



Age impact on human papillomavirus vaccination in France in 2014: A study from the National Health Insurance Database

Delphine Héquet^{1,2}, Nicolas Pouget¹, Juan-Pablo Estevez¹, Mathieu Robain³, Roman Rouzier^{1,2}

Received 29 June 2015
Accepted 18 September 2015
Available online: 30 October 2015

1. Institut Curie-René-Huguenin, département d'oncologie chirurgicale, 35, rue Dailly, 92210 St-Cloud, France
2. Université Versailles-Saint-Quentin, équipe d'Accueil 7285, risques cliniques et sécurité en santé des femmes et en santé périnatale, 2, rue de la source de la Bièvre, 78180 Montigny-le-Bretonneux, France
3. Institut Curie, département de biostatistiques, 26, rue d'Ulm, 75005 Paris, France

Correspondence:

Delphine Héquet, Institut Curie-René-Huguenin, département d'oncologie chirurgicale, 35, rue Dailly, 92210 St-Cloud, France.
delphine.hequet@gmail.com

Keywords

HPV
Vaccine
Compliance

Summary

Introduction > Human papillomavirus (HPV) is the main cause of cervical cancer. In France, since March 2007, HPV vaccination has been recommended for girls aged 14, in addition to a catch-up program for girls aged 15 to 23. In October 2012, the target population was changed to 11- to 14-year-old girls. The main objective of the present study was to evaluate the impact of the recommendation change on HPV vaccination coverage and compliance.

Methods > We conducted a descriptive study of the Échantillon Généraliste des Bénéficiaires (EGB), which is a random 1/97 permanent sample from the French National Health Insurance Database. We focused our analyses on girls aged 11 to 17 years who were covered by the main insurance scheme (which covers 77% of the French population).

Results > We included 16,195 girls in this analysis. At the last update of the database (06/15/2014), 42% of 17-year-old girls had been vaccinated, with more than 50% of them having been vaccinated at age 14. Between January 2012 and June 2014, patients were reimbursed for a total of 7698 doses of the HPV vaccine. During the first trimester of 2013, the number of vaccinated 11- to 13-year-old girls increased, growing by more than 20-fold between the last trimester of 2012 ($n = 8$) and the last trimester of 2013 ($n = 178$). Less than 60% of the vaccinated patients received 3 injections.

Discussion > Implementation of the new recommendations was rapid but had only a slight impact on vaccination coverage.

Mots clés
HPV
Vaccination
Compliance

■ Résumé

Impact de l'âge sur la couverture vaccinale anti-HPV en France en 2014 : une étude réalisée à partir des données de l'échantillon généraliste des bénéficiaires (EGB)

Introduction > Le papillomavirus humain (HPV) est la principale cause de cancer du col. En France, la vaccination anti-HPV est recommandée depuis mars 2007 chez les jeunes filles âgées de 14 ans, avec un programme de rattrapage des jeunes filles âgées de 15 à 23 ans. En octobre 2012, la population cible a été modifiée comprenant les jeunes filles de 11 à 14 ans. L'objectif de cette étude est d'évaluer l'impact des modifications des recommandations sur la couverture vaccinale anti-HPV et l'observance.

Méthodes > Nous avons mené une étude rétrospective à partir des données de l'EGB (échantillon généraliste des bénéficiaires) qui correspond à 1/97 de la population présente dans la base de l'Assurance maladie. Nous avons ciblé les jeunes filles de 11 à 17 ans couvertes par le Régime Général (couvrant 77 % de la population française).

Résultats > L'analyse a concerné 16 195 filles. À la dernière mise à jour avant analyse, 42 % des jeunes filles de 17 ans avaient été vaccinées, dont plus de 50 % à l'âge de 14 ans. Entre janvier 2012 et juin 2014, 7 698 doses de vaccins ont été remboursées. Lors du 1^{er} trimestre 2013, la part des 11-13 ans vaccinées a augmenté, jusqu'à être multipliée par 20 entre le dernier trimestre 2012 et le dernier trimestre 2013. Moins de 60 % des patientes ont reçu les 3 doses recommandées à l'époque.

Discussion > L'implémentation des nouvelles recommandations concernant l'âge a été rapide. Toutefois, la couverture vaccinale anti-HPV est toujours basse.

Introduction

Human papillomavirus (HPV) is the main cause of cervical cancer [1]. The high-risk subtypes HPV 16 and 18 are responsible for 70% of cervical cancer cases [2]. In France, in 2012, there were 3028 new cases of cervical cancer and 1102 deaths from the disease [3]. HPV is also responsible for cervical intraepithelial neoplasia (CIN), a precancerous lesion that can necessitate surgical procedures and that requires close follow-up of patients [2]. In several countries (Australia, Great Britain, and the United States) with a national HPV vaccination program, we have observed a decrease in HPV prevalence in the vaccinated population [4-6]. In addition, HPV vaccination has been shown to reduce CIN prevalence in vaccinated patients in Australian studies [7,8]. HPV vaccination has been recommended and its costs covered by the French health authorities since March 2007 [9]. However, there is no national HPV vaccination program in France. From March 2007 to September 2012, HPV vaccination was recommended for girls aged 14, in addition to a catch-up program for girls aged 15 to 23 who had become sexually active within the previous year or who had not yet initiated sexual activity [10]. Since October 2012, the target population has changed from 14-year-old girls to 11- to 14-year-old girls [11]. In early 2014, the French health authorities revised their existing recommendations from a 3-dose schedule to a 2-dose schedule [12,13]. The impact of the target age change on HPV vaccination coverage and compliance is unknown.

The main objective of this study was to evaluate the implementation of recommendations concerning target age and the impact of these recommendations on HPV vaccination coverage and compliance.

Materials and methods

Data source

Data were extracted from the Échantillon Généraliste des Bénéficiaires (EGB), which is a random 1/97 permanent sample from the French National Health Insurance Database [14]. This national database includes reimbursement within the three main insurance schemes, which cover nearly 85% of the French population. On June 15, 2014, the EGB covered 708,208 people, including both those who consume health services and those who do not. The data in the EGB include patient characteristics, all reimbursed medical costs, prescriptions, administered laboratory tests, private hospital data, partial public hospital data and vital status. The use of the EGB is regulated, and the data are anonymous. We obtained authorization to access the EGB database from the French National Health Insurance system (CNAM, or Caisse Nationale d'Assurance Maladie). The data were prospectively collected beginning in 2005. No clinical investigation was conducted, and no personal identifiers were included; therefore, no IRB approval was sought for this study.

Study population

We restricted analysis to individuals insured by the main health insurance scheme, covering 77% of the population, because data on the two other schemes of the EGB were only available after 2011. The patients had to be insured by the main health insurance scheme at the date of analysis and since the beginning of data collection to avoid loss of reimbursement information. We focused our analysis on girls aged 11 to 17 years. Indeed, girls younger than 11 are not administered HPV vaccination in France, and girls older than 17 often change health insurance schemes when they become students in secondary education. For all of the girls in the selected population, we obtained information concerning their month and year of birth. For each vaccinated girl, the following information was available: the date of each vaccine injection (month and year), the type of vaccine (Cervarix[®] or Gardasil[®]), and the number of injections. In our study, we assumed that every dose registered had been administered and that patients had been reimbursed for all administered doses.

Statistical methods

All statistical analyses were performed using R software (<http://cran.r-project.org>, The R Foundation for Statistical Computing, Vienna, Austria, version 0.98.978, ©2009–2013 RStudio, Inc.). We used classic descriptive statistical methods. The study population was considered to be exhaustive and did not represent a sample; therefore, confidence intervals are not given with the results. Comparisons of compliance between the different periods were performed using Pearson's chi-square test.

Results

Number of covered vaccine doses

Between January 2012 and June 2014, patients were reimbursed for a total of 7698 doses of the HPV vaccine. The Gardasil[®] vaccine represented 84% of these doses ($n = 7698$). Analysis by trimester showed an increase in covered doses from June to December 2013, followed by a decrease in the number of both Gardasil[®] and Cervarix[®] doses in 2014 compared with the rate observed in 2012.

Coverage of the study population

We examined the vaccination rates (at least one vaccine dose with reimbursement) as of June 15, 2014, the date that the database was last updated. The vaccination rates were described by age at the time of the last update (*figure 1a*). Of the 16,195 girls aged 11 to 17, 18.2% ($n = 2940$) had been vaccinated by the time of analysis. The majority of vaccinated girls who were 15, 16 or 17 years old on June 15, 2014, had received their first HPV vaccine injection at 14 years of age (54%, $n = 1208$). The age at vaccination was lower for girls who were younger at the time of analysis (*figure 1b*), demonstrating implementation of the current recommendations.

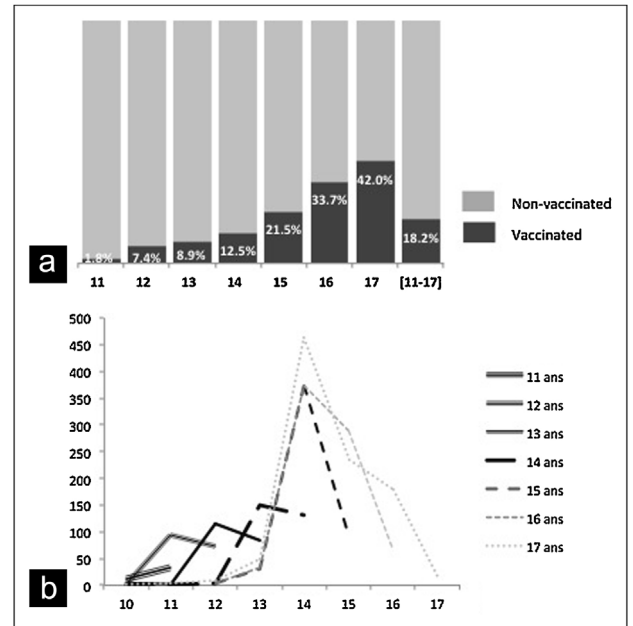


FIGURE 1

HPV vaccination coverage of girls aged 11 to 17 years at the last database update (06/15/2014). a: vaccination rates; b: age at the time of vaccination

Evolution of the vaccination rates by age from January 2012 to June 2014

The evolution of the vaccination rates by age is reported in *figure 2*. Globally, we observed an increase in the vaccination rate among 11- to 17-year-old girls (at least one vaccine dose with reimbursement), from 5.4% in 2012 to 8.1% in 2013. Moreover, the vaccination rate among 11- to 13-year-olds increased by 10-fold between 2012 and 2013 (from 0.6% to 6.2%). In addition, when we performed analysis by quarter, we observed that the number of vaccinated girls aged 11 to 13 years increased, growing more than 20-fold between the last quartile of 2012 ($n = 8$) and the last quartile of 2013 ($n = 178$). The numbers of 14-year-old and 15- to 17-year-old girls who had received a vaccination were globally stable, even though seasonality was obvious. This finding suggests that moving the target population from 14-year-old girls to 11- to 14-year-old girls increased the coverage rate.

Evolution of HPV vaccination compliance by age between January 2012 and June 2014

We studied the number of injections for which vaccinated patients were reimbursed between January 2012 and June 2013. We did not consider the period from July 2013 to June 2014. However, certain patients did not have time to complete the vaccination because it is recommended that the last dose be administered 6 months after the first dose, with an elasticity of one year. Among

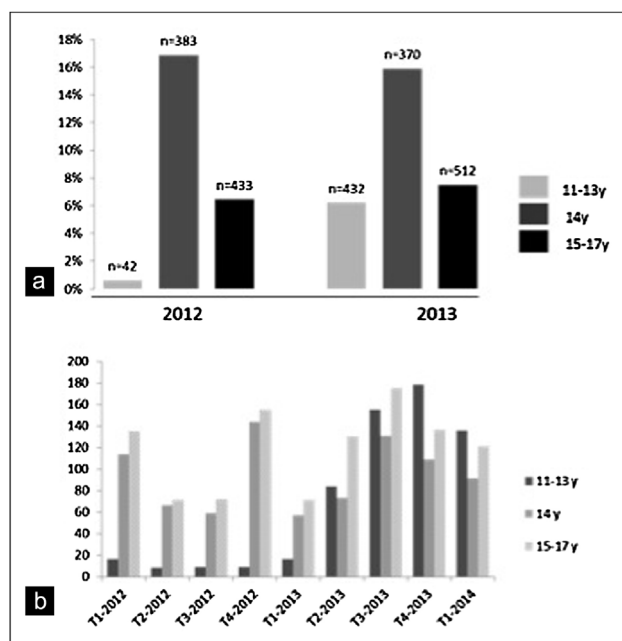


FIGURE 2 Evolution of vaccination coverage by age in 2012/2013. a: vaccination rates by age in 2012/2013; b: number of first injections by age

the 1289 vaccinated girls in this period, 766 (59.4%) received 3 injections, as recommended by the French health authorities during this time period. Compliance with the vaccination scheme was better for the target population (14-year-old girls) compared with 15- to 17-year-old girls ($P = 0.009$), as presented in *table 1a*. Of concern, we observed a decrease in compliance from January 2012 (72%) to June 2013 (56.1%, $P = 0.0005$). *Table 1b* reports the evolution of compliance between January 2012 and June 2013. *Figure 3* shows the evolution of the number of doses covered by insurance among vaccinated patients from 2012 to 2013 by age.

Discussion

This study analyzed HPV vaccination rates in a huge population of French girls (16,195) ranging in age from 11 to 17 years old. The data on the study population came from the EGB, which is a random 1/97 permanent sample from the French National Health Insurance Database, a national database that covered 708,208 people at the last update (06/15/2014). Data are available on both patients who consume health services and those who do not, which permitted us to evaluate vaccination rates. Moreover, the database provides exhaustive data on reimbursement for medicines and is a fantastic tool for epidemiological analyses [15]. However, the EGB presents certain limitations. First, we had access to reimbursement data, but not administration data; consequently, we cannot be sure that medicine delivered at the pharmacy was really administered to the patient. Studies using this database are strongly controlled to protect individuals; that is, certain data are considered to be "sensitive" and cannot be obtained. Second, in this particular

TABLE 1A HPV vaccination compliance depending on the age at first injection

	Target age, $n = 504$		Catch up age, $n = 611$		P
	n	%	n	%	
1 dose	80	15.9	141	23.1	0.009
2 doses	82	16.3	99	16.2	
3 doses	342	67.9	371	60.7	

TABLE 1B HPV vaccination compliance depending on the period of first injection (among 14- to 17-year-old girls)

	January-June 2012, $n = 375$		July-December 2012, $n = 426$		January-June 2013, $n = 314$		P
	n	%	n	%	n	%	
1 dose	56	14.9	86	20.2	79	25.2	0.0005
2 doses	49	13.1	73	17.1	59	18.8	
3 doses	270	72.0	267	62.7	176	56.1	

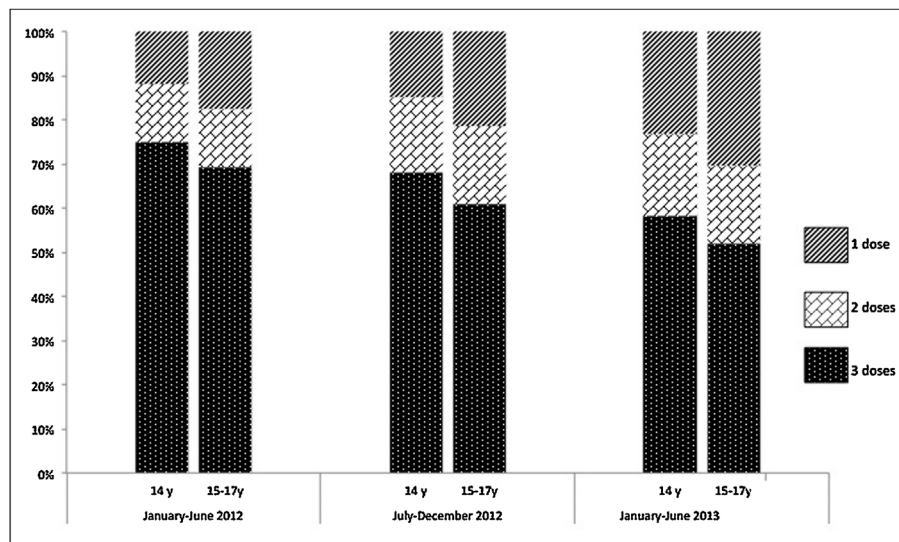


FIGURE 3
Evolution of vaccine doses delivered, depending on the age at vaccination

study, we were fettered by the health insurance scheme change for patients over 17 who became secondary education students. Therefore, we focused our study on patients aged 11 to 17 years. Finally, because the primary objectives of the database are reimbursement and protection of patient confidentiality, there are few social or medical data on the patients. However, the EGB currently remains the most useful tool to evaluate vaccination rates and is therefore used by the national health authorities to set up new recommendations [16].

In this study, we reported vaccination rates (at least one injection with reimbursement) of 33.7% among girls aged 16 years and 21.5% among girls aged 15 years in June 2014. In 2011, the vaccination rate for girls aged 15 was higher, reaching 26% [16]. Similar results were described in a French study published in 2014 concerning 1136 mothers of girls 14 to 16 years of age [17]. Based on a self-administered questionnaire, the authors describe that 31.7% of 14–16-year-old girls had started the vaccination schedule. Based on *figure 1b*, we do not suspect that better coverage of younger girls explains this decrease. These rates are very low compared with those in other countries, such as Australia (70%), Denmark (82%), Great Britain (80%) and Canada (75%) [6,7,18,19].

In October 2012, the French authorities changed the recommendations on HPV vaccination: the target population changed from girls aged 14 years to girls aged 11 to 14 years. As early as January 2013, we observed a large increase in vaccinated girls aged 11 to 13 years. However, even if the new recommendations were rapidly implemented and had a positive impact, vaccination coverage remains too low. We showed higher

numbers of doses and patients vaccinated in 2013 after the new recommendations of October 2012. However, this effect was temporary because a decrease was observed in the first trimester of 2014. An anticipated effect of the two-dose schedule is suspected, but further studies are warranted.

We observed poor adherence to the vaccination protocol, with only 59% of patients receiving 3 injections between January 2012 and June 2013. Better compliance was observed in the girls of the target age compared with the catch-up population. In 2010, a study on HPV vaccination coverage in Paris found that only 43% of vaccinated patients had received a complete vaccination scheme, with 3 doses [20]. Moreover, vaccination coverage rate had decreased (–11 to –16 points depending of age) between 2009 and 2012 [17]. The better compliance observed in the youngest girls is a clear benefit of lowering the target age for HPV vaccination. A positive effect is also expected for the two-dose schedule [12,13].

In France, there is no national vaccination program. However, the last report from the health authorities introduced a project to organize an extensive vaccination campaign at schools [16]. National HPV vaccination programs have been already set up in several countries, including Australia, Denmark, Great Britain, New Zealand, the United States (only certain states), Sweden, Germany and Canada. This approach seems to be the most effective for improving vaccination coverage. Therefore, vaccination coverage in these countries is up to 82% [18]. The French national health authorities' decision to establish a national program is a consequence of both poor vaccination coverage and the growing number of publications on HPV vaccination

efficiency. Indeed, in Australia and the United States, decreases in HPV prevalence were observed in 77% and 56% of vaccinated patients, respectively [12,13]. Moreover, decreases in CIN prevalence were observed in vaccinated patients in Australia and Canada [7,8,4].

Conclusion

This observational study conducted to evaluate a large French population revealed a poor HPV vaccination coverage rate. National health authorities often change recommendations to improve vaccination rates. In fact, we observed very rapid implementation of the new recommendations. However,

despite the slight increase in the number of vaccinated girls, HPV vaccination coverage is still too low in France. It is currently too soon to appreciate the effects of the last recommendation (2 injections instead of 3) on HPV vaccination coverage. Nonetheless, foreign experience has shown that national vaccination programs at schools are the most effective way to improve HPV vaccination coverage. Consequently, this solution is currently being discussed in France and should be established soon.

Disclosure of interest: the authors declare that they have no competing interest.

References

- [1] Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. *Vaccine* 2008;26(Suppl.10):K1-6.
- [2] Centre national de référence des Papillomavirus humains (CNR HPV), Institut Pasteur. <http://www.pasteur.fr/ip/easysite/pasteur/fr/sante/info-hpv>.
- [3] Les cancers en France en 2013. Collection état des lieux et des connaissances, ouvrage collectif édité par l'INCa, Boulogne-Billancourt, janvier 2014. <http://www.e-cancer.fr/publications/69-epidemiologie/758-les-cancers-en-france-edition-2013> (consulté le 27/06/2014). Avis du Comité technique des vaccinations et du Conseil supérieur d'hygiène publique de France relatif à la vaccination contre les papillomavirus humains 6, 11, 16 et 18. 9 mars 2007. http://www.cngof.asso.fr/D_TELE/vaccin_hpv_0307.pdf.
- [4] Tabrizi SN, Brotherton JM, Kaldor JM, Skinner SR, Cummins E, et al. Fall in human papillomavirus prevalence following a national vaccination program. *J Infect Dis* 2012;206(11):1645-51.
- [5] Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. *Infect Dis* 2013;208(3):385-93.
- [6] Mesher D, Soldan K, Howell-Jones R, Panwar K, Manyenga P, et al. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. *Vaccine* 2013;32(1):26-32.
- [7] Gertig DM, Brotherton JM, Budd AC, Drennan K, Chappell G, Saville AM. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC Med* 2013;11:227.
- [8] Crowe E, Pandeya N, Brotherton JM, Dobson AJ, Kisely S, et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. *BMJ* 2014;348:g1458.
- [9] Institut de veille Sanitaire. Calendrier des vaccinations et recommandations vaccinales 2012 selon l'avis du haut conseil de la santé publique (2012 vaccination schedule and recommendations from the « Haut Conseil de la santé publique » in France). *Bull Epidemiol Hebd* 2012;14-15:163.
- [10] Groupe de travail sur la vaccination contre les papillomavirus. Comité technique des vaccinations. Conseil Supérieur d'Hygiène Publique de France. 23 Mars 2007. <http://www.sante.gouv.fr/IMG/pdf/1.pdf>.
- [11] Haut Conseil de la santé publique. Avis relatif à la révision de l'âge de vaccination contre les infections à papillomavirus humains des jeunes filles; [7 p]. 2012, <http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=302>.
- [12] Haut Conseil de la santé publique. Avis relatif à l'utilisation du vaccin contre les infections à papillomavirus Cervarix®; 2014, <http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=411>.
- [13] Haut Conseil de la santé publique. Avis relatif à l'utilisation du vaccin contre les infections à papillomavirus Gardasil®; 2014, <http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=416>.
- [14] Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. *RESP* 2010;58(2010):286-90.
- [15] Martin-Latry K, Bégaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! *Pharmacoepidemiol Drug Saf* 2010;19:256-65.
- [16] Haut Conseil de la santé publique. Vaccination contre les infections à papillomavirus humains. Données actualisées; 2014, <http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=454>.
- [17] Denis F, Cohen R, Stahl JP, Martinot A, Dury V, Le Danvic M, et al. Papillomavirus vaccination in France according to 2008 to 2012 Vaccinocopie® data. *Med Mal Infect* 2014;44(1):18-24.
- [18] Baandrup L, Blomberg M, Dehrendorff C, Sand C, Andersen KK, Kjaer SK. Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program. *Sex Transm Dis* 2013;40(2):130-5.
- [19] Institut national de santé publique du Québec. Comité sur l'immunisation du Québec. La vaccination contre les VPH au Québec : mise à jour des connaissances et propositions du comité d'experts. <http://www.inspq.qc.ca/>.
- [20] Rouzier R, Giordanella JP. Coverage and compliance of Human Papilloma Virus vaccines in Paris: demonstration of low compliance with non-school-based approaches. *J Adolesc Health* 2010;47(3):237-41.