Original Study

Vaccination against Human Papillomavirus in relation to Financial Crisis: The "Evaluation and Education of Greek Female Adolescents on Human Papillomaviruses' Prevention Strategies" ELEFTHERIA Study

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A B S T R A C T

Study Objective: In this study we aimed to explore financial and other sociodemographic factors that affect nonvaccination against the human papillomavirus (HPV) in Greece, one of the first European Union countries to introduce the vaccination against HPV into its National Immunization Programme in 2008.
Design, Setting, Participants, Interventions, and Main Outcome Measures: Six hundred thirty-two female adolescents (aged 11-16 years) from Greece completed a pilot cross-sectional questionnaire-based survey (ELEFTHERIA study) from 2008 to 2014.
Results: Overall, only 8.9% (56 of 632) of the female adolescents reported that they had received all 3 doses of the HPV vaccination. The HPV vaccination uptake rates increased gradually from 3.2% (3 of 95) in 2008 to 17.1% (14 of 82) in 2011. However, it abruptly decreased to 2.1% (2 of 95) in 2012 and it reached 9.2% (8 of 87) in 2013 and 11.5% (11 of 96) in 2014. The most common factors for nonvaccination included fear of side effects, which decreased (Spearman $\rho = -0.860$; $P = .024$) and financial issues, which increased statistically significantly (Spearman $\rho = 0.890$; $P = .012$) during the years 2008 to 2014.
Conclusion: In our study we addressed the novel topic of the association of financial issues with HPV vaccination compliance and highlighted the urgent need to provide and maintain health insurance coverage to children in Greece, a country in financial crisis.
Key Words: Human papillomavirus, HPV, Vaccination, Adolescents, Financial crisis, Greece

Introduction

Human papillomavirus (HPV) is a small nonenveloped double-stranded DNA virus, which belongs to the *Papillomaviridae* family and infects epithelial cells, exclusively.[1] To date, HPV is considered a common pathogen in humans and has been associated with a wide range of cutaneous and mucosal infections in multiple anatomical sites in adults and in children.[2] Different genotypes of HPV can cause common warts, anogenital warts, recurrent respiratory papillomatosis, low-grade and high-grade squamous intraepithelial lesions of the human cervix and cervical cancer.[2,3] HPV infection represents the most widespread sexually transmitted infection especially in adolescence and young adulthood and after a variable incubation period it can culminate in latent, subclinical, or clinical epithelial lesions, leading to benign or malignant neoplasms; however, in most cases it is self-sustained by the host cellular immune system and undergoes spontaneous resolution.[4]

Despite the revolutionary invention of the Papanicolaou smear test by Dr George N. Papanicolaou (Kyme, Island of Euboea, Greece, 1883-Miami, Florida, 1962), HPV is considered the most frequent carcinogen in humans causing approximately 530,000 incident cases of cervical cancer per annum, with most cases occurring in developing countries.[5–7] The link between HPV and cervical cancer was first suspected by Professor Harald zur Hausen (Gelsenkirchen, Germany, 1936-) in the early 1970s.[3] Subsequently, the first genotypes of HPV were isolated and cloned using molecular techniques and just 1 decade later further molecular and epidemiological studies supported HPV as the principal causative factor for cervical cancer.[1] In parallel to these studies, the beginning of the 1980s provided all of the valuable background for research attempts to develop human vaccines against 'high-risk' HPV genotypes.[3] In 2008, the year that Professor Harald zur Hausen received the Nobel Prize in Physiology and Medicine, 2 vaccines against HPV, the bivalent 16/18 and the quadrivalent 6/11/16/18, were implemented into clinical practice in several countries, worldwide, including the European Union.[8] To date, several cost-effectiveness analyses have been conducted to calculate the expected health benefits because of the implemented HPV vaccination programs, which have been hailed as among the most significant advances of the recent

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years in cancer prevention.[9,10] However, current trends indicate a low HPV vaccination uptake rate among female adolescents in several countries in the European Union.[11–16] These studies have also focused on potential factors that influence parents' decisions to decline HPV vaccination of their daughters. Because data on HPV vaccination among female adolescents is Greece were limited, we designed the ELEFTHERIA study entitled "Evaluation and education of Greek female adolescents on human papillomaviruses' prevention strategies." The name of this project was inspired by 'Eleftheria,' the name of the first adolescent who was recruited to our study. The aim of the ELEFTHERIA study was: (1) to assess HPV vaccination uptake among female adolescents in Greece during the period from 2008 to 2014; and (2) to investigate sociodemographic reasons for declining HPV vaccination.

Materials and Methods

Study Setting and Participants

We conducted a questionnaire-based pilot cross-sectional questionnaire-based survey during a 7-year period spanning from January 2008 to December 2014 at the pediatric outpatient clinics of the 'Aghia Sophia' Children's Hospital and the 'Penteli' Children's Hospital in Athens, Greece. These are tertiary pediatric centers providing acute primary, secondary, and tertiary health care to pediatric patients from Attica and mainland Greece up to the age of 16 years. In view of our research objectives, we attempted to interview randomly selected female adolescents and their parents, who agreed to participate in the ELEFTHERIA study. All participants attended a pediatric outpatient clinic accompanied by their parents, were female, and their age ranged from 11 to 16 years. Adolescents not accompanied by their parent(s) were excluded to eliminate erroneous reporting. Adolescents whose parents did not provide consent were also excluded.

Study Design

All participants were interviewed by our research team after obtaining informed written consent from their parents. The responders were informed of their right to refuse at any time of the study. The confidentiality and anonymity of the data was maintained at all times. Interviews were performed using a structured questionnaire. At the end of each interview, all adolescents and their parents were counseled on the need and positive aspects of HPV vaccination and attempts were made to shun any false beliefs.

Ethical Approval

Our study was approved by the Department of Paediatric Infectious Diseases at the University of Athens School of Medicine in Athens (Greece). It was performed anonymously using a self-administered questionnaire and did not involve access to identifiable private information, thus all participants remained not identifiable according to the principles of the Declaration of Helsinki. Moreover, no access to hospital files or case notes was performed and no human specimens were involved. For these reasons, our project did not meet our institutional criteria to require an institutional review board and was excluded from institutional review board review.

Definitions

Adolescents who had received the full course of HPV vaccination according to their age as per the National Immunization Programme in Greece (having received all 3 shots) were defined as 'fully vaccinated.' Adolescents who had been vaccinated at least once against HPV, but had failed to complete the full course of HPV vaccination according to their age as per the National Immunization Programme in Greece were defined as 'partially vaccinated.' Adolescents who had never been vaccinated against HPV according to their age as per the National Immunization Programme in Greece were defined as 'not vaccinated.'

Study Questionnaire

The questionnaire used in our study was comprised of 2 groups of questions. The first consisted of 2 sections. Section 1A was concerned with the demographic characteristics of the adolescents and included variables such as age, ethnicity, type of school (public or private), and a history of their current HPV vaccination status. Section 1B was concerned with the demographic characteristics of the parents and inquired about their age, number of children, educational status, annual income, and insurance status. The second group of questions was comprised of 3 sections. Section 2A was only completed by adolescents considered 'fully vaccinated' and 'partially vaccinated' against HPV and included the factors that convinced them to be vaccinated against HPV. Section 2B was completed only by adolescents 'partially vaccinated' against HPV and investigated their intentions to fulfill the 3-dose scheme of the HPV vaccination. Questions in section 2C were completed only by adolescents considered as 'partially vaccinated' or 'not vaccinated' against HPV and included reasons that prevented them from being 'fully vaccinated' against HPV. These were divided into primary and secondary factors. The primary reason referred to the single most important factor reported by the responders for nonvaccination against HPV. The question had an open-ended connotation and no options were given in this case. The response was then classified according to a preformed list of factors. After the responder had successfully answered the question, the reasons (excluding the primary reason) were inquired individually and the responder was supposed to answer using a 'yes or no' approach, meaning that the responders were allowed to select more than 1 reason, as opposed to the primary factor, for which they were allowed to select only one.

Statistical Analyses

Data from the questionnaire was entered in SPSS version 17 for analysis and the results were compared. Descriptive statistics formed the mainstay of the statistical analysis. *P*

values were calculated to determine the significance of the associations between variables and were on the basis of the χ^2 test. Spearman ρ correlation (nonparametric test) was used to assess statistical trends in frequencies of the 3 most common factors for nonvaccination across the years. A *P* value of less than .05 was considered statistically significant.

Results

Demographic Characteristics

A total of 632 of the 681 adolescents approached agreed to be interviewed, which yielded a response rate of (632 of 681; 92.8%). The mean age of the investigated adolescents was 13.2 ± 9 years. The mean maternal and paternal ages were 34.7 ± 4.9 years and 41.4 ± 7.9 years, respectively. Most of the participants (501 of 632; 79.3%) were Greek and attended public high schools (598 of 632; 94.6%).

Vaccination Status

Overall, of the 632 female adolescents only 56 (56 of 632; 8.9%) adolescents reported that they were 'fully vaccinated' against HPV, 18 (18 of 632; 2.8%) were 'partially vaccinated' against HPV, and 558 (558 of 632; 88.3%) had never been vaccinated. Of those who were 'partially vaccinated,' 10 (10 of 18; 55.6%) intended to complete the 3-dose scheme. In Figure 1, the reported HPV vaccination rates during the years 2008 (3 of 95; 3.2%), 2009 (7 of 85; 8.2%), 2010 (9 of 92; 9.8%), 2011 (14 of 82; 17.1%), 2012 (2 of 95; 2.1%), 2013 (8 of 87; 9.2%), and 2014 (11 of 96; 11.5%) are presented.

Reasons for Vaccination

The most common provocative factors for HPV vaccination compliance were internet information (56 of 62; 90.3%), mass media (47 of 62; 75.8%) and friends' advice (25 of 62; 40.3%), followed by relatives' advice (19 of 62; 30.6%), family physician's or pediatrician's advice (8 of 62; 12.9%), gynecologist's advice (2 of 62; 3.2%), and school information (1 of 62; 1.6%).

Reasons for Nonvaccination

The most common primary factors for nonvaccination against HPV were fears of side effects (386 of 574; 67.2%) and financial issues (110 of 574; 19.2%), followed by lack of knowledge (61 of 574; 10.6%), busy schedule (7 of 574; 1.2%), vaccination not deemed necessary (3 of 574; 0.5%), religious taboos (3 of 574; 0.5%), fear of exposure to needles (2 of 574; 0.3%), medical contraindications (1 of 574; 0.2%), and physician advising against vaccination (1 of 574; 0.2%). When primary and secondary reported factors were analyzed, the most common factor for nonvaccination against HPV included fear of side effects (400 of 574; 69.7%) and financial issues (300 of 574; 52.2%), followed by lack of knowledge (246 of 574; 42.9%), busy schedule (21 of 574; 3.7%), vaccination not deemed necessary (15 of 574; 2.6%), religious taboos (3 of 574; 0.5%), fear of exposure to needles (2 of 574; 0.3%), medical contraindications (2 of 574; 0.3%), and physician advising against vaccination (2 of 574; 0.3%). Figure 2 shows a graphical comparison of the different factors implicated in HPV nonvaccination choice.

Sociodemographic Associations

The HPV vaccination status revealed a statistically significant association with Greek ethnicity ($P = .002$) and private insurance status ($P = .003$). However, no significant association was found with type of school ($P = .061$) and maternal or paternal age ($P = .105$ and $P = .206$, respectively). During the period 2008 to 2014, a shift was noted in 2 of the 3 most common factors for declining HPV vaccination (Fig. 3). The fear of side effects decreased gradually (Spearman $\rho = -0.860$; $P = .024$), the self-perception of insufficient knowledge remained stable (Spearman $\rho = 0.070$; $P = .906$), and financial issues increased statistically significantly (Spearman $\rho = 0.890$; $P = .012$) during the years 2008 to 2014. In 2012, the most common factor for

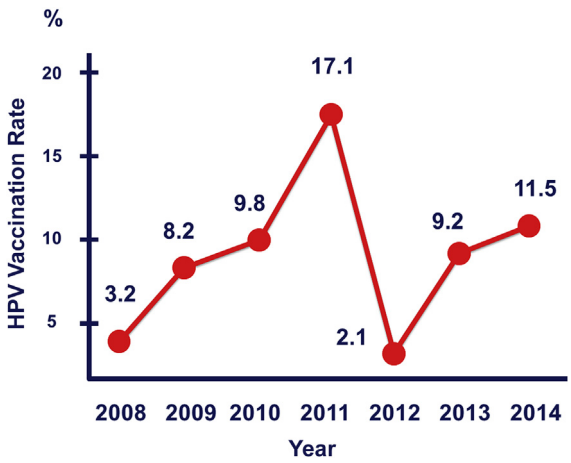

Fig. 1. Annual human papillomavirus vaccination rates among female adolescents in Greece during the period 2008-2014 (2008: n = 95; 2009: n = 85; 2010: n = 92; 2011: n = 82; 2012: n = 95; 2013: n = 87; 2014: n = 96).

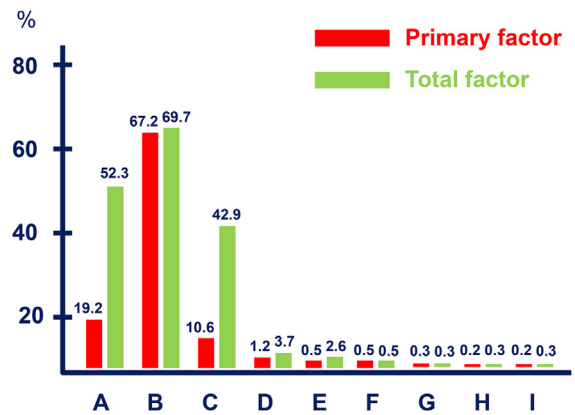

Fig. 2. Factors for nonvaccination among 574 not 'fully-vaccinated' against human papillomavirus female adolescents in Greece (A: financial issues; B: fears about side effects; C: lack of knowledge; D: busy schedule; E: vaccination not deemed necessary; F: religious taboos; G: fear of exposure to needles; H: medical contraindications; and I: physician advising against vaccination).

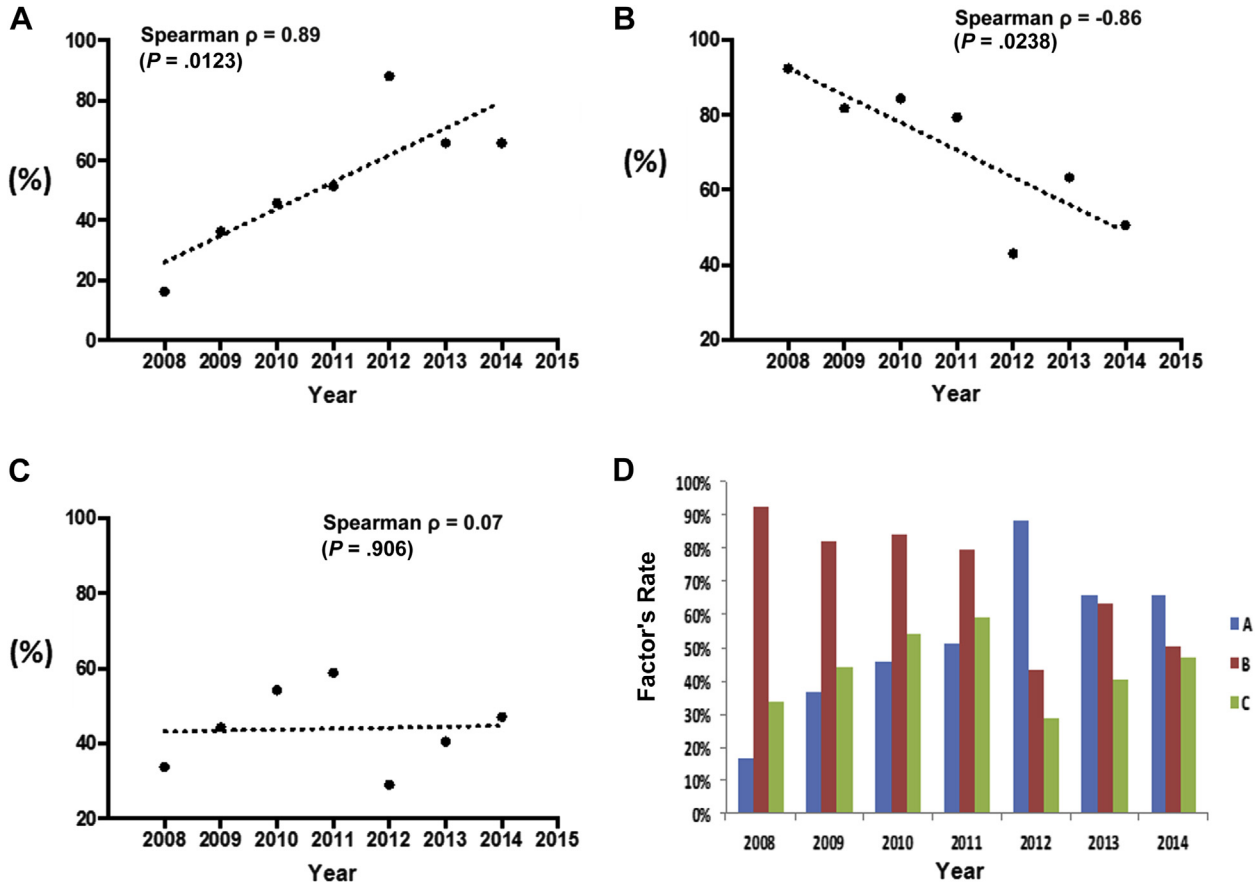

Fig. 3. Statistical trends (Spearman ρ) of financial and other issues as factors for nonvaccination among not 'fully-vaccinated' against human papillomavirus female adolescents in Greece during the period 2008-2014 (A: financial issues; B: fears of side-effects; C: lack of knowledge).

nonvaccination against HPV was parental financial weakness (82 of 93; 88.2%).

Discussion

Although to date a number of studies have aimed to assess the HPV vaccination status of adolescents in relation to sociodemographic factors, including age, ethnicity, receipt of childhood vaccines, knowledge, attitudes, and parental and community acceptability, this is the first European study to attempt to elucidate the financial reasons behind nonvaccination against HPV.[11–16] According to our findings, the HPV vaccination uptake in Greece increased gradually during the years 2008 to 2011 from 3.2% (3 of 95) to 17.1% (14 of 82). However, it decreased significantly after lack of insurance coverage during the second semester of 2012 (2 of 95; 2.1%), and in 2013 and 2014 it reached the 2010 rate (8 of 87; 9.2% and 11 of 96; 11.5%, respectively). During the period 2008 to 2014, an interesting shift was noted in 2 of the 3 most common factors for declining HPV vaccination; the fear of side effects decreased, the self-perception of insufficient knowledge remained stable, and the financial issues significantly increased.

In our study, the most common factor for nonvaccination against HPV in 2012 was parental financial weakness. Indeed, this period was characterized by the disability of the public insurance to cover the cost of the vaccines as a consequence of the current financial crisis. Recently, Vandoros et al[17] aimed to evaluate the effect of the recent financial crisis on health in Greece using a quasiexperimental approach. The results of this research team provide interesting evidence that trends in self-rated health in Greece have worsened as a result of the recent financial crisis. Similar findings have also been shown thus far by other researchers, who have highlighted the deterioration of health indexes due to the recent financial crisis.[18,19] These findings stress the need for urgent health policy responses to the recent financial collapse in Greece as the full effect of austerity measures unfolds in the coming years.

The strength of our study is that it addresses the novel topic of the association of financial issues with HPV vaccination acceptance in a country in financial crisis. To date, several researchers have associated HPV vaccination uptake with the presence or absence of parental health insurance.[20,21] Moreover, individuals enrolled in private health insurance are more likely to be aware of the vaccine compared with the uninsured and those enrolled in public health insurance.[22] For this reason, it has been proposed that strategies to increase HPV vaccination should consider insurance and cost barriers for adults and those with medical care expenditures.[23] Indeed, during the period of uninsurance, the health needs for medical care, dental care, and prescription drugs among children have increased.[17] Our findings showed the positive effect of providing

health insurance coverage to children regardless of parental income.

In our study, HPV vaccination uptake among adolescents during the years 2008, 2009, 2010, 2011, 2013, and 2014 was unacceptably low despite the fact that during this period the HPV vaccination was free of charge. Our reported rate was much lower compared with the 25.8% rate described by Donadiki et al[24] among higher education female students. In the study by Tsakiroglou et al[25] among the Greek female population aged 16 to 28 years, 11% had been vaccinated against HPV and an additional 23% intended to be vaccinated within the next 6 months. In the study by Bakogianni et al[26] of 573 students aged 18 to 25 years only 10.5% had been administered the HPV vaccine. Recently, Papagiannis et al[27] reported a vaccination coverage of 44.3% among second-year and third-year female students pursuing degrees in medicine, nursing, and paramedical health disciplines in central Greece. In all of these studies on the Greek population, the low HPV vaccination uptake was attributed to the low level of parental and adolescents' knowledge about HPV infections and the increased fear of side effects.[24–27] For this reason, in parallel to the financial improvement, further health education efforts are still needed to improve knowledge and facilitate the incorporation of HPV vaccination into clinical practice.[28,29]

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References

1. zur Hausen H: Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer 2002; 2:342
2. Mammas IN, Sourvinos G, Spandidos DA: Human papilloma virus (HPV) infection in children and adolescents. Eur J Pediatr 2009; 168:267
3. zur Hausen H: Papillomaviruses in the causation of human cancers – a brief historical account. Virology 2009; 384:260
4. Einstein MH, Schiller JT, Viscidi RP, et al: Clinician's guide to human papillomavirus immunology: knowns and unknowns. Lancet Infect Dis 2009; 9:347
5. Mammas IN, Spandidos DA, George N: Papanicolaou (1883-1962): fifty years after the death of a great doctor, scientist and humanitarian. J BUON 2012; 17:180
6. Tota JE, Chevarie-Davis M, Richardson LA, et al: Epidemiology and burden of HPV infection and related diseases: implications for prevention strategies. Prev Med 2011; 53:S12
7. Mammas IN, Sourvinos G, Zaravinos A, et al: Vaccination against human papilloma virus (HPV): epidemiological evidence of HPV in non-genital cancers. Pathol Oncol Res 2011; 17:103
8. Kahn JA: HPV vaccination for the prevention of cervical intraepithelial neoplasia. N Engl J Med 2009; 361:271
9. Kim JJ, Goldie SJ: Health and economic implications of HPV vaccination in the United States. N Engl J Med 2008; 359:821
10. Raffle AE: Challenges of implementing human papillomavirus (HPV) vaccination policy. BMJ 2007; 335:375
11. Fisher H, Audrey S, Mytton JA, et al: Examining inequalities in the uptake of the school-based HPV vaccination programme in England: a retrospective cohort study. J Public Health (Oxf) 2014; 36:36
12. Stöcker P, Dehnert M, Schuster M, et al: Human papillomavirus vaccine uptake, knowledge and attitude among 10th grade students in Berlin, Germany, 2010. Hum Vaccin Immunother 2013; 9:74
13. Steens A, Wielders CC, Bogaards JA, et al: Association between human papillomavirus vaccine uptake and cervical cancer screening in the Netherlands: implications for future impact on prevention. Int J Cancer 2013; 132:932
14. Marek E, Dergez T, Rebek-Nagy G, et al: Adolescents' awareness of HPV infections and attitudes towards HPV vaccination 3 years following the introduction of the HPV vaccine in Hungary. Vaccine 2011; 29:8591
15. Fagot JP, Boutrelle A, Ricordeau P, et al: HPV vaccination in France: uptake, costs and issues for the National Health Insurance. Vaccine 2011; 29:3610
16. Deleré Y, Böhmer MM, Walter D, et al: HPV vaccination coverage among women aged 18-20 years in Germany three years after recommendation of HPV vaccination for adolescent girls: results from a cross-sectional survey. Hum Vaccin Immunother 2013; 9:1706
17. Vandoros S, Hessel P, Leone T, et al: Have health trends worsened in Greece as a result of the financial crisis? A quasi-experimental approach. Eur J Public Health 2013; 23:727
18. Simou E, Koutsogeorgou E: Effects of the economic crisis on health and healthcare in Greece in the literature from 2009 to 2013: a systematic review. Health Policy 2014; 115:111
19. Rajmil L, Fernandez de Sanmamed MJ, Choonara I, et al: Impact of the 2008 economic and financial crisis on child health: a systematic review. Int J Environ Res Public Health 2014; 11:6528
20. Fisher H, Trotter CL, Audrey S, et al: Inequalities in the uptake of human papillomavirus vaccination: a systematic review and meta-analysis. Int J Epidemiol 2013; 42:896
21. Kessels SJ, Marshall HS, Watson M, et al: Factors associated with HPV vaccine uptake in teenage girls: a systematic review. Vaccine 2012; 30:3546
22. Duderstadt KG, Hughes DC, Soobader MJ, et al: The impact of public insurance expansions on children's access and use of care. Pediatrics 2006; 118:1676
23. Chou B, Krill LS, Horton BB, et al: Disparities in human papillomavirus vaccine completion among vaccine initiators. Obstet Gynecol 2011; 118:14
24. Donadiki EM, Jiménez-García R, Hernández-Barrera V, et al: Human papillomavirus vaccination coverage among Greek higher education female students and predictors of vaccine uptake. Vaccine 2012; 30:6967
25. Tsakiroglou M, Bakalis M, Valasoulis G, et al: Women's knowledge and utilization of gynecological cancer prevention services in the Northwest of Greece. Eur J Gynaecol Oncol 2011; 32:178
26. Bakogianni GD, Nikolakopoulos KM, Nikolakopoulou NM: HPV vaccine acceptance among female Greek students. Int J Adolesc Med Health 2010; 22:271
27. Papagiannis D, Rachiotis G, Symvoulakis EK, et al: Vaccination against human papillomavirus among 865 female students from the health professions in central Greece: a questionnaire-based cross-sectional study. J Multidiscip Healthc 2013; 6:435
28. Donadiki EM, Jiménez-García R, Hernández-Barrera V, et al: Knowledge of the HPV vaccine and its association with vaccine uptake among female higher-education students in Greece. Hum Vaccin Immunother 2013; 9:300
29. Mammas IN, Theodoridou M: Financial crisis and childhood immunization: when parents disagree. Acta Paediatr 2013; 102:e145