

EFFICACY AND SAFETY OF HPV VACCINE: A REVIEW OF THE LITERATURE

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INTRODUCTION

Despite being highly preventable, the cervical cancer (CC) is nevertheless the fourth most common cancer among women worldwide, with an estimated 604,127 new cases and 341,831 deaths in 2020. (GLOBOCAN 2020). In Armenia CC is the second most common female cancer in women aged 15 to 44 years. It ranks* as the eighth leading cause of female cancer in Armenia. The age standardized incidence of the condition per 100 000 females composes 7.8, while the age standardized mortality per 100 000 females is 4.6 (65 deaths in 2020 year) [1].

Efficacy of CC primary prevention can be ensured by high coverage of HPV immunization among girls aged 9–14, which is the important measure in achieving the target of 4 cases per 100 000 female population, indicated by WHO in 2020 [2]. It is considered one of two “best-buy” interventions in low and middle-income countries (the second one is the CC screening) [3], proved that the measure leads to the reduction of pre-cancerous conditions and cancers verified by screening, ultimately resulting in decline of CC mortality rates [4,5].

To develop the adequate strategy of CC elimination, 135 (45 in Europe) countries in the world have implemented routine HPV vaccination programs in 2022 with

Abstract

We have undertaken a generalized presentation of data on aspects of the effectiveness and safety of various HPV vaccination measures available in the English-language literature. The review includes 50 sources (5 of which are systematic reviews) published over the past 10 years. The selection was made by matching the subjects of the studies to current concepts of HPV infection control and including all the predefined keywords. The data studied included reports and recommendations of the WHO, health authorities of European countries and USA, the results of observational studies and clinical trials studying the effectiveness of different vaccinations programs, as well as systematic reviews. The core part of the review presents data published by WHO and special task forces of US preventive services, as well as the authors of multi-center studies in European countries, devoted to a comparative analysis of the effectiveness of various vaccination programs in countries with different income levels. The analysis attempts to highlight efficacy of HPV vaccine and its safety issues.

The reviewed provides the basis and motivational framework to analyze the clinical efficacy, safety and cost efficacy of the vaccine used in RA. The subsequent implementation of community based study will contribute to the adequate evaluation of the anti-HPV vaccination program in RA as a primary prevention measure for cervical cancer.

Keywords: HPV, vaccination, papillomavirus, vaccination efficacy, safety

involvement of 58% proportion of young female population. Routine vaccination of males as well contribute to decline of HPV-related cancers in males and females [6]. Today, already 20 countries vaccinate males as well.

HPV vaccination was included in the Armenian National Immunization Calendar for females aged 13 starting in December 2017 and was then expanded in February 2019 to include females aged 13–45 and males aged 14–45. Vaccinations are provided through primary health care clinics using the 4-valent (Gardasil) vaccine with a 2 dose schedule (0 and 6 months). HPV vaccination coverage rates in 2021 and 2022 were 10.8% and 13.3% respectively, and increased to 23.7% for the period from January to April 2023 (girls aged ≤15, last dose) [7].

This literature review aimed to conclude recent international data regarding the efficacy of HPV vaccine’ as well as its influence on fertility function and pregnancy outcome.

METHOD

A literature search for the topic was conducted from Google Scholar and PubMed using appropriate keywords (HPV, Vaccination, efficacy, safety). The initial search has identified 1030 works published. The review includes 50 sources (5 of which are systematic reviews)

published over the past 10 years. The selection was made by matching the subjects of the studies to current concepts of HPV infection control and including all the predefined keywords. The data studied included reports and recommendations of the WHO, health authorities of European countries and USA, the results of observational studies and clinical trials studying the effectiveness of different vaccinations programs, as well as systematic reviews. The core part of the review presents data published by WHO and special task forces of US preventive services, as well as the authors of multi-center studies in European countries, devoted to a comparative analysis of the effectiveness of various vaccination programs in countries with different income levels.

HPV VACCINE EFFICACY

Multiple studies were undertaken in different countries to verify the real efficacy of HPV vaccination. The overall analysis of studies estimating the prevalence of HPV associated cancers included 9.529 vaccinated at age 14-17 and 17 838 non-vaccinated women. The comparative analysis of the results showed the complete absence of HPV associated cancer cases in vaccinated group vs prevalence 8.0 (CI 95% 4.3-15) (cervical, vulvar, oro-pharyngeal, vaginal, anal) in non-vaccinated group with particular prevalence of CC 6.4 (CI 95% 3.2-13) [8].

The evaluated studies have shown that the vaccine provides close to 100% protection against the infection and pre-cancerous conditions caused by certain types of HPV. Administering the vaccine to boys and girls between 9 and 12 years old can prevent more than 90% of HPV cancers when they get older [9-12].

According to results obtained by Scottish researchers Kavanagh K, Pollock KG, Cuschieri K et al (2017), vaccination with a bivalent vaccine resulted in an unprecedented reduction in the circulation of the HPV types included in the vaccine and all HPV types against which the vaccine provided cross-protection [13].

Australian researchers Ali et al (2013) came to similar conclusions. They have found, that quadrivalent vaccine led to the total disappearance of genital warts among young people from vaccinated cohorts [14]. Genital warts related efficacy of HPV vaccine was similarly positively evaluated by multiple researchers [15,16].

A monitoring study in the state of Connecticut (USA) aimed to analyze rates of CIN2+ among women aged 21-39 years between 2008 and 2015, as well as conduct a comparative assessment of rates taking into account levels of vaccination coverage (4-valent HPV vaccine). It was began with offering the 4-valent HPV vaccine to girls aged 11 and 12 in 2006, along with catch-up immunization through age 26 [17,18]. As a result, significant reduction in CIN2+ incidence rates among women aged 21-26 years was revealed, with the utmost reduction in incidence among women aged 21-22 years (the highest vaccination coverage rates).

The investigation conducted by C. Spinner, L. Ding, D. I. Bernstein et al., in 2019 [19] has aimed to deter-

mine the prevalence of vaccine-type HPV in adolescent and young adult population including vaccinated (to evaluate vaccine effectiveness) and non-vaccinated (to evaluate herd protection) women in post-vaccination 11 years period.

Female patients 13 to 26 years of age were recruited for 4 studies from 2006 to 2017. The proportion of vaccinated and non-vaccinated positive for vaccine-type HPV women across the studies, and the odds of positivity for vaccine-type HPV using logistic regression were determined. As a result, HPV detection decreased from 35% to 6.7% in vaccinated women (4-valent vaccine-type H (80.9% decline; odds ratio 0.13, 95% confidence interval 0.08 to 0.22)).

Among non-vaccinated women, 4-valent vaccine-type HPV detection declined from 32.4% to 19.4% (40% decrease; odds ratio 0.50, 95% confidence interval 0.26 to 0.97). The HPV trends in US community within >10 years post 4-valent HPV vaccine and post 9-valent vaccine period were investigated. The evidence of vaccine effectiveness and herd protection was determined.

The Swedish investigators have showed decreased risk of CC in women under 28 years of age vaccinated before age 17. It was 88% lower than in non-vaccinated Swedish women in the same age group [20].

The systematic review and meta-analysis performed by Drolet M, Bénard É, Pérez N in 2019, includes data describing up to 8 years of post-vaccination follow-up of 60 million individuals. The received data showed compelling evidence of the substantial impact of HPV vaccination programs on HPV persistence and CIN2+ among girls and women, as well as on anogenital warts incidence among girls, women, boys, and men. Besides of that, the programs with multi-cohort vaccination and high vaccination coverage demonstrated a greater direct impact and herd protection effects [21].

HPV VACCINE SAFETY

HPV vaccines have demonstrated an excellent safety profile in clinical trials in the post-licensing period:

- 270 million doses of HPV vaccine have been administered since 2006
- Research on safety issues of more than 1 million people.
- No other limitations have been identified with vaccines, except for 1) syncope, which was affected by the stress of injections, 2) anaphylactic shock [22].

The WHO Global Committee on Vaccine Safety has reviewed the safety of HPV vaccines for the following:

- Adverse effects regarding pregnancy
- Aluminum adjuvant (quadrivalent vaccine)
- Syncope and anaphylaxis
- Vein thrombosis and stroke
- Autoimmune diseases (multiple sclerosis and Guillain-Barre syndrome) and cerebral vasculitis
- Complex regional pain syndrome and/or other chronic pain conditions
- Postural orthostatic tachycardia syndrome
- Primary ovarian failure

The WHO Global Committee on Vaccine Safety considers the safety of HPV vaccination to be very high [22].

HPV VACCINE AND ADVERSE PREGNANCY OUTCOMES (APO)

The study involving U.S. military women aged 17–28 years who had at least one pregnancy between 2017–2014 showed no relationship between HPV vaccination during pregnancy and adverse outcomes for the mother or the newborn [23].

Wang A, Liu C, Wang Y, et al., performed systematic review for comparison of HPV vaccine exposed pregnancies with the unexposed pregnancies. The RR was calculated. No higher risk for spontaneous abortion (RR, 0.99 [95% CI, 0.90 to 1.08]); stillbirth (RR, 1.16 [95% CI, 0.71 to 1.90]); small for gestational age (RR, 0.96 [95% CI, 0.86 to 1.07]); preterm birth (RR, 1.04 [95% CI, 0.91 to 1.18]); or birth defects (RR, 1.18 [95% CI, 0.97 to 1.43]) or any adverse pregnancy outcomes was revealed [24].

Yan X, Li H, Song B, Huang G, Chang Q, et al. (2023) conducted investigation of vaccinated and non-vaccinated female cohorts to estimate the risks of adverse pregnancy outcomes, including spontaneous abortion, birth defects, stillbirth, SGA, preterm birth and ectopic pregnancy. No additional risks for HPV vaccine exposures in periconceptional period or during pregnancy was revealed [25].

Scheller NM, Pasternak B, Mølgaard-Nielsen D, et al (2017) investigated a cohort of Denmark female population with registered pregnancy termination between October 1, 2006, and November 30, 2013. National registry content was examined to compare the data on vaccination (with adverse pregnancy outcomes - spontaneous abortion, stillbirth, major birth defect, small size for gestational age, low birth weight, and preterm birth) with the data of non-vaccinated cohort. The propensity score in a 1:4 ratio was matched with non-vaccinated women. The authors came to conclusion that quadrivalent HPV vaccination during pregnancy was not associated with a significantly higher risk of APO comparatively with the non vaccinated cohort. [26].

Some other researches have also investigated the association between human papillomavirus (HPV) vaccination and adverse pregnancy outcomes. This study set out to verify any association between HPV vaccination during pregnancy and subsequent risk of spontaneous abortion, stillbirth, and one-year infant mortality. It was found no increased risk of spontaneous abortion, stillbirth, or infant mortality following unintended HPV vaccination during pregnancy [27]. Analysis of multiple other researches targeting APO revealed no increased risk of spontaneous abortion, stillbirth, neonatal mortality or negative infant outcomes associated with HPV vaccination during pregnancy [28–30]. Some additional benefits of HPV vaccination in reducing APO was reported by Yuill S, Velentz LS, Smith M et al., in 2021 [31]. Having analyzed the data of 1380424 individuals the researchers came to the conclusion that HPV vacci-

nation during pregnancy is better postponed until after this period. However, no significant evidence was found to indicate that vaccination was dangerous and unsafe during pregnancy [30]. Further studies are needed to draw a more definitive conclusion. The deep further investigation is required to acquire results that could become milestone in the management of cervical precancerous lesions and prevention of APOs.

Two studies defined SGA as birthweight less than the 10th percentile for gestational age [32, 33], one study¹⁵ defined by additionally accounting for sex. Compared with the unexposed pregnancies, HPV vaccine exposed pregnancies were associated with no higher risk for SGA

HPV VACCINE AND FERTILITY

Currently there is no estimated evidence on the impact of the HPV infection and anti HPV vaccine on the rates of fertility disorders.

The net protection effect of 9-valent HPV genotypes against female infection and miscarriage/infertility is not clear, yet the impact of this virus on health reproduction is evident. Accordingly, the value of HPV vaccination in adolescent females is supported for not only preventing cancer but also couple infertility [34].

CDC has published official data regarding fertile function of female after HPV vaccination. The report provided an uncertain conclusion: “HPV vaccine does not cause fertility problems” [35].

HPV vaccination has no effect on fertility, no confirmed cases of primary ovarian failure among HPV vaccine recipients in the United States was revealed in accordance with USA Vaccination Adverse Event Reporting Registration system (VAERS), 2014–2017. The research includes follow up of 28 million vaccine doses administered to female and male population with 7244 reports of adverse reactions (259 reports per 1,000,000 doses). 97.4% of these had non-serious character (dizziness, headache, injection site reactions) and three reports were comparable to diagnosis of primary ovarian failure, but eventually were not confirmed. No unusual or unexpected manifestations after vaccination were revealed. The incidence of serious manifestations, including primary ovarian failure, was within the range registered in the period before the introduction of the HPV vaccine [36, 37].

The data received via prospective study - follow-up of 996,300 adolescent girls and young women aged 11–34 years from 2007 to 2016 revealed the identical frequency of primary ovarian failure with complete absence of its association with HPV vaccine administration [38].

A comparison of the average probability of fertilization was made in a study of vaccinated and non-vaccinated women, including 3.483 women planning pregnancy, as well as 1.222 of their partners over a 12-month follow-up period. The results showed that HPV vaccination had no effect on the ability to get pregnant. The researchers evaluated fecundability and 95% confidence

intervals (CI) for pre - HPV vaccination Pap test. The obtained data revealed that patients with history of STD & PID (risk group of HPV), had higher post vaccination fecundability than those not vaccinated (FR=1.35, 95% CI: 0.99, 1.86). Authors concluded, that anti-HPV vaccine is positively associated with fecundability in women with positive STD history in spite of the fact that the latter had insignificant general effect on fecundability [39].

Another research results demonstrate a polygenic role of HPV infection in all stages of human reproduction, especially the pathogenetical involvement of oxidative stress caused by HPV 16, 18, inducing DNA damage and genomic affect as well as the reproductive system HPV-infected cells-directed immune response. HPV infection associated reproductive impairment, and the availability of highly effective and safe prophylactic anti-HPV vaccines are composing another strong importance of the vaccination to achieve significant decrease HPV-associated cancers' prevalence the HPV-associated human reproduction impairment and even mediated improvement of fertility indicators on population levels [40].

There is substantial concern over infertility after HPV vaccination, particularly in light of case studies that revealed early menopause or premature ovarian insufficiency (POI) in six young women between the ages of 13 and 21 within a year of immunization [41, 42].

POI is a clinical condition characterised by decreased estradiol levels, high gonadotrophins, and menstrual cycle disorders (amenorrhoea or oligomenorrhoea) before the age of 40 [42]. There have been some documented occurrences of spontaneous pregnancies in women with POI, and there is currently no established treatment that might induce ovarian activity and increase the likelihood of natural fecundability [43].

Multiple backgrounds of POI - HPV vaccines relationship have been put out, including autoimmune reactions to the aluminum adjuvant in the vaccine and purported ovarian toxic effects [44].

Postvaccination autoimmunity (POI) has not been proven to have a specific cause, but it is theoretically possible, and vaccine-induced polysorbate 80 exposure levels are quite low compared to dangerous levels. Consequently, such a risk ought to be seen as theoretically irrational [44, 45].

Conversely, several vaccines that do not raise the risk of POI contain polysorbate 80, including those against rotavirus, tetanus, influenza, hepatitis A and B, meningococcal and pneumococcal infections, diphtheria, tetanus, pertussis, and poliomyelitis [45,46]. Furthermore, a recent study established the safety of HPV vaccination in relation to the reproductive and pregnancy outcomes of women undergoing IVF.. In comparison to unvaccinated women, Demir et al. demonstrated that HPV-vaccinated patients had an identical frequency of retrieved oocytes and mature oocytes. However, there were no statistically significant changes in implantation, clinical, and continuing pregnancy rates [47, 48]. It follows that the HPV vaccine's impact on fertility is justified.

Tatang et al. examined the VAERS database for POI cases and discovered a possible safety signal regarding POI following HPV immunization [46]. They claimed that the true risk would be lower as compared to the CC lifetime risk if that signal was supported by more epidemiological research [48, 49].

Another researchers have reported on the potential adverse impact of the anti-HPV vaccine on fecundability. According to the results, women who had the HPV vaccination had a lower likelihood of ever becoming pregnant than women in the same age range who did not. Therefore, more research on how the HPV vaccine affects fertility is necessary [50].

Conclusion. Not all investigators are unanimous in their opinion regarding the safety of the Vaccine and the absolute absence of its impact on reproductive functions.

Having analyzed the results of the studies, point out the need for further deep research to scope the results of various types of anti-HPV vaccines' implementation. Its particular importance should be also emphasized in context of provision greater confidence to primary care workers who carry out direct outreach work with the vaccination program potential beneficiaries.

The reviewed data allow to conclude regarding the high appropriateness of analyzing the clinical efficacy, safety and cost efficacy of the vaccine used in RA. The implementation of community based study will contribute to the adequate evaluation of the anti-HPV Vaccination Program in RA as a primary prevention measure for cervical cancer.

ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ ВАКЦИНЫ ВПЧ.
ОБЗОР ЛИТЕРАТУРЫ

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Абстракт

В работе предпринято обобщенное изложение данных по аспектам эффективности и безопасности различных мер вакцинации против ВПЧ, имеющихся в англоязычной литературе. В обзор вошли 50 источников (из коих 5 являются систематическими обзорами), опубликованных за последние 10 лет. Отбор источников производился на основе принципа соответствия субъектов проводимых исследований современным представлениям об отдельных аспектах контроля над инфекцией ВПЧ и включения всех заранее определенных ключевых слов. Изученные данные включали отчеты и рекомендации ВОЗ, органов здравоохране-

ния европейских стран и США, результаты обсервационных исследований и клинических испытаний по изучению эффективности различных программ вакцинации, а также систематические обзоры. В основной части обзора представлены данные, опубликованные ВОЗ и специальными группами профилактических служб США, а также результаты многоцентровых исследований в европейских странах, посвященных сравнительному анализу эффективности различных программ вакцинации в странах с разным уровнем заболеваемости и различными уровнями доходов. Основной фокус в данном обзоре литературы поставлен на освещение и различных оценок эффективности и безопасности вакцин против ВПЧ. Обзор обеспечивает мотивационную основу для анализа клинической эффективности, безопасности и экономической эффективности вакцины, используемой при РА. Последующее проведение исследования на уровне сообщества будет способствовать адекватной оценке программы вакцинации против ВПЧ при РА как меры первичной профилактики рака шейки матки.

Ключевые слова: ВПЧ, вакцинация, вирус папилломы, эффективность вакцинации, безопасность

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Վահե Տեր-Մինասյան^{1*}, Վադիմ Ֆրոլով², Գագիկ
Բազիլյան¹, Վահան Մանվելյան¹, Հռիփսիմե
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ազգային ինստիտուտ

²«Աստիկ» բժշկական կենտրոն, Երևան, Հայաստան

Ամփոփագիր

Այս աշխատանքում մենք ձեռնարկել ենք ՄՊՎ պատվաստման տարբեր միջոցառումների արդյունավետության և անվտանգության տեսակետերի վերաբերող անգլալեզու գրականության տվյալների ընդհանրացված ներկայացում: Վերլուծվել է վերջին 10 տարվա ընթացքում հրատարակված 37 աղբյուր: Ընտրությունը կատարվել է հետազոտության առարկաների համապատասխանության սկզբունքի հիման վրա ՄՊՎ վարակի վերահսկման արդյունավետության և անվտանգության տեսակետերի վերաբերյալ ժամանակակից պատկերացումներին: Ակնարկում ընդգրկված են ԱՀԿ-ի, առանձին երկրների առողջապահական մարմինների ուսումնասիրված տվյալները, հտհաշվետվությունները և առաջարկությունները,

առանձին հեղինակների հետազոտության արդյունքները, ինչպես նաև գրականության համակարգված ակնարկներ՝ պատվաստումների տարբեր ծրագրերի արդյունավետության ուսումնասիրության արդյունքներ: Հասկապես ուշագրավ են ԱՀԿ-ի հատուկ թիրախավորված կանխարգելիչ ծառայությունների կողմից հրապարակված տվյալները, ինչպես նաև տարբեր եկամտների մակարդակ ունեցող երկրներում պատվաստումների տարբեր ծրագրերի կիրառական և արդյունավետության համեմատական վերլուծության վերաբերյալ բազմակենտրոն հետազոտությունների արդյունքները: Այս գրականության ակնարկի հիմնական նպատակն է ներկայացնել հակա-HPV-ի պատվաստանյութերի արդյունավետությունն ու անվտանգությունը տարբեր գնահատականներ:

Վերանայված տվյալները թույլ են տալիս եզրակացնել ՀՀ-ում կիրառվող պատվաստանյութի կիրառական արդյունավետության, անվտանգության և ծախսարդյունավետության վերլուծության բարձր նպատակահարմարության մասին: Նման ուսումնասիրության իրականացումը կնպաստի ՀՀ-ում ՄՊՎ-ի դեմ պատվաստումների ծրագրի՝ որպես արգանդի պարանոցի քաղցկեղի առաջնային կանխարգելման միջոցի համարժեք գնահատմանը:

Հիմնաբառեր: ՄՊՎ, պապիլոմավիրուս, պատվաստում, պատվաստման արդյունավետություն, անվտանգություն

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