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Cost-effectiveness analysis of organized HPV DNA screening in Romania

Bianca Florentina Niculescu

Supervised by: Lumbwe Chola

University of Oslo,
The Faculty of Medicine, Department of Health Management and Health Economics

Thesis submitted as a part of the Master of Philosophy Degree in Health Economics, Policy and Management

May, 2023

Acknowledgements

I would like to express my deepest gratitude to my supervisor, Lumbwe Chola for supporting me during this journey. You were always available to answer my questions and helped me overcome the challenges of economic evaluation. I would also like to thank Emily Burger for always making time to share her invaluable knowledge on economic modelling and HPV.

I'm extremely grateful for my family who has always supported me and encouraged me to start this Master's programme, even if it meant leaving home. I also wish to thank my friends from home Gab, Catalina, Nadina and Bogdan for always being there for me. Special thanks to my friend Ioana for inspiring me to choose this path.

Finally, my experience studying in Oslo would not have been so beautiful without my best friends Adrian, Nora, Maren, Lea and my partner LeoPål. You constantly supported and motivated me during these two years.

Abstract

Introduction: Cervical cancer represents a major health issue in Romania. However, there is no organized HPV screening program available at the moment, despite studies showing its cost-effectiveness in other countries. Moreover, there are also no cost-effectiveness studies on HPV screening in Romania. Therefore, we wanted to explore the cost effectiveness of an organized HPV screening strategy using HPV DNA testing every five years for women over 30 until 65.

Methods: The analysis was done using a Markov tree built in Amua to reflect the natural history of HPV. Transition probabilities for high-risk HPV strands were selected after a literature review. A cohort of 10,000 women was simulated. We adopted a provider perspective, including only direct medical costs and QALYs as outcomes. We calculated the incremental cost-effectiveness ratio (ICER) and assessed the cost-effectiveness of the strategies using a 50,000 euro threshold. Different cost scenarios were analyzed and sensitivity analyses were ran.

Results: The cost-effectiveness analysis showed HPV DNA screening to be the most cost-effective strategy in all the scenarios, with ICERS below the 50,000 euro threshold. However, the value of the ICER differed greatly between the scenarios. Moreover, the PSA showed that HPV DNA screening is the most cost-effective option as the willingness to pay threshold increases. However, for our willingness to pay it showed a relatively low probability of being the most cost-effective choice.

Conclusion: Organized HPV DNA screening can be the cost-effective option depending on the resources available and the willingness to pay for health. Further research on the cost and effectiveness data of HPV screening for Romania would be very useful for removing a high degree of analytic uncertainty.

Table of contents

List of abbreviations

CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CIN	Cervical Intraepithelial Neoplasia
EU	European Union
EVPI	Expected Value of Perfect Information
EVPPI	Expected Value of Perfect Parameter Information
HPV	Human Papilloma Virus
hrHPV	High Risk Human Papilloma Virus
ICER	Incremental cost-effectiveness ratio
NATO	North Atlantic Treaty Organization
PSA	Probabilistic sensitivity analysis
UK	United Kingdom
UN	United Nations
US	United States
WHO	World Health Organization
WTO	World Trade Oranization
WTP	Willingness to pay
QALY	Quality Adjusted Life Years

List of Figures

List of Tables

1. Introduction

Human Papillomavirus (HPV) is one of the most spread viruses worldwide; studies show that almost 80% of women will acquire the infection during their lifetime (Chesson et al., 2014). HPV is a sexually transmitted infection that usually does not require treatment, going away on its own. However, 10-15% of cases can develop into cancer, negatively impacting patients and the health system (Seong et al., 2021).

Nowadays, most countries in the European Union have implemented screening and vaccination programs to prevent the development of cervical cancer in the population (Todor et al., 2021). Research has shown that countries that have successfully implemented organized screening and vaccinations have drastically reduced and, in some cases, even eliminated cervical cancer (Ilisiu et al, 2019). Despite being part of the European Union, Romania represents an extreme case for cervical cancer, presenting the highest incidence and mortality rate in the EU (Ilisu et al., 2019).

Romania has the EU's highest cervical cancer incidence and mortality rate, 19.9 and 8.9 per 100.000 women, respectively (Ilisu et al., 2019). It is estimated that 3308 women in Romania are diagnosed with cervical cancer yearly, and 1805 die from it (Bruni et al., 2021). Despite the very high incidence of HPV and cervical cancer, at present there is no organized screening or vaccination for HPV.

In addition, there is little research on cervical cancer in the Romanian context. A literature review showed no studies on organized screening or vaccination cost-effectiveness. The only available research studies the society's attitudes toward the vaccine and the factors that led to the failure of past campaigns targeting cervical cancer. Those studies have found that society is generally very poorly informed about HPV (Grigore et al., 2018; Todor et al., 2021; Craciun & Baban, 2012). Most people get their information from unofficial sources and know very little about HPV and its consequences.

Despite being a significant health challenge in Romanian society, the general population is poorly informed, and there are no economic studies on this topic. However, previous studies focusing on

other EU states have found organized screening to have a positive health and economic impact (Todor et al., 2021). For example, countries like Austria, Germany and Belgium had similar mortality rates to Romania in the 1970s before organized screening was introduced (Todor et al., 2021). Nowadays, these countries have a death rate of about two deaths per 100.000 women, reducing cervical cancer mortality by 75% in some cases (Todor et al., 2021).

Hence, considering the evidence from other EU countries, introducing an organized screening programme can potentially improve Romania's drastic HPV situation. This paper thus aims to fill a gap in the literature by investigating the cost-effectiveness of introducing organized HPV screening (compared to no screening) in Romania.

2. Background information

2.1 The natural history of HPV

HPV are small double-stranded DNA viruses, and there are over 80 types of HPV strands that can be divided into two categories: low and high-risk strands (Bedell et al., 2020, pp.28-29). While low-risk strands can lead to the development of genital, oral or anal warts, it does not cause cancer (Bedell et al., 2020, p.28). Instead, the high-risk strands can lead to different types of cancers, the most common being cervical cancer (Bedell et al., 2020, p. 29). About 15 types of high-risk HPVs can cause cancer (Stanley, 2010, p. 1).

Studies show that HPV infections are most common in women under 25 (Stanley, 2010, p. 56). There is a decline in acquiring HPV infections after the age of 30 and then a rise again in the postmenopausal age group (Stanley, 2010, p. 56). HPV is contracted through any type of sexual intercourse that involves direct skin contact (Stanley, 2010, p.57). Factors that affect one's likelihood of acquiring HPV are mostly related to one's sexual behaviour, such as the age of first sexual intercourse, the number of sexual partners or the number of lifetime partners (Stanley, 2010, p.57).

Most women worldwide are affected by the HPV virus, presenting a 50-80% chance of infection in a lifetime (Stanley, 2010, p. 56). In addition, around 10% of women with a normal cervix present an HPV infection at any given time (Stanley, 2010, p. 56). However, in most cases, HPV infection clears itself out in about two years.

In a minority of cases, the body does not have a successful immune response; consequently, the virus does not regress (Stanley, 2010, p. 56). Instead, these women remain HPV positive, continually producing the infectious virus and causing changes in cervical cells (Stanley, 2010, p. 56). Hence, this leads to the appearance of cervical intra-epithelial neoplasia (CIN), the precancerous stage of cervical cancer. CIN can be defined as an abnormal growth of cells on the surface of the cervix caused by hrHPV strands (Cleaveland Clinic, 2022). CIN has multiple stages depending on how much epithelial tissue presents abnormal cells, as shown in *Figure 1*. For

example, CIN1 is the stage in which one-third of the thickness of the epithelium is affected, CIN2 is the stage in which one-third to two-thirds is affected, and CIN3 refers to more than two-thirds of the epithelium is affected. (Cleaveland Clinic, 2022). If the infection does not regress on its own or is not treated, it will first develop into local cancer, followed by regional and distant (Cleaveland Clinic, 2022).

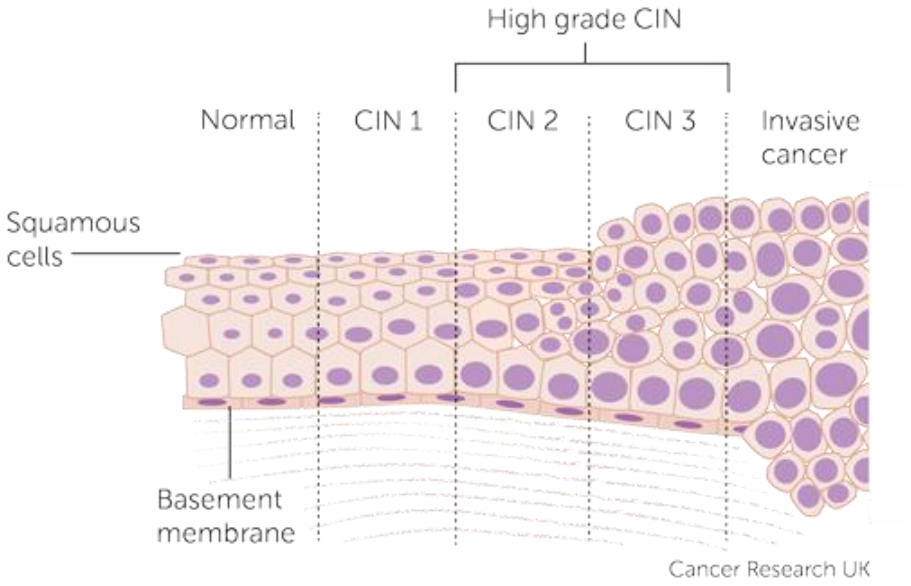

Figure 1:Evolution of HPV infection to cancer (Source: Cancer Research UK, 2020)

2.2 Screening of HPV

Because HPV infections have no symptoms, screening is the only way to detect such an infection early and prevent cervical cancer development. The three most common screening tests are visual inspection with acetic acid (VIA), the Pap test and HPV DNA testing (Bedell et al., 2020).

Pap test

This screening method was invented in the 1940s when George N. Papanicolaou and H. F. Traut managed to exfoliate cells from the cervix and interpret them morphologically with the help of a microscope (Bedell et al., 2020, p. 30). They demonstrated that by using the microscope, we can differentiate between normal and abnormal cervix smears (Bedell et al., 2020, p. 30). From that moment on, it became the standard HPV screening method, as it had little cost and was relatively

easy to conduct (Bedell et al., 2020, p. 30). Over the years, updates have been made to the test, and nowadays, studies suggest that it has a specificity of around 98% and lower varying sensitivity between 55 and 80% (Bedell et al., 2020, p. 31). In developed countries, it has proved to be one of the most cost-effective screening methods, significantly lowering the incidence and mortality of cervical cancer (Bedell et al., 2020, p. 31). However, it proved very hard to implement in developing countries as it is resource intensive, making it too costly (Bedell et al., 2020, p. 31). Moreover, because of low sensitivity, it must be redone frequently, necessitating an excellent medical infrastructure that is often missing in developing countries (Bedell et al., 2020, p. 31).

Visual inspection by acetic acid

A second screening method is the visual inspection by acetic acid (VIA), which is less costly compared to the pap test, making it more accessible for low-resource settings. This method entails the practitioner applying acetic acid on the cervix, making precancerous lesions visible to the naked eye (Bedell et al., 2020, pp. 32-33). Studies have shown this to be the most cost-effective screening for low-resource countries, as it requires few resources and is easy to perform (Bedell et al., 2020, pp.32-33). However, while this screening method has acceptable sensitivity and specificity levels, it relies heavily on the subjectivity of the practitioner. It has higher rates of false negatives, which can ultimately lead to higher costs as further tests are required.

HPV DNA testing

Finally, HPV DNA is a screening method that involves a sample collection of cells from the cervix, which are then analyzed by the clinician in the lab. Studies have shown HPV DNA testing to be more accurate than cytology-based screening as it has higher sensitivity for CIN2 or CIN3 cells (Origoni et al., 2012). Moreover, HPV DNA testing is essential for the follow-up of patients already treated for CIN2+. The test can accurately detect residual or recurrent disease, which is essential as these patients have a higher risk of relapsing (Origoni et al., 2012, p. 5). Countries such as the US have adopted HPV DNA testing as its main primary screening method, and it is expected in the following decades for this to become the standard in many countries (Bedell et al., 2020, p. 31). A significant advantage of the HPV DNA test is that it does not necessitate a medical provider to take the cell sample (Bedell et al., 2020, p.32). Instead, women can do it themselves,

with studies showing acceptable sensitivity and specificity for self-collected samples (Bedell et al., 2020, p. 32).

One disadvantage of HPV DNA is that it attracts high costs. Because it needs to be analyzed in a laboratory and requires sophisticated technology, it can to too costly for developing countries (Bedell et al., 2020, p. 32). However, HPV tests specifically designed for developing countries have been made at a substantially lower price, making them an accessible option (Bedell et al., 2020, p. 32).

2.3 HPV vaccination

In 2006 the first HPV vaccine was approved, called Gardasil. Currently, two more approved vaccines protect against multiple strains of HPV, Gardasil 9 and Cervarix (Bedell et al., 2020, p. 29). All these vaccines protect against HPV16 and 18, the most widespread cancerous strains. The vaccine is recommended for both men and women between the ages of 9 and 26 (Bedell et al., 2020, p.29). However, research studies have shown it to be effective for people up to the age of 45 (Bedell et al., 2020, p.29). Even if an individual has already been infected with one type of HPV, the vaccine can protect them against other strands.

Trials have shown the vaccines to be 100% effective against cervical cancer (Bedell et al., 2020, p.29). Moreover, a study from the UK has demonstrated that by introducing HPV vaccination in the national immunization program, cervical cancer has been completely eliminated for women born since 1995 (Falcaro et al., 2021). Hence, vaccination can effectively prevent and even eradicate cervical cancer. Vaccinated people are still recommended to get screened, but as societies reach higher vaccination rates, different screening protocols might be needed.

However, the global vaccination rates are still relatively low, with statistics showing that in 2021 only 13% of girls worldwide were fully vaccinated against HPV (World Health Organization, 2022). In addition, in the past few years, very high demand for the vaccine has led to supply shortages, with low-income countries being the most affected (World Health Organization, 2022). For example, it was estimated that by 2015, 59 million women received one dose of the vaccine,

out of which only 1,4 million were from low-income countries (Bedell et al., 2020, p.30). Therefore, access to HPV vaccination is still limited, especially in developing countries.

2.4 Treatment of cervical cancer

If the screening test has been positive, a colposcopy, sometimes in combination with a biopsy, will be recommended (Prendiville & Sankaranarayanan, 2017). This allows the medical providers to establish if the HPV infection has developed into cancer and at what stage exactly.

If the HPV infection develops into one of the CIN stages, it is considered a precancerous stage. Usually, the treatment at this stage will involve the excision of the cervical transformation zone (Prendiville & Sankaranarayanan, 2017, p.87). This procedure can be done using different methods. Two common techniques are the conization of the cervix and the LEEP procedure (Prendiville & Sankaranarayanan, 2017). Both have proved to be very efficient and only required local anaesthesia. Cryotherapy is another alternative that implies the destruction of the transformation zone by freezing (Prendiville & Sankaranarayanan, 2017, p.87). However, it takes substantially longer than LEEP and requires CO_2, which can raise costs considerably (Prendiville & Sankaranarayanan, 2017, pp.87-88). Lastly, cold-knife cone biopsy is the oldest procedure and is still used in areas where technology is not widely available (Prendiville & Sankaranarayanan, 2017, p.91). It is done under general anaesthesia and implies the removal of the transformation zone but usually results in the removal of a more extensive tissue zone than necessary (Prendiville & Sankaranarayanan, 2017, pp.91-92). Overall, it is a more complex procedure and has more complications later on (Prendiville & Sankaranarayanan, 2017, pp.91-92).

If the colposcopy or the biopsy indicates the presence of cervical cancer, a different treatment procedure will be adopted. Four main cervical cancer stages are determined based on the size of the cervical tumour or its extension in the pelvis (Waggoner, 2003, p 2218.). Then, depending on the patient and the cancer stage, treatment can include conization, hysterectomy, radiotherapy or different types of chemotherapy (Waggoner, 2003, p.2220).

2.5 Vaccination and screening of cervical cancer in the EU

The HPV vaccine is available under different conditions in all EU countries. In 2018, out of the 27 official EU countries, including the UK, 25 had added HPV vaccination to their national immunization programs (Chrysostomou et al., 2018, pp.12-13). However, no EU country has yet achieved more than 90% vaccine uptake for the final dose (European Cancer Organisation, 2021). Studies have shown that the most common reasons for refusing vaccination among EU countries are: insufficient or inadequate information about the vaccine, worries about adverse side effects, mistrust in authorities and doubts about the efficiency of the vaccine (Karafillakis et al., 2019, p.1618).

While vaccination can be a form of primary prevention against HPV cancer, screening is still necessary as vaccination does not protect against all types of HPV, and the coverage is not big enough in many parts of Europe. However, with an efficient screening strategy, studies have shown that HPV cancer mortality can be significantly reduced, and the quality of life for the patients can also be greatly improved (Peirson, et al., 2013). Hence, countries around Europe have developed and implemented various screening strategies. Screening can either be opportunistic or organized population-based screening.

In 1993, the first edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening published the first official guidelines for organized population-based screening (Chrysostomou et al., 2018, p.6) The second edition further emphasized the importance of organized screening, inviting all European countries to adhere to this screening model (Chrysostomou et al., 2018, p.6). This type of screening entails that each person from the population eligible for screening will be personally invited to screening, this way reaching a high screening coverage (Chrysostomou et al., 2018, p. 6). It also requires a regional or national team that can oversee the implementation of the guidelines, rules, and protocols while also taking responsibility for quality assurance (Chrysostomou et al., 2018, p.7). Finally, population-based screening allows for vast data collection and implicit evaluation of the burden of diseases. This facilitates further research and offers authorities an overview of the healthy population.

In contrast, opportunistic screening is not organized on a national or regional level, but rather it is an individual choice that requires personal awareness and effort (Chrysostomou et al., 2018, p. 7). Therefore, this type of screening leads to only a subtype of the population getting screening, usually people with a higher socio-economic status.

For the above reasons, the European guidelines recommend organized screening over opportunistic one. However, the organization of screening varies significantly from country to country. It is influenced by many factors, such as the available economic resources, the existing medical infrastructure, and society's attitudes towards screening (Chrysostomou et al., 2018, p.11). In 2018, surveys showed that organized screening was fully implemented in only nine countries: Denmark, Estonia, Finland, Latvia, Poland, Slovenia, Sweden, The Netherlands, and the United Kingdom (Chrysostomou et al., 2018, p.11). However, 22 member states are in the process of implementing, piloting, or planning organized screening (Chrysostomou et al., 2018, p. 11). At that moment, some countries such as Bulgaria, Greece, and Austria do not have organized population-based screening, but most have guidelines or recommendations (Chrysostomou et al., 2018, p.11). For example, there is no organized screening in Switzerland, but the Swiss Gynecological Society recommends it, and the Pap test is covered by health insurance (Chrysostomou et al., 2018, p.11).

Regarding the type of test used, The European Guidelines and the World Health Organization recommend HPV DNA testing over the Pap test or other tests because of its high cost-effectiveness (Chrysostomou et al., 2018). HPV DNA testing is very effective, having a high sensitivity, high negative predictive value and requires lower costs because of low training requirements and less frequent screening (Origoni et al, 2012). The European Guidelines recommend that HPV DNA testing should be done every 5 to 10 years, depending on the patient's characteristics (Chrysostomou et al., 2018). Considering the natural history of cervical cancer, the European Guidelines recommend that screening starts at 30 or 35 (Chrysostomou et al., 2018, p. 8). For cytology-based screening, it is recommended to start no earlier than 20 years old (Chrysostomou et al., 2018, p. 8). It is recommended for both HPV DNA testing and cytology that screening is stopped at age 65 (Chrysostomou et al., 2018, p. 8).

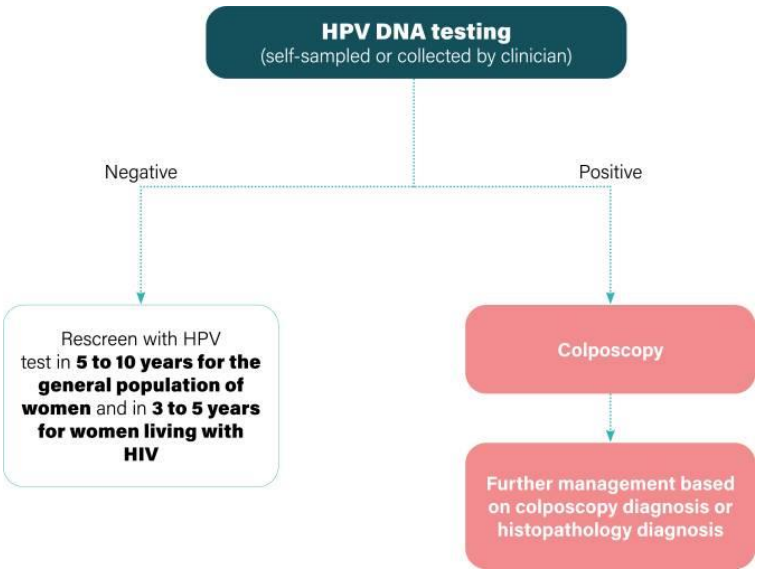

Figure 2: Screening algorithm for HPV infection (Source: World Health Organization, 2021, p.69)

Figure 2 illustrates a screening algorithm proposed by WHO. A patient is first screened with an HPV DNA test. If the result is negative, the patient will be screened again in 5 or 10 years, depending on the country's protocol. If the test is positive, a colposcopy is done to determine the exact stage of the HPV infection. Depending on the colposcopy result, the necessary medical intervention will be made.

2.6 Background information on Romania

2.7 Sociodemographic context

Romania is situated in South-Eastern Europe, bordering Moldova, Ukraine, Hungary, Serbia and Bulgaria. It has a population of 19 million, representing Europe's seventh-largest population (Vlădescu et al., 2016, p. 4). Romania presents an ethnically mixed population with a Romanian majority of 88,9%. The Hungarian ethnicity represents 6.5% of the population, 3.3% identify as Roma, and 1,3% are different nationalities (Vlădescu et al., 2016, p. 4). In 2021, 46% of the population lived in rural areas, while the remaining 54% in urban areas (World Bank, 2021). The life expectancy is one of the lowest in the EU; for men is 70.5 years, while for women, 's is 78 (Statista, 2023). The infant mortality rate is 6.4 per 1000 births (World Bank, 2023).

2.8 Political context

Romania had a communist political and economic system from 1947 until 1989, when the anticommunist revolution occurred. Romania had one of the harshest dictatorships in Europe under Nicolae Ceausescu. The revolution was also one of the deadliest communist revolutions in Europe, with 1,100 people dying (Paun, 2019). In 1991, a new Constitution was adopted, establishing Romania as a presidential republic with a free-market economy and guaranteed property rights (Vlădescu et al., 2016, p. 6). In 2007, Romania joined the EU; nowadays, it is a member of NATO, WTO and UN (Vlădescu et al., 2016, p. 6).

One of Romania's most significant political challenges has been corruption (Vlădescu et al., 2016, p. 7). The Romanian health authorities and the EU authorities have been battling political corruption for years, leading to many major political arrests. For example, one of the most high-profile arrests on the basis of corruption was the arrest of former Prime Minister Adrian Nastase (Marinas, 2014). In 2021, Transparency International ranked Romania as the 66th least corrupt country in the world out of 180, with a score of 45.

2.9 Economic context

Romania used to be one of the least-performing economies in the EU when it joined the alliance. The instability from the fall of the communist regime led to two big recessions, resulting in a simple and poorly performing and a significant poverty gap (Vlădescu et al., 2016, p. 4). In 2015, Romania had the highest inequality gap in the EU, with the wealthiest households earning 7.2% or times? more than the poorest (European Parliament, n.d.).

However, since joining the EU, Romania underwent significant economic reforms, which resulted in an increasingly sophisticated economy and the biggest economic growth in the Union since 2010 (World Bank, 2023). As a result, in 2023, Romania is classified by the World Bank as an upper-middle-income country. In 2021, the GPD per capita was 14,858, being ranked as the 44th richest economy in the world (World Bank, 2021). Hence, Romania's economy is ever-evolving,

making significant progress since the fall of the communist regime. Still, nowadays, the economy faces increasing challenges from the COVID-19 pandemic and the ongoing war in neighboring Ukraine (World Bank, 2023).

2.10 Health care system

There are two main levels in the Romanian healthcare system: the national and the district level. The national level is represented by the Minister of Health, the leading actor responsible for developing and implementing health policy (Vlădescu et al., 2016, p. 16). On a district level, the main responsible actor is the National Health Insurance House (NHIH), which oversees the health insurance system and ensures that the healthcare provider works according to the national rules (Vlădescu et al., 2016, p. 16). The legal framework within which the healthcare system operates is Law 95/2006 on Health Reform (Vlădescu et al., 2016, p. 17). This legal act regulates all health system sectors, such as the finance, policy and organization of healthcare, and the provision of all healthcare services or medical practice (Vlădescu et al., 2016, p.17).

In 2020, Romania had one of the EU's lowest healthcare expenditures per capita (Eurostat, 2020). Even if spending has doubled since communist times, it still lags behind other EU countries (Vlădescu et al., 2016, p. 45). The primary source of financing for the healthcare system is the national health insurance contribution, which represented 65% of the total funding in 2013 (Vlădescu et al., 2016, p. 45). The second source is out-of-pocket payments, accounting for 19% in 2014 (Vlădescu et al., 2016, p. 45). However, a substantial amount of money comes from informal payments, which represents a big issue as it raises many ethical issues, leading to unequal access to healthcare (Vlădescu et al., 2016, p. 45). Health insurance is mandatory for all citizens by law (Vlădescu et al., 2016, p. 45). However, around 14% of the population is uninsured, mostly people that are officially unemployed or marginalized groups such as the Roma population (Vlădescu et al., 2016, p.46). Insurance allows access to a comprehensive benefits package, which includes most healthcare services except the dentist. At the same time, uninsured people have the right to emergency care, infectious diseases care and pregnancy care (Vlădescu et al., 2016, p. 46).

The main challenge that the Romanian healthcare system faces is achieving financial stability. The system has been struggling over the years to accumulate the necessary funding (Vlădescu et al., 2016, p. 126). Moreover, corruption affects not only the political and economic system but the health care system too. Informal payments represent a substantial percentage of Romanian healthcare funding, despite being illegal and corrupt. According to a study done by Asociatia Sf. Damian (2010), almost 75,5% of patients admitted to the hospital in a year offered informal payments to healthcare providers (Vlădescu et al., 2016, p. 65).

A second significant challenge for the healthcare system is the unequal access to services between rural and urban areas (Vlădescu et al., 2016, p. 107). This is caused mainly by a shortage of primary doctors willing to move to rural areas, poor infrastructure, and long distances to healthcare centres (Vlădescu et al., 2016, p. 107). In 2014, only about 40% of all primary care providers worked in rural areas, and about 300 communities did not have even one primary health provider (Vlădescu et al., 2016, p. 107).

Finally, there is a shortage of medical providers caused by the "brain drain" phenomenon (Vlădescu et al., 2016, p. 154). Many medical providers choose to emigrate and work in Western Europe, where they enjoy higher salaries and better working conditions. The free movement principle of the EU facilitates their immigration, accelerating the brain drain phenomenon.

Considering the healthcare challenges and resource constraint, value for money considerations are thus important in health decision-making in Romania. However, the use of health technology assessment is not yet officially regulated. Therefore, there are no official guidelines for cost-effectiveness analysis in Romania. However, studies have shown that healthcare experts believe there is a strong need to establish a national technology assessment program and invest in postgraduate education in this area (Rais et al., 2020).

2.11 HPV cancer in Romania

In Romania, the prevalence of cervical cancer caused by HPV is very high; being the second most common type of cancer and cause of death for women aged 15 to 44 (Bruni et al.,2021).
As stated in the introduction, the incidence and mortality are three times higher than in other European countries (Ilisu et al., 2019).

When it comes to HPV prevention, there is no organized screening program. Opportunistic screening is available in private hospitals, which usually leads to unequal access to healthcare. Studies have shown that women with higher education in Romania are four times more likely to get screened for cervical cancer than those without one (Afectiunile Ocoligice Feminine in Romania)(Todor, 2021). Most women claim a lack of time or lack of financial resources when explaining why they don't get screened for HPV (Todor, 2021, p.10)

Between 2012 and 2017, an organized screening program using the Pap test was introduced. The guidelines indicated that women over 25 with no prior cancer history should be screened with a Pap test every five years (Coravu et al., 2021). However, the program failed to reach its objective; out of the 6 million women it was supposed to reach, only 260,000 got tested. The reasons behind this failure include limited national coverage, as the program failed to reach rural areas. Moreover, there was not enough promotion of the program on social media or among general practitioners. The application to the program was also time-consuming, requiring many documents, which discouraged many women from applying. Finally, the program was poorly organized and sometimes discontinued due to a lack of funds (Todor, pp.9-10). Since 2017, no organized screening program has been introduced.

When it comes to vaccination, there were two extensive vaccination campaigns organized on a national level in 2008 and 2011. Both campaigns had poor results, being able to reach very little of the targeted population. The campaign in 2008 only reached 2.5% of the targeted population (Craciun & Baban, 2012). Studies have shown that most parents refused to vaccinate their daughters, as they perceived it as dangerous (Craciun & Baban, 2012). Most parents thought there was insufficient official information regarding the vaccine and its effect. They thought the

government imposed the vaccine on them without being educated about it (Craciun & Baban, 2012, p. 6791). Later studies reveal that only 50.7% of Romanian women would get vaccinated (Grigore et al., 2018, p.157). The reason for declining the vaccine is still that it is perceived as having dangerous side effects (Grigore et al., 2018, p.157). After those failed campaigns, HPV vaccination has not been introduced in the national immunization program but can be administered on request for free for girls under 18. However, the Minister of Health has announced that starting this year, the vaccine will be administered for free on request to women until the age of 45.

To conclude, the Romanian authorities have tried to lower cervical cancer's high incidence and mortality rates by introducing vaccination and screening. However, the poor organization of these programs and the lack of education on the subject led to the failure of these programs, as they did not reach their goals. Therefore, all studies recommend educational campaigns on the subject and a better organization and promotion of future organized screening and vaccination programs.

3. Theoretical framework

3.1 Economic Evaluation

Economic evaluations are increasingly used worldwide to help societies effectively distribute their finite resources in the healthcare system (Briggs et al., 2006, p.1). The first countries to adopt the official use of economic evaluation in their healthcare systems were Australia and Canada (Briggs et al., 2006, p.1). Nowadays, many governments around the world use economic evaluations to decide the reimbursement of new pharmaceuticals or health interventions (Briggs et al., 2006, p.1).

In healthcare, it is unavoidable that some choices will need to be made on how to distribute resources since they are limited. The scope of economic evaluation is to inform us of the costs and consequences of a specific choice based on some defined criteria, allowing us to make an informed decision (Drummond et al., 2015). Hence, Drummond et al. (2015) define economic evaluation in healthcare as the comparison of alternatives based on the costs and consequences. There are multiple types of economic evaluations depending on the nature of the consequences.

3.2 Types of economic evaluation

Cost-effectiveness analysis

A CEA is a type of economic evaluation that compares the costs and outcomes of two or more strategies with the same outcome, such as life years (Drummond et al., 2015, p.5). Hence, the defining feature of a CEA is that all strategies compared have the same consequence, but they achieve it to different degrees. Common measurements of consequences used in CEA are life years gained, number of cases detected, and number of episode-free days (Drummond et al., 2015, p.5). In addition, the results are usually reported as incremental cost per unit or effects per unit of cost (Drummond et al., 2015, p.5). Hence, in a CEA, the strategy that produces the most optimal outputs at the lowest or acceptable cost is the most cost-effective strategy. Generally, CEAs are used by decision-makers who must choose between limited options and within a specific budget (Drummond et al., 2015, p.7).

Cost-utility analysis

CUA is described by Drummond et al. (2015, p. 8) as "a variant of CEA", and it is often referred to as a CEA. It has the same logic as a CEA, comparing the magnitudes of the same type of outcome. However, the consequences of CUA are all measured using the same generic measurement of health benefits, making it possible to compare health interventions in different healthcare sectors (Drummond et al., 2015, p. 8). To calculate health benefits, utilities for different health states are used. These utilities represent the value someone assigns to their present health state. For example, a person with light flu will probably assign a different utility to their current health state than a person with cervical cancer. These utilities are mostly calculated using surveys or questionnaires, and they range from 0, associated with being dead, to 1, representing perfect health. The most widely used measurement for CUA is quality adjusted life years (QALY), which is calculated by multiplying the utility someone gets from being in a particular health state with the time they spend in that state (Drummond et al., 2015, p.8). The results of CUA are usually reported as cost per QALY, making it easy for decision-makers to compare a wide range of interventions (Drummond et al., 2015, p.8).

Cost-benefit analysis

In a CBA, the consequences of intervention are expressed in monetary terms, allowing for a more obvious comparison between the costs and the consequences (Drummond et al., 2015, p. 10). Hence, in a CBA, consequences such as life years gained or QALYs are transformed into monetary values (Drummond et al., 2015, p. 10). the results of a CBA are expressed in the form of a ratio or a sum.

3.3 Decision modelling in economic evaluation

Decision modelling has become an important vehicle for economic evaluation, due to the features of an economic evaluation, which seek to inform decision-making (Briggs et al., 2006, p.6-7). Decision analysis is defined as “a formalized approach to making optimal choices under conditions of uncertainty.” (Muenning, 2017, p. 211). In economic evaluation, decision analytic models use complex mathematical relationships to evaluate the costs and outcomes that result from two or

more alternative interventions being compared. Decision models can either be microsimulation models, which consider variations between individual patients, or cohort models, which characterize experiences of an average patient from a cohort. The most common cohort models are described below

Decision tree

One of the most used models in economic evaluations is the decision tree. In such a model, there are a set of mutually exclusive pathways that an individual can take, each resulting in different costs and outcomes (Briggs et al., 2006, p.23). A decision tree often starts with a decision node, which separates the two health interventions being compared (Drummond et al., 2015, p. 329). The decision nodes are continued by branches, each representing a particular event a patient might experience (Drummond et al., 2015, p. 329). Branches can end in a chance node, which signals an important point of uncertainty in the model (Drummond et al., 2015, p. 329). Hence, the branches coming out of a chance node lead to very different consequences and costs. The likelihood that a patient will experience the event of a specific branch is referred to as the branch probabilities (Drummond et al., 2015, p. 329). Consequently, multiple branches form a pathway a patient might experience, depending on the pathway probabilities (Drummond et al., 2015, pp. 329-330). In such a model, different interventions can be compared by summing up the costs and consequences of each pathway and then assessing how the results for each strategy compare. *Figure 3* illustrates a hypothetical decision tree.

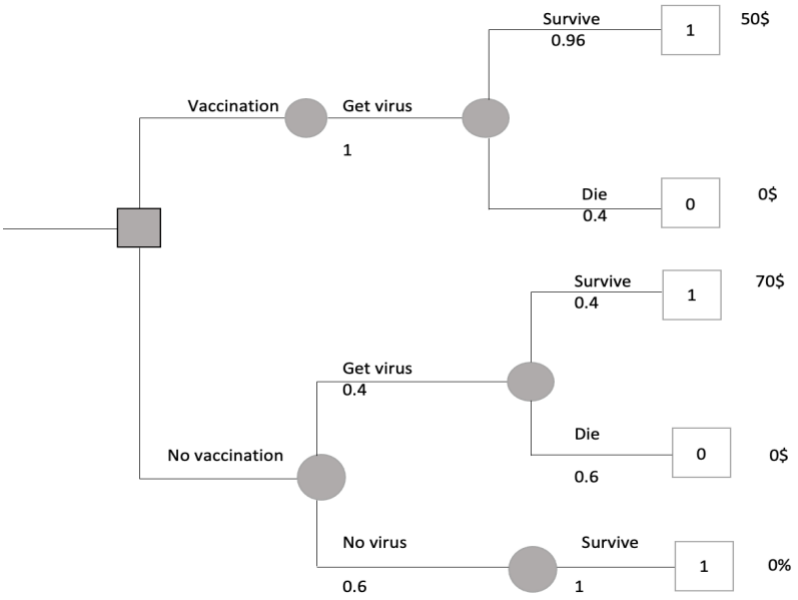

Figure 3: A hypothetical decision tree

While decision trees are very accessible, they also present some limitations. For example, time cannot be defined so simply in a decision tree. It is often assumed that the events happen instantly over an undefined period (Drummond et al., 2015,p. 331). Therefore, decision trees cannot be used for interventions in which time represents a crucial element. For example, one cannot use QALYs as a consequence because, in a decision tree, one cannot measure how much time a patient spends in one health state (Drummond et al., 2015, p. 331). Finally, it can be challenging to build decision trees for complex chronic diseases, as the tree will become very bushy (Drummond et al., 2015, p. 331).

Markov model

A Markov model resolves some of the limitations of the decision tree. First, this model is characterized by multiple health states a patient can be in at a specific time (Drummond et al., 2015, p. 331). Unlike a decision tree, in a Markov model, time plays an essential role in all events happening during a cycle (Drummond et al., 2015, 332). Cycles are defined as the probability of a patient being in a specific health state evaluated over a series of discrete time periods (Drummond et al., 2015, p. 332). Depending on the nature of the intervention studied, the researcher can choose how long they want their cycles to be, from one month to a year. Transition probabilities determine

how patients move between health states (Drummond et al., 2015, p. 332). Finally, each health state has certain costs and outcomes. In the case of QALYs, each state has a specific HRQoL weight (Drummond et al., 2015, p. 332). The final costs and outcomes are calculated depending on how long patients occupy the different states. A hypothetical Markov model is illustrated by *Figure 4.*

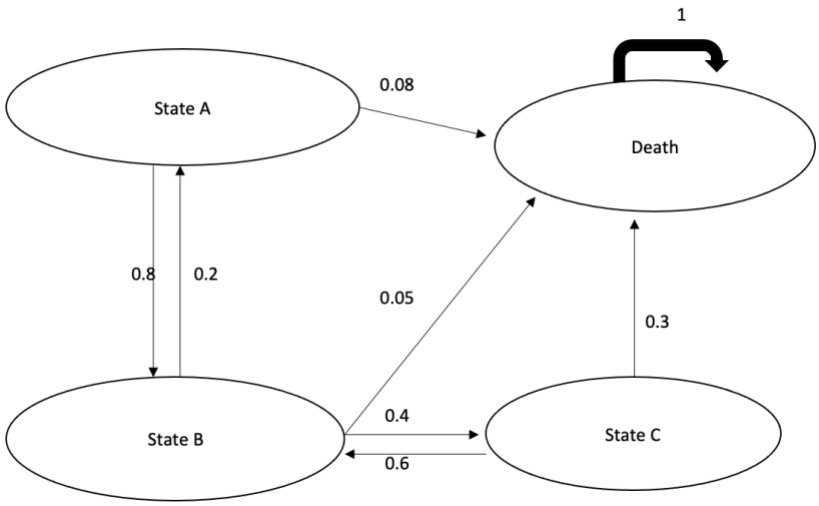

Figure 4: A hypothetical Markov model

Markov tree

A Markov tree, which has been used in this research, represents a combination between a decision tree and a Markov model (Drummond et al., 2015, p. 333). This model type has a decision tree structure, with chance nodes and branches representing different pathways. However, unlike a decision tree, a Markov tree has multiple health states that the simulated patients can transition between based on the transition probabilities. Moreover, it has a time dimension, with events happening only at the beginning of one cycle. Markov models are memoryless, meaning that the model cannot trace back a patient's trajectory between health states. The Markov tree also has possible costs and rewards or utility weights for each branch.

3.4 Measuring effectiveness

Measuring health benefits

As mentioned above, health and, consequently, health outcomes can be measured in different ways in economic evaluations. The first method is to collect data from clinical studies and measure the health gain produced by an intervention (Drummond et al., 2015, p.124). This type of measurement is useful for health interventions that have only one major objective. For example, a therapy intended to prolong one's life can be measured in life-years gained. Hence, this type of measurement can be helpful for decision-makers when they are choosing between health interventions in the same health field and with the same health objective (Drummond et al., 2015, p.124). However, interventions with different objectives cannot be compared using the measuring method (Drummond et al., 2015, p.124). For example, a treatment that measures its health outcomes in the number of severe asthma episodes cannot be compared with the intervention that measures life-years gained.

A second way of measuring health outcomes is by using a generic health measurement. This represents a comprehensive measurement as it does not only include the time a person spends in a health state but also the person's preference for being in that health state. QALY is the most used generic measurement of health. The quality of life can be measured for a specific health condition, such as asthma, or the general population (Drummond et al., 2015, p.126). the quality of life is usually measured through standardized surveys or questionaries administered to the population of interest.

Measuring costs

In health economic evaluations, costs are usually measured in monetary terms. However, what type of costs are included in an economic evaluation depends on the perspective adopted by the researchers. There are two main perspectives in healthcare evaluation: the provider and the societal perspective (Drummond et al., 2015, p. 219). The first one should include only costs that directly affect the provision of healthcare (Drummond et al., 2015, p.219). Hence, direct costs usually include the actual medical costs of an intervention, such as the cost of medical equipment and hourly medical wage.

A societal perspective is concerned with both direct and indirect costs. Hence, while it includes the direct medical costs, it also includes hidden costs that don't directly affect the healthcare provider as they are supported by the patient (Drummond et al., 2015, p. 219). For example, the cost the patient must pay on transportation to the hospital or the hourly wage the patient loses while being in the hospital.

Discounting

In the case of many healthcare interventions, including HPV screening, the health benefits are not always obtained at the current moment but in future periods. However, these interventions have costs at the present time. This is because these resources invested in the screening could have been invested in other parts of the economy that would offer an immediate positive rate of return (Drummond et al., 2015, p.108). Hence, costs in the near future have a higher value than those in the more distant future (Drummond et al., 2015, p.108). Therefore, there needs to be a common period where all costs can be expressed. Usually, costs are discounted to the present value based on the time they are inquired and discounted with a discount rate that reflects the real rates of return (Drummond et al., 2015, p.108).

ICER

Finally, a measurement of cost-effectiveness that was used in this research is the incremental cost-effectiveness ratio (ICER). The ICER is defined as the extra cost per another unit of effect from the more effective strategy (Briggs et al., 2006, p.5). It is calculated using the following formula:

$$\text{ICER}=\frac{Cost2-Cost}{Outcome2-Outcome1}$$

The way ICERs of different interventions are compared can be illustrated by the cost-effectiveness plane shown in *Figure 5* (Drummond et al., 2015, p.55). For example, if we have a base-case strategy named O and a competing strategy called A, we can tell which strategy has a dominant ICER depending on its position in the four quadrants. If the ICER of A is in quadrant II, it dominates strategy O, as it costs less and produces more health outcomes. However, the opposite is true if the ICER of A is quadrant IV. Then, strategy A is dominated by O as it costs more and

produces fewer health outcomes. If A is in quadrants I or III, the most cost-effective strategy depends on the decision maker's willingness to pay (Drummond et al., 2015, p. 55). For example, many countries, such as the United Kingdom, have an official state willingness to pay per QALY, which acts as guidelines for assessing intervention cost-effectiveness in healthcare. For example, the willingness to pay threshold in the United Kingdom is 20,000-30,000 pounds per QALY (Drummond et al., 2015, p.56). Hence, if strategy A is in the first quadrant and is below the WTP threshold, it can be regarded as the cost-effective choice.

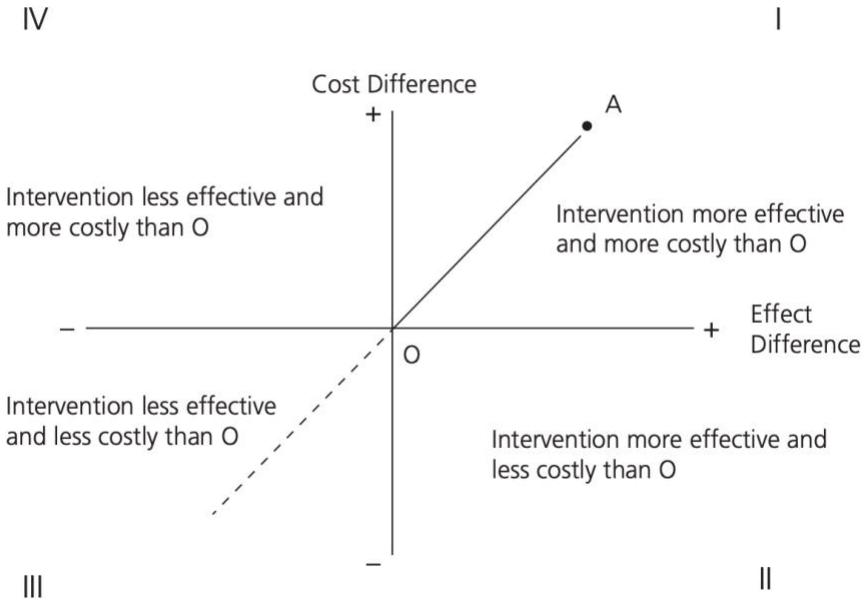

Figure 5:Cost-effectiveness plane (Source: Drummond et al., 2015, p. 55)

The WTP can be calculated in multiple ways depending on one's scope and resources and consequently it varies depending on the country. Hence, some countries have calculated official WTP threshold that is used by both researchers and policymakers. Where there is no official threshold, researchers guide themselves based on the ICER of interventions that have already been adopted. Finally, WHO recommends that the WTP is three times GDP per capita (Drummond et al., 2015, p.56).

3.5 Dealing with uncertainty

An essential feature of any economic evaluation model is uncertainty. Parameters such as costs and consequences can cause uncertainty in the model, as they might change and differ in real life. Consequently, the results of the study might not be accurate. For example, policy changes are frequently costly, as many resources are needed for structural change to happen (Drummond et al., 2015). Moreover, some changes might be irreversible or very expensive to change. Hence, uncertainty must be reduced as much as possible when making policy choices based on economic evaluations. To solve this issue, researchers must account for the study's uncertainty by performing different tests depending on the study's features.

Deterministic sensitivity analysis

A one-way sensitivity analysis is one of the most widespread methods of researching and presenting existing uncertainty. In this type of sensitivity analysis, each input parameter is varied one at a time to investigate its effect on the model outputs (Drummond et al., 2015, p. 393). In a one-way sensitivity analysis, the researcher varies the input parameter by a certain amount (Drummond et al., 2015, p. 393). For example, a parameter can be varied by the minimum and maximum values reported during data collection.

Probabilistic sensitivity analysis

PSA represents one of the most reliable methods of exploring parameter uncertainty. During a PSA, all parameters of interest are varied at the same time. When conducting a PSA, a statistical distribution is applied to all parameters, and then empirical distributions of the costs and consequences are generated by random sampling from the distributions (Drummond et al., 2015, p. 60). Hence, it is essential to assign the right type of distribution to each parameter. This should be an informed choice based on the nature of the parameter, how it was estimated, and the reported summary statistics (Drummond et al., 2015, p. 400). There are several statistical distributions that can be used in PSA. Two distributions that have been used in this are the gamma and beta distributions.

The gamma distribution is constrained to the interval of 0 and positive infinite and represents count data (Briggs et al., 2006, p.91). Because these are two of the main characteristics of costs, the gamma distribution is usually assigned to costs. In Amua and other software used for economic evaluations, the gamma distribution is parameterized as gamma (α,β) (Briggs et al., 2006, p.91). The α and β are defined by the following formulas:

$$\alpha=\frac{\bar{\mu}^2}{s^2} \; ; \quad \beta=\frac{s^2}{\mu}$$

The beta distribution has values between 0 and 1 and is characterized by the parameters α=r and β=r-n (Briggs et al. 2006, p. 87). Therefore, it is used for binominal data such as transition probabilities or utilities.

3.6 Expected Value of Perfect Information and Expected Value of Perfect Parameter Information

There is always a risk that even if we choose the best option given our current data, there is a chance that another option is more cost-effective once the uncertainty is eliminated (Briggs et al., 2006, p.170). Taking the wrong decision can result in both health and monetary costs. Hence, the probability of a wrong decision based on current data and the consequences of this decision determine the expected cost of uncertainty. The expected cost of uncertainty can be calculated with the estimated probability of error and the opportunity cost of error (Briggs et al., 2006, p.170). Because perfect information eliminates the probability of making the wrong decision, we can define the expected costs of uncertainty as the EVPI (Briggs, 2006, p.170). Therefore, the EVPI indicates the maximum value that can be gained from obtaining new information and reducing uncertainty. Hence, policymakers shouldn't pay more than the value of EVPI for acquiring new information.

The EVPPI is similar to the EVPI in the way it is calculated and interpreted. Once we know the EVPI, it is useful to know exactly which parameters might require further research and how much that should cost (Briggs et al., 2006, p.179). Therefore, it is calculated by subtracting the expected

value with the present information from the expected net-benefit with perfect information for the parameter (Briggs et al., 2006, p.180).

4. Methods and data

4.1 Analytical overview

A model was built using an existing mathematical model of the natural history of HPV, to estimate the cost-effectiveness of organized screening vs no screening for HPV in Romania. In each scenario, incremental costs and benefits were calculated to compare the two strategies. Costs were measured using euros, and health benefits were measured using QALYs. The provider perspective was adopted in this study, which includes only direct costs. Both the costs and the health benefits were discounted by 3%, as recommended by WHO (2003, p.71). Finally, a strategy was considered cost-effective if it presented an incremental cost-effectiveness ratio under the willingness to pay threshold of 50,000 euros per QALY. Because Romania does not have an official WTP threshold, the US threshold has been chosen as it is one of the most used thresholds in international research (Grosse, 2008). In this research, only the high-risk HPV strands are analyzed, as these are the most likely to develop into cervical cancer.

When running the Markov model, events are assumed to happen only at the cycle's beginning or end. This can lead to overestimating or underestimating costs and QALYs, as in real life, events can happen randomly at any point in the cycle (Naimark et al., 2013). A half-cycle correction can be applied to the model to fix this issue. When applying half-cycle correction, Amua sets the value of the cost or utility parameter to a half-cycle value (Naimark et al., 2013, p. 961).

4.2 Model description

A Markov tree was developed to simulate the natural history of high-risk HPV types, comparing the two strategies (Figure 1). There are 27 possible health states, each tree branch representing a possible event in the infection's development. The tree has two strategies: the baseline "No screening" and the competing alternative "Screening". A cohort of 10.000 women starting from age 16 until 100 was simulated. Each woman continuously moved throughout the model, according to the age-dependent transition probabilities, until they reached an end state. It was assumed that

at all times, the women were in one of the 27 health states. Each cycle lasted for one year, and the model's time horizon was a lifetime.

4.3 The natural history of HPV

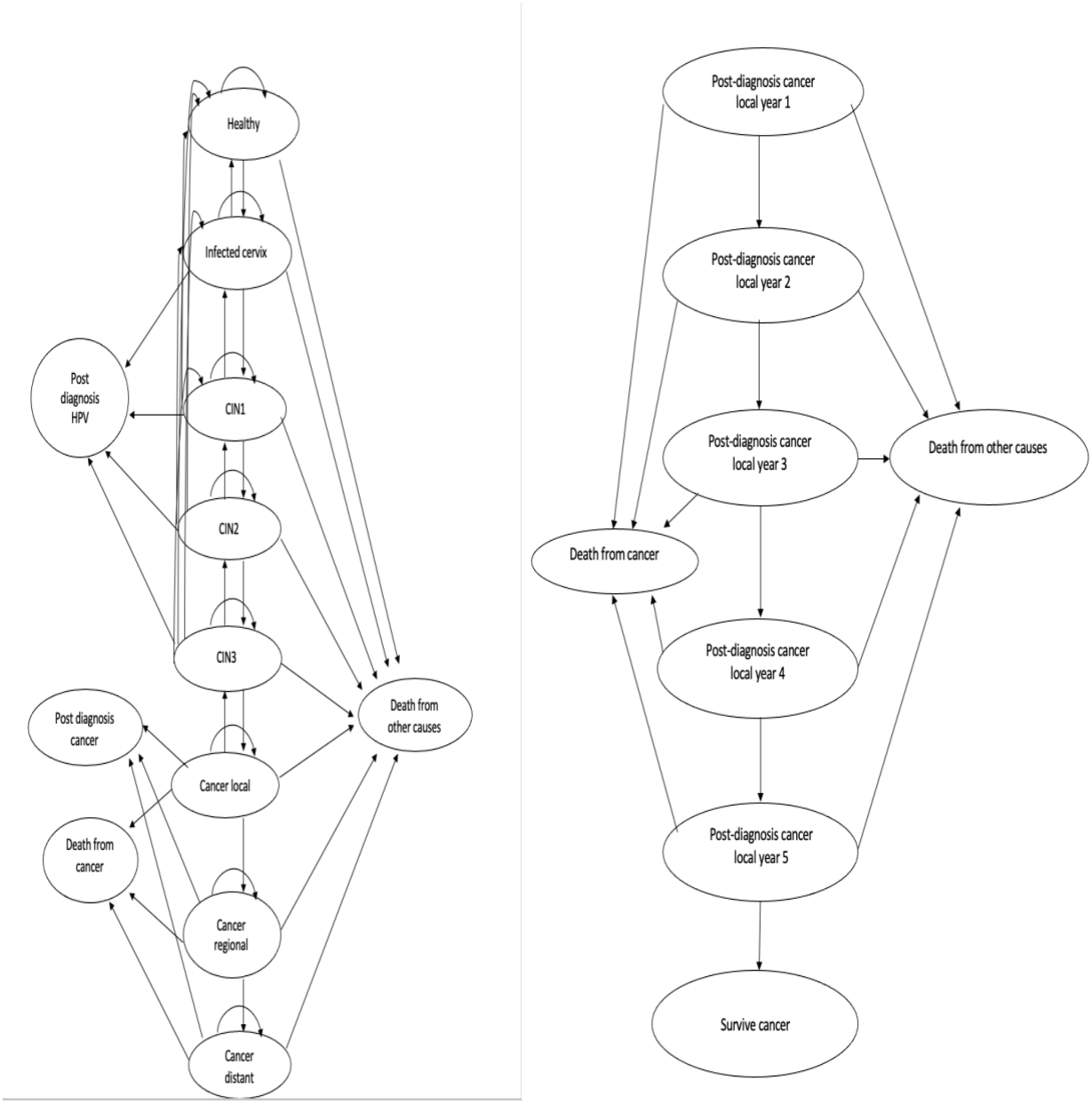

Fig.6A: Natural history of hrHPV strands Fig.6B:Tunnel state for the post-diagnosis cancer state
Figure 6

All women entered the model illustrated in *Figure 6A* at the age of 16 in the first health state, healthy. From this health state, they had an age-dependent probability of acquiring the HPV infection or remaining healthy. The three health states they could progress to were CIN1, CIN2 and CIN3. The women could progress or regress between these health states according to the age-specific probabilities. Probabilities were age specific because the HPV incidence and regression greatly depend on age. Finally, women could develop cancer, which was divided into three health states: local, regional, and distant. Once they entered this health state, they could not regress but only progress to the final three health states. Women with undiagnosed cancer were assumed to progress through the three cancer states until they died from cancer or other causes.

In both strategies, there was a chance that women could detect cancer through symptoms. Alternatively, in the "Screening" strategy, a woman could get screened and thus cancer could be detected. Once cancer was detected, women moved to one of the cancer post-diagnosis health states. These health states were modelled as tunnel states, which allowed us to add "memory" to the model (Briggs, 2006, p.58). In these reoccurring states, the rewards, costs and probabilities depended on the patient's history. For example, a patient with local cancer for two years might have a different mortality rate than one with cancer for four years.

If a woman was diagnosed with local cancer, she moved to the first year of local cancer post-diagnosis, illustrated in *Figure 6B.* It was assumed that she received the proper treatment for local cancer in this health state. If she did not die from cancer or other causes, she would progress to the state of second-year local cancer post-diagnosis. It was assumed that women could be in one of these health states for only one year, after which they moved to the next tunnel state or exited the model. This process could continue for a maximum of five years in this model.

The tunnel states are essential in capturing the effects of this study, respectively QALYs. The moment cervical cancer is detected is crucial for the quality and length of a patient's life. For example, if a woman detects her cancer in a local state, she will undergo a very different treatment. As a result, she will have much higher chances of survival and quality of life than if she detects her cancer in a distant stage.

The three final health states from which women could not return to the model: surviving cancer, death from other causes and death from cancer. Women entered the "survived cancer" health state if they survived five years while having cancer. Because the mortality rate from cancer decreases with time, the model only monitored the women for five years, after which they existed the model. They could not reenter the model because women diagnosed with cervical cancer must be monitored differently. In addition, some of them might undergo treatments such as cervix removal surgery that will not allow them to rejoin the "healthy" state.

4.4 The screening and treatment protocol

WHO (2021) recommend HPV DNA testing as the primary screening method, as it is the most efficient in detecting high-risk HPV types (World Health Organization, 2021). Given the current recommendations and the relevance of this method to the scope of this research, HPV DNA testing was used as the screening method in this model.

Since both the WHO and most European guidelines recommend starting HPV DNA screening at 30, this was also used as the starting age for this model (WHO, 2021; Wang et al., 2022). On the other hand, research is inconclusive on the best age to stop screening. While some research suggests that screening after 65 is no longer efficient, other studies show that women over 65 are just as likely as younger women to develop cervical cancer (Dilley et al., 2021). Since Romania is a European state, the European guidelines were followed (Wang et al., 2022). Hence, the screening stopped at 65 in the model.
Finally, both WHO and most European guidelines recommend screening with HPV DNA every five years (WHO, 2021; Wang et al., 2022). This practice was adopted in the model as well.

According to the current international screening guidelines, patients who receive a positive HPV DNA test will undergo a colposcopy (National Health Services, 2022; WHO, 2021). This model assumed that the colposcopy was 100% accurate and that all patients fully complied with the entire screening and treatment procedure. Hence, the women with a true positive test discovered their true health state after the colposcopy and underwent treatment.

Regarding the specificity and sensitivity of the HPV DNA test, results from various research differ. The values used in this paper are form Mustafa et al. (2016), who did a systematic literature review of the accuracy of three different HPV screening methods. By pooling together five different studies, they found an estimated sensitivity of 95% and specificity of 84% (Mustafa et al, 2016).

4.5 Data

The data for the transition probabilities were selected based on a literature review. Most probabilities in the model were chosen from the research done by Canfell & al. (2004) in the UK context. As younger women tend to have more HPV infections that regress without treatment, the probabilities from HPV infection to CIN and between different CIN stages were age dependent. The cancer detection and progression probabilities were from an existing mathematical model of the natural history of HPV infection (Campos et al, 2014).

Utility weights were used to calculate the QALY and were supposed to reflect the quality of life of a person in a certain health state. For example, in this model a healthy person had a utility weight of 1, while a death was assigned a 0 utility. Through utility weights we measured a person's quality of life, on a scale from 0 to 1, with 1 being healthy and 0 death. The value and source of the utility data are listed in *Table 1*.

Table 1. Utility parameters used in the model

Health state	Value of the utility weight	Source
Healthy	1	
Infected cervix	0.92	Ju X, Canfell K, Howard K, Garvey G, Hedges J, Smith M, et al. (2021)
CIN1	Age 16-40 : 0.9 Age 16-100: 0.91	Ju X, Canfell K, Howard K, Garvey G, Hedges J, Smith M, et al. (2021)

CIN2	0.9	Ju X, Canfell K, Howard K, Garvey G, Hedges J, Smith M, et al. (2021)
CIN3	0.9	Ju X, Canfell K, Howard K, Garvey G, Hedges J, Smith M, et al. (2021)
Cancer local	Age 16-40: 0.83 Age 41-100: 0.84	Ju X, Canfell K, Howard K, Garvey G, Hedges J, Smith M, et al. (2021)
Cancer regional	Age 16-40: 0.68 Age 40-100: 0.70	Ju X, Canfell K, Howard K, Garvey G, Hedges J, Smith M, et al. (2021)
Cancer distant	Age 16-40: 0.68 Age 40-100: 0.70	Ju X, Canfell K, Howard K, Garvey G, Hedges J, Smith M, et al. (2021)
Survive cancer	0.74	K. Robin Yabroff, William F. Lawrence, Steven Clauser, William W. Davis, Martin L. Brown (2004)
Post diagnosis HPV Infection	0.95	
Death	0	

As this research adopts a healthcare perspective, only direct medical costs were used in the base-case. Therefore, the costs reflect the final value of an HPV DNA test, a colposcopy, HPV infection treatment and cancer treatment.

After a literature search no official data on medical costs were found. Therefore, costs for the HPV DNA test, the colposcopy and the conization procedure were taken from private hospitals. The cheapest price was selected but most hospitals have the same prices with differences being of maximum 10 euros. This was considered to be a suitable substitute given lack of official data, as

in Romania private and public hospitals work in a hybrid regime, with the national insurance covering some services offered by private clinics.

Moreover, no official information exists on the cost of treating cervical cancer in Romania. The only information on this subject comes from the study "Povara cancerului in Romania si impactul sau asupra economiei" by Clara Volintiriu, presented at the conference "Health- a source of competition: Investing in the sanitary system and the benefits of healthy life to the economy." (Bechir, 2021). According to this study, treatment of a cancer patient costs at least 10.000 ron which is approximately 2026 euros. Because as cancer progresses, the costs of treatment also increase, 1000 euros was added to each cancer stage.

The price for the HPV DNA test and the cancer treatment in scenarios two and four are taken from Swedish healthcare system (Fogelberg et al., 2020). The productivity loss from dying prematurely of cancer in Romania is 51,683 euros (Hanly & Soerjomataram, 2022).

Table 2. Overview of costs

Cost of	Value of cost (in euros)
HPV DNA test	65
Colposcopy	96
Conization for HPV infection	49
Treatment for local cancer	2,026
Treatment for regional cancer	3,026
Treatment for distant cancer	4,026
HPV DNA test (scenarios two and four)	26
Treatment for local cancer (scenario four)	27,579
Treatment for regional cancer (scenario four)	52,774
Treatment for distant cancer (scenario four)	62,925
Premature mortality cost	51,683

Age-dependent mortality rates for women in Romania were taken from Eurostat (2023), the main European organization responsible for gathering official data for EU states. To adapt the model to

the Romanian context, the HPV prevalence was taken from the study by Ilisiu et al. (2019), in which the overall high-risk HPV prevalence for all age groups was 16.9%. In addition, the study includes women of different ethnicities from multiple regions of the country, being representative data for the entire country.

4.6 Scenario analysis

Because most costs are not from official studies, we wanted to test how uncertainty can impact and change the results. Hence, four different scenarios were analyzed to comprehensively understand the "Screen" strategy's cost-effectiveness. Firstly, the base-case scenario was run using only the direct costs with the values found at the present moment for Romania.

Secondly, after a literature search, it was found that countries with organized screening have lower HPV DNA test prices, even if these countries are economically more developed than Romania. This can be explained through the market economy. Because a state buys a large amount of tests, the cost per test becomes lower. Moreover, wages in private hospitals tend to be higher than in public ones, driving the price of the test up. So, a scenario with a lower price per test was simulated.

In the third scenario, the productivity loss from dying prematurely from cancer was added, to show the societal impact. Productivity losses were not added in the initial base-case analysis as it may be argued that use of such indirect costs in CEA can be unfair and inequitable, as older or retired people generally present a lower value than younger people actively working. Therefore, it would make health interventions for older people less cost-effective than for younger people, creating discriminatory results.

However, productivity losses have an important impact on the healthcare system, as taxes primarily fund health in Romania. Moreover, studies show that cervical cancer is mainly developed between the ages of 30 and 50, and the screening will stop at age 65 (Montalvo et al., 2011, p. 701). In Romania, the retirement age for women is 61. Hence, these represent ages when most people are active at the workplace and in society (European Commission). Therefore, it seems that

productivity losses from premature death can significantly impact the cost-effectiveness of cervical cancer screening, and to explore this potential impact, it was included in this scenario.

Lastly, in the fourth scenario, the cost of the HPV DNA test has a lower value, while the cost of treating cancer has a higher value. The productivity loss from premature cervical cancer death was also added. As discussed in the data section on page X, official cost data is not available. However, previous studies in other countries, such as Sweden, did show that treating cancer is significantly more expensive than what has been assumed based on the available data for Romania. Because of such a significant economic difference between Romania and countries like Sweden, these costs were not used in the base-case scenario. However, this scenario will be run to explore how higher cancer treatment costs, productivity losses, and lower test costs from organized screening would affect the ICER.

4.7 Sensitivity analyses and EVPI

This paper has drawn data on all the parameters from multiple sources, making sensitivity analysis the appropriate solution. During a sensitivity analysis, the different parameters are varied to assess their impact on the results (Drummond, 2015, p.57). In this paper multiple one-way sensitivity analyses and a PSA were carried out. For the one-way sensitivity analysis, the cost parameters were varied +/-50%, while the prevalence, sensitivity and specificity were varied with the minimum and maximum values reported by the source research. In this case of the PSA, the Gamma distribution was applied for the cost parameters, as this is a discrete and always positive type of data. Because the transition probabilities and the utility weights represent binominal data, the Beta distribution was assigned. Each probability parameter was assigned a value between 0 and 1.

The EVPI informs us on how much more economic benefits we could earn by acquiring more information and reducing the uncertainty in the model. It also indicates the maximum amount that should be spend on future research. It is calculated using the estimated probability of error and the opportunity cost of error (Briggs, 2006, p.170). The EVPPI is similar to the EVPI in the way it is

calculated and interpreted, but it only informs us about the benefits and costs of acquiring more information for a specific parameter.

4.8 Software

The software used to create and run the model is called Amua. It is a free software described as being “an open-source modeling framework and probabilistic programming language” (Ward, 2019).

5. Results

5.1 Base-case scenario

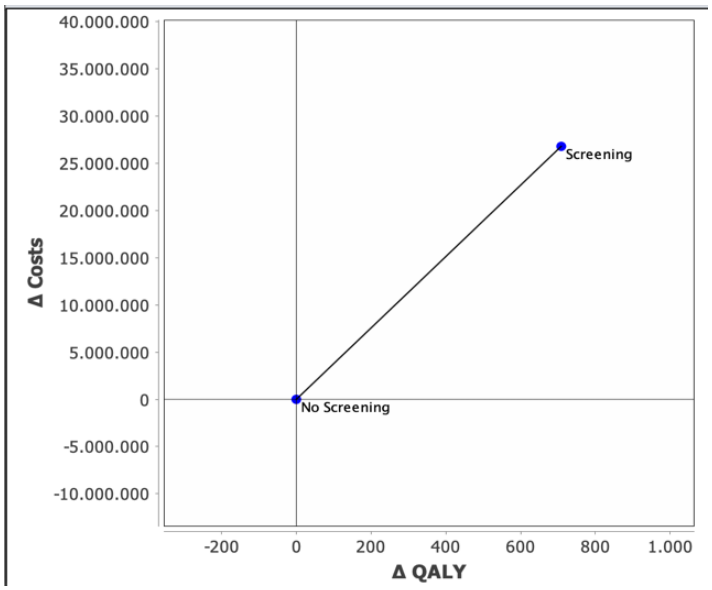

Figure 7: Base-case cost-effectiveness analysis

Table 3 and *Figure 7* show the results of the base-case scenario. The "Screening" strategy has significantly higher costs than the "No screening" strategy. It costs 2700 euros per woman in a lifetime, while the "No screening" strategy costs 6,38 euros per woman. However, the "Screening" strategy also produces more QALYs than its comparator. While the baseline strategy produces 26,5067 QALYs per woman, the alternative strategy produces 26,5775 QALYs. Therefore, this scenario has an ICER of 37,829 euros, which is below the 50,000 euros threshold.

Table 3. Base-case cost-effectiveness analysis

Strategy	Cost (euros)	Cost per woman	Incremental cost (I.C.)	Outcome (QALYs)	QALYs per woman	Incremental outcome (I.O.)	Cost Effectiveness Ratio	ICER (I.C./I.O.)
No screening	63,800	6,38		265,067	26,5067		0,24069386	
Screening	27,000,000	2,700	26,936,200	265,775	26,5775	708	101,589691	37,829

5.2 Scenario two

The second scenario has the same parameters as the base-case, but a lower HPV DNA test price. For this scenario, the cost of the "Screening" strategy is 2560 euros per woman, while the "No screening" cost remain 6,38. The QALY results are still 26,5067 per woman for the baseline strategy and 26,5775 for the competing strategy. The ICER is 35,342.

Table 4. Scenario analysis – lower HPV DNA price

Strategy	Cost (euros)	Cost per woman	Incremental cost (I.C.)	Outcome (QALYs)	QALYs per woman	Incremental outcome (I.O.)	Cost Effectiveness Ratio	ICER (I.C./I.O.)
No screening	63,800	6,38		265,067	26,5067		0,24069386	
Screening	25,600,000	2560	25,536,200	265,775	26,5775	708	96,3220769	35,342

5.3 Scenario three

The third scenario has the same parameters as the base-case one, but we added the productivity loss from premature cervical cancer death. In this case, the "No screening" strategy has lower costs

than the “Screening”, respectively, 2000 and 3400 euros per woman and per lifetime. However, “Screening” produces 26,5775 QALYs per women, while “No screening” produces 26,5067 QALYs. The ICER in this scenario is 20,039 euros, still under the WTP threshold.

Table 5. Scenario analysis – inclusion of productivity losses

Strategy	Cost (euros)	Cost per woman	Incremental cost (I.C.)	Outcome (QALYs)	QALYs per woman	Incremental outcome (I.O.)	Cost Effectiveness Ratio	ICER (I.C./I.O.)
No screening	20,000,000	2,000		265,067	26,5067		75,4526214	
Screening	34,000,000	3,400	14,000,000	265,775	26,5775	708	127,927758	20,039

5.4 Scenario four

In the final scenario a lower price for the HPV DNA test was assumed, higher costs for treating cancer and the productivity loss from premature cancer death was included. The costs for “No screening” were 2900 euros per woman in a lifetime, while for the “Screening” strategy it was 3800 euros. The outcomes stayed the same as in the other scenarios. Finally, the ICER is 13,310 euros, which is under the 50,000 euros threshold.

Table 6. Scenario analysis: higher treatment costs plus productivity losses

Strategy	Cost (euros)	Cost per woman	Incremental cost (I.C.)	Outcome (QALYs)	QALYs per woman	Incremental outcome (I.O.)	Cost Effectiveness Ratio	ICER (I.C./I.O.)
No screening	29,000,000	2,900		265,067	265,067		109,406301	
Screening	38,000,000	3,800	9,000,000	265,775	26,5775	708	142,978083	13,310

5.5 One-way sensitivity analysis

Table 7 presents the results of one-way sensitivity analysis for the input parameters. All parameters led to a change in the ICER. Parameters such as the cost of local and distant cancer treatments had relatively low changes in the ICER, while the cost of the colposcopy resulted in the biggest ICER range, with a difference of 150% between the minimum and the maximum value.

Table 7. Results from one-way sensitivity analysis

Parameter name	Base estimates	ICER
Prevalence	16.9%	33,500-37,200 (10.4 %)
Sensitivity	95%	34,800-37,400 (7.47%)
Specificity	84%	28,000- 43,000 (54%)
Cost test HPV DNA	65	35,345-35,420 (0.21%)
Cost colposcopy	97	20,000-50,000

		(150%)
Cost HPV conization	49	35,340-35,430 (0.40%)
Cost treatment cancer local	2026	35,355-35,415 (0.17%)
Cost treatment cancer regional	3026	30,500-35,500 (16,39%)
Cost treatment cancer distant	4026	35,370-35,396 (0.07%)

5.6 Probabilistic Sensitivity Analysis

Figure 8 is the cost effectiveness acceptability curve which presents the result of the PSA. Axis X shows the range of values for WTP thresholds starting from 0 to 140,000 euros, while Axis Y shows the probability that a strategy is cost effective, from 0 to 1 being the most effective. It can be seen that the higher the WTP, the more cost effective the "Screen" strategy is. It seems that starting from the threshold of around 70,000 euros, the "Screen" strategy is the cost effective one, reaching its maximum efficiency around the threshold of 140,000 euros. *Figure 8* shows that for a WTP threshold of 50,000 euros, the "No screening" strategy has higher chances of being cost-effective.

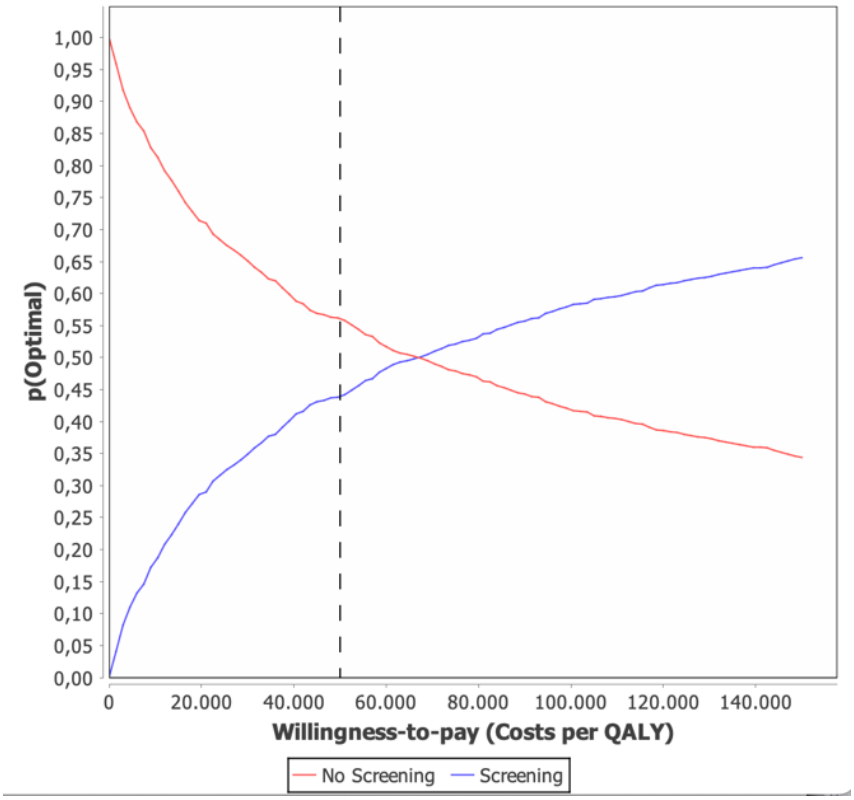

Figure 8: CEAC

5.7 EVPI and EVPPI

The EVPI of this study is 20 million euros. *Figure* 9 shows the information (EVPPI) for the cost parameters. The EVPPI for local cancer treatment is 8,089,880 euros. For the cost of regional cancer, it is 7,365,321 euros and for distant cancer it is of 6,666,112 euros. The cost of the HPV DNA test has an EVPPI of 6,709,016, while the cost of the conization intervention is 5,982,388. The colposcopy presents the highest value of 10 million euros.

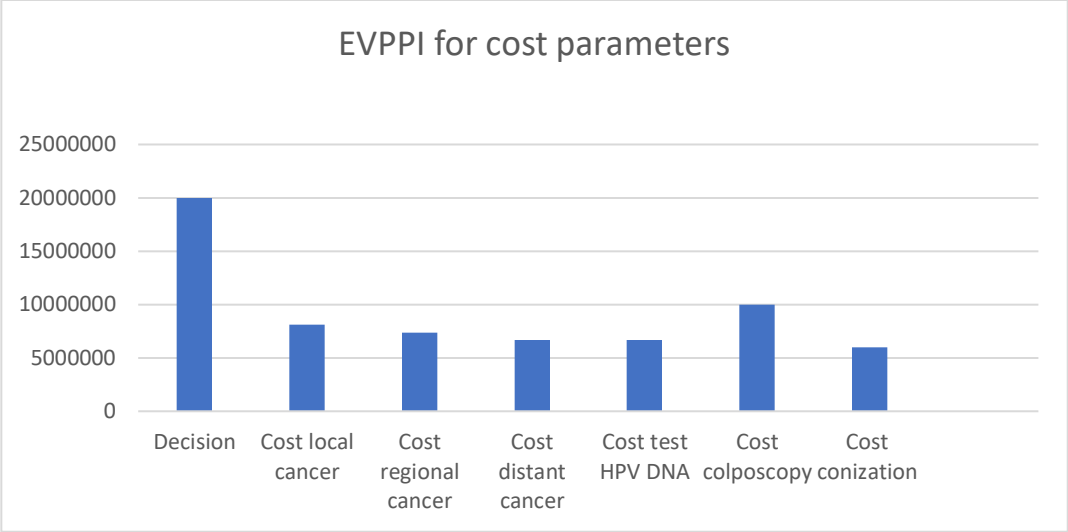

Figure 9: EVPPI results

6. Discussion

The CEA shows that screening with the HPV DNA test is cost-effective, presenting an ICER below the 50,000 WTP threshold in all the scenarios. Moreover, if we would used the method recommended by WHO to calculate the WTP threshold, for Romania it would be 44,000 euros. Hence, the ICERs would still be under our WTP threshold. These results seems to align with the recommendation of WHO and confirmed studies that found it to be one of the most cost-effective strategies (Goldie, Kim & Wright, 2004; Kim, Wright & Goldie, 2005; Andrés-Gamboa et al., 2008). The difference between the ICERs in the scenarios shows how essential it is to have exact cost measurements. Just by reducing the test cost, the ICER fell by 2487 euros. The CEA confirmed the assumption that productivity losses have an important effect on the ICER, as the ICER was substantially lower in both the third and fourth scenarios. The last scenario presented the lowest ICER of 13,310, indicating that HPV DNA testing can be more cost-effective than in the base case scenario if the test price is lowered, productivity losses are accounted for and the full costs of cancer treatment are considered. Moreover, when running the 10.000 women cohort, the "No screening" strategy resulted in 44 deaths from cervical cancer, while the "Screening" strategy led to 16 cancer deaths. Hence, introducing "Screening" led to the prevension of 28 deaths in our cohort.

For our threshold of 50,000 euros, there is a low probability of around 45% of HPV DNA testing being cost-effective. Moreover, at that threshold, there is a higher probability of the "No Screening" strategy being cost-effective, almost 60%. As the WTP increases, so does the cost-effectiveness of HPV DNA testing, becoming the dominant strategy around the threshold of 70,000 euros. However, this WTP might be too costly for Romanian society. Overall, the CEA and PSA combined results indicate that HPV DNA testing can be a cost-effective strategy, depending on one's WTP.

The one-way sensitivity analysis showed varying levels of uncertainty in the parameters. Some parameters, such as cancer treatment costs, produce relatively few changes in the ICER. In comparison, the cost of colposcopy and the specificity had a very big impact on the ICER, implying that more data and research is needed. This is also supported by the results of the EVPI and EVPPI,

which shows that more accurate information could bring benefits of 20 million euros. Moreover, there are high additional benefits to getting more accurate information on each cost parameter.

6.1 Implications for policy and further research

This research indicates that HPV DNA testing could be cost-effective for Romania, depending on the WTP. This threshold was chosen based on past international studies, but this varies greatly depending on a country's economy and healthcare system. Therefore, further research to determine a suitable WTP for Romania could significantly impact researchers' and policymakers' recommendations and decisions.

Moreover, the different scenarios showed that the value of the costs greatly influences the cost-effectiveness of the "Screening" strategy. Hence, future research must be carried out on the exact value of the medical costs to reduce uncertainty and find the most cost-effective screening strategy for Romania. For example, introducing higher cancer treatment costs in the fourth scenario reduced the ICER. Hence, further research reporting the exact cost of cervical cancer treatment in Romania would allow for developing less uncertain CEA studies. Furthermore, the EVPPI results also showed additional value in obtaining more information, and data such as cancer treatment can be obtained in the same study, reducing the costs of obtaining information.

Accounting for indirect costs caused a significant change in the ICER. Because of the nature of HPV, which mainly affects young women, it seems crucial to consider these types of costs as well when analyzing the cost-effectiveness of HPV-related interventions. Therefore, future research that includes a societal perspective as well should be done.

Finally, it could be investigated if a different screening protocol would be more cost-effective. For example, perhaps the Pap test might be a better choice for Romania, as it is more affordable or a co-screening strategy with HPV DNA testing, and the Pap test could be examined. Moreover, the government has announced new measures for increasing vaccination rates (Pratama, 2023). Hence,

a new generation of vaccinated women might require a new screening protocol. Further research can clarify which screening protocol would be the most cost-effective for a population with high HPV vaccination rates.

6.2 Related research

Results from related research in Eastern Europe have shown that HPV DNA testing is usually cost-effective when combined with another prevention method, such as the Pap test or vaccination. For example, A CEA of different screening protocols in Slovenia have found a combination of the Pap test and HPV DNA testing after 30 to be the most cost-effective choice (Jansen et al., 2021). The protocol studied in this paper was the second-best option with an ICER of 45,406 euros with HPV DNA testing every five years from the age of 30 until 65. Similarly, a study focusing on Central and Eastern Europe found that the most cost-effective prevention strategy in countries like Poland is vaccination combined with an HPV DNA test every ten years (Berkhof et al., 2013). However, de Kok et al. (2012) studied the cost-effectiveness of HPV screening in different scenarios and found that primary cytology is more cost-effective for countries like Romania, with lower resources.

Overall, this study's results seem to align with the existing studies in the region, indicating that HPV DNA testing could be cost-effective depending on the resources available. Furthermore, cytology screening could also be effective on its own or in combination with HPV DNA; as stated above, more research is needed on the data and the different screening scenarios.

6.3 Limitations

There are a few limitations to this research that need to be taken into consideration. First of all, the costs are not from an official data source. The actual costs of treating cervical cancer are probably much higher in reality than the ones used in the base-case scenario, especially in the regional and distant stages. However, Romanian Government officials have unveiled plans to establish a National Cancer Register in 2024, which may include official cervical cancer costs, enabling more certain future research (Lazar, 2023).

Secondly, the medical costs in the base-case scenario come from analyzing private clinics' prices and not from public hospitals. Therefore, even if the costs can be similar, it is still uncertain what the exact costs are in a public hospital. For example, with organized screening, the state could buy substantial amounts of tests that can significantly lower the price of each test. Hence, obtaining more accurate data would reduce the uncertainty in the model, giving a more precise answer on the most cost-effective strategy for HPV screening in Romania.

A third limitation of this study is that there is not 100% compliance with the screening and treatment procedure in real life. Patients often don't get screened or comply with the treatment scheme because they find the costs or effort too much. For example, coming to the doctor's office could require a day off work or hiring someone to look after their children. Therefore, it might be that the QALYs have a different value if not all women comply. Still, the state can ensure a high compliance rate by educating women and giving them incentives such as paid holidays to get screened. For example, in Stockholm, sending women self-testing HPV kits at home led to an increase of 10% in screening compliance (World Health Organization, 2022).

Fourthly, in this model, the screening in the "No screening" strategy was assumed to be 0%. However, in real life, people engage in opportunistic screening by getting screened privately. Previous studies have shown that this type of screening can cause harm and makes all screening less cost-effective, as it does not promote equity and has no quality assurance (Arbyn et al., 2009). Consequently, implementing an organized screening protocol can make the strategy studied here even more cost-effective (Jansen et al., 2021, p.125).

Finally, the utility weights for being in an HPV-related health state were used in both strategies. However, this does not accurately reflect reality, as people in the "No screening" strategy do not have any symptoms before developing cancer. Hence, in reality, they would not present the HPV-related utility weight. To perfect the conceptualization of the health utility, further research needs to be done on the health utilities of the general Romanian population and the population affected by HPV.

6.4 Strength of the research

Despite its limitation, this research does fill a gap in the literature, as there are no economic evaluations of HPV screening in Romania. Furthermore, as discussed in the introduction, Romania is an extreme case in the EU, with a big HPV incidence and cervical cancer mortality. Therefore, it is important to start researching this subject and find the most fitting solutions. This research does offer insight into the HPV situation in Romania and the feasibility of HPV DNA testing in different scenarios. Moreover, this paper identified topics of future research that are essential for carrying out future economic evaluations.

7. Conclusion

To conclude, HPV is a viral infection that affects women all over the world. In Romania, it is a significant public health concern as its link to cervical cancer causes a high mortality rate. However, this mortality can be prevented through screening and vaccination, as practices in other EU countries have shown. The results of this paper have shown that HPV DNA testing can be the cost-effective choice for Romania, depending on the available resources and the WTP of decision-makers. Still, there is uncertainty in the model which indicates that further research is needed, especially on the data. Because policy change is expensive, it should only be made based on accurate data and precise research results. Hence, in this situation, there is much value in obtaining more information.

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Appendix

1.Table with the transition probabilities used in the model taken from the study by Canfell et al. (2004).

Parameter	Annual probability		Reference
Healthy to HPV infected cervix	16-19 20-24 25-29 30-34 40-49 50+	0.0855 0.2500 0.1500 0.0576 0.0333 0.0222	Barnabas and Garnett, 2004; Schiffman and Kjaer, 2003; Melkert et al, 1993
HPV infected cervix to healthy	16-29 30+	0.7000 0.4130	Myers et al, 2000; Hildesheim et al, 1994; Moscicki et al, 1998; Koutsky et al, 1992; Ho et al, 1998; Molano et al, 2003
HPV infected cervix to CIN1 or CIN2	0.0959		Myers et al, 2000; Moscicki et al, 1998
CIN1 to HPV infected cervix	16-34 35+	0.2248 0.1124	Myers et al, 2000; Yokoyama et al, 2003; Syrjanen et al, 1992; de Brux et al, 1983
CIN1 to CIN2	16-34 35+	0.0297 0.1485	de Brux et al, 1983; Syrjanen et al, 1992; Myers et al, 2000
CIN1 to CIN3	0.0301		Yokoyama et al, 2003
CIN2 to HPV infected cervix or healthy	0.1901		Yokoyama et al, 2003
CIN2 to CIN1	0.2430		Syrjanen et al, 1992
CIN2 to CIN3	16-34 35-44 45+	0.0389 0.0797 0.1062	Syrjanen et al, 1992; de Brux et al, 1983; Yokoyama et al, 2003
CIN3 to HPV infected cervix or healthy	16-44 45+	0.0135 0.0100	Syrjanen et al, 1992
CIN3 to CIN1	0		Canfell et al., 2004
CIN3 to CIN2	0.0135		Canfell et al., 2004
CIN3 to cancer	0.0099		Syrjanen et al, 1992; Ostor, 1993; McIndoe et al, 1984
Symptom detection local cancer	0.0174		Campos et al, 2014
Local cancer to regional cancer	0.020		Campos et al, 2014
Symptom detection regional cancer	0.0735		Campos et al, 2014

Regional cancer to distant cancer	0.025	Campos et al, 2014
Symptom detection cancer distant	0.1746	Campos et al, 2014

2. Table showing cancer mortality from the study by Campos et al. (2014)

Cancer type	Per year	Probability	Reference
Local cancer	Year 1 Year 2-3 Year 4-5	0.0016 0.0014 0.0009	Campos et al, 2014
Regional cancer	Year 1 Year 2-3 Year 4-5	0.0095 0.0078 0.0036	Campos et al, 2014
Distant cancer	Year 1 Year 2-3 Year 4-5	0.0293 0.0195 0.0076	Campos et al, 2014

3. Table with mortality rates for women in Romania taken from Eurostat (2023)

Age	Mortality rate
16	0.00021
17	0.00021
18	0.00022
19	0.00032
20	0.00038
21	0.00045
22	0.00032
23	0.00027
24	0.00025
25	0.00032
26	0.00030
27	0.00029
28	0.00049
29	0.00050
30	0.00072
31	0.00057
32	0.00073

33	0.00078
34	0.00076
35	0.00075
36	0.00098
37	0.00106
38	0.00114
39	0.00105
40	0.00136
41	0.00168
42	0.00176
43	0.00195
44	0.00228
45	0.00234
46	0.00287
47	0.00303
48	0.00329
49	0.00382
50	0.00390
51	0.00449
52	0.00457
53	0.00581
54	0.00572
55	0.00677
56	0.00733
57	0.00815
58	0.00927
59	0.00972
60	0.01131
61	0.01177
62	0.01309
63	0.01481
64	0.01587
65	0.01710
66	0.01856
67	0.01962
68	0.02165
69	0.02508
70	0.02724
71	0.02990

72	0.03320
73	0.03549
74	0.03982
75	0.04628
76	0.04839
77	0.05731
78	0.06131
79	0.06978
80	0.07652
81	0.09138
82	0.09849
83	0.11033
84	0.12599
85-100	0.19987