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# Vaccine Regulations in Croatia

Bernard Kaić<sup>1</sup>, Ira Gjenero-Margan<sup>1</sup>, Milka Brzović<sup>2</sup>, Danijela Lakošeljac<sup>3</sup>, Borislav Aleraj<sup>1</sup>, Tatjana Nemeth-Blažić<sup>1</sup>, Branko Kolarić<sup>1</sup>, Viola Macolić-Šarinić<sup>4</sup>, Aleksandar Šimunović<sup>1</sup> and Jasmina Pavlić<sup>1</sup>

<sup>1</sup> Department of Infectious Disease Epidemiology, Croatian Institute of Public Health, Zagreb, Croatia

<sup>2</sup> Split-Dalmatia County Institute of Public Health, Vukovarska 46, HR-21000 Split, Croatia

<sup>3</sup> Primorsko-Goranska County Institute of Public Health, Krešimirova 52a, HR-51000 Rijeka, Croatia

<sup>4</sup> Agency for Medicinal Products and Medical Devices, Ksaver 4, HR-10000 Zagreb, Croatia

## ABSTRACT

*In this paper legal prerequisites for vaccine licensure in Croatia are discussed. The Croatian legislation concerning vaccine licensing, marketing authorisation and utilization is reviewed. The procedures for including a vaccine into the Mandatory Childhood Vaccination Programme are also discussed with focus on Human papillomavirus (HPV) vaccines. Non-obligatory vaccination recommendations are given when according to professional opinion; vaccination is beneficial for the vaccinee. There is little doubt that HPV vaccines should be recommended for preadolescent girls in Croatia. However, reaching a decision on its possible introduction into the Childhood Vaccination Programme will require careful consideration of the larger picture and a comparison of the cost-effectiveness of a mandatory vaccination against other competing public health priorities.*

**Key words:** vaccination, regulations

## Introduction

The first prerequisite for a vaccine to be legally used in Croatia is licensure. The Agency for Medicinal Products and Medical Devices (AMPMD) is responsible for the licensing procedure and for marketing authorization of vaccines<sup>1</sup>. However, it is very important to understand that licensing and marketing authorization only guarantee the quality, safety and efficacy of vaccines but this does not determine the way a vaccine will be used.

Each lot of vaccine regardless of the manufacturer is subject to quality control performed by the AMPMD, Division for Immunological Medicinal Products. Further, the AMPMD undertakes a variety of other tasks including postmarketing surveillance and this is done in collaboration with the Croatian National Institute of Public Health which is responsible for surveillance of adverse events following immunization. Based on this surveillance, the AMPMD can request that the manufacturer review and change the summary of product characteristics, as well as the prescribing information.

The way a vaccine will be used depends on a number of epidemiological, regulatory and financial factors. Vac-

cines may be mandatory for the entire eligible population such as specific birth cohorts according to the Childhood Vaccination Programme<sup>2</sup>, or for specific at-risk groups such as hepatitis B vaccination for health care workers. Then, there are vaccines that are recommended for specific groups such as typhoid fever vaccination for travelers to endemic areas and influenza vaccination for the elderly, health care workers and chronically-ill patients.

## Mandatory Vaccinations

Each year, the Minister of Health announces the Childhood Vaccination Programme (»the Programme«) based on the recommendation from the Croatian Institute of Public Health (CIPH). The declaration of mandatory vaccination or the provision of free-of-charge vaccines is regulated by health care legislation, primarily the Act on the Protection of the Population from Infectious Diseases, which is further elaborated by the implementing provisions that are issued by the Minister of Health<sup>3,4</sup>. Mandatory vaccinations that are covered by

the Childhood Vaccination Programme are obligatory for all in the defined target population because it is in the interest of the community to have all its members / citizens vaccinated, as well as being in the interest of the individual vaccinee. All mandatory vaccinations according to the Programme are free of charge for the vaccinee, because the vaccines are purchased and vaccination is reimbursed to primary health care physicians by the Croatian Health Insurance Institute. The current Childhood Vaccination Programme is presented in Table 1.

**TABLE 1**  
CHILDHOOD VACCINATION PROGRAMME IN CROATIA  
FOR YEAR 2007

Age	Vaccine
Birth*	BCG, Hepatitis B
2 months	Hib, Hepatitis B
3 months	DTP, IPV
4 months	DTP, OPV, Hib
6 months	DTP, OPV, Hib, Hepatitis B
12–18 months	MMR, DTP, OPV, Hib
3 years	DTP
6 years	MMR, Td, OPV
12 years	Hepatitis B **
13 years	PPD, BCG***
14 years	Td, OPV
19 years	TT
60 years	TT

BCG – Bacillus Calmette-Guerin, Hib – Haemophilus influenzae type B, DTP – Diphtheria, tetanus, pertussis, IPV – Inactivated polio vaccine, OPV – Oral polio vaccine, MMR – Measles, mumps, rubella, PPD – Purified protein derivative testing, Td – Tetanus, diphtheria, adult formulation, TT – Tetanus toxoid, \* Newborns to HBsAg positive mothers receive HBIG at birth together with the first dose of hepatitis B vaccine, which is continued according to a 0, 1, 2, 12 scheme, \*\* Three doses of hepatitis B vaccine according to a 0, 1, 6 scheme. Vaccination at the age of 12 will be discontinued when children vaccinated as newborns reach this age, \*\*\* BCG revaccination is administered only to PPD negative children

Mandatory vaccination carries with it the responsibility of the government to secure safe and effective vaccines and to organise the health care system in such a way that it makes vaccination accessible to all within the designated target population. This is also regulated by law, primarily the Health Care Act, the Act on the Protection of the Population from Infectious Diseases (noted above), as well as various bylaws and ordinances arising from these acts<sup>5</sup>. According to these documents, it is the duty of primary health care providers to vaccinate pre-school children according to the Programme. Newborns are vaccinated in the maternity wards, while elementary school pupils are vaccinated at school by the school medical service that is affiliated to the County Institutes of Public Health.

As you will see, mandatory vaccination involves an enormous commitment on the part of the community, institutions and individuals so the decision to include a vaccine into the Programme or not must be based on solid scientific evidence and the highest professional expertise.

The Croatian Institute of Public Health (CIPH) is the institution responsible for designing the Childhood Vaccination Programme in Croatia. In collaboration with the relevant partners (representatives of paediatric associations, school health associations, epidemiologist associations, family doctors, etc.), the CIPH analyses the epidemiological situation regarding vaccine-preventable diseases, the performance of the proposed vaccination programme and all suggestions relevant to the Programme to develop and present a recommendation to the Minister. In certain instances, public opinion is taken into account in the decision-making process even if it is at odds with the scientific evidence and professional knowledge.

There are also a number of vaccinations which are mandatory for specific groups, e.g. hepatitis B (HBV) vaccination for health-care workers and for sexual partners of HBV carriers, then prophylaxis for persons exposed to rabies; these vaccines are free of charge for individuals and reimbursed by the Croatian Health Insurance Institute.

## Recommended Vaccination

Non-obligatory vaccination recommendations are those considered to be of interest for the individual but not to the whole community, and these can be either paid for by public Health Insurance or the individual. For example, influenza vaccination for health-care workers, the elderly and chronically-ill patients, pneumococcal vaccination for asplenic patients and the elderly in nursery homes, etc. are examples of vaccinations that are recommended and paid for by public Health Insurance. Then, all vaccinations recommended to travellers to prevent diseases that are endemic in the countries they are going to such as cholera, meningococcal meningitis, yellow fever or hepatitis A are paid for by the vaccinee. The same applies to tick-borne encephalitis vaccine, which is recommended for persons exposed to ticks in endemic areas, either professionally or recreationally.

## HPV Vaccination

As far as Human papillomavirus (HPV) vaccine is concerned, as soon as the vaccine is licensed and the batch control is finished, the vaccine will receive marketing authorization and can be used in Croatia. Then, recommendations for the use of vaccination will be issued by professional medical associations, e.g. gynaecology, paediatrics or epidemiology associations, or other non-governmental associations. Whether it will be reimbursed or not depends on the Health Insurance Institute. Any of the associations which issue recommendations can suggest the reimbursement of vaccination by the Health Insurance Institute or request the Ministry of Health to initiate the process for covering expenses by the Health

Insurance Institute. In both cases, the Health Insurance Institute establishes a committee of the relevant medical experts and eventually decides whether the Health Insurance Institute will cover the expenses or not.

The vaccination strategy that is anticipated to have the greatest impact on the incidence of cervical carcinoma in the future would involve at least universal vaccination of preadolescent girls<sup>6</sup>. In Croatia, this means introducing the vaccine into the mandatory Childhood Vaccination Programme.

Although the public health burden of cervical carcinoma in Croatia is well-known, together with the general epidemiology of HPV infection and the general characteristics of available vaccines, there are still uncertainties which must be clarified before considering the introduction of HPV vaccine into the Programme.

The reduction of precancerous and invasive cervical lesions achieved by vaccination with reasonably high coverage rates is anticipated to be substantial, but not enough to eliminate the need for cervical screening<sup>6,7</sup>. In order to calculate how substantial this reduction of precancerous lesions and cancer will be, a systematic review of available information on the prevalence of HPV types in our population is necessary. Then, this will need to be compared to the impact that could be achieved through improvements to the cervical screening system. Nevertheless, the potential of HPV vaccines to prevent precancerous lesions caused by HPV types included in the vaccine would appear to favour vaccine introduction regardless of the reductions in cancer that could be achieved by improvements to screening.

A characteristic of the HPV vaccine that could be an obstacle to the wide acceptance of the vaccine in public as well as in the professional community is the fact that a significant impact on the burden of disease can not be expected within 20–30 years of the introduction of the vaccination into the Programme, provided always that high coverage rates would be achieved and maintained continuously. And finally, the price of introducing this vaccine into the Programme is an important issue. In case it would be established that vaccination would achieve better results in reducing cervical cancerous lesions than alternative interventions (e.g. enhanced screening), the cost-effectiveness would have to be assessed against other interventions in the health care system, waiting to be implemented or improved. Since the health budget is

a single source, money for screening programmes, paper towels or antibiotics all comes from the same source as the funds for vaccination, there are numerous needs competing with each other for the funds.

So far, the introduction of vaccines into the Programme was never limited by the health care budget, mostly due to the fact that it was clear the vaccines (at their given prices) were the most cost-effective interventions. However, it is expected that one dose of HPV vaccine would cost about 100 Euros and therefore, introducing this vaccine into the Programme to vaccinate only one birth cohort of girls (e.g. 11-year-old girls) would raise the annual cost of the Programme by 130% (the HPV vaccine would cost about 6.7 million Euros which is 30% more than all the other vaccines used in the Programme at the moment 5.1 million Euros<sup>8</sup>).

## Conclusion

The HPV vaccine will soon be licensed in Croatia and will have an important role in the prevention of cervical cancer in this country. Immediately after licensure physicians will be able to use it on individual, patient-pay basis. In order to ensure reimbursement of the vaccine by the Croatian Health Insurance Institute, a request would need to be issued and an expert committee would then decide if the request should be accepted.

Regardless of the reimbursement policy for recommended vaccinations, no effect on the public health burden of cervical cancer can be expected unless vaccination is implemented to the whole target population within a well designed vaccination programme. This could be achieved by introducing HPV vaccination into the mandatory Childhood Vaccination Programme.

Still, much information must be gathered in order to assess the potential public health benefit of this vaccine in Croatia (type specific epidemiology of HPV in Croatia, potential of improved screening for cervical cancer in Croatia, etc.). From the perspective of an institution responsible for the introduction of new vaccines into the Childhood Vaccination Programme and the allocation of considerable amounts of public funding into one specific intervention, we believe that these associations advocating introduction of a new vaccine should make every effort to demonstrate this is the best available option.

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*B. Kaić*

*Hrvatski zavod za javno zdravstvo, Služba za epidemiologiju zaraznih bolesti,  
Rockefellerova 7, HR-10000 Zagreb, Croatia  
e-mail: bernard.kaic@hzjz.hr*

## **ZAKONSKA REGULATIVA VEZANO UZ CJEPIVA U HRVATSKOJ**

### **S A Ž E T A K**

U ovom članku raspravlja se o legislativi koja mora biti udovoljena da bi se cjepiva koristila u Hrvatskoj. Korišteni su zakoni i pravilnici kojima se regulira registracija, puštanje lijeka u promet, te način korištenja cjepiva. Postupci za uključivanje cjepiva u Program obveznih cijepljenja su također prodiskutirani, s naglaskom na cjepivo protiv humanog papilomavirusa (HPV). Preporuke za cijepljenja koja nisu obvezna se izdaju na temelju stručnog stava da je cijepljenje korisno za pojedinca. Nema sumnje da se cijepljenje protiv HPV-a može preporučiti djevojčicama u preadolescentnoj dobi. Međutim, da bi se donijela odluka o uvođenju cjepiva u Program obveznih cijepljenja potrebno je sa različitih medicinskih stajališta razmotriti uvođenje cijepljenja u odnosu na druge javnozdravstvene prioritete koji se nadmeću za ista sredstva.