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Ethical Challenges in Human Papillomavirus Vaccination

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Abstract

The Human Papillomavirus (HPV) is the most common sexually transmitted infection that manifests clinically through anogenital warts which may progress to precancerous lesions or different types of cancers. To prevent morbidity and mortality, the World Health Organization (WHO) recommends HPV vaccines as part of routine vaccinations in all countries, along with other prevention measures. In Romania, the Ministry of Health recommends HPV vaccinations based on the fact that countries that included HPV vaccination in their national programs reported significant reductions in the prevalence of anogenital warts and different types of cancers. One of the essential aspects of vaccination in general and more specifically in HPV vaccination is the ethical aspect. It will be discussed in detail in the present paper.

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ETHICAL CHALLENGES IN HUMAN PAPILOMAVIRUS VACCINATION

Antoanela Naaji,¹ Gratiana Chicin²

INTRODUCTION

The Human papillomavirus (HPV) infection is now a global concern. It is the most common sexually transmitted infection that manifests clinically through anogenital warts and it may progress to precancerous lesions or different types of cancers. It is now well established that this infection is the cause of cervical cancer and there is growing evidence of HPV being a relevant factor in other anogenital cancers as well as head and neck cancers.

Data on the HPV role in anogenital cancers other than the cervix are limited, but there are some evidence linking HPV DNA with cancers of the anus, vulva, vagina, and penis. Their association with HPV makes them potentially preventable and subject to similar preventative strategies as those for cervical cancer. According to the HPV Information Centre, About 569,847 new cervical cancer cases are diagnosed annually in the world (estimates for 2018). Cervical cancer ranks as the 3rd leading cause of female cancer and it is the 2nd most common female cancer in women aged 15 to 44 years.³

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³ Laia Bruni, G. Albero, B. Serrano, M. Mena, D. Gómez, J. Muñoz, Xavier Bosch, Silvia de Sanjosé, *Human Papillomavirus and Related Diseases in the World. Summary Report*. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre), 17 June 2019. <https://www.hpvcentre.net/statistics/reports/XWX.pdf> (accessed August, 2019).

Considering that the Human papillomavirus is mostly acquired during adolescence or young adulthood, in order to prevent morbidity and mortality, the World Health Organization (WHO) recommends HPV vaccines as part of routine vaccinations in all countries, along with other prevention measures. Thus, institutionalized vaccination programs have become part of routine health care worldwide.⁴

Monitoring of HPV vaccination coverage is essential in order to assess the performance of vaccination programmes. Since their licensure in 2006, HPV vaccines have been progressively introduced in many countries, mainly targeting girls around the ages of ten to fourteen. Comparison of coverage statistics is limited by differences in age at vaccination, programme delivery strategy, and year. However, global estimates of the extent and impact of vaccine coverage are still unavailable.⁵

According to literature, trials and studies investigated different issues related to HPV vaccination, such as vaccination status and results, the efficiency of human papillomavirus vaccines, parents' HPV vaccine knowledge, attitudes and behavior, ethical issues related to human papillomavirus vaccination programs, HPV vaccination policy, inequalities in cervical cancer burden and prevention, etc. Some of the studies are presented in the "Literature review" section.

In Romania, the Ministry of Health recommends HPV vaccinations based on the fact that countries that included HPV vaccination in their national programmes, reported significant reductions in the prevalence of anogenital warts and different types of cancers. The most important cause for which the HPV types 16 and 18 vaccines was introduced in Romania was the high prevalence of cervical cancer. The current vaccine is for 9 HPV types, including those that cause genital warts. More aspects regarding these issues are presented in "The HPV vaccination in Romania" section.

One of the most important aspects of vaccination in general and more specifically in HPV vaccination is the ethical one. It will be discussed in more detail in the "Ethical Challenges" section.

⁴ WHO, "Human papillomavirus vaccines: WHO position paper," *WER* 43 (2014), 89, 465–492. www.who.int/wer/2014/wer8943.pdf?ua= (accessed July 2019).

⁵ Lauri E. Markowitz, Vivien Tsu, Shelley L. Deeks, et al., "Human papillomavirus vaccine introduction - the first five years," *Vaccine* 30 (suppl. 5) (2010): F139-F148.

LITERATURE REVIEW

According to Bruni et al., worldwide, from June 2006 to October 2014, 64 countries nationally, four countries subnationally, and 12 overseas territories had implemented HPV immunization programs. Between 2006 and 2014, on the global level, about 47 million women received a full course of the HPV vaccine, and 59 million women received at least one dose of the vaccine⁶. For optimum cost-effectiveness, HPV vaccination coverage in women should be about 70%. At a vaccination rate of 50%, a 68% reduction in HPV types 16 and 18 were found and also a 61% decrease in anogenital warts. Thus, 379,000 cases of cervical cancer and 156,000 deaths were prevented until the age of 75. Even if an estimated 118 million women had been targeted through these programmes, only 1% were from low-income or lower-middle-income countries. However, the impact of the vaccine was higher in upper-middle-income countries than in high-income countries, despite the lower number of vaccinated women.⁷

According to the literature, recent trials and studies investigated different issues related to HPV vaccination, such as HPV vaccination policy, vaccination status and results, the efficiency of human papillomavirus vaccines, etc.⁸ These studies were carried out all over the

⁶ Laia Bruni, G. Albero, B. Serrano, M. Mena, D. Gómez, J. Muñoz, Xavier Bosch, Silvia de Sanjosé, *Human Papillomavirus and Related Diseases in the World. Summary Report*. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre), 17 June 2019. www.hpvcentre.net/statistics/reports/XWX.pdf (accessed August, 2019).

⁷ Laia Bruni, Mireia Diaz, Leslie Barrionuevo-Rosas, Rolando Herrero, Freddie Bray, F. Xavier Bosch, Silvia De Sanjosé, Xavier Castellsagué, “Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis,” *Lancet Glob Health* 4(7) (2016): e453-e463.

⁸ See the following articles: Catherine De Martel, Martyn Plummer, Jerome Vignat, Silvia Franceschi, “Worldwide burden of cancer attributable to HPV by site, country and HPV type,” *International Journal of Cancer* 141(4) (2017): 664-670. Rolando Herrero, Wim Quint, Allan Hildesheim, Paula Gonzalez, Linda Struijk, Hormuzd A Katki, Carolina Porras, Mark Schiffman, Ana Cecilia Rodriguez, Diane Solomon et al. (CVT Vaccine Grp), “Reduced Prevalence of Oral Human Papillomavirus (HPV) 4 Years after Bivalent HPV Vaccination in a Randomized Clinical Trial in Costa Rica,” *PLOS ONE* 8(7): 2013. Hammad Ali, Basil Donovan, Handan Wand, Tim R. H. Read, David G. Regan, Andrew E. Grulich, Christopher K. Fairley, Rebecca J. Guy, “Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data,” *British Medical Journal* 346 (2013). Anisa Mburu, Peter Itsura, Hillary Mabeya, Alice Kaaria, Darron R. Brown, “Knowledge of Cervical Cancer and

world. There are also some studies which investigate ethical related issues such as: parents' HPV vaccine knowledge, attitudes and behavior, ethical issues related to human papillomavirus vaccination programs, inequalities in cervical cancer burden and prevention, etc. Furthermore, we will present a few of them.

In "Who calls the shots? The ethics of adolescent self-consent for HPV vaccination,"⁹ the authors investigated the factors which influence the rate of human papillomavirus vaccination based on the fact that even the HPV is indicated to reduce the risk of genital warts and certain types of cancer, rates of vaccination are low in the USA. Their hypothesis was that the individual-level factors have an important contribution to low vaccination rates. One of the most important factors was considered to be the need for parental consent. In their study, the authors explored the ethical acceptability of vaccinating adolescents for HPV without parental

Acceptability of Prevention Strategies among Human Papillomavirus-Vaccinated and Human Papillomavirus-Unvaccinated Adolescent Women in Eldoret, Kenya," *BioResearch Open Access* 8(1) (2019): 139-145. Kristina Thorsteinsson, Steen Ladelund, Merete Storgaard, Terese Katzenstein, Isik Somuncu Johansen, Gitte Pedersen, et al., "Persistence of cervical high-risk human papillomavirus in women living with HIV in Denmark - the SHADE," *BMC Infectious Diseases* 19(1) (2019): 740. Tanja Y. Walker, Laurie D. Elam-Evans, James A. Singleton, David Yankey, Lauri E. Markowitz, Benjamin Fredua, Charnetta L. Williams, Sarah A. Meyer, Shannon Stokley, "National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13-17 Years - United States 2018," *Morbidity and Mortality Weekly Report*, 68(33) (2019): 718-723. Witness Mapanga, Brendan Girdler-Brown, Elvira Singh, "Knowledge, attitudes and practices of young people in Zimbabwe on cervical cancer and HPV, current screening methods and vaccination," *BMC Cancer* 19(1) (2019): 845. Shyamji Rawat, Sulekha Yadav, Pranijl Mandloi, Chinkal Panihar, P.V. Barde, "High Incidence of Human Papillomavirus Types 16 and 18 in Cervical Carcinoma Patients in a Tertiary Care Unit, Jabalpur, MP, India," *Indian Journal of Gynecologic Oncology* 17(3) (2019): 66. Lin Zhu, Shumenghui Zhai, Philip T. Siu, Helen Y. Xia, Sarah Lai, Cristina N. Zambrano, Grace X. Ma, "Factors Related to Chinese Parents' HPV Vaccination Intention for Children," *American Journal of Health Behavior* 43(5) (2019): 994-1005. Bo Zhu, Yunyong Liu, Tingting Zuo, Xiaoli Cui, Mengdan Li, Jing Zhang, Huihui Yu, Haozhe Piao, "The prevalence, trends, and geographical distribution of human papillomavirus infection in China: The pooled analysis of 1.7 million women," *Cancer Medicine* 8(11) (2019): 5373-5385. Sylvie Abel, Fatiha Najioullah, Jean-Luc Volumenic, Laetitia Accrombessi, Gabriel Carles, Dominique Catherine et al. (HP2V Study Grp), "High prevalence of human papillomavirus infection in HIV-infected women living in French Antilles and French Guiana," *PLOS ONE* 14(9) (2019): e0221334.

⁹ Suchi Agrawal, Stephanie R. Morain, "Who calls the shots? The ethics of adolescent self-consent for HPV vaccination," *Journal of Medical Ethics* 44(8) (2018): 531-535.

consent. Based on the analysis that they carried out, the conclusion was that allowing adolescents to self-consent for being immunized by HPV vaccine is justifiable from an ethical point of view and it should be reflected in United States policies.

In “Ethical issues related to human papillomavirus vaccination programs: an example from Bangladesh,”¹⁰ the authors present the current situation in Bangladesh where the HPV vaccine was introduced in 2016, as a pilot project, in Gazipur district, targeting grade five female students and non-school going girls (age range 10-12 years). The paper investigates the various ethical aspects related to the introduction and implementation of such a vaccination program. The study was conducted based on interviews with policy-makers, vaccine implementers, vaccine recipients and ethics specialists from Bangladesh. The authors concluded that more ethical discussion and debate should be done among the public health professionals. Also, adolescent health education should contain more detailed information about HPV, its mode of transmission, risk factors and prevention in order to make an informed choice.

In “Assessing the acceptability of incentivising HPV vaccination consent form return as a means of increasing uptake”¹¹ the influence of an incentive intervention for obtaining the HPV vaccination consent forms was investigated. The methodology of the study was based on applying a qualitative free-text questionnaire to 181 adolescent girls and 61 parents, assessing the acceptability of an incentive intervention to increase HPV vaccination consent form return. Telephone interviews were also conducted with six members of the staff participating, assessing the acceptability of the incentive. The results of the study showed that the use of an incentive intervention to encourage the return of HPV vaccination consent forms were moderately acceptable. Another conclusion was that improving communication about the nature of the incentive to reduce misconceptions is vital.

¹⁰ Marium Salwa, Tarek Abdullah Al-Munim, “Ethical issues related to human papillomavirus vaccination programs: an example from Bangladesh,” *BMC Medical Ethics* 19 (2018).

¹¹ Lauren Rockcliffe, Amanda J. Chorley, Emily McBride, Jo Waller, Alice S. Forster, “Assessing the acceptability of incentivising HPV vaccination consent form return as a means of increasing uptake,” *BMC Public Health* 18 (2018).

Another study carried out in Canada¹² examined the ‘girls only’ policy for publicly funded human papillomavirus (HPV) vaccination programmes, which is criticized by some ethicists as inequitable. This ethical issue is based on some recent studies that indicate increasing rates of other HPV-related cancers among cisgender men and women. The authors consider that these exclusionary practices that leave out those who form their gender identities across the spectrum are unethical. Their conclusion, based on deontological and utilitarian frameworks, is that a collective mobilization is needed in order to fund more inclusive HPV vaccination policies.

The other two studies carried on in 2014 emphasize the role of advertising and professional communication in the decision-making process related to HPV vaccination.

The first study¹³ explores the methodological and ethical issues of engaging in health research using social media. As methodology, the authors searched seven electronic databases using search terms related to Human papillomaviruses (HPV) and HPV vaccination. The conclusion was that most researchers did not engage enough virtual users in the research. Most studies did not seek ethical approval from an institutional research board or permission from web service hosts (providers). To respect the principles of concern for welfare, respect for the person, and justice in research using social media, the authors recommend researchers and ethics review boards to work together to develop expertise in evaluating the design of studies where the virtual communities are involved.

The second study¹⁴ was carried out in Sweden and investigated why parents refuse to vaccinate their 10-12 years old daughters with the HPV vaccine. The methodology consisted of interviewing 25 parents. The conclusions showed that, besides other subjective reasons, the main reason was related to the lack or insufficient information necessary for

¹² Victoria Law, Diana L. Gustafson, “Challenging ‘girls only’ publicly funded human papillomavirus vaccination programmes,” *Nursing Inquiry* 24(1) (2017).

¹³ Diana L. Gustafson, Claire F. Woodworth, “Methodological and ethical issues in research using social media: a meta method of Human Papillomavirus vaccine studies,” *BMC Medical Research Methodology* 14 (2014), <https://bmcmmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-14-127>, (accessed August, 2019).

¹⁴ Maria Grandahl, Marie Oscarsson, Christina Stenhammar, Trygve Neveus, Ragnar Westerling, Tanja Tyden, “Not the right time: why parents refuse to let their daughters have the human papillomavirus vaccination,” *Acta Paediatrica* 103(34) (2014): 436-441.

giving documented informed consent. The results also pointed out that a more flexible HPV vaccination schedule could improve vaccine uptake.

A recent study¹⁵ focuses on the challenges in obtaining the informed consent necessary for carrying out the immunization programs in schools, in England. These programs requested parental informed consent for HPV vaccinations. The methodology of the study consisted of analyzing the results of the data collected from 39 interviews with immunization managers and providers and a descriptive statistical analysis of data resulted from questions related to consent for adolescent vaccination, included in a survey applied to parents and adolescents in 2017. The main conclusions were: (1) parents and adolescents generally agreed on vaccine decisions although only 32% of parents discussed vaccination with their daughters, (2) health professionals were not always clear about the best way to manage the consent process and (3) improving the communication and developing related interventions to improve the logistics and practice of consent in school-based adolescent immunization programmes could help improve uptake.

HPV VACCINATION IN ROMANIA

According to Human Papillomavirus and Related Diseases Report,¹⁶ the HPV infection is the main cause of cervical cancer and, based on the recent evidence, it represents an important factor in other anogenital cancers as well as head and neck cancers. Moreover, HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases globally.

In Romania, about 3,308 new cervical cancer cases are diagnosed annually (estimates for 2018). Cervical cancer ranks as the 2nd leading cause of female cancer in Romania and it is the 2nd most common female cancer in women aged 15 to 44 years. Figure 1 represents a comparison of cervical cancer incidence to other cancers in women of all ages in Romania.

¹⁵ Tracey Chantler, Louise Letley, Pauline Paterson, Joanne Yarwood, Vanessa Saliba, Sandra Mounier-Jack, "Optimising informed consent in school-based adolescent vaccination programmes in England: A multiple methods analysis," *Vaccine* 37(36) (2019): 5218-5224.

¹⁶ Laia Bruni, G. Albero, B. Serrano, M. Mena, D. Gómez, J. Muñoz, Xavier Bosch, Silvia de Sanjosé, *Human Papillomavirus and Related Diseases in the World. Summary Report*. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre), 17 June 2019. www.hpvcentre.net/statistics/reports/XWX.pdf, (accessed August, 2019).

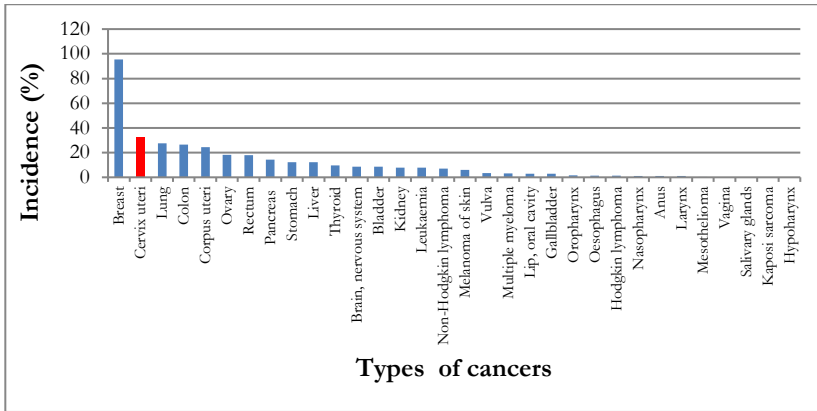


Fig. 1. Incidence of different types of cancers in Romania

In particular, in Romania, cervical cancer represents a critical problem of the public healthcare system, its incidence being very high¹⁷ (Fig. 2).

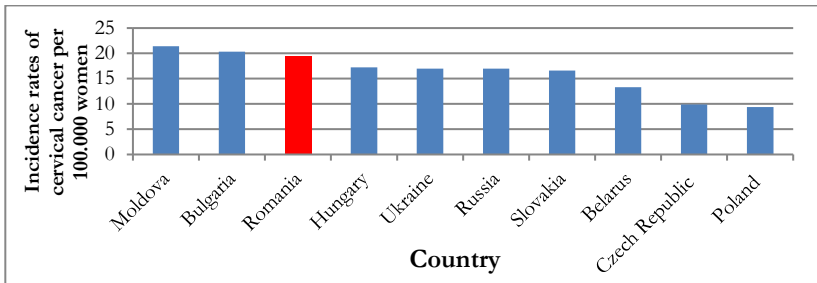


Fig. 2. Age-standardized incidence rates of cervical cancer per 100.000 women

Regarding cervical cancer mortality in Romania, about 1,743 cervical cancer deaths occur annually (estimates for 2018). Cervical cancer ranks as the 3rd leading cause of female cancer deaths in Romania and it is the 2nd leading cause of cancer deaths in women aged 15 to 44 years in Romania.¹⁸ Figures 3 and 4 show a comparison of cervical cancer mortality to other cancers in women of all ages in Romania and a

¹⁷ Ibidem.

¹⁸ Ibidem.

comparison of age-standardized cervical cancer mortality rates in Romania and respectively, in countries within the region.

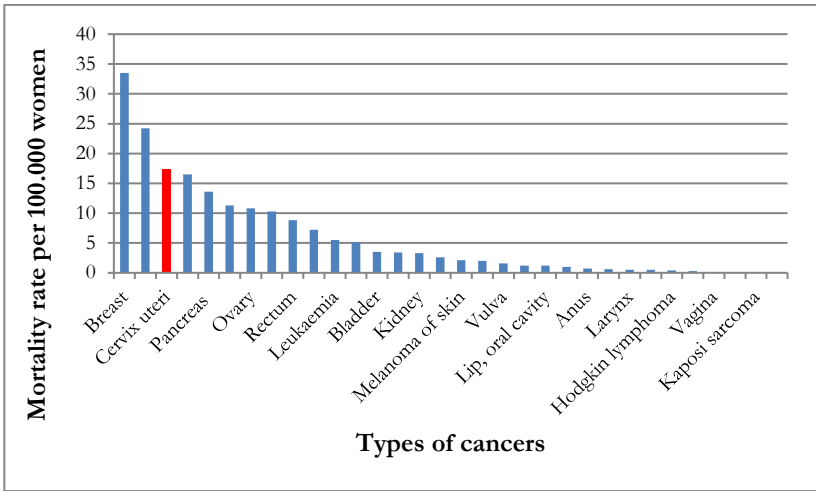


Fig. 3. Mortality rate caused by different types of cancers per 100,000 women

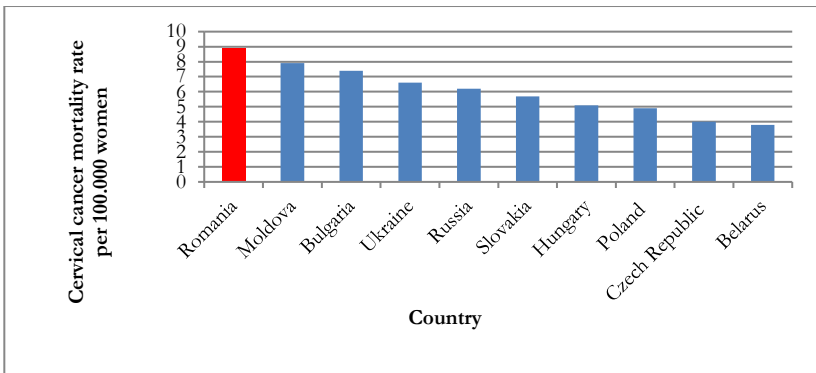


Fig. 4. Age-standardised cervical cancer mortality rates in Romania and countries within the region

The report also presents data related to the influence of HPV in other types of cancers.

Regarding the HPV prevention strategies, it is known that cervical screening programmes can reduce cervical cancer incidence and mortality. Also, there are studies that demonstrated the efficacy of the HPV vaccination in reducing the burden of cervical cancer.

Romania did not have a nationwide, population-based screening programme until 2012 when a National Programme was implemented for women aged 25-64. Therefore, this programme was not a successful one, due to the low rate of attendance and opportunistic participation in screening procedures.¹⁹

In April 2016, the Romanian Ministry of Health launched the first National plan for control of cancer in Romania, a project that included a comprehensive set of measures for the prevention, reduction of the incidence and mortality of cancer in Romania. Although this plan was in accordance with other programmes existing in Western Europe and it could have a major benefit for cancer patients in Romania, the project has never been implemented.²⁰

Regarding the HPV vaccination strategies around the world, in 2006 and 2009 respectively, two human papillomavirus (HPV) vaccines, Gardasil/Silgard (Merck & Co. Inc.) and Cervarix (GlaxoSmithKline, GSK) were licensed by the US Food and Drug Administration. By May 2012, 19 EU countries have implemented HPV vaccination programmes.²¹ In 2008, the Romanian Ministry of Health started an immunization campaign in schools, providing free vaccines for 10 to 11

¹⁹ Marcela Penta, Adriana Baban, "Mass media coverage of HPV vaccination in Romania: a content analysis," *Health education research* 29(16) (2014): 977-992, www.academia.edu/23787954/Mass_media_coverage_of_HPV_vaccination_in_Romania_a_content_analysis?auto=download, (accessed June, 2019). Iuliana Raluca Gheorghe, "Human papillomavirus (HPV) vaccination campaign in Romania. A case study from a social marketing perspective," in *Advances in Business-Related Scientific Research Conference* (Venice, 2012).

²⁰ Ramona Gabriela Ursu, Luminita Smaranda Iancu, "Epidemiological Data on HPV Infection in Romania in the Context of the Lack of Correct Cervical Cancer Screening" in *Human Papilloma Virus* (Avid Science, 2017), www.researchgate.net/publication/317433912_Epidemiological_Data_on_HPV_Infection_in_Romania_in_the_Context_of_the_Lack_of_Correct_Cervical_Cancer_Screening, (accessed August, 2019).

²¹ *** *Public consultation on draft guidance for introduction of HPV vaccines in EU countries: focus on 9-valent HPV vaccine and vaccination of boys and people living with HIV*, European Centre for Disease Prevention and Control (ECDC) (Stockholm, 2019), www.ecdc.europa.eu/sites/portal/files/documents/hpv-public-consultation-3-April.pdf, (accessed June, 2019).

years old girls who have received written parental consent. Statistics revealed that only 2.57% of the 110000 girls were vaccinated.

Starting with 2009, an information campaign was launched, followed by a second vaccination programme, targeting 12 to 14 years old girls. Moreover, the programme was made available for adult women, who had the opportunity to get the vaccine free of charge through their health provider. Despite the accessibility of the vaccine, the coverage remained low and the programme for schools was discontinued at the end of 2011. In April 2013, the programme was launched again. At present, HPV vaccination is included in the National Vaccination Program in the category “Vaccination of Population at Risk” and is addressed to girls aged 11–14 years.

Unfortunately, in recent years the vaccination has not been done due to the limited funds and low interest from decision-makers.

ETHICAL CHALLENGES RELATED TO HPV VACCINATION

There are numerous studies that focus on ethical aspects related to HPV vaccination, few of them being presented in the “Literature review” section.

In this section, we present some ethical issues that should be considered in connection with the HPV vaccination and immunization programmes. The main issue is how governments, which are responsible for the health of citizens, and in this case, for immunization programmes, are able to achieve this goal in an equitable and transparent way. One of the most essential means, in order to prevent the spread of HPV infection, is vaccination. From an ethical point of view, the balance between benefits and harms should be established. Also, the autonomy of the individual must be respected, a thing which can lead to a conflict between public and individual interest.²²

²² *** *Health Technology Assessment (HTA) of HPV vaccination of boys*, Health Information and Quality Authority (Dublin, 2018), www.hiqa.ie/sites/default/files/2018-12/HTA-for-HPV-Vaccination-boys.pdf, (accessed June, 2019).

The principle of autonomy

The principle of autonomy is based on the respect for persons, which means that every person has the right to make his/her own choices. In healthcare systems, the principle of autonomy translates into the principle of informed consent.

In healthcare systems, vaccination is provided to individuals in order to prevent different illnesses, but its benefits may not be visible to the individuals who receive the vaccination, some of them perceiving it as unnecessary. Evaluating the results according to the rate of coverage, the vaccination is sometimes misunderstood. Thus, a high rate of coverage is considered to have a social benefit, and not an individual one. In this case, even in situations where vaccination is not mandated, individuals may feel that they are losing their autonomy. On the other hand, vaccination continues to be a widely accepted public health intervention. Thus, the interplay between autonomy, informed consent and shared decision-making should exist.

The elements of valid informed consent are capacity, understanding of information disclosed and voluntary agreement. In HPV vaccination programmes, one of the most challenging tasks is obtaining consent from adolescents or their parents/guardians. Considering that most of the immunization programmes are targeting children who are too young to have the capacity to consent themselves, parents or guardians are requested to give consent on their behalf. The debate here is if, in order to exercise autonomy, the children should be involved in the decision-making process. Our opinion is that, given the age at vaccination, it may be appropriate to consider the participation of the child in each part of the informed consent process, even if together with the parent. Meanwhile, the informed consent materials must provide sufficient information in a form, manner and language that is understandable to parents. So, in our opinion, the best option for obtaining informed consent for vaccination is to involve both children and parents on the basis of understanding the specific information.

Informed consent is underpinned by the provision of sufficient information. In the absence of clear information then it may be speculated, for example, that the policy decision was on the basis of safety concerns. Also, clear communication in relation to policy decisions

on HPV immunization may minimize the risk of misperceptions amongst the public.²³

Another issue regarding autonomy, in some countries, as mention in a study from Bangladesh,²⁴ is the use of an implied consent procedure. This means that parents or guardians are informed about vaccination through social media or different official ways of communication, and thus if they send their children to be vaccinated, it means that they are giving the consent to receive the vaccine, and vice versa. An important issue is, even if the consent is implied or written, it should be well informed.

In Romania, the first HPV vaccination campaign has failed due to a lack of communication and information presented in the public space. At the same time, there was no firm position of the authorized institutions about the importance of HPV vaccination, so, in many cases, a misunderstanding of the vaccine's risks/benefits. In this way, the principle of autonomy was respected, but the coverage rate was very low, especially due to the lack of information.

Currently, in Romania, consent is presumed, which means that everyone was supposed to be vaccinated, and only those who refused had to express their choice in writing or verbally. Even so, many of the parents or guardians continued to refuse the vaccine. As a result, the Ministry of Health increased the age of eligible women up to 24 years, then, in 2010, up to 45 years.

The principles of beneficence and non-maleficence

Beneficence requires that the procedure be provided in the patient's interest, with the intent of doing good. Thus, the healthcare providers should develop and maintain skills and knowledge, continually update

²³ *** *Health Technology Assessment (HTA) of HPV vaccination of boys*, Health Information and Quality Authority (Dublin, 2018), www.hiqa.ie/sites/default/files/2018-12/HTA-for-HPV-Vaccination-boys.pdf, (accessed June, 2019). Jeroen Luyten, Bart Engelen, Philippe Beutels, "The Sexual Ethics of HPV Vaccination for Boys," in *HEC Forum* (Springer, 2013), https://pure.uvt.nl/ws/portalfiles/portal/5039613/luyten_engelen_beutels_sexual_ethics_of_hpv_vaccination_for_boys.pdf, (accessed June, 2019).

²⁴ Marium Salwa, Tarek Abdullah Al-Munim, "Ethical issues related to human papillomavirus vaccination programs: an example from Bangladesh," *BMC Medical Ethics* 19(1) (2018).

training, consider individual circumstances of all patients, and strive for net benefit.

Non-maleficence requires that a procedure does not harm the patient involved or others in society. In some cases, this principle is difficult for doctors to fully apply it due to some conditions or factors which are influencing the medical act. In practice, sometimes, “the do no harm principle” is understood as minimizing as much as possible the harm and maximize the benefits.

In the case of HPV vaccination, the benefit-harm balance must be considered not only at the population level, translated into coverage rate, but also at the individual level. The decision to be vaccinated is made by individuals, based on the evaluation of risks and benefits, perceived personally. Thus, the policy decision-maker should consider this aspect even if they consider the benefit-harm balance at the population level.

Based on the existing literature, the only harms that could be generated by vaccination are related adverse events, which usually are non-serious reactions, such as soreness or redness at the injection site. Only a small minority reported severe adverse events, such as anaphylactic reactions.

One of the difficulties in evaluating the harm is due to collecting clinical outcome data from children and adolescents who receive the vaccine. However, non-serious adverse events can be noticed after the vaccination, so the quantification of such harm is easy to assess.

Regarding the benefits, an important issue is that the time lag between vaccination and future benefits could be very long. In the case of HPV-related tumors, onset is typically decades after vaccination, so the effects of the implementation of an HPV immunization programme could take many years before the impact is observed. This means that it may never be possible to accurately determine the full benefits of vaccination.

Therefore, in countries where HPV vaccination was implemented, there is international evidence that for anogenital warts, the benefits are more evident through the decline of the incidence of these infections. Considering other prevention strategies, like cervical screening programmes, which are in the real benefit of the targeted population by reducing morbidity and mortality, both strategies should be applied.

In Romania, when the first HPV immunization programme was introduced, there were opinions against the HPV vaccination. The main arguments of adolescents or their parents who refused to enter HPV

immunization programmes were: the insufficient tests and fear of adverse effects. Also, an assumption that the entire program was an experiment of big pharmaceutical companies in the local population circulated during that period. Thus, in the first year, only 2.5% of the families of the targeted population accepted the vaccination, and in 2010-2011 the Romanian state began to destroy the purchased doses of vaccine, because they expired. All these facts have had a negative impact on the correct understanding of the benefits of the HPV vaccination²⁵.

As conclusion, vaccination is often used as a mechanism to achieve benefits for the greater good, even if only a few will experience a substantial benefit to the detriment of many individuals who experience a minor burden. In the case of HPV vaccination, the incidence of HPV-attributable diseases being higher, a larger proportion of the population will experience some form of benefits.

The principle of justice

The principle of justice requires, in the medical field, a fair distribution of services. The health care provider must consider when evaluating justice some issues such as fair distribution of resources, competing needs, rights and obligations, and potential conflicts with the established legislation.

Regarding this principle, there is an ethical dilemma because in many countries the HPV vaccination policies are available only for girls, so the immunization programmes are not equally available to all the targeted people. Considering the fact that boys can also benefit from vaccination, the existing girls-only programmes may be viewed as discriminating against boys. When HPV vaccination was initially introduced, it was as a means to reduce the incidence of cervical cancer and hence seen as benefiting girls only. The HPV vaccination of boys is a very important issue that could be analyzed in a future study.

The evaluation of how the principle of justice is applied in the case of HPV immunization programmes, should be done according to the financial resources of each country.

25 *** *Public consultation on draft guidance for introduction of HPV vaccines in EU countries: focus on 9-valent HPV vaccine and vaccination of boys and people living with HIV*, European Centre for Disease Prevention and Control (ECDC) (Stockholm, 2019), www.ecdc.europa.eu/sites/portal/files/documents/hpv-public-consultation-3-April.pdf, (accessed June, 2019).

Other ethical considerations

One of the ethical aspects which are less discussed in literature is related to the use of an intervention to encourage the HPV vaccination consent. In one of the mentioned studies²⁶, the conclusion was that incentives were moderately acceptable to those receiving and delivering the intervention and according incentives could be an acceptable means of improving HPV vaccination rates.

Another ethical issue, which we consider important in case of HPV vaccination, is respecting the privacy of individuals, which of course, should be part of the informed consent. The non-discrimination restriction will direct selective vaccination policies as much as possible towards relevant characteristics at the individual level. However, this can lead to infringements of privacy, since characteristics like sexual activity or other behaviours, in which disease transmission can occur, typically belong to an individual's privacy.

CONCLUSIONS

As conclusion, we consider that HPV vaccination is an essential measure in preventing anogenital warts and different types of cancers, but it must be done in compliance with ethical principles.

An important issue from an ethical point of view, in case of HPV immunization programmes, is obtaining informed consent. Considering that the target population is usually underage, the information of the parents/guardians must be done correctly. Thus, medical authorities should organize information campaigns that encourage vaccination and, at the same time, annihilate campaigns that misinform, especially if they are not based on studies and are not scientifically substantiated.

For a successful HPV immunization programme and for obtaining a high HPV vaccination coverage, communication remains one of the most important aspects of the advertising campaigns.

²⁶ Lauren Rockliffe, Amanda J. Chorley, Emily McBride, Jo Waller, Alice S. Forster, "Assessing the acceptability of incentivising HPV vaccination consent form return as a means of increasing uptake," *BMC Public Health* 18 (2018).

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