufficiently safe and effective in both sexes. The main problem with HPV vaccination in men occurs economically. Due to the current high price of vaccines, paying for HPV vaccination in men would be financially unfeasible in several countries. There are several reasons for subsidizing HPV vaccination in men as well. One of them is that it is not possible to protect homosexual men from the virus by vaccinating women. In addition, the HPV virus is transmitted to both sexes to the same extent, and HPV-induced diseases are common in men and their treatment is more costly than prevention. [84]

### 2.3.2 HPV vaccines

Currently, three vaccines are known in Slovakia, which are used as primary prevention against HPV. The first of them, registered since 2006, is called Silgard. This vaccine was marketed by Merck Sharp & Dohme Corp. (MSD) and registered in the US by the Food and Drug Administration (FDA) as Gardasil, in Europe by the European Medicines

Agency (EMA) as Silgard. The second vaccine, Cervarix, manufactured by GlaxoSmithKline Biological (GSK), has been registered with the EMA since 2007. The latest vaccine is Gardasil 9, manufactured by Merck Sharp & Dohme Corp. (MSD) and has been a registered EMA since 2015. [81, 91]

All three vaccines protect people who are vaccinated against high-risk HPV types, namely HPV 16 and 18. The bivalent Cervarix vaccine has been shown to be effective in individuals from 9 years of age, especially HPV types 16 and 18. The quadrivalent vaccine Gardasil has been shown to be effective in both women and men aged 9-26 years. Gardasil 9, a nonavalent vaccine, has been shown to be effective in both women and men aged 9-26 years, in addition to HPV types 16, 18, 6, 11 in addition to HPV types 31, 33, 45, 52 and 58. [92, 93] In Cervarix 93% protection against high-risk HPV types has been demonstrated, but protection against low-risk HPV types has not been demonstrated with this vaccine. Silgard shows 83% protection against high-risk HPV types, and protection against low-risk HPV types is higher, at more than 95%. Gardasil 9 provides up to 96% protection against high-risk HPV types. [50] Cervarix contains an adjuvant of 500 mg aluminum hydroxide and 50 mg monophosphoryl lipid A. The antigen content is 20/20 mg HPV VLPs (virus-like particles) 16, 18. Silgard adjuvant consists of 225 mg aluminum hydroxyphosphate sulphate. The antigen content is 20/40/40/20 µg HPV VLPs 6, 11, 16, 18. Gardasil 9 adjuvant consists of 500 mg aluminum hydroxyphosphate sulfate. The antigen content is 30/40/60/40/20/20/20/20 mg HPV VLPs 6, 11, 16, 18, 31, 33, 45, 52, 58. [94]

### 2.3.3 Cervarix

This 2-valent vaccine contains vortex particles of two types of HPV, namely HPV 16 and 18, which are adsorbed on aluminum hydroxide. This vaccine contains more aluminum than Gardasil. In addition to the aluminum salt, the vaccine contains a lipopolysaccharide that enhances the immune response. [81] This vaccine is a prophylaxis before the development of pre-tumor changes in the cervix, vulva, vagina and prior to the development of cervical and anus cancer. The dosage depends on the age of the patient. This vaccine can be given to people over 9 years of age by intramuscular administration, most often into the deltoid muscle. It is given as two doses of the vaccine, with the second dose to be given five to thirteen months after the first dose. This is characteristic of children from 9 to 14 years. People over 15 years of age are vaccinated with three doses of the vaccine, with the second dose given one month and the third dose six months after the first dose. During vaccination, the patient may suddenly lose consciousness and fall away. After administration of this vaccine, the patient is most likely to experience adverse reactions such as visual disturbances, headache, fatigue, pain or run-off at the injection site, par aesthesia or limb cramps. The only known

contraindication to the use of this vaccine is hypersensitivity to any of the substances contained in the vaccine. Bleeding conditions, immunodeficiency conditions or infectious diseases accompanied by high fever should not be present in the patient receiving the vaccine. However, it is not recommended to vaccinate patients during pregnancy or breastfeeding. [95]

### 2.3.4 Silgard

It is a 4-valent vaccine that contains vortex particles of four types of HPV that are adsorbed on amorphous aluminum hydroxyphosphate sulfate. This vaccine is a prophylaxis for four types of HPV, namely HPV 16 and 18, which cause pre-tumor changes in the cervix, vulva, vagina and cervical or anal canal carcinoma, and HPV 6 and 11, which cause genital warts. [81] The vaccine is given intramuscularly in the deltoid region of the upper arm or in the upper thigh. Other methods of application are not permitted. This vaccine can be used to vaccinate people over 9 years of age. Children aged 9 to 13 years are vaccinated with two doses of the vaccine, with the second dose being given six months after the first dose. People over 14 years of age receive the vaccine in three doses, the second dose being given two months later and the third dose six months after the first dose. The entire vaccine dosage schedule must be administered to the patient within one year. Differently from the other vaccines this vaccine may be given at the same time as certain vaccines. A contraindication to the administration of the vaccine to humans is their hypersensitivity to any of the substances contained in the vaccine. Vaccination with this vaccine should be postponed in people suffering from severe infectious diseases. The same applies during pregnancy. However, women might be vaccinated during breastfeeding. The most common side effects associated with vaccination are headache, run-off, redness or pain at the injection site. [96]

### 2.3.5 Gardasil 9

This 9-valent vaccine contains vortex particles of nine types of HPV that are adsorbed on amorphous aluminum hydroxyphosphate sulfate. There are four types of HPV that Silgard (Gardasil) also contains, and HPV 16, 18, 6, 11 and five other types of HPV, and HPV 31, 33, 45, 52 and 58. Gardasil 9 is a vaccine a substance that is an effective prevention against pre-tumor changes and carcinoma of the cervix, vulva, vagina, anal canal and genital warts. This vaccine can be used to vaccinate people over 9 years of age. The vaccine is given in two doses to people aged 9 to 14 years, with the second dose to be given five to thirteen months after the first dose. People 15 years of age and older are vaccinated with three doses of the vaccine, with the second dose given two months later and the third dose six months after the first dose. All three doses of the vaccine should be given within one year. Side effects that often occur in patients after

receiving this vaccine include headache, pain, run-off or redness at the injection site, tiredness or dizziness. A contraindication to the administration of this vaccine is hypersensitivity to any of the substances contained in the vaccine. It is not appropriate for women to be vaccinated with this vaccine during pregnancy. [97]

### 2.3.6 HPV vaccines and their side effects

Experts from various institutions have controversial views on the side effects of HPV vaccines. Although vaccine users have reported a number of adverse reactions to the Vaccine Adverts Events Reporting System (VAERS), there are still many proponents of these vaccines who claim that the vaccines are safe enough. The most commonly reported side effect was injection site pain, fatigue or headache. In addition, patients have experienced more serious side effects, such as disorders of the blood and lymphatic system, immune disorders, disorders of organs such as the gallbladder, liver, heart, kidneys, gastrointestinal tract, nervous system, movement problems, mental problems or breathing problems. The most serious adverse reactions reported were abnormal pregnancies, fetal development or even miscarriage. Most of these side effects are not accepted and are considered serious, so it is nevertheless concluded that vaccines are safe. [81] The European Medicines Agency has alerted the National Institute for Drug Control to two deaths in women vaccinated with Gardasil. As neither of these cases has a direct link to vaccination confirmed and vaccination with this vaccine has been shown to have more benefits than risks for patients, patients can continue to be vaccinated with this vaccine. [82] A number of studies compare the effectiveness of Cervarix and Silgard vaccines. Preventive vaccination is known to be of the greatest importance in people who have not yet come into contact with the HPV virus. It is also clear that people aged 12-14 should be vaccinated before the first sexual intercourse. The vaccines are approximately equally effective in preventing pre-tumor cervical changes caused by HPV 16 and 18. Silgard has been found to be a more effective vaccine in preventing genital warts and Cervarix in preventing cervical lesions caused by related HPV types. [83]

### 2.3.7 Price of HPV vaccines and insurance coverage

The price of one dose of Cervarix is around € 50, the Silgard vaccine is around € 65 and the price of one dose of Gardasil 9 is around € 112, with the insurance company paying € 6.30 of the total price, the rest being paid by the patient. [85, 86, 87]

In Slovakia, the health insurance company (Union) provides girls aged 13-15, and most recently boys aged 13-15, with a 50% allowance for vaccination with HPV vaccines (Cervarix, Silgard and Gardasil 9). [88,

89] The health insurance company (Dôvera) provides girls and boys from the age of 13 to the age of 18 with a 30-70% contribution for vaccination with HPV vaccines (Cervarix, Silgard). In comparison, in the Czech Republic, based on the Amendment to the Public Health Insurance Act, vaccination against HPV is the least demanding economic option for girls from 13 to 14 years of age. Likewise, for boys in the same age range, since 2017. [90]

The summary information of the State Institute for Drug Control on the supply of medicinal products to distributors and operators entitled to issue in the Slovak Republic and abroad shows the volume of distribution by individual. Doctors and pharmacies are the most represented end customers (excluding distributors and exporters). The number of withdrawals of individual medicinal products for the first quarter of 2018 is shown in the Table 1. [109]

**Table 1: Distribution of HPV vaccines in Slovak Republic**

| Vaccine | Customer type | Number of packages | Average price *per* package without sales charge and VAT | Price for all packages without sales charge and VAT |
|---|---|---|---|---|
| Cervarix® 1× 0,5 ml | DOCTOR | 6 199 | 49 € | 303 751 € |
| | PHARMACY | 1 153 | 49 € | 56 497 € |
| Silgard® 1× 0,5 ml | DOCTOR | 12 437 | 60 € | 746 220 € |
| | PHARMACY | 1 119 | 65 € | 72 735 € |
| Gardasil® 9 1× 0,5 ml | DOCTOR | 4 295 | 112 € | 481 040 € |
| | PHARMACY | 1 169 | 112 € | 130 928 € |
| **Total number of packages** | | 26 372 | | |

In the Table 1 we may observe that by far the most widely used vaccine is Silgard® despite the fact that Cervarix happens to be a more economic option. This might be explained by Silgards® wider scale of protection compared to Cervarix®. Silgard® provides protection against four basic types of HPV strains (strains 6,11,16 and 18) while Cervarix®, a fully covered vaccine, protects only against two of these HPV strains (strains 16 and 18). The reason for the higher level of demand of Silgard® is admittedly is protection against a larger number of HPV strains and also the fact that its price or surcharge is lower than the price of Gardasil®9, as shown in the Table 1. This results in people's relative willingness to pay for a vaccine with a wider range of HPV strains.

The main end customers are doctors. Pharmacies take hundreds of rows of packaging a month. There are several reasons. Doctors argue with the comfort of their patients who receive or buy a vaccine directly at doctor's office. On the other hand, doctors are interested in administering the vaccines they have purchased, because they can be reported to the insurance companies for the compensation, or they may be sold to a patient with a permitted market surcharge which is then the profit of the doctor. Therefore, some doctors do not want to vaccinate people with the vaccines they have purchased in pharmacies, because they then lose funds from the sale of vaccines.

Unfortunately, from the data in the Table 1 it is not possible to determine how many doses were actually applied in a given period, nor how many of the applied vaccines were covered by the public health insurance, neither is possible to determine these data what was the proportion of vaccinated men. These accurate data are only available to individual health insurance companies.

The maximum reimbursement from the public health insurance is € 65 per dose. The maximum price of the manufacturer - meaning the upper price limit at which the manufacturer or importer can place the medicinal product on the Slovak market, is € 49 per dose for Cervarix® vaccine, € 60 for Silgard® and € 110 for Gardasil®9.

For both products, the maximum selling price of the manufacturer is determined by law. The final price of the products is further influenced by the higher trade surcharge and VAT. Information on pricing is shown in Table 2. [126]

**Table 2: Pricing of HPV vaccines in Slovak Republic**

| Vaccines | Cervarix | Silgard | Gardasil |
|---|---|---|---|
| **Maximum manufacturer price / Guide price** | **52 €** | **95 €** | **115 €** |
| **Maximum reimbursement from health insurance** | **65 €** | **65 €** | **65 €** |
| **Indicative selling price +** | **65 €** | **125 €** | **150 €** |
| **Orientation surcharge ++** | **0,0 €** | **60 €** | **85 €** |

\+ the maximum price of the manufacturer plus the maximum allowable trade fee and VAT

++ the difference between the approximate sales price and the maximum reimbursement from health insurance, this is the highest possible patient supplement

The condition for payment is the commencement of vaccination in the range from the completion of the third to the completion of the first year of life. From January 1th 2018, boys also have this option if the same conditions are met. The remaining age groups of both titles can be vaccinated at their own expense. The reimbursement system set up in this way puts other age groups at a disadvantage for whom vaccination could be beneficial. One of the possibilities of at least partial reimbursement of expenses associated with vaccination is the use of one of the health programs, organized by most health insurance companies.

### 2.3.8 Health insurance programs

Today, all Slovak health insurance companies provide a number of financial contributions to their policyholders, primarily for various types of preventive activities. There is no legal claim to these contributions and it is only up to the insurance company to decide how the contributions will be provided to its clients and in what amount. These programs are changed annually, but the basic structure remains similar to previous years. The largest domestic health insurance company – General Health Insurance Company of the Slovak Republic (Union) within the framework of financial contributions from the prevention fund, offers its clients up to €

37 against HPV. Boys and girls can use this post between 14 and 18 years of age. [128] Between the 13th and 14th year of life, the vaccination is fully covered by health insurance. The application of a vaccine is not recommended before the age of 13. The Dôvera employee insurance company offers a contribution of up to € 150 for vaccination against HPV infection as part of the 2018 health program. The contribution can be drawn by men and women from 12 to 18 years of age. The contribution does not apply to insured persons for whom vaccination is covered by public health insurance. Dôvera also offers a contribution of up to € 30 for vaccination against HPV for women under 45 years of age. The condition is the indication of vaccination within 6 months after the conization of the uterine plug for the precancerous [129]. The branch health insurance company for employees of banks, insurance companies and the construction industry offers all its policyholders a contribution for the prevention of € 11. [130] Similarly, an insured person of the Health Insurance Company of the Ministry of the Interior of the Slovak Republic is entitled to draw a contribution of up to € 19 per year. In both cases, the amount can be used for any vaccination not covered by public health insurance, ie also against HPV. [132] The Slovak Industrial Health Insurance Company enables its clients to draw a contribution in the amount of € 37 or € 55.

Adults can apply for € 37, and insured persons under the age of 18 can apply for € 55. The contribution is provided for any dose/vaccine of the vaccination cycle, it is not provided for the administration of the vaccine. The Military Health Insurance Company of the Slovak Republic provides up to € 55 for HPV vaccination to its policyholders from 14 to 18 years of age. Adults have the opportunity to draw up to € 19 per year for vaccination not covered by public health insurance. The Revolutionary Fraternal Treasury, the Health Insurance Company contributes within the bonus program to girls and women from 12 to 30 years of age and to boys from 12 to 15 years of age up to € 150 per person against HPV. If policy holders are entitled to health insurance, they can also pay a surcharge for the more expensive vaccine from the bonus program. Clients who do not meet the age range can draw a contribution of up to € 37 for any preventive vaccination not covered by public health insurance. In general, it can be stated that all health insurance companies provide a contribution for vaccination, either specifically against HPV or for vaccination according to the policyholder's choice.

### 2.3.9 Foreign Countries

Gardasil and Cervarix vaccines are available on the market in the United Kingdom. Vaccination is not mandatory for any group of inhabitants. Under The UK HPV vaccination program, the vaccine is reimbursed to girls aged 11 to 14. The parents of these girls are informed about the possibility of vaccination by letter. It is vaccinated in two or

three dose regimens, similar to the Slovak Republic. Vaccination of boys and men, as well as other women, is not included in the preventive immunization program. These people have the opportunity to get vaccinated, but they have to pay for the cost of the vaccine from their own resources. The price of one dose is around $130. [132] A very interesting case is India – a country with a large percentage of population struggeling with poverty. Between the years 1982 and 2005 the number of tumors caused by HPV continued to grow. In the last ten years, the number of these cancers has been declining. India's share of the world's CA number is 25.4%. The mortality rate for this disease is 26.5 %. The reduction in the incidence of cancer due to HPV infection is largely due to the mandatory screening program for women and thus the possibility of vaccination. (For men, support for preventive vaccination programs is not significant). [136] However, the fact that India has managed to negotiate a reduction in the price of a single dose of HPV vaccines from 130 USD to 4,5 USD, more than 96 %, can be a great benefit. [137] When converted to euro, the price of one dose was around 3,7€, which reduced the financial burden of the local health care system.

## 2.4 Cost of treating anal cancer.

### 2.4.1 Great Britain

A 2014 study examined the cost of treating anal cancer in the United Kingdom. In the first part, a retrospective study of outpatient and inpatient treatment of anal cancer was performed. Data for the time period from 2006 to 2011 were provided by the national database Hospital Episode Statistics. On average, 642 men were admitted to inpatient treatment each year and 139 for outpatient treatment, with an average age of 64 years. Further, the costs of the treatment were calculated, when the data used came from the National Health Service tariffs for 2010/11. The annual cost of treating a male patient was £4 562 for inpatients and £1335 for outpatients. There is a significant difference in the price of treatment. In the second part, the development and progression of the disease was simulated using the Markov model. The model was set for 10 years with a one-month cycle. Based on this modeling, the average cost of treatment per patient was calculated to be £16 473. Procedures used are mainly radiotherapy and chemotherapy. [138]

### 2.4.2 Germany

The aim of the 2012 study was to quantify the costs of treating anal cancer caused by HPV infection in Germany. The study was based on a retrospective cross-sectional analysis of five German databases providing information on hospital care, inpatient rehabilitation and healthcare, all

from 2008. Identification and selection of loads from individual databases was performed using a diagnosis with the code C21, which according to ICD-10 corresponds to anal cancer. This code had to continue to meet the condition of the main diagnosis. In total, the study included data from 2,238 men and 3,536 women. Costs were divided between direct costs (hospitalization, rehabilitation) and indirect costs (incapacity for work). The quantification was done especially for men and women. The total cost to men was €13 020 000 of which €11 880 000 were direct costs (€11 430 000 Hospitalization, €443 731 rehabilitation) and €1 150 000 represented the indirect costs (incapacity for work). Based on data from a 2009 meta-analysis of the prevalence of HPV infection in anal cancer, the results were subsequently recalculated. Meta-analysis data prevalence 84.3 % more than five out of six cases of anal cancer are caused by HPV infection. The estimated total cost of treating men with anal cancer caused by HPV viruses is €10 976 000.

### 2.4.3 Denmark

The aim of this 2012 study was to estimate the incidence and health care costs of anal cancer, penile cancer, vaginal cancer, and vulvar cancer. Patient data were obtained from Danish national registries, mainly from the Danish National Oncology Registry, between 2004 and 2007. These registers record all patient data (from personal data, medical history, to records of the use of any work in the healthcare sector). The analysis was performed from the perspective of the hospital in which the patients were treated. The costs were quantified using the DRG system in the framework of hospitalization and Danish outpatient fees (DAGS fees). The cost of treating cancer was calculated using regression analysis, which compared cancer patients with a group of healthy individuals of the same age and sex. Total costs were calculated by deducting the cost of healthy individuals from the cost of cancer patients. [138] The results were presented as annual cost estimates for the year before diagnosis, the first, second and third year after diagnosis. Costs for the year prior to diagnosis were included in the study due to the estimated cost of initial examination and diagnostics. The costs of medicine, radiotherapy, chemotherapy and specialized rehabilitation were also included in the total costs. The costs for the second and third year after the diagnosis were discounted (3 % annual discount rate). [138] The total cost of treating anal cancer by patient was € 38 289, the cost by man was € 41 347. The total cost of all male patients with anal cancer in Denmark accounted for €2 434 623 by year. The total cost of all male patients with anal cancer caused by HPV infection by year was estimated at €1 154 461. The total number of new cancers in Denmark is about 270 per year. In comparison, the total number of new cases of cervical cancer is around 390 per year. The total cost of anogenital cancer to the hospital sector was estimated to be €7 600 000 per year (€2 400 000 per year for men and €5 200 000 per year for women). Costs associated with anal and vulvar cancer comprised 53 % and 27 % of

the total cost, respectively. In comparison, the total hospital cost of cervical cancer (excluding precancerous lesions) is estimated to be €10 200 000 per year (2008 price level, estimated on the basis of Olsen and Jepsen, 2010. [138] The total health care sector costs of genital warts is estimated to be €8 000 000 per year (2008 price level).[1]

A limited number of international publications on the cost-of-illness of anogenital cancers are available. The present cost estimates are markedly higher than those by Borget et al. (2011) and Abramowitz et al. (2010) but similar to US cost estimates from Hu and Goldie (2008). Discrepancies may be due to differences in cost levels between countries (especially salaries for health professionals). Other important factors, however, are differences in methodology (prevalent vs. incident patients), health service organization and clinical practice, and in time horizon for the analyses (longitudinal vs. cross-sectional approach). The strengths of these studies were the use of comprehensive national registers that include all incident patients in the years 2004–2007 and the estimation of costs for four separate years. In comparison, for example, Borget et al. used a 1year cross-sectional approach. [158]

The German study used data on the prevalence of HPV infection from a 2009 meta-analysis 84.3 % to calculate the estimate. The highest treatment costs were in the first 12 months after the diagnosis due to the use of diagnostic methods, surgical procedures, radiotherapy. The analysis did not take into account any indirect costs. It can be burdened with an error with respect to the patients selected for the study – not all patients with this cancer were selected. Not all patients with anal cancer are diagnosed and treated within hospitals, but there are practitioners in the field of primary care who have not been included in the study.

# 3 METHODS

The chapter describes the procedures and methods that were used in the practical part of the work. The basis is a literature search of clinical results and analysis of costs, especially for the vaccination and treatment of anal cancer. Based on this information, a Mark's model is compiled, whose theoretical basis is described in this chapter. Also, the cost-effectiveness will be calculated and a sensitivity analysis will be performed, which are also explained in this chapter.

[1] OLSEN, Jens, Tine Rikke JØRGENSEN, Kristian KOFOED a Helle Kiellberg LARSEN. Incidence and cost of anal, penile, vaginal and vulvar cancer in Denmark. BMC Public Health. 2012, 12(1), 1082- . DOI: 10.1186/1471-2458-12-1082. ISSN 1471-2458. Available from: http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-12- 1082

## 3.1 Literary search of clinical results

It is a review of the literature, which includes current knowledge, including factual findings, as well as theoretical and methodological contributions to a particular topic. The review of the literature is a secondary source of information and the latest new findings. [139] It is very often focused on a specific research question, it seeks to identify, evaluate, select and synthesize all the quality research evidence and arguments relevant to this question. This evidence and information can then be processed using statistical methods to achieve a more reliable result. The information obtained serves to clearly and convincingly formulate one's own ideas and are subsequently used as a theoretical basis of work. [140]

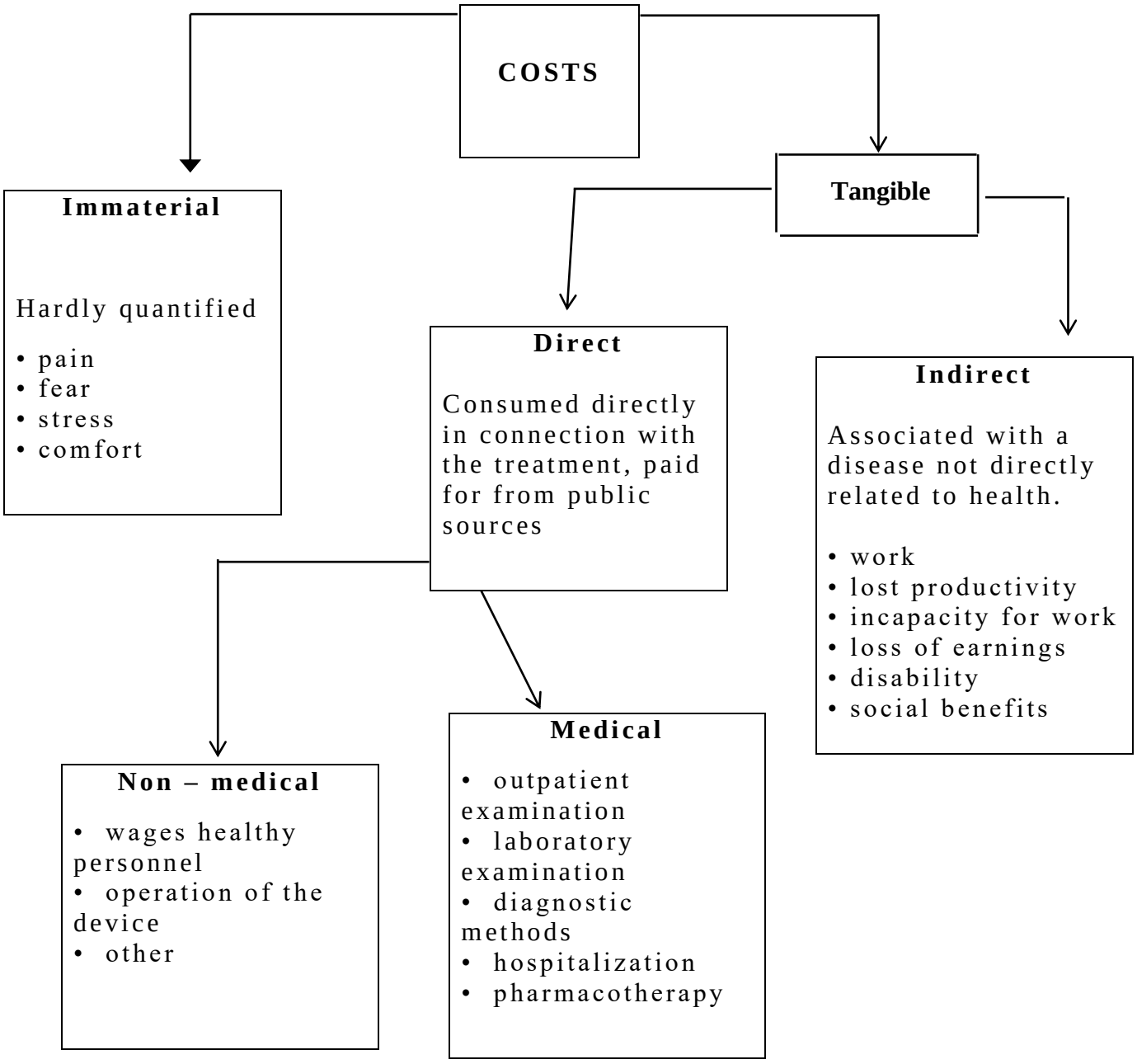
## 3.2 Cost analysis

Health care costs can be defined as the sum of resources expressed in monetary units consumed in the production of health services (provision of health care). [141] Categorization of costs can be done from different points of view, such as:

- according to the goal of the study (relevant, irrelevant),
- according to sources (direct medical and non-medical and indirect costs),
- according to their nature (fixed and variable). [142]

Different analytical approaches are applied when valuing costs. The general point of view includes all types of direct and indirect costs associated with a given treatment process. Providers of health care or payers usually only include items that appear in their accounting in connection with the intervention. One of the possible divisions of medical expenses is shown in Figure 1. In comparative analyzes between foreign states, it is necessary to take into account the exchange relations between the currencies of individual countries. [141]

**Figure 1**: Division of medical costs [143]




## 3.3 Cost-effectiveness analysis

The Cost Effectiveness Analysis (CEA) is a method for assessing the benefits of health in relation to the costs of various health interventions. To do this, it uses a comparison of costs in currency units with results in quantitative non-monetary units, for example reduced mortality or morbidity. The CEA can only compare technologies or processes whose results are measured in the same units. [144] One of the advantages of using the cost-effectiveness ratio is the absence of some ethical dilemmas and analytical difficulties that arise when trying to

analyze the cost and benefits of "Cost benefit analysis". [145] The CEA indicator is an efficiency criterion that can be monitored using the following indicators.

• Cost by unit of output (cost efficiency)

$$\frac{Ca}{Ea} < \frac{Cb}{Eb}$$

where Ca is the current value of the costs of program A, Cb the current value of the costs of program B, Ea is the natural effect of expenditure program A and finally Eb the natural effect of expenditure program B.

• Efficiency by unit of charge on costs (efficiency as the inverse value of costs) [146]

$$\frac{Ea}{Ca} > \frac{Eb}{Cb}$$

Approaches to accounting for costs and the results of cost analysis may vary in a number of important aspects, such as the choice of comparator, the perspective of economic analysis, and the time horizon of analysis.

## Comparator:

The comparator is a relevant, comparable, effective and safe technology or intervention that is usualy used for a given stage of the disease and is at the same time paid for by the health care system. If there are significant reasons and if more than one relevant comparator is identified, it is recommended to make a comparison with other comparators as well. It should be done against each other separately. It is also true that the choice of comparator must be duly justified. [147]

**Perspective:**

This is the point of view that we look at the evaluation of cost-effectiveness. There are several points of view, for example from the point of view of the patient, family, doctor, provider (health care facility), payer (health insurance company) or from a macroeconomic (society-wide) point of view. Determining the perspective is crucial for calculating the corresponding costs. Most often, economic analyzes are performed from the point of view of the payer or the provider, although in general the societal point of view is considered to be the most suitable. [148]

**Time horizon:**

The time horizon is the time for which the costs and benefits associated with the disease and its treatment are evaluated. The time horizon should be long enough to allow a reliable and reasoned conclusion regarding the assessment of the differences in costs and the benefits of comparisons of the interventions available for evidence. Costs and benefits must always be measured in the same long time frame for the evaluated and compared intervention.

**Discounting:**

Is a method used to adjust future costs and the benefits of their current market value. The usual higher discount rate (according to the Slovak Pharmaco-economic Society) is 3 % per year for costs and benefits over one year. Discounting is performed if the time horizon is longer than one year. In the long run (for example lifetime), higher discount rates have a very significant effect on the outcome of the pharmaco-economic evaluation. For sensitivity analysis, it is recommended to state a scenario without a discount rate (0 %) and a scenario with for example 5 % discount rate (this is a methodological uncertainty). The formula for calculating the current value of money in individual years is as follows:

$$Pv = \sum_{t=0}^{N} \left( \frac{Pt}{(1+r)^t} \right)$$

where (PV) is the current value in EURO, (N) the number of years, (t) the time period, (P) the nominal value of the costs and (r) the discount rate. [149]

### 3.3.1 Incremental costs

Incremental Cost-Effectiveness (ICER), from the English "Incremental Cost-Effectiveness Ratio" or such an incremental cost-effectiveness ratio is used in the calculation of CEA and is defined by the difference in two possible interventions, divided by the difference in their effect. It represents the average cost associated with an additional unit of measurement effect. We can estimate it as follows:

$$ICER = \frac{\Delta C}{\Delta E} = \frac{(C_{1-}\ C_0)}{(E_{1-}\ E_0)}$$

where C1 and E1 are the costs and effects of an intervention and Co and Eo are the costs and effects of a comparator. [150] ICER can be used as a decision rule when allocating resources. If the decision-maker is able to determine the value of willingness to pay for the result of the interest, this value can be accepted as a threshold. If ICER is above the threshold for a given intervention, it will be considered too expensive and should therefore not be funded. If ICER is below the threshold, the intervention can be considered as cost-effective. [150]

## 3.4 Modeling

The real effectiveness of vaccination can only be objectively assessed after a sufficiently long period of time. If vaccination has already taken place for a sufficiently long time, it is mainly a retrospective evaluation based on realistic clinical and economic data. Prospective data collection is unlikely in the long run. When it is necessary to predict the development of the situation several years in advance, we approach modeling, which helps us, on the basis of current facts, to estimate a situation that would actually occur in a few years or decades. It should be noted that this is only an estimate, which can be more or less accurate. The actual accuracy of the model can only be verified after its duration has elapsed. The choice of a suitable model depends on the specific solution of the problem. Markov's model is widely used in the evaluation of medical technologies. The Markov model is an analytical framework, often used in decision-making processes, and is probably the most common type of model used in the economic evaluation of health care

interventions. Markov models are based on the definition of interconnected stages and situations in which a patient with a given disease may find himself. Each patient represented in the model can only be in one of these stages at a time. Due to changes in health status over time, individual patients move between disease states. The time itself is considered discrete. The time period (typically a certain number of weeks, months of years) is called a cycle. The length of the cycle and the number of its repetitions determines the specific solution of the problem. Movements from one state to another (in the following time period) are represented as transition probabilities. The time spent in each disease state for one model cycle (and the transition between stages) is associated with cost and health outcomes. Health outcomes and outcomes of the modeled patient group are collected over the course of the cycles. Subsequently, they can be compared with aggregate data from a similar cohort, for example with another (comparative) intervention. Markov model has a limited ability to store information about previous events in individual cycles of models. For example, the probability of what will occur after disease progression may be related to the time of progression. Although to some extent this situation can be solved, other modeling approaches may be required for more complex diseases.

## 3.5 Sensitivity analysis

Sensitivity analysis is a tool that examines how different values of independent variables at the input affect a particular dependent variable at the output. It is generally used in a wide range of areas, from biology and geography to economics and engineering. [151] Deterministic sensitivity analysis (DSA) is a method in which one or more parameters are changed manually. The result is the extent to which the impact on the output values has changed. The range of variability of each parameter is usually pre-specified and, where appropriate, corresponds to the uncertainty in that parameter. In the one-dimensional sensitivity analysis, only one parameter is measured at a time, the other parameters of the model remain constant. In this way, the influence of the tested parameter on the result can be clearly determined. The disadvantage is the fact that in real applications only one input at a time changes only very rarely and the scenario tested in this way is therefore unlikely. [152] In multivariate sensitivity analysis, more than one parameter is measured at a time. It is usually not possible to change more than 4 to 5 parameters. Probabilistic sensitivity analysis (PSA) is required to assess the impact of simultaneous changes in many input parameters. It is a procedure in which all input parameters are considered to be random variables and are related to the probability distribution. Different distributions are generally suitable for

different types of variables. The key output of PSA is the proportion of results that are favorable (considered cost-effective) in relation to a given cost-effectiveness threshold. This can be represented by a curve of cost acceptability and efficiency. [153]

The purpose of the sensitivity analysis is:

• identify key variables that affect the cost flows and benefits of the intervention;

• investigate the consequences of possible adverse changes in all of the variables;

• identify actions that could mitigate the possible adverse effects of the intervention.

Only unfavorable changes are typically considered in the sensitivity analysis. [154]

# 4 RESULTS

The chapter contains an analysis of the cost-effectiveness of human papillomavirus vaccination and the further steps that lead to its implementation. The basis is the calculation of relevant costs from the perspective of the payer of health care, followed by the establishment of the Markov model and the calculation of cost-effectiveness. It compares people vaccinated against HPV with unvaccinated people. This is followed by a scenario analysis and a sensitivity analysis.

## 4.1 Cost Calculation

For the purpose of the thesis, the costs are divided into the costs of vaccination and the costs of treating cancer from the point of view of the healthcare payer.

### 4.1.1 Vaccination costs

The amount of vaccine costs is determined by two basic components – the price of the vaccine and the price of the medical service, in this case the application of the vaccine. Both components are regulated by valid legal regulations. The price of medical service is determined by the Ministry of Health which issues a list of medical procedures with point values. According to this list of procedures an application of HPV vaccine is a procedure covered by the public health insurance including the vaccine itself. Meaning this procedure is fully covered by public health insurance, it can only be performed on an outpatient basis with a frequency limit of 2/ day. The procedure does not include a clinical examination before the

vaccination to rule out any contraindications to the vaccination, but it does include a check of the patient's health after the application of the vaccine. Clinical examination before the application of the vaccine to exclude possible contraindications to vaccination can be reported separately only for an unregistered insured person at fully cost without insurance. For a registered insured person, it is included in the capitalization payment. Clinical examination in this case means a control examination by a general practitioner, which is performed before the mass vaccination or the individual vaccination. The total price of one vaccination fee is shown in Table 3. It is assumed that most of the vaccinated men will receive the vaccine from a registered general practitioner. (If, for any reason, an individual chooses another – unregistering general practitioner for vaccination services, he is entitled to obtain the general examination together with the application of the vaccine.) Another possibility is the application of the vaccine by a practicing pediatrist for children and adolescents, in case the person interested in vaccination is in the care of such a doctor or has not reached the legal age. The difference between the application of the vaccine by registered a non-registering doctor is the same as in the previous case of an adult general practitioner. Performances differ only in reported codes. The resulting price is the same for both specialists. The difference would occur when vaccinating a boy under 14 years of age. In that case, a two-dose vaccination scheme would be used instead of a three-dose vaccination scheme for people 13 years of age or older. This variant seems unlikely. At this age, most of the sex and sexual preferences and orientations are still not clearly defined, and it is not possible to place individuals in the group of men with a homosexual orientation, nor the MSM.

**Table 3:** Price for the application of the vaccine

| ITEM | Number of points | Point Value | Price |
|---|---|---|---|
| Vaccination including eyelets. paid from SI | **184** | **0,041** | **7,54 €** |
| Check-up examination by a general practitioner | **119** | **0,04** | **4,76 €** |
| Vaccines (max. Payment from SI) | **.....** | **.....** | **65,40 €** |
| The total price of one dose – registered patient | | | **73 €** |
| The total price of one dose – an unregistered patient | | | **77,80 €** |
| Total cost of three doses – registered patient | | | **219 €** |
| Total cost of three doses – unregistered patient | | | **233,37 €** |

### 4.1.2 Cost of treating anus cancer presumably in men

The costs associated with the treatment of anal cancer are quantified from the point of view of their payers. All four health insurance companies were contacted for this purpose. The content included a request for anonymised information on the costs associated with anus cancer (C21) as the main diagnosis in men over the past five years. At the time of the application of the request, it was not clear whether the information for 2018/19 would be available. Therefore, the requested time interval was specified from 2012 to 2016, eventually 2017. The application also contained a question on the number and age of individual patients, or the average age of patients in individual years or for the whole period. Insurance companies were asked to keep the data they provide as detailed as possible, for example age of individual patients instead of average age. The request was accepted and data were obtained from four health insurance companies, namely the General Health Insurance Company, the Military Health Insurance Company, the Dôvera Insurance Company and the Union health insurance companies. Although all health insurance companies have been asked for the same information since 2012, there are significant differences between them. The first significant difference is the different length of the time interval of the provided information, when the UZP provided information only for 2016, VoZP for three years (2015–2017), DPS from 2013 to 2017 and VZP from 2012 to 2017. Another difference was the format of the quantified costs. VZP, UZP and DPS have calculated the costs separately for each patient in each year. VoZP calculated the average cost per patient for each year. For this reason, a procedure was chosen for this dissertation, in which the average costs per patient for one year were calculated. Table 4 shows the annual average costs per patient related to the diagnosis of C21 in individual years, broken down by health insurance company.

**Table 4:** Expenses of health insurance companies – diagnosis C21

| Health Insurance | Average cost by patient | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | $\bar{x}$ |
| UZP | 0 | 0 | 0 | 0 | 1 354€ | 0 | 1 354€ |
| VZP | 380 € | 1 350€ | 1 347€ | 1 492€ | 2 471€ | 338 € | 1 220€ |
| VoZP | 0 | 0 | 0 | 2 400€ | 1 389€ | 1 399€ | 1 730€ |
| DPS | 0 | 2 567€ | 222 € | 652 € | 1 606€ | 819 € | 1 009€ |

The last column of the table expresses the average costs of the respective health insurance company for the provided period. PWD provided data for only one year, therefore they are taken as average costs for the whole monitored period. The final amount of costs to be used in the simulation was calculated as the average of the average annual costs of all insurance companies for each year. The resulting average amount is **€** 1 328 by patient by year. The data on the number of patients and their age are summarized in Table 5. VoZP did not provide any information on the age of the patient.

**Table 5:** Numbers of patients with C21 by health insurance companies in individual years

| Health Insurance | Number of patient | | | | | | Age | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | $\bar{x}$ | $Q_{0,5}$ | s | $s^2$ |
| UZP | x | x | x | x | 51 | x | 66,8 | 70 | 14,35 | 206,04 |
| VZP | 12 | 14 | 17 | 16 | 12 | 17 | 61,5 | 62 | 9,13 | 83,4 |
| VoZP | x | x | x | 46 | 55 | 50 | x | x | x | x |
| DPS | x | 7 | 4 | 4 | 7 | 6 | 66,4 | 70,5 | 12,35 | 152,17 |
| Total | 12 | 21 | 21 | 66 | 125 | 73 | 63,9 | 66 | 11,71 | 137,17 |

Further statistical processing is given in Table 6, which shows the average annual costs by patient, the median annual costs by patient, the standard deviation and variance.

**Table 6:** Descriptive statistics – costs of CA treatment by patient by year

| **Symbol** | **€** |
|---|---|
| $\bar{x}$ | 1 328 |
| $Q_{0,5}$ | 1 354 |
| S | 753 |
| $s^2$ | 15 294 040 |

## 4.2 Creation of Markov model

For the purposes of this dissertation, a Markov model was used. This represents conditions associated with the development of anal cancer. The input data for the model are the cost of vaccination, the average annual cost of treating anal cancer by patient by year and the probability of transition between conditions. The cost of vaccination was the total cost of the three doses of vaccine administered by the registrant. The average annual costs of health insurance companies by patient by year were taken as costs for the treatment of anal cancer. The transitional probabilities were taken over from two foreign studies published in 2014–2017. [155,156] The first addressed the clinical and cost-effective effects of quadrivalent HPV vaccine, used as a prevention against recurrence of high-grade and anal intraepithelial neoplasia in HIV-negative MSMs. [155] The second study focused on the benefits of targeted vaccination of MSM against HPV in Australia. [156] The reason for the selection of these studies was a detailed model that included a more intermediate stage between HPV infection and cancer development, and these stages were assigned annual transitions between probabilities. Figure 2 shows the structure of the constructed Markov model. The "Z" status represents a healthy 15year-old MSM entering a model that may be infected with HPV – the "HPV" status. In an infected individual, HPV infection may subside (so-called virus clearance – meaning return to the Z state) or cause the development of various degrees of epithelial lesions – the “LGAIN, HGAIN” stages. High-grade lesions can lead to anal cancer – the state of "CA". An individual can reach the stage of death from all other stages of the model based on the probability of natural mortality by age in the Slovak Republic (the model was used in the WHO online database from 2015). A summary of the model status is given below.

Z – population of 15-year-old HPV negative men having sex with men

HPV – HPV-infected men

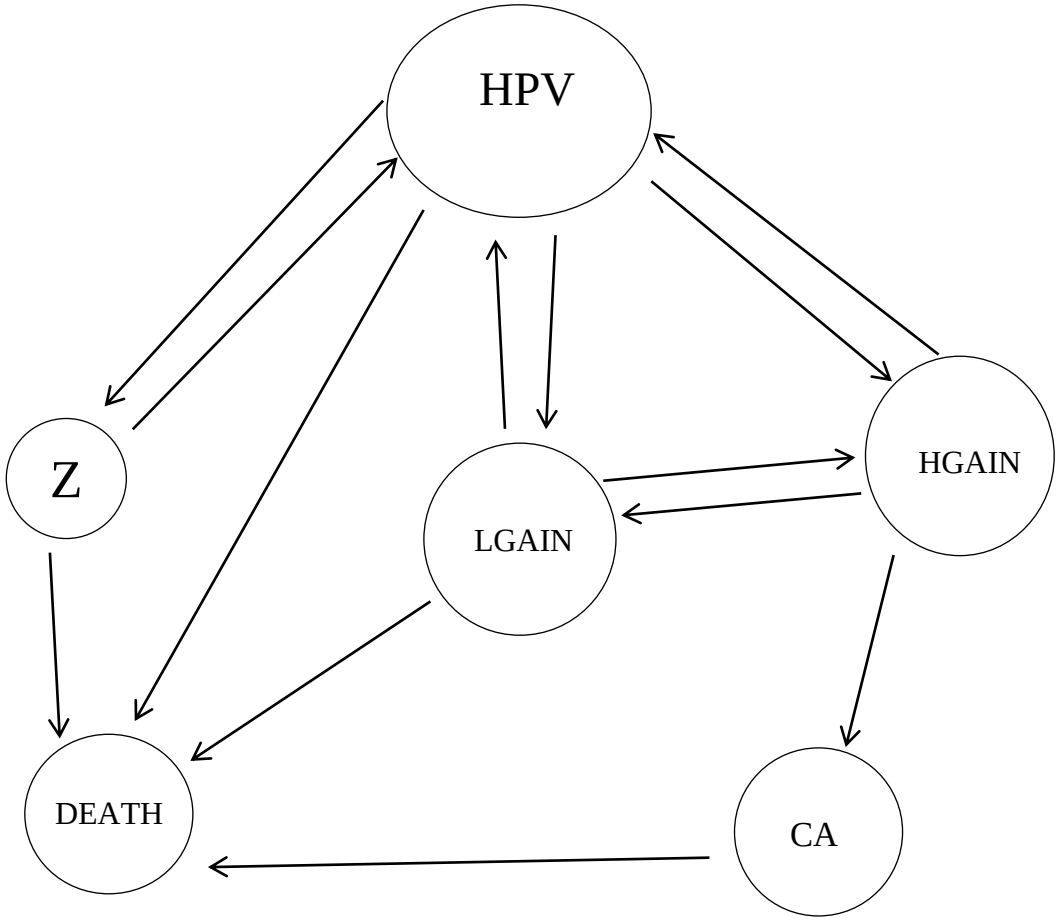
LGAIN – men with low-grade anal intraepithelial lesions

HGAIN – men with high-grade anal intraepithelial lesions

CA – men with anal cancer

Death – death due to anal cancer or other causes

**Figure 2:** Graphic construction of the Markov state model




The probabilities of transition between the conditions in the population (men) of unvaccinated persons are shown in Table 7 and the probabilities of the transition between the conditions in the population (men) of vaccinated persons are shown in Table 8, where "P" is the probability of death by age and "C" is the calculation of the probability of remaining in the current state, varying in time according to the value of P. The probability of death from cancer is "q". From the CA stage, an individual can move to the stage of death due to cancer (q) and from other causes (P)

**Table 7:** Transition probabilities for the unvaccinated population (men). (The values of P and C are variable and change over time).

| Condition | Z | HPV | LGAIN | HGAIN | CA | Death |
|---|---|---|---|---|---|---|
| Z | C | **0,179** | x | x | x | P |
| HPV | 0,445 | C | 0,072 | 0,057 | x | P |
| LGAIN | x | 0,071 | C | 0,35 | x | P |
| HGAIN | x | 0,301 | 0,05 | C | 0,000239 | P |
| CA | x | x | x | x | C | q + (1-q).P |
| Death | x | x | x | x | x | 1 |

+ P and C are variable and they change in time

**Table 8:** Transition probabilities for the vaccinated population (men). (The values of P and C are variable and change over time).

| Condition | Z | HPV | LGAIN | HGAIN | CA | Death |
|---|---|---|---|---|---|---|
| Z | C | **0,0179** | x | x | x | P |
| HPV | 0,0445 | C | 0,072 | 0,057 | x | P |
| LGAIN | x | 0,071 | C | 0,35 | x | P |
| HGAIN | x | 0,301 | 0,05 | C | 0,000239 | P |
| CA | x | x | x | x | C | q + (1-q).P |
| Death | x | x | x | x | x | 1 |

As shown above in the Table 7 and Table 8 the tranistion probability for Z condition category (15year-old HPV negative MSM) lowers significantly by 10 % for the vaccinated population. The construction of the model took place in the programming language R with the help of the hememod source, which is intended for the creation of Markov models and economic evaluation of medical technologies. The outcome is years of life gained. During each cycle, people in all states except death receive one year of life. The state of death has a value of acquired years of life equal to zero. The cost of treating anal cancer is assigned to the condition "CA". Vaccination costs are a one-time input in the first cycle. The model is set to 60 cycles, where one cycle expresses one year. The reason is the time of development of anal cancer and the long time horizon in which the effects of vaccination can manifest themselves. The input population is estimated by the following procedure. The basis is the number of 15year-old men in 2016 - approximately 47,200. The age of 15 is chosen with regard to the limit of legal capacity for sexual intercourse. At this age, there is already a refinement of sexual preference and orientation. The estimation of the size of the population of homosexuals or MSM is based on the research of sex and sexual practices of the Faculty of Science of Charles University. According to the commentary of one of the research leaders - prof. RNDr. Jaroslav Flegr, CSc, approximately 11 % of the total population is MSM, of which about 90 % are homosexuals and about 10 % are bisexuals. [157] Assuming that not all of the above men practice anal sex, the baseline MSM in the model is 7.5 %. It follows from the above that the initial number of people in the model, after rounding, is set to 3,540. The comparator is the treatment of anal cancer without prior vaccination. The expected benefit is primarily in the reduction of HPV infection, which is an essential precursor of anal cancer. The efficacy of the vaccine is set at 90 % after studying the official materials issued for the vaccines. However, there is lack of knowlege in Slovakia about HPV and young people as well as older ones don’t take this problem too serious. There is lack of knowlege and If there is some, people are not that concerned about this problematic situation. They don’t see the outcomes (good or bad dones). As well finding HPV in our health system is difficult,

because in Slovakia only girls getting tested on HPV while visiting gynecologist. [124]

## 4.3 Cost effectiveness

The calculation of cost efficiency was performed according to the above-mentioned model in the RStudio program. Table 9 shows the results of the CEA, where the cost of treating anal cancer is discounted at an annual discount rate of 3 %. The costs are stated in euro. The effect is expressed in years of life gained. The costs and effects are calculated for the whole population (women and men). ΔC is the difference between the cost of vaccination and the comparator of one person. Similarly, the difference between the years of life of both interventions is recalculated to one person. ICER represents the average incremental cost, this is costs spent on gaining one year of life. C/E ratio is the ratio of costs and effects – it expresses the‘‘price‘‘ of one year of life gained.

**Table 9:** Cost-effectiveness of interventions in discounting the cost of cancer treatment 3 % p.a.

| | Comparator | Vaccination |
|---|---|---|
| Cost | 12 830 € | 777 511 € |
| ΔC | N/A | 216 € |
| Effect | 193 516,30 | 193 577,60 |
| ΔE | N/A | 0,01733773 |
| ICER | N/A | 12 459 € |
| C/E ratio | 1,79 | 108,45 |
| Vaccination costs | 0,00 € | 775 653 € |
| Costs of cancer treatment | 12 830 € | 1 857 € |

The cost of vaccination intervention is approximately 60 times greater than the cost of the comparator. The life years gained obtained show a minimal difference between interventions. In terms of one person,

it is about 0.017 years, less than a day. The small difference in the age of life originated in the small absolute difference in the number of people in the CA state. The largest absolute difference was about 0.45 persons. The relative difference where about 13 % of vaccinated persons and 87 % of unvaccinated persons are in the CA state around the 30th cycle. In total, the number of cancers in vaccinated persons decreased by 84.53 % as compared to non-vaccinated persons. The number of high-grade lesions is 85.11 % lower and the number of low-grade lesions is 85.09 % lower.

The second basic variant of CEA is based on the previous one and is supplemented by a discounting effect of a 3 % annual discount rate (see Table 10). The principle of discounting the acquired years of life corresponds to the observation that the (subjective) price of life decreases with increasing age for a given person. A significant change is the increase in the difference in effect by two rows from 0.017 to 1.61. Conversely, ICER reacted differently to the discounting effect, falling by two orders of magnitude from € 12 459 to € 134.

**Table 10:** The cost-effectiveness of interventions to discount cancer treatment costs and years of life at a discount rate of 3 % p.a in men.

| | Comparator | Vaccination |
|---|---|---|
| Cost | 12 830 € | 777 511 € |
| ΔC | N/A | 216 € |
| Effect | 193 516,30 | 193 577,60 |
| ΔE | N/A | 1,60954 |
| ICER | N/A | 134 € |
| C/E ratio | 1,79 | 108,45 |

## 4.4 Scenario analysis

Scenario analysis suggests potential situations or conditions that could occur. It monitors the behavior of the model in these situations and analyzes the impacts of individual situations on the final results.

### 4.4.1 No discount

The first scenario is a variant where neither the costs nor the effect will be discounted. This situation is summarized in Table 11. Compared to the 3 % discounted load variant, a significant increase in comparator loads can be seen here. This is because the value of money does not decrease with increasing cycles, as is the case with discounting. The absence of discounting has little effect on the increase in vaccination intervention costs, as it has lower discounting costs for cancer treatment.

**Table 11:** Cost-effectiveness of interventions without discounting in men.

| | Comparator | Vaccination |
|---|---|---|
| Cost<br>ΔC<br>Effect<br>ΔE<br>ICER<br>C/E ratio | 31 991 €<br>N/A<br>7 167<br>N/A<br>N/A<br>4,46 | 780 390 €<br>211 €<br>193 577,60<br>0,01733773<br>12 194 €<br>108,45 |
| Vaccination costs<br><br>Costs of cancer treatment | 0,00 €<br><br>31 991 € | 775 653 €<br><br>4 737 € |

### 4.4.2 Discounting 5%

The next scenario assumes a discount rate of 5 %. Table 12 first lists the variant in which only the costs of treating CA are discounted. The higher discount rate reduces the cost of the comparator by more than 3 703 €, slightly increases ICER and the difference in costs. This is again due to the reduced value of money in later cycles. In the second part, the years of life gained are also discounted. This fundamentally measures the values of ΔE and ICER. The difference in effect increased by from 0.0173 to 2.62. Conversely, ICER reacted differently to the discounting effect, falling from € 12 530 to € 83. ΔE increased and ICER dicreased by about 150 times, while during 3 % discount rate it was only by about 60 times. From the above scenarios, which calculate the different value of the discount rate in various variants, it is clear that a significant influence on the result of my calculation methodology is thought to be decided. Whether to discount the life years gained or not. This mainly affects the ICER value,

which is used to decide whether to mark the evaluated intervention as cost-effective or to reject it.

**Table 12:** Cost-effectiveness of interventions – discount rate 5 % in men

| | Discounted costs | | Discounted costs and effect | |
|---|---|---|---|---|
| | Comparator | Vaccination | Comparator | Vaccination |
| Cost | 7 728 € | 776 754 € | 7 728 € | 776 754 € |
| ΔC | N/A | 217 € | N/A | 217 € |
| Effect (years) | 193 516 | 193 577 | 193 516 | 193 577 |
| ΔE (years) | N/A | 0,01733773 | N/A | 2,62 |
| ICER | N/A | 12 530 € | N/A | 83 € |
| C/E ratio | 1,08 | 108,34 | 1,08 | 108,34 |
| Vaccination costs | | | 0,00 | 775 653 € |
| Costs of cancer treatment | | | 7 728 € | 1 100 € |

## 4.4.3 Vaccine efficiency 70%

In the following scenario, the effect of the efficacy of the HPV vaccine on the outcome of the cost-effectiveness is investigated. The model is based on the introductory version – 3 % discount rate of costs, effect without discounting. The effectiveness of the vaccine was reduced to 70 %, and thus the likelihood of contracting HPV infections (moving from Z to HPV). The original probability of a transition increased from 0.0179 to 0.0537. The change has an effect on the increase in the ICER value, which increased by more than € 3 704 compared to the variant with 90 % vaccine efficiency, see Table 13.

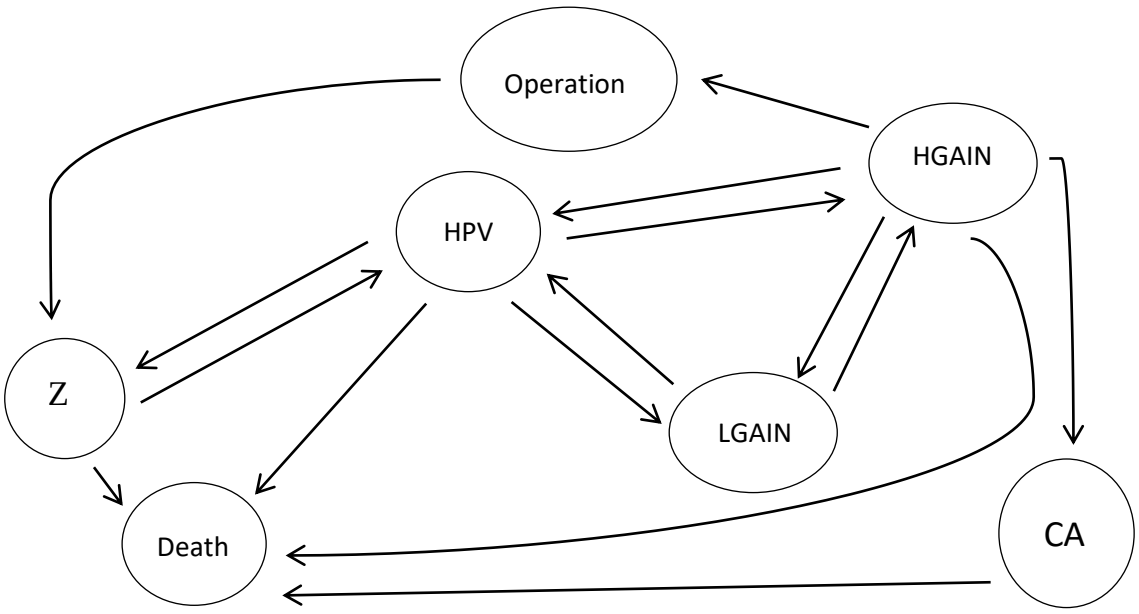
**Table 13:** The cost-effectiveness of interventions in vaccine efficacy is 70 % and the cost of cancer treatment is discounted in men.

| | Comparator | Vaccination |
|---|---|---|
| Cost<br>ΔC<br>Effect<br>ΔE<br>ICER<br>C/E ratio | 12 830 €<br>N/A<br>193 516<br>N/A<br>N/A<br>1,79 | 780 722 €<br>216 €<br>193 559<br>0,01228411<br>17 658 €<br>108,45 |
| Vaccination costs<br><br>Costs of cancer treatment | 0,00 €<br><br>12 830 € | 775 653 €<br><br>5 069 € |

## 4.4.4 High-grade surgical solutions

The following scenario considers a surgical procedure that removes high-grade epithelial lesions in the anal region and is thus a preventive measure against cancer. For this scenario, the original model has been modified and the state of the operation to which persons from the HGAIN state enter has been added (see below).

**Figure 3:** Graphic construction of Markov's state model with the state of operation HGAIN




The probability of transition from HGAIN to surgery is determined for 50 % of people remaining in HGAIN (exactly 32.5 % of the total). The

state of the operation is continuous and with probability 1, people move to the stage of health, natural mortality is neglected. The cost of high-grade surgery is taken from the DRG clinical classification system for analgesic and ostomy procedures without complications. Its amount is € 654. The results are summarized in Table 14. Significantly higher costs for high-grade surgical solutions lie in unvaccinated individuals. This is a consequence of the number of people with high-grade lesions indicated for surgery in unvaccinated intervention.

**Table 14:** Cost-effectiveness of interventions in high-grade epithelial lesion surgery

| | Comparator | Vaccination |
|---|---|---|
| Cost<br>ΔC<br>Effect<br>ΔE<br>ICER<br>C/E ratio | 751 333 €<br>- 36,30<br>193 778<br>0,04608826<br>- 788 €<br>104,69 | 879 903 €<br>N/A<br>193 615<br>N/A<br>N/A<br>122,70 |
| Vaccination costs | 0,00 € | 775 653 € |
| Costs for HGAIN operation | 744 830 € | 103 348 € |
| Costs of cancer treatment | 6 504 € | 900 € |

Despite the higher costs of operating a high-grade solution for the unvaccinated, the total costs are less than the total costs of vaccination intervention. The benefit of the operation is in the acquired years of life. These have increased significantly among the unvaccinated. The cause is the transfer of the operated persons to a healthy state.

## 4.5 Sensitivity analysis

In the context of deterministic sensitivity analysis (DSA), the same variables are considered, which are varied in the analysis of scenarios. Their basic values are retained. For DSA needs, it is necessary to specify the lower and upper limits of each variable. The values of the changed

limits are determined according to the available information, or estimated, see table 15. All costs are expressed by person.

**Table 15:** Baseline values of deterministic sensitivity analysis

| | Basic values | Lower limit | Upper limit |
|---|---|---|---|
| Vaccination costs | 219 € | 148 € | 259 € |
| Costs for HGAIN operation | 654 € | 555 € | 913 € |
| Costs of cancer treatment | 1 320 € | 568 € | 2 073 € |
| Discount rate [% / p.a.] | 3 | 0 | 5 |
| Vaccine efficiency [%] | 90 | 70 | 95 |
| Share of persons in operation HGAIN [%] | 50 | 25 | 65 |

The lower and upper limits of vaccination costs are determined by estimation. The lower limit simulates a reduction in the amount of vaccine that could occur, for example during all consumption. The increase is less likely, so the increase is relatively smaller than the decrease. The basic costs of high-grade epithelial lesion surgery are taken from the DRG system. Cost reductions are unlikely, so the lower limit is set at € 555. The upper limit represents the costs according to the DRG system for the same performance with complications. For cancer treatment costs, the basic value is an average calculated from data provided by health insurance companies.

The limits are then the sum or difference of the basic values of the loads and their standard deviations. The discount rate is 3 % according to generally accepted rules, the recommended limits are 0 % and 5 %. The efficacy limits of the vaccine were estimated at 70 % to 95 %. Cases have

been reported in which vaccinated people become infected with HPV infection. Therefore, efficiency is considered to be less than 100 %. The proportion of people undergoing high-grade climbing surgery is also estimated. The lower limit is set at 25 %. Due to the often asymptomatic manifestation of high-grade lesions and the absence of effective screening, the proportion of people may be smaller. The upper limit of 65 % represents rather a theoretical situation where it would be possible to capture a substantial part of the resulting lesions.

The main influence of the price of the vaccine on the resulting costs is evident. A reduction in the cost of vaccination costs by €71 will result in a reduction in the average cost etc. person by approximately € 74. The so-called total costs are directly proportional to the cost of vaccination. Reducing the effectiveness of the vaccine to 70 % increases the average cost to a value of over € 296. More people will reach a stage where they will be indicated for high-grade surgery or need cancer treatment. The zero discount rate affects the average cost negatively, because the value of money remains the same throughout the simulation. Conversely, a 5 % discount rate reduces the average cost, albeit not so much because the value of money decreases over time. Especially in later simulation cycles, the resulting price of individual cost items is reduced. The cost of the operation does not have a significant effect on the average cost, nor does the percentage of people with HGAIN undergoing surgery. The costs of treating anal cancer have a negligible effect.

The average cost of unvaccinated individuals is mostly increased by the discount rate, according to the principle stated in the previous paragraph. The zero rate increases the resulting costs roughly to double and thus significantly increases the cost of treating unvaccinated people. The cost of treating anal cancer in relation to the results is negligible, as is the case of the vaccinated. The effectiveness of the vaccine and the cost of vaccination have no effect in this case.

Among the variables examined, only the effectiveness of vaccination and the proportion of people undergoing high-grade surgery have an impact on the years of life gained. The reason is a greater transition of people to the HGAIN state, followed by surgery and a state of health. As a result, the value of the years of life gained increases. The proportion of people with high-grade lesions undergoing surgery is directly related to the effect obtained. The more HGAIN operations performed, the more years of life gained. Obviously, the only way to influence the life expectancy in this case is to change the number of high-grade lesions.

# 5 DISCUSSION

The issue of human papillomaviruses and the diseases they have caused recently has been of interest to many scientific teams around the World. Today, it is proven that human papillomaviruses are a cause of a large number of skin abnormalities and diseases ranging from minor to malignant transformation which in some cases might lead to death. The dissertation examines the clinical and economic benefits of vaccinating men against human papillomaviruses. Unequivocal clinical benefit is a reduction in the number of people infected with HPV and people with epithelial lesions and anal cancer. The clinical efficacy of the vaccine against high-grade lesions is 85.11 %. It was calculated from the number of vaccinated and unvaccinated persons in the HGAIN state. In a 2011 study, Palefsky reported a vaccine efficacy against high-grade intraepithelial neoplasia of 77.5 %.[125] The lower efficacy of the vaccine against computation may be due to the presence of heterogeneous HPV-infected individuals at the very beggining of the study. For those, the effectiveness of the vaccine is significantly reduced. To prevent this in the present dissertation, the entry age was limited to 15 years, for which it is assumed that the number of infected persons is negligible.

Lei Zhang [2] claims that with an re-vaccination greater than 84 % in the MSM population between the ages of 15 and 26, low-grade and high-grade epithelial lesions will be reduced by 90 %.[156] This statement cannot be exactly confirmed nor denied, as the results within the dissertation show a decrease in the changed LGAIN and HGAIN by 85.09 % and 85.11 %. However, no statistical deviation was included here, such as the confidence interval. It is possible that the model created would confirm Zhang's assertion. Lei Zhang's claim is interesting because he counts with MSM under the age of 26. It is more than likely that, at this age, some men will be infected with HPV and the effectiveness of the vaccine will be reduced. Therefore, in this dissertation the age of the focus group is limited to 15 year, as mentioned above.

The average annual cost of cancer treatment in the Slovak Republic was set at € 1 320 according to data from Slovak health insurance companies. To compare, in the UK the average annual cost of treatment for one patient with anal cancer, according to a 2014 study, was £ 4 562, which is approximately € 4 937 and even higher for Denmark. [135] These costs are higher than in the Slovak Republic, but the Slovak average costs are not cleared of outpatient treatment. Greater co-operation between

[2] ZHANG, Lei, David G. REGAN, Jason J. ONG, et al. Targeted hu- man papillomavirus vaccination for young men who have sex with men in Australia yields significant population benefits and is cost-effective. DOI: 10.1016/j.vaccine.2017.07.078. ISBN 10.1016/j.vaccine.2017.07.078. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0264410X17310046

health care payers would be needed to analyze cost data in detail and assign it to individual health conditions and types of health care.

It is imposible to compare the cost-effectiveness and ICER value, because the examined foreign studies use as value the QALY - (Quality Adjusted Life Year) which was not used in the Dissertation since there is no relevant QALY data for the anal cancer in Slovak Republic. Related to this is the issue of the discounting, when mainly by discounting the acquired years of life significantly changes the value of ICER. Opinions on the discounting the years of life are not uniform. The question is whether it is even possible to evaluate the value of the acquired years of human life in an appropriate way. Distortion of the resulting information may easily occur in this area.

The sensitivity analysis examines the relationship between HPV infection, high-grade lesions, and their surgical treatment and anal cancer. High-grade operations fundamentally affect the outcome of cost-effectiveness. ICER is most sensitive to the discount rate, the low value of which significantly increases the cost of HGAIN surgery and cancer treatment.

From a cost point of view, the vaccination is the largest item in the considered model. These costs should be spent comprehensively and efficiently. The vaccine is for prophylactic use only and has no effect on active HPV infection or clinically proven disease. The vaccine does not prevent lesions in individuals already infected with the relevant HPV type at the time of vaccination. It follows that an individual should not undergo HPV infection by the appropriate type of HPV against which he or she should be vaccinated until the time of vaccination. This would be cost-effective and clinically inefficient. The fact whether the organism has already encountered HPV infection can be determined by serological examination (ELISA) or by DNA testing. From a clinical point of view, it would be appropriate to use one or a combination of the two above-mentioned tests to verify HPV negativity before the vaccination is performed. At present, no pre-vaccination testing is performed in Slovakia. Althought some studies indicate that vaccination may have a positive effect in people with a history of infection, [155] this procedure is currently not professionally indicated.

From a cost point of view, the introduction of the above testing would be worth a more detailed examination. It would be necessary to quantify the number of detected HPV-positive individuals and the associated cost of vaccination and compare them with the cost of testing (for example very accurate PCR test for high-risk HPV costs approximately between € 33-55). The preventive pre-vaccination testing is however very unlikely to be preformed in Slovak Republik at least in the near future.

In connection with the diagnosis of earlier tumor changes in the cervix, a cytological examination is performed, which is a part of regular gynecological examinations. The aim of the screening is the early detection of possible precancerous lesions of the cervical mucosa and possible preventive surgical treatment. Abidance to regular intervals of screening examinations, early diagnosis and surgery of epithelial lesions lead to a significant reduction in the development of malignancies. According to European data, states that have included more than 80 % of the population aged 30-55 in the screening program have reduced the overall incidence of cervical cancer by as much as 80 %.[158] In the case of this dissertation, a similar trend showed that the inclusion of high-grade lesions in the model meant a reduction in the cost of treating of anal cancer in vaccinated and unvaccinated men and also an increase in the number of years of life gained, especially in the case of unvaccinated individuals.

The significant increase in the cost of the HGAIN operation in the unvaccinated patients was offset by the number of years of life gained, and the ICER value indicated a smaler cost-effectiveness in the unvaccinated individuals.

In women the screenings are performed only for the prevention of cervical cancer. Other locations where the virus occurs predilection are not tested. This is mainly due to the significantly lower incidence of other malignancies caused by HPV. In men, cytological testing is not performed regularly. There is no significantly high incidence of one type of tumor, such as cervical cancer. The incidence of other HPV-positive tumors is also lower than in woman. Exceptions are risk groups of men, especially the already mentioned men having sexual intercourse with men. In the event of multiple sexual partners, frequent HPV reinfections occur and there is a higher risk of epithelial lesions and malignancies based on HPV.

The question is: how much clinical benefit the introduction of a comprehensive cytological examination of men would bring? And who would possibly carry out such an examination? For women it is a gynecologist who perform the cytological examination in the context of preventive examinations? For men, only general practicioner is a option. A suitable solution might be to selectively test only endangered groups of men – homosexuals or bisexuals (MSM). This would raise both social and ethical issues. Some people keep their sexual orientation secret from a general practitioner. He can then hardly invite them for a cytological examination, or perform it in the framework of preventive examinations.

Another fact to consider is the other consequences of HPV infection. In men, human papillomaviruses are not only the cause of possible cancer (although it predominates), but also other malignancies altered in the current state. These are mainly cancers of penis and oropharyngeal area. Another unpleasant (not life-threatening) consequence of HPV can be a papilloma of the larynx and genital warts. None of these diseases were

included in the creation of the population model, because the scope of the diploma thesis would be considerably extended.

Theoretically, the cost of treating each additional disease associated with HPV should increase the cost-effectiveness of vaccination, because vaccination will reduce the cost of treatment, and increase the effect. This statement needs to be verified. It would be necessary to determine which other diseases and with what probabilities are caused by HPV, to find out their possible coincidences and possible influences to quantify their costs and finally to base the strategy to obtain the needed results. It is obvious that different groups of people (for example MSM) will need to be treated differently.

Vaccinating males can provide direct protection against certain HPV-related conditions (including genital warts, anal and penile cancer), but efficacy trials of clinical disease endpoints are still in progress. Vaccinating boys could also offer indirect protection to women by reducing the transmission of HPV. Although this approach does not seem to be cost-effective if a high vaccine coverage of females can be achieved, vaccinating boys may be attractive in some countries, in order to promote gender equity and to prevent rumours that vaccines offered only to females may cause sterility in girls, an ill-founded rumour associated with other vaccines.

In spite of the benefits of the vaccination, current economic models show that including boys in the current HPV vaccination programmes is unlikely to be cost-effective. However, one major limitation is that the models published in literature reflect assumptions that are not entirely evidence-based, such as duration of protection, coverage rates in girls, and incidence of HPV-related morbidities in the general population. Nevertheless, in all scenarios economic analyses render a much higher cost-effectiveness ratio for campaigns aimed at improving vaccination coverage rates in females. The cost-effectiveness of including boys in HPV vaccination programmes can be re-assessed when more solid data are available for baseline assumptions, and especially if vaccination costs are significantly reduced in the future. When more data on vaccine protection against HPV re-infection are available, one strategy worth exploring is that of targeted immunisation programmes for men who have sex with men (MSM). MSM may benefit more from HPV vaccination than the general male population, and might be an important group for targeted vaccination campaigns. Despite foreseeable obstacles in implementation, offering vaccination to MSM, even after sexual debut and exposure to HPV, might prove cost-effective.

# 6 CONCLUSION

The main goal of the dissertation was to perform cost-effectiveness analysis of vaccination of men against human papillomavirus in the Slovak Republic. In order to successfully achieve this goal, it was necessary to choose appropriate sub-steps leading to completing the aim. First, it was necessary to analyze the current state of the issue in the field of vaccination of men against human papillomavirus in the Slovak Republic and in the World, which has been done in the theoretical section of the dissertation. On this basis an endangered group of men having sexual intercourse with men was selected and the corresponding costs of vaccination were calculated from the perspective of the health care payer. After determining the clinical outcomes of vaccination, a Mark's model was performed, on the basis of which the cost-effectiveness of vaccination of MSM was calculated and sensitive analysis was also performed.

The main and partial goals of the work were met. Vaccination costs were calculated on the basis of valid legislative regulations. For the purpose of this dissertation they were rounded to € 219 for all three doses. The costs of treating cancer have been calculated on the basis of data from four health insurance companies. For the purpose of the work, the costs were determined as the average annual costs by patient with a diagnosis of C21, which amounted to € 1 320 a median of € 1 354, with a standard deviation of € 753 and a variance of € 15 294 040 (table 6).

During the development of the Markov ratios model and the subsequent calculation of cost-effectiveness, the costs of vaccination, the average annual cost of treating anal cancer and the probability of cancer by year were selected as input data for the model. CEA was performed in two variants. At first, it assumed a 3% discount rate on costs, and the ICER value was € 12 459 in favor of vaccinations. Then the effect of years of life gained was discounted at the same rate. The ICER value was € 134 in favor of vaccination.

An analysis of four feasible district scenario carried out were reflecting potential situations or conditions that could occur. The first scenario was a variant without discounting both costs and effects. In this scenario, a significant increase in the cost of intervention without vaccination is evident. At a discounted rate of 5 %, first only the costs of cancer treatment were discounted, and then the life expectancy gained. There was probably an even more significant reduction in ICER than at a discount rate of 3 %. In the variant of reducing the effectiveness of the vaccine to 70 %, the ICER value increased by more than € 3 704. In the last scenario, a high-grade lesion surgical solution was considered as a preventive measure against cancer. The cost of high-grade surgical treatment was almost as high as the cost of vaccination, but the resulting effect outweight the effect of vaccination. In this case, high-grade surgical

treatment was more cost-effective for non-vaccinated people. The scenarios mentioned above were jointly varied within the Deterministic Sensitivity Analysis. This analysis showed the considerable dependence on the discount rate and showed high-grade operations as cost-effective variants.

The most prudent and efective form of preventing the spread of the HPV infection would definitely be to focus on higher education on this matter and better access to the information about its possible threads and consequences. When asked, 8 out of 10 males do not know what the HPV infection is or how it spreads. This is alarming since as many as aprroximately 80% of adult population suffers from the HPV virus at some point of their lives and many of them are not even aware of the presence of the infection in their body as in numerous cases the course of the disease is symphtomless. These carriers unintentionally keep spreading the infection among others without their knowledge. In Slovak Republic females get tested anually for the presence of HPV infection by their gynecologist as a part of a routine check. Males on the other hand are never tested unless they specifically request it. Here arises the main problem, due to the lack of information on this matter, males are hardly aware of the existence of the HPV infection and do not realize it might affect them as well, therefore it is very unlikely for them to request the examination. Other problem is that in Slovak Republic there aren't reported many MSM mainly because this is still a sensitive subject to a public discussion. The cost-effectivnes would be much better, if MSM would not be scared to speak up, and if the society would start educate men about HPV infection as well. Other important step would be if Health Insurances would be able to cover the vaccination. To implement this into our Health Insurance system would be expensive and the effectiveness won´t be seen at first, but in the future, it might help to prevent other cancers and other HPV-related diseases, what should directly increase the cost-effectiveness of vaccination as this shall reduce the cost of other HPV-related diseses treatment.

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