

# Cervical Cancer as a Public Health Issue – What Next?

Ante Ćorušić<sup>1,4</sup>, Lana Škrgatić<sup>1,4</sup>, Vesna Mahovlić<sup>2</sup>, Vjekoslav Mandić<sup>3</sup>, Pavao Planinić<sup>1</sup>  
and Magdalena Karadža<sup>1</sup>

<sup>1</sup> Division of Gynecologic Oncology, University Department of Obstetrics and Gynecology, University Hospital Center Zagreb, Zagreb, Croatia

<sup>2</sup> Division of Gynecologic Cytology, University Department of Obstetrics and Gynecology, University Hospital Center Zagreb, Zagreb, Croatia

<sup>3</sup> Department of Obstetrics and Gynecology, University Clinical Hospital Mostar, Mostar, Bosnia and Herzegovina

<sup>4</sup> University of Zagreb, School of Medicine, Zagreb, Croatia

## ABSTRACT

*Cervical cancer is the second most common cancer in women worldwide. There are about 60,000 newly detected cases and 30,000 deaths annually in Europe, with the highest incidence reported from Eastern Europe countries. According to data from the National Institute of Public Health, in Croatia the incidence of cervical cancer was 14.9/100,000 in 2006, ranking eighth most common malignancy in women. Croatia has a lower incidence of the disease compared to many countries of Central and Southeast Europe. A large study carried out in 1995 by the International Agency for Research on Cancer, which included cervical cancer material collected from 22 countries all over the world revealed HPV genome in 99.7% of cases. Efficient methods of cervical cancer detection and screening methods for identification of precancerous lesions (conventional Pap smear) are available. Cervical cancer prevention programs should include education (of health care providers and women), stressing the benefits of screening, the age of the peak cervical cancer incidence, and the signs and symptoms of precancerous lesions and invasive disease. The aim of screening actions is to detect precancerous lesions that may lead to cancer if left untreated. Screening can only be effective if there is a well-organized system of follow up, diagnosis and treatment. Cervical cytology, or Papanicolaou (Pap) testing, has for decades been a cornerstone of cervical cancer screening. According to recent guidelines issued by the World Health Organization Regional Office for Europe, the primary task of the public health system is the introduction of secondary prevention through properly organized screening programs. Launching the national immunization program is only possible in the countries with well-organized secondary prevention programs and in those that can afford it.*

**Key words:** cervical cancer, HPV infection, prevention program, HPV vaccine

## Introduction

Cervical cancer is the second most common cancer in women worldwide. There are 500,000 new cases and 270,000 deaths recorded in the world *per year*. The highest incidence of the disease has been reported from developing countries of South-West Africa, South America and South-East Asia (Figure 1). Nearly 80% of newly detected cases of cervical cancer are reported from these countries<sup>1</sup>. In Europe, there are about 60,000 newly detected cases and 30,000 deaths *per year*, with the highest incidence of the disease in the Eastern Europe countries<sup>2–5</sup>.

## Cervical Cancer Trends in the EU

In the European Union (EU), the incidence of cervical cancer is 4.0/100,000 to up to 29.9/100,000 women in the EU eastern member countries<sup>6</sup>. Analysis of cervical cancer mortality in 25 EU member countries showed the incidence to be lowest in Finland and highest in Lithuania<sup>2</sup>. The risk of developing cervical cancer increases with age and reaches peak at about 35 to 55 years of age in unscreened populations<sup>7</sup>.

According to the International Agency for Research on Cancer (IARC) data for 2004, there were 34,300 newly registered cervical carcinoma cases in 27 EU member

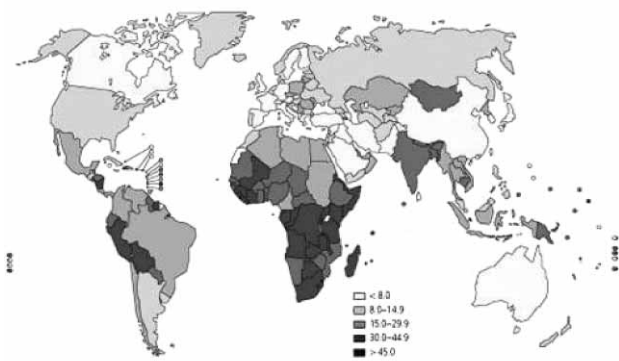


Fig. 1. Incidence of cervical carcinoma worldwide<sup>1</sup>.

countries and 16,300 women died from the disease. The EU countries before 2005 enlargement had a lower incidence of the disease thanks to organized screening programs. In these countries, cervical carcinoma ranked tenth of all cancers in women. The highest cervical cancer mortality is found in Romania (13.7/100,000) and lowest in Finland (1.1/100,000). With the exception of Malta, 11 new EU member countries have a higher cervical carcinoma prevalence and mortality than old EU member countries (Figure 2)<sup>5</sup>.

Therefore Candice Pettifer concludes:

- cervical cancer remains an important problem in the EU,
- the primary cause of cervical cancer is a persistent infection with a cancer-causing genital human papillomavirus (HPV),
- HPV infections are very common and acquired soon after onset of sexual activity,
- most HPV infections clear spontaneously,
- persistent HPV infections with a high-risk type can cause cellular changes that can result in cervical cancer,
- HPV 16 and 18 are together associated with an estimated 73% of cases of cervical cancer in Europe, and
- cervical cancer can be prevented by screening and treating precancerous lesions<sup>7</sup>.

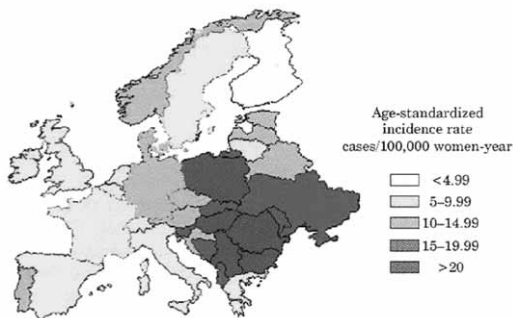


Fig. 2. Incidence of cervical cancer in European countries (on 100 000 women) standardized by age<sup>5</sup>.

According to data from the National Institute of Public Health, in 2006 the incidence of cervical cancer was 14.9/100,000 in Croatia, with cervical cancer ranking eighth most common malignant disease in women. Croatia has a lower incidence of the disease as compared to many countries of Central and Southeast Europe (Figure 3). The mortality from cervical cancer in Croatia is estimated to 4.3/100,000 women<sup>8</sup>.

Cervical carcinoma is a disease of younger women. The highest incidence is found in the 35–50 age group. In the population of women aged 25–40, cervical cancer is the second most prevalent malignancy, just behind breast cancer. Given that today, women often decide to accomplish their reproduction after their thirties, one can say that this disease seriously affects human procreation (Figure 4).



Fig. 3. The geographic distribution of cervical cancer mortality – age standardized rate (mortality /100 000 woman-year) (W-ASMR World age-standardized mortality) in 11 countries of SouthEast Europe, the estimates for year 2002/2004<sup>2,5,9</sup>.

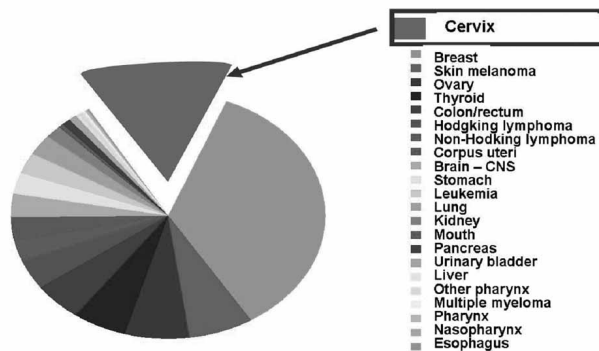


Fig. 4. Incidence of cervical cancer in young European women (aged 15–44) (source: Ferlay J et al. Lyon, France: IARC Press, 2004)<sup>5</sup>.

### The Etiopathogenesis of Cervical Carcinoma

A large study carried out by IARC in 1995 on cervical cancer material collected from 22 countries all over the

world revealed HPV genome in 99.7% of cases<sup>10</sup>. Subsequent IARC meta-analysis on 13,000 cervical cancer specimens showed the presence of eight most common high-risk oncogenic HPV strains, i.e. HPV 16, 18, 45, 31, 33, 52, 58 and 35. These eight high-risk strains are responsible for about 90% of all cervical carcinoma cases. Subsequent study confirmed the HPV 16 and 18 strains to be responsible for about 70% of cervical carcinoma of squamous origin and 86% of adenocarcinoma<sup>5</sup>. HPV is a small DNA virus that has a circular genome consisting of several thousand base pairs incorporated into icosahedral capsid surrounded by two capsid proteins L1 and L2 (Figure 5). More than 100 HPV types have been isolated to date, with about 40 of them able to cause infection of the anogenital mucous membranes. They primarily infect the superficial layer of squamous epithelium of the skin and mucous membranes<sup>11,12</sup>.

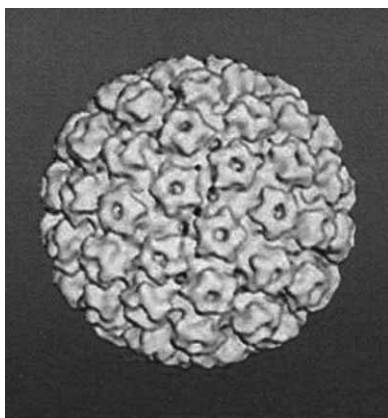


Fig. 5. Icosahedral structure of HPV virus<sup>13</sup>.

Genital HPV strains are divided into three groups, as follows:

- high-risk oncogenic strains (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59),
- possibly carcinogenic strains (26, 53, 66, 68, 73 and 82), and
- low-risk oncogenic strains (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and 89).

The latter can cause benign proliferation of epithelium of the anogenital region but these changes are not associated with cervical carcinoma<sup>13</sup>.

### The Significance of Persistent HPV Infection

HPV infection is the most common sexually transmitted disease. Many studies using HPV DNA testing in asymptomatic women show the prevalence of HPV infection in the general population to be 2–44%<sup>14</sup>. This large difference in the prevalence results from different population groups studied as well as from variation in molecular sensitivity of different methods used on HPV DNA

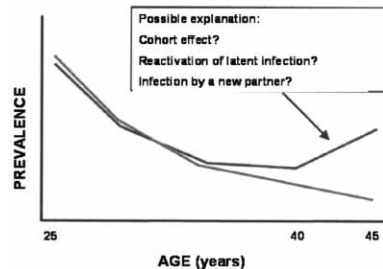


Fig. 6. Prevalence of HPV infection according to age<sup>17</sup>.

detection. Many epidemiologic studies have shown the prevalence of HPV infection to be highest in sexually active women younger than 25, then abruptly declining to the age of 45–50, when the second prevalence peak occurs<sup>15,16</sup> (Figure 6)<sup>17</sup>.

This second prevalence peak at peri- and postmenopause can be explained by the following:

- reactivation of prior latent infection,
- new infection with a new partner,
- changes in sexual behavior in recent decades may have an effect on HPV exposure, and
- infection in different cohorts of women examined (cohort effect).

HPV infection will resolve spontaneously in 90–95% of cases. For precancerous lesions of the cervix (cervical intraepithelial neoplasm, CIN) and cervical cancer to develop, permanent infection with a high-risk HPV strain is required. Yet, there is no consensus on what is permanent infection with HPV. Recent studies show that a woman that is positive for infection with a high-risk oncogenic HPV strain will show a tendency to develop precancerous lesion of the cervix in 6–12 months<sup>16–19</sup>.

### Risk Factors for HPV Infection

According to numerous prospective studies, the risk of HPV infection increases with:

- early age at first sexual activity,
- large number of partners,
- cigarette smoking,
- use of oral contraceptives,
- association with other sexual infections (*Chlamydia trachomatis*, Herpes simplex virus type II),
- chronic inflammation of the lower genital tract, and
- immunosuppressive states.

According to some findings, the use of condoms may reduce the risk of HPV infection by up to 70%. However, other studies show that the use of condoms may increase the risk of developing HPV infection. People usually use condoms with partners that they expect to be at an increased risk of STD (a new partner, a prostitute), but not with a partner with which they expect safe sex (a long-term partner, a spouse). This mode of behavior may ex-

plain the results of some studies where the use of condoms did not reduce the risk of HPV infection<sup>20–22</sup>. A few studies suggest that food rich in fruit and vegetables, high doses of vitamins C and E, and alpha and beta carotene may reduce the risk of HPV infection<sup>20–22</sup>. There is a well-known fact that the infection with high-risk oncogenic HPV strain need not necessarily lead to neoplastic conversion, which indicates the possible role of the host's immune system. The host's immune system can cause virus elimination; however, if the immune mechanism of the host is inadequate to eliminate the virus, the infection can become permanent and lead to precancerous lesion of the cervix and finally to cancer. It is possible that the human leukocyte antigen (HLA) system gene plays an important role in the emergence of persistent HPV infection. Specifically, protein products of HLA genes play an important role in antigen presentation to T cells of the host. In two separate studies, Maciag et al.<sup>23</sup> and Wang and Hildesheim<sup>24</sup> isolated different haplotypes of HLA II system. Some of these haplotypes were found to reduce the risk of persistent HPV infection three to four times, whereas carriers of other haplotypes had up to sevenfold risk of developing persistent HPV infection<sup>23,24</sup>. Permanent infection with high-risk oncogenic HPV strains causes changes in epithelial cells that can be mild (low-grade squamous intraepithelial lesions, LSIL) or severe (high-grade squamous intraepithelial lesions, HSIL). Preinvasive lesions are relatively easily treated with ablative surgical procedures (conization with cold knife or LLETZ). It is assumed that persistent infection with HPV leads to invasive cancer of the cervix in 7–10 years. Thus, there is enough time for preventive actions. The natural course of the disease from persistent infection with high-risk HPV strain to the development of cervical cancer is shown in Figure 7<sup>17</sup>.

Theoretically, cervical cancer is a disease that should not be permitted to develop in any woman and no woman should die from it. Cervix is an organ available to direct visualization on gynecologic examination. There are efficient methods of cervical cancer detection and screening methods for precancerous lesion identification (conventional Papanicolaou (Pap) smear).

Cervical cancer prevention programs should include education (of health care providers and women) that stresses the benefits of screening, the age of peak cervical cancer incidence, and the signs and symptoms of precancerous lesions and invasive disease<sup>25</sup>. Screening aims to detect precancerous changes that may lead to cancer if left untreated. Screening is only effective if there is a well-organized system for follow up, diagnosis and treatment.

The World Health Organization (WHO) recommends specific target ages and frequency of cytologic screening:

- new programs should start screening women at age 30 or older, and should only screen younger women when the older age groups have been adequately screened; the existing programs should not screen women younger than 25;

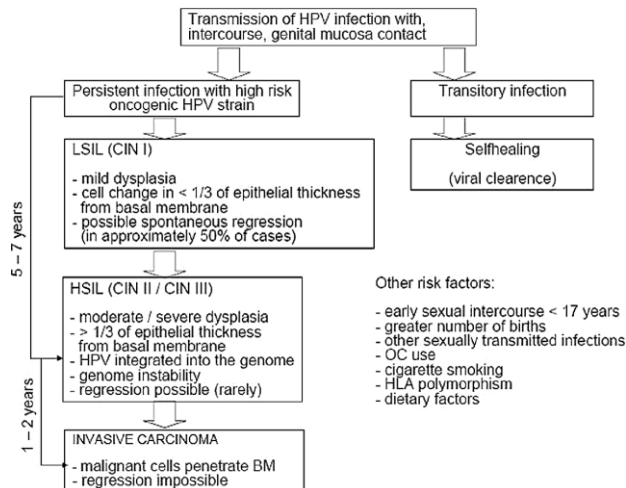


Fig. 7. Natural course of permanent HPV infection to cervical carcinoma<sup>17</sup>; HPV – Human papillomavirus, HSIL – High-grade Squamous Intraepithelial Lesion, LSIL – Low-grade Squamous Intraepithelial Lesion, BM – Basal Membrane, HLA – Human Leukocyte Antigen.

- if a woman can undergo screening only once in her lifetime, the best age is between 35 and 45;
- in women aged over 50, a five-year screening interval is appropriate;
- in women aged 25–49, a three-year interval can be considered if resources are available;
- annual screening is not recommended at any age;
- screening is not necessary in women aged over 65, provided the last two previous smears in mid-life were negative.

Table 1 shows WHO recommendations for primary and secondary prevention of cervical carcinoma<sup>25</sup>.

Regular cervical cancer screening is especially important in women with HIV infection because they are at a higher risk of acquiring oncogenic HPV types, and being infected with HPV, they are at a higher risk of rapid progression to precancerous lesions and cancer<sup>26</sup>.

Cervical cytology or Pap testing has been a cornerstone of cervical cancer screening for decades. Most cervical cancer cases and deaths can be prevented by cytologic screening followed by appropriate diagnosis and treatment<sup>27,28</sup>. It has been demonstrated in countries with well-organized screening programs or extensive opportunistic screening with effective follow-up for patients with abnormal or borderline smears, quality control procedures and high coverage<sup>29</sup>.

Many countries use different methods of cervical cancer screening depending on the level of development and gross national product (GNP). Table 2 shows the most widely used methods of screening and assessment and their sensitivity and specificity<sup>30</sup>.



**TABLE 1**  
WHO RECOMMENDATIONS FOR PREVENTION AND CONTROL OF CERVICAL CANCER CAUSED BY HPV INFECTION<sup>25</sup>

Primary prevention	Early detection and screening	Treatment
Reduce high-risk sexual behaviours	Periodic screening using: cytology (Pap test) for women aged 25+ years, preferably in organized programmes	Precancerous lesions: cryotherapy, loop electrosurgical excision procedure, or surgical excision.
Condom use	In pilot or carefully monitored settings periodic screening with: HPV DNA tests; or visual inspection of cervix with acetic acid or Lugol's iodine	»Screen and treat« in low-resource settings using cryotherapy
Avoid or reduce tobacco use		Cancer: surgery, chemotherapy, radiotherapy, brachytherapy, paliative care
Seek prompt treatment of sexually transmitted infections	Prompt diagnostic follow-up if screening test abnormal (e.g. colposcopy and biopsy)	

**TABLE 2**  
CHARACTERISTICS OF SCREENING TESTS FOR SECONDARY PREVENTION (SOURCE SANKARANARAYAN ET AL. 2005)<sup>30</sup>

Characteristics	Conventional cytology	HPV DNA tests	Visual inspection test	
			VIA	VILI
Sensitivity	47–62%	66–100%	67–79%	78–98%
Specificity (for high – grade lesions and invasive cancer)	60–95%	62–96%	49–86%	73–91%
Comments	Assessed over the last 50 years in a wide range of settings in developed and undeveloped countries	Assessed over the last decade in many settings in developed countries and a few developing countries	Assessed over the last decade in many settings in developing countries	Assessed by IARC over the last four years in India and three countries in Africa. Need further evaluation for reproducibility
Number of visits required for screening and treatment	Two or more	Two or more	Can be used in a single-visit or see-and treat approach where outpatient treatment is available	

IARC – International Agency for Research on Cancer, VIA – visual inspection with acetic acid application; VILI – visual inspection with Lugol's iodine

## The Situation in Croatia

The conventional Pap smear has been widely used since 1962, although the first laboratory of gynecologic cytology was founded in 1953. Croatia has a good model of public health and sufficient number of gynecologists and cytologists. Croatia is one of the few countries in Europe that have residency in cytology that includes post-graduate study in gynecologic cytology<sup>31</sup>. However, in the last ten years Croatia has a 'stable' incidence of cervical cancer of 14–16/100,000 women. This figure has been attributed to the opportunistic screening program used in Croatia. Women present for Pap smears on their own initiative, mainly involving the same group of women. We assume that only 30–35% of the female population are covered by opportunistic screening, while a large proportion of women are not included in the screening, and it is the group where 90% of cervical cancer cases are found. Therefore, it is necessary to launch an organized screening program as soon as possible, in which we will be committed by conclusions of the ministers of EU Health Council Committee from 1994. At that meeting it was concluded that there was a sufficient body of scientific

ally based data to justify the introduction of organized screening program for breast and cervical cancer in women and for colon cancer in women and men. During 2003, the national health ministers of all EU member countries adopted a document on the need of an organized screening program, thus pointing to organized cancer control in Europe. With a well organized cancer screening program, cervical cancer can be reduced by 80%<sup>32,33</sup>. The Working Group of the Ministry of Health and Social Welfare of Croatia made a proposal for early detection of cervical cancer in Croatia. The program proposed clearly indicates the objectives of the program, program organization, technical performance, as well as evaluation and monitoring of the program. We believe that in the near future the Ministry of Health and Social Welfare will accept our proposal<sup>34</sup>.

## HPV Vaccines

Secondary prevention now poses the issue of primary prevention. Researchers have isolated the genome of the HPV gene encoding protein L1. Installation of this gene

**TABLE 3**  
 QUADRIVALENT AND BIVALENT HPV VACCINE CHARACTERISTICS<sup>29</sup>

	Quadrivalent vaccine	Bivalent vaccine
Manufacturer and trade name	Merck; Gardasil®	GlaxoSmithKline; Cervarix®
Virus-like particles of genotypes	6, 11, 16, 18	16, 18
Substrate	Saccharomyces cerevisiae	Baculovirus expression system
54 Adjuvant	Proprietary aluminium hydroxyphosphate sulfate (225µg) (Merck aluminium adjuvant)	Proprietary aluminium hydroxide (500 µg) plus 50 µg 3-deacylated monophosphoryl lipid A (GSK AS04 adjuvant)
Schedule. 3 doses at intervals of	2 months between doses 1 and 2 6 months between doses 1 and 3	1 months between doses 1 and 2 6 months between doses 1 and 3

in the appropriate expressional systems enabled production of L1-virus like particles (L1-VLP). L1-VLP is conformationally identical to the natural virus containing the viral epitopes of capsid making it antigenic even if it does not contain the genome of HPV. The process from conclusion to vaccine took ten years.

Currently, two HPV vaccines are licensed and marketed<sup>35</sup>:

- one manufactured by Merck & Co. (known by the brand name Gardasil), first licensed in 2006 and here referred to as the »quadrivalent vaccine«; and
- one manufactured by GlaxoSmithKline (known as Cervarix), first licensed in 2007.

By March 2008, both vaccines were licensed in several countries for use in girls and women. Differences between the two vaccines are shown in Table 3<sup>29</sup>. Both vaccines have been registered in Croatia and are available on the market. Both vaccines are equally effective in protection against HPV infection. According to recent guidelines issued by the WHO Regional Office for Europe, the primary task of the public health system is the introduction of secondary prevention through well-organized screening programs. Organization of a national immunization program is only possible in countries with well-organized secondary prevention programs and in those that can afford it<sup>18,36,37</sup>.

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A. Ćorušić

*Department of Obstetrics and Gynecology, School of Medicine, University of Zagreb, Petrova 13, 10 000 Zagreb, Croatia  
e-mail: ante.corusic@mef.hr*

## **KARCINOM CERVIKSA KAO JAVNOZDRAVSTVENI PROBLEM – KAKO DALJE?**

### **S A Ž E T A K**

Karcinom vrata maternice drugi je najčešći karcinom u žena u svijetu. U Europi se godišnje otkrije oko 60 000 novooboljelih i oko 30 000 žena umre od ove bolesti. Najveća incidencija je u zemljama istočne Europe. U Hrvatskoj prema podacima Hrvatskog zavoda za javno zdravstvo (HZJZ) incidencija je 2006. godine bila 14.9 i po učestalosti je na osmome mjestu svih malignoma u žene. Hrvatska ima nižu incidenciju ove bolesti od mnogih država srednje i jugoistočne Europe. Veliko istraživanje International Agency for Research in Cancer (IARC) iz 1995. godine na materijalu iz 22 zemlje diljem svijeta otkrilo je u 99,7% svih karcinoma vrata maternice genom HPV-a. Danas postoje dobre metode otkrivanja ove bolesti kao i dobra metoda probira (konvencionalni PAPA-obrisak). Program prevencije karcinoma vrata maternice mora uključivati edukaciju (za zdravstvene radnike i žene) o dobrobiti programa probira, vršnoj dobi pojave karcinoma kao i edukaciju o znakovima i simptomima preinvazivnih i invazivnih promjena. Programi probira su usmjereni prema preinvazivnim lezijama koje mogu dovesti do invazivnih ako se ne liječe. Probir je učinkovit samo ako postoji dobro organiziran sustav praćenja, dijagnostike i liječenja. Citologija cerviksa ili Papanicolau obrisak temeljna je metoda probira za karcinom vrata maternice kroz desetljeća. Prema zadnjim smjernicama Europskog odjela Svjetske zdravstvene organizacije primarna zadaća javnoga zdravstvenog sustava je uvođenje sekundarne prevencije dobro organiziranim programima probira. Organizaciju nacionalnih imunizacijskih programa moguće je aplicirati samo u zemljama s dobro organiziranim programima sekundarne prevencije i u zemljama koje to mogu platiti.