CORRELATION BETWEEN HPV VACCINATION COVERAGE AND HPV INFECTION PREVALENCE

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Abstract: Human papillomavirus infection is one of the most widespread sexually transmitted infections and represents a major etiological factor for cervical cancer and other anogenital malignancies. Despite the availability of effective prophylactic vaccines, the global burden of human papillomavirus infection remains significant, particularly in countries with insufficient vaccination coverage. The objective of this paper is to examine the association between human papillomavirus vaccination coverage and the prevalence of human papillomavirus infection in the female population in North Macedonia. The study is based on a retrospective analysis of data obtained from the national immunization program and organized human papillomavirus screening activities conducted over several consecutive years. The analysis includes data from more than seventeen thousand tested women and evaluates trends observed before and after the introduction and expansion of the vaccination program. The results demonstrate a gradual increase in vaccination coverage accompanied by a measurable reduction in the prevalence of vaccine-covered human papillomavirus types. However, infections associated with non-vaccine virus types remain present, indicating that vaccination does not eliminate all infection risks. The findings suggest that higher vaccination coverage contributes to a lower overall prevalence of infection, but long-term disease prevention requires additional public health measures. In conclusion, the study confirms the positive impact of vaccination while emphasizing the importance of continuous screening and health education as essential components of comprehensive human papillomavirus prevention strategies.
Keywords: human papillomavirus, vaccination coverage, infection prevalence, cervical cancer prevention

1. INTRODUCTION

Human papillomaviruses belong to the family Papillomaviridae, with approximately 120 genotypes described to date. These viruses are etiological agents of infections affecting the skin and mucosal membranes of various parts of the human body. Based on their oncogenic potential, HPV types are classified into three groups: (1) high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, 70, 73, 82, 83, and IS39), (2) potentially high-risk HPV types (26, 53, 62, and 66), and (3) low-risk HPV types (6, 11, 34, 40, 42, 44, 57, 31, 64, 67, 69, 72, 74, 81, 84, CP6108, CP8061, and LVX100) (Arsova et al., 2014).

HPV is a sexually transmitted infection and the leading causative agent of cervical cancer, a disease responsible for more than 200,000 deaths among women annually. Most HPV infections resolve spontaneously within approximately two years, while a small proportion persist and may progressively develop into cervical cancer (Das et al., 2018).

Globally, it is estimated that approximately 12% of sexually active women carry HPV DNA at any given time, with higher prevalence observed among younger women (<25 years), reaching up to ~24% in some regions. In Europe, the highest prevalence is reported in Eastern Europe, while in North Macedonia the incidence rate of cervical cancer is approximately 10.9 per 100,000 women per year (IARC/WHO, 2024). High-risk HPV types, particularly HPV16 and HPV18, are responsible for approximately 70% of cervical cancer cases worldwide. Understanding genotype distribution is essential for assessing the effectiveness of vaccination programs and for adapting national immunization strategies (Falcaro et al., 2024). Currently available HPV vaccines provide protection against the most clinically relevant HPV types. The bivalent vaccine targets HPV16 and HPV18, the quadrivalent vaccine covers HPV6, HPV11, HPV16, and HPV18, while the nonavalent vaccine offers broader protection against HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, and HPV58 (Saccucci et al., 2018).

The World Health Organization (WHO) includes vaccination against human papillomavirus (HPV) as a core component of the global strategy to eliminate cervical cancer as a public health problem by 2030. According to the WHO guidelines (2024), HPV immunization is recommended as routine vaccination for girls aged 9–14 years, preferably prior to the onset of sexual activity (WHO, 2024).

According to the national immunization schedule, HPV vaccination in North Macedonia is voluntary but strongly recommended, with the aim of achieving coverage of at least 80% of the target population. The HPV vaccine provides the highest level of protection against serious HPV-related diseases, and each vaccinated individual contributes to reducing viral transmission. The currently used HPV vaccine provides protection against nine HPV

types (6, 11, 16, 18, 31, 33, 45, 52, and 58) and is administered in two doses at a six-month interval (e-zdravstvo.mk).

2. MATHERIALS AND METHODS

The study was conducted as a retrospective observational study. Secondary data on HPV vaccination coverage and the percentage of HPV-positive cases for the period 2020–2024 were analyzed, obtained from the Ministry of Health and the University Clinic of Gynecology and Obstetrics – Skopje. The sample consisted of aggregated data from more than 17,000 women.

The analysis included a comparison of annual trends in vaccination coverage and infection prevalence, as well as a review of the most common HPV genotypes (16, 18, 31, and 45) based on relevant clinical sources. All data were processed in anonymized form, in accordance with ethical principles and data protection standards.

3. RESULTS

The data were processed using descriptive statistical methods, including the calculation of percentage values, arithmetic means, and aggregated differences for the analyzed period 2021–2024. Table 1 enables a direct comparison between vaccination coverage and the percentage of HPV-positive results.During the analyzed period, a continuous increase in HPV vaccination coverage was observed among the female population, rising from 44.0% in 2021 to 60.4% in 2024. The average vaccination coverage for the period was 53.2%, indicating a gradual improvement in immunization uptake within the national vaccination program.

Figure 1. Comparison of HPV Vaccination Coverage and HPV Positivity (2021–2024)

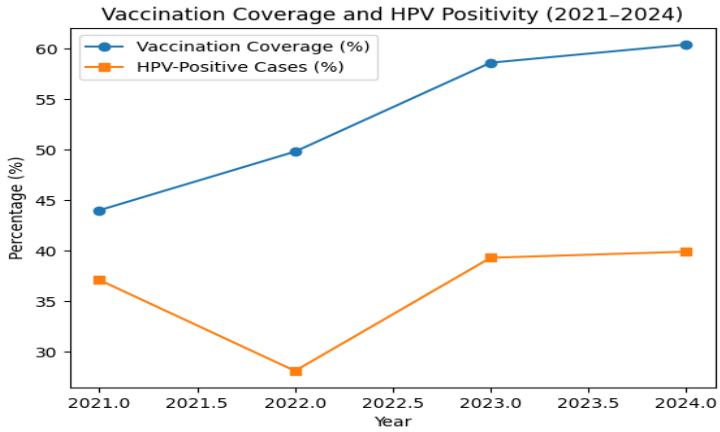
Year	Vaccination Coverage (%)	HPV-Positive Cases (%)	Δ%
2021	44.0	37.1	–6.9
2022	49.8	28.1	–21.7
2023	58.6	39.3	–19.3
2024	60.4	39.9	–20.5
Average	53.2	36.1	–17.1

Source: Authors research

The percentage of HPV-positive cases demonstrated a variable trend, with the lowest value observed in 2022 (28.1%), followed by an increase in 2023 and 2024 (39.3% and 39.9%, respectively). The average HPV positivity for the entire analyzed period was 36.1%.

The difference between vaccination coverage and HPV positivity was negative in all analyzed years, with the largest gap recorded in 2022 (–21.7 percentage points). The average difference for the entire period was –17.1 percentage points, indicating a favorable trend toward increased vaccination coverage relative to the prevalence of infection (figure 1, figure 2).

Figure 2. Vaccination coverage and HPV posiitive cases(2021–2024)



Source: Authors research

Although a direct causal relationship cannot be fully established due to the observational nature of the data, the observed trend suggests a potential positive effect of increased vaccination coverage on the control of HPV infection.

4. DISCUSSIONS

Although a clear linear association cannot be established, the descriptive analysis indicates a tendency toward stabilization of HPV infection as vaccination coverage increases. This suggests that the impact of vaccination is becoming apparent; however, longer follow-up and higher coverage in younger age groups are needed for the effect to be statistically demonstrable.

These findings are consistent with the World Health Organization's global report (2024), which indicates that countries achieving vaccination coverage levels of 70–80% have experienced reductions in HPV infection of 60–90% within 5–10 years after the introduction of vaccination. Similar trends have been reported in Australia and Sweden, where, following a decade of high vaccination coverage, HPV infection has been nearly eliminated among women under 25 years of age.

According to the World Health Organization report (WHO, 2024), the global average for complete HPV vaccination coverage (two doses) in 2023 was only 21%, while in the European region it was approximately 33%. With more than 50% complete coverage in the past two years, North Macedonia exceeds the regional average and represents a positive example in Southeast Europe. This finding is particularly relevant given that several Balkan countries (Serbia, Bosnia and Herzegovina, and Albania) reported vaccination coverage below 25% among girls aged 9–14 years during the initial years of program implementation.

Additional analysis of clinical data from the University Clinic of Gynecology and Obstetrics – Skopje identified a single case of a patient who, despite complete immunization with the bivalent HPV vaccine, tested positive for an HPV genotype not covered by the vaccine formulation. This finding indicates the possibility of infection with non-vaccine genotypes even among vaccinated individuals. According to available studies, the overall prevalence of HPV infection among women in North Macedonia ranges between 18% and 20% (Shabani, 2024). In the same study, which analyzed 300 cervical samples, high-risk HPV types accounted for 94.5% of all positive cases. The most frequently detected genotypes were HPV16 (11%), HPV31 (7%), and HPV18 (5%), which is consistent with global trends (Stanojević et al., 2024). Several studies have demonstrated that introduction of HPV vaccines in real-world settings has led to a dramatic decline in the prevalence of vaccine-type HPV among vaccinated individuals (Drolet et al., 2015; Kahn et al., 2016).

The clinical relevance of this observation can be considered from several perspectives. First, it confirms the need for continued screening in vaccinated populations, as vaccination substantially reduces but does not eliminate the risk of infection and the development of precancerous lesions. Second, the finding indirectly highlights the potential advantage of the nonavalent vaccine, which provides broader coverage of high-risk genotypes compared with the bivalent vaccine. Third, the occurrence of infection with a non-vaccine genotype suggests ongoing circulation of multiple oncogenic HPV types in the population, underscoring the importance of continuous epidemiological surveillance and adaptive prevention strategies.

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5. CONCLUSIONS

The results of this study indicate a clear increase in HPV vaccination coverage among the female population in the Republic of North Macedonia during the period 2021–2024, accompanied by a relatively lower prevalence of HPV-positive cases. Although infection dynamics show year-to-year variation, the aggregated trend suggests a positive effect of increased vaccination on the control of HPV infection and the reduction of risk associated with vaccine-covered genotypes.

The identification of a single case of infection with a non-vaccine HPV type in a vaccinated patient further underscores the need for continuous screening and systematic epidemiological surveillance, as well as the importance of expanding vaccine coverage through broader vaccine formulations. These findings support the role of integrated preventive strategies combining vaccination, regular screening, and health education as a key approach for achieving long-term reduction in the burden of HPV infections and associated malignancies.

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