University Library

MINERVA ACCESS

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Castellsagué, X;Ault, KA;Bosch, FX;Brown, D;Cuzick, J;Ferris, DG;Joura, EA;Garland, SM;Giuliano, AR;Hernandez-Avila, M;Huh, W;Iversen, OE;Kjaer, SK;Luna, J;Monsonego, J;Muñoz, N;Myers, E;Paavonen, J;Pitisuttihum, P;Steben, M;Wheeler, CM;Perez, G;Saah, A;Luxembourg, A;Sings, HL;Velicer, C

Title:
Human papillomavirus detection in cervical neoplasia attributed to 12 high-risk human papillomavirus genotypes by region

Date:
2016-12-01

Citation:
Castellsagué, X., Ault, K. A., Bosch, F. X., Brown, D., Cuzick, J., Ferris, D. G., Joura, E. A., Garland, S. M., Giuliano, A. R., Hernandez-Avila, M., Huh, W., Iversen, O. E., Kjaer, S. K., Luna, J., Monsonego, J., Muñoz, N., Myers, E., Paavonen, J., Pitisuttihum, P. ,... Velicer, C. (2016). Human papillomavirus detection in cervical neoplasia attributed to 12 high-risk human papillomavirus genotypes by region. Papillomavirus Research, 2, pp.61-69. https://doi.org/10.1016/j.pvr.2016.03.002.

Persistent Link:
https://hdl.handle.net/11343/260973

License:
CC BY-NC-ND

Papillomavirus Research 2 (2016) 61–69

Contents lists available at ScienceDirect

Papillomavirus Research

journal homepage: www.elsevier.com/locate/pvr

Human papillomavirus detection in cervical neoplasia attributed to 12 high-risk human papillomavirus genotypes by region ☆

Xavier Castellsagué [a,*], Kevin A. Ault [b], F. Xavier Bosch [a], Darron Brown [c], Jack Cuzick [d], Daron G. Ferris [e], Elmar A. Joura [f], Suzanne M. Garland [g], Anna R Giuliano [h], Mauricio Hernandez-Avila [i], Warner Huh [j], Ole-Erik Iversen [k], Susanne K. Kjaer [l], Joaquin Luna [m], Joseph Monsonego [n], Nubia Muñoz [°], Evan Myers [p], Jorma Paavonen [q], Punnee Pitisuttihum [r], Marc Steben [s], Cosette M. Wheeler [t], Gonzalo Perez [u,v], Alfred Saah [u], Alain Luxembourg [u], Heather L Sings [u], Christine Velicer [u]

[a] Institut Catala d'Oncologia (ICO), IDIBELL, CIBERESP, L'Hospitalet de Llobregat, Catalonia, Spain
[b] Department of Obstetrics and Gynecology, University of Kansas Medical Center, Kansas City, KS, USA
[c] Department of Medicine, Indiana University School of Medicine, Indianapolis IN, USA
[d] Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom
[e] Department of Obstetrics and Gynecology, Georgia Regents University Cancer Center, Georgia Regents University, Augusta, GA, USA
[f] Department of Gynecology and Obstetrics, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria
[g] Department of Microbiology and Infectious Diseases, The Royal Women's Hospital, Murdoch Childrens Research Institute, Department of Obstetrics and Gynecology, University of Melbourne, Australia
[h] Moffitt Cancer Center, Tampa, FL, USA
[i] National Institute of Public Health, Cuernavaca, Morelos, Mexico
[j] Division of Gynecologic Oncology, University of Alabama, Birmingham, AL, USA
[k] Institute of Clinical Medicine, University of Bergen/Haukeland University Hospital, Bergen, Norway
[l] Danish Cancer Society Research Center, Copenhagen Denmark and Department of Gynecology, Rigshospitalet, University of Copenhagen, Denmark
[m] Department of Obstetrics and Gynecology, Clinica Colsanitas, Fundacion Universitaria Sanitas, Bogota, Colombia
[n] Institut du col, Paris, France
[°] National Institute of Cancer, Bogotá, Colombia
[p] Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC, USA
[q] Department of Obstetrics and Gynecology, University Central Hospital, Helsinki, Finland
[r] Faculty of Tropical Medicine, Mahidol University, Thailand
[s] Direction des Risques Biologiques et de la Santé au travail, Institut National de Santé Publique du Québec, Montréal, QC, Canada
[t] Departments of Pathology and Obstetrics and Gynecology, University of New Mexico Health Sciences Center, Albuquerque, NM, USA
[u] Merck & Co., Inc., Kenilworth, NJ, USA
[v] Universidad del Rosario, Bogota, Colombia

ARTICLE INFO

Article history:
Received 2 June 2015
Received in revised form
2 March 2016
Accepted 7 March 2016
Available online 14 March 2016

Keywords:
Human papillomavirus
Cervical cancer
Cervical intraepithelial neoplasia
Adenocarcinoma in situ

ABSTRACT

Background: We estimated the proportion of cervical intraepithelial neoplasia (CIN) cases attributed to 14 HPV types, including quadrivalent (qHPV) (6/11/16/18) and 9-valent (9vHPV) (6/11/16/18/31/33/45/52/58) vaccine types, by region

Methods: Women ages 15–26 and 24–45 years from 5 regions were enrolled in qHPV vaccine clinical trials. Among 10,706 women (placebo arms), 1539 CIN1, 945 CIN2/3, and 24 adenocarcinoma in situ (AIS) cases were diagnosed by pathology panel consensus.

Results: Predominant HPV types were 16/51/52/56 (anogenital infection), 16/39/51/52/56 (CIN1), and 16/31/52/58 (CIN2/3). In regions with largest sample sizes, minimal regional variation was observed in 9vHPV type prevalence in CIN1 (~50%) and CIN2/3 (81–85%). Types 31/33/45/52/58 accounted for 25–30% of CIN1 in Latin America and Europe, but 14–18% in North America and Asia. Types 31/33/45/52/58 accounted for 33–38% of CIN2/3 in Latin America (younger women), Europe, and Asia, but 17–18% of CIN2/3 in Latin America (older women) and North America. Non-vaccine HPV types 35/39/51/56/59 had

☆ ClinicalTrials.gov: NCT00092521, NCT00092534, and NCT00090220.

* Correspondence to: Cancer Epidemiology Research Program (CERP). Institut Català d'Oncologia (ICO), Avda. Gran Via 199-203, L'Hospitalet de Llobregat, 08908 Barcelona, Catalonia, Spain.
E-mail address: xcastellsague@iconcologia.net (X. Castellsagué).

http://dx.doi.org/10.1016/j.pvr.2016.03.002
2405-8521/© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

similar or higher prevalence than qHPV types in CIN1 and were attributed to 2–11% of CIN2/3.
Conclusions: The 9vHPV vaccine could potentially prevent the majority of CIN1-3, irrespective of geographic region. Notwithstanding, non-vaccine types 35/39/51/56/59 may still be responsible for some CIN1, and to a lesser extent CIN2/3.
© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

A 9-valent HPV (9vHPV) vaccine was licensed in 2014 in the United States and in 2015 in Canada, the European Union and Australia for the prevention of cervical, vulvar, vaginal, and anal cancers, their respective pre-cancerous lesions, and genital warts caused by HPV types 6/11/16/18/31/33/45/52/58 in females and males aged 9–26 years. The vaccine was developed to protect against cancer and precancer beyond what is already provided by the current quadrivalent vaccine (qHPV vaccine), which targets the high risk (HR) (i.e., cancerous) HPV types 16/18. The 9vHPV vaccine additionally targets the 5 next most common HPV types found in cervical cancer worldwide (HPV 31/33/45/52/58). Both the 9vHPV and qHPV vaccines also protect against the low risk (i.e., not likely to cause cancer) types 6/11 responsible for 90% of genital warts cases.

In a pivotal Phase III efficacy study, the 9vHPV vaccine prevented approximately 97% of cervical, vaginal and vulvar precancers caused by HPV 31/33/45/52/58. The vaccine also generated antibody responses to HPV6/11/16/18 that were non-inferior to those generated by the qHPV vaccine and had a favorable safety profile [1].

Approximately 90% of cervical cancers worldwide are attributed to infection with the 7 HR HPV types targeted by the 9vHPV vaccine (i.e., HPV16/18/31/33/45/52/58) [2,3]. A previous study of women in Brazil, Mexico, India and China also found that approximately 90% of cervical cancer cases in these countries are attributed to the 9vHPV types, with some minor regional variation in the proportion of these cancers attributed to HPV 31/33/45/52/58 (12–19% variability) [7]. Similarly, a previous study using qHPV clinical trial data found that approximately 85% or more of cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS), and approximately 50% of CIN1 lesions are attributed worldwide to the types targeted by the 9vHPV vaccine [4]. However, regional data on the proportion of CIN and AIS attributed to the 9vHPV vaccine types are sparse. Such data are essential for estimating the regional impact of HPV vaccines on the rates of cervical lesions. For example, the greatest impact of HPV vaccination is expected in low- and middle-income countries where the current qHPV and bivalent HPV vaccines targeting HPV16/18 are estimated to potentially reduce cancer risk by 40–50% at 70% vaccine uptake and where well organized screening programs are lacking [5–7].

Using data from the qHPV vaccine clinical trials, we estimated the proportion of CIN1-3 in North America, Latin America, Europe, Asia, and Oceania [8–11] attributed to the 14 HPV types tested in the trials (HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59), as well as the proportion attributed overall to the 9vHPVvaccine types (6/11/16/18/31/33/45/52/58) and by the 9vHPV vaccine's constituent qHPV types (6/11/16/18) and 5 new types (31/33/45/52/58).

2. Materials and methods

2.1. Objective

The objective of this analysis was to determine the proportion of low and high grade cervical lesions (CIN1-3) attributed to the 9vHPV vaccine types (6/11/16/18/31/33/45/52/58), to the qHPV types (6/11/16/18), to the 5 new types targeted by the 9vHPV vaccine (31/33/45/52/58), as well as to 5 other measured non-vaccine HR HPV types (35/39/51/56/59), across the 5 regions studied.

2.2. Study designs and population

Data from 3 randomized double-blind, placebo-controlled clinical trials of the qHPV vaccine were used in this analysis. Protocols 013 and 015 included 17,622 women (8798 in placebo group) 15–26 years old from 23 countries enrolled between December 2001 and May 2003, while Protocol 019 included 3819 women (1908 in placebo group) 24–45 years old from 7 countries enrolled between June 2004 and April 2005. Participants in the trials were followed for approximately 4 years. As Protocols 013 and 015 enrolled only a small percentage of women above the age of 23, the age range for Protocol 019 was chosen to overlap with these studies. The proportions of subjects enrolled from the following regions for the younger and older age groups, respectively, are: North America (13%, 14%), Latin America (32%, 42%), Europe (51%; 13%), Asia (2%; 31%) and Oceania (2%, only included for women aged 15–26 years). Further details of subjects and patients with lesions and the countries included in these trials are provided in Supplementary Appendix Table A.1

The study designs, protocols, and results of the primary hypotheses for each of the studies have been previously described [8–10]. The studies were conducted in accordance with principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies.

2.3. Analyses for infection

HPV anogenital infection prevalence was reported as one potential measure of HPV types circulating in the study population, and it can be compared to HPV types responsible for causing low and high grade cervical lesions. An endo/ectocervical swab (one specimen) and a combined labial/vulvar/perianal swab were obtained from all subjects across the trials. Prevalence of HPV infection at day 1 was assessed in the vaccine and placebo arms combined to increase precision (given the randomized nature of the trials, it is expected that the placebo arm infection prevalence will be similar to the prevalence in the combined trial arms). In each study, day 1 swabs were tested for 14 HPV types (6/11/16/18/31/33/35/39/45/51/52/56/58/59) using a PCR-based assay as previously described [12–14].

2.4. Cervical neoplasia diagnosis

All biopsies and excisional procedure specimens were tested for the 14 HPV types as previously described [4]. All specimens were processed and adjacent histological sections of each specimen were first read for clinical management by pathologists at a central laboratory (Diagnostic Cytology Laboratories, Indianapolis, IN) and then read for endpoint determination by a panel of up to 4 pathologists who were blinded to central laboratory and clinical diagnoses, treatment group, and HPV status. The following

histological endpoints were included in the analyses reported here: CIN grade 1, 2 and 3, and/or AIS. There were no cases of cervical cancer.

Over approximately 4 years of follow-up of 10,706 women in the placebo arms of the 3 trials, 1539 cases of CIN1, 945 cases of CIN2 or CIN3 (CIN2/3), and 24 cases of AIS were diagnosed. Of these, most were identified among the 8798 women aged 15–26, as follows: 1366 CIN1, 456 CIN2, 393 CIN3, and 19 AIS. The remaining lesions were diagnosed among the 1908 women aged 24–45 (Table A.1).

2.5. Statistics

Analyses of the prevalence of the 14 tested HPV types in cervical lesions (defined as a biopsy or surgical excisional specimen) was performed in 10,706 women randomized to the placebo arms of the trials (representing over 99% of the total number randomized to the placebo arms). Because some women developed more than one lesion during the studies, an individual could be counted multiple times in the tables and figures.

We used 4 approaches (described below) to estimate the attribution of cervical lesions to individual HPV types, with 2 approaches to adjust for lesions with more than one HPV type detected. In this analysis, to avoid unstable estimates resulting from small sample sizes, attribution was reported only for regions with >20 lesions of a given CIN grade (e.g., CIN1). For each of the 4 analyses, all lesions (i.e. both HPV positive and HPV negative) were included in the denominator, as the HPV negative lesions might have been caused by a non-tested type.

1) *Minimum (Min) Estimate:* The minimum estimate of attribution was calculated by including in the numerator only those lesions in which a respective HPV type was present as a single infection.
2) *Proportional (Prop) Attribution Estimate:* Consistent with the literature [15,16], this estimate was calculated following the method of Insinga et al., [17] in which a fractional allocation for each individual HPV type was used when evaluating lesions with more than one HPV type detected. This was based on the relative number of instances in which each HPV type was observed as a single infection in a lesion of a given grade. For example, if one were to derive an apportionment for two CIN3 lesions found to test positive for HPV16 and 51, and if there were nine CIN3 lesions with HPV16 only and a single CIN3 lesion with HPV51 only, then $[2^*9/(9+1)]$ or 1.8 of these 2 multiple infected lesions would be attributed to HPV16 and $[2^*1/(9+1)]$ or 0.2 attributed to HPV51.
3) *Hierarchical:* A modified version of the hierarchical attribution estimate of Wentzensen et al. was also performed for lesions with more than one HPV type detected [18]. We attributed the cervical lesion to the HPV type that is most commonly detected in invasive cervical cancer [19]. For example, a lesion with HPV16 and 59 would be attributed to HPV16 because HPV16 is more commonly found in cervical cancer. A lesion was attributed to HPV 31/33/45/52 or 58 (i.e. the additional high-risk HPV types included in the 9vHPV vaccine), only if there were no co-infection with HPV16 and/or 18; and to HPV35/39/51/56/59 (i.e. the other high-risk HPV types tested which are less commonly detected in invasive cervical cancers) [19]. only if there were no co-infection with HPV16/18/31/33/45/52 and/or 58.
4) *Any type estimate:* This estimate was calculated by including in the numerator any lesion in which a respective HPV type was present, regardless of co-infection with other types.

3. Results

3.1. HPV anogenital infection prevalence on day 1 (placebo and vaccine arms combined)

The most commonly detected HPV type in young women (aged 15–26) within any given region was generally HPV16, followed by HPV56 and 51, while in older women (aged 24–45), HPV56 infection was most common, followed by HPV51 and 52 (Table 1, Fig. 1, Supplementary Appendix Table A.2). However, in Asia, HPV52 had the highest prevalence in both age groups. Approximately 10–15% of the younger age group and 10% of the older age group had more than one HR HPV type (i.e., "coinfections") measured at day 1, with the exception of Asia (2–3% coinfections in both age groups).

Overall, the prevalence of anogenital infection with any of the 14 measured HPV types on day 1 (placebo and vaccine arms combined) was fairly similar across all regions and both age groups ($\sim$28–33%), with the exceptions of Asia, which had a lower prevalence in both age groups (12–14%), and Latin America, where the younger cohort had higher prevalence than the older cohort (38% vs 30%). Irrespective of age, in North America, Europe, and Oceania, anogenital infection prevalence was similar for any non-vaccine HPV type (16–20%), any qHPV type (12–16%), and 9vHPV type (20–25%), while in Latin America and Asia, HPV prevalence was also similar, though lower than in the other regions: any non-vaccine type (6%), and qHPV type (3–4%), and any 9vHPV type (7–8%).

3.2. HPV prevalence in CIN lesions (placebo arms)

Among the high-risk 9vHPV types and non-vaccine types, there was less than a 5% difference across each region for each of the proportional, hierarchical, or any attribution estimates. Thus, the proportionally-weighted results are discussed below, with additional findings provided in Supplementary Appendix Figs. A.2 and A.3.

3.2.1. CIN1 lesions

The most commonly detected HPV types in CIN1 lesions within any given region were generally similar to the most common types in HPV anogenital infection (Table 1, Supplementary Appendix Table A.3). HPV16 was typically the most common, followed by HPV39, 51, 52, and 56. Across North America, Europe, and Asia, approximately 30–40% of CIN1 lesions were coinfected in young women, with approximately twice as many coinfections as in the older age group: 15% (Asia) and 20% (Europe). In contrast, in Latin America, the proportion of co-infections in CIN1 lesions was similar in both the younger and older age groups (21–22%).

The non-vaccine HPV types (35/39/51/56/59) accounted for approximately 25–30% of CIN1 lesions in Latin America and Europe in both age groups, and 36% in North America (young women) (Table 1, Fig. 2, Fig. 3). In Oceania and Asia, where there were substantially fewer lesions, the 5 non-vaccine types accounted for 47% and 15–19% of CIN1 cases, respectively (Table 1, Fig. 3, Supplementary Appendix Fig. A.3).

In comparison to the qHPV types, in North America, Asia, and Oceania, the 5 new HPV types addressed by the 9vHPV vaccine accounted for an additional 18%, 14%, and 11% of CIN1 cases, while in Latin America and Europe, the 5 new types accounted for a higher proportion of these lesions (25–28%) (Table 1, Fig. 2, Supplementary Appendix Fig. A.3). HPV6/11 accounted for less than 10% of CIN1 lesions in any region or age group (approximately 4% of the CIN1 in young women in North America, Europe, and Latin America; 8% in Asia, and 2% in the older age group in Latin America).

Table 1
Summary of HPV prevalence (%) in cervical infections and HPV attribution (%) to cervical lesions, by age (15–26 and 24–45 years old), region, and HPV type combinations.

HPV type	HPV infection		CIN1 adjusted*		CIN2/3 adjusted*	
	15–26	24–45	15–26	24–45	15–26	24–45
North America						
Number of lesions	–	–	162	14	85	3
Most prevalent types	16/51/56	56/16/52	16/39/56	56/16/45	16/31/52	NA
> 1 HR type	12%	10%	34%	NA	28%	0%
Any non-vaccine type	17%	20%	36%	NA	7%	NA
Any qHPV type	14%	12%	26%	NA	63%	NA
Any 9vHPV type	20%	21%	44%	NA	85%	NA
Latin America						
Number of lesions	–	–	549	103	239	37
Most prevalent types	16/56/51	56/52/16	16/56/58	16/58/56	16/58/31	16/52/58
> 1 HR type	15%	9%	21%	22%	23%	11%
Any non-vaccine type	6%	6%	30%	25%	8%	11%
Any qHPV type	4%	3%	21%	28%	50%	61%
Any 9vHPV type	9%	8%	48%	56%	83%	78%
Europe						
Number of lesions	–	–	606	15	496	14
Most prevalent types	16/56/51	56/16/51	16/51/56	51/31/39	16/31/52	16/31/52
> 1 HR type	15%	11%	38%	20%	40%	43%
Any non-vaccine type	19%	19%	29%	NA	9%	NA
Any qHPV type	16%	13%	28%	NA	44%	NA
Any 9vHPV type	25%	22%	53%	NA	82%	NA
Asia						
Number of lesions	–	–	21	40	10	42
Most prevalent types	52/16/51	52/51/39	16/39/51	52/16/51	16/52/33	16/52/31
> 1 HR type	3%	2%	29%	15%	30%	14%
Any non-vaccine type	6%	6%	19%	15%	NA	2%
Any qHPV type	4%	3%	43%	22%	NA	34%
Any 9vHPV type	9%	8%	57%	38%	NA	71%
Oceania						
Number of lesions	–	–	28	–	19	–
Most prevalent types	51/16/56	–	51/16/58	–	31/16/51	–
> 1 HR type	11%		39%	–	42%	–
Any non-vaccine type	16%	–	47%	–	NA	–
Any qHPV	13%	–	28%	–	NA	–
Any 9vHPV	22%	–	39%	–	NA	–

NA: not applicable (sample size too small); – population not included in trial;
HR= high risk HPV type (total of 12 HR types tested); non-vaccine types: 35/39/51/56/59; qHPV type: 6/11/16/18; 9vHPV types: 6/11/16/18/31/33/45/52/58
* Proportional weighted.

Overall, approximately 50% (44–53%) of CIN1 in young women in North America, Europe and Latin America were attributed to the 9vHPV vaccine types, consistent with the estimate for all regions combined (Table 1, Fig. 2). In Asia and Oceania, where there were substantially fewer CIN1 lesions in young women, the 9vHPV types respectively accounted for 57% and 39% of CIN1. In the older women in Asia and Latin America, the 9vHPV types respectively accounted for 38% and 56% of CIN1 lesions (Table 1, Supplementary Appendix Fig. A.3).

3.2.2. CIN2/3 lesions

Other than HPV16, the next most commonly detected HPV types in CIN2/3 lesions were generally different than the most common types in HPV anogenital infection and CIN1 lesions, and included in the 9vHPV vaccine types (HPV 31, 52, 58) (Table 1, Supplementary Table A.3).

In all regions, approximately 30–40% of CIN2/3 in young women were coinfected with other types, with the exception of Latin America (23%) (Table 1). In the older age groups, a smaller proportion of CIN2/3 were coinfected (14% Asia, 11% Latin America), while in Europe, approximately 40% of CIN2/3 lesions were coinfected in both age groups.

There was also minimal regional variation in the prevalence of the 5 other non-vaccine types in CIN2/3 cases, ranging from 7% to 11%, except for Asia (2%, older women only) (Table 1, Fig. 3). In both age groups and all regions, the relative contribution of the non-vaccine HPV types decreased as lesion severity increased. For example, in young women, the relative contribution of the 5 non-vaccine types was 20–36% for CIN1, 8–15% for CIN2, and 2–4% for CIN3.

In comparison to the qHPV vaccine types, the 5 new vaccine types generally accounted for approximately 30–40% of CIN2/3 in both age groups, with the exception of North America and Latin America (older age group), where the 5 new types accounted for 16–18% of CIN2/3 lesions (Table 1, Fig. 2, Supplementary Appendix Fig. A.3).

Approximately 80% (78–85%) of CIN2/3 in North America, Europe and Latin America were attributed to the 9vHVP vaccine types, whereas in Asia (older women only), 71% of the CIN2/3 lesions were attributed to these types (Table 1, Fig. 2, Supplementary Fig. A.3). It is important to note that by grade, the 9vHPV vaccine types were attributed to 72–80% of CIN2 but to 90–97% of CIN3 lesions.

3.2.3. Adenocarcinoma in situ

Very few AIS lesions were detected within any region, and all but 1 lesion were infected with HPV16. Of the 9 total AIS lesions in Latin America (both age groups combined), 7 had HPV16 only, one was co-infected with HPV16/58, and one with HPV16/52. Of the 13 total AIS lesions in Europe, 5 had HPV16/18 only, 6 had HPV16/18

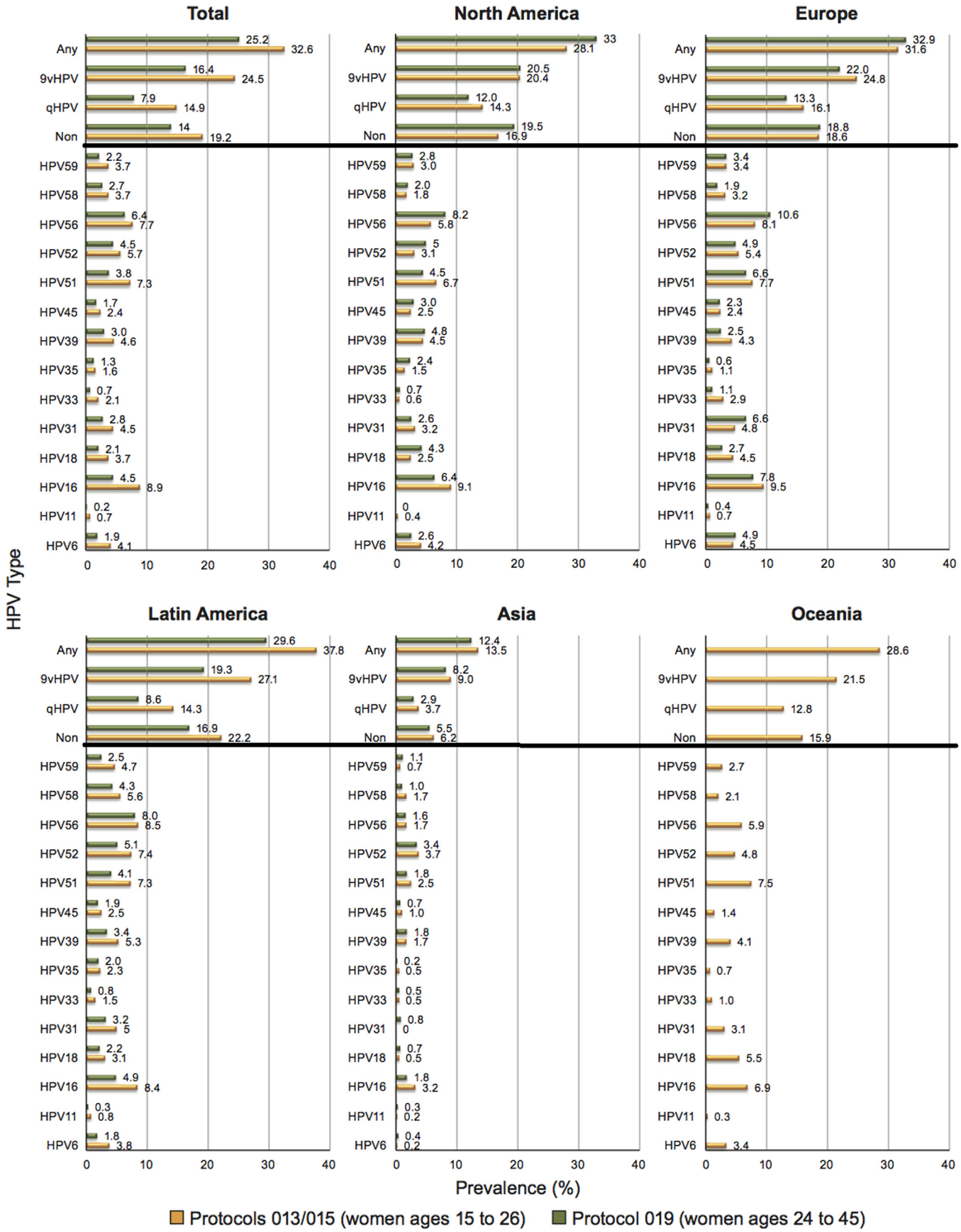

Fig. 1. Prevalence of cervical HPV infection at baseline by region, irrespective of co-infections, vaccine and placebo arms combined. Non = non-vaccine type (HPV35/39/51/56/59); qHPV = quadrivalent vaccine HPV type (HPV6/11/16/18); 9vHPV = 9-valent vaccine HPV type (HPV6/11/16/18/31/33/45/52/58). Total data adapted from reference 4.

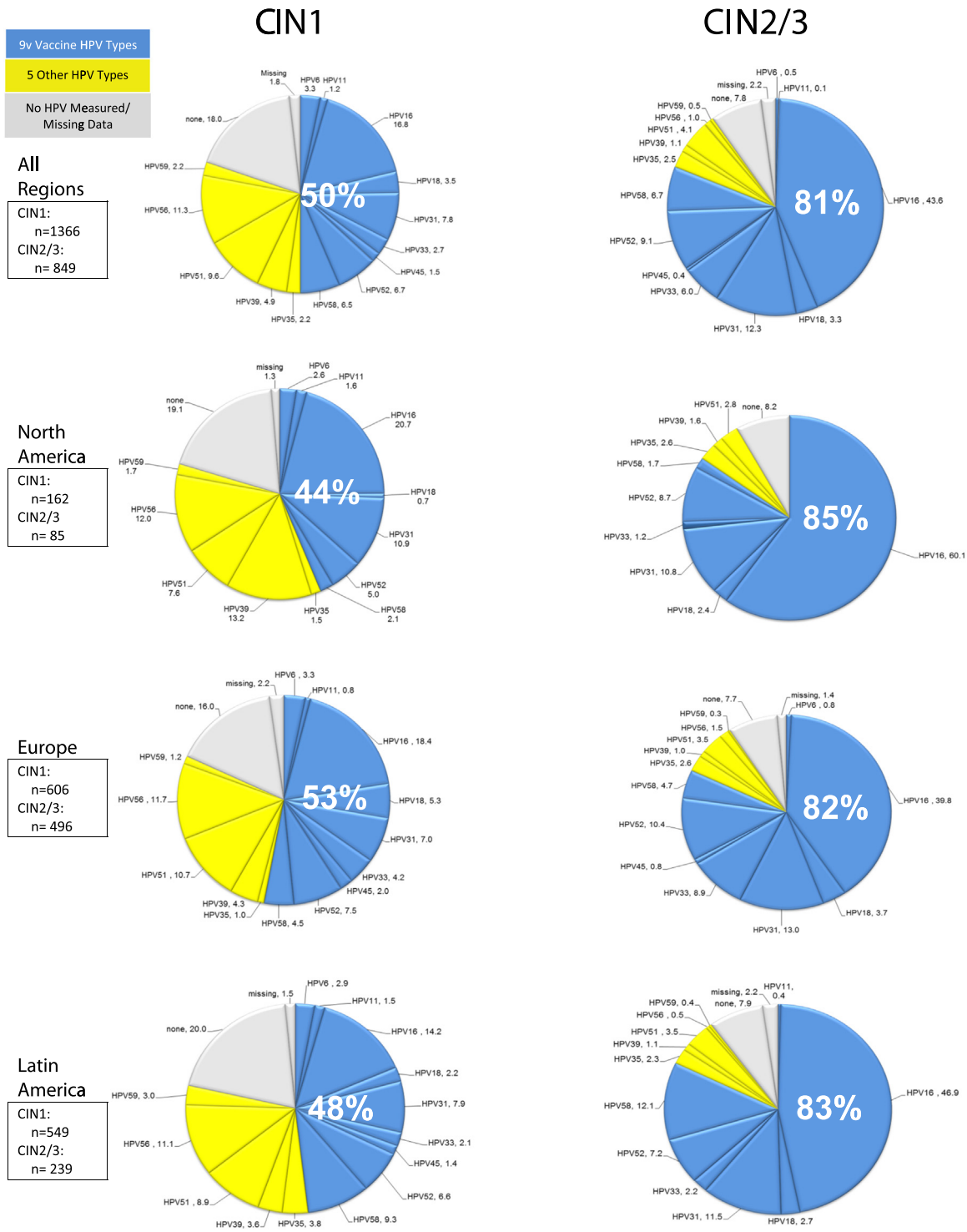

Fig. 2. Percent of CIN1-3 attributed to the respective HPV types in women ages 15–26, by region, proportional method. Total data adapted from reference (4).

plus a co-infection with another high-risk type, and one had no HPV type detected. Of the 2 AIS lesions in Asia (older women only), both had HPV16 only.

4. Discussion

The present study is one of the first to assess HPV type-specific attribution to CIN by geographical region. With respect to CIN1, the 5 new HPV types (31/33/45/51/58) in the 9vHPV vaccine accounted for approximately 25–30% of lesions in Latin America and Europe, and 14–18% of lesions in North America and Asia. With respect to CIN2/3, the 5 new types accounted for 33–38% of lesions, with the exception of North America and the older age group in Latin America (17–18%). Notwithstanding this regional variance between the qHPV vaccine types and the 5 new types, our study shows that the majority (71–85%) of pre-cancerous cervical lesions (CIN2/3) in all the regions studied are attributed to 9vHPV vaccine types.

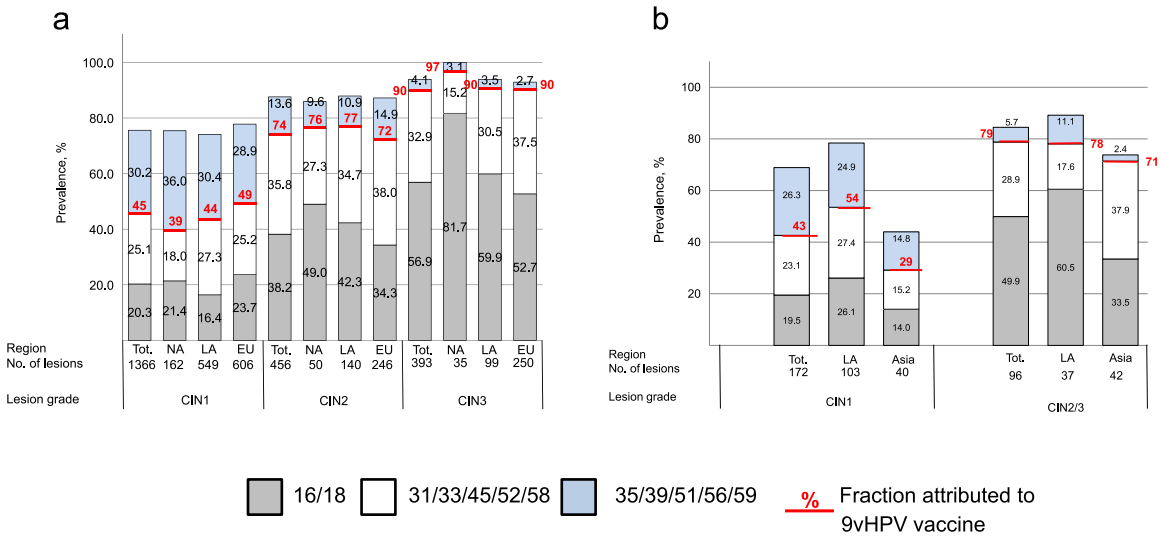

Fig. 3. Percent of CIN1-3 attributed to HPV16/18, HPV 31/33/45/52/58, and HPV 35/39/51/56/59, by region, proportional method, in women ages 15–26 *(panel A)* and 24 to 45 *(panel B)*. Only regions with >20 CIN2 or CIN3 lesions are shown.

These regional HPV attribution results are consistent with a worldwide study of 8977 HPV-positive invasive cervical cancers, in which there was also minimal regional variation [19]. Approximately 96%, 88%, 88%, 91%, 86% and 87% of the HPV-positive cervical cancers in North America, Central South America, Europe, Asia, Oceania, and Africa, respectively, were attributed to the high risk 9v HPV vaccine types in that study. Our study results for the attribution of cervical neoplasia to the 9vHPV vaccine types are also consistent with 2 recent, large US studies of cervical neoplasia [20,21]. One study was a population-based study of 5378 cervical lesions conducted by the US Centers for Disease Control (CDC) in 5 catchment areas across the US among women aged 21–39 between 2008 and 2011. The other study was also population-based and included 21,297 females aged 13–90 (mean ages at CIN2 and CIN3 diagnosis: 25 and 28, respectively) who had cervical biopsies in New Mexico between 2006 and 2009. The attribution of CIN2/3 to the high risk 9vHPV vaccine types was 75% (65.3% for CIN2 and 86.2% for CIN3/AIS) in the CDC study, while in the New Mexico study, the attribution of CIN2 and CIN3 to any 9vHPV vaccine type was 65.9% and 82.3%, respectively [20,21]. Similarly, we estimated that 76% of CIN2 lesions in women aged 15–26 are attributed to the high risk 9vHPV vaccine types in North America and 79% of CIN2/3 lesions in women aged 24–45 (in all regions combined) are attributed to these types (Fig. 3). While we also found that 97% of CIN3 lesions in women aged 15–26 in North America are attributable to the high risk 9vHPV types, our sample size was small ($n=35$). Our estimate of 90% attribution of CIN3 lesions in all regions combined was within 4–6% of the CDC and New Mexico studies for CIN3. The estimates of attribution of CIN2 and CIN3 to individual HPV types (e.g., 16/18) varied among these 3 studies, and they also varied by region in our study. The reason for this variation is not clear. Importantly however, when attribution of these lesions is assessed for the high risk 9vHPV vaccine types combined, the differences among the studies and regions are minimal.

Both our study and the New Mexico study [20] also evaluated CIN1 attribution to the 9vHPV types. We found that among women aged 15–26 years, approximately 44% of CIN1 was attributable to the 9vHPV types in North America, and 46–50% of CIN1 in all regions combined in both age groups studied. In contrast, the New Mexico study found that only 25% of CIN1 lesions were attributed to the 9vHPV vaccine types overall, whereas in the age 26 years old and under, the attribution of CIN1 to the 9vHPV vaccine types was 30–35%.

Since diagnostic criteria and terminology varies in real world practice, a strength of our study is the adjudicated consensus diagnosis of CIN1-3 lesions by an expert pathology panel, reasonably ruling out important potential misclassification of our lesion grades. Several large studies examining the percent agreement between clinical center diagnoses and quality control (QC) pathology diagnoses of cervical lesions have found poor agreement, with the QC pathologists tending to give less severe diagnoses [22,23].

For women aged 15–26 years, the mathematical approaches (proportional, hierarchical and any) for assessing HPV type attribution converged for the high-risk vaccine HPV types, regardless of region. The proportional attribution methods showed that the 7 high-risk types contained in the 9vHPV vaccine contributed to 85%, 83% and 81% of CIN2/3 in North America, Latin America, and Europe respectively. In women aged 24–45 years, these types contributed to 71%, and 78% of CIN2/3 in Asia and Latin America, respectively. Several studies have now shown good consistency between the proportional and hierarchical attribution methods. For example, in the CDC study described above the proportional and hierarchical attribution methods yielded the same estimates for the attribution of HPV16/18/31/33/45/52/58 to CIN2/3 (~75%).

Under the proportional attribution method, the next most common HPV types (other than the 9vHPV vaccine types) that have been found in invasive cervical cancers at a proportion of >1% are: HPV35 (1.9%), HPV39 (1.6%), HPV51 (1.3%), HPV59 (1.1%), and HPV56 (0.83%) [19]. In our study, these types collectively contributed to 7%, 8% and 9% of CIN2/3 in North America, Latin America, and Europe in women aged 15–26, respectively. In women aged 24 to 45, these types contributed to 2%, and 11% of CIN2/3 in Asia and Latin America. In 2012, the International Agency for Research on Cancer concluded there was sufficient evidence of carcinogenicity to humans for the 7 high-risk HPV types in the 9vHPV vaccine in addition to these 5 HPV types which are not contained in the 9vHPV vaccine [24]. Less evidence was available for HPV68, and 7 other phylogenetically related types (HPV26/53/66/67/68/70/73) were considered possibly carcinogenic [24]. These conclusions are supported by a recent Swedish study that estimated the HPV type-specific risks of CIN2 and CIN3 using a randomized primary HPV screening trial with 14.6 years follow-up. In that study, substantial differences were found in risk

of CIN2 and CIN3 between different oncogenic HPV types – HPV16/18/31/33/45/52/58 together contributed to 73.9% of CIN2/3 lesions whereas HPV39/51/56/59/66/68 had risks of $<10\%$ [25]. Collectively, these data inform HPV screening and vaccination strategies.

We found approximately 8% of CIN2/3 lesions to be negative to the 14 tested HPV types across all regions and age groups with the exception of Asia, where 21% (9 of 42) of the CIN2/3 lesions in women aged 24–45 were negative to all of the 14 tested types. As we cannot determine if our HPV negative lesions are attributed to a non tested type, we included all lesions in our analyses, irrespective of their HPV status. When considering only HPV positive lesions in women aged 15–26, the 7 high-risk types contained in the 9vHPV vaccine contributed to 92%, 89.7% and 88.0% of CIN2/3 cases in North America, Latin America, and Europe, respectively. In women aged 24–45 years, these types contributed to 90.9%, and 85.0% of CIN2/3 lesions in Asia and Latin America. These estimates of 9vHPV attribution are closer to the de Sanjosé worldwide study of 8977 HPV-positive invasive cervical cancers [19]. Also, the proportion of our samples that were HPV positive is generally consistent with that study, in which 8%, 18%, 13%, and 12% of cancers were HPV negative in North America, Central South America, Europe, and Asia, though the study tested for 30 HPV types [19].

The study has some limitations. The clinical trial populations are not entirely representative of the general population of women aged 15–45 due to the per-protocol exclusion/inclusion criteria used in the trials. Although this study provides data from 27 countries in 5 regions, some regions had small numbers of lesions and not every country was represented for each region. Thus the proportion and hierarchical attribution methods were only applied to regions/countries where more than 20 lesions were detected. Very few AIS lesions were detected across each region. Of the 24 total, 23 (95.8%) were attributed to the 9vHPV vaccine types.

According to recent literature from 5 countries with organized cervical screening programs (the US and 4 Nordic countries), the incidence of CIN2/3 is approximately 10 or more times higher than the incidence of cervical cancer [26–29]. In all regions, CIN2/3 incidence is generally not well measured or consistently reported and rates are likely to vary mainly due to differences in sexual behaviors and screening and treatment programs. Nonetheless, the CIN2/3 disease burden worldwide is clearly substantial, and mostly attributable to the high risk 9vHPV vaccine types.

5. Conclusions

In summary, the 5 new HPV types (31/33/45/51/58) in the 9vHPV vaccine accounted for approximately 25–30% of CIN1 in Latin America and Europe, 14–18% of CIN1 in North America and Asia, 33–38% of CIN2/3 in most regions, and 17–18% of CIN2/3 in North America and Latin America (older age group). Irrespective of region, if future 9vHPV vaccination programs are effectively implemented in HPV naïve adolescents and young women, a substantial number of cervical lesions could be prevented in settings where HPV immunization programs have yet to be implemented, as well as in settings currently implementing qHPV (HPV6/11/16/18) and/or bivalent (HPV16/18) vaccines. 9vHPV vaccination programs would also eliminate many invasive procedures (colposcopy, biopsy, excisional surgery of the cervix) associated with CIN treatment in countries with existing cervical cancer screening programs, and a substantial number of cervical cancers everywhere, including countries without screening programs. Broad immunization with the 9vHPV vaccine of adolescent populations may thus necessitate evaluation of optimal screening algorithms in HPV vaccinated women. Notwithstanding, and regardless of screening practices and vaccine uptake, our data suggest that the non-vaccine types 35/39/51/56/59 may still be responsible for some CIN1, and to a lesser extent CIN2/3.

Funding support

This study was funded by Merck and Co., Inc., Kenilworth, NJ (ClinicalTrials.gov: NCT00092521, NCT00092534, and NCT00090220). *This systematic review was designed, managed, and analyzed jointly by authors employed by Merck & Co. and external authors who were not paid for their work.*

Conflicts of interest

Xavier Castellsagué reports having received institutional research grants from Merck and Co., Inc., Sanofi Pasteur MSD, GlaxoSmithKline, and Genticel, and occasional personal travel grant and speakers honorarium from Sanofi Pasteur MSD and Vianex

Kevin A. Ault reports having received grants to his institution from Merck and the National Institutes of Health and advisory committee fees from the American College of Obstetricians and Gynecologists. He also serves on the editorial board for the National Cancer Institute (USA).

Xavier Bosch reports having received institutional research and educational grants from Sanofi Pasteur MSD and GlaxoSmithKline and personal travel grant and speakers honorarium from Sanofi Pasteur MSD and GlaxoSmithKline.

Darron Brown has served on an Advisory Board at Merck and Co., Inc. and has lectured on the quadrivalent HPV vaccine (honoraria received from Merck and Co., Inc. are donated to charities). His laboratory has received research funding from Merck and Co., Inc. Indiana University and Merck and Co., Inc. have an agreement that pays the University, based on certain landmarks related to vaccine development. DB receives a portion of these funds as income.

Jack Cuzick reports having received advisory board fees from Merck and GlaxoSmith Kline.

Daron G. Ferris reports having received grants to his institution, lecture fees from MSD, and advisory board and consultant fees from Merck.

Suzanne M. Garland reports having received grant support paid to her institution from GlaxoSmithKline, Merck and CSL Bio and speakers honoraria for work performed in own time from Sanofi Pasteur and Merck.

Anna R Giuliano reports having received grant support and advisory board member fees to her institution from Merck.

Mauricio Hernandez-Avila reports nothing to disclose.

Warner Huh reports having received honoraria for advisory board participation with Merck.

Ole-Erik Iversen reports having received compensation from Merck and GlaxoSmithKline to conduct vaccine clinical trials and scientific advisory board fees from Merck.

Elmar A. Joura reports having received grant support paid to his institution from Merck and GlaxoSmithKline; advisory board fees from Merck and Sanofi Pasteur MSD, and lecture fees from Sanofi Pasteur MSD, Merck, GSK and Roche.

Susanne K. Kjaer reports having received scientific advisory board and speaker's fees and unrestricted research grants through her institution from Sanofi Pasteur MSD and Merck, and scientific advisory board fee from Roche.

Joaquin Luna reports nothing to disclose.

Joseph Monsonego reports having received honorarium as a member of scientific advisory board of Sanofi Pasteur MSD, Merck,

Roche Diagnostic, Genprobe and Genticel and compensation from Merck and GlaxoSmith Kline to conduct vaccine trials.

Nubia Muñoz reports having received honorarium from Merck for being a member of HPV Global Advisory Board.

Evan Myers reports having received personal fees from Merck and grant support from GlaxoSmithKline, Gen-Probe/Hologic, and the NIH. He is a member of the American Cancer Society's Guidelines Committee for Cervical Cancer Screening and is a member of the advisory panel for the CDC's National Breast and Cervical Cancer Early Detection Program.

Jorma Paavonen reports having received research funding from Merck and GlaxoSmithKline through his institution.

Punnee Pitisuttihum reports having researched funding from Merck through her institution.

Marc Steben reports having received grants and personal fees from Merck and personal fees from Cepheid, Paladin and Valeant.

Cosette M Wheeler reports having received equipment and reagents for HPV genotyping from Roche Molecular Systems and contracts for HPV vaccine studies from GlaxoSmith Kline and Merck through her institution, the University of New Mexico.

Gonzalo Perez, Alfred Saah, Alain Luxembourg, Heather L Sings, and Christine Velicer are employees of Merck Sharp & Dohme Corp and hold stock/stock options.

Acknowledgments

We thank Scott Vuocolo, Ph.D. and Karyn Davis (Merck & Co., Inc.) for assistance in the preparation of this manuscript and Kathy Harkins, Jane Liao, Mary Anne Rutkowski, Weifeng Xu, Se Li, and Xingshu Zhu (Merck & Co., Inc.) for statistical programming support.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pvr.2016.03.002.

References

[1] E.A. Joura, A.R. Giuliano, O.E. Iversen, C. Bouchard, C. Mao, J. Mehlsen, et al., A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women, N. Engl. J. Med. 372 (2015) 711–723.
[2] International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100, A Review of Human Carcinogens, Part B: Biological Agents, WHO Press, Lyon, France, 2012.
[3] B. Serrano, L. Alemany, S. Tous, L. Bruni, G.M. Clifford, T. Weiss, et al., Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease, Infect. Agent Cancer 7 (2012) 38.
[4] E.A. Joura, K.A. Ault, F.X. Bosch, D. Brown, J. Cuzick, D. Ferris, et al., Attribution of 12 high-risk human papillomavirus genotypes to infection and cervical disease, Cancer Epidemiol. Biomark. Prev. 23 (2014) 1997–2008.
[5] S.J. Goldie, M. O'Shea, M. Diaz, S.Y. Kim, Benefits, cost requirements and cost-effectiveness of the HPV16,18 vaccine for cervical cancer prevention in developing countries: policy implications, Reprod. Health Matters 16 (2008) 86–96.
[6] J.M. Brotherton, D.M. Gertig, Primary prophylactic human papillomavirus vaccination programs: future perspective on global impact, Expert Rev. Anti Infect. Ther. 9 (2011) 627–639.
[7] B. Serrano, L. Alemany, P.A. Ruiz, S. Tous, M.A. Lima, L. Bruni, et al., Potential impact of a 9-valent HPV vaccine in HPV-related cervical disease in 4 emerging countries (Brazil, Mexico, India and China), Cancer Epidemiol. 38 (2014) 748–756.
[8] S.M. Garland, M. Hernandez-Avila, C.M. Wheeler, G. Perez, D.M. Harper, S. Leodolter, et al., Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases, N. Engl. J. Med. 356 (2007) 1928–1943.
[9] FUTURE II Study Group, Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions, N. Engl. J. Med. 356 (2007) 1915–1927.
[10] N. Munoz, R. Manalastas, P. Pitisuttihum, D. Tresukosol, J. Monsonego, K. Ault, et al., Safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women between 24 and 45 years of age: a randomized, double-blind trial, Lancet 373 (2009) 1949–1957.
[11] X. Castellsague, N. Munoz, P. Pitisuttithum, D. Ferris, J. Monsonego, K. Ault, 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 105 (2011) 28–37.
[12] International Patent Numbers WO 2003/019143 A2, WO 2006/116276 A2, and WO 2006/116303 A2. 〈http://www.wipo int/portal/index html〉. (accessed 21.02.11).
[13] L.L. Villa, R.L.R. Costa, C.A. Petta, R.P. Andrade, K.A. Ault, A.R. Giuliano, et al., Prophylactic quadrivalent human papillomavirus (types 6, 11, 16 and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial, Lancet Oncol. 6 (2005) 271–278.
[14] C. Mao, L.A. Koutsky, K.A. Ault, C.M. Wheeler, D.R. Brown, D.J. Wiley, et al., Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial, Obstet. Gynecol. 107 (2006) 18–27.
[15] V.V. Sahasrabuddhe, P.E. Castle, S. Follansbee, S. Borgonovo, D. Tokugawa, L. M. Schwartz, et al., Human papillomavirus genotype attribution and estimation of preventable fraction of anal intraepithelial neoplasia cases among HIV-infected men who have sex with men, J. Infect. Dis. 207 (2013) 392–401.
[16] R.P. Insinga, G. Perez, C.M. Wheeler, L.A. Koutsky, S.M. Garland, S. Leodolter, et al., Incident cervical HPV infections in young women: transition probabilities for CIN and infection clearance, Cancer Epidemiol. Biomark. Prev. 20 (2011) 287–296.
[17] R.P. Insinga, K.L. Liaw, L.G. Johnson, M.M. Madeleine, A systematic review of the prevalence and attribution of human papillomavirus types among cervical, vaginal, and vulvar precancers and cancers in the United States, Cancer Epidemiol. Biomark. Prev. 17 (2008) 1611–1622.
[18] N. Wentzensen, M. Schiffman, T. Dunn, R.E. Zuna, M.A. Gold, R.A. Allen, et al., Multiple human papillomavirus genotype infections in cervical cancer progression in the study to understand cervical cancer early endpoints and determinants, Int. J. Cancer 125 (2009) 2151–2158.
[19] S. de Sanjose, W.G. Quint, L. Alemany, D.T. Geraets, J.E. Klaustermeier, B. Lloveras, et al., Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study, Lancet Oncol. 11 (2010) 1048–1056.
[20] N.E. Joste, B.M. Ronnett, W.C. Hunt, A. Pearse, E. Langsfeld, T. Leete, et al., Human papillomavirus genotype-specific prevalence across the continuum of cervical neoplasia and cancer, Cancer Epidemiol. Biomark. Prev. 24 (2015) 230–240.
[21] S. Hariri, E.R. Unger, S. Schafer, L.M. Niccolai, I. Park, K.C. Bloch, et al., HPV type attribution in high grade cervical lesions: assessing the potential benefits of vaccines in a population-based evaluation in the United States, Cancer Epidemiol. Biomark. Prev. 24 (2014) 393–399.
[22] P.E. Castle, M.H. Stoler, D. Solomon, M. Schiffman., The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 (CIN2) to the quality control pathology-reviewed diagnosis: an ALTS report, Am. J. Clin. Pathol. 127 (2007) 805–815.
[23] M.H. Stoler, M. Schiffman, Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL triage study, JAMA 285 (2001) 1500–1505.
[24] M. Arbyn, M. Tommasino, C. Depuydt, J. Dillner, Are 20 human papillomavirus types causing cervical cancer? J. Pathol. 234 (2014) 431–435.
[25] V. Smelov, K.M. Elfstrom, A.L. Johansson, C. Eklund, P. Naucler, L. Arnheim-Dahlstrom, et al., Long-term HPV type-specific risks of high-grade cervical intraepithelial lesions: a 14-year follow-up of a randomized primary HPV screening trial, Int. J. Cancer 136 (2015) 1171–1180.
[26] E.W. Flagg, S.D. Datta, M. Saraiya, E.R. Unger, E. Peters, L. Cole, et al., Population-based surveillance for cervical cancer precursors in three central cancer registries, United States 2009, Cancer Causes Control 25 (2014) 571–581.
[27] M. Nygard, B.T. Hansen, J. Dillner, C. Munk, K. Oddsson, L. Tryggvadottir, et al., Targeting human papillomavirus to reduce the burden of cervical, vulvar and vaginal cancer and pre-invasive neoplasia: establishing the baseline for surveillance, PLoS One 9 (2014) e88323.
[28] S. Hariri, E.R. Unger, S.E. Powell, H.M. Bauer, N.M. Bennett, K.C. Bloch, et al., The HPV vaccine impact monitoring project (HPV-IMPACT): assessing early evidence of vaccination impact on HPV-associated cervical cancer precursor lesions, Cancer Causes Control 23 (2012) 281–288.
[29] National Cancer Institute. Surveillance, epidemiology, and end results program. 〈http://seer.cancer.gov/faststats/selections.php?#Output〉. (accessed 29.01.15).