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EVALUATION OF ECONOMIC FEASIBILITY OF CANCER PREVENTION BY VACCINATION FROM PAPILLOMAVIRUS INFECTION IN UKRAINE

Serhii Hryshchuk[1,2*], Alla Harlinska[1], Nataliya Korneichuk[1]

[1] Zhytomyr Ivan Franko State University, Zhytomyr, Ukraine
[2]Zhytomyr Medical Institute of Zhytomyr Regional Council, Zhytomyr, Ukraine

Abstract. *Infection with human papillomavirus (HPV) presents a serious problem for modern healthcare. The most common manifestations of the papillomavirus infection include anogenital warts, cervical intraepithelial neoplasia, cervical cancer. The purpose of the work is to determine the economic feasibility of preventing cervical cancer in Ukraine by introducing a continuous vaccination against a papilloma virus infection. Markov simulation was used to determine the incremental cost-effectiveness ratio (ICER) based on epidemiological data on morbidity and mortality from cervical cancer in Ukraine. Taking into account the accepted assumptions and limitations of the introduction of HPV vaccination in Ukraine, it will prevent 1380 cervical cancer cases, preserve 2058 quality-adjusted life years and the reduce the cost of medical care for cervical cancer in the amount of $1,479,972. The amount of additional costs for the vaccine and its introduction is $12,009,684 (all results per 100,000 vaccinated persons). The ICER index is $4,729, which is 1.4 times higher the gross domestic product in Ukraine per 1 person in 2019 ($3,464). Taking into account the actual cost of the vaccine, vaccination against HPV infection with a view of preventing cervical cancer in Ukraine is currently economically feasible.*

Keywords: *Human papillomavirus, vaccination, Markov simulation, economic feasibility, Ukraine*

1. INTRODUCTION

Infection with human papillomavirus (HPV) presents a serious problem for modern health care. About 2.5-3 million cases of infection are diagnosed annually in the world. The most common manifestations of the papillomavirus infection include anogenital warts, cervical intraepithelial neoplasia, cervical cancer, vulvar and vaginal cancer. According to World Health Organization (WHO), up to 82% of women are infected with different types of HPV two years after sexual intercourse. HPV causes cervical cancer, which is the most common cancer in women, with estimated 266,000 deaths and 528,000 new cases in 2012. A large majority (about 85%) of the global burden occurs in developed regions, where it accounts for almost 12% of all female cancers [1, 2, 3]. The only way to effectively prevent HPV-associated diseases is the vaccine prophylaxis. Three HPV vaccines are now being marketed in many countries throughout the world - a bivalent, a quadrivalent, and nonavalent vaccines. All three vaccines are highly efficacious in preventing infection with virus types 16 and 18, which are together responsible for approximately 70% of cervical cancer cases globally [4, 5, 6].

According to numerous scientific studies, after vaccination, the frequency of detection of HPV 16 and type 18 decreases [7, 8]. According to meta-analyzes, 68% and provided 80% of girls were vaccinated, the previous reduction of HPV 16 among women and men was 93% [9, 10, 11].

In May 2018, 81 countries (42% of UN Member States, corresponding to 25% of target population) had introduced HPV to the national routine immunization schedules [12]. Cost-effective vaccination against HPV has been proven in many countries [13, 14, 15, 16, 17, 18]. However, due to different indicators of social-economic development, it is not always possible to use the results of an assessment of a particular medical technology conducted in other states [19]. Therefore, one of the topical issues is the study of the possibility of including vaccination against a papillomavirus infection in a mandatory vaccination calendar in Ukraine.

HPV-associated diseases and, in particular, cervical cancer is a significant health problem in Ukraine. According to the National Cancer Registry of Ukraine (NCRU) [20], in the structure of the incidence of women with malignant neoplasia, cervical cancer is 5.9% (ranked fifth). About 1,700 women (5.8% of patients with malignant tumors) die every year from the cervical cancer in Ukraine.

Mortality from cervical cancer is noted in women of the most able-bodied period of life, when they are actively engaged in raising children, have the maximum professional and life experience, participate in public life. In addition to the medical and social problem of cervical cancer, a major socio-economic damage is the precancerous and pre-invasive forms of this disease that can lead to infertility and disability. Taking into account the above mentioned facts, the conduct of this study is very relevant.

* gsmlk@ukr.net

The purpose of the study – to calculate the economic feasibility of cervical cancer prevention by vaccination against papillomavirus infection in Ukraine.

2. Materials and methods

To achieve the purpose of the study, we have used a method of analyzing economic feasibility, which allows comparing two alternative medical technologies, provided that the results of treatment can be measured in the same degree of health.

We carried out simulation of two technologies - vaccination against papillomavirus infection of the entire cohort of 12-year-old girls in Ukraine ("new" technology) and the current situation (without vaccination, "comparison" technology). Expenditures in both variants (without vaccination and in case of it) were evaluated in monetary units. The results of the introduction of the "new" health (vaccination) technology were assessed using the quality-adjusted life-year (QALY) indicator, which is most often used to compare the relative improvement in the health of the population as a result of the application of a variety of health technologies.

It is economically feasible to have a technology in which one unit of incremental health improvement (in our case, one QALY) can be achieved at an acceptable incremental cost of the "new" technology (in our case, a vaccination) to an alternative to comparison (the current situation without vaccination) (Formula 1).

$$ICER = (C2 – C1) / (QALY2 – QALY1) \quad (1),$$

where ICER is an incremental cost-effectiveness ratio; C2 - costs for "new" technology in monetary units; C1 - costs of comparative technology (as a rule existing); QALY2 - the number of years of quality of life when using the "new" technology; QALY1 - the number of years of quality life when using the technology of comparison.

The study was conducted considering the long-term social perspective, the definition of economic feasibility was carried out using the Markov modeling method [21] in the Microsoft Excel program. The Markov model investigates a hypothetical cohort of patients who are in the initial state before the study (in our case, the "healthy" state) and are converted to different states during the cycle according to definite probabilities. The patient may be in only one of the classes, so each subsequent cycle is determined by the number of patients that are distributed by the states. This allows you to calculate the costs and quantity of QALY during the cycles for each state of the investigated technology.

The study program included the following steps:

1. Development of the Markov model (the definition of the Markov's states and variants of transition between them).

2. Search for scientific and statistical data to calculate the matrix of the probabilities of transition between Markov states.

3. Calculation of the number of QALYs of the cost of medical care (direct costs) due to the incidence of cervical cancer without vaccination (in the present situation, the model of comparison).

4. Calculation of the number of QALYs and the cost of medical care due to the incidence of cervical cancer under vaccination (direct costs, based on the cost of vaccination - the model of the experiment).

5. Determination of ICER and decision making on recommendations.

During the simulation, we assumed that vaccination was conducted for all 12-year-old girls in Ukraine, and the effect of vaccination is maintained throughout life. In carrying out the assessment, only the effect in the vaccinated population was considered, without considering cross-vaccination. Economic feasibility was determined only for cervical cancer (the effect of vaccination for other diseases that can be caused by HPV, due to lack of reliable statistical data, was not considered).

Demographic indicators (the population of females under the age of 12 years as of 01.01.2019, the total mortality of the population by age) were obtained from the site of Statistics of Ukraine [22]. Indicators of age-related cervical cancer incidence, mortality due to cervical cancer, distribution of patients with cervical cancer by stages, 5-year survival in cervical cancer, depending on the stage of the disease, recurrence rate of cervical cancer after treatment, rates of use of different types of treatment by stages were obtained from the NCRU [20].

Necessary amount of funding for diagnosis in the stage of cervical cancer, monitoring the severity of relapses (for those who are in the stage of remission), surgical treatment, chemotherapy and radiotherapy of cervical cancer was determined by the data of the prices of the private clinic [23], as in the public clinics in the Ukraine official payment is not established. The cost of the vaccine, vaccination and examination of the pediatrician in front of it also determined from the websites of private clinics (in Ukraine it is not mandatory) [23].

Table 1. The matrix of probabilities of transitions between Markov states (without vaccination)

From state to state	1.A	2.B	3.C	4.D
1.A	0.999516	0.000017*	0	0.000467**
2.B	0	0.12	0.72	0.16
3.C	0.55	0.22	0.13	0.1
4.D	0	0	0	1

Note: * from 1 (A) state to 2 (B) state according to the incidence of cervical cancer by age; ** from 1 (A) state to 4 (D) state according to the indicators of total mortality by age (without mortality from cervical cancer).

Creating the model, we identified the following Markov states for the female population: 1. A - healthy; 2. B - primary patients with cervical cancer (acute period) - receive diagnosis and different types of treatment depending on the stage of the disease; 3. C - cervical cancer patients during remission - need to be diagnosed with relapses; 4. D - death.

Time horizon - the period of survival of girls, who at the beginning of the study is 12 years old. The duration of the Markov cycle is 1 year. Discounting the duration of life and the amount of costs considered at a rate of 3% per year.

Considering the initial data, we determined the probabilities of transitions between states, given in Table 1 (the model of comparison, when vaccinated, the probability of transition from the state 1 (A) to the state 2 (B) decreases by 65%).

According to statistics, as of 01.01.2019, in Ukraine there were 209 930 girls aged 12 years [22]. The indicator of total mortality of the female population in all age groups was 13.89 per 1,000 women. The standardized incidence rate of female population in the cervical cancer in 2018 was 19.3 per 100,000 female population, and standardized mortality rate from cervical cancer was 7.1 per 100,000 women. The age-related indicators of overall mortality, morbidity and mortality from cervical cancer were used [20, 22].

In modeling, we considered that according to the data of the NCRU (data for 2019), cervical cancer manifests itself in the following stages: I st. and II st. – 69.6%, III st. – 17.6%, IV st. -7.9%, stage not defined – 4,5%. The consumption of patients directly depends on the stage of the disease, its five-year indicators are for stage I – 78.1%, II – 57.0%, III – 31.0%, IV – 7.8%, all stages - 55.0% [21]. It was therefore assumed that 5 years after the discovery of the disease in the absence of relapses, 55% of patients from the category "remission" went into the category "healthy". In the first year after the diagnosis of cervical cancer in Ukraine, about 15.2% of women die.

According to [20], the rate of recurrence of cervical cancer (tumor growth, the appearance of metastases) in Ukraine is about 24.0% (transition from the state 3 (C) to the stage 2 (B), requiring predominantly chemotherapeutic treatment). With regard to the quality of life factors during stay in different states (taken into account when calculating lost QALY), taking into account world data, we have taken the following: healthy (A) - 0.9, primary ill (acute period) (B) - 0.5; patients with cervical cancer in the period of remission (C) -0.7, death (D) - 0.

To calculate the direct costs of diagnosis and treatment of cervical cancer, we considered the order of the Ministry of Health of Ukraine of 02.04.2014 №236 "Unified clinical protocol of primary, secondary (specialized), tertiary (highly specialized) medical care. Dysplasia of the cervix. Cervical cancer" [24], which transmits the necessary volume of diagnostic and medical services depending on the stage of the disease. The cost of diagnosis of the stage of cervical cancer and the presence of relapses (for those who are in the stage of remission) is determined at a rate of $355.

This includes a gynecologist's review, colposcopy, biopsy, cytological, histological, ultrasound examination, blood tests on oncomarkers, computer and magnetic resonance imaging. Diagnosis should be performed for all patients with cervical cancer and in cases of suspected relapse. Treatment costs were determined by us depending on the stage of the disease.

1. Costs for surgical treatment of cervical cancer are defined in the amount of $1333 (abdominal or laparoscopic removal of the uterus, considering the cost of anesthesia and hospital stay). Only surgical treatment was performed for 17.0% of the patients first diagnosed with cervical cancer.

2. Expenditures for chemotherapy of cervical cancer. Two cycles of neoadjuvant therapy with carboplatin and paclitaxel were administered in 50% of patients and six adjuvant therapy cycles in 25% of patients. The cost of all courses of chemotherapy was accepted by us for $1852.

3. Costs of radiotherapy of cervical cancer were about $148, received 40.0% of patients.

4. Combinations of these methods of treatment were used in the provision of medical care in 78.0% of patients.

In general, considering the above data, we calculated that the average cost of treatment of one case of cervical cancer in terms of direct costs is $4074. According to the NCRU [20], 22.0% of patients who were diagnosed with cervical cancer were not covered by treatment.

For the given values, we calculated the cost of diagnosis and treatment of cervical cancer, as well as the number of QALYs from the unvaccinated population (model of comparison).

At the next stage, the calculation was made based on the simulation of the vaccination against HPV by a bivalent vaccine (it was assumed that vaccination reduces the risk of contracting a cervical cancer (the probability of transition from state 1 (A) to state 2 (B))).

The predicted effectiveness of HPV vaccination in the prevention of cervical cancer was determined considering that according to research [2, 3, 4, 5, 6], the cause of cervical cancer in 74% of cases is HPV 16th and 18th types. Consequently, we consider that vaccination will reduce the risk of cervical cancer to fall by 65% (considering that 88% vaccination reduces the presence of HPV in the body).

Initially, the costs of diagnosis and treatment of cervical cancer (for a fraction of those who were ill) were calculated, cost estimates for one case were identical with the comparison group. At the next stage, the cost of vaccination was calculated. The price of a bivalent vaccine "Cervarix" was established at $46. It is used for children from 9 to 14 years including two doses of 0.5 ml. The second dose is administered between 5 and 13 months after the first dose. The cost of 2 vaccinations is $ 92. It was assumed that before the introduction of each dose of the vaccine, the pediatrician's examination is carried out (cost $ 10.1) [23].

Having got these indices, we calculated the cost of vaccination for the entire cohort of 12-year-old girls in Ukraine (model of experiment). The number of QALYs for the vaccinated population was determined. Based on the obtained results, the value of the ICER was established.

During the analysis of sensitivity, the changes of the following parameters were evaluated: increasing the effectiveness of vaccination in the part of prevention of cervical cancer to a level of 85% (from 65%); reduction of the cost of the vaccine by 50% (cost $23); and increase in the cost of treatment for one case of cervical cancer by 50%.

3. Results

According to the results of modeling in the first variant (preserving the existing situation with regard to the incidence of cervical cancer), it has been established that in Ukraine during the lifetime of 209 930 girls, who at the beginning of 2019 were 12 years old, with the preservation of existing indicators of morbidity, 4459 people (2124 per 100 000 women's population).

With regard to the simulation of the second option - HPV vaccination for all 12-year-old girls, the expected reduction in the number of patients with cervical cancer to 1563 (out of 4459) (Fig. 1) is expected, which is 744 people per 100 000 female population. That is, considering the assumptions made, the vaccination of 100,000 girls with an HPV vaccine will prevent 1380 cases of cervical cancer.

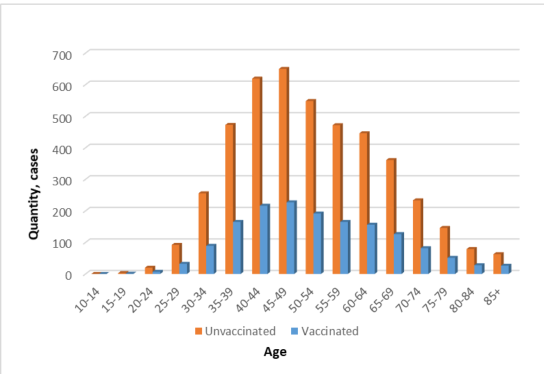

Figure 1. Comparison of the number of cases of cervical cancer in a vaccinated and unvaccinated female population (209930 persons)

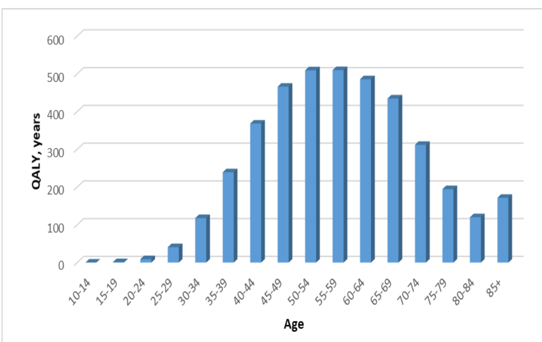

Figure 2. The number of additional QALYs by age groups obtained as a result of vaccination against HPV infection for the prevention of cervical cancer for the population of 209 930 females (with discounting, years).

With regard to QALY, the first option, due to morbidity and premature mortality from cervical cancer, has determined that this indicator for a given population of 12 years of age will be based on discounting (3%) of 5,580,791 years (26.58 years for 1 person), without discounting – 58.55 years.

The calculated QALY, with allowance for discounting for the cohort of vaccinated persons, will be 5 585 112 years, which in the amount of 1 person will be 26.60 years (without discounting - 58.63 years). According to the simulation, the introduction of vaccination will add 4321 QALY (2058 QALY per 100 000), the greatest number of them will be obtained as a result of prevention of the disease in persons aged 45-64 (Fig. 2).

The total cost of providing medical care related to cervical cancer for unvaccinated persons with a discount of 3% will be $4 776 689 ($22.7 per person). The total cost of providing medical care related to cervical cancer vaccinated persons, considering discounting at 3%, will be $1 669 781 ($7,9 per person). Consequently, the vaccination will enable to prevent the costs associated with the disease in the cervical cancer, the vaccinated population (209930 women) to $3 106 908 or $1 479 972 per 100,000 female population.

The maximum increase in the prevented costs (with discounting) can be predicted at the time of reaching the vaccinated age of 35-49 years (Fig. 3).

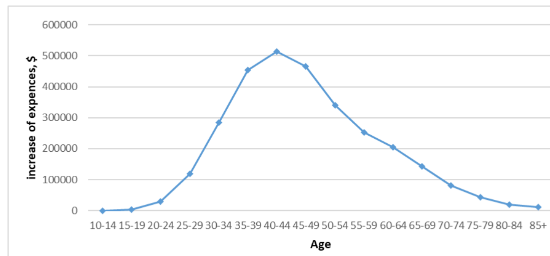

Figure 3. The size of direct expenses for provision of medical care under cervical cancer in age groups, forewarned as a result of vaccination against HPV, $, for the population of 209 930 women (with discounting).

Table 2. Results of calculation of evaluation of vaccination effectiveness from HPV infection in the part of prevention of cervical cancer

Indicator	Unvacci -nated	Vacci - nated	The difference between the groups
The incidence of cervical cancer, per 100 000	2124	744	-1380
Average QALY, per person, years (discount -3%)	26.58	26.60	0.02
Average life expectancy after 12 years without discount	58.55	58.63	0.08
Costs of rendering of medical care, which relates to cervical cancer, per 1 person, $. (discount - 3%)	22.7	7.9	14.8
Costs for vaccination, $ per person	0	112.1	-112.1
Average cost per person, $	22.7	120.0	-97.3

To these costs, it is necessary to add a cost of vaccination (the cost of double-administration of the bivalent vaccine, considering the pediatrician's review for the entire cohort of 12-years girls will be $23 542150). The total cost for the experiment group will be $25 211 931 ($12 009 685 per 100 000). Summarized results of calculation are given in Table 2.

By the formula given above, we have determined the ICER (cost of one additional QALY) when vaccinated with a divalent vaccine.

ICER = ($25 211 931– $4 776 689) / (5 585 112 - 5 580 791) = $ 4729

We have analyzed the sensitivity of individual parameters, which may vary depending on various factors, or there are different data in scientific sources. The results of the analysis of the sensitivity of the results to the change in modeling parameters are shown in Table 3.

Table 3. Sensitivity analysis

Parameter	Estimated indicator ICER ($/QALY)	Per capita GDP in Ukraine ($3464)
Basic version (2-valent vaccine)	4729	1.4
Increased vaccination efficiency in the prevention of cervical cancer to the level 85% (from 65%)	3452	1.0
Reducing the cost of a vaccine by 50% (cost $ 23)	2473	0.7
An increase in the cost of cervical cancer by 50%	4379	1.3

4. Discussion

In countries with economics in transition (including Ukraine), where pharmacoeconomic assessments are not applied at the state level [25], the WHO has previously recommended to determine the acceptable value of economic feasibility based on the size of the gross domestic product (GDP) [26, 27]. If the cost per QALY is less than or equal to the value of GDP, then the technology is definitely economically feasible, even if it exceeds the value of GDP by 1-3 times, technology is still considered economically expedient, if it exceeds more than 3 times – expense. In accordance with the WHO updated recommendation, a fixed rate of cost-effectiveness should not be used as a separate criterion for financing decision-making, price setting or reimbursement of the cost of a new medical product or other intervention.

The gross domestic product (GDP) in 2019 amounted to $3,464 per capita in Ukraine [28]. In our case, we received an additional QALY value of $4,729, which is 1.4 times the GDP per capita.

According to the sensitivity analysis, it has been found that only in the case of a 50% reduction in the cost of the vaccine, it will be economically feasible (1 QALY will be less than 2 GDP per capita). By changing the remaining sensitivity parameters, the results allow recommending the technology for implementation, considering the current economic situation in Ukraine.

4.1. Restriction of research

The study is characterized by several limitations. The high efficacy of vaccination against acute condyloma and other HPV-associated diseases (due to lack of reliable statistical data on morbidity) was not considered. Screening costs were not considered at cervical cancer (they were the same for both models). When assessing costs, tariffs for private clinics were used, which may differ from spending in other health care facilities.

Modeling did not consider the population effect of vaccination, found in several countries where vaccination against HPV is included in the vaccination calendar. Also, there was no calculation of indirect costs (lost profits). The accounting of these factors would allow to predict the higher value of the cost of vaccination against the papillomavirus infection in Ukraine. This will be one of the areas for further research.

5. Conclusion

According to the results of the review of scientific sources, high efficiency (70-100%) of vaccination against HPV infection was determined in terms of the prevention of the occurrence of HPV associated diseases, including cervical cancer.

Established with the help of Markov simulation, in the basic version, the cost of one additional year of quality of life during vaccination with a divalent vaccine will be $4,729 which is 1,4 times the per capita GDP in Ukraine. Taking into account the obtained results and the actual cost of the vaccine, the total vaccination against HPV infection to prevent cervical cancer in Ukraine is currently economically feasible.

References

1. World Health Organization, *Human papillomavirus (HPV)*.
Retrieved from:
http://www.who.int/immunization/diseases/hpv/en/
Retrieved on: June 10, 2019
2. A. B. Berenson, J. M. Hirth, M. Chang, "Change in Human Papillomavirus Prevalence Among U.S. Women Aged 18-59 Years, 2009-2014," *Obstetrics and Gynecology*, vol. 130, no. 4, pp. 693–701, Oct. 2017.
https://doi.org/10.1097/AOG.0000000000002193
3. T. Malagón, C. Laurie, E. L. Franco, "Human papillomavirus vaccination and the role of herd effects in future cancer control planning: a review", *Expert Review of Vaccines,* vol. 17, no. 5, pp. 395–409, May 2018.
https://doi.org/10.1080/14760584.2018.1471986
4. R. Luckett, S. Feldman "Impact of 2-, 4- and 9-valent HPV vaccines on morbidity and mortality from cervical cancer", *Human Vaccines & Immunotherapeutics,* vol. 12, no. 6, pp. 1332–1342, Mar. 2016.
https://doi.org/10.1080/21645515.2015.1108500
5. C. Spinner et al., "Human papillomavirus vaccine effectiveness and herd protection in young women", *Pediatrics*, vol. 143, no. 2, article no. e20181902, Feb. 2019.
https://doi.org/10.1542/peds.2018-1902
6. J. A. Kahn et al., "Substantial decline in vaccine-type human papillomavirus (HPV) among vaccinated young women during the first 8 years after HPV vaccine introduction in a community", *Clinical Infectious Diseases*, vol. 63, no. 10, pp. 1281–1287, Nov. 2016.
https://doi.org/10.1093/cid/ciw533
7. K. Kavanagh et al., "Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely

related HPV types", *Br. J. Cancer,* vol. 110, pp. 2804–2811, May 2014.
https://doi.org/10.1038/bjc.2014.198

8. L. Ding, L. E. Widdice, J. A. Kahn, "Differences between vaccinated and unvaccinated women explain increase in non-vaccine-type human papillomavirus in unvaccinated women after vaccine introduction", *Vaccine*, vol. 35, no. 52, pp. 7217–7221, Dec. 2017. https://doi.org/10.1016/j.vaccine.2017.11.005
9. M. Brisson et al., "Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models", *The Lancet Public Health*, vol. 1, no. 1, pp. e8–e17, Nov. 2016. https://doi.org/10.1016/S2468-2667(16)30001-9 PMID: 29253379
10. M. Drolet, É. Bénard, M. Boily, H. Ali, L. Baandrup, H. Bauer et al., "Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis", *The Lancet Infectious Diseases*, vol. 15, no. 5, pp. 565–580, May 2015. https://doi.org/10.1016/s1473-3099(14)71073-4 PMID: 25744474 PMCID: PMC5144106
11. A. Hammer, A. Rositch, F. Qeadan, P. E. Gravitt, J. Blaakaer, "Age-specific prevalence of HPV16/18 genotypes in cervical cancer: A systematic review and meta-analysis", *International Journal of Cancer,* vol. 138, no. 12, pp. 2795–2803, Dec. 2015. https://doi.org/10.1002/ijc.29959
12. *Global Market Study HPV,* World Health Organization, 2019, pp. 1–4. Retrieved from: https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/WHO_HPV_market_study_public_summary.pdf Retrieved on: Mar. 10, 2019
13. D. A Machalek et al., "Very low prevalence of vaccine human papillomavirus types among 18- to 35-year old Australian women 9 years following implementation of vaccination", *The Journal of Infectious Diseases,* vol. 217, no. 10, pp. 1590–1600, May 2018. https://doi.org/10.1093/infdis/jiy075
14. D. Mesher, K. Panwar, S. L. Thomas, S. Beddows, K. Soldan, "Continuing reductions in HPV 16/18 in a population with high coverage of bivalent HPV vaccination in England: an ongoing cross-sectional study", *BMJ Open,* vol. 6, no. 2, article no. e009915, Feb. 2016. https://doi.org/10.1136/bmjopen-2015-009915
15. S. E. Oliver, E. R. Unger, R. Lewis, D. McDaniel, J. W. Gargano, M. Steinau et al., "Prevalence of human papillomavirus among females after vaccine introduction-national health and nutrition examination survey, United States, 2003-2014", *The Journal of Infectious Diseases,* vol. 216, no. 5, pp. 594–603, Sept. 2017. https://doi.org/10.1093/infdis/jix244
16. Q. Zhang, Y. Liu, S. Hu and F. Zhao, "Estimating long-term clinical effectiveness and cost-effectiveness of HPV 16/18 vaccine in China", *BMC Cancer*, vol. 16, no. 1, article no. 848, Dec. 2016. https://doi.org/10.1186/s12885-016-2893-x
17. J. Brotherton et al., "Age-specific HPV prevalence among 116,052 women in Australia's renewed cervical screening program: A new tool for monitoring vaccine impact", *Vaccine*, vol. 37, no. 3, pp. 412–416, Jan. 2019. https://doi.org/10.1016/j.vaccine.2018.11.075
18. R. L. Cameron et al., "Human papillomavirus prevalence and herd immunity after introduction of vaccination program, Scotland, 2009-2013", *Emerging Infectious Diseases*, vol. 22, no. 1, pp. 56–64, Jan. 2016. https://doi.org/10.3201/eid2201.150736
19. Z. Kaló, K. Landa, T. Doležal, Z. Vokó, "Transferability of National Institute for Health and Clinical Excellence recommendations for pharmaceutical therapies in oncology to Central-Eastern European countries", *Eur. J. Cancer Care*, vol. 21, no. 4, pp. 442–449, Jul. 2012. https://doi.org/10.1111/j.1365-2354.2012.01351.x PMID: 22510226
20. "Cancer in Ukraine, 2018-2019," *Bulletin of National Cancer Registry of Ukraine,* vol. 21, 2020. Retrieved from: http://www.ncru.inf.ua/publications/BULL_21/index_e.htm Retrieved on: June 27, 2020
21. P. Menn, R. Holle, "Comparing three software tools for implementing Markov models for health economic evaluations", *PharmacoEconomics,* vol. 27, no. 9, pp. 745–753, Mar. 2009. https://doi.org/10.2165/11313760-000000000-00000
22. *Population statistics of Ukraine.* Retrieved from: http://database.ukrcensus.gov.ua Retrieved on: June 05, 2020
23. *The cost of medical services in private clinics in Ukraine.* Retrieved from: https://feofaniya.org/wp-content/uploads/2020/05/price.pdf, https://oberig.ua/media/files/Price_05.05.20.pdf, https://www.lissod.com.ua/prices/consultation Retrieved on: May 05, 2020
24. Міністерство охорони здоров'я України. (квітень 02, 2014). *N 236 Про затвердження та впровадження медико-технологічних документів зі стандартизації медичної допомоги при дисплазії та раку шийки матки.* (Ministry of Health of Ukraine. (April 02, 2014). N 236 Unified clinical protocol of primary, secondary (specialized), tertiary (highly specialized) medical care. Dysplasia of the cervix. Cervical cancer.) Retrieved from: https://zakon.rada.gov.ua/rada/show/va236282-14 Retrieved on: May 10, 2019
25. M. Csanádi et al. "Health technology assessment implementation in Ukraine: current status and future perspectives", *International Journal of Technology Assessment in Health Care*, vol. 35, no. 5, pp. 393-400, Oct. 2019. https://doi.org/10.1017/S0266462319000679
26. A. T. Newall, M. Jit, R. Hutubessy, "Are current cost-effectiveness thresholds for low- and middle-income countries useful? Examples from the world of vaccines", *PharmacoEconomics*, vol. 32, no. 6, pp. 525–531, Jun. 2014. https://doi.org/10.1007/s40273-014-0162-x
27. M. Fesenfeld, R. Hutubessy, M. Jit, "Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: a systematic review", *Vaccine*, vol. 31, no. 37, pp. 3786–3804, Aug. 2013. https://doi.org/10.1016/j.vaccine.2013.06.060
28. *Data Bank World Development Indicators.* Retrieved from: https://databank.worldbank.org/reports.aspx?source=2&country=UKR Retrieved on: June 10, 2020