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HPV VACCINATION ROLE IN CERVICAL CANCER ELIMINATION: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Cervical cancer is a socially significant disease in the development of which the human papillomavirus (HPV) plays a central role. HPV is the most common sexually transmitted virus, affecting 80% of sexually active men and women by age 45. Since 2017, the World Health Organization has recommended that all countries implement HPV vaccination programs to reduce and eliminate cervical cancer.*

The study aimed to *examine the role of HPV vaccination in eliminating cervical cancer over the past decade.*

Methods: *The literature search was done in the PUBMED, MEDLINE, and Cochrane databases for the last ten years using the keywords "cervical cancer", "vaccination", and "human papillomavirus". The review included the results of randomized studies and meta-analyses.*

Results: *The literature provides evidence of the effectiveness and safety of HPV vaccination in countries that have introduced HPV vaccine immunization. The compelling evidence for the effectiveness of HPV vaccination in preventing HPV urges to move from control to elimination of HPV-related diseases.*

Conclusion: *Cervical cancer is the only cancer that can be prevented by vaccination. The development of HPV vaccines and the introduction of HPV immunization into national vaccination schedules helped many countries reduce HPV prevalence and thus reduce HPV incidence.*

Keywords: *cervical cancer, vaccination, human papillomavirus (HPV).*

Introduction: Cervical cancer is one of the most common female cancers. Cervical cancer ranks 1st among oncological diseases of the female reproductive system.

According to Globocan 2020, cervical cancer ranks 4th in the global female cancer structure after breast cancer (2,261,419 cases), colorectal cancer (865,630 cases), and lung cancer (770,828 cases). 604,000 new cases and 341,000 deaths from cervical cancer are registered annually [1].

The morbidity and mortality from cervical cancer are high in Africa. In 2020, cervical cancer became the leading cause of cancer mortality among women in African countries. The highest mortality – 55.7 per 100,000 women – was registered in Eswatini (South Africa) [1]. In low- and middle-income countries, cervical cancer is a significant public health issue (Fig. 1).

Chronic persistence of the human papillomavirus (HPV) in the body was established as the cause of cervical cancer development. HPV is responsible for nearly 4.5% of all new cervical cancer cases worldwide. This urges the control over HPV prevalence through vaccination programs [2].

Globocan reported 353,497 new cases and 200,736 deaths from cervical cancer in Kazakhstan in 2020 [1]. The morbidity and mortality from this disease remain high despite the National Screening Programme for cervical cancer introduction in 2008. Vaccination against HPV is the only way to prevent cervical cancer except for screening. A pilot immunization HPV vaccination program was implemented in four regions of Kazakhstan in the Pavlodar and Atyrau regions, the cities of Nur-Sultan and Almaty, in 2013-2015. 17,295 girls underwent complete vaccination [3]. The vaccination was carried out in schools with the parent's consent. However, the project was suspended due to many refusals to vaccinate and two fainting schoolgirls after vaccination, which subsequently led to an anti-vaccine movement.

The study aimed to examine the role of HPV vaccination in eliminating cervical cancer over the past decade.

Materials and methods: The literature search was done in the PUBMED, MEDLINE, and Cochrane databases for the last ten years using the keywords "cervical cancer", "vaccination", and "human papillomavirus". The review included the results of randomized studies and meta-analyses for the previous decade.

Data collection relied on the publication year and the reliability of results. The review included the results of 3 meta-analyses from WHO and a review of Australian vaccination programs as an example of successful HPV vaccination.

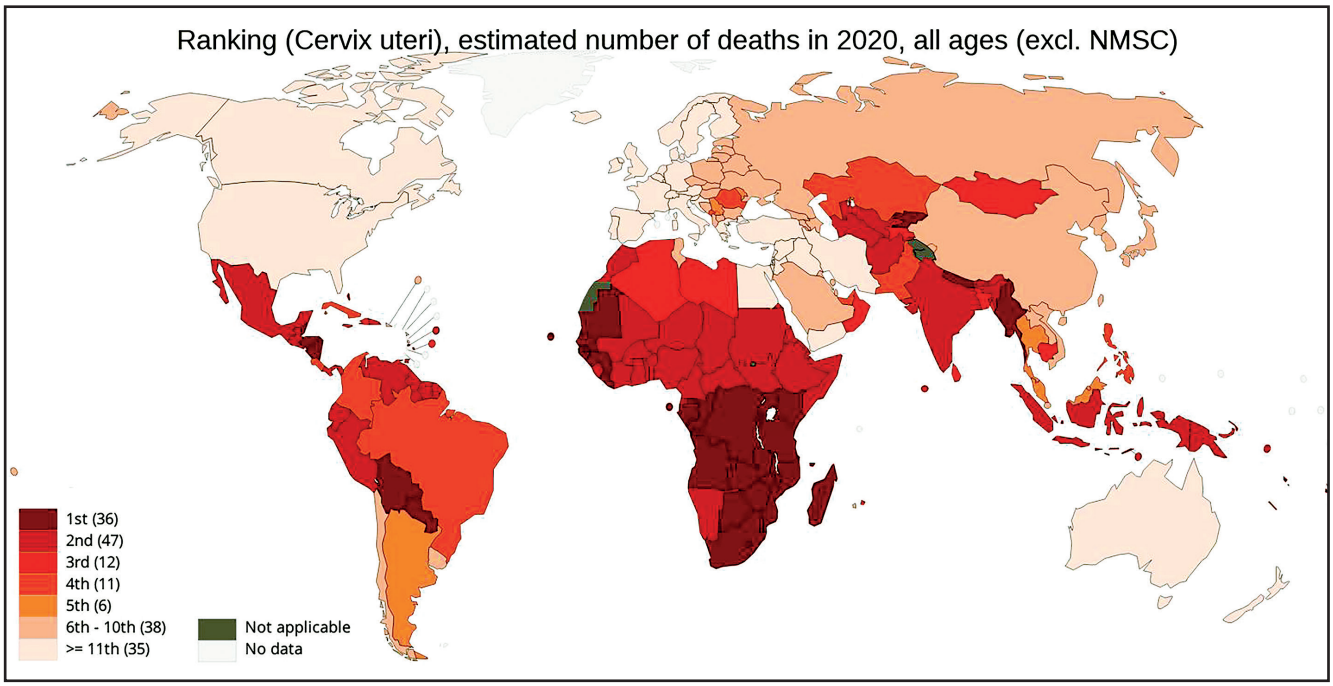

Figure 1 – Global mortality from cervical cancer, as per Globocan 2020 [1]

Results: HPV has been identified as the cause of cervical cancer development. Today, more than 200 types of HPV are known, of which 12 types (HPV 16/18/31/35/39/45/51/52/58/66/68) have high oncogenic risk. They are dangerous to humans since the long-term persistence of high-risk HPV in the female body can cause cervical cancer. HPV types 16 and 18 are the most common and responsible for 70% of cervical cancer cases. HPV types 6 and 11 with a low risk of cervical cancer development are responsible for 90% of genital warts [2].

Cervical cancer is the only cancer that can be prevented through primary and secondary prevention. The development of HPV vaccines began in the mid-1980s. Vaccine against HPV has been available since 2006 and recommended by the World Health Organization (WHO) since 2009. The vaccination against HPV was gradually introduced into national vaccination calendars in many countries, but an optimal full-scale introduction and vaccination coverage have not yet been achieved [4, 5]. Only 107/194 WHO countries have introduced HPV vaccination into the national immunization calendars partially or nationwide [6] (Fig. 2).

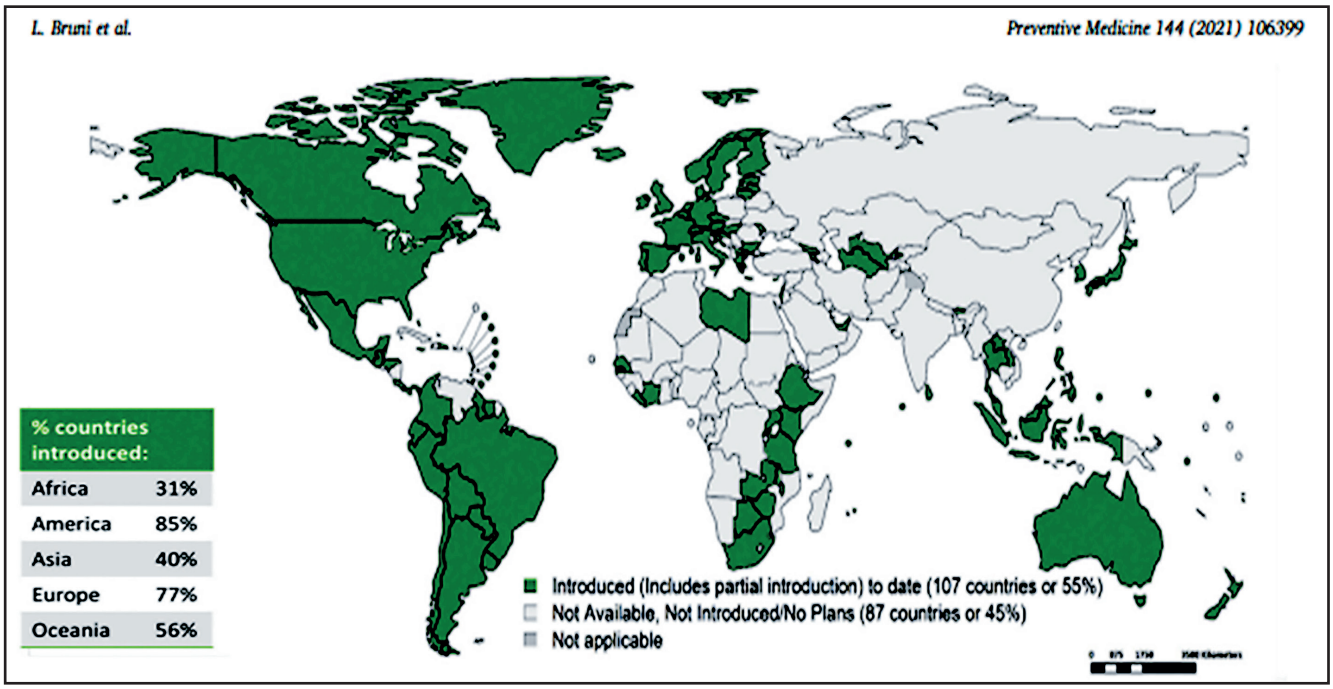

Figure 2 – WHO member countries that have included HPV vaccination in their national immunization programs as of June 2020 [7]

The share of high-income countries that have introduced HPV vaccination is higher than among low- and middle-income countries (Fig. 3, 4). The US and Europe have the highest vaccination coverage of 85% and 77%, respectively. Asia has the lowest vaccination coverage at 40%. Australia has been the first to implement a national, state-funded HPV vaccination program. The vaccination program introduced in Australia in 2007 provided for immunization with quadrivalent vaccines of girls aged 12-13 years; boys joined the program in 2009 [8]. In Australia, the vaccination program showed promising results. In particular, the prevalence of HPV types 6, 11, 16, and 18 after the introduction of vaccination decreased from 29% to 7% [9, 10]. The prevalence of HPV types covered by vaccination has declined over ten years from 22.7% to 1.5% among women aged 18 to 24 and 11.8% to 1.1% among women aged 25 to 35. In total, the prevalence of HPV types covered by the quadruple HPV vaccine (HPV 6, 11, 16, 18) has decreased by 92% among women aged 18 to 35. In this group of women, the prevalence of vaccine types of HPV has decreased by 90% despite incomplete (40%) coverage by vaccination [11]. The subsequent evidence of vaccination effectiveness in Australia was a reduction in the incidence of high-level intraepithelial injury in the vaccinated age groups [12-14].

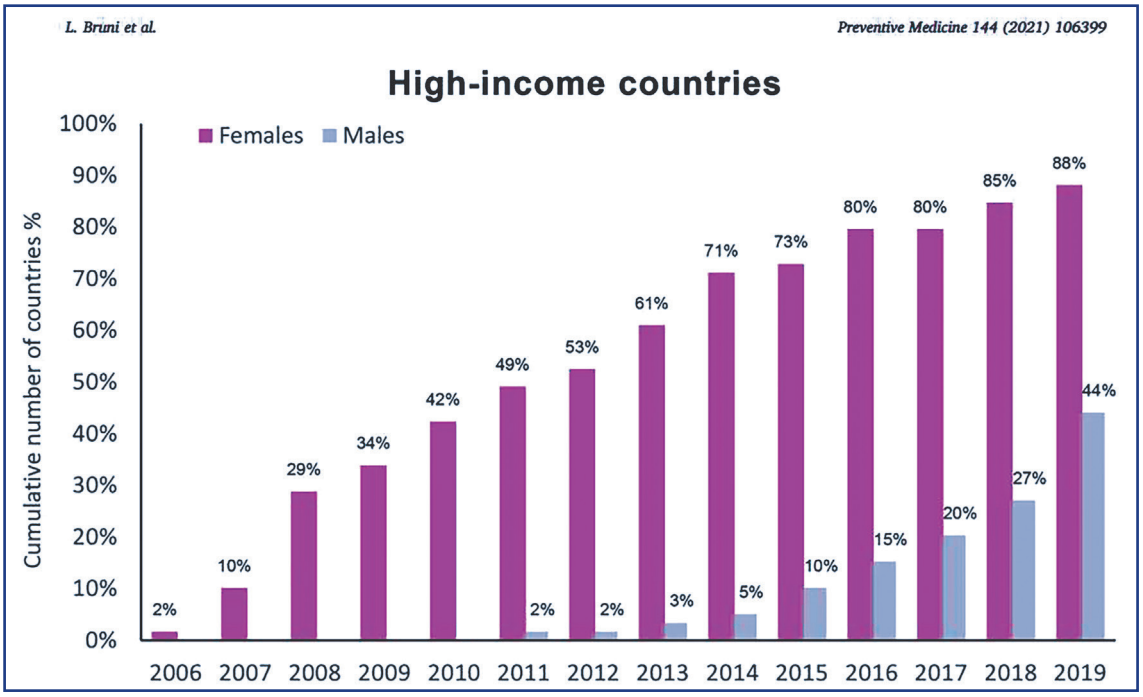

Figure 3 – Share of high-income countries that have introduced HPV vaccination [7]

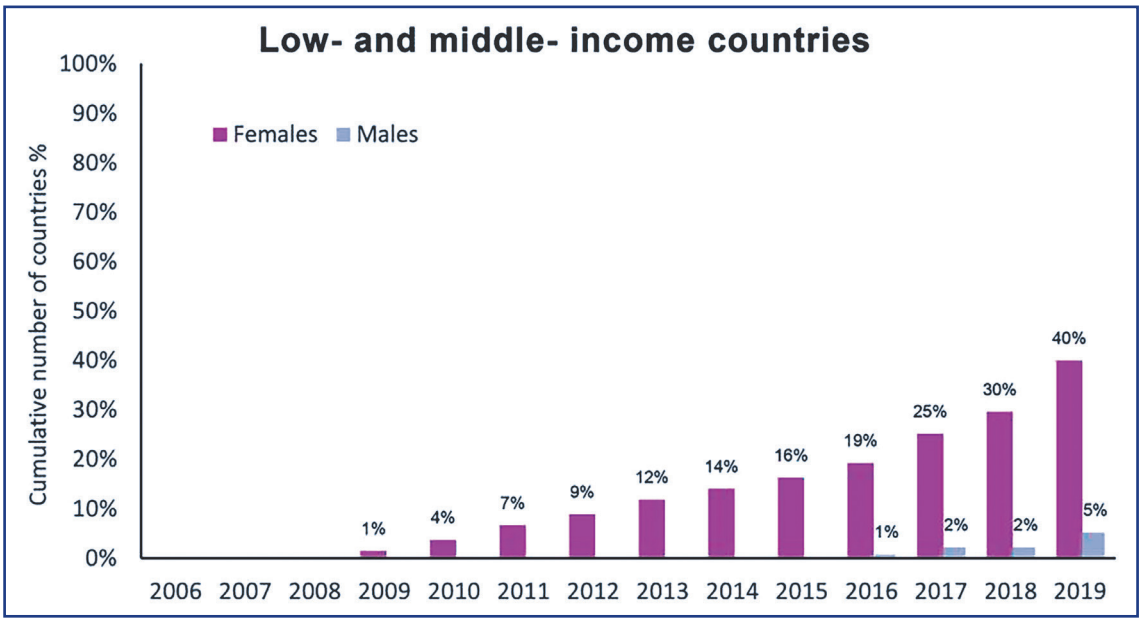

Figure 4 – Share of low- and middle-income countries that have introduced HPV vaccination (Romania, Lesotho, Peru, and Kazakhstan terminated their programs in 2011, 2012, 2013, and 2015) [7]

The introduction of the vaccination program has decreased the prevalence of HPV In the US: by 70-80% - for low cancer risk HPV types 6 and 11 types, and by 26-56% – for HPV of high-risk types 16, 18. European countries are also witnessing the impact of the vaccination program on the prevalence of HPV vaccine strains. For example, in Sweden, the prevalence of HPV types 6, 11 decreased by 40 and 72%, respectively; HPV types 16, 18 – by 35-45% [15, 16]. A meta-analysis revealed a decrease in the prevalence of high-risk HPV (16/18) by 68%, plus a significant decrease in HPV types 31, 33, 45 prevalence by 28% in the countries where at least 50% of women were covered by vaccination in 2007-2014. This implies the cross-protection capacity of the vaccine [4].

Since the introduction of the HPV immunization program, only 12% of young girls have been targeted by vaccination. By the end of 2014, only 6% of girls aged 10 to 20 had been vaccinated worldwide. In 2016, it was estimated that HPV immunization programs targeted only 12% of adolescent girls worldwide, and only 6% of girls aged 10 to 20 were vaccinated by the end of 2014 worldwide. [17]. In May 2018, WHO General Director announced a new strategy to eliminate cervical cancer, calling for active action to reduce the cervical cancer incidence to 4 cases per 100,000 people worldwide [18]. The HPV elimination strategy includes targets to increase HPV vaccination to 90% of all adolescent girls worldwide by 2030.

Discussion: This work overviews meta-analyses, randomized studies, and WHO/UNICEF data on HPV elimination. Despite the successful vaccination results achieved over the past five years, there is a long way to go before the WHO 2030 plan can be achieved. This review testifies the significant effectiveness of vaccination against HPV and intraepithelial cervical disorders in countries with high coverage of the target population. After 5-8 years of programs in countries with high vaccination coverage, there has been a 100 percent reduction in intraepithelial cervical changes, further demonstrating the positive effect of HPV immunization as cervical cancer prophylaxis [19, 20].

It is also worth noting that vaccination programs are more effective when reaching adolescents of both sexes. Thus, vaccinating up to 40% of girls ensures the protection of 53% of women and 36% of men. In comparison, the same coverage of both sexes increases the share of protected persons to 71% of women and 71% of men. Eliminating HPV types 16, 18, 6, and 11 requires reaching 80% of girls and boys [15, 21].

Conclusion: The extensive multi-center studies and meta-tests show positive HPV vaccination results. Countries that have introduced HPV vaccination achieve effective primary prevention of cervical cancer. The fullest possible coverage of the target population and the introduction of vaccination into national vaccination schedules are required to fulfil the vaccination program's potential and ensure the early protection of the female population.

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ЖАТЫР МОЙНЫ ОБЫРЫН ЖОЮДАҒЫ HPV ВАКЦИНАЦИЯСЫНЫҢ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

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ТҰЖЫРЫМ

Өзектілігі: *Жатыр мойнының қатерлі ісігі әлеуметтік маңызды ауру болып табылады, оның дамуында адам папилломавирусы басты рөл атқарады. Адам папилломавирусы (АПВ) жыныстық жолмен берілетін ең көп таралған вирус болып табылады, 45 жасқа дейінгі жыныстық белсенді ерлер мен әйелдердің 80%-на әсер етеді. 2017 жылы Дүниежүзілік Денсаулық Сақтау ұйымы (ДДСҰ) АПВ вакцинациясына қатысты өз ұстанымын жариялады. ДДСҰ барлық елдерге АПВ вакцинациясын ұлттық деңгейде енгізуді ұсынып жатыр мойны қатерлі ісігінің (ЖМҚІ) кездесу жиілігін айтарлықтай төмендететінін жариялады.*

Зерттеудің мақсаты *– қайталанатын гинекологиялық қатерлі ісік кезінде вагинэктомияның тиімділігін зерттеу.*

Әдістері: *соңғы 10 жылдағы әлемде жатыр мойнының қатерлі ісігін жоюдағы АПВ вакцинациясының рөлін зерттеу.*

Нәтижелер: *АПВ вакцинациясын енгізген елдерде АПВ вакцинациясының тиімділігі мен қауіпсіздігі анықталды. Вакциналардың АПВ инфекциясының таралуын болдырмаудағы тиімділігінің дәлелі болып АПВ-мен байланысты ауруларды жоюға көшетін уақыттың пайда болғанын анықтады.*

Қорытынды: *Жатыр мойны обыры – вакцинация арқылы алдын алуға болатын жалғыз ісік. HPV-ге қарсы вакциналарды жасау және ұлттық егу күнтізбесіне енгізу көптеген елдерге HPV таралуын азайтуға және сол арқылы жатыр мойны обырының сырқаттануын азайтуға мүмкіндік берді.*

Түйінді сөздер: *жатырмойныобыры, вакцинация, адампапилломавирусы.*

РОЛЬ ВАКЦИНАЦИИ ПРОТИВ ВПЧ В ЭЛИМИНАЦИИ РАКА ШЕЙКИ МАТКИ: ОБЗОР ЛИТЕРАТУРЫ

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АННОТАЦИЯ

Актуальность: *Рак шейки матки (РШМ) является социально-значимым заболеванием, в развитии которого основную роль играет вирус папилломы человека (ВПЧ). ВПЧ является часто распространенным вирусом у сексуально активных мужчин и женщин – до 80% из них могут оказаться инфицированы к 45 годам. Всемирная организация здравоохранения с 2017 г. рекомендует всем странам мира внедрять программы ВПЧ-вакцинации с целью снижения заболеваемости и элими-нации РШМ.*

Цель исследования *– изучить роль вакцинации против ВПЧ в элиминации РШМ в мире за последние 10 лет.*

Методы: *Проведен литературный обзор по базам данных PUBMED, MEDLINE, Cochrane по ключевым словам «рак шейки матки», «вакцинация», «вирус папилломы человека» за последние 10 лет. В обзор были включены результаты рандо-мизированных исследований и мета-анализов.*

Результаты: *Установлена эффективность и безопасность вакцинации от ВПЧ в странах, внедривших иммунизацию вакцинами от ВПЧ. Данные по эффективности вакцинации против ВПЧ в отношении профилактики РШМ показывают, что необходимо перейти от контроля к элиминации РШМ, связанных с ВПЧ.*

Заключение: *РШМ – единственное онкологическое заболевание, которое поддается профилактике с помощью вакцинации. Создание вакцин от ВПЧ и внедрение иммунизации против ВПЧ в национальные календари прививок позволило многим странам снизить распространенность ВПЧ и тем самым снизить показатели заболеваемости РШМ.*

Ключевые слова: *рак шейки матки (РШМ), вакцинация, вирус папилломы человека (ВПЧ).*

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