

Utilization Evaluation of Human Papilloma Virus Vaccine (GARDASIL®) in Iran; A Cross-Sectional Study.

Fateme Mohammadpour^a, Ava Mansouri^{a*} and Molouk Hadjibabaie^{a, b}

^aResearch Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran. ^bFaculty of Pharmacy, Department of Clinical Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Vaccination against HPV seems to be a good approach for prevention of cervical cancer and genital warts. But in Iran we are confronted with lack of evidence for its cost-effectiveness whereas its consumption is dramatically increasing.

This was a cross-sectional study. We used a questionnaire including 5 sections as follows; Patients demographic information, Patients medical history, Pregnancy and lactation considerations, Gardasil prescription characteristics and HPV infection characteristics. Prescriber with adherence to guideline were defined as those prescribing Gardasil for correct age range and indication with accurate dosage and administration. Descriptive statistics for variables was shown by frequency (percent) or mean (\pm SD) and evaluation of relation between categorical variables was performed by using Chi-square test.

Total 566 Gardasil recipients participated in the study. There were mostly female with mean age of 28.1 (\pm 6.68). For 128 (22.6%) participants Gardasil prescribed correctly considering both age range (9-26 years) and indication (prophylactic). From this group, 80 participants (14.1%/566) have received accurate Gardasil dosage and interval (prescriber had adherence to guideline). Patients' out of pocket payment in guidelines adherent prescriptions was a seventh of total costs obtained from 566 consumers. Gynecologists significantly prescribed for prophylaxis higher than other specialties (p -value = 0.01).

Prescribers' practice in administrating Gardasil is obviously not appropriate and it is imposing burdensome cost to community and government. On the other hand, we have encountered with increasing rate of its use in Iran in past years. Therefore, we are in urgent need for appropriate interventions in national level and prompt supervision to regulate Gardasil consumption.

Keywords: Gardasil; Human papilloma virus vaccine; Utilization, Iran; Guideline adherence.

Introduction

Cervical cancer is the second common cancer in women (1, 2) and one of the most frequent causes of mortality all over the world (3). Majority of these cervical cancers occur in developing countries (1).

Prevention of cervical cancer is done by two approaches: Pap screening program in order to early diagnosis of cancer precursor

(1) and vaccination against Human papilloma virus (HPV) as the main cause of cervical cancers (4). HPV is the most common sexually transmitted infection which is contaminated at least 50% of adults in their lifetime (5). The U.S.FDA (American Food and Drug Administration) approved Gardasil 4 for prevention of anogenital cancer and genital warts for women and men in 2006 and 2009, respectively (6) and also, Gardasil 9 in 2015 (7).

* Corresponding author:

E-mail: ava_mansouri_j@yahoo.com

Persistent HPV infections by high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, and 58) are the reason of 99% of cervical cancers and cancers and 70% of them attributed to HPV type 16 and 18 (8). Among cervical cancer population in Iran, 77.7 % (61.9% to 83.7 % depending on their geographical regions) were infected with HPV. The Frequency of Subtypes in this Iranian population were; 50.1% subtype 16, 14.4% subtype 18, 8.1% subtype 31 and 6.1% subtype 33 (9). Frequencies of these subtypes are similar worldwide (10), except subtype 31 which is higher in Iran (8.1-9.5%) (9, 10) in comparison to its worldwide reported rate (3.5%) (10). So, vaccination against HPV in Iran also seems to be a good approach for prevention of cervical cancer and genital warts, especially new generation of vaccine which cover subtype 31.

Until now, three type of antipapilloma virus vaccine manufactured: Gardasil 4, Cervarix and Gardasil 9. Gardasil 4 currently is available in Iran and Gardasil 9 does not exist in Iran drug list.

Gardasil 4 is expensive. Although Gardasil is covered by insurance in 19 countries (5) or it is funded by the government for vaccination program in some other countries (e.g. USA and Australia) (11, 12), its expenditure is not entirely or partly covered by Iran public insurance companies. On the other hand, Khatib *et al.* stated that quadrivalent HPV vaccine (Gardasil 4) is not cost-effective in Iran based on their base-case parameters value study (5). Nevertheless, Gardasil sale pattern dramatically increased in the last five years, about 19 times, based on the available data of Iran pharmaceutical wholesale data (provided by Food and Drug department of the I.R. Iran Ministry of Health).

Assessing Gardasil use situation in Iran seems necessary, considering increasing consumption of this vaccine while we are confronted with lack of evidence for its cost effectiveness. Hence, we evaluated utilization of Gardasil and assessed prescribers' adherence to U.S.FDA and ACIP (Advisory Committee to Immunization Practice) guidelines for Gardasil administration (6, 13).

Method

Setting and Study design

This was a cross-sectional, Drug Utilization Evaluation (DUE) study. It was carried out from February 2014 to July 2015 at 13 Aban Foghe-Takhasosi Pharmacy affiliated with pharmacy faculty, Tehran University of Medical Sciences (TUMS), in Tehran, Iran. 13 Aban Foghe-Takhasosi pharmacy is one of the few authorized pharmacies in Iran for Gardasil distribution. The study was approved by the research council of Research Center for Rational Use of Drugs, and TUMS institutional review board and Committee for Research Ethics.

Participants' characteristics

We included all the individuals who referred to the pharmacy with a prescription containing Gardasil, regardless of their age, gender, insurance, and physician specialty. Patients were excluded if they refuse to cooperate, not willing to give any contact information for further evaluation and could not provide sufficient information since Gardasil was not prescribed for them or they have filled the questionnaire in their former visit.

Data acquisition

Questionnaire

We used a questionnaire to collect the information. The questionnaire was designed according to guidelines. It contains 19 questions (3 open ended questions and 16 multiple choice questions) which was self-administered. The questionnaire included 5 sections as follows:

1. *Patients demographic information:* age, sex, and educational level,
2. *Patients medical and drug history:* underlying diseases and drugs,
3. *Pregnancy and lactation considerations:* Pregnancy and lactation status,
4. *Gardasil prescription characteristics:* number of prescribed dose, number of received dose, dose interval, physician specialty, prescribing intention (prophylactic or therapeutic based on patients' information),

patients' perception about Gardasil insurance,

5. *HPV infection characteristics*: HPV infection existence, wart presence, HPV PCR (polymerase chain reaction) test result, Papanicolaou test (Pap smear) program (former or later tests).

Filling instructions

Individuals received the questionnaire at the admission time from the pharmacy technician. They have responded to the questions during the dispensing process and until they were called by the pharmacist. Whenever the prescription was filled, the pharmacist in charge would take the questionnaire, and check that all of the questions were answered. The questions about PCR laboratory test and HPV types were asked face to face by pharmacist to reduce the probable confusion. If the test results were unavailable at the time, pharmacist would request for their contact information and permission for further evaluation by calling them. Afterwards, the pharmacist would obtain the omitted information few days later over a phone call.

Data extraction analysis

Frequency of different variables was calculated, i.e.: sex, age, educational level, underlying disease, physician specialty and pregnancy and lactation, Gardasil prescription indication, and PCR-test result.

To assess Gardasil practice, we used US-FDA protocol (13) and the Advisory Committee on Immunization Practices (ACIP) protocol (6) of HPV vaccination. According to these guidelines, Gardasil could be used in male and female in age of 9-26 years old in order to prevent from HPV infection. Although, ACIP recommended routine vaccination of HPV vaccine for age 11-12, and catch up vaccination was also offered to 13-26. Therefore, for accuracy of Gardasil indication we evaluate the participants regarding their age, sex, and Gardasil prescribing intention based on the mentioned guidelines criteria.

Accurate Gardasil dosage and administration was defined as three doses of Gardasil within correct intervals according to FDA and ACIP guidelines. Frequency of correct administration was reported based on the approved protocols; there should

be 1 to 2 months between first and second administration of vaccine, 4 months between second and third administration and minimum interval of 6 months between first and third administration.

The individuals were categorized regarding the adherent to the guidelines and their amount of payment was compared to identify the amount of total paid out expenditure in inaccurate practices. Guideline adherence was defined as prescribing Gardasil for correct age range and indication with accurate dosage and administration.

Finally correlation between physician specialty and patient educational level within correct or incorrect prescription indications was evaluated.

Statistical methods

Descriptive statistics were shown by using frequency (percent) for qualitative variables and mean (\pm SD) for quantitative variables. In analytic phase, evaluation of relation between categorical variables was performed by using Chi square test. *P*-values less than 0.05 were considered as significant.

Results

A total of 566 participants filled out the questionnaire. Most of participants were female and their age ranged between 9 to 68 years old with mean age of 28.1 (\pm 6.68). Table 1 represents patients' demographic and medical information.

Underlying diseases were reported in 22 patients as follows: asthma ($n = 10$), multiple sclerosis ($n = 7$), autoimmune disease ($n = 4$), organ transplantation ($n = 3$), and rheumatoid arthritis ($n = 1$).

Gardasil were mostly prescribed for prophylaxis by gynecologists (53.0%) and in 3 doses. Details about prescription characteristics are shown in Table 2.

Information about prescribed doses of Gardasil was documented for 493 consumers. Of these participants, 459 (93.1%) had three prescribed doses, which 379 (82.6%) of them were informed correctly about dose intervals.

We categorized some of participants and prescriptions characteristics based on Gardasil indication in Table 3. In incorrect indication

Table 1. Patient’s demographic and medical information.

Patients characteristic	N (%)
Age	
>26	292 (51.6)
9-26	206 (36.4)
Unanswered	68 (12.0)
Sex	
Male	92 (16.3)
Female	466 (82.3)
Unanswered	8 (1.4)
Educational level	
BS and Above the BS	380 (67.1)
lower than BS	120 (21.2)
Unanswered	66 (11.7)
Underlying disease	
Positive	22 (3.9)
Negative	544(96.1)
PCR test result*	
Negative	31(6.7)
Positive for one of vaccine subtypes**	67(14.4)
Positive all four types in a case	0
Positive other types***	24(5.2)
Not available	39(8.4)
No PCR	221(47.4)
Unanswered	84(18)
Awareness of routine Pap test checkup*	
Yes	183(39.3)
No	182(39.1)
Do not know	101(21.7)
Pregnancy*	
Positive	4 (0.9)
Negative	343 (73.6)
Unanswered	119 (25.5)
Lactation*	
Positive	6 (1.3)
Negative	333 (71.5)
Unanswered	127 (27.2)
Total	566

* PCR test result, Pregnancy, Lactation and Contraceptive method were reported only in females (N = 466), **subtypes 6 or 11 or 16 or 18, *** There are 13 persons which have other types in addition to one of vaccine subtypes.

Table 2. Gardasil prescription characteristics.

Prescription characteristics	N (%)
Indication	
Correct (Prophylaxis)	348 (61.5)
Incorrect (Treatment)*	168(29.7)
Don't know	29 (5.1)
Unanswered	21 (3.7)
Interval	
Correct	432(76.3)
Incorrect	89(15.7)
Unanswered	45(8)
Prescribed dose	
3 doses	459(81.1)
Other	34(6)
Unanswered	73(12.9)
Physician specialty**	
Gynecologist	300(53.0)
Dermatologist	82(14.5)
Urologist	16(2.8)
Infectious disease specialists	14(2.5)
Other	35(6.2)
Unknown	119(21)
Total	566

*45 person claimed to receive vaccine for both Prophylaxis and Treatment, **Specialties with more than 10 prescriptions in the study.

group (treatment), 168 participants ranged between 17 to 68 years old (29.1 ± 6.8) and in correct indication category (prophylaxis), 348 participants ranged between 9 to 50 years old (28 ± 6.7) and in both groups they were mostly female. More details are provided in Table 3.

About 206 (36.4%) participants aged between 9-26 years and 348 (61.5%) interviewees were received Gardasil for prophylaxis indication. By putting these findings together, Gardasil practice was concordant to the guidelines for 128 (22.6%) participants. Among them 80 (14.1%/566 participants) have accurate Gardasil dosage

and interval administration (guideline adherent participants).

Patients' out of pocket payment in guidelines adherent users (80; 14.1%) was 6*108 IRR which was a seventh of total costs obtained from 566 consumers (some costumers did not received 3 doses). From 470 participants who answered to the impact of the insurance coverage in Gardasil uptake, 370 (78.7%) stated that insurance coverage can have a positive impact on Gardasil utilization.

Gynecologists prescribed for prophylaxis significantly higher than other specialties (191 Out of 300; 63.7% and $p = 0.01$). We

Table 3. Patient and prescription characteristic based on the Gardasil indications.

Characteristic	Correct indication	Incorrect indication [€]	Do Not know	Not answered
Age				
>26	181(32)	86(15.2)	17(3)	8(1.4)
9-26	128(22.6)	63(11.2)	8(1.4)	7(1.2)
Unknown	39(6.9)	19(3.4)	4(0.7)	6(1.1)
Sex				
Male	43(7.6)	41(7.3)	4(0.7)	4(0.7)
Female	302(53.4)	123(21.7)	25(4.4)	16(2.8)
Unknown	3(0.5)	4(0.8)	0	1(0.2)
Educational level				
BS and Above the BS	239(42.2)	116(20.5)	11(1.9)	14(2.5)
lower than BS	75(13.3)	30(5.3)	13(2.3)	2(0.4)
Unknown	34(6)	23(3.9)	5(0.9)	5(0.9)
Prescribed dose				
3 doses	285(50.4)	144(25.5)	17(3)	12(2.1)
Other	22(3.9)	10(1.8)	1(0.2)	1(0.2)
Unknown	42(7.4)	14(2.5)	11(1.9)	7(1.2)
Interval				
Correct	272(48.1)	133(23.5)	17(3)	10(1.8)
Incorrect	53(9.4)	26(4.6)	5(0.9)	5(0.9)
Unknown	23(4.1)	9(1.6)	7(1.2)	6(1.1)
Physician specialty [¥]				
Gynecologist	191(33.7)	82(14.4)	16(2.8)	11(1.9)
Dermatologist	41(7.2)	36(6.3)	3(0.5)	2(0.4)
Urologist	11(1.9)	9(1.6)	0	1(0.2)
Infectious disease specialists	8(1.4)	6(1.1)	0	0
Other	27(4.8)	2(0.4)	0	1(0.2)
Unknown	70(12.4)	33(5.8)	10(1.8)	6(1.1)
PCR-test result (female=466)				
Negative PCR	24(5.2)	3(0.6)	3(0.6)	1(0.2)
Positive type 6	14(3)	18(3.9)	1(0.2)	2(0.4)
Positive type 11	5(1.1)	6(1.3)	0	0
Positive type 16	8(1.7)	7(1.5)	2(0.4)	1(0.2)
Positive type 18	1(0.2)	2(0.4)	0	0
Positive all four types	0	0	0	0
Positive other types*	16(3.4)	6(1.2)	0	2(0.4)
PCR result not available	18(3.9)	16(3.5)	5(1.1)	0
No PCR	166(35.6)	42(9)	8(1.7)	5(1.1)
Unknown	50(10.7)	23(4.9)	6(1.3)	5(1.1)
Awareness/knowledge Pap test (female=466)				
Yes				
No	124(26.6)	48(10.3)	7(1.5)	4(0.9)
Unknown	120(25.8)	47(10)	11(2.3)	4(0.9)
	58(12.4)	28(6)	7(1.5)	8(1.7)
Total	348	168	29	21

[€] 45 person claimed to receive vaccine for both Prophylaxis and Treatment, [¥] Specialties with more than 10 prescriptions in the study *other types; 31,35,39,40,43,44,45,51,52,53,55,56,58,66,67,68,82

didn't found any significant correlation between patient's education level and Gardasil prophylaxis indication based on above mentioned guidelines ($p = 0.95$).

Discussion

In this study we have evaluated the Gardasil utilization among its recipients which Gardasil was prescribed for them by any healthcare professional. We found out that a large number of prescribed Gardasil were out of the specified age range and did not comply with the approved indication. Hence, large amounts of money are wasted due to non-adherent to guideline.

Gardasil is indicated for cancer prophylaxis in both male and female aged 9 to 26 years old (6, 13). In 124 countries vaccination against HPV is part of the national immunization program (5). The recommended vaccination age varies from 9 to 14 for both boys and girls (5, 6, 14). In our study, only about 14 recipients (2.5%) fall in this range. So, in fact, in Iran Gardasil is not administered in recommended beginning age of vaccination and is shifted towards the older ages.

Regardless of the beginning age of vaccination, for the best result, Gardasil should be administered before possible HPV exposure via sexual intercourse (15, 16). The efficacy of vaccination among those who sexually are active is expected to be lower (16), but it is recommended that they follow the age-based guidelines (17). Gardasil is not approved for use in older than 26 years {F., 2014 #32}(6). It has been reported by most studies in the United States that HPV prevalence after 25 would decrease (15). In Iran, also Shafaghi *et al.* found a peak of HPV incidence in women aged 18-25, and a decrease when they get older (18). In our study more than half of the recipients are older than 26 years old (52%). So, based on our result, prescribers practice is not acceptable by considering the beginning and the final recommended age for vaccination.

Another important consideration in vaccine administration is the intended indication. Quadrivalent vaccine (Gardasil) is indicated for prevention of HPV-associated anogenital diseases (6, 17, 19, 20). It is not recommended

for active external genital lesions and cancers treatment (1, 17, 21, 22). In our study, about 30% of recipients claimed to receive vaccine for wrong indication (treatment) of the presented lesion without receiving any of Gardasil doses before the infection. As previously mentioned, it is best to take the vaccine even before that recipient expose to the risk of HPV infection due to sexual activity not after infection (15, 16). Based on our findings, prescribers are not fully in compliance with the suggested indication by the guidelines.

Pregnancy/lactating and patient underlying disease are the areas that doctors should pay more attention due to the lack of effectiveness or safety evidence. In the present study, only 4 and 6 females respectively were pregnant or lactating. Gardasil Safety has not been established in these specific groups (13). Although they were few, but still should be considered as a problem especially during pregnancy. Twenty two patients had an underlying disease which might diminish response to Gardasil, naturally or due to the consumed drugs. These include Immunosuppressive therapies in immunocompetent persons and or immunocompromised patients (6). It seems that informing prescribers in this regard can be useful.

In our study, we also found that 50% of respondents were not informed by their healthcare professionals that they should do their Pap smear, routinely afterward. This is important for patient to know that vaccination is not an alternative for routine cervical cancer screening, since there are several HPV types which are not covered or prevented by Gardasil (6, 14, 16, 18).

We found that gynecologists prescribed the right indication significantly more than other specialists, whereas in Dempsey *et al.* study pediatrician and family physician significantly chose eligible recipients more than gynecologist (23). However, in our study only 6 pediatricians and 6 GPs were among prescriber.

The frequency of received dose and their interval is also important in the success of vaccination. There is not enough evidence to support less than 3 doses vaccine efficacy (14). It has been stated that adolescents out

of trials have lower immunity to HPV than those participated in clinical trials due to their lack of compliance to the vaccination schedule (6, 24). This non-adherence could be in the forms of not receiving vaccine at all or receiving it in other than suggested times (14, 24).

In most of the studies the rate of uptake is reported as an indicator for adherence of target group to vaccination (9, 11). Since the subject here is prescriber practice, instead of uptake rate, we assessed the number of doses prescribed by prescriber and the information about the dose intervals which should be given to the patient. In our study, most participants received 3 doses and stated the correct interval within vaccine administration as well. So it seems that prescribers are aware of the Gardasil dosage and interval administration.

Khatibi *et al.* which assessed cost effectiveness of Gardasil in Iran, stated that in current situation of Iran, Gardasil vaccination is not cost-effective (5). Yet Gardasil sale in Iran in a period of 5 years (March 2011 till March 2015) started from 1,250 vials in first year and reached to 23,500 vials in last year based on available data of Iran pharmaceutical wholesale data (provided by Food and Drug department of the I.R. Iran Ministry of Health). As reported by other studies high cost of Gardasil has been mentioned in several studies as vaccination barrier (11, 14, 24, 25). The abovementioned data represents Gardasil sales situation while it is not insured by Iran public health insurance and only for those who has private health insurance its expenses might be partly covered by the contractor. So, as most of our participants answered, the insurance coverage would have a positive impact on Gardasil uptake and utilization, and in our case, its irrational utilization.

Based on our study, by considering the correct indication in correct age group with correct frequency of doses and intervals as appropriate prescribing; Gardasil is prescribed appropriately according to the guidelines only in 14.1% cases (6). The money which is spent by this group for Gardasil vaccination is about 6*10⁸ IRR which was a seventh of total costs obtained from all 566 consumers. This means that about 85% of the money spending on Gardasil is wasted due

to one of the following reason; wrong age, wrong indication, wrong frequency, or wrong interval.

Conclusion

Our study provides a picture of Gardasil utilization situation in Iran. Based on our findings, prescribers' practice for administering Gardasil is obviously not appropriate, since only about 14% is prescribed according to guidelines. This wrong practice imposes burdensome cost to community and government. According to Gardasil growing rate of use, this cost expected to be increased. The underlying reasons for this behavior cannot be extracted by this study and there are uncertainties about it. But, we are certainly in urgent need for appropriate interventions and supervision in National level to regulate Gardasil consumption.

Acknowledgement

This study was supported by grant number 27887-156-04-93 of the Deputy of Research in Tehran University of Medical Sciences.

References

1. Harper DM, Vierthaler SL and Santee JA. Review of gardasil. *J. Vaccines. Vaccin.* (2010) 1: 107.
2. Gizzo S, Noventa M and Nardelli GB. Gardasil administration to hr-HPV-positive women and their partners. *Trends. Pharmacol. Sci.* (2013) 34: 479-80.
3. Khorasanizadeh F, Hassanloo J, Khaksar N, Taheri SM, Marzaban M, Rashidi BH, Sari AA and Zendehtdel K. Epidemiology of cervical cancer and human papilloma virus infection among Iranian women - analyses of national data and systematic review of the literature. *Gynecol. Oncol.* (2013) 128: 277-81.
4. Franco EL and Harper DM. Vaccination against human papillomavirus infection: a new paradigm in cervical cancer control. *Vaccine.* (2005) 23: 2388-94.
5. Khatibi M, Rasekh HR, Shahverdi Z and Jamshidi HR. Cost-effectiveness evaluation of quadrivalent human papilloma virus vaccine for hpv-related disease in Iran. *Iran. J. Pharm. Res.* (2014) 13: 225-34.
6. Markowitz LE, Dunne EF, Saraiya M, Chesson HW, Curtis CR, Gee J, Bocchini Jr JA and Unger ER. Human Papillomavirus Vaccination

- Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Recomm. Rep.* (2014) 63(RR-05): 1-30.
7. Kirby T. FDA approves new upgraded Gardasil 9. *Lancet. Oncol.* (2015) 16: e56.
 8. Braaten KP and Laufer MR. Human Papillomavirus (HPV), HPV-Related Disease, and the HPV Vaccine. *Rev. Obstet. Gynecol.* (2008) 1: 2-10.
 9. Jalilvand S, Shoja Z, Nourijelyani K, Tohidi HR and Hamkar R. Meta-analysis of type-specific human papillomavirus prevalence in Iranian women with normal cytology, precancerous cervical lesions and invasive cervical cancer: Implications for screening and vaccination. *J. Med. Virol.* (2015) 87: 287-95.
 10. Castellsague X, de Sanjose S, Aguado T, Louie KS, Bruni L, Munoz J, Diaz M, Irwin K, Gacic M, Beauvais O, Albero G, Ferrer E, Byrne S and Bosch FX. HPV and Cervical Cancer in the World: 2007 Report. *Vaccine* (2007) 1: C1-C230.
 11. Mazza D, Petrovic K, Grech C and Harris N. HPV vaccination in women aged 27 to 45 years: what do general practitioners think? *BMC. Women. health.* (2014) 14: 91.
 12. Dempsey AF and Patel DA. HPV vaccine acceptance, utilization and expected impacts in the US: Where are we now? *Hum. Vaccin.* (2010) 6: 715-20.
 13. Highlights of prescribing information, available at <https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/pprovedproducts/ucm111263.pdf>. date of access data: 4.29.2017.
 14. Fagot J-P, Boutrelle A, Ricordeau P, Weill A and Allemand H. HPV vaccination in France: uptake, costs and issues for the National Health Insurance. *Vaccine* (2011) 29: 3610-6.
 15. Dunne EF, Markowitz LE. Genital human papillomavirus infection. *Clin. Infect. Dis.* (2006) 43: 624-9.
 16. Insinga RP, Dasbach EJ, Allen SE, Carides GW and Myers ER. Reductions in Human Papillomavirus-Disease Resource Use and Costs with Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) Recombinant Vaccination: The FUTURE Study Economic Evaluation. *Value Health* (2008) 11: 1022-32.
 17. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, Tang GW, Ferris DG, Steben M, Bryan J, Taddeo FJ, Railkar R, Esser MT, Singhs HL, Nelson M, Boslego J, Sattler C, Barr E and Koutsky LA. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N. Engl. J. Med.* (2007) 356: 1928-43.
 18. Shafaghi B, Jarollahi A, Yousefzadeh B, Ameri A, Moghadam S and Mostafavi M. Human Papilloma Virus Prevalence and Types among Iranian Women Attending Regular Gynecological visits. *Rep. Radiothe. Oncol.* (2013) 1: 73-79.
 19. Brotherton JM, Gertig DM, May C, Chappell G and Saville M. HPV vaccine impact in Australian women: ready for an HPV-based screening program. *Med. J. Aust.* (2016) 204: 184-184e1
 20. Bryan JT, Buckland B, Hammond J and Jansen KU. Prevention of cervical cancer: journey to develop the first human papillomavirus virus-like particle vaccine and the next generation vaccine. *Curr. Opin. Chem. Biol.* (2016) 32: 34-47.
 21. Villa J, Muñoz N, Perez G, Krüger Kjaer S, Paavonen J, Lehtinen M, Sigurdsson K, Hernandez-Avila M, Iversen OE, García P, Majewski S, Tay EH, Bosch FX, Dillner J, Olsson SE, Ault K, Brown D, Ferris D, Koutsky L, Kurman R, Myers E, Barr E, Bryan J, Boslego J, Esser M, Hesley T, Lupinacci L, Railkar R, Saah A, Sattler C, Taddeo F, Thornton A and Vuocolo S. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. *J. Infect. Dis.* (2007) 196: 1438-46.
 22. Medeiros LR, Rosa DD, da Rosa MI, Bozzetti MC and Zanini RR. Efficacy of human papillomavirus vaccines: a systematic quantitative review. *Int. J. Gynecol. Cancer.* (2009) 19: 1166-76.
 23. Dempsey A, Cohn L, Dalton V and Ruffin M. Patient and clinic factors associated with adolescent human papillomavirus vaccine utilization within a university-based health system. *Vaccine* (2010) 28: 989-95.
 24. Kessels SJ, Marshall HS, Watson M, Braunack-Mayer AJ, Reuzel R and Tooher RL. Factors associated with HPV vaccine uptake in teenage girls: a systematic review. *Vaccine* (2012) 30: 3546-56.
 25. Gerend MA, Shepherd MA and Shepherd JE. The multidimensional nature of perceived barriers: Global versus practical barriers to HPV vaccination. *Health Psychol.* (2013) 32: 361-9.