

Human papillomavirus vaccine efficacy in the prevention of anogenital warts: systematic review and meta-analysis

Romina A Tejada, MD, MSc,⁽¹⁾ Kris G Vargas, MD, MHS,⁽²⁾ Vicente Benites-Zapata, MD, MSc,⁽³⁾
Edward Mezones-Holguín, MD, MSc,^(4,5) Rafael Bolaños-Díaz, MD, MSc,^(1,6) Adrián V Hernández, MD, PhD.^(5,7)

Tejada RA, Vargas KG, Benites-Zapata V, Mezones-Holguín E, Bolaños-Díaz R, Hernández AV. Human papillomavirus vaccine efficacy in the prevention of anogenital warts: systematic review and meta-analysis. *Salud Publica Mex* 2017;59:84-94.

<http://dx.doi.org/10.21149/7824>

Tejada RA, Vargas KG, Benites-Zapata V, Mezones-Holguín E, Bolaños-Díaz R, Hernández AV. Eficacia de la vacuna contra el virus del papiloma humano en la prevención de verrugas anogenitales: revisión sistemática y metanálisis. *Salud Publica Mex* 2017;59:84-94.

<http://dx.doi.org/10.21149/7824>

Abstract

Objective. To review evidence on the efficacy of HPV vaccines in the prevention of non-cancer lesions (anogenital warts [AGW], recurrent laryngeal papillomatosis and oral papillomatosis). **Materials and methods.** We conducted a systematic review of randomized trials. We performed random effect models and effects were reported as relative risks (RR) and their confidence intervals (95%CI) following both intention to treat (ITT) and per protocol (PP) analyses. **Results.** We included six studies (n=27 078). One study was rated as high risk of bias. One study could not be included in the meta-analysis because it provided combined results. We found that quadrivalent vaccine reduced the risk of AGW by 62% (RR: 0.38, 95%CI:0.32-0.45, I2:0%) in the ITT analysis and by 95% (RR: 0.05, 95%CI:0.01-0.25, I2:66%) in the PP analysis. Subgroup analyses of studies in women or with low-risk of bias provided similar results. **Conclusion.** HPV quadrivalent vaccine is efficacious in preventing AGW in men and women.

Keywords: Papillomavirus vaccines; *Condyloma acuminata*; papillomatosis; meta-analysis

Resumen

Objetivo. Revisar la evidencia sobre la eficacia de las vacunas contra el virus del papiloma humano en la prevención de lesiones no oncológicas (verrugas anogenitales [VAG], papilomatosis recurrente respiratoria y papilomatosis oral). **Material y métodos.** Realizamos una revisión sistemática de ensayos clínicos aleatorizados. Empleamos modelos de efectos aleatorios, calculando riesgos relativos (RR) y sus intervalos de confianza al 95% (IC95%), utilizando el análisis por intención a tratar (ITT) y por protocolo (PP). **Resultados.** Seleccionamos seis estudios (n=27 078). Un estudio tuvo alto riesgo de sesgo y otro no fue incluido en el metanálisis. La vacuna cuadrivalente reduce el riesgo de VAG en 62% (RR: 0,38; IC95%:0,32-0,45; I2:0%) en el análisis ITT y en 95% (RR: 0,05; IC95%:0,01-0,25; I2:66%) en el análisis PP. Los análisis de subgrupos (mujeres y estudios con bajo riesgo de sesgo) proporcionaron resultados similares. **Conclusión.** La vacuna cuadrivalente es eficaz en la prevención de VAG en hombres y mujeres.

Palabras clave: vacunas contra apillomavirus; condiloma acuminado; papilomatosis; metanálisis

- (1) Unidad de Análisis y Generación de Evidencias en Salud Pública, Centro Nacional de Salud Pública, Instituto Nacional de Salud. Lima, Perú.
- (2) Department of Epidemiology, Erasmus MC. Rotterdam, Netherlands.
- (3) Centro de Investigación de Salud Pública, Instituto de Investigación, Facultad de Medicina Humana, Universidad de San Martín de Porres. Lima, Perú.
- (4) Intendencia de Investigación y Desarrollo, Superintendencia Nacional de Salud. Lima, Perú.
- (5) School of Medicine, Universidad Peruana de Ciencias Aplicadas. Lima, Perú.
- (6) Organización médica para el desarrollo de la salud. Lima, Perú.
- (7) Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic. Ohio, USA.

Received on: March 3, 2016 • Accepted on: June 10, 2016

Corresponding author: Romina A. Tejada. Unidad de Análisis y Generación de Evidencias en Salud Pública, Centro Nacional de Salud Pública, Instituto Nacional de Salud. Av. Defensores del Morro 2268. Lima, Perú.
E-mail: rtejada@ins.gob.pe

Human papillomavirus (HPV) represents one of the most frequent sexually transmitted infections. There are more than 150 HPV genotypes, which have been grouped according to their oncogenic capacity into high risk and low risk subtypes.¹

Anogenital and respiratory papillomatosis are clinical manifestations of HPV infection caused by low oncogenic risk genotypes. Anogenital warts (AGW) are not only a problem associated with physical discomfort and pain but also with emotional stress,² whose effects may become greater than the physical discomfort.³ These effects include impairments in their sex life, a fear of developing cancer, and worsening of their emotional relationship with their partner.⁴ Thus, the quality of life of those infected with HPV papillomatosis is greatly affected. Furthermore, from the public health standpoint, the estimated cost of treatment of new or recurrent cases of AGW in the United Kingdom is 22.4 million sterling pounds per year.⁵

High incidence of AGW has been reported, ranging from 58 to 319 cases per 100 000 persons/year; with most cases occurring among young women (below 25 years).⁶⁻⁸ These rates may be underestimated because many patients do not seek medical care and go undiagnosed. Recurrent respiratory papillomatosis is less frequent, with an incidence of 0.35-0.38 per 100 000 persons/years.⁶

There are several interventions for the prevention of HPV infection, though none is totally effective. The use of barrier methods, such as condoms, does not eliminate the possibility of HPV infection as there can be injuries in the unprotected epithelium during sex. Vaccination against HPV could be a useful strategy in the prevention of non-oncological diseases.⁹⁻¹⁴ It has been proposed that HPV vaccination could reduce cases of recurrent respiratory papillomatosis, both by decreasing maternal infection during pregnancy and by the passage of vaccine-induced HPV antibodies from the vaccinated mother to the fetus,¹⁵ nevertheless this is still controversial due to lack of evidence.

At the moment of the systematic search there were two vaccines available for HPV: a bivalent vaccine which protects against HPV 16 and 18, and a quadrivalent vaccine further including genotypes 6 and 11. Currently there is a nonavalente vaccine, which also protects against HPV 31/33/45/52/58.^{10,16,17} The HPV vaccine has been proven safe¹⁸⁻²⁰ and is recommended by the US Center for Disease Control and Prevention (CDC), World Health Organization (WHO) and Global Alliance for Vaccines and Immunization (GAVI) among others, for both oncological and non-oncological lesions prevention.²¹⁻²³ HPV vaccine has been integrated into national immunization programs of various countries for the prevention of cervical disease.^{24,25}

Our aim was to summarize the available evidence on the efficacy of HPV vaccines in preventing non-oncological lesions: AGW, recurrent laryngeal papillomatosis and oral papillomatosis.

Materials and methods

We carried out a systematic review of randomized clinical trials (RCTs) following a protocol available upon request to the authors. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for the preparation of this report.²⁶

Systematic search

We conducted a systematic search in seven online databases, without language restrictions: Medline (PubMed), Embase, Cochrane Library, Scopus, LILACS, SciELO and Web of Knowledge, from its inception until August 2013. We also reviewed abstracts presented at conferences from 2007 to August 2013 (American Society of Clinical Oncology [ASCO], European Society of Medical Oncology [ESMO], Infectious Disease Society of America [IDSA], European Society of Clinical Microbiology and Infectious Diseases [ESCMID]) and records of RCTs from the National Institutes of Health (www.clinicaltrials.gov) and Europe (www.clinicaltrialsregister.eu). We finally reviewed the list of references of selected studies to include others which may have been missed in our initial search. We ran the search strategy again in July 2015 and did not find any new articles that met the inclusion criteria.

We developed three search strategies, one for each outcome (oral and respiratory papillomatosis, and AGW), which included both descriptors (MeSH) and free terms, related to HPV vaccination (human papillomavirus vaccine, bivalent human papillomavirus vaccine, quadrivalent papillomavirus vaccine) and outcome (condyloma, AGW, laryngeal papillomatosis, recurrent respiratory papillomatosis, and oral papillomatosis). We included only RCT studies. The search strategies for each database are available in Dataverse (<https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/HCMDYJ>, MD5: 6fc48d4df57678d60bdf71f8f598a739).²⁷ Summaries of conferences and references of selected articles were reviewed manually to find abstracts that met the selection criteria.

Selection of studies

We included RCTs which assessed the efficacy of HPV vaccines in preventing non-cancerous lesions. Among

the components of the research question (population, intervention, control, outcome)²⁸ we considered both male and female participants. Age or other demographic characteristic were not considered as limits. The intervention arm consisted of HPV vaccine (bivalent or quadrivalent) at any dose and schedule, whereas comparison group consisted was placebo or another vaccine. We also considered three possible outcomes: AGW, recurrent laryngeal papillomatosis and oral papillomatosis. In vitro studies, animal models and therapeutic studies were excluded.

We combined all three search results through the software EndNote basic (Thomson Reuters [Scientific] Inc., New York, NY, USA) eliminating repeated publications. After reading titles and abstracts, two authors independently selected articles that met the inclusion criteria. Cases of disagreement were resolved by consensus, and if necessary with the help of a third author. The same authors independently selected studies to be included in the quality assessment, after reading full text. Again, cases of discrepancies were resolved by consensus, and if necessary with the help of a third author.

Risk of bias assessment

We carried out a risk of bias assessment using tools proposed by Cochrane for RCTs.²⁸ This tool assesses the risk of bias for each study based on seven domains: generation of the randomization sequence, allocation concealment, blinding of participants and study personnel, blinding of persons responsible for measuring outcomes, incomplete information on outcomes, selective reporting and other potential biases. Two authors independently assessed the risk of bias; discrepancies were resolved with the help of a third author when consensus could not be achieved.

Data extraction

Two authors independently performed data extraction. We included information on RCTs phase, number of centers, and number of countries included. Period of enrollment, follow-up time, percentage loss per group and source of funding were also collected. Among the criteria for selection of participants, we collected information on gender, age, number of sexual partners, and exclusion criteria. Regarding the intervention and comparison, we collected information on its components, adjuvants, and the administration schedule. Finally, information on the primary and secondary outcomes of each study and the populations for efficacy analysis were collected both for

intention to treat (ITT) and per protocol (PP) analyses. Cases of disagreement were resolved by consensus and with the help of a third author when necessary.

Data analysis

Where studies were sufficiently similar in relation to the population and the intervention as well as follow-up times, the management of the participants and the measurement of outcomes, we carried out a meta-analysis to assess the clinical efficacy of HPV vaccines in the prevention of non-oncological lesions. Outcomes were measured dichotomously (presence or absence of non-oncological lesions) in each group. We used random effects model, with inverse variance method. We calculated the relative risk (RR) and their respective intervals 95% confidence, both for ITT and PP analyses. We also carried out subgroup analysis according to gender, and risk of bias assessment.

Sources of heterogeneity were considered and described in this review. We calculated the Cochrane Q test and Higgins I² statistic with a 95% confidence interval for assessment of the degree of heterogeneity between studies.²⁸ We used STATA version 12.0 (StataCorp LP, College Station, Texas, USA) for analysis.

Assessment of publication bias

We evaluated the presence of publication bias using the funnel plot graph and Egger's test.²⁹

Results

We identified 1 599 references, of which 448 were repeated. After reading titles and abstracts we excluded 1 131 articles, mostly because they were not related to HPV vaccines, were not RCTs or did not study the outcomes of interest. We excluded 14 studies after reading full text reports because they were pooled analyses of RCTs, interim analyses, did not evaluated the outcome of interest, did not have results, were narrative reviews or comments on RCTs (figure 1). Finally, we included the remaining six studies that evaluated the efficacy of HPV vaccine and our outcomes of interest.^{10,30-34} In the case of Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE II) study we included two reports of pooled analysis (with FUTURE I study) as data was not provided individually for AGW.^{11,35} All selected studies corresponded only to the quadrivalent vaccine. No studies reported on the efficacy of HPV vaccines on respiratory or oral papillomatosis.

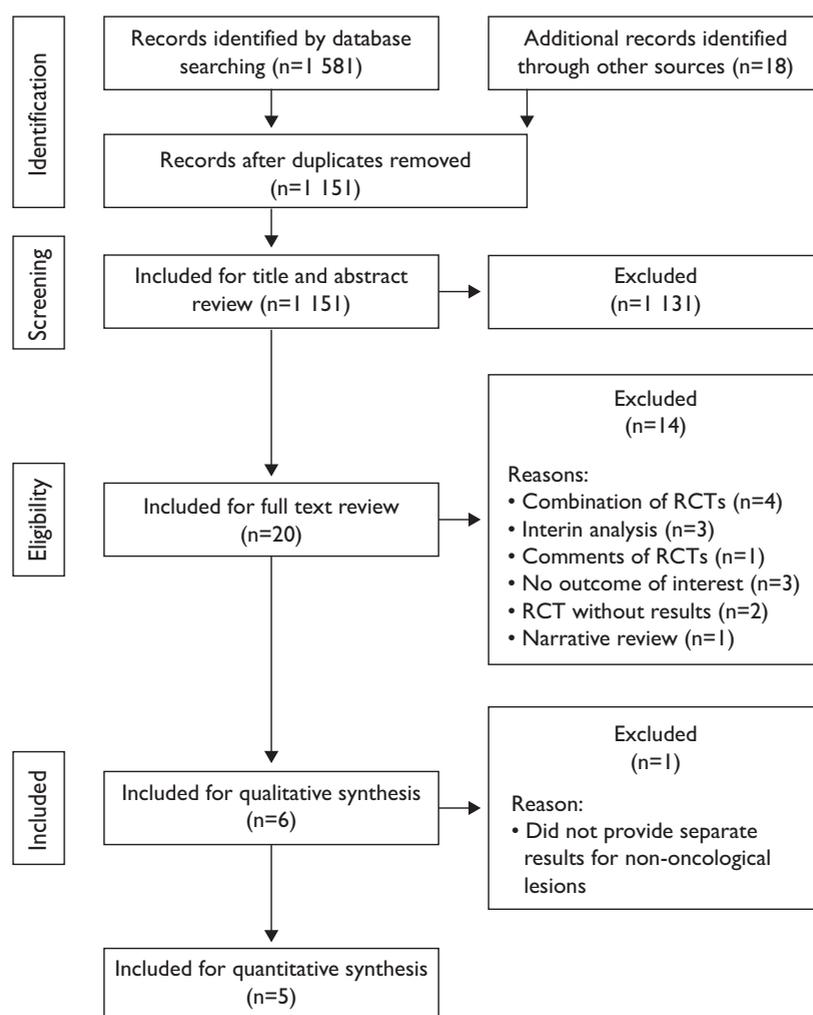


FIGURE I. FLOWCHART OF SELECTED STUDIES. LIMA, PERÚ, 2014

Characteristics of included studies

A total of 27 079 participants were enrolled. All studies were double-blind, phase II or III, multicenter and conducted in adults (table I). Five studies included women^{10,30,31,33,34} and one study included men.³² Participants had no current or prior history of anogenital lesions, and in the case of women, they had no current or previous history of cervical lesions, were not pregnant and should use birth control methods during the study. Follow-up times varied between 26 and 60 months. All studies used a quadrivalent vaccine composition of 20/40/40/20 μ g + 225mg of amorphous aluminum hydroxyphosphate sulfate (AAHS) in the intervention group and 225mg AAHS in the placebo group. Villa and

colleagues also considered two different compositions of the vaccine (40/40/40/40 and 80/80/40/80mg) and a different doses of placebo (450mg AAHS) in the first stage of the study.³⁰

Most studies had follow-up periods between 26 and 36 months, except for one study that had a follow-up period of 60 months. However, only 56.3% of women were enrolled in the extended follow-up phase (37-60 months), and groups were not comparable in percentage and reasons of loss of follow-up during this second phase of the study.³⁰

Per-protocol analysis included population who were seronegative and had negative results in HPV-DNA test for the genotypes included in the vaccine at enrollment, received three doses of either vaccine or

Table I
CHARACTERISTICS OF INCLUDED STUDIES

	Villa et al (2006) ³⁰	Garland et al (2007) ¹⁰	Future II (2007) ³⁴	Giuliano et al (2011) ³²	Castellsagué et al (2011) ³¹	Yoshikawa et al (2013) ³³
Design characteristics						
Study phase	II	III	III	III	III	II
Age, media (SD)	I: 20.2 (1.7) P: 20.0 (1.7)	I: 20.2 (1.8) P: 20.3 (1.8)	I: 20.0 (2.2) P: 19.9 (2.1)	20.5 (2.0)	34.3 (6.3)	I: 22.7 (2.1) P: 22.9 (2.1)
Number of centers	>1	62	90	71	38	≥1
Number of countries	5	16	13	18	7	1
Enrollment period	05/2000 -¿?	01/2002-03/2003	06/2002 - 05/2003	3/09/2004 - 29/08/2008	18/06/2004 - 30/04/2005	NS
Follow-up (months)	60	36	36	36	48	30
Loss of follow-up	43.7% enrolled in follow-up phase I: 3,5% y P: 9,5%	ITT no losses PP I: 17% y P: 16,6%	ITT no losses; PP I: 12.8% y P: 13.5%	ITT I: 2.4% P: 4.7%	ITT I: 5% P: 4.4%; PP I: 17.4% P: 17%	I: 15.1% P: 16.4%
Selection criteria						
Age (years)	16-23	16-24	15-26	16-26	24-45	18-26
Number of sexual partners	≤4	≤4	≤4	≤5	No restriction	≤4
Exclusion criteria	Pregnancy, history of abnormal cervical cytology or genital warts	Pregnancy, history of cervical disease or genital warts	Pregnancy, abnormal cervical cytology at enrollment	STDs, vaccination in the last 21 days, history of severe allergic reaction, immune or coagulation disorders, having received Ig or blood products and drug abuse and being enrolled in studies that collected genital specimens	Pregnancy, history of cervical disease or genital warts, cervical biopsy in the past 5 years, immune disease	Pregnancy, history of abnormal cervical cytology
Vaccine and control characteristics						
Vaccine	20/40/40/20µg VLP + 225mg AAHS	20/40/40/20µg VLP + 225mg AAHS	20/40/40/20µg VLP + 225mg AAHS	20/40/40/20µg VLP + 225mg AAHS	20/40/40/20µg VLP + 225mg AAHS	20/40/40/20µg VLP + 225mg AAHS
Control	Placebo + 225mg or 450mg AAHS	Placebo + 225mg AAHS	Placebo + 225mg AAHS	Placebo + 225mg AAHS	Placebo + 225mg AAHS	Placebo + 225mg AAHS
Outcome						
Primary	Combined outcome: persistent infection, cervical, anogenital or vaginal lesions associated with HPV 6,11,16,18	AGW, cervical, anogenital or vaginal lesions or cancer associated with HPV 6,11,16,18	Cervical lesion grade 2 or greater associated with HPV 16,18	External genital lesions associated with HPV 6,11,16,18 and severe adverse events	Combined outcome: persistent infection, CIN, VIN, VaIN, AIN, gynecological cancer, and AW associated with 1) HPV 6,11,16,18 or 2) HPV 16, 18. Adverse events.	Combined outcome: persistent infection, NIC, VIN, VaIN, AIN, gynecological cancer, and AW associated with HPV 6,11,16,18
Secondary	NS	NS	Persistent infection, CIN grade 1, VIN, VaIN, and AGW	Persistent infection associated with HPV-6,11,16,18	Combined outcome: persistent infection, CIN, VIN, VaIN; AIN, gynecological cancer, and AW associated with HPV 6,11	Adverse events
Analysis						
Per protocol analysis	Women negative to HPV 6,11,16,18 until the 7th month, who received 3 doses and followed protocol	Women negative to HPV until the 7th month, who received 3 doses within a year time, had at least 1 follow-up visit, and followed protocol	Women negative to HPV 16/18 until the 7th month, who received 3 doses within a year time, and followed protocol	Men negative to HPV until the 7th month, who received 3 doses, had at least 1 follow-up visit and followed protocol	Women negative to HPV until the 7th month, who received 3 doses, had at least 1 follow-up visit, and followed protocol	Women negative to HPV until the 7th month, who received 3 doses, and followed protocol
Intention to treat analysis	MITT: women negative to HPV at enrollment who received ≥1 doses	Women who received ≥1 doses and had at least 1 follow-up visit	All randomized subjects	Men who received ≥1 doses and had at least 1 follow-up visit	Women who received ≥1 doses and had at least 1 follow-up visit	NS

SD: Standard deviation; I:Vaccine group; P: placebo group; ITT: intention to treat analysis; MITT modified intention to treat analysis; PP: per protocol analysis; NS: not specified; AGW: anogenital warts; STD: sexual transmitted diseases; VLP: Virus-like particles; AAHS: amorphous aluminum hydroxyphosphate sulfate; HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia, VaIN: vaginal intraepithelial neoplasia; AIN: anal intraepithelial neoplasia

placebo, and had no protocol violations. In this analysis, case count began a month after receiving the last dose (7th month). On the other hand, ITT analysis included participants who received at least one dose of either vaccine or placebo, regardless of their infection status at enrollment, case counting began after day one. Villa and colleagues conducted a modified ITT (MITT) analysis in women not infected by HPV strains included in the vaccine on enrollment and who received at least one dose of vaccine or placebo.³⁰

Most studies reported outcomes separately using both ITT and PP analysis, except for the study by Yoshikawa and colleagues where the authors reported a combined outcome for persistent infection or disease caused by HPV, and only for a PP analysis.³³ We were unable to reach the authors for the separate data and therefore, this study could not be included in the meta-analysis.

HPV vaccines efficacy in AGW

Intention to treat analysis

We found some sources of heterogeneity between studies due to population characteristics, for example age at enrollment, genre, and number of previous sexual partners, as well as sample sizes which varied from 552 to 12 167. Other sources of heterogeneity were percentage of loss to follow-up, which was high and different between groups in a study, and time between visits which varied between 6 and 12 months. All studies had similar protocols in the composition and administration of the vaccine, as well as in assessing outcomes; thus, we consider that differences in subject's characteristics were a probable cause of heterogeneity. Consequently, we used a random effects model and carried-out sub-analysis in studies that only included women. Incidence of AGW in the intervention group was lower compared with the placebo group (1.28 vs 3.40%). Quadrivalent vaccine reduced the risk of AGW associated to HPV 6/11/16/18 by 62% (RR: 0.38, 95%CI: 0.32-0.45, I²: 0%) as shown in figure 2. No differences were observed when we included only studies conducted in women (RR 0.39, 95%CI: 0.32 to 0.47, I² = 0%) or low risk of bias (RR: 0.38, 95%CI 0.32 -0.45, I² = 0%).

Per protocol analysis

Quadrivalent HPV vaccine reduced the relative risk of AGW associated to HPV 6/11/16/18 in 95% (RR: 0.05, 95%CI: 0.01-0.25, I²: 66%) as shown in figure 3. No differences were observed when we only included studies conducted in women (RR: 0.03; 95%CI: 0.01-0.18; I² =

43%) or with low risk of bias (RR: 0.04; 95%CI: 0.01-0.27; I² = 75%)

Publication bias

No publication bias was observed in the analysis, with an Egger coefficient of 0.082 (95%CI: -1.348 to 1.185; p=0.808).

Assessment of risk of bias

Only one study³⁰ was rated as high risk of bias (table II). Randomization of patients and appropriate concealment of randomization were carried out in all studies as well as blinding of both participants and staff conducting evaluations. Villa and colleagues had unequal losses among research groups during their follow-up (3.5% in the vaccine group and 9.5% in the placebo group), which was considered as high risk of bias. In the domain of selective reporting, Yoshikawa and colleagues received an undetermined risk qualification because, although the analysis was performed as specified in the methods section, it was incomplete, presenting only the PP analysis, and as a compound result.³³ Finally, five studies were funded by Merck or the National Institutes of Health, and in one study funding source was not mentioned. In all studies the authors reported receiving funding from a pharmaceutical company.

Discussion

In this systematic review we found that the quadrivalent HPV vaccine is effective in preventing AGW, both in healthy men and women, between ages 15 to 45, with no history of anogenital lesions and no more than five sexual partners. This result was expected as adequate immunogenicity of the quadrivalent vaccine against virus strains 6 and 11 has been previously reported;³¹⁻³⁶ this strains are responsible for 90% of AGW.^{37,38}

Our findings are consistent with those reported previously in two systematic reviews and an observational study.^{19,39,40} Rambout and colleagues found a risk reduction of external genital lesions by 70% in the MITT analysis and by 87% in the PP analysis. However, the authors defined external genital lesions as AGW, vulvar intraepithelial neoplasia, and vaginal intraepithelial neoplasia while we performed an individual analysis for AGW. Also, this review only included two studies while we considered five studies in the meta-analysis.¹⁹ Schiller and colleagues did not carry out a meta-analysis and only reported a pooled analysis from the FUTURE I and II studies, with a risk reduction of 79.5% in the ITT analysis.³⁹ A systematic review of vaccine impact

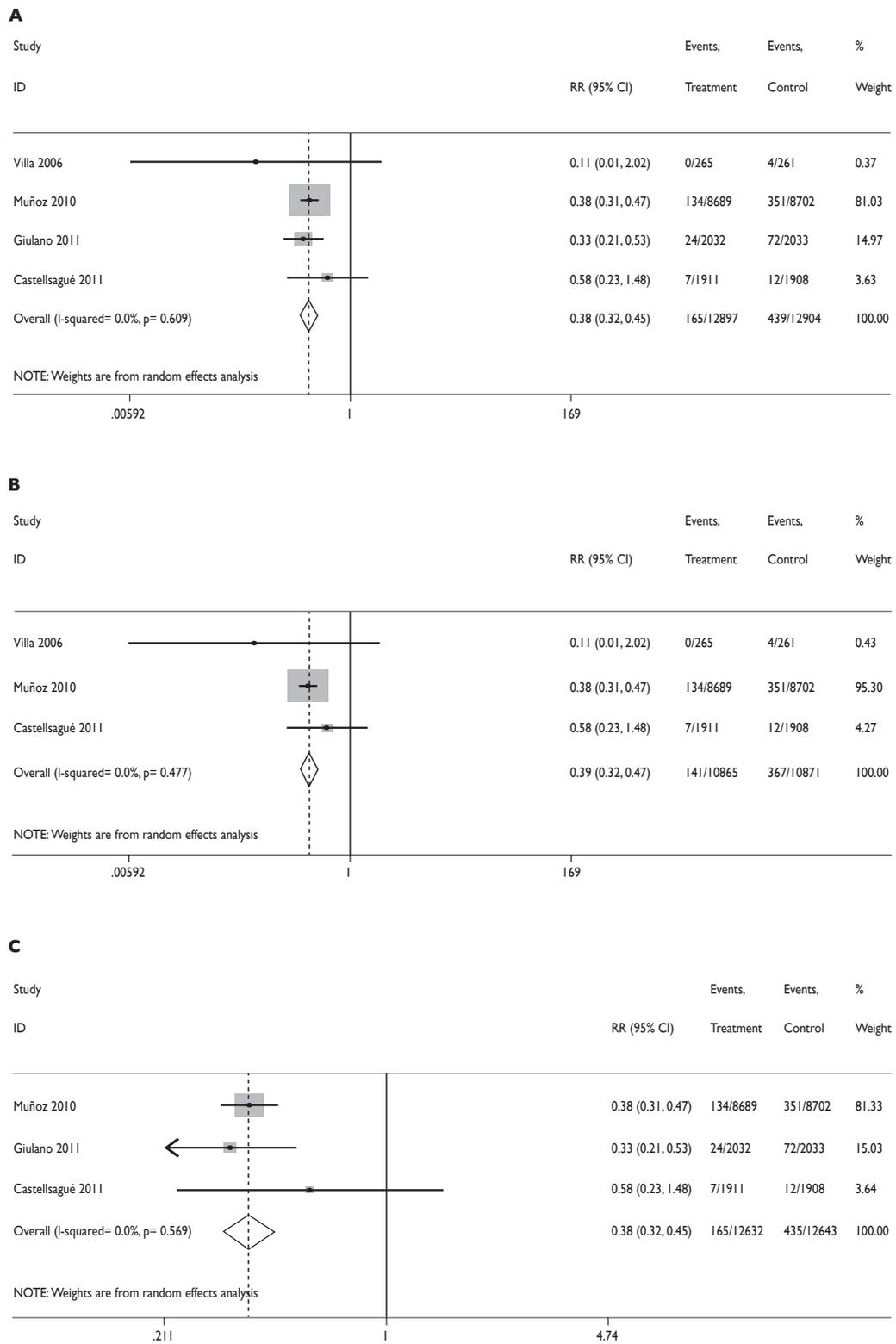


FIGURE 2. FOREST PLOT OF THE EFFICACY OF HPV QUADRIVALENT VACCINE IN THE PREVENTION OF ANOGENITAL WARTS IN THE INTENTION TO TREAT ANALYSIS IN (A) ALL STUDIES, (B) STUDIES IN WOMEN, AND (C) STUDIES WITH LOW RISK OF BIAS. LIMA, PERU, 2014

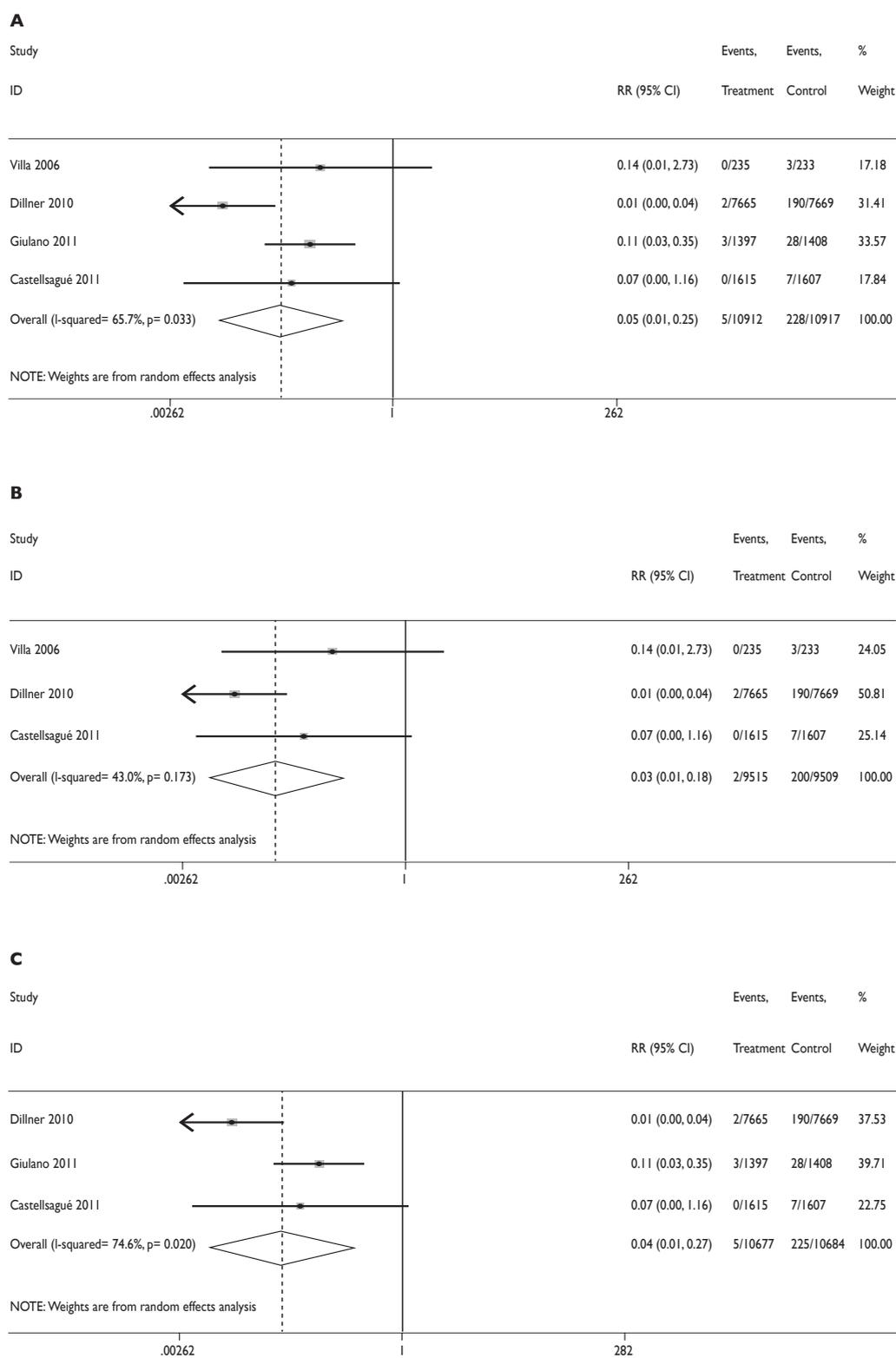


FIGURE 3. FOREST PLOT OF THE EFFICACY OF HPV QUADRIVALENT VACCINE IN THE PREVENTION OF ANOGENITAL WARTS IN THE PER PROTOCOL ANALYSIS IN (A) ALL STUDIES, (B) STUDIES IN WOMEN, AND (C) STUDIES WITH LOW RISK OF BIAS. LIMA, PERU, 2014

Table II
QUALITY ASSESSMENT OF INCLUDED STUDIES

	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Villa <i>et al</i> (2007)	●	●	●	●	●	●	●
Garland <i>et al</i> (2007)	●	●	●	●	●	●	●
Future II (2007)	●	●	●	●	●	●	●
Giuliano <i>et al</i> (2011)	●	●	●	●	●	●	●
Castellsague <i>et al</i> (2011)	●	●	●	●	●	●	●
Yoshikawa <i>et al</i> (2013)	●	●	●	●	●	●	●

in general populations showed a reduction on the incidence of AGW after vaccination.⁴⁰ Also, an observational study after the introduction of the HPV vaccine in the Australian national immunization program also showed a decrease in unvaccinated heterosexual males due to herd immunity.⁴¹

We acknowledge some limitations in this systematic review. We were unable to evaluate the efficacy of HPV vaccines in respiratory and oral papillomatosis as there were no available data. Although one study was rated as high risk of bias, the results were not affected when only studies with low risk of bias were included. Because of the possibility of publication bias in systematic reviews, we also included online records of RCTs, collections of abstracts presented at oncology and infectious diseases scientific conferences and references of selected articles, without language restrictions. Moreover, the Egger test for publication bias was not significant. Therefore we consider that publication bias did not markedly affect our study. However, we should keep in mind that only four articles were included in the meta-analysis and that the Egger test power is low to detect publication bias in this situation. Finally, since the inclusion of HPV vaccine on national immunizations programs, there are many observational studies on its effectiveness in preventing HPV associated diseases that could increase knowledge about its application in populations different from those included in RCTs such as adolescents. Unlike cervical cancer, AGW occurs earlier during HPV infection and can be assessed directly, which makes it an important endpoint for the evaluation of HPV vaccines efficacy.

To the best of our knowledge, no previous meta-analysis has assessed the efficacy of HPV vaccines in AGW. We also believe that we are the first study to carried-out a combined analysis in men and women and not only women, as well to carried-out an analysis taking into consideration the risk of bias. Therefore, we believe our results could be of great utility to help decision makers on the inclusion of HPV vaccines to national immunizations programs. Our results could also be used as efficacy parameters in health economic studies instead of the data from a single clinical trial.

At the time we designed the present review, the Peruvian national immunization scheme included HPV vaccine for 10 years old girls.⁴² However, it did not specify which of the two currently available vaccines should be employed. This review was part of a series of studies, including cost-effectiveness and budget impact studies, to help decision makers design and implement a national HPV vaccination program as well as to choose which vaccine to include. After consideration of available evidence, the Ministry of Health decided to include the quadrivalent vaccine on national immunization program.

Based on our review of the literature, we conclude that quadrivalent vaccine is efficacious in preventing AGW. Despite great breakthroughs on HPV vaccines, there is still much to investigate. We lack information on long term vaccine efficacy, as we only have data up to eight years.²⁰ Finally, HPV vaccine efficacy on recurrent laryngeal papillomatosis and oral papillomatosis associated with HPV have not been evaluated despite their important burden disease.⁴³

Acknowledgment

We thank Dr. Kelika A. Konda for her help reviewing the final manuscript.

Funding

This study was funded by Instituto Nacional de Salud. Lima, Perú.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

References

- Rodríguez M, García F, Aragón J. Virus del papiloma humano: situación actual, vacunas y perspectivas de su utilización [Internet]. Andalucía: Consejería de Salud, 2008 [accessed 2013 December 17]. Available from: http://www.juntadeandalucia.es/salud/sites/ksalud/galerias/documentos/p_4_p_3_prevenccion/vacunas/virus_papiloma.pdf

2. Maw RD, Reitano M, Roy M. An international survey of patients with genital warts: perceptions regarding treatment and impact on lifestyle. *Int J STD AIDS* 1998;9:571-578. <http://doi.org/bp2dgt>
3. Voog E, Löwhagen GB. Follow-up of men with genital papilloma virus infection. Psychosexual aspects. *Acta Derm Venereol* 1992;72:185-186.
4. Filiberti A, Tamburini M, Stefanon B, Merola M, Bandieramonte G, Ventafridda V, et al. Psychological aspects of genital human papilloma-virus infection: a preliminary report. *J Psychosom Obstet Gynaecol* 1993;14:145-152. <http://doi.org/db27pr>
5. Brown RE, Breugelms JG, Theodoratou D, Bénard S. Costs of detection and treatment of cervical cancer, cervical dysplasia and genital warts in the UK. *Curr Med Res Opin* 2006;22:663-670. <http://doi.org/dzmk2p>
6. Hartwig S, Syrjänen S, Dominiak-Felden G, Brotons M, Castellsagué X. Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review. *BMC Cancer* 2012;12:30. <http://doi.org/ffxxrkg>
7. Scarbrough-Lefebvre CD, Van Kriekinge G, Gonçalves MA, de Sanjose S. Appraisal of the burden of genital warts from a healthcare and individual patient perspective. *Public Health* 2011;125:464-475. <http://doi.org/c7bhcx>
8. Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. *BMC Infect Dis* 2013;13:39. <http://doi.org/bj2j>
9. HPV 6, 11, 16, 18 vaccine in men. Inadequate assessment. *Prescrire Int* 2012;21:208.
10. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356:1928-1943. <http://doi.org/bjwvb3>
11. FUTURE I/II Study Group, Dillner J, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen OE, et al. Four year efficacy of prophylactic human papilloma-virus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. *BMJ* 2010;341:c3493. <http://doi.org/bdv96h>
12. Erickson BK, Landers EE, Huh WK. Update on Vaccination Clinical Trials for HPV-Related Disease. *Clin Ther* 2014;36:8-16. <http://doi.org/bj2k>
13. Chow EP, Danielewski JA, Fehler G, Tabrizi SN, Law MG, Bradshaw CS, et al. Human papillomavirus in young women with Chlamydia trachomatis infection 7 years after the Australian human papillomavirus vaccination programme: a cross-sectional study. *Lancet Infect Dis* 2015;15:1314-1323. <http://doi.org/bj2m>
14. Drolet M, Bénard É, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2015;15:565-580. <http://doi.org/f27h4q>
15. Matys K, Mallary S, Bautista O, Vuocolo S, Manalastas R, Pitisuttithum P, et al. Mother-infant transfer of anti-human papillomavirus (HPV) antibodies following vaccination with the quadrivalent HPV (type 6/11/16/18) virus-like particle vaccine. *Clin Vaccine Immunol* 2012;19:881-885. <http://doi.org/bj2n>
16. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomized study in young women. *Lancet* 2009;374:301-314. <http://doi.org/crczfw>
17. Zhu FC, Chen W, Hu YM, Hong Y, Li J, Zhang X, et al. HPV-039 study group. Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18-25 years: results from a randomized controlled trial. *Int J Cancer* 2014;135:2612-2622. <http://doi.org/bj2p>
18. Medeiros LR, Rosa DD, da Rosa MI, Bozzetti MC, Zanini RR. Efficacy of human papillomavirus vaccines: a systematic quantitative review. *Int J Gynecol Cancer* 2009;19:1166-1176. <http://doi.org/dqtfmz>
19. Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *CMAJ* 2007;177:469-479. <http://doi.org/btg9kw>
20. De Vincenzo R, Conte C, Ricci C, Scambia G, Capelli G. Long-term efficacy and safety of human papillomavirus vaccination. *Int J Womens Health* 2014;6:999-1010. <http://doi.org/bj2q>
21. Centers for Disease Control and Prevention (CDC). FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2010;59:626-629.
22. Centers for Disease Control and Prevention (CDC). Recommendations on the use of quadrivalent human papillomavirus vaccine in males-Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep* 2011;60:1705-1708.
23. De Sanjosé S, Serrano B, Castellsagué X, Brotons M, Muñoz J, Bruni L, et al. Human papillomavirus (HPV) and related cancers in the Global Alliance for Vaccines and Immunization (GAVI) countries. A WHO/ICO HPV Information Centre Report. *Vaccine* 2012;30(Suppl4):D1-83, vi. <http://doi.org/bj3v>
24. Arbyn M, Simoons C, Van Damme P, Scharpantgen A, Meijer CJLM, Beutels P. Introduction of human papillomavirus vaccination in Belgium, Luxembourg and the Netherlands. *Gynecol Obstet Invest* 2010;70:224-232. <http://doi.org/dkkmhg>
25. Donovan B, Franklin N, Guy R, Grulich AE, Regan DG, Ali H, et al. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. *Lancet Infect Dis* 2011;11:39-44. <http://doi.org/bwz84f>
26. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336-341. <http://doi.org/d969xc>
27. Tejada RA, Vargas KG, Benites-Zapata V, Mezones-Holguín E, Bolaños-Díaz R, Hernández AV. Human papillomavirus vaccine efficacy in the prevention of anogenital warts: systematic review and meta-analysis [dataset]. In: Harvard Dataverse [Internet]. 1 file: 33.1 KB [accessed on June 1, 2016]. Available at: <https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/HCMDYJ>, MD5: 6fc48d4df57678d-60bd71f8f598a739.
28. Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [Internet]. The Cochrane Collaboration, 2011; 2011 [accessed 2013 July 3]. Available from: www.cochrane-handbook.org.
29. Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634. <http://doi.org/d36qsc>
30. Villa LL, Costa RLR, Petta CA, Andrade RP, Paavonen J, Iversen OE, et al. High sustained efficacy of a prophylactic quadrivalent human papilloma-virus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer* 2006;95:1459-1466. <http://doi.org/dftf6z>
31. Castellsagué X, Muñoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. *Br J Cancer* 2011;105:28-37. <http://doi.org/fvwmjq>
32. Giuliano AR, Palefsky JM, Goldstone S, Moreira ED Jr, Penny ME, Aranda C, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N Engl J Med* 2011;364:401-411. <http://doi.org/d8qw6k>
33. Yoshikawa H, Ebihara K, Tanaka Y, Noda K. Efficacy of quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine (GARDASIL) in Japanese women aged 18-26 years. *Cancer Sci* 2013;104:465-472. <http://doi.org/bj2r>
34. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915-1927. <http://doi.org/c8n9s8>
35. Muñoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. *J Natl Cancer Inst* 2010;102:325-339. <http://doi.org/d975sh>

36. Hillman RJ, Giuliano AR, Palefsky JM, Goldstone S, Moreira ED Jr, Vardas E, et al. Immunogenicity of the quadrivalent human papillomavirus (type 6/11/16/18) vaccine in males 16 to 26 years old. *Clin Vaccine Immunol* 2012;19:261-267. <http://doi.org/d33fjh>
37. Menton JF, Cremin SM, Canier L, Horgan M, Fanning LJ. Molecular epidemiology of sexually transmitted human papillomavirus in a self referred group of women in Ireland. *Viol J* 2009;6:112. <http://doi.org/br9qxq>
38. Aubin F, Prétet JL, Jacquard AC, Saunier M, Carcopino X, Jaroud F, et al. Human papillomavirus genotype distribution in external acuminata condylomata: a Large French National Study (EDiTH IV). *Clin Infect Dis* 2008;47:610-615. <http://doi.org/dwq8qz>
39. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine* 2012;30Suppl5:F123-138. <http://doi.org/bj2s>
40. Mariani L, Vici P, Suligoi B, Checucci-Lisi G, Drury R. Early direct and indirect impact of quadrivalent HPV (4HPV) vaccine on genital warts: a systematic review. *Adv Ther* 2015;32:10-30. <http://doi.org/bj2t>
41. Ali H, Donovan B, Wand H, Read TRH, Regan DG, Grulich AE, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ* 2013;346:f2032. <http://doi.org/bj2v>
42. Ministerio de Salud. Norma técnica de salud que establece el esquema nacional de vacunación. RM N°510-2013/MINSA [Internet]. 2013 [accessed 2013 December 17]. Available from: ftp://ftp2.minsa.gob.pe/normas-legales/2013/RM510_2013_MINSA.pdf
43. Chang Y, Brewer NT, Rinas AC, Schmitt K, Smith JS. Evaluating the impact of human papillomavirus vaccines. *Vaccine* 2009;27:4355-4362. <http://doi.org/bfh5np>