ŚLIWIŃSKA, Martyna, WIKLIŃSKA, Agata, SZYDLIK, Julia and WÓJTOWICZ, Katarzyna. Current status of HPV vaccination - recommendation and introduction in European countries. Quality in Sport. 2024;21:53870. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.21.53870
https://apcz.umk.pl/QS/article/view/53870

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 28.07.2024. Revised: 17.08.2024. Accepted: 20.08.07.2024. Published: 23.08.2024.

CURRENT STATUS OF HPV VACCINATION - RECOMMENDATIONS AND INTRODUCTION IN EUROPEAN COUNTRIES

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ABSTRACT

Introduction and aim of study: HPV infection is estimated to underlie 5.2% of all cancers. These can affect the cervix, vagina, vulva, anus, penis and head and neck. The main aim of this systematic review was to assess the current knowledge about primary prevention of HPV infection and compare the vaccination data between European countries.

Materials and methods: The authors based this review paper on an extensive analysis of scientific articles published in PubMed, Science Direct, UpToDate, Springer, Cochrane and Google Scholar, vaccine reports from 2021 and later years, healthcare-oriented media reports and government information pages.

Results: Currently, one of the most effective methods of dealing with HPV-dependent cancers is primary prevention. It is estimated that vaccination can prevent up to 70% of cases of cervical cancer, and with the 9-valent vaccine, this rate can increase to 90%. There are currently 3 types of vaccines available on the market: 2-, 4- and 9-valent. A 2- or 3-dose vaccination schedule can be followed depending on the age of the patient. The main target group of vaccination are children between the ages of 9 and 14. However, adults up to the age of 45 may still gain some benefits from the injection. A 1-dose regimen is under examination in order to increase vaccination rates in regions with the highest incidence of HPV-associated cancers. Due to major differences in vaccination programs and monitoring, it is difficult to compare vaccination coverage in European countries.

Conclusion: The HPV vaccine is a very effective method of primary prevention. It is crucial to improve the vaccination rates in European countries, including Poland, in order to lower the incidence of HPV-dependent cancers.

Keywords: HPV, Vaccination, Cancer Prevention

BACKGROUND

The high prevalence of human papillomavirus (HPV) infection makes this problem extremely relevant in clinical practice. It has been calculated that in the sexually active population, 91% of men and 85% of women will become infected with HPV during their lifetime. [1]

Until now, more than 182 HPV types have been isolated. Of these, types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 have the greatest oncogenic impact. Other types such as 6, and 11 are responsible for the development of benign lesions. [2] HPV is also responsible for the development of cancers of the cervix, vagina, vulva, anus, penis and head and neck. [3] It is estimated that up to 5.2 per cent of all cancers are linked to HPV infection. [4]

In 2022, approximately 660,000 cases of cervical cancer were documented worldwide, establishing this type of neoplasm as the fourth most common type of cancer in women. [5] The invention of HPV vaccines was a groundbreaking moment in the history of oncology. It has been calculated that they can prevent up to 70% of cases of cervical cancer, and with the 9-valent vaccine, this rate can increase to as much as 90%. [6]

MATERIALS AND METHODS

The authors based this review paper on an extensive analysis of scientific articles published in PubMed, Science Direct, UpToDate, Springer, Cochrane and Google Scholar. For vaccine coverage rate description, reports from 2021 and later years have been considered. Healthcare-oriented media reports and government information pages have also constituted a source of information.

PROPHYLACTIC VACCINES

The creation of many breakthrough vaccines against HPV, as well as poliomyelitis and COVID-19 vaccines, among others, was made possible by work on the "HeLa" cell line. It was initiated thanks to cancer cells collected from the cervix of 31-year-old Henrietta Lacks in 1951. The cell line established shortly after her death is used to date in many experiments, including cancer research. [7,8]

The European Union, following the EMA's (European Medicines Agency) standpoint, has approved the promotion of 3 vaccines for the prevention of HPV infection. [9] Gardasil is a 4-valent vaccine targeting HPV 6,11, 16 and 18, and was approved by the Food and Drug Administration (FDA) in 2006. [10] It is dedicated to the prevention of high-grade Cervical Intraepithelial Neoplasia (CIN 2/3), cervical cancer, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3) and condyloma acuminata. [11] Cervarix is a 2-valent vaccine, which protects against HPV 16 and 18 infections. The EMA approved the product in 2007 and the FDA in 2009. It is an effective vaccine for the prevention of precancerous lesions of the genitals and anus, as well as cervical cancer and anal cancer. Due to the lack of HPV 6 and 11 antigens, it does not prevent lesions such as condyloma acuminata. [12,13] The last of these specimens is Gardasil 9. It is a 9-valent vaccine that protects against infection with HPV serotypes 6, 11, 16, 18, 31, 33, 45, 52, 58. It was approved by the FDA in 2014. It provides protection against precancerous lesions and cancers of the cervix, vulva, vagina and rectum caused by the types of HPV virus contained in the vaccine, as well as against condyloma acuminata. [14]

The effect shared by all three vaccines is based on the introduction of the virus capsid protein (L1 protein), produced using recombinant DNA techniques. It enables the avoidance of a pathogenic effect. The genetic material of the virus is not introduced into the patient’s body and thus the virus cannot replicate while the immunization of the patient is maintained. Produced with yeast (Gardasil, Gardasil 9) or baculoviruses (Cervarix), L1 protein monomers group into pentamers and then self-assemble into virus-like particles (VLPs). Administration of such antigens to the patient enables the development of a humoral response by producing appropriate neutralizing antibodies. They prevent the virus from entering the cell and, consequently, from multiplying its genetic material in the vaccinated person.

An important aspect of vaccine efficacy is the resulting cross-immune response. Due to similarities in the structure of the L1 proteins of different types of HPV, vaccinated individuals may show immunity to infection not only with the type against which the vaccine is directed but also against those not included in the vaccines. New prophylactic vaccines are being developed, with the antigen in the form of the L2 protein of the virus capsid. It has less immunogenic properties than the L1, but it is produced in a similar form by many types of the HPV virus, which would make it possible to create one vaccine against numerous types. [15]

THERAPEUTIC VACCINES

Current prophylactic vaccines available on the market do not show significant therapeutic efficacy against pre-existing lesions caused by HPV infection. [12] Research is underway on therapeutic vaccines that would rely more on a cellular than a humoral response, as is the case with prophylactic vaccines.

One concept is based on the use of an attenuated vector in the form of a virus or bacteria which would allow the gene encoding HPV-specific antigens (E6, E7) to enter the cell. This would enable it to induce an immune response against the virus. This solution has its limitations like high immunogenicity, which may pose a risk to the patient. In addition, the body's response to the administered vector may be disproportionate to the effect on HPV-specific antigen. [12]

A second idea is to give the patient viral peptides or proteins that would be presented via the major histocompatibility complex (MHC) to T lymphocytes after contact with dendritic cells. However, these vaccines have shown relatively little immunogenicity in studies.

A third route to create a therapeutic vaccine is the use of nucleic acids. DNA-based vaccines contain plasmids that encode viral antigens. When administered, the vaccine enters the cell nucleus, allowing the production of antigens, which are then presented via MHC class I to Tc lymphocytes. However, the low ability to self-replicate free DNA is the reason for its low immunogenicity. A vaccine based on the virus' mRNA is also under study.

Researchers are also working on the use of dendritic cells to treat HPV infection. Two strategies for obtaining such a vaccine are in development. The first involves in vitro cultured dendritic cells, which would then be stimulated with E6/EF antigen. The second option is to transfer dendritic cells, which had previously been transfected with a vector expressing viral antigens, to the patients. The disadvantages of this concept are its high cost and the difficulty of large-scale production. The above-mentioned vaccines are still in clinical trials. [12,16]

SCHEDULES AND RECOMMENDATIONS

In Poland, vaccination against HPV is possible from the age of 9. The vaccine is administered intramuscularly in the shoulder muscle area. Dosage varies in different age groups of patients. Until the age of 14, the basic regimen is a two-dose regimen regardless of the type of vaccine. The recommended interval between the first and second dose is from 5 to 13 months.

If the minimum interval between injections is not observed, the regimen should be corrected, and a third dose of the product should be given at an interval of at least 5 months after the first dose and at least 3 months after the second dose.

If vaccination is started at age 15, the regimen includes an additional, third injection. Intervals between doses depend on the type of the vaccine:

- for a bivalent vaccine, a schedule of 0, 1, 6 months is recommended;

- a quadrivalent or nonavalent vaccine should be given in a 0, 2, 6-month schedule. [17]

After the age of 26, the decision to vaccinate is made depending on the patient's individual medical history. Patients up to the age of 45 can benefit from vaccination. [18] HPV DNA testing is not recommended before qualifying for vaccination. A positive test result does not disqualify from the injection. [19]

A recent WHO position paper mentions the single-dose regimen as potentially effective in preventing HPV-16 and -18 infections. [20] In their randomized study, P. Basu et al. demonstrated that a single dose of vaccine showed similar protective effects against persistent HPV 16 and HPV 18 infection as 2 and 3-dose immunization schedules. [21] At present, there are still insufficient data to evaluate adequately the efficacy and long-term immunity gained from the single-dose regimen. [22] The introduction of a single-dose schedule would result in organisational simplification and increased vaccination coverage, especially in low- and middle-income countries, where the vast majority of cervical cancer cases worldwide are diagnosed. [23] Vaccinability of the population could be increased by improving accessibility to vaccines and reducing distribution costs. [24] In 2022, according to WHO recommendations, each country had the option to introduce shortened vaccination schedules, i.e. 1-dose for 9–20-year-olds and 2-dose for other patient groups, in order to increase the vaccination coverage of the population. [20]

During pregnancy, HPV vaccination is not recommended, but there is no need for a pregnancy test at the time of vaccine eligibility. [18] Breastfeeding is not a disqualifying criterion – previously unvaccinated women should receive the vaccine. [19] Prophylactic vaccination according to a three-dose schedule is recommended for immunocompromised individuals due to their increased risk of HPV infection. [25]

The guidelines in secondary prevention after vaccination have not changed so far - women should still undergo screening at 5-year intervals. This interval will not be changed until new data on the effectiveness of vaccination in preventing CIN2+ lesions are available. [26]

EFFICACY

All HPV vaccines have significant immunogenicity and a high safety profile. In contrast to the natural course of infection, vaccination results in tens to hundreds of times higher antibody concentrations.[27] Several randomised trials have shown that vaccine efficacy is higher in patients with negative HPV DNA status. If HPV-infected and HPV-uninfected women were eligible for the study, efficacy was lower. [28] Children <16 years of age achieve higher antibody levels compared to other age groups. A similar dependency also existed regarding the gender of the patients - antibody levels were significantly higher in women compared to men. [29]

According to studies, the bivalent vaccine reduces the risk of developing condylomata acuminata by up to 95%, and the 2- and 4-valent vaccines show more than 90% effectiveness in preventing HPV-related intraepithelial neoplasia. [30] An 11-year follow-up of patients showed that the 2-valent vaccine was almost 100 % effective in preventing the development of CIN2+ lesions in women who - prior to vaccine administration - had not been diagnosed with HPV 16 and HPV 18. Remarkably, the protective effect was maintained throughout the entire follow-up period. [31]

In the case of the 4-valent vaccine, vaccine efficacy of over 90% has been shown to last for at least 10 years. [32] Warner K. Huh et al. conducted a study comparing the efficacy of the 4-valent and 9-valent vaccines in a female population aged 16-26 years. They showed that both vaccines were comparably effective in preventing lesions caused by HPV 6,11,16 and 18. In contrast, for lesions caused by HPV 31, 33, 45, 52, and 58, the efficacy of the 9-valent vaccine was 97.4 %. [33] Furthermore, antibody levels against HPV 6, 11, 16 and 18 reached comparable values with the 4- and 9-valent vaccines. [34]

Worldwide, it is estimated that the 9-valent vaccine can prevent up to 90% of cervical cancers, 90% of vaginal and vulvar cancers associated with HPV infection, 70-85% of CIN2/CIN3 lesions and about 90% of HPV-associated anal cancers and condylomas. [35]

HPV VACCINATION COVERAGE IN EUROPEAN COUNTRIES

The organization of HPV vaccination programs varies vastly among European countries. The first countries to introduce the HPV vaccine into their national immunization schedules in 2006 and 2007 were Austria, Germany, France, Italy, and the UK.[36] On the contrary, several countries such as Turkey, Ukraine, and Belarus have not yet included the vaccination in any official immunization schedules or programs. [37] Additionally, in the last three years, the following countries have decided to launch a national HPV vaccination campaign: Kosovo (2024) [38], Poland (2023) [39], Albania (2022) [37,40], Serbia (2022) [37,40] and Montenegro (2022) [40].

The vaccination coverage rates are difficult to compare, as target age groups differ significantly between countries and in some cases official monitoring systems are unavailable. According to the most recent accessible data, European countries with a coverage of above 80% of female individuals in target groups, who have had the first dose of the vaccination administered, are the UK [41], Denmark [42], Norway [43], Sweden [44], Iceland [45], Ireland [46], Hungary [47], Lithuania [47], Portugal [47,48] and Spain [47,49]. All those countries have also offered the male population the HPV vaccination within the national immunization schedule [41,42,43,44,46,47,48,49,50]. Examples that are particularly worth mentioning in terms of high vaccine uptake, are Sweden, Norway, Portugal, and Denmark. In the first two countries, not only the first dose but also the final dose coverage rate in target groups in both sexes exceeds 80% [43,44]. In Denmark and Portugal, only the first dose administration covers above 80% of the targeted group in both sexes [42,47].

Some of the countries that introduced the vaccination first have a coverage rate that was reported as insufficient by national institutions [51,53]. It had been estimated that until 2023 55% of French eligible girls younger than 15 years old have initiated, whereas 45% have finished the vaccination course. In the male population, coverage rates for first and second-dose administration in individuals under 15 were estimated at 26% and 16%, respectively [52]. Also, the Robert Koch Institute (national German Disease Control and Prevention Institute) has described the HPV vaccine uptake in Germany as low, based on data from 2021. Until that year around 54% of German girls and 27% of German boys younger than 15 years old had been fully vaccinated against HPV [53].

The countries with the lowest vaccination rates include those, which have started state-funded vaccination programs only in the most recent three years. In some of them, a monitoring system has not yet been developed. Albania and Poland have a coverage rate of vaccine initiation in target groups of around 15 and 20%, respectively [54,55]. In Slovakia, 20% of targeted girls and 6.2% of targeted boys aged 12-13 have completed the vaccination course according to data from 2022 [56]. The lowest official coverage rates are observed in Bulgaria. According to media reports the vaccine coverage for eligible girls in Bulgaria was 1,5% in 2023 without dose specification [57], while official reports from 2023 estimate coverage of around 6% for full vaccination scheme [47]. Unofficial estimations also highlight Romania as another country with a potential deficient uptake. In a cross-sectional survey from 2023, only 22 women out of 524 (4,2%) female respondents aged from 19 to 69 declared that they were HPV vaccinated [58].

A lack of an official monitoring system may hinder an objective judgment of vaccination coverage, as is also the case with Croatia and Greece. In light of unavailable official data, a cross-sectional survey coverage rate is to be reported. In a Croatian survey from 2022 among 1,197 individuals aged 18-25 years only 18.3% of participants (25.0% of women and 11.7% of men) reported that they were HPV vaccinated [59]. Regarding Greece, a study from 2022 investigated parents' attitudes towards the HPV vaccine. The results revealed that only 35% of children had received all the recommended doses [60].

CONCLUSIONS

Vaccination of children and screening tests constitute the basis of the elimination of cervical cancer. The efficacy of the already existing vaccines is very high, which could raise hope for a significant decrease in cervical cancer morbidity in the future. Further research directions imply promising data regarding the increased valency of new vaccines. Currently, vaccines, which may target more HPV types, are being investigated. Vaccination promotion and focus on education regarding infection routes, mainly in countries with high cervical cancer incidence and low vaccination coverage, are of relevance.

DISCLOSURE

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All authors have read and agreed with the published version of the manuscript.

Funding Statement: The study did not receive special funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: There is no conflict of interest for the authors.

Acknowledgments: Not applicable.

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