CHARLES UNIVERSITY

FACULTY OF SOCIAL SCIENCES

Institute of Economic Studies

Bachelor's Thesis

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Is women's vaccination against HPV in the Czech Republic cost-effective?

Bachelor's Thesis

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Study programme: Economics and Finance

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Year of the defence: 2021

Declaration

1. I hereby declare that I have compiled this thesis using the listed literature and resources only.
2. I hereby declare that my thesis has not been used to gain any other academic title.
3. I fully agree to my work being used for study and scientific purposes.

In Prague on 27th of July 2021 Martina Lušková

References

Lušková, M. (2021) *Is women's vaccination against HPV in the Czech Republic cost-effective?* Praha. 54 pages. Bachelor's thesis (Bc). Charles University, Faculty of Social Sciences, Institute of Economic Studies. Supervisor Mgr. Lenka Šlegerová

Length of the Thesis: 56,122 characters with spaces

Abstract

This thesis approaches the cost-effectiveness of women's vaccination against human papillomaviruses (HPV) in the Czech Republic. HPV is a pathogen responsible for the majority of diagnosed cervical carcinomas. The aim is to assess the current reimbursement setting of HPV vaccination compared to the designed change. In order to increase the vaccination coverage and subsequently decrease the future treatment costs, two strategies were proposed. A homogenous multistate Markov model is developed to model the transition among states representing the stages of progression of the cervical carcinoma. Transition analysis is performed based on the data collected for the purpose of healthcare reimbursement under public health insurance. The incremental cost-effectiveness ratio suggests that increased immunization coverage (from 65.8% to 80%) fuelled by the campaign promoting vaccination seems to be cost-effective assuming the threshold of 1.2 million CZK per one quality-adjusted life year. The strategy promoting the vaccination together with extending the age (from thirteen-year-olds by cohorts of fourteen- and fifteen-year-olds) at which vaccination is reimbursed delivers analogous outcome. The main setback of the thesis is that the data for the purpose of reimbursement and not data from the clinical register were used. Thus, the epidemiological situation in the Czech Republic was not reflected precisely. Despite the limitations, the increased immunization coverage of women's vaccination against HPV appears to be cost-effective and therefore, the corresponding policy change should be implemented.

Keywords

Cost-effectiveness, Markov model, HPV, vaccination, cervical carcinoma, women, Czech Republic

Abstrakt

Táto práca sa zaoberá nákladovou efektivitou očkovania žien proti ľudským papilomavírusom (HPV) v Českej republike. HPV je patogén zodpovedný za väčšinu diagnostikovaných prípadov rakoviny krčka maternice. Zámerom je posúdiť súčasné nastavenie úhrady očkovania proti HPV v porovnaní s navrhovanou zmenou. S cieľom zvýšiť preočkovanosť a následne znížiť budúce náklady na liečbu boli navrhnuté dve stratégie. Na modelovanie prechodu medzi stavmi predstavujúcimi stupne progresie rakoviny krčka maternice je vyvinutý homogénny viacstupňový Markov model. Analýza prechodov medzi stavmi sa vykonáva na základe dát zhromaždených na účely úhrady zdravotnej starostlivosti z verejného zdravotného poistenia. Koeficient prírastkovej efektivity nákladov naznačuje, že zvýšená preočkovansť (zo 65,8% na 80%) podporovaná kampaňou propagujúcou očkovanie sa javí ako nákladovo efektívna pri predpoklade prahovej hodnoty 1,2 milióna CZK na jeden rok získaného života štandardizovanej kvality. Stratégia propagujúca očkovanie spolu s rozšírením veku (z trinástich o kohorty štrnásť a pätnásťročných), pri ktorom sa očkovanie uhrádza, prináša analogický výsledok. Hlavným problémom práce je, že boli použité dáta na účely úhrady a nie dáta z klinického registra. Epidemiologická situácia v Českej republike teda nebola reflektovaná presne. Napriek obmedzeniam sa zvýšená preočkovanosť žien proti HPV javí ako nákladovo efektívna, preto by sa príslušná zmena úhrady pre toto očkovanie mala uskutočniť.

Klíčová slova

Nákladová efektivita, Markův model, HPV, vakcinace, rakovina děložního čípku, ženy, Česká republika

Název práce

Je očkování žen proti HPV v České republice nákladově efektivní?

Acknowledgement

I would like to express my gratitude to Mgr. Lenka Šlegerová for her professional insights, valuable guidance, advice, and support, which she has provided throughout writing this thesis. Without her, the thesis would not be completed.

Additionally, I would like to thank my family and friends for the provided support.

Table of Contents

List of Tables

List of Figures

Acronyms

CIN	Cervical intraepithelial neoplasia
ČPZP	Czech Industry Health Insurance Fund, CR
CR	Czech Republic
ČSÚ	Czech Statistical Office
CZK	Czech crown
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FIGO	International Federation of Gynaecology and Obstetrics
GCO	Global Cancer Observatory
HG SIL	high grade squamous intraepithelial lesion
HPV	Human papillomavirus
HRQoL	Health-related Quality of Life
ICER	Incremental Cost-effectiveness Ratio
LG SIL	low grade squamous intraepithelial lesion
NICHSR	National Information Centre on Health Services Research and Health Care Technology
NOR	National Cancer Register, CR
NRHZS	National Register of Reimbursed Health Services, CR
NSC	National Screening Centre
NZIS	National Health Information System, CR
OZP	Occupational Health Insurance Company for Employees of the Banking, Insurance and Building Industry, CR
PAP test	Papanicolaou test
QALY	Quality Adjusted Life Year
RBP	Coalfield Brotherhood Cash Office, a health insurance company, CR
SÚKL	State Institute for Drug Control, CR
TNM	tumour, nodes, and metastases
ÚZIS	Institute of Health Information and Statistics of the Czech Republic
VoZP	Military Health Insurance Fund, CR
VZP	General Health Insurance Fund, CR
WHO	World Health Organization
ZPMV	Ministry of the Interior Health Insurance Fund, CR
ZPŠ	Škoda Employees Health Insurance Fund, CR

Introduction

Cervical carcinoma belongs to the most common cancer diseases diagnosed in women worldwide (GCO, 2021). In the Czech Republic every year approximately eight hundred women are diagnosed with the disease. And about three hundred women die from the disease annually (NSC, ÚZIS, 2018). Human papillomavirus (HPV) is the originator of the majority of diagnosed cervical cancers (Harsh, 2011; Serrano et al., 2015). The epidemiological data from the Global Cancer Observatory suggest that the implementation of the vaccination against HPV types typically associated with the cervical carcinoma decreases its incidence and mortality (GCO, 2021; Májek et al., 2021a). In accordance with Act No. 48/1997 Coll., on Public Health Insurance, the costs of non-obligatory vaccination against human papillomavirus for thirteen-year-olds is fully reimbursed for both girls and boys. However, the immunization coverage rate in the Czech Republic suggests that only 65.8% of women whose vaccination would have been reimbursed have been vaccinated (NSC, ÚZIS, 2018). The average costs of treating female genital cancer are approximately 30,000 CZK a year per patient (VZP, 2020).

This thesis, therefore, studies the cost-effectiveness of vaccinating women against HPV in the Czech Republic. The thesis assesses the cost-effectiveness of the current reimbursement setting of HPV vaccination compared to the designed change. The author proposes two strategies to improve the vaccination coverage in the Czech Republic. Firstly, the increase in vaccination coverage fuelled by a campaign promoting the vaccination under the current reimbursement conditions. Secondly, the extension of reimbursed vaccination to the age group of thirteen to fifteen years old women together with the increase in the vaccination coverage achieved by the vaccination campaign as well.

The contribution of this thesis lies primarily in its focus on the Czech Republic because, as far as the author knows, no cost-effectiveness analysis of vaccinating women against HPV was published. To perform the analysis, the multistate Markov model for modelling over-the-time transitions among the states representing disease progression was built. The model's outputs are used to calculate the incremental cost-effectiveness ratio (ICER), which is used to evaluate the cost-effectiveness of an intervention compared to the current setting.

The thesis firstly describes HPV and its linkage to cervical carcinoma. Then the epidemiology of the disease in the Czech Republic is depicted. Chapter 1 includes a brief overview of progression, treatment, and prevention of cervical carcinoma. Chapter 2 deals with the vaccination against HPV. The description of the current state of vaccination in the Czech Republic, as well as the status of vaccination abroad, are included. To better understand the costs of vaccination, different types of vaccines are presented together with the maximal reimbursement. Chapter 3 includes the literature review of conducted cost-effectiveness analyses of HPV vaccination.

Chapter 4 firstly defines the methodology of Markov chains. Then the approach used to assess the cost-effectiveness is introduced and the input data are presented. Additionally, the built model, together with the enumeration of the states and values specifically assigned to them, are interpreted. Chapter 5 presents the results, and chapter Conclusion summarises the whole thesis.

1. Human papillomavirus

Papillomavirus is a relatively small virus containing circular double-stranded DNA belonging to the *Papillomaviridae* family, replicating their genomes using the host's enzymatic machinery. Generally, lesion formations, like micro-wounds or micro-abrasions, on the surface of the epithelium allow the virus to enter and insert the viral genome into the basal cells (Manini & Montomoli, 2018). Papillomaviruses infect mentioned cells of vertebrates, including humans.

Human papillomaviruses (HPV) are substantially resistant DNA viruses that form a group of more than 100 genotypes infecting epithelial, mucosal (e.g., cervical and other anogenital mucosae), and cutaneous (skin) cells (Bednář et al., 1996). HPV is proven to be significantly involved in the development of cervical cancer. Based on the HPV type, two main classes can be differentiated. High-risk HPV genotype represented primarily by HPV 16 and 18. These were diagnosed in 70% of cases of cervical cancer. And low-risk HPV genotype – especially 6 and 11. The second group is said to be less invasive, and HPV infection is usually cleared up on its own by activating immune system reactions (Harsh, 2011). The human papillomavirus type affecting the rectogenital area is the most common sexually transmitted infection, and skin-to-skin genital contact is sufficient for virus transmission (Manini & Montomoli, 2018).

In addition, HPV causes other clinical manifestations such as genital, anal, skin warts, oropharynx, anus, and rectum lesions that could progress to cancer. Table 1 shows which are the most common HPV types for particular clinical manifestations.

Table 1: Most common clinical manifestations and HPV types causing them

Clinical manifestation	**Most common HPV type**
Cervical dysplasia and carcinoma	16, 18
Rectum, anus, and anal carcinoma	6, 11
Benign skin warts	1, 2, 4, 7, 27, 57, 65
Other skin manifestations	1, 2, 3, 4, 5, 7, 8, 10, 16
Oral infection	6, 11
Laryngeal papillomatosis	6, 11

Note: author's creation, source of the data: (Handisurya et al., 2009)

1.1. Cervical carcinoma

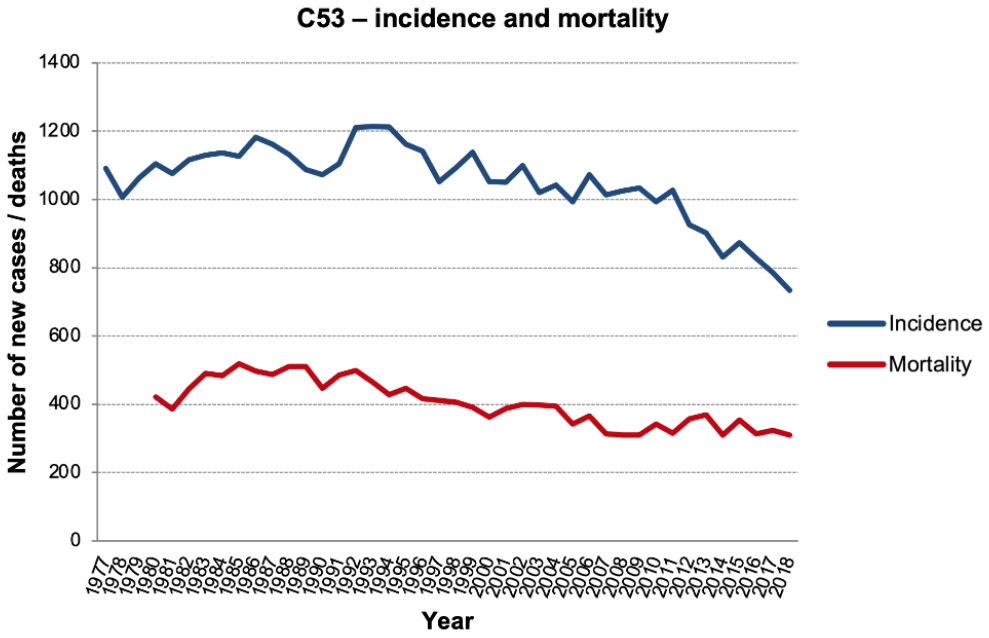
HPV infection is a well-established cause of cervical cancer, and there is strong evidence connecting HPV DNA with other anogenital cancers such as the anus, vulva, vagina, and penis. In addition, more than 85% of female HPV-related cancers are invasive cervical cancer cases (Serrano et al., 2015).

The following chapter contains a description of the current situation regarding cervical carcinoma in the Czech Republic. A critical aspect affecting the number of reimbursed costs by health insurance companies is cervical cancer progression and its treatment.

1.2. Cervical carcinoma in the Czech Republic

Approximately eight hundred women are annually diagnosed with cervical cancer in the Czech Republic (incidence), and more than three hundred women die from the disease every year (mortality). Figure 1 depicts the absolute numbers of the incidence (blue curve) and mortality (red curve) of cervical carcinoma in the Czech Republic. Even though the tendency of newly diagnosed cases is decreasing, as shown in Figure 1, the number of deaths is relatively stable over the last decade (Májek et al., 2021a). In 2018, 734 patients were diagnosed with cervical carcinoma, and 310 patients died of this diagnosis. The prevalence of cervical carcinoma in the Czech Republic as of December 31st of 2018 was 17,653 patients. This number refers to the absolute number of women living with the diagnosis (ÚZIS et al., 2018).

Figure 1: Incidence and mortality of cervical cancer in the Czech Republic: historical development of the absolute number of cases



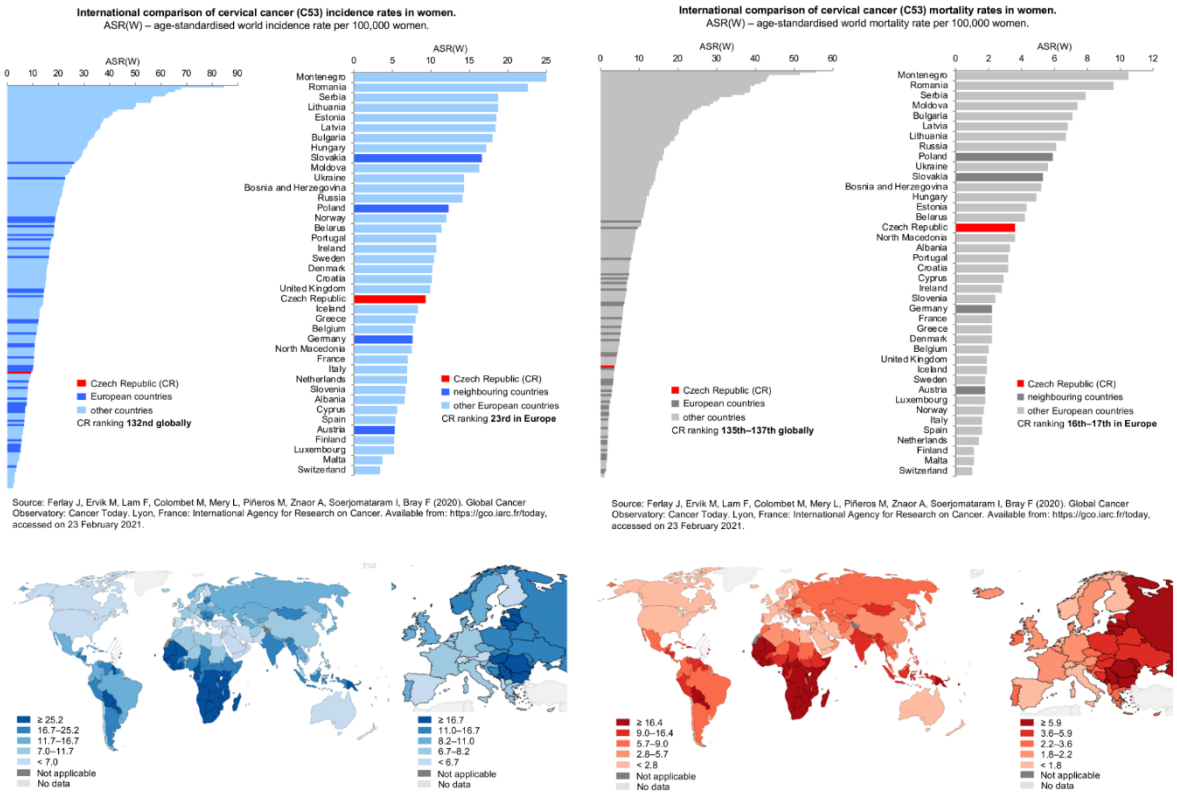
Note: source: (Májek et al., 2021a), source of the data: NOR (incidence throughout the whole period, mortality until 1993), ČSÚ (mortality since 1994)

Within the European Union, there are significant differences between western and eastern countries. In the countries of the former Eastern Bloc, cervical carcinoma is much more widespread. While screening and vaccination programmes in Western Europe were established a long time ago, these programmes have only recently begun to be systematically established in post-communist countries (Májek et al., 2021a).

Figure 2 shows the incidence (in blue colours) and mortality (in red colours) per 100,000 women, age-standardized to the world age standard. In comparison to the western European

countries, the Czech Republic struggles to implement a stable, functional vaccination and screening programme in order to lower the number of newly diagnosed cases and mortality rate.

Figure 2: Incidence and mortality of cervical cancer: an international comparison based on data from 2018.



Note: source: *(Májek et al., 2021a)*, source of the data: *Global cancer observatory: Cancer today., Lyon, France: International Agency for Research on Cancer*

Data sourced from the National Cancer Register of the Czech Republic (NOR), Institute of Health Information and Statistics of the Czech Republic (ÚZIS) for the time period from 2012 till 2016 suggest that the average age, as well as median age, at which cervical cancer is diagnosed is fifty-five years. The twenty-fifth and seventy-fifth quantile interval represents age ranging from forty-one to sixty-seven years at which cervical carcinoma is diagnosed (NSC, ÚZIS, 2018).

1.3. Stages and progression of cervical carcinoma

Persistent infections with a high-risk genotype of human papillomaviruses participate in the development of cervical precancerosis and, if left untreated, could mature to the malignant cervical carcinoma and later on spread to the even more distant parts of the female reproductive organs. Continual infection is necessary, however, not a sufficient condition. For the development of the carcinoma, other cofactors need to be present. For instance, tobacco

smoking, immune system disorders, long-term use of hormonal contraception, early onset of sexual life, promiscuity, or simultaneous infection with other sexually transferred diseases (e.g., chlamydia) (Chovanec & Náležinská, 2014).

1.4. Treatment of cervical carcinoma

The treatment of cervical carcinoma differs based on the progression of the disease, and so do its costs. There are several modalities: surgical treatment, radiotherapy, and chemotherapy. Selection of the treatment is made with the consideration of the patient's health status and progression of the tumour. For young women, the desire to maintain fertility is a crucial factor determining the treatment options.

Surgical treatment is an appropriate treatment for patients at the early stages of cervical cancer. Such treatment includes conization of the cervix, consisting of the removal of a specific part of the cervix with the ambition to eliminate affected cells completely. Another surgery option is a trachelectomy. In contrast, the almost whole body of the cervix is removed. Both conization and trachelectomy preserve the fertility of a patient. Invasive surgical options are different types of hysterectomy – the extraction of the uterus (and surrounding tissues). Based on the area where cancer has spread. The hysterectomy does not preserve fertility.

Radiotherapy is the core treatment method in advanced stages. The basis is the application of ionizing radiation in doses that are lethal for the tumour with regard to the minimal damage of surrounding tissues.

Chemotherapy is a treatment that involves the administration of drugs with a cytotoxic effect. The disadvantage is that these drugs also impact the patient's healthy cells. Chemotherapy is mainly used as a therapy in advanced stages (Chovanec & Náležinská, 2014).

1.5. Prevention of cervical carcinoma

Prevention is a crucial factor determining the incidence of cervical carcinoma. The sooner the cytological changes are identified, the better is the prognosis for a patient. Regular preventive check-ups are crucial to diagnose cervical (pre)cancerosis at an early stage. There are currently two screening tests. A cytological smear – PAP test, which is recommended to women aged 21 to 65. Consistent testing on a yearly basis is essential, considering that cervical cancer occurs in up to 1/3 of negatively tested women.

Another screening option is an HPV DNA test, which is used to identify the presence of high-risk HPV types. HPV DNA testing is recommended for women aged 30 to 65. The negative result of a test indicates that the tested HPV types are not present, and the risk of development of cervical carcinoma is indeed low not only at the time the test was carried out but during the next period of 5 to 10 years as well. Since January 2021, the HPV DNA test is a mandatory part of routine cervical cancer screening and is indicated as a part of screening control together with cytological examination for women who are 35 or 45 years of age (Moje medicína, 2021).

Additional preventive measures include protected sexual intercourse, avoiding promiscuity, a healthy lifestyle, and, most importantly, vaccination against HPV.

2. Vaccination against HPV

Vaccination against HPV has become one of the most important prevention programmes in the world in the last decade (HPV College, 2021a). Complete vaccination prevents both cancer and pre-cancer changes that could develop into carcinoma. They contain non-infectious viral proteins that can trigger the production of antibodies in the immune system. If the body subsequently encounters a viral infection, the immune system is able to suppress such infection. The highest effect can be achieved by vaccinating both girls and boys before the beginning of sexual life, i.e., before they can encounter HPV infection. Nevertheless, even vaccination after the onset of sexual life brings a reduction in the risk of developing any of the conditions caused by HPV (Markowitz, 2007; Májek et al., 2021a, 2021b).

2.1. The current state of the vaccination in the Czech Republic

As in most developed European countries, a vaccination programme against human papillomaviruses has been introduced in the Czech Republic. Health insurance companies bear the costs of non-obligatory vaccination against human papillomaviruses since April 1st of 2012 for girls aged thirteen. The costs are reimbursed if the vaccination is initiated after a girl reaches her thirteenth year of life up to the reached fourteenth year of life. In addition, by the amendment Act no. 290/2017 in august 2017, the vaccination covered by the public health insurance was extended to boys (NSC, ÚZIS, 2018).

Immunization coverage (number of vaccinated female patients in relation to the size of the population) of female patients who initiated the vaccination in their thirteenth year of age is reported to be 65.8% in 2017 for the whole Czech Republic. However, the immunization coverage differs across the regions, ranging from 51.5% to 82.7% in 2017. It is essential to mention that reported percentages concern only women who have fulfilled the age limit for vaccination reimbursed by public health insurance (NSC, ÚZIS, 2018). The data used to carry out the analysis published by the National Screening Centre, CR (NSC), Institute of Health Information and Statistics of the Czech Republic (ÚZIS) are sourced from the National Register of Reimbursed Health Services (NRHZS).

Currently, there are three medical products used in vaccination against HPV. The extent of protection is determined by the number of HPV types that the vaccine protects against (HPV College, 2021b). A bivalent (protecting against two HPV types) vaccine *CERVARIX* protects against high-risk HPV types 16 and 18. A quadrivalent vaccine, *GARDASIL* is protecting against four HPV types (low-risk types 6 and 11 along with high-risk types 16 and 18). Furthermore, a nonavalent vaccine *GARDASIL 9*, providing protection against nine HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58).

Table 2: Overview of vaccines used in the Czech Republic, their characteristics, prices, and reimbursement

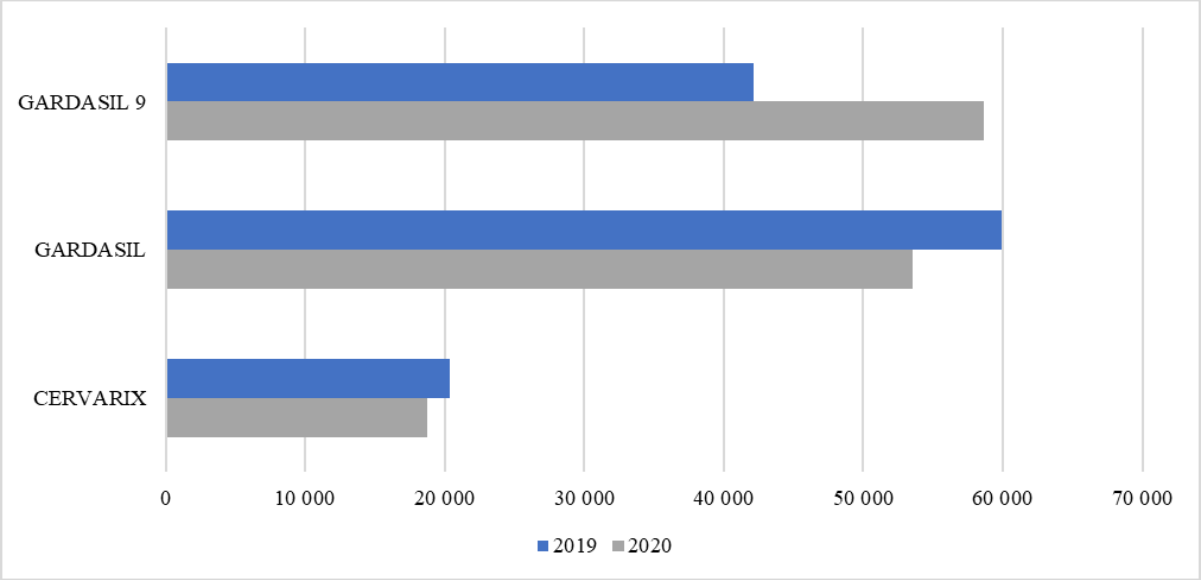
Name of the vaccine	Providing protection against HPV types:	An indicative selling price [CZK]	The maximum reimbursement from public health insurance [CZK]	An indicative surcharge paid by the patient [CZK]
CERVARIX	16, 18	1,765.79	1,765.79	0.00
GARDASIL	6, 11, 16, 18	3,138.54	1,765.79	1,372.75
GARDASIL 9	6, 11, 16, 18, 31, 33, 45, 52, 58	4,032.63	1,765.79	2,266.84

Note: author's creation, source of the data: (SÚKL, 2021b)

As seen in Table 2, the maximum reimbursement from public health insurance, in accordance with the law, equals to the amount of the least economically costly medical product. However, the amount of prices and surcharges shown in Table 2 represent the price for the one dose of the vaccine only. The number of doses needed for the full immunization depends on the age at which the vaccination was initiated. *CERVARIX* could be injected in a two-dose scheme if the age of administration of the first dose was from nine to fourteen years included. If a woman is first vaccinated at fifteen or more years, three doses are needed (SÚKL, 2021b). For vaccines *GARDASIL* and *GARDASIL 9*, two doses are sufficient if the patient received the first dose from nine to thirteen years of age. For the patients first vaccinated at the age of fourteen or more, three doses need to be administered (SÚKL, 2021b).

Patients in the Czech Republic are able to choose the type of medical product used for the vaccination. SÚKL publishes the summary information on the supply of medicinal products obtained from the monthly reports of entities authorized to distribute medicinal products in the Czech Republic pursuant to Article 23 of the Act on Medicinal Products. Figure 3 demonstrates the distribution of medical products used for vaccination against HPV supplied to medical doctors and pharmacies. These two types of purchasers represent the direct way, how a patient could access the medical product. The number of medical products supplied to the distribution centres was omitted. The most preferred medical product in 2019 was *GARDASIL*. However, in 2020 *GARDASIL 9* was supplied the most. In both years, the proportion of fully reimbursed vaccine *CERVARIX* was around 15% (SÚKL, 2020a, 2021a). Nevertheless, it is necessary to take into consideration that the supplied medical products were used to vaccinate both female and male patients.

Figure 3: Proportion of the medical products supplied to the medical doctors and pharmacies in the year 2019 and 2020.



Note: author's creation, source of the data: (SÚKL, 2020a, 2021a)

2.2. Vaccination programmes of insurance companies

In addition to the mentioned vaccination programme, almost all health insurance funds offer various vaccination programmes and financial contributions for the patients to carry out the vaccination against HPV infection.

Ministry of the Interior Health Insurance Fund (ZPMV) provides the financial contribution of up to 1,000 CZK for adults without age restriction and for children aged fourteen to eighteen up to 1,500 CZK (ZPMV, 2021). Coalfield Brotherhood Cash Office, a health insurance company (RBP) contribute to children from twelve years up to the 4,000 CZK. Women up to thirty years of age could get up to 4,000 CZK, women older than thirty, and men could get up to 1,000 to carry out the vaccination against HPV (RBP, 2021). Czech Industry Health Insurance Fund (ČPZP) offers a contribution for children up to the age of seventeen in the amount of 1,500 CZK. For adults, the amount of financial contribution is up to 1,000 CZK (ČPZP, 2021). Occupational Health Insurance Company for Employees of the Banking, Insurance and Building Industry (OZP) provides financial contributions for children and adults without any age restriction up to 1,000 CZK (OZP, 2021). Škoda Employees Health Insurance Fund (ZPŠ) offers beneficence in an amount up to 4,000 CZK for children older than twelve years. Women up to the age of forty-five could get up to 800 CZK (ZPŠ, 2021).

However, there could be some additional conditions to be fulfilled and strict dates by which the application must be submitted in order to receive a financial contribution for HPV vaccination. General Health Insurance Company of the Czech Republic (VZP) and Military Health Insurance Company of the Czech Republic (VoZP) do not provide financial contributions for HPV vaccination (VZP, 2021; VoZP, 2021).

2.3. Status of vaccination abroad

According to The European Centre for Disease Prevention and Control (ECDC), most of the European Union (EU) and European Economic Area (EEA) countries have established a recommended, not obligatory HPV vaccination programme (ECDC, 2021). There are three vaccines (listed in Table 2) used in immunization programmes in the EU. This chapter contains a description of the vaccination strategies, including the catch-up programmes in the selected European countries. Catch-up vaccination refers to the practice of vaccinating the patients who did not receive a dose/doses at recommended age (cancer.gov, 2011).

In Austria, there is a non-obligatory vaccination offered to both girls and boys aged ten to twelve. Additionally, the catch-up programme has been established for patients aged thirteen to thirty, however, the vaccination is funded by the national health system until the age of fifteen only (ECDC, 2021). Vaccination coverage in Austria is assumed to be 60% for girls and 40% for boys (Boiron et al., 2016). In 2018 the age-standardised number of new cases in Austria was estimated to be 5.5 per 100,000 women compared to 9.9 in the Czech Republic. Additionally, the cervical cancer mortality rate estimates were 1.7 deaths per 100,000 women, compared with 4.0 in the Czech Republic (Bruni et al., 2019). In conclusion, the number of deaths due to cervical cancer is almost 2.4 times higher in the Czech Republic. Considering the age structure of women diagnosed with cervical cancer, the Czech Republic and Austria immunization programs were established only recently (2012 and 2014, respectively). The difference could be found in the implementation of a national screening programme. While Austria implemented such a programme in the year 1974, the Czech Republic only in 2009 (Dušková et al., 2014; Australian Institute for Health Technology Assessment, 2018).

In Germany, a gender-neutral immunization programme has been established for patients from nine up to fourteen years of age, followed by the female-only catch-up programme up to the age of seventeen. Estimates from 2018 suggest the number of newly diagnosed cases per 100,000 women to be 7.5 and the age-standardised number of deaths to be 2.2. The study from 2017 assumed the vaccination coverage among the young to be 50% (Damm et al., 2017).

A specific case of vaccination programme occurs in Latvia, where female-only vaccination is compulsory at twelve years of age (ECDC, 2021). This is possibly due to the cervical cancer incidence of 25.0 cases per 100,000 women (Bruni et al., 2019). Note that the vaccination strategies and catch-up programmes could change each year. The actual effect of implementing the immunization programme is yet to be seen after vaccinated women will reach the average age at which cervical carcinoma is usually diagnosed.

3. Literature review of cost-effectiveness analyses

The following chapter contains a review of some of the conducted cost-effectiveness analyses of HPV vaccination and cervical cancer prevention in Europe.

A study from 2011 focused on vaccinating women in the Netherlands analysed the health-economic and clinical impact for women aged twelve to fifty in one year age cohorts. A Markov

transition model was used to analyse the transition among the stages (HPV susceptible, HPV infected, pre-cancer, cancer, and cancer mortality stages were used). The results suggest that vaccinating women against HPV is highly cost-effective for twelve to sixteen-year-olds. Remarkably, with the age of vaccinees increasing up to twenty-five years, the cost-effectiveness declines only slowly. The study proposes that by vaccinating such age groups, substantial health benefits can be obtained at acceptable costs. However, the cost-effectiveness of vaccinating women older than twenty-five declines rapidly. To conclude, vaccinating women is cost-effective even after the onset of sexual life (Westra et al., 2011).

Another study from 2013 explored the incremental cost-effectiveness of vaccinating women pre- and post-sexual debut in Belgium. The already published multiple staged Markov model for modelling a cohort of women over a lifetime, reproducing the natural history of HPV infection, the effect of screening, and the effect of HPV vaccination (Debicki et al., 2008) was used. The base scenario assumed vaccinating twelve-year-old women only. In addition, a catch-up programme was assessed. The results suggest that bivalent HPV-16/18 vaccination combined with screening provided to women after the offset of sexual life would contribute to a substantial reduction in cervical carcinoma disease burden in Belgium. In conclusion, a bivalent HPV-16/18 vaccine is said to be cost-effective in women up to the age of thirty-three to forty (Demarteau et al., 2013).

A study from 2012 examined a health economic evaluation of vaccination strategy to prevent HPV-related diseases. The study was oriented toward Italy. A Bayesian multicohort Markov model using the probability distributions reflecting the observed data or expert opinion of unknown parameters was used. The results implicate that the base scenario of vaccinating two cohorts of women aged twelve and sixteen as well as a multicohort scenario where an additional cohort aged eighteen along with cohorts aged eighteen and twenty-five was assumed shown to be cost-effective (Favato et al., 2012).

More recent studies on providing vaccination to older women as well using the methodology of Markov models are available for countries located in Asia only. According to the author's knowledge, there are no published cost-effectiveness analyses of vaccination women against HPV in the Czech Republic. There is only one master's thesis written on the topic; nevertheless, it is aimed at vaccinating men with a greater focus on homosexual men (Stach, 2018).

4. Methodology, data, and model

The following chapter contains a theoretical background and a characterization of the methodology of Markov chains, as well as a description of the data used to construct a model for the transition analysis among the states. Furthermore, the concrete model and the cost-effectiveness analysis, which uses the outputs of the Markov model for economic evaluation, are explained.

4.1. Methodology of Markov chains

Markov models are widely used in health economic modelling to assess health care strategies regarding their cost-effectiveness and inform public policies (Russell, 1996). They are used to analyse uncertain processes over the time. Markov models are suited to decisions where the timing of events is essential and where events could happen more than once, and therefore they are appropriate where the strategies being evaluated are of sequential or repetitive nature (Gray et al., 2011).

Markov model uses a Markov process to model the transitions among the states. A stochastic process $\{X(t), t \in T\}$ is called a first-order Markov process if for any $t_0 < t_1 < \cdots < t_n$, the conditional cumulative distribution function of $X(t_n)$ for given values of $X(t_0), X(t_1), \ldots, X(t_{n-1})$ depends only on $X(t_{n-1})$. That is,

$$P[X(t_n) \leq X_n | X(t_{n-1}) = x_{n-1}, X(t_{n-2}) = x_{n-2}, \ldots, X(t_0) = x_0] = P[X(t_n) \leq x_n | X(t_{n-1}) = x_{n-1}] \quad (1)$$

Markov chains can be used to model over-the-time transitions among the states represented as a health status. The discrete-time process $\{X_k, k = 0, 1, 2, \ldots\}$ is called a homogenous Markov chain if for all $i, j, k, \ldots, m$ the following holds:

$$P[X_k = j | X_{k-1} = i, X_{k-2} = n, \ldots, X_0 = m] = P[X_k = j | X_{k-1} = i] = p_{ij} \quad (2)$$

Where the quantity p_{ij} is the state transition probability which does not depend on the time. Meaning that the probability p_{ij} of a process which is at time *k – 1* at state *i* will transit to the state *j* at time *k* does not depend on time. In other words, given the present state of the Markov process, the future state is independent of the past. Such attribute is usually referred to as a Markov property (Filipović-Pierucci et al., 2017; Ibe, 2013).

The homogenous state transition probability p_{ij} has the following properties:

1. The probability p_{ij} must be in an interval between zero and one.

$$0 \leq p_{ij} \leq 1 \quad (3)$$

2. The sum of probabilities of transition from state *i* to all possible states must be equal to one.

$$\sum_j p_{ij}, i = 1, 2, \ldots, n \quad (4)$$

Such property follows from the states being mutually exclusive and collectively exhaustive.

The probability of each state transitioning to the other states could be displayed by the state transition probability matrix *P*. Such matrix *P* is an object of *n* rows and *n* columns, where p_{ij} is the entry in the *i*-th row and *j*-th column. The sum of entries in each row is equal to one, implying that the state transition probability matrix *P* is a stochastic matrix. The Markov chain

could be represented apart from the state transition probability matrix by the state transition diagram.

$$P = \begin{bmatrix} p_{11} & p_{12} & \cdots & p_{1n} \\ p_{21} & p_{22} & \cdots & p_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ p_{n1} & p_{n2} & \cdots & p_{nn} \end{bmatrix} \tag{5}$$

Assuming a finite Markov chain, state transition probability of *n*-th step can be defined as a probability $p_{ij}(n)$ of the system being in a state j after n transitions, knowing that system is at a state *i* presently. The probability $p_{ij}(n)$ can be defined as:

$$p_{ij}(n) = P[X_{m+n} = j | X_m = i] \tag{6}$$

Additionally, the probability $p_{ij}(n)$ could be similarly found for all possible combinations of *i* and *j*. In that manner, it is possible to construct an *N*-state Markov chain matrix P^n consisting of all possible probabilities $p_{ij}(n)$. Where $p_{ij}(n)$ is the entry at the *i*-th row and *j*-th column in the matrix P^n. The matrix P^n could be obtained by multiplication of the matrix *P* by itself n-times.

$$P^n = \begin{bmatrix} p_{11}(n) & p_{12}(n) & \cdots & p_{1N}(n) \\ p_{21}(n) & p_{22}(n) & \cdots & p_{2N}(n) \\ \vdots & \vdots & \ddots & \vdots \\ p_{N1}(n) & p_{N2}(n) & \cdots & p_{NN}(n) \end{bmatrix} \tag{7}$$

The Markov chain could be formed by the different types of states. A state *j* is said to be accessible/reachable from state *i* if the probability $p_{ij}(n) > 0$ for some $n > 0$. Accessibility refers to the possibility of ever entering the state. Two states that are mutually accessible are said to communicate with each other. A Markov chain is said to be irreducible if each state communicates with every other state present in the model.

A state *i* is said to be absorbing/trapping state if the process cannot enter any other state *j* once state *i* is reached. $p_{ij} = 0$ for every $j \neq i$. Thus, for absorbing state the probability of remaining in the state *i*, $p_{ii} = 1$ for every $j \neq i$. A Markov chain where there is a nonzero probability of entering an absorbing state from every other state is called an absorbing Markov chain (Ibe, 2013).

4.2. Economic evaluation carried out by the cost-effectiveness analysis

Cost-effectiveness analysis is one of the methods used for economic evaluation in health care. The inputs in the cost-effectiveness analysis are costs and effects representative for the current setting. Costs and effects could be calculated for one or more interventions as well. To assess the economic value of an intervention, the summary measure – an incremental cost-

effectiveness ratio (ICER) is applied (York Health Economic Consortium, 2016). ICER is calculated as follows:

$$ICER = \frac{C_A - C_B}{E_A - E_B} = \frac{\Delta C}{\Delta E} \quad (8)$$

Where C_A and E_A refer to the costs and effect of the intervention A. In a similar manner, C_B and E_B represent the costs and effect of current setting (Gray et al., 2011).

The effect of an intervention is in the case of this study evaluated by an indicator of quality-adjusted life years (QALY). QALY combines the length of life with the quality of life. The calculation of QALY multiplies the duration of life in years by the health-related quality of life (HRQoL) measure connected to the respective years.

$$QALY = T * HRQoL \quad (9)$$

HRQoL is a utility measure of a health state displayed on a numerical scale acquiring values from zero to one, where zero represents the utility of the "dead" state. The utility of a state lived in "perfect health" is corresponding to the HRQoL of one. This measure of wellbeing arises from the patients' surveys such as EQ-5D where they assess a wide range of aspects such as mobility, pain, mental health, and others. (Prieto & Sacristán, 2003; Whitehead & Ali, 2010; Komorowski & Raffa, 2016).

To be able to assess whether an intervention is cost-effective or not, one needs a cost-effectiveness threshold. Following the decision-making practice of SÚKL, the 1.2 million CZK/QALY limit is applied as a usual acceptable limit when deciding on cost-effectiveness (SÚKL, 2020b).

4.2.1. Costs in health care

In health care, the costs could be divided into direct and indirect costs. Direct costs represent the monetary value of all resources (goods, services) spent on providing health care and settling the side effects, current and future consequences. Direct costs could be health-care and non-health-care related.

- Direct health-care related costs include medication, hospital services, medical examination, laboratory tests, etc.

- Direct non-health-care related costs indicate the wages of medical professionals, operation of the medical facilities, transportation costs, etc.

Indirect costs signify the productivity losses of a patient. For instance, the loss of productivity at work, the cost to the social system due to the inability to work, or early retirement. Other indirect costs include the costs that cannot be quantified, such as suffering, pain, discomfort, or distress. (Andersen et al., 2008; NICHSR, 2020, 2021).

4.3. Data description

This sub-chapter contains a description of data used to conduct a cost-effectiveness analysis of women's vaccination in the Czech Republic.

4.3.1. Data used for survival analysis

To determine the length of survival a request for data from the National Health Information System (NZIS) was filed. The length of the survival is for the purpose of this thesis divided into three possible states according to the health condition of a patient. For more detail see subchapter 4.4. The data consists of the number of women in each of these three health states in 2018 and of their state in the next year. Overall, 5,446,053 women were included. Where each of them is exactly in one of the defined health states. Such data were used to calculate the transition probabilities among the states, including the probability of dying. The states were defined based on the reported diagnosis in the corresponding year. The diagnoses were identified according to the International Classification of Diseases and Related Health Problems (ICD-10), which codifies the system of labeling and classification of human diseases, disorders, health problems, and other symptoms, situations, or circumstances (ÚZIS, 2021). Considered diagnoses are N87 – cervical dysplasia (precancerous stage) and C53 – cervical carcinoma (cancerous stage). The third state is defined as a "healthy" i.e., none of these diagnoses. The description of data subject to the request can be find in Appendix no. 3: Request for the data from NZIS.

The provider of the data (ÚZIS) informed about the limitations resulting from the fact that the identification of patients was based on the reporting of data for the purpose of reimbursement of health care within the framework of public health insurance. It is not a clinical database; simultaneously, cases outside public health insurance were not considered.

The provided data were compared to the incidence, prevalence, and mortality numbers of cervical carcinoma in the Czech Republic. Unfortunately, differences were observed. These inaccuracies are given primarily by the above stated difference between a clinical register and reimbursement data. Other causes might be the incorrectness in reported diagnoses, patients who did not come to their check-ups during the observed time period (the patient does not appear in the reimbursement data). Another reason could be numerous diagnoses of a single patient.

4.3.2. Health-related quality of life

The health-related quality of life is a value assigned to each health state (i.e., state of the Markov model), acquiring values from zero to one. HRQoL of precancerous and cancerous stages was taken from the literature. The state *N87* is representing the precancerous stage. For such stage values, HRQoL ranged from 0.87 to 0.91 based on the progression of precancerosis (CIN I, II,

III). State *C53* represents the cervical carcinoma. HRQoL for such state was dependant on the progression of the carcinoma (local, regional, distant) and acquired the values from 0.48 to 0.76 (Elbasha et al., 2007; Boiron et al., 2016). For the purpose of this thesis, the HRQoL of *N87* and *C53* was set to 0.89 and 0.67, respectively. The HRQoL of the state *D* was set to zero. State *H* was assigned the HRQoL value of one, even though the HRQoL of a person who does not suffer from either C53 or N87 does not equal to the "perfect health" state. The decision was made because of the fact that the average HRQoL of the whole population with no condition would be lower than the value assigned to the state *N87* (Elbasha et al., 2007), which would cause a problem in the model.

4.3.3. Costs of vaccination and vaccine efficacy.

The costs of vaccination for the purpose of this analysis include only direct health-care related costs of medical products and their administration. Costs are dependent on the woman's age at which the vaccination is initiated. Total costs of vaccination are determined as costs of medical products and costs of its administration. The costs of the medical product are equal to the amount of the least economically costly option, meaning only vaccine *CERVARIX* is fully reimbursed.

The costs of administering the vaccine include the application of the vaccine itself and a general examination by a medical doctor. The Decree No. 269/2019 Coll. amending the Decree No. 134/1998 Coll., which issues a list of medical services with point values, as amended and the Decree No. 428/2020 Coll. on the determination of point values, the amount of payments for reimbursed services and regulatory restrictions for the year 2021 were used. Table 3 displays the total costs of vaccination for two and three doses.

Table 3: Costs associated with vaccination

Price per one dose of vaccine	1,765.79 CZK
Price of application and examination per one dose	263.32 CZK
Total costs of administration per one dose	2,029.11 CZK
Total costs of administration of two doses	4,058.22 CZK
Total costs of administration of three doses	6,087.33 CZK

Note: author's creation, data source:(Ministry of Health, CR, 2019, 2020; SÚKL, 2021b)*; Point values of application of the vaccine and general examination are 138 and 89 points respectively. Value of a point is 1.16 CZK* (Ministry of Health, CR, 2019, 2020).

Vaccine efficacy against a precancerous stage could be taken from the summary of the product characteristics available for every vaccine at SÚKL (SÚKL, 2021b). Efficacy of vaccines against precancerous stages was ranging from 78% to 100% (all three vaccines are considered). The efficacy against the cancerous stage is not available yet, due to the long time period needed for cervical carcinoma development. *CERVARIX* was authorised by European Medicines Agency (EMA) for use in 2007, *GARDASIL* in 2006 and *GARDASIL 9* in 2015 (EMA, 2007, 2008, 2015). The efficacy was set to 90%.

4.3.4. Costs assigned to the specific states

The costs assigned to the specific states were taken from the 2019 Yearbook of VZP. The number of insured persons at VZP was almost 6 million in 2019, i.e. approximately 60% of insured persons (VZP, 2020). Thus, persons insured at VZP could be taken as a good approximation of the population of the Czech Republic.

The costs assigned to the *H* (healthy) state were calculated as a median value of average total annual costs of five-year age groups ranging from ten to fourteen years up to eighty to eighty-four years. This value was 22,270 CZK. The costs for state *D* (dead) were set to zero. The costs for state *N87* were computed as costs of *H* state added up to the average costs for a group of diagnoses N80 – N98 taken from the 2019 yearbook. This value was 22,270 CZK. + 1,621.34 CZK = 23,891.34 CZK. The costs for *C53* state were similarly calculated as costs of *H* state added up to the average costs for a group of diagnoses C51 – C58 taken from the 2019 yearbook. This value was 22,270 CZK. + 30,113.38 CZK = 52,383.38 CZK (VZP, 2020). Table 4 summarises the average total annual costs of each state.

Table 4: Average total annual costs assigned to each state

H	22,270.00 CZK
N87	23,891.34 CZK
C53	52,383.38 CZK
D	0.00 CZK

Note: author's creation

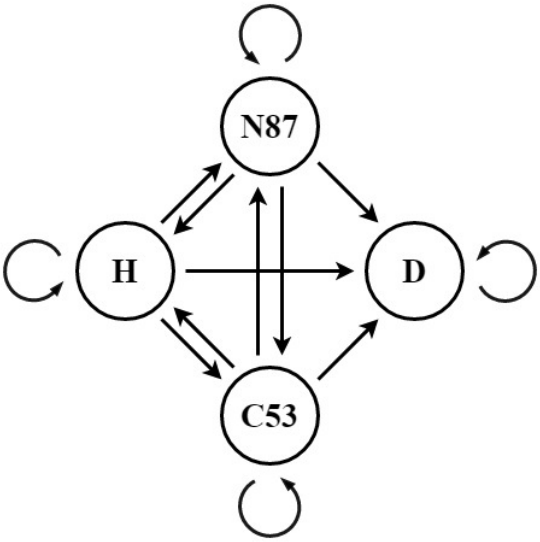
The total costs for states *N87* and *C53* do not reflect the costs for these stages completely because the costs of these diagnoses are already included in the average total costs. However, the number of women diagnosed with these diagnoses is relatively low compared to the number of women insured at VZP. The main problem regarding the costs is that these are not costs for specific diagnoses, but the costs of a group of diagnoses. Unfortunately, the author was not able to obtain better data.

4.4. Model

To perform a cost-effectiveness analysis, the costs and benefits of different vaccination strategies were computed. The ICER coefficient implements these costs and benefits to determine which alternative is more cost-effective. We quantify the benefits as a length of survival multiplied by HRQoL. To obtain the length of survival a transition analysis is needed. Details of the transition analysis are described below. The obtained length of persistence in individual states is also used to calculate the costs. For individual states different costs are assumed, see Table 4 for more detail. For the purpose of this thesis, a homogenous multistage Markov model for modelling the transitions among the states was created.

Figure 4 shows a graphical representation of the developed model. There are four states: *H, N87, C53,* and *D.* From the methodology of Markov's chains follow that the states are mutually exclusive and collectively exhaustive, meaning that only being at precisely one state at a time (i.e., in each cycle) is possible. Costs and values assigned to each state are described below.

Figure 4: Graphical representation of Markov model



Note: authors' creation

- *H* (healthy) is a state which represents women whose medical condition was neither N87 nor C53 and are not dead at a particular cycle. The name *H* was chosen to identify the state better and does not mean that a woman at this state cannot be diagnosed with any other disease apart from N87 and C53.
  State *H* is accessible from states *H*, *N87,* and *C53.*
  From state *H,* all other states – *H, N87, C53,* and *D* could be accessed.
  Costs assigned to the state: 22,270 CZK per cycle and person
  HRQoL assigned to the state: 1

- *N87* (cervical neoplasia, precancerous state) is a state which represents women whose medical condition was precisely N87 at a particular cycle.
  State *N87* is accessible from states *H*, *N87,* and *C53.*
  From state *N87,* all other states – *H, N87, C53,* and *D* could be accessed.
  Costs assigned to the state: 23,891.34 CZK per cycle and person
  HRQoL assigned to the state: 0.89

- *C53* (cervical carcinoma, cancerous state) represents women whose medical condition was precisely C53 at a particular cycle.
  State *C53* is accessible from states *H*, *N87,* and *C53.*
  From state *C53,* all other states – *H, N87, C53,* and *D* could be accessed.
  Costs assigned to the state: 52,383.38 CZK per cycle and person
  HRQoL assigned to the state: 0.67

- *D* (dead) is a state representing women who are dead at a particular cycle. Those women naturally do not fulfill conditions of being in any other "alive" states at a time.
  State *D* is accessible from states *H*, *N87, C53,* and *D.*
  From state *D,* only state *D* can be accessed. Thus, this state is defined as absorbing.
  Costs assigned to the state: 0 CZK per cycle and person
  HRQoL assigned to the state: 0

Women entering the model is a cohort of thirteen-year-olds who start at state *H*. The age of thirteen was chosen because it is the age at which health insurance companies fully reimburse vaccination against HPV. The size of cohorts was set to 50,000 women in consideration of the age composition of the population (ČSÚ, 2021b). The model was set for 68 cycles. This number was computed as average life expectancy, which is 81 years for women in the Czech Republic (ČSÚ, 2021a) minus the age at which women enter the model (thirteen). One cycle of the model represents one year. According to the methods for assessing cost-effectiveness analysis, discounting of both costs and effect was set to 3%. For the purpose of sensitivity analysis, recalculation using discount rates of 0% and 5% was performed (SÚKL, 2020b).

To be able to assess the benefits of vaccination against HPV, two state-transition matrices are needed. The one for unvaccinated women was obtained from the data provided by the ÚZIS. The provided data represented the transitions among states for the whole population, including women who were already vaccinated, since HPV vaccination started in 2012 for women in the Czech Republic. However, the women vaccinated since 2012 would affect the number of diagnosed cases and thus the transition probabilities only marginally because of the relatively long time period needed to develop a pre(cancerous) condition.

The matrix for vaccinated was obtained by decreasing the probability of transition from state *H* to *N87* and from state *H* to *C53* by 90%. (90% efficacy of the vaccine was assumed.) The missing values needed for the row, to sum up to one, were added to the probability of transition from state *H* to state *H*. The transition from state *H* to *D* was not altered. These two matrices reflect the transition probabilities for the whole life of a cohort of women because the women are transitioning among the states for 68 cycles, i.e., years. Transition matrices can be seen in Table 5 and Table 6.

Table 5: Transition matrix for unvaccinated

	H	N87	C53	D
H	0.9740	0.0150	0.0010	0.0100
N87	0.5510	0.4450	0.0020	0.0020
C53	0.2620	0.0270	0.6550	0.0560
D	0.0000	0.0000	0.0000	1.0000

Note: Author' creation

Table 6: Transition matrix for vaccinated

	H	N87	C53	D
H	0.9884	0.0015	0.0001	0.0100
N87	0.5510	0.4450	0.0020	0.0020
C53	0.2620	0.0270	0.6550	0.0560
D	0.0000	0.0000	0.0000	1.0000

Note: Author's creation

At each cycle, a woman in states *H*, *N87,* and *C53* gains one year of life; in state *D,* zero years of life are gained. This number of gained years of life at each state of each cycle is multiplied by the HRQoL. Thus, the effect is QALY. Subsequently the total costs are obtained as a multiplication of length of persistence in a state by the total annual cost of corresponding state.

The model was developed in the R software using the package *heemod*, programmed for writing Markov models for health economic evaluations (Filipović-Pierucci et al., 2017).

4.5. Proposed strategies

The subchapter introduces the two vaccination strategies proposed by the author.

Strategy 1 proposes increasing vaccination coverage of thirteen-year-olds from 65.8% (NSC, ÚZIS, 2018) (the number of last known vaccination coverage of thirteen-year-olds from 2017) to 80%. The costs and QALYs are calculated proportionally according to the percentage of vaccinated women. The costs of vaccination are ten added to the costs of the proposed intervention. Appendix no. 4: Calculations of costs and QALY for strategy 1 show the concrete values. The proposed increase is assumed to be achieved by the campaign promoting the vaccination. The costs of the campaign were estimated to be 100,000,000 CZK[1]. Such amount is believed to be overestimated for purpose of HPV vaccination campaign. However, in order to increase immunization coverage, the campaign should be continuous in contrast to the Covid-19 campaign. Additionally, this is the maximum amount expected, the real costs of campaign would likely be lower.

Strategy 2 proposes the extension of vaccination to women aged thirteen to fifteen together with the increase of vaccination coverage to 80%. To assess the cost-effectiveness of the second strategy compared to the current setting, the current setting needs to be modelled differently compared to the first strategy. At the beginning of the first cycle 50,000 women were present in the state *H*, and after each of the first and the second cycle 50,000 women (inflow) were added to the state *Z*. Such method was chosen so that a situation where only 13-year-olds are vaccinated (gradual vaccination of thirteen-year-olds only), i.e., the current setting can be

[1] 100,000,000 CZK are the costs, that will be incurred for the campaign promoting vaccination against Covid-19 in the Czech Republic (E15.cz, 2021). Simmilar amount would be allocated to the campaign in Slovakia (SME.sk, 2021).

simulated. The vaccination costs were computed as a sum of costs incurred at the current period and discounted costs incurred after the first and after the second cycle. That is the representation of the current vaccination strategy.

On the other hand, the vaccination for women aged thirteen to fifteen was modelled as one big cohort of 150,000 women. Assuming the equal counts of thirteen-, fourteen- and fifteen-year-olds, one-third of vaccinated women in the cohort would need three doses of vaccine (for women aged fifteen three doses of vaccine need to be administered), and two-thirds of vaccinated women would need the two doses. Costs of vaccination are calculated according to this assumption. Calculations can be seen in Appendix no. 5: Calculations of costs and QALY for strategy 2.

The proposed increase would be achieved by the vaccination campaign valued at 300,000,000 CZK because the group of triple the size needs to be addressed. This originates from the overestimated value of the campaign addressing one cohort of women only. The amount indeed represents upper cost limit, the real value would very likely be lower.

5. Results

The chapter results include the cost-effectiveness analysis of two vaccination strategies proposed by the author.

Table 7 shows the ICER computation using the different discount rates for both costs and QALY for the first strategy. As shown in Table 7, the values of ICER are below the cost-effectiveness threshold of 1.2 million CZK/QALY. To conclude, such intervention shows to be cost-effective at 327,868 CZK/QALY. The base case uses the 3% discount rate; however, the intervention would be cost-effective even at 0% and 5%. The value of discount rates for sensitivity analysis was chosen according to the methods for assessing cost-effectiveness analysis (SÚKL, 2020b). Considering the strategy 1 being cost-effective taking into account the overestimated campaign costs, such strategy would be cost-effective even at lower costs associated with the vaccination campaign.

Table 7: ICER computation - Strategy 1, 90% vaccine efficacy assumed

Discount rate	0%	3%	5%
Δ C [CZK]	71,907,936	105,312,653	113,545,063
Δ QALY	487	321	252
ICER [CZK/QALY]	147,637	327,868	450,081

Note: author's creation, The campaign costs were added to the total costs of the strategy 1 and thus are included in the ICER calculation.

Since the vaccine's efficacy is known only against precancerous stages, the analysis was performed again, assuming the efficacy of the vaccine to be only 80%. As seen in Table 8, the intervention would be cost-effective even at lower vaccine efficacy taking into account the cost-effectiveness threshold of 1.2 million CZK/QALY.

Table 8: ICER computation - Strategy 1, 80% vaccine efficacy assumed

Discount rate	0%	3%	5%
Δ C [CZK]	78,368,191	107,979,623	115,277,062
Δ QALY	432	285	224
ICER [CZK/QALY]	181,483	379,073	515,435

Note: author's creation, The campaign costs were added to the total costs of the strategy 1 and thus are included in the ICER calculation.

The strategy 2 seems cost-effective at the base case scenario using 3% discounting at 50,877 CZK/QALY. Table 9 displays the ICER values at different discount rates. Considering the strategy 2 being cost-effective taking into account the overestimated campaign costs, such strategy would be cost-effective even at lower costs associated with the vaccination campaign.

Table 9: ICER computation - Strategy 2, 90% vaccine efficacy assumed

Discount rate	0%	3%	5%
Δ C [CZK]	306,156,596	696,091,339	795,551,553
Δ QALY	1,743	13,682	16,502
ICER [CZK/QALY]	175,688	50,877	48,209

Note: Author's creation, The campaign costs were added to the total costs of the strategy 2 and thus are included in the ICER calculation.

For strategy 2, the recomputation assuming the 80% efficacy was performed in a similar manner. As seen in Table 10, the intervention would be cost-effective even at lower vaccine efficacy, considering the cost-effectiveness threshold of 1.2 million CZK/QALY.

Table 10: ICER computation - Strategy 2, 80% vaccine efficacy assumed

Discount rate	0%	3%	5%
Δ C [CZK]	325,921,761	704,480,901	801,796,162
Δ QALY	1,571	13,564	16,383
ICER [CZK/QALY]	207,510	51,937	48,941

Note: Author's creation, The campaign costs were added to the total costs of the strategy 2 and thus are included in the ICER calculation.

Considering the values of ICER of both strategies, the author would suggest the policy change in the women's vaccination against HPV in the Czech Republic. Either increased vaccination coverage powered by the campaign promoting vaccination of both campaign and extending the vaccination to the women aged thirteen to fifteen would be beneficial.

Conclusion

The thesis assesses the cost-effectiveness of vaccinating women against HPV in the Czech Republic. Vaccination against HPV has become one of the most critical prevention programmes globally in the last decade (HPV College, 2021a) due to its ability to protect women against HPV, which is the originator of the majority of diagnosed cervical cancers.

In order to assess the cost-effectiveness, a transition analysis needs to be performed to estimate time spent in the defined health states. To model over-the-time transitions among predefined states, a multistage homogenous Markov model with four states was constructed. State for women with cervical precancerosis, another state for women with cervical cancer, a state defining death, and a state for alive women without cancer or precancerosis. To each state, total average costs per cycle and health-related quality of life were assigned. Transition probabilities for every possible transition were derived from the data provided by ÚZIS. Outputs of the model – total costs and quality adjusted life years were obtained and used to compute the incremental cost-effectiveness ratio (ICER).

ICER is a summary measure used to assess the cost-effectiveness of an intervention compared to the current situation. The author introduced two designed strategies. The first proposes the increase in vaccination coverage of thirteen-year-old women, whose vaccination costs are fully reimbursed by the health insurance funds. The increase in immunization coverage would be fuelled by a campaign promoting vaccination. The second strategy introduced the vaccination of women aged thirteen to fifteen together with a vaccination campaign. Both strategies appear to be cost-effective considering the cost-effectiveness threshold of 1.2 million CZK/QALY. Such result is in compliance with the reviewed literature.

Despite the fact that the results are in line with the literature, the analysis has its setbacks. The arose problems are the following. Firstly, there was a problem with obtaining the data needed for the analysis. The data obtained from the NZIS do not precisely reflect the epidemiology of cervical cancer and cervical precancerosis. In order to model the transition among the states more precisely, one needs clinical data. Additionally, the cost data that were not provided would increase the precision of the analysis. Secondly, the decrease in HRQoL after overcoming the disease is not taken into. The main problem of HRQoL is an assumption, that a woman who do not suffer from either precancerous or cancerous stage of cervical carcinoma has a HRQoL value equal to the perfect health. Therefore, when a disease would be adverted, a substantial drop in HRQoL would be adverted as well. In reality, the adverted drop would not be that significant.

Limitations of the model include the relatively low number of states. Already published models had included numerous states representing both precancerous and cancerous stages of progression of the disease. Additionally, the age adjustment of the probabilities, especially the probability representing the natural mortality, would be wise to implement. However, the Markov model with such improvement would require a more advanced methodology of Markov chains.

Overcoming the issues and limitations of this analysis is a topic for further research.

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List of Appendices

Appendix no. 1: Additional information about cervical precancerosis

Cervical precancerosis, known as dysplasia or intraepithelial neoplasia (CIN), is a precancerous condition in which the growth of abnormal cells and the changes in the surface of the cervical epithelium occurs. Precanceroses could be divided into the following stages. Usually, there are no symptoms associated with these conditions.

- CIN I - low grade squamous intraepithelial lesion (LG SIL)
  Refers to the acute HPV infection. In most cases of CIN I in young women (approximately up to the 35th year of age), the immune system is able to clear the condition on its own. CIN I indicate dysplasia that involves about one-third of the thickness of the epithelium.

- CIN II - high grade squamous intraepithelial lesion (HG SIL)
  CIN II characterizes the chronic HPV infection, which affects about one-third to two-thirds of the epithelial layer.

- CIN III - high grade squamous intraepithelial lesion (HG SIL)
  Indicate the chronic HPV infection with severe changes of cervical epithelium affecting more than two-thirds of its thickness (Cleveland Clinic, 2014).

Since 2013, there is an effort to divide the stages into LG SIL and HG SIL. However, CIN I/II/III is still being used.

Appendix no. 2: Additional information about cervical carcinoma stages

Early cervical cancer is often asymptomatic, while locally advanced disease could cause symptoms including abnormal vaginal bleeding (between menstrual periods, during or after sexual intercourse), vaginal discharge, or pelvic pain (Marth et al., 2017). The time interval needed for cervical cancer to develop is said to be from 15 to 20 years in a woman with a regular immune system. However, it can take only 5 to 10 years in women with a weakened immune system, such as those with untreated HIV or other sexually transferred infections and diseases (World Health Organization, 2020). To evaluate the progression of cervical cancer, two classifications of staging are being used: TNM (where "T" stands for the size of the tumour, "N" for regional lymph nodes, and "M" stands for distant metastasis). And The International Federation of Gynaecology and Obstetrics classification (FIGO). The table below shows the TNM, FIGO, and the description of surgical-pathological findings.

TNM	FIGO	Surgical-pathological findings
Tis		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma restrained to the cervix
T1a	IA	Invasive carcinoma, stromal invasion with a maximum depth of < 5.0 mm, measured from the base of the epithelium
T1a1	IA1	Measured stromal invasion < 3.0 mm in depth
T1a2	IA2	Measured stromal invasion ≥ 3.0 mm and < 5.0 mm
T1b	IB	Invasive carcinoma with measured most profound invasion ≥ 5 mm, lesion limited to the cervix
T1b1	IB1	Invasive carcinoma with ≥ 5 mm depth of stromal invasion and < 2 cm in the greatest dimension
T1b2	IB2	Invasive carcinoma, 2 cm to < 4 cm in greatest dimension
T1b3	IB3	Invasive carcinoma, ≥ 4 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina
T2a	IIA	Involvement is limited to the upper two-thirds of the vagina without parametrial invasion
T2a1	IIA1	Invasive carcinoma < 4 cm in greatest dimension
T2a2	IIA2	Invasive carcinoma ≥ 4 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion but not up to the pelvic wall
T3	III	Carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes
T3a	IIIA	A tumour involves the lower third of the vagina, with no extension to the pelvic wall
T3b	IIIB	Tumor extends to the pelvic wall and/or causes hydronephrosis or non-functional kidney
T3c	IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent
T3c1	IIIC1	Pelvic lymph node metastasis only
T3c2	IIIC2	Para-aortic lymph node metastasis
T4	IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum.

Note: author's creation, source of the data:(Boardman, 2020)

Appendix no. 3: Request for the data from NZIS

1. The number of women who had a reported diagnosis of C53 at any time during the year 2018 and at the same time did not have a reported diagnosis of N87. Only women who did not die in 2018 and were born before 2018 would be identified.

- The number of women from the part **1.**, who had a reported diagnosis of C53 in 2019 as well. At the same time, did not have a reported diagnosis of N87 and did not die in 2019.
- The number of women from the part **1.**, who had a reported diagnosis of N87 in 2019 and did not die in 2019. (These women may or may not have a reported diagnosis of C53 in 2019.)
- The number of women from the part **1.**, who did not have a reported diagnosis of either C53 or N87 in 2019 and did not die in 2019.
- The number of women from the part **1.**, who died in 2019.

Each woman from the part **1.**, would thus fall into just one of the above sub-points.

2. The number of women who had a reported diagnosis of N87 at any time during the year 2018 and at the same time did not have a reported diagnosis of C53. Only women who did not die in 2018 and were born before 2018 would be identified.

- The number of women from the part **2.**, who had a reported diagnosis of N87 in 2019 as well. At the same time, did not have a reported diagnosis of C53 and did not die in 2019.
- The number of women from the part **2.**, who had a reported diagnosis of C53 in 2019 and did not die in 2019. (These women may or may not have a reported diagnosis of N87 in 2019.)
- The number of women from the part **2.**, who did not have a reported diagnosis of either C53 or N87 in 2019 and did not die in 2019.
- The number of women from the part **2.**, who died in 2019.

Each woman from the pert **2.**, would thus fall into just one of the above sub-points.

3. The number of women who did not have a reported diagnosis of either N87 or C53. Only women who did not die in 2018 and were born before 2018 would be identified.

- The number of women from the part **3.**, who had a reported diagnosis of N87 in 2019. At the same time, did not have a reported diagnosis of C53 in 2019 and did not die in 2019.

- The number of women from the part **3.**, who had a reported diagnosis of C53 in 2019 and did not die in 2019. (These women may or may not have a reported diagnosis of N87 in 2019.)
- The number of women from the part **3.**, who did not have a reported diagnosis of either C53 or N87 in 2019 and did not die in 2019.
- The number of women from the part **3.**, who died in 2019.

Each woman from the part **3.**, would thus fall into just one of the above sub-points.

Appendix no. 4: Calculations of costs and QALY for strategy 1

Total costs and QALY of the whole cohort assuming the efficacy of the vaccine to be 90%

	90%	Costs 0%	QALY 0%	Costs 3%	QALY 3%	Costs 5%	QALY 5%
0% VACC		55301787262	2459371	26008927163	1157091	18247508124	812018.3
100% VACC		54901044828	2462801	25843429211	1159353	18139984894	813794.9

Current	90%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Vacc.	0.658	36124887497	1620523.06	17004976421	762854.27	11936110060	535477.04
Unvacc.	0.342	18913211244	841104.88	8895053090	395725.12	6240647778	277710.26
SUBTOTAL		55038098740	2461627.94	25900029511	1158579.40	18176757839	813187.30
VACC	32900	133515438		133515438		133515438	
TOTAL		55171614178		26033544949		18310273277	

Intervention	90%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Vacc.	0.8	43920835862	1970240.8	20674743369	927482.4	14511987915	651035.92
Unvacc.	0.2	11060357452	491874.2	5201785433	231418.2	3649501625	162403.66
SUBTOTAL		54981193315	2462115	25876528801	1158900.6	18161489540	813439.58
VACC	40000	162328800		162328800		162328800	
TOTAL		55143522115		26038857601		18323818340	

Note: The table displays the calculation of total costs and QALY for strategy 1 as well as for the current situation. The campaign costs were added when calculating the ICER, thus are not included here. 90% vaccine efficacy was assumed. The percentages of vaccinated and unvaccinated women were calculated proportionally according to the orange and green row representing 0% and 100% vaccination coverage. The vaccination costs were added.

Total costs and QALY of the whole cohort assuming the efficacy of the vaccine to be 80%

	80%	Costs 0%	QALY 0%	Costs 3%	QALY 3%	Costs 5%	QALY 5%
0% VACC		55301787262	2459371	26008927163	1157091	18247508124	812018.3
100% VACC		54946539582	2462412	25862210688	1159097	18152182065	813593.3

Current	80%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Vacc.	0.658	36154823045	1620267.10	17017334633	762685.83	11944135799	535344.39
Unvacc.	0.342	18913211244	841104.88	8895053090	395725.12	6240647778	277710.26
SUBTOTAL		55068034289	2461371.98	25912387722	1158410.95	18184783577	813054.65
VACC	32900	133515438		133515438		133515438	
TOTAL		55201549727		26045903160		18318299015	

Intervention	80%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Vacc.	0.8	43957231666	1969929.6	20689768550	927277.6	14521745652	650874.64
Unvacc.	0.2	11060357452	491874.2	5201785433	231418.2	3649501625	162403.66
SUBTOTAL		55017589118	2461803.8	25891553983	1158695.8	18171247277	813278.30
VACC	40000	162328800		162328800		162328800	
TOTAL		55179917918		26053882783		18333576077	

Note: The table displays the calculation of total costs and QALY for strategy 1 as well as for the current situation. The campaign costs were added when calculating the ICER, thus are not included here. 80% vaccine efficacy was assumed. The percentages of vaccinated and unvaccinated women were calculated proportionally according to the orange and green row representing 0% and 100% vaccination coverage. The vaccination costs were added.

Appendix no. 5: Calculations of costs and QALY for strategy 2

Total costs and QALY of the whole cohort assuming the efficacy of the vaccine to be 90% for the current setting

13 only	90%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Inflow	I	6085366039	272366.6	5814521764	260249.40	5645471993	252686.30
Inflow	II	160600785715	7141114.0	72276389749	3214450.00	48978290429	2178617.69
0% VACC		166686151754	7413480.6	78090911513	3474699.40	54623762422	2431303.99
Inflow	I	6075368988	272716.0	5805029318	260581.30	5636293285	253007.30
Inflow	II	159418293867	7151216.0	71799290386	3220858.71	48674364199	2183529.25
100% VACC		165493662855	7423932.0	77604319704	3481440.01	54310657484	2436536.55

Current	90%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Vacc.	0,658	108894830159	4884947.26	51063642365	2290787.52	35736412624	1603241.05
Unvacc.	0,342	57006663900	2535410.37	26707091738	1188347.19	18681326748	831505.96
SUBTOTAL		165901494058	7420357.62	77770734102	3479134.72	54417739373	2434747.02
VACC	32900	400546314		388993182		381775436	
TOTAL		66302040372		78159727285		54799514809	

Note: The table displays the calculation of total costs and QALY for the current situation. 90% vaccine efficacy was assumed. The percentages of vaccinated and unvaccinated women were calculated proportionally according to the orange and green row representing 0% and 100% vaccination coverage. The vaccination costs were added.

Total costs and QALY of the whole cohort assuming the efficacy of the vaccine to be 90% for strategy 2

13 - 15	90%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Inflow	I	6628984053	296499.2	6342558632	283695.20	6163608212	275695.50
Inflow	II	160069766152	7117204.0	72039248214	3203641.25	48818498690	2171268.93
0% VACC		166698750205	7413703.2	78381806846	3487336.45	54982106902	2446964.43
Inflow	I	6615825607	296956.5	6330051635	284130.00	6151506480	276116.30
Inflow	II	158884544552	7127243.0	71559081434	3210056.56	48511611246	2176204.08
100% VACC		165500370159	7424199.5	77889133069	3494186.56	54663117726	2452320.38

Intervention	90%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Vacc.	0,8	132400296127	5939359.60	62311306455	2795349.25	43730494181	1961856.31
Unvacc.	0,2	33339750041	1482740.64	15676361369	697467.29	10996421380	489392.89
SUBTOTAL		165740046168	7422100.24	77987667824	3492816.53	54726915561	2451249.19
VACC	120000	568150800		568150800		568150800	
TOTAL		166308196968		78555818624		55295066361	

Note: The table displays the calculation of total costs and QALY for strategy 2. 90% vaccine efficacy was assumed. The percentages of vaccinated and unvaccinated women were calculated proportionally according to the orange and green row representing 0% and 100% vaccination coverage. The vaccination costs were added.

Total costs and QALY of the whole cohort assuming the efficacy of the vaccine to be 80% for the current setting

13 only	80%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Inflow	I	6085366039	272366.6	5814521764	260249.40	5645471993	252686.30
Inflow	II	160600785715	7141114.0	72276389749	3214450.00	48978290429	2178617.69
0% VACC		166686151754	7413480.6	78090911513	3474699.40	54623762422	2431303.99
Inflow	I	6076483255	272677.1	5806087318	260544.30	5636293285	253007.30
Inflow	II	159553137615	7150095.0	71853715343	3220142.33	48709037541	2182979.59
100% VACC		165629620870	7422772.1	77659802661	3480686.63	54345330826	2435986.89

	80%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Vacc.	0,658	108984290532	4884184.04	51100150151	2290291.80	35759227684	1602879.38
Unvacc.	0,342	57006663900	2535410.37	26707091738	1188347.19	18681326748	831505.96
SUBTOTAL		165990954432	7419594.41	77807241888	3478639.00	54440554432	2434385.34
VACC	32900	400546314		388993182		381775436	
TOTAL		166391500746		78196235071		54822329868	

Note: The table displays the calculation of total costs and QALY for the current situation. 80% vaccine efficacy was assumed. The percentages of vaccinated and unvaccinated women were calculated proportionally according to the orange and green row representing 0% and 100% vaccination coverage. The vaccination costs were added.

Total costs and QALY of the whole cohort assuming the efficacy of the vaccine to be 80% for strategy 2

13 - 15	80%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Inflow	I	6628984053	296499.2	6342558632	283695.20	6163608212	275695.50
Inflow	II	160069766152	7117204.0	72039248214	3203641.25	48818498690	2171268.93
0% VACC		166698750205	7413703.2	78381806846	3487336.45	54982106902	2446964.43
Inflow	I	6617292882	296905.5	6331446227	284081.50	6152855857	276069.40
Inflow	II	159019609201	7126125.0	71613808527	3209338.30	48546586455	2175649.89
100% VACC		165636902083	7423030.5	77945254754	3493419.80	54699442312	2451719.29

	80%	**Costs 0%**	**QALY 0%**	**Costs 3%**	**QALY 3%**	**Costs 5%**	**QALY 5%**
Vacc.	0,8	132509521666	5938424.40	62356203803	2794735.84	43759553850	1961375.43
Unvacc.	0,2	33339750041	1482740.64	15676361369	697467.29	10996421380	489392.89
SUBTOTAL		165849271707	7421165.04	78032565172	3492203.13	54755975230	2450768.32
VACC	120000	568150800		568150800		568 150 800	
TOTAL		166417422507		78600715972		55324126030	

Note: The table displays the calculation of total costs and QALY for strategy 2. 80% vaccine efficacy was assumed. The percentages of vaccinated and unvaccinated women were calculated proportionally according to the orange and green row representing 0% and 100% vaccination coverage. The vaccination costs were added.

Appendix no. 6: Costs, QALY, and number of women at each state for each cycle for strategy 1 (0% vaccinated)

strategy name	Markov cycle	H count	N87 count	C53 count	D count
S1 zero	1	49350	375	25	250
S1 zero	2	48280,08	907,8	66,475	745,65
S1 zero	3	47542,41	1129,967	93,6368	1233,989
S1 zero	4	46953,45	1218,5	111,1344	1716,917
S1 zero	5	46433,17	1249,535	122,1835	2195,112
S1 zero	6	45946,41	1255,839	128,9624	2668,785
S1 zero	7	45477,56	1251,527	132,9285	3137,982
S1 zero	8	45019,56	1242,682	135,0488	3602,705
S1 zero	9	44569,16	1231,933	135,9619	4062,949
S1 zero	10	44124,78	1220,419	136,0881	4518,718
S1 zero	11	43685,64	1208,632	135,7033	4970,028
S1 zero	12	43251,32	1196,79	134,9886	5416,901
S1 zero	13	42821,58	1184,986	134,0624	5859,367
S1 zero	14	42396,28	1173,262	133,0024	6297,46
S1 zero	15	41975,29	1161,637	131,8594	6731,218
S1 zero	16	41558,54	1150,118	130,6665	7160,678
S1 zero	17	41145,97	1138,709	129,4453	7585,881
S1 zero	18	40737,51	1127,41	128,2101	8006,867
S1 zero	19	40333,13	1116,222	126,9699	8423,676
S1 zero	20	39932,77	1105,144	125,7309	8836,351
S1 zero	21	39536,4	1094,175	124,4968	9244,929
S1 zero	22	39143,96	1083,315	123,2701	9649,454
S1 zero	23	38755,42	1072,563	122,0525	10049,96
S1 zero	24	38370,74	1061,917	120,845	10446,5
S1 zero	25	37989,88	1051,377	119,648	10839,1
S1 zero	26	37612,8	1040,942	118,4621	11227,8
S1 zero	27	37239,46	1030,609	117,2873	11612,64
S1 zero	28	36869,83	1020,38	116,1239	11993,67
S1 zero	29	36503,87	1010,252	114,9717	12370,91
S1 zero	30	36141,54	1000,224	113,8309	12744,4
S1 zero	31	35782,81	990,2964	112,7012	13114,2
S1 zero	32	35427,64	980,4669	111,5827	13480,32
S1 zero	33	35075,99	970,735	110,4752	13842,8
S1 zero	34	34727,83	961,0998	109,3787	14201,69
S1 zero	35	34383,13	951,5601	108,2931	14557,01
S1 zero	36	34041,85	942,1151	107,2182	14908,81
S1 zero	37	33703,96	932,7639	106,154	15257,12
S1 zero	38	33369,42	923,5055	105,1004	15601,97
S1 zero	39	33038,21	914,339	104,0572	15943,4
S1 zero	40	32710,28	905,2635	103,0243	16281,44
S1 zero	41	32385,6	896,2781	102,0017	16616,12
S1 zero	42	32064,15	887,3818	100,9893	16947,48
S1 zero	43	31745,89	878,5739	99,98691	17275,55
S1 zero	44	31430,79	869,8534	98,99446	17600,37
S1 zero	45	31118,81	861,2194	98,01186	17921,96
S1 zero	46	30809,93	852,6711	97,03902	18240,36
S1 zero	47	30504,12	844,2077	96,07584	18555,59
S1 zero	48	30201,34	835,8283	95,12221	18867,7
S1 zero	49	29901,57	827,5321	94,17805	19176,72
S1 zero	50	29604,78	819,3182	93,24326	19482,66
S1 zero	51	29310,93	811,1858	92,31775	19785,57
S1 zero	52	29019,99	803,1342	91,40142	20085,47
S1 zero	53	28731,95	795,1624	90,49419	20382,4
S1 zero	54	28446,76	787,2698	89,59597	20676,37
S1 zero	55	28164,41	779,4556	88,70666	20967,43
S1 zero	56	27884,85	771,7189	87,82618	21255,6
S1 zero	57	27608,07	764,059	86,95444	21540,91

S1 zero	58	27334,04	756,4751	86,09135	21823,39
S1 zero	59	27062,73	748,9665	85,23682	22103,07
S1 zero	60	26794,11	741,5325	84,39078	22379,96
S1 zero	61	26528,16	734,1722	83,55314	22654,11
S1 zero	62	26264,85	726,885	82,72381	22925,54
S1 zero	63	26004,15	719,6701	81,90271	23194,28
S1 zero	64	25746,04	712,5268	81,08977	23460,35
S1 zero	65	25490,49	705,4544	80,28489	23723,77
S1 zero	66	25237,48	698,4522	79,488	23984,58
S1 zero	67	24986,97	691,5196	78,69902	24242,81
S1 zero	68	24738,96	684,6557	77,91787	24498,47

strategy names	Markov cycle	costs	QALY	costs 3%	QALY 3%	costs 5%	QALY 5%
S1 zero	1	1,11E+09	49700,5	1,08E+09	48252,91	1,06E+09	47333,81
S1 zero	2	1,1E+09	49132,56	1,04E+09	46312,15	9,98E+08	44564,68
S1 zero	3	1,09E+09	48610,81	9,98E+08	44485,78	9,42E+08	41991,85
S1 zero	4	1,08E+09	48112,37	9,6E+08	42747,22	8,89E+08	39582,17
S1 zero	5	1,07E+09	47627,12	9,23E+08	41083,57	8,39E+08	37317,09
S1 zero	6	1,06E+09	47150,52	8,88E+08	39487,81	7,91E+08	35184,44
S1 zero	7	1,05E+09	46680,48	8,53E+08	37955,5	7,46E+08	33174,95
S1 zero	8	1,04E+09	46216,03	8,2E+08	36483,36	7,03E+08	31280,83
S1 zero	9	1,03E+09	45756,67	7,89E+08	35068,68	6,63E+08	29495,16
S1 zero	10	1,02E+09	45302,13	7,58E+08	33709,04	6,26E+08	27811,58
S1 zero	11	1,01E+09	44852,24	7,29E+08	32402,21	5,9E+08	26224,18
S1 zero	12	9,99E+08	44406,91	7,01E+08	31146,11	5,56E+08	24727,43
S1 zero	13	9,89E+08	43966,04	6,73E+08	29938,74	5,24E+08	23316,13
S1 zero	14	9,79E+08	43529,59	6,47E+08	28778,19	4,95E+08	21985,4
S1 zero	15	9,69E+08	43097,49	6,22E+08	27662,64	4,66E+08	20730,63
S1 zero	16	9,6E+08	42669,69	5,98E+08	26590,34	4,4E+08	19547,48
S1 zero	17	9,5E+08	42246,14	5,75E+08	25559,61	4,15E+08	18431,85
S1 zero	18	9,41E+08	41826,81	5,53E+08	24568,84	3,91E+08	17379,9
S1 zero	19	9,32E+08	41411,64	5,31E+08	23616,48	3,69E+08	16387,99
S1 zero	20	9,22E+08	41000,59	5,11E+08	22701,03	3,48E+08	15452,69
S1 zero	21	9,13E+08	40593,63	4,91E+08	21821,07	3,28E+08	14570,77
S1 zero	22	9,04E+08	40190,7	4,72E+08	20975,23	3,09E+08	13739,19
S1 zero	23	8,95E+08	39791,78	4,54E+08	20162,17	2,91E+08	12955,06
S1 zero	24	8,86E+08	39396,81	4,36E+08	19380,62	2,75E+08	12215,69
S1 zero	25	8,77E+08	39005,77	4,19E+08	18629,37	2,59E+08	11518,51
S1 zero	26	8,69E+08	38618,61	4,03E+08	17907,24	2,44E+08	10861,13
S1 zero	27	8,6E+08	38235,29	3,87E+08	17213,11	2,3E+08	10241,26
S1 zero	28	8,52E+08	37855,77	3,72E+08	16545,88	2,17E+08	9656,767
S1 zero	29	8,43E+08	37480,02	3,58E+08	15904,51	2,05E+08	9105,634
S1 zero	30	8,35E+08	37108,01	3,44E+08	15288,01	1,93E+08	8585,956
S1 zero	31	8,26E+08	36739,68	3,31E+08	14695,4	1,82E+08	8095,937
S1 zero	32	8,18E+08	36375,01	3,18E+08	14125,76	1,72E+08	7633,884
S1 zero	33	8,1E+08	36013,96	3,05E+08	13578,21	1,62E+08	7198,202
S1 zero	34	8,02E+08	35656,49	2,94E+08	13051,88	1,53E+08	6787,385
S1 zero	35	7,94E+08	35302,58	2,82E+08	12545,95	1,44E+08	6400,014
S1 zero	36	7,86E+08	34952,17	2,71E+08	12059,63	1,36E+08	6034,752
S1 zero	37	7,78E+08	34605,24	2,61E+08	11592,17	1,28E+08	5690,335
S1 zero	38	7,71E+08	34261,76	2,51E+08	11142,82	1,21E+08	5365,576
S1 zero	39	7,63E+08	33921,69	2,41E+08	10710,89	1,14E+08	5059,351
S1 zero	40	7,55E+08	33584,99	2,32E+08	10295,71	1,07E+08	4770,602
S1 zero	41	7,48E+08	33251,63	2,23E+08	9896,616	1,01E+08	4498,334
S1 zero	42	7,41E+08	32921,58	2,14E+08	9512,995	95413409	4241,604
S1 zero	43	7,33E+08	32594,81	2,06E+08	9144,244	89967960	3999,527
S1 zero	44	7,26E+08	32271,28	1,98E+08	8789,787	84833294	3771,265
S1 zero	45	7,19E+08	31950,97	1,9E+08	8449,069	79991674	3556,031
S1 zero	46	7,12E+08	31633,83	1,83E+08	8121,559	75426377	3353,081
S1 zero	47	7,05E+08	31319,84	1,76E+08	7806,744	71121631	3161,713
S1 zero	48	6,98E+08	31008,96	1,69E+08	7504,132	67062565	2981,267
S1 zero	49	6,91E+08	30701,18	1,62E+08	7213,25	63235160	2811,12
S1 zero	50	6,84E+08	30396,44	1,56E+08	6933,644	59626193	2650,683

S1 zero	51	6,77E+08	30094,74	1,5E+08	6664,876	56223197	2499,403
S1 zero	52	6,7E+08	29796,02	1,44E+08	6406,526	53014418	2356,757
S1 zero	53	6,64E+08	29500,27	1,39E+08	6158,191	49988770	2222,251
S1 zero	54	6,57E+08	29207,46	1,33E+08	5919,481	47135803	2095,423
S1 zero	55	6,5E+08	28917,55	1,28E+08	5690,025	44445661	1975,832
S1 zero	56	6,44E+08	28630,53	1,23E+08	5469,464	41909051	1863,067
S1 zero	57	6,38E+08	28346,35	1,18E+08	5257,451	39517211	1756,738
S1 zero	58	6,31E+08	28064,99	1,14E+08	5053,657	37261879	1656,477
S1 zero	59	6,25E+08	27786,42	1,09E+08	4857,763	35135263	1561,939
S1 zero	60	6,19E+08	27510,62	1,05E+08	4669,462	33130017	1472,795
S1 zero	61	6,13E+08	27237,55	1,01E+08	4488,46	31239216	1388,74
S1 zero	62	6,07E+08	26967,2	97052604	4314,475	29456326	1309,481
S1 zero	63	6,01E+08	26699,53	93290565	4147,233	27775190	1234,746
S1 zero	64	5,95E+08	26434,52	89674354	3986,475	26190000	1164,277
S1 zero	65	5,89E+08	26172,13	86198318	3831,947	24695280	1097,829
S1 zero	66	5,83E+08	25912,36	82857022	3683,41	23285867	1035,174
S1 zero	67	5,77E+08	25655,16	79645245	3540,63	21956892	976,0939
S1 zero	68	5,71E+08	25400,51	76557966	3403,385	20703765	920,3861

Appendix no. 7: Costs, QALY, and number of women at each state for each cycle for strategy 1 (100% vaccinated)

strategy name	Markov cycle	H count	N87 count	C53 count	D count
S1 hundred	1	49710	37,5	2,5	250
S1 hundred	2	49154,68	91,32	6,6835	747,315
S1 hundred	3	48636,56	114,5499	9,475801	1239,419
S1 hundred	4	48137,97	124,1854	11,2994	1726,544
S1 hundred	5	47650,96	127,7745	12,46328	2208,805
S1 hundred	6	47171,88	128,6726	13,18409	2686,268
S1 hundred	7	46699,03	128,3731	13,61011	3158,982
S1 hundred	8	46231,63	127,5421	13,84127	3626,992
S1 hundred	9	45769,24	126,4774	13,94428	4090,338
S1 hundred	10	45311,66	125,3128	13,96338	4549,064
S1 hundred	11	44858,75	124,1087	13,92781	5003,213
S1 hundred	12	44410,42	122,8925	13,85681	5452,829
S1 hundred	13	43966,6	121,6769	13,76304	5897,955
S1 hundred	14	43527,24	120,4678	13,6548	6338,635
S1 hundred	15	43092,28	119,2677	13,53756	6774,913
S1 hundred	16	42661,67	118,0781	13,41486	7206,833
S1 hundred	17	42235,37	116,8994	13,28906	7634,437
S1 hundred	18	41813,34	115,7321	13,16167	8057,769
S1 hundred	19	41395,52	114,5762	13,03369	8476,87
S1 hundred	20	40981,88	113,4316	12,90577	8891,785
S1 hundred	21	40572,37	112,2983	12,77833	9302,553
S1 hundred	22	40166,96	111,1763	12,65164	9709,217
S1 hundred	23	39765,59	110,0655	12,52587	10111,82
S1 hundred	24	39368,24	108,9657	12,40114	10510,39
S1 hundred	25	38974,86	107,8769	12,2775	10904,99
S1 hundred	26	38585,4	106,799	12,155	11295,64
S1 hundred	27	38199,84	105,7319	12,03366	11682,39
S1 hundred	28	37818,14	104,6754	11,9135	12065,27
S1 hundred	29	37440,24	103,6294	11,79451	12444,33
S1 hundred	30	37066,13	102,5939	11,67668	12819,6
S1 hundred	31	36695,75	101,5687	11,56003	13191,12
S1 hundred	32	36329,07	100,5538	11,44453	13558,93
S1 hundred	33	35966,06	99,54907	11,33018	13923,06
S1 hundred	34	35606,67	98,55434	11,21697	14283,56
S1 hundred	35	35250,88	97,56955	11,10489	14640,45
S1 hundred	36	34898,64	96,5946	10,99393	14993,77
S1 hundred	37	34549,92	95,62939	10,88408	15343,57
S1 hundred	38	34204,68	94,67382	10,77532	15689,87
S1 hundred	39	33862,9	93,72781	10,66765	16032,71
S1 hundred	40	33524,52	92,79124	10,56106	16372,12
S1 hundred	41	33189,53	91,86404	10,45553	16708,15
S1 hundred	42	32857,89	90,9461	10,35105	17040,81
S1 hundred	43	32529,56	90,03733	10,24762	17370,15
S1 hundred	44	32204,52	89,13765	10,14522	17696,2
S1 hundred	45	31882,72	88,24695	10,04385	18018,99
S1 hundred	46	31564,13	87,36515	9,943486	18338,56
S1 hundred	47	31248,73	86,49217	9,844127	18654,93
S1 hundred	48	30936,48	85,62791	9,745761	18968,14
S1 hundred	49	30627,36	84,77228	9,648378	19278,22
S1 hundred	50	30321,32	83,9252	9,551967	19585,21
S1 hundred	51	30018,33	83,08659	9,456521	19889,12
S1 hundred	52	29718,38	82,25636	9,362027	20190
S1 hundred	53	29421,42	81,43442	9,268479	20487,88
S1 hundred	54	29127,43	80,6207	9,175865	20782,77
S1 hundred	55	28836,38	79,81511	9,084176	21074,72
S1 hundred	56	28548,24	79,01757	8,993403	21363,75
S1 hundred	57	28262,97	78,22799	8,903538	21649,9

S1 hundred	58	27980,56	77,44631	8,814571	21933,18
S1 hundred	59	27700,97	76,67244	8,726492	22213,64
S1 hundred	60	27424,17	75,9063	8,639294	22491,29
S1 hundred	61	27150,13	75,14781	8,552967	22766,16
S1 hundred	62	26878,84	74,39691	8,467502	23038,3
S1 hundred	63	26610,26	73,65351	8,382892	23307,71
S1 hundred	64	26344,36	72,91753	8,299127	23574,43
S1 hundred	65	26081,11	72,18892	8,216199	23838,48
S1 hundred	66	25820,5	71,46758	8,1341	24099,9
S1 hundred	67	25562,49	70,75345	8,052821	24358,7
S1 hundred	68	25307,06	70,04645	7,972354	24614,92

strategy name	Markov cycle	costs	QALY	costs 3%	QALY 3%	costs 5%	QALY 5%
S1 hundred	1	1,11E+09	49745,05	1,08E+09	48296,17	1,06E+09	47376,24
S1 hundred	2	1,1E+09	49240,43	1,03E+09	46413,83	9,95E+08	44662,53
S1 hundred	3	1,09E+09	48744,85	9,94E+08	44608,45	9,38E+08	42107,64
S1 hundred	4	1,08E+09	48256,07	9,56E+08	42874,89	8,85E+08	39700,39
S1 hundred	5	1,06E+09	47773,03	9,19E+08	41209,43	8,34E+08	37431,42
S1 hundred	6	1,05E+09	47295,23	8,83E+08	39609,01	7,87E+08	35292,43
S1 hundred	7	1,04E+09	46822,41	8,49E+08	38070,9	7,42E+08	33275,81
S1 hundred	8	1,03E+09	46354,41	8,16E+08	36592,6	6,99E+08	31374,49
S1 hundred	9	1,02E+09	45891,15	7,84E+08	35171,74	6,59E+08	29581,84
S1 hundred	10	1,01E+09	45432,54	7,54E+08	33806,08	6,22E+08	27891,64
S1 hundred	11	1E+09	44978,54	7,24E+08	32493,45	5,86E+08	26298,02
S1 hundred	12	9,93E+08	44529,08	6,96E+08	31231,8	5,53E+08	24795,46
S1 hundred	13	9,83E+08	44084,12	6,69E+08	30019,14	5,21E+08	23378,75
S1 hundred	14	9,73E+08	43643,61	6,43E+08	28853,57	4,91E+08	22042,99
S1 hundred	15	9,63E+08	43207,5	6,18E+08	27733,25	4,63E+08	20783,55
S1 hundred	16	9,54E+08	42775,75	5,94E+08	26656,43	4,37E+08	19596,06
S1 hundred	17	9,44E+08	42348,32	5,71E+08	25621,43	4,12E+08	18476,43
S1 hundred	18	9,35E+08	41925,16	5,49E+08	24626,61	3,88E+08	17420,77
S1 hundred	19	9,25E+08	41506,23	5,28E+08	23670,42	3,66E+08	16425,42
S1 hundred	20	9,16E+08	41091,48	5,07E+08	22751,36	3,45E+08	15486,95
S1 hundred	21	9,07E+08	40680,88	4,88E+08	21867,98	3,26E+08	14602,09
S1 hundred	22	8,98E+08	40274,38	4,69E+08	21018,9	3,07E+08	13767,79
S1 hundred	23	8,89E+08	39871,94	4,5E+08	20202,78	2,89E+08	12981,16
S1 hundred	24	8,8E+08	39473,53	4,33E+08	19418,36	2,73E+08	12239,47
S1 hundred	25	8,71E+08	39079,09	4,16E+08	18664,39	2,57E+08	11540,16
S1 hundred	26	8,62E+08	38688,6	4E+08	17939,7	2,43E+08	10880,81
S1 hundred	27	8,54E+08	38302,01	3,84E+08	17243,15	2,29E+08	10259,13
S1 hundred	28	8,45E+08	37919,28	3,69E+08	16573,64	2,16E+08	9672,967
S1 hundred	29	8,37E+08	37540,38	3,55E+08	15930,12	2,03E+08	9120,297
S1 hundred	30	8,29E+08	37165,26	3,41E+08	15311,59	1,92E+08	8599,203
S1 hundred	31	8,2E+08	36793,89	3,28E+08	14717,08	1,81E+08	8107,882
S1 hundred	32	8,12E+08	36426,23	3,15E+08	14145,66	1,7E+08	7644,634
S1 hundred	33	8,04E+08	36062,25	3,03E+08	13596,41	1,61E+08	7207,853
S1 hundred	34	7,96E+08	35701,9	2,91E+08	13068,5	1,52E+08	6796,028
S1 hundred	35	7,88E+08	35345,15	2,8E+08	12561,08	1,43E+08	6407,733
S1 hundred	36	7,8E+08	34991,97	2,69E+08	12073,36	1,35E+08	6041,623
S1 hundred	37	7,72E+08	34642,32	2,59E+08	11604,59	1,27E+08	5696,432
S1 hundred	38	7,65E+08	34296,16	2,49E+08	11154,01	1,2E+08	5370,963
S1 hundred	39	7,57E+08	33953,46	2,39E+08	10720,93	1,13E+08	5064,09
S1 hundred	40	7,49E+08	33614,18	2,3E+08	10304,66	1,06E+08	4774,75
S1 hundred	41	7,42E+08	33278,3	2,21E+08	9904,554	1E+08	4501,942
S1 hundred	42	7,34E+08	32945,77	2,12E+08	9519,984	94627589	4244,721
S1 hundred	43	7,27E+08	32616,56	2,04E+08	9150,347	89220986	4002,196
S1 hundred	44	7,2E+08	32290,65	1,96E+08	8795,061	84123292	3773,528
S1 hundred	45	7,13E+08	31967,99	1,88E+08	8453,57	79316858	3557,925
S1 hundred	46	7,06E+08	31648,55	1,81E+08	8125,339	74785042	3354,641
S1 hundred	47	6,98E+08	31332,31	1,74E+08	7809,852	70512155	3162,972
S1 hundred	48	6,92E+08	31019,22	1,67E+08	7506,615	66483401	2982,253
S1 hundred	49	6,85E+08	30709,27	1,61E+08	7215,151	62684833	2811,861
S1 hundred	50	6,78E+08	30402,41	1,55E+08	6935,005	59103297	2651,203

S1 hundred	51	6,71E+08	30098,62	1,49E+08	6665,735	55726396	2499,725
S1 hundred	52	6,64E+08	29797,86	1,43E+08	6406,921	52542435	2356,902
S1 hundred	53	6,58E+08	29500,11	1,37E+08	6158,156	49540392	2222,239
S1 hundred	54	6,51E+08	29205,33	1,32E+08	5919,05	46709872	2095,27
S1 hundred	55	6,45E+08	28913,5	1,27E+08	5689,228	44041076	1975,556
S1 hundred	56	6,38E+08	28624,59	1,22E+08	5468,329	41524763	1862,681
S1 hundred	57	6,32E+08	28338,56	1,17E+08	5256,007	39152221	1756,256
S1 hundred	58	6,25E+08	28055,39	1,13E+08	5051,93	36915236	1655,911
S1 hundred	59	6,19E+08	27775,05	1,08E+08	4855,776	34806062	1561,299
S1 hundred	60	6,13E+08	27497,51	1,04E+08	4667,238	32817397	1472,094
S1 hundred	61	6,07E+08	27222,75	1E+08	4486,02	30942356	1387,985
S1 hundred	62	6,01E+08	26950,73	96123865	4311,839	29174446	1308,681
S1 hundred	63	5,95E+08	26681,43	92391611	4144,421	27507547	1233,909
S1 hundred	64	5,89E+08	26414,81	88804272	3983,503	25935887	1163,409
S1 hundred	65	5,83E+08	26150,87	85356220	3828,834	24454024	1096,937
S1 hundred	66	5,77E+08	25889,56	82042047	3680,169	23056829	1034,263
S1 hundred	67	5,71E+08	25630,86	78856556	3537,277	21739464	975,1696
S1 hundred	68	5,66E+08	25374,75	75794750	3399,934	20497366	919,4527