HPV-vaccination and cancer cervical screening in 53 WHO European Countries: An update on prevention programs according to income level

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Abstract
Human papillomavirus (HPV) is the most common sexually transmitted disease in the world. The aim of our study is to describe the differences in HPV-vaccination coverage and screening programs in WHO European Countries notably according to income levels. Multiple correspondence analysis was applied to examine the association among the following variables: Gross National Income (GNI) levels (Lower-Middle Income, LMI; Upper-Middle Income, UMI; and High Income, HI); type of CC screening program (coverage; opportunistic/organized); vaccination payment policies (free or partial or total charge); mortality rates/100 000 (≤3; >3-6; >6-9; >9); incidence rates/100 000 (≤7; >7-15; >15-21; >21). Data HPV-vaccination start (years) (2006-2008; 2009-2011; 2012-2014; >2014; no program); coverage HPV-vaccination percentage (≤25; 26-50; 51-75; >75); data screening start (years) (<1960; 1960-1980; 1981-2000; >2000); primary screening test (HPV, cytology), and screening coverage percentage (≤25; >25-50; >50-75; >75). A high income is associated with: start of screening before 1960, medium-high screening coverage, organized screening, start of vaccination in the periods 2009-2011 and 2012-2014 and high immunization coverage. On the other hand, lower-middle income is associated with: late start of vaccination and screening programs with cytology as primary test, high mortality and incidence rates and lower-medium vaccination coverage. Our results show a useful scenario for crucial support to public health decision-makers. Public health authorities should monitor the HPV-vaccinated population in order to determine more precisely the effects on short- and long-term incidence and mortality rates. In fact, the greater the vaccination coverage, the greater will be the efficacy of the program for the prevention of CC and other HPV-related diseases.

KEYWORDS
cervical cancer, coverage, HPV vaccination, income level, screening programs, surveillance

1 INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted disease in the world.1 The persistent infection with high-risk HPV causes Cervical Cancer (CC).2 In female population it is the fourth cancer and the second most common from 25 to 40 years of age.3 Strategies against HPV infection are vaccination and safe sex education.4 Countries...
that have performed HPV-vaccination programs have showed a decrease in the prevalence in the population of the HPV 16, 18 genotypes. HPV-related disease incidence and mortality are the most common measures used to evaluate the impact of vaccination in European Countries. In Europe, HPV-vaccination coverage rates vary from 30% to 80% with school-based programs. Information campaigns of health interventions are closely linked to the success of a vaccination program. In fact, the greater the vaccination coverage, the greater will be the efficacy of the program for the prevention of CC and other HPV-related diseases. In 2006, the European Medicines Agency (EMA) endorsed the quadrivalent HPV vaccine, in 2007 the bivalent, while in June 2015 a 9-valent vaccine was recommended.

It is important to underline that the two primary (HPV vaccination) and secondary strategies (screening, early diagnosis) will lead to the reduction of incidence and mortality for CC. Relatively to Europe, with regard to CC, vaccination and screening programs show differences among Countries; indeed, relatively to screening, there are organized and nonorganized (opportunistic) programs. Knowledge of the onset of CC, new technologies, HPV test as primary screening test along with home self-sampling modified screening programs in many European Countries.

Cervical cancer screening programs together with primary prevention could contribute to reducing social inequalities between central and eastern European Countries.

The aim of the study was to describe the differences in HPV-vaccination coverage and screening programs in WHO European Countries notably according to income levels.

2 MATERIALS AND METHODS

2.1 Gross national income (GNI)

According to the World Bank, economies can be divided into low income (LI), lower-middle income (LMI), upper-middle income (UMI), and high income (HI) in relation to GNI per capita (Figure 1). In this study, the 53 WHO ER Countries were thus divided into: LMI, $1026-4035 (Armenia, Georgia, Kyrgyzstan, Moldova, Tajikistan, Ukraine, and Uzbekistan); UMI, $4036-12,475 (Albania, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Kazakhstan, FYR of Macedonia [FM], Hungary, Montenegro, Romania, Serbia, Turkey, and Turkmenistan); and HI, $12,476 (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Norway, Poland, Portugal, Slovakia Republic, Slovenia, Spain, Sweden, Switzerland, the Netherlands, and the United Kingdom, Andorra, Croatia, Cyprus, Malta, Monaco, Latvia, Lithuania, Russian Federation, and San Marino) (World Bank and Lending Groups 2016) (Table 1).
| Country       | 2008  | 2012  | 2008  | 2012  | Date start | Age at beginning | Policy payment          | Organization Start date | Region  | Coverage % (year) | Year  | 500.000 | Year  | Cancer screening |
|---------------|-------|-------|-------|-------|------------|-------------------|-------------------------|------------------------|---------|------------------|-------|----------|-------|------------------|
|               | Incidence | National immunization | Mortality | Cancer screening |
|               | 100.000 | 100.000 | Mortality | Regions Coverage % (year) | Primary Test | Age target | Screening Interval Years | Payment Policy |
| Austria       | 5.7    | 5.8    | 2.2    | 2.6    | 2014       | 9-12              | Fully covered by patient health authorities | Opportunistic 1970   | National | 86.6 (2014) | Cytology PAP | >18   | 1       | Free of Charge   |
| Andorra       | NR     | NR     | NR     | NR     | 2014       | 12                | Opportunistic NR | Opportunistic NR | NR | 61.4 (2011) | Cytology PAP | >18   | 1       | NR               |
| Belgium       | 8.4    | 8.6    | 2.5    | 2.3    | 2007       | 12                | 75% supported by national health authorities | Opportunistic 1965   | Regional | 68.7 (2013) | Cytology PAP | 25-64  | 3       | Free of Charge   |
| Croatia       | 11.8   | 10.0   | 4.2    | 3.4    | 2016       | NR                | Fully covered by national health authorities | Opportunistic 1960   | National | 65.3 (2003) | Cytology PAP | 25-64  | 3       | Free of Charge   |
| Cyprus        | 4.5    | 4.1    | 2.6    | 1.3    | 2016       | 11-12             | Opportunistic NR | Opportunistic NR | NR | 67.4 (2012) | Cytology PAP | 24-65  | NR     | NR               |
| Czech Republic| 14.0   | 14.1   | 4.6    | 4.8    | 2012       | 13                | Covered by general health insurance for routine | Opportunistic 1947   | National | 87.2 (2014) | Cytology PAP | 25-60  | 1       | Free of Charge   |
| Denmark       | 12.1   | 10.6   | 3.1    | 2.6    | 2009       | 12                | Fully covered by national health authorities | Opportunistic 1962   | National | 57.7 (2014) | Cytology PAP | 30-59  | 5       | Free of Charge   |
| Estonia       | 15.8   | 19.9   | 7.3    | 7.5    | No program | -                 | Organized 2006 | Organized 2006 | National | 69.0 (2015) | HPV PAP | 4-64  | 3       | 5-64 HPV | Free of Charge   |
| Finland       | 4.5    | 4.3    | 1.5    | 1.3    | 2013       | 11-12             | Fully covered by national health authorities | Organized 1963 | National | 69.0 (2015) | HPV PAP | 30-64  | 5       | Free of Charge   |
| France        | 7.1    | 6.8    | 1.9    | 1.8    | 2007       | 11-14             | 65% supported by national health authorities | Organized 1991 | Regional 75.4 (2014) | Cytology PAP | 25-65  | 3       | Insurance Copayment |
| Germany       | 6.9    | 8.2    | 2.6    | 2.6    | 2007       | 9-14              | Fully covered by national health authorities | Organized 1971 (west) | National | 80.4 (2014) | Cytology PAP | >20   | 1       | Free of Charge   |
| Greece        | 4.1    | 5.2    | 1.4    | 1.9    | 2008       | 11-15             | Fully covered by national health authorities | Opportunistic 1991 | National | 75.5 (2014) | Cytology PAP | >20   | 1       | NR               |

(Continues)
| Country                  | 2008 | 2012 | Date start | Age at beginning | Policy payment | Coverage% (year) | Organization Start date | Regions Coverage % (year) | Primary Test | Age target Age | Screening Interval Years | Payment Policy |
|-------------------------|------|------|------------|------------------|----------------|------------------|-------------------------|---------------------------|--------------|----------------|--------------------------|----------------|
| Hungary                 | 16.6 | 18.0 | 6.6        | 2014             | NR             | NR               | Opportunistic 1950     | National 40.1 (2015)       | Cytology PAP  | 25-65          | 3                         | Free of Charge |
| Iceland                 | 8.4  | 7.9  | 0.8        | 2011             | Fully covered by national health authorities 84.0 (2013) | NR             | Organized 1964     | National 71.0 (2015)       | Cytology PAP  | 20-69          | 2 (20-39) 4 (40-69)   | NR             |
| Ireland                 | 10.9 | 13.6 | 3.6        | 2010             | Fully covered by national health authorities 849 (2014) | Organized 2008 | National 78.7 (2015) | Cytology PAP  | 25-60          | 3 (25-44) 5 (45-60) | Free of Charge |
| Israel                  | NR   | 4.6  | 2.4        | NR               | NR             | NR               | Opportunistic NR     | Regional 32.0 (2008)       | Cytology PAP  | 25-65          | 3                         | Free of Charge |
| Latvia                  | 12.4 | 17.3 | 6.9        | 2010             | Fully covered by national health authorities 65.0 (2011) | Organized 1960 | National 25.2 (2016) | Cytology PAP  | 25-70          | 3                         | Free of Charge |
| Lithuania               | 21.0 | 26.1 | 10.6       | 2016             | NR             | NR               | Organized 2004       | National 74.0 (2014)       | Cytology PAP  | 25-60          | 3                         | Free of Charge |
| Luxembourg              | 6.3  | 4.9  | 5.6        | 2008             | Fully covered by national health authorities 17.0 (2009) | Organized 1962 | National 83.6 (2014) | Cytology PAP  | >15            | 1                         | NR             |
| Malta                   | 2.1  | 3.8  | 2.1        | 2012             | Fully covered by national health authorities NR | Organopportunistic NR | National 49.3 (2008) | HPV Cytology PAP | >30 HPV 25-50 Cytol. | 5 HPV 3 Cytology | Free of Charge |
| Monaco                  | NR   | NR   | NR         | 2011             | NR             | NR               | Opportunistic NR  | National 74.0 (2015)       | Cytology PAP  | 25-69          | 3                         | NR             |
| Norway                  | 9.4  | 9.8  | 3.0        | 2009             | Fully covered by national health authorities 63.0 (2011) | Organopportunistic 1970 | National 74.1 (2015) | HPV Cytology PAP | 25-69          | 3                         | NR             |
| Poland                  | 11.6 | 12.2 | 7.3        | No Program       | Opportunistic 1970 | Organized 2006 | National 21.2 (2013) | Cytology PAP  | 25-59          | 3                         | Free of Charge |

(Continues)
| Country                      | National immunization | Cancer screening | Screening Interval Years | Payment Policy |
|------------------------------|-----------------------|------------------|--------------------------|----------------|
|                              | Incidence 100,000     | Mortality 100,000|                          |                |
|                              | 2008 2012             | 2008 2012        | Date start Age at beginning | Policy payment Coverage % (year) | Organization Start date | Regions Coverage % (year) | Primary Test | Age target | Year | Screening Interval Years | Payment Policy |
| Portugal                     | 12.2 9.0              | 3.4 2.8          | 2008 13                  | Fully covered by national health authorities 84.0 (2011) | Organized Central Region 1990 Akentejo Region 2008 | Regional 70.7 (2014) | Cytology PAP | 25-64     | 3     |                    | Free of Charge |
| Russian Federation Outside European institutions | 13.3 15.3            | 6.6 6.9          | Partial program 2009 12-13 | NR NR            | Organized NR | NR 72.0 (2012) | Cytology PAP | >18       | 1     |                    | NR |
| San Marino                  | NR NR NR             | 2008 11-14       | Fully covered by national health authorities NR | Opportunistic 1968 Organized 2006 | National 82.0 (2017) | HPV Cytology PAP | 30-65 HPV 25-30 Cytol. | 5 HPV 3 Cytology | NR |
| Slovakia Republic           | 15.8 16.1            | 6.5 6.9          | 2014 12                  | NR 55.0 (2012) | Opportunistic 1980 Organized 2008 | National 69.0 (2014) | Cytology PAP | 23-64     | 1     |                    | Free of Charge |
| Slovenia                     | 11.1 10.5            | 3.1 2.9          | 2009 11                  | Fully covered by national health authorities 70.8 (2012) | Opportunistic 1960 Organized 2003 | National 71.9 (2016) | Cytology PAP | 20-64     | 3     |                    | Free of Charge |
| Spain                       | 6.3 7.8              | 2.1 2.1          | 2007 11-14               | Fully covered by national health authorities 78.5 (2010) | Organized 1993 | National 72.7 (2014) | HPV Cytology PAP | 30-65 HPV 25-65 Cytol. | 5 HPV 3 Cytology | Free of Charge |
| Sweden 4,100,000             | 7.8 7.4              | 2.2 2.8          | 2010 10-12               | Fully covered by national health authorities 82.0 (2012) | Opportunistic 1950 Organized 1967 | National 81.7 (2015) | HPV Cytol. PAP | 30-64 HPV 23-29 Cytol. | 3 (30-50) HPV 7 (51-64) 3 (23-29) Cytology | Free of Charge |
| Switzerland                 | 4.0 3.6              | 1.4 1.5          | 2008 11-14               | NR NR            | Opportunistic NR | NR 74.5 (2012) | Cytology PAP | >20       | 3     |                    | Insurance Copayment |
| Netherlands                 | 6.8 6.8              | 2.3 1.9          | 2010 12                  | Fully covered by national health authorities 79.5 (2014) | Opportunistic 1970 Organized 1980 | National 64.4 (2015) | HPV Cytology PAP | 30-60     | 5 HPV 5 Cytology | Free of Charge |
| United Kingdom              | 7.2 7.1              | 2.4 2.2          | 2008 12-13               | Fully covered by national health authorities 91.4 (2013) | Opportunistic 1964 Organized 1988 | National 77.5 (2016) | Cytology PAP | 25-64     | 3 (25-49); 5 (50-64) | Free of Charge |
| Albania                     | 7.1 5.0              | 1.5 1.8          | No Program               | NR NR            | Opportunistic NR | NR 2.7 (2002) | Cytology PAP | >20       | 2-3   |                    | NR |

(Continues)
| Country                      | Regions | Primary Test | Age target | Screening Interval Years | Payment Policy |
|------------------------------|---------|--------------|------------|--------------------------|----------------|
| Azerbaijan Outside European institutions | NR | Acetic acid visualization VIA | NR | 11 | NR |
| Belarus Outside European institutions | NR | Cytology PAP | >18 | 1 | NR |
| Bosnia and Herzegovina      | Organized | National | 21-70 | 1 | NR |
| Bulgaria                    | Opportunistic NR | National | 30-59 | 3 | NR |
| Kazakhstan Outside European institutions | Organized NR | National | 30-60 | 5 | NR |
| FRY of Macedonia            | Organized 2015 | National | 30-55 | 3 | NR |
| Montenegro                  | Opportunistic NR | National | 25-64 | 3 | NR |
| Romania                     | Opportunistic 1965 Organized 2012 | National | 25-64 | 5 | Free of Charge |
| Serbia                      | Opportunistic 1960 Organized 2011 | National | 25-65 | 3 | Free of Charge |
| Turkey                      | Opportunistic 1985 Organized 2004 | National | 30-65 | 5 | NR |
| Turkmenistan Outside European institutions | Opportunistic NR | National | >20 | 1 | NR |
| Country | Incidence 100.000 | Mortality 100.000 | Date start | Policy payment | Coverage % (year) | Organization Start date | Regions Coverage % (year) | Primary Test | Age target | Screening Interval Years | Payment Policy |
|---------|-------------------|------------------|------------|----------------|-------------------|-------------------------|---------------------------|--------------|------------|--------------------------|----------------|
| Armenia | NR 13.8           | 3.7 5.5          | No Program | NR NR           | Opportunistic NR   | NR 9.3 (2010)           | Cytology PAP              | 30-60        | 3          | NR                       |                |
| Georgia | NR 14.2           | NR 5.7           | NR NR      | NR NR           | Opportunistic NR   | NR 9.0 (2011)           | Cytology PAP²              | 25-60        | 3          | Free of Charge            |                |
| Kyrgyzstan Outside European institutions | NR 23.7 | 12.6 11.4 | No Program | NR 53.4 | Opportunistic NR | NR 10-50 (2015) | Cytology PAP | NR | 5          | NR                       |                |
| Republic of Moldova | 17.1 19.6 | 8.6 7.5 | NR NR | Organized NR | National 70.0 (2015) | Cytology PAP | >20 | 2          | NR                       |                |
| Tajikistan Outside European institutions | NR 9.9 | NR 4.9 | NR | Opportunistic NR | NR 65.0 (2012) | Cytology PAP | >20 | NR | NR                       |                |
| Ukraine | NR 16.6           | 7.4 7.5          | No Program | NR 86.7 (2014) | Opportunistic NR   | NR 73.7 (2003)         | Cytology PAP              | 18-65        | 1          | NR                       |                |
| Uzbekistan Outside European institutions | NR 13.5 | NR 6.4 | Announced 12 | NR NR | Opportunistic NR | NR | Cytology PAP | 25-49 | NR | NR                       |                |

R: Not Reported.

aAcetic acid visualization VIA HPV secondary test as a triage to borderline cytology and as a follow-up after treatment of severe cervical lesions.

bInterval between negative screens is three years for women aged 23-49 and five years for women aged 50-64. The primary screening test is cytology for women aged 23-59 with HPV as a triage test. HPV DNA test is primary screening for women aged 60-64 years.

cPrimary screening test is predominantly cytology but can also be HPV. The sample is examined for cell changes (the traditional Pap test) or the Human Papillomavirus. If there is cancer-related HPV, the screening sample is checked for possible cervical cell changes (Pap test).

dHPV testing is not reimbursed.

eScreening ages: Above 25 (cytology), Above 30 (HPV test). Screening interval: Cytology every 3 years (ages 25-50), VIA every 5 years (above 50). HPV test every 5 years.

f1, 3 after 2 consecutive annual negative Cytology test.

ghReflex testing with HPV is done for cytology positive test (ASCUS/LSIL or worse) below the age of 30 and reflex testing with cytology for HR HPV positive test above the age of 30. A double test (cytology and HPV) is recommended for women at age 41. Women with HPV positive/cytology negative tests should repeat screening after 3 years. Women with ASCUS/LSIL (regardless of HPV status) below the age of 28 are not referred to colposcopy, but repeat cytology.

iReplace Pap-test with hrHPV DNA test as primary screening test (since 2016).

jIf slightly abnormal cells are present, the human papillomavirus (HPV) will be tested.

kHPV test since 2015.
lHPV test undergoing project.
(1960; 1960–1980; 1981–2000; ≥2000); primary screening test (HPV, cytology); screening coverage percentage (≤25; >25–50; >50–75; >75).

These variables were coded as ordinal, nominal or dummy, as appropriate, and incorporated into the model.

3 | RESULTS

3.1 | Multiple correspondence analysis

The results of MCA are shown in Figures 2 and 3. We identified two dimensions that explain 82% of the variance: the first is 49% and the second being 33%.

The first quadrant (top right) identified the following variables: an early initiation of vaccination programs based on HPV screening as primary test; a high-screening coverage and low incidence and mortality rates. In addition,
and screening with cytology as primary test, medium-high mortality and incidence rates, and medium vaccination coverage (Figure 2). It is important to highlight that most EU-28 Countries are mainly located between the first and fourth quadrants with high income. On the contrary, the Countries outside of the EU-28 are located between the second and third quadrant with upper-middle income and lower-middle income (Figure 3).

4 | DISCUSSION

In 2015, 526,000 women developed CC worldwide and caused 239,000 deaths.39 The pap-test screening programs, allowing an early diagnosis of precancerous lesions and a timely treatment of the same, have allowed to reduce the incidence of cervical cancer. Vaccination prevents precancerous lesions, reduces cancer and related treatments to eliminate precancerous lesions. Vaccination, acting much earlier in the history of disease development, prevents chronic infection resulting in pre-cancerous lesions. Vaccination and screening programs are fundamental because they are potentially cost-effective and allow decreasing incidence and mortality rates of CC.40 Screening, however, will remain fundamental for prevention of CC despite HPV vaccines.41 In fact, a factor that determines the differences in the incidence of CC among Countries is the screening coverage of the population.7

Monitoring HPV-vaccination coverage is important to evaluate the performance of vaccination programs and the potential impact of HPV vaccine on cervical cancer. In fact, cervical cancer screening programs will need to be adjusted to the number of vaccinated people eligible for screening. However, despite the documented effectiveness of HPV vaccine, there is still an incomplete availability to this prevention action in the world population. Bruni et al42 showed high differences in number of women vaccinated according to gross income level countries; in fact, high-quality primary and secondary cancer prevention is nearly always available in wealthy countries with gross national income (GNI) level.42 Moreover, higher income allows access to better resources and living standards and can increase the ability to maintain healthy behaviors.43 Syse and Lyngstand showed that high income is also related to higher survival rate.44

Our study shows that European Countries with higher income have higher screening and immunization coverage probably due to organized screenings starting before 1960 that determined low incidence and mortality rates, respect to those with lower-middle income. High-income countries have HPV screening test as the primary test and total or free partial charge HPV vaccination.

Eastern European and Asian Countries have lower-middle income and show high incidence and mortality rates. These countries have an opportunistic screening with lower-screening coverage and lower-immunization coverage probably because HPV vaccine was introduced later. Globally, the coverage of vaccination is higher in countries with high income; by 2016, 71% of HI countries, 35% UMI countries, 8% of LMI countries, and 6% of LI countries had introduced the HPV vaccine.45

Only eight of the 70 countries who reported HPV vaccine introduction by the end of 2016, made the vaccine available to boys in addiction to girls (Australia, Austria, Barbados, Brazil, Canada, Italy, Switzerland, and the United States).46 According to Brisson et al,47 greater benefits can be acquired for both female and male by increasing HPV-vaccination coverage among girls. In addition, vaccination of both sexes would be more equitable.48

In light of this, we would like to point out that: first, the strategy of including males in vaccination campaigns has, without a doubt, the function of reducing the circulation of the virus (herd-effect) and the transmission of infection between the two sexes. It has also the advantage of countering the occurrence of HPV-related diseases affecting male anatomic sites, such as the penis. Second, it is important to stress that both sexes have the same right to benefit from the advantages of anti-HPV vaccination. In fact, according to European regulations, it is a right of every citizen to take advantage of disease prevention programs, where there is an effective means of prevention like the anti-HPV vaccine. Third, a universal anti-HPV vaccination program reduces the prejudices created around a female-only vaccination, helping to reduce sociocultural barriers and thereby increasing acceptability and vaccination coverage.

Public health authorities should monitor the HPV-vaccinated population in order to determine more precisely the effects on short- and long-term incidence and mortality rates.

A useful scenario for crucial support to public health decision-makers is the strength of our paper. On the other hand, a limitation could be that the data that came from low-income countries must be considered with caution, both because they come from local registries (rather than the population-based cancer registries used for the other countries) and because the International Classification Disease, 9th revision, codes are not always accurate.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Altobelli E, Rapacchietta L, Profeta VF, Fagnano R. HPV‐vaccination and cancer cervical screening in 53 WHO European Countries: An update on prevention programs according to income level. Cancer Med. 2019;8:2524‐2534. https://doi.org/10.1002/cam4.2048