MAJOR ARTICLE

Cervical Human Papillomavirus Prevalence in 5 Continents: Meta-Analysis of 1 Million Women with Normal Cytological Findings

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Background. Baseline information on human papillomavirus (HPV) prevalence and type distribution is highly desirable to evaluate the impact of prophylactic HPV vaccines in the near future.

Methods. A meta-analysis was performed of studies published between 1995 and 2009 that used polymerase chain reaction or Hybrid Capture 2 for HPV detection in women with normal cytological findings.

Results. The analysis included 194 studies comprising 1,016,719 women with normal cytological findings. The estimated global HPV prevalence was 11.7% (95% confidence interval, 11.6%–11.7%). Sub-Saharan Africa (24.0%), Eastern Europe (21.4%), and Latin America (16.1%) showed the highest prevalences. Age-specific HPV distribution presented with a first peak at younger ages (<25 years) and, in the Americas and Africa, a rebound at older ages (⩾45 years). Among the women with type-specific HPV data ($n = 215{,}568$), the 5 most common types worldwide were HPV-16 (3.2%), HPV-18 (1.4%), HPV-52 (0.9%), HPV-31 (0.8%), and HPV-58 (0.7%).

Conclusions. Although the prevalence of HPV in women with normal cytological findings is high and variable across world regions, HPV types 16, 18, 31, 52, and 58 are consistently found among the 10 most common types in all of them. These results represent the most comprehensive assessment of HPV burden among women with normal cytological findings in the pre–HPV vaccination era worldwide.

Epidemiological knowledge of the distribution of cervical human papillomavirus (HPV) infection in the general population is critical. HPV vaccines are being widely introduced in Western countries [1, 2], promising new broad-spectrum HPV vaccines are in development [3, 4], and the use of novel strategies based on the use of HPV DNA assays as primary cervical screening is increasingly recommended [5, 6].

In 2007, a comprehensive meta-analysis was published to assess the burden of HPV infection in women without cervical disease [7]. These data were subsequently updated and made available on the WHO/ICO Information Centre on HPV and Cervical Cancer Web site, which provided estimates by country and world region [8]. Since the last update, a large number of additional studies have been published, especially from understudied regions.

Genital HPV infection is one of the most common sexually transmitted infections worldwide. It has been estimated, on the basis of cross-sectional observations [7, 9], that ~10% of women worldwide with normal

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cytological findings carry a detectable cervical HPV infection, although a broad range of estimates (6.1%–35.5%) has been documented, depending on the HPV testing technology, study size, and the age groups and geographical region studied [7].

Here, we present a meta-analysis of cervical HPV prevalence, HPV type, and age-specific prevalence distributions restricted to women with normal cytological findings, including studies published between January 1995 and May 2009. The aim of the study was to provide robust and standardized statistics on the burden of cervical HPV infection in the female population worldwide and comparable regional estimates. Regional and country-based type-specific HPV prevalences provide baseline values against which the global impact of HPV vaccination might be assessed in the future.

METHODS

Identification and Eligibility of Relevant Studies

The literature was systematically reviewed by performing a PubMed database search, using the keywords "human papillomavirus," "cervical cancer," or "normal cytology" and restricting the search to publication dates between January 1995 and May 2009. References cited in retrieved articles were also evaluated and included if appropriate. Inclusion criteria comprised the use of polymerase chain reaction (PCR) or Hybrid Capture 2 (HC2) techniques for HPV detection, the inclusion of $\geqslant$90 women with normal cytological findings, and a detailed methodological description of cervical sampling techniques, cell transport medium, and the different PCR HPV DNA assays and HPV genotyping techniques used. Women with human immunodeficiency virus (HIV) infection were excluded when this information was available. When data proved to be incomplete or it was impossible to distinguish women with normal cytological findings from those with cervical disease or HIV coinfection, authors were contacted to obtain further details. In populations with a high prevalence of HIV, such as in Zimbabwe [10], case ascertainment was specially attempted to exclude HIV-infected women, but testing for HIV was not done in all studies.

Data Extraction

Data were extracted by 2 independent investigators (L.B. and E.F.) with discrepancies resolved by forced consensus (S.d.S.). For each study, information was retrieved regarding population characteristics (age, sample type and size, catchment through routine cervical screening), study characteristics (design, period), number of HPV-positive and HPV-negative women by age and HPV type, detailed HPV detection and genotyping methodology (eg, tests, probes, targeted HPV types), and sample collection methods. When HPV prevalence was assessed by both HC2 and PCR in the same study, only the prevalence obtained using PCR was included.

Overall, >500 articles were evaluated, from which 194 studies were included in the final analyses. Analyses were restricted to women with normal cytological findings to obtain the best comparable prevalence estimates across studies and to avoid an overrepresentation of women with abnormal cytological findings from convenience samples [11]. Table 1 lists all included studies.

Statistical Analyses

HPV prevalence by region. Studies were grouped using the United Nations classification, which categorizes the world into 5 macrogeographical (continental) regions and 22 geographical subregions [12]. HPV crude prevalence was calculated by pooling the number of HPV-positive women divided by the total number of women tested from selected studies. Binomial 95% confidence intervals were calculated for each HPV prevalence.

Weighted regression models with logit transformation of the prevalences were used to estimate HPV prevalences, adjusting for variables that were selected by stepwise introduction. The weighting variable was the number of women from each study. The final model included the following study characteristics: geographical subregion; mean age of the group of women (5 categories); ending year of the study (3 categories); HPV testing method (HC2 or PCR using the GP5/6 or GP5+/6+ primer set, MY09/11 or PGMY09/11, GP5/6[+] and [PG]MY09/11 combined, SPF10, HPV DNA chip, other PCR); tested high-risk HPV spectrum (<75% high-risk HPV types tested vs $\geqslant$75%) and tested low-risk HPV spectrum (<75% low-risk HPV types tested vs $\geqslant$75%). As previously reported [7], a set of prevalence clusters was identified by analyzing mixtures with the computer package C.A.MAN (Computer-Assisted Mixture Analysis), and it was added to the regression model [11].

Regionally adjusted HPV prevalences were further standardized by the country-specific population sizes using United Nations population data [13]. When country-specific HPV prevalence was not available, the subregion-adjusted HPV estimate was applied.

Age-specific prevalence. For this analysis, 114 studies provided the necessary information (Table 1). HPV prevalence was estimated within 6 broad age groups ($\leqslant$25, 25–34, 35–44, 45–54, 55–64, and >64 years), using for each a specific weighted regression model with logit transformation of the prevalences and standardized by the world's population geographical structure, as described above.

Type-specific HPV prevalence. One hundred thirty-six

Table 1. Studies Included in the Meta-analysis of Human Papillomavirus (HPV) and Their Characteristics by Region

This table is available in its entirety in the online version of the *Journal of Infectious Diseases*.

studies provided type-specific HPV prevalence data in women with normal cytological findings (Table 1). Type-specific HPV prevalence was expressed as the proportion of women positive for a given HPV type among all women tested for this type. Evaluation of types was always based on the ability of the assay to detect them. Type-specific HPV prevalence was always provided as a crude estimate weighted by the number of women tested and further standardized by the world's population geographical structure. Each HPV type was evaluated independently of others; estimations show the presence of a given type either as a single type or combined with the presence of other concomitant types (multiple infections).

RESULTS

Our analysis included 194 studies testing for cervical HPV infection in women with normal cytological findings, for a total of 1,016,719 women tested. Of these studies, 17.0% were population-based surveys, 33.0% were from routine screening programs, 23.2% were case-controls studies, and 26.2% were other types of cross-sectional studies with convenience sampling. Studies of routine cervical screening programs (not necessarily population based) provided the large majority of women (76.3%). Close to half of the women analyzed came from a single study in the United States from a private insurance plan [14].

The estimated crude and adjusted HPV prevalences among women with normal cytological findings worldwide were 7.2% and 11.7%, respectively (Table 2). Sub-Saharan African regions (24.0%), Latin America and the Caribbean (16.1%), Eastern Europe (14.2%), and Southeastern Asia (14.0%) had the highest prevalences. However, there were remarkable differences in the estimates, not only between regions but also between countries and among studies within the same region. Figure 1 shows point estimates of adjusted HPV prevalences by geographical region and the contributing study-specific HPV prevalences by country. This intracountry and intraregion heterogeneity was illustrated by countries such as the United States, with 19 studies and HPV prevalence estimates ranging from 2.9% to 80.8% [15, 16] (see Table 1 for more details). The large American study by Castle et al [14], which had an HPV prevalence of 4.0% for women aged ⩾30 years attending screening, strongly determined the global estimate (4.7%) for the Northern America region (10.2% excluding Castle's study) but had less of an effect on the world estimate (from 11.7% to 12.8%).

This heterogeneity was partially explained and controlled for by the variables selected in the adjusted model (Table 3). Women aged 35–54 years were the most represented in the studies included and therefore had a higher weight in the overall estimate. Regarding the spectrum of tested HPV types, if the analysis was restricted to studies reporting results from generic PCR primers (able to identify both high- and low-risk types) or the 2 probes of HC2, covering both high- and low-risk HPV types, the worldwide HPV prevalence increased >2-fold in comparison with high-risk testing only (12.0% vs 5.0%). HPV prevalence varied according to the HPV testing method used. The adjusted HPV prevalence for the MY09/11 family of consensus PCR primers was 70.4% higher than that observed for GP5/6 or GP5+/6+. The PCR SPF10 primer presented the highest HPV detection rates. Population-based studies showed an HPV prevalence of 9.8%, which was higher than that observed among women attending screening programs or participating in case-control studies.

Figure 2 and Table 4 present HPV prevalence by age and region, adjusted by factors described in Table 3. In all regions, a peak in HPV infection was found at younger ages (<25 years), declining to a plateau in middle age. In some regions, a modest second peak was observed at age ⩾40 years. This second peak was clearly identified at age >45 years in Central America and South America and >55 years in Western Africa. A less pronounced second peak was also observed in Southern Asia, Southern Europe, and Southern Africa. In the rest of the regions, this second peak was not observed.

The most common HPV types found among 215,568 women with normal cytological findings worldwide were the oncogenic types, namely, HPV types 16, 18, 52, 31, 58, 39, 51, and 56 (Figure 3). HPV-6 was the most frequent low-risk type in the Americas (0.9% and 2.0% in Latin and Northern America, respectively) but was less common in Asia (0.2%). In Africa, HPV-6 had an estimated prevalence of 0.8%, similar to HPV types 83, 72, 70, and 51 (not shown in Figure 3). Compared with other types, HPV-31 was especially frequent in Europe (2.3%), and HPV-52 was especially frequent in Northern America (2.1%), Africa (2.4%), and Asia (0.7%). HPV-18 was second after HPV-16 in the overall estimate, with some international variability. HPV-45 was rare (0.5%), usually ranking after the rest of the oncogenic types.

Of the global HPV burden, 22.5% (95% confidence interval, 21.9%–23.2%) of HPV infections were estimated to be produced by HPV-16. A significant inverse correlation was observed between overall HPV prevalence and the contribution of HPV-16 (correlation coefficient, −64.8%; $P = .017$), with the lowest HPV-16 proportions in the regions with the highest prevalences. Sub-Saharan African regions had the lowest HPV-16 contributions estimates (13.7%, 11.3%, and 11.1% for Southern, Eastern, and Western Africa, respectively), and Northern America (24.3%), Western Europe (24.4%), Southern Europe (28.9%), and Southern Asia (32.3%) had the highest.

Approximately 3.2% of women tested had infections with multiple HPV types, corresponding to 20.0% among HPV-positive women. Further multivariate analyses could not identify any clear pattern of determinants for multiple infections within the available data by study (analysis not shown).

Table 2. Human Papillomavirus (HPV) Prevalence by Region

Region	Countries (no. of studies)	Women, no.		HPV prevalence, % (95% CI)	
		Total tested	HPV positive	Crude	Adjusted[a]
World		1,016,719	73,018	7.2 (7.1–7.2)	11.7 (11.6–11.7)
Less developed regions[b]		120,008	17,207	14.3 (14.1–14.5)	11.8 (11.6–12.0)
More developed regions[c]		895,862	55,747	6.2 (6.2–6.3)	11.3 (11.2–11.3)
Africa		8568	1829	21.3 (20.5–22.2)	21.1 (20.2–22.0)
Northern Africa	Tunisia (1), Morocco (2), Egypt (1), Algeria (1)	863	94	10.9 (8.9–13.2)	9.2 (7.3–11.3)
Sub-Saharan Africa		7705	1735	22.5 (21.6–23.5)	24.0 (23.1–25.0)
Eastern Africa	Zimbabwe (1), Mozambique (1), Kenya (1)	751	252	33.6 (30.2–37.1)	33.6 (30.2–37.1)
Southern Africa	South Africa (3)	2485	521	21.0 (19.4–22.6)	17.4 (15.9–18.9)
Western Africa	Senegal (2), Nigeria (2), Guinea (1), Gambia (1), Cote d'Ivoire (2)	4469	962	21.5 (20.3–22.8)	19.6 (18.5–20.8)
America		692,964	39,522	5.7 (5.6–5.8)	11.5 (11.4–11.6)
Latin America and Caribbean		48,171	8279	17.2 (16.9–17.5)	16.1 (15.8–16.4)
Caribbean	Trinidad and Tobago (1)	212	75	35.4 (29.0–42.2)	35.4 (29.0–42.2)
Central America	Mexico (8), Honduras (2), Guatemala (1), Costa Rica (2), Belize (1)	24,783	5110	20.6 (20.1–21.1)	13.0 (12.6–13.5)
South America	Peru (3), Paraguay (2), Colombia (3), Chile (1), Brazil (6), Argentina (3)	17,500	2302	13.2 (12.7–13.7)	15.3 (14.7–15.8)
Northern America	United States (19), Greenland (1), Canada (6)	644,793	31,243	4.8 (4.8–4.9)	4.7 (4.6–4.7)
Asia		84,710	9235	10.9 (10.7–11.1)	9.4 (9.2–9.6)
Eastern Asia	Mongolia (1), South Korea (6), Japan (12), China (14)	55,365	6983	12.6 (12.3–12.9)	10.7 (10.4–10.9)
Southern Asia	India (12)	23,061	1816	7.9 (7.5–8.2)	7.1 (6.7–7.4)
Southeastern Asia	Vietnam (2), Thailand (7), Philippines (1), Indonesia (1)	4849	405	8.4 (7.6–9.2)	14.0 (13.0–15.0)
Western Asia	Turkey (1), Bahrain (1)	1435	31	2.2 (1.5–3.1)	1.7 (1.1–2.5)
Europe		229,628	22,368	9.7 (9.6–9.9)	14.2 (14.1–14.4)
Eastern Europe	Russian Federation (2), Poland (1), Hungary (1), Belarus (1), Latvia (1)	4053	904	22.3 (21.0–23.6)	21.4 (20.1–22.7)
Northern Europe	United Kingdom (8), Sweden (3), Norway (3), Lithuania (1), Ireland (1), Finland (1), Denmark (4)	97,242	10,531	10.8 (10.6–11.0)	10.0 (9.8–10.2)
Southern Europe	Spain (5), Italy (12), Greece (3), Croatia (1)	41,726	3820	9.2 (8.9–9.4)	8.8 (8.5–9.0)
Western Europe	Switzerland (1), Netherlands (4), Germany (2), France (7), Belgium (4)	77,445	5652	7.3 (7.1–7.5)	9.0 (8.8–9.2)

NOTE. CI, confidence interval.

[a] Adjusted HPV prevalence standardized by the world's geographical structure. Model adjusted by geographical subregion, mean age of women, ending year of the study, HPV testing method, proportion of high-risk HPV types tested, proportion of low-risk HPV types tested, and cluster (analysis of mixtures).

[b] Africa, the Americas (excluding Northern America), Caribbean, Central America, South America, Asia (excluding Japan), and Oceania (excluding Australia and New Zealand) [12].

[c] Northern America, Europe, Japan, Australia, and New Zealand [12].

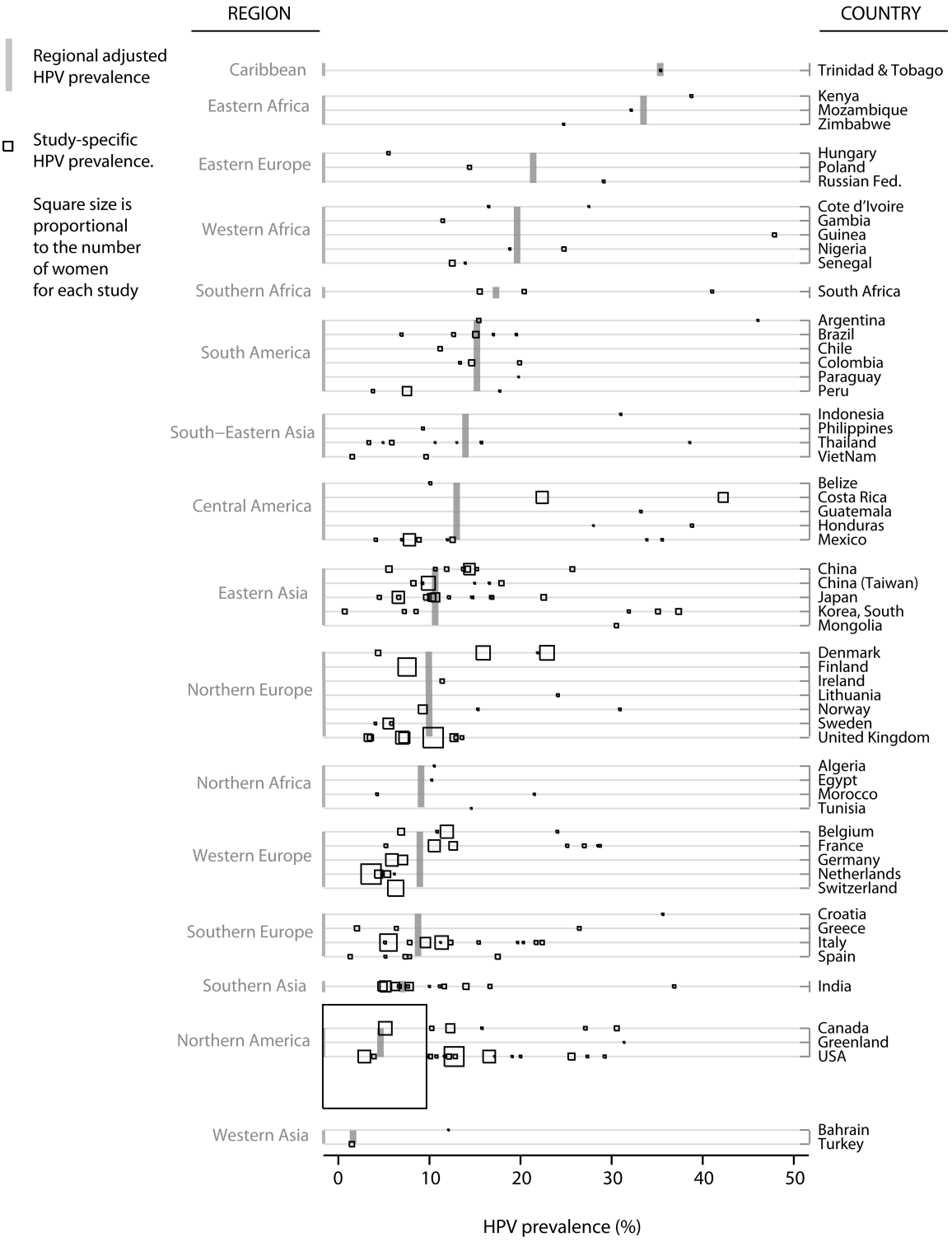

Figure 1. Adjusted human papillomavirus (HPV) prevalence estimates by geographical region and study-specific HPV prevalence by country. Square sizes represent the number of women for each study. Vertical bars represent the resulting adjusted HPV prevalence from the regression models for each corresponding region. Some extreme values (HPV prevalences of >50%) have been omitted (see Table 1 for specific values). Because of the size of the study by Castle et al [14] (*largest square at bottom of figure*), its square appears to overlap adjacent countries but corresponds only to the United States.

Table 3. Overall Human Papillomavirus (HPV) Prevalence by Selected Variables

Variable	Women, no.		HPV prevalence, % (95% CI)	
	Total tested	HPV positive	Crude	Adjusted[a]
Mean age of enrolled women				
<25 years	27,343	5960	21.8 (21.3–22.3)	24.0 (23.5–24.5)
25–34 years	60,475	8901	14.7 (14.4–15.0)	13.9 (13.6–14.1)
35–44 years	263,740	27,962	10.6 (10.5–10.7)	9.1 (9.0–9.2)
45–54 years	658,695	28,691	4.4 (4.3–4.4)	4.2 (4.2–4.3)
⩾55 years	328	44	13.4 (9.9–17.6)	7.5 (5.0–11.0)
Last year of study				
⩽1999	109,392	13,340	12.2 (12.0–12.4)	10.4 (10.2–10.5)
2000–2003	167,263	16,574	9.9 (9.8–10.1)	8.2 (8.0–8.3)
⩾2004	740,064	43,104	5.8 (5.8–5.9)	4.8 (4.8–4.9)
Spectrum of HPV types tested for				
High and low risk	164,818	25,747	15.6 (15.4–15.8)	12.0 (11.9–12.2)
High risk	851,901	47,271	5.5 (5.5–5.6)	5.0 (5.0–5.1)
Main HPV testing method				
PCR				
GP5/6 or GP5+/6+	81,792	7266	8.9 (8.7–9.1)	7.1 (7.0–7.3)
MY09/11 or PGMY09/11	48,762	7333	15.0 (14.7–15.4)	12.1 (11.8–12.4)
GP5/6(+) and (PG)MY09/11 combined	3597	664	18.5 (17.2–19.8)	14.8 (13.7–16.0)
SPF10	5526	2285	41.3 (40.0–42.7)	41.3 (40.0–42.6)
HPV DNA chip	4096	1016	24.8 (23.5–26.2)	15.1 (14.0–16.2)
Other PCR	60,269	8013	13.3 (13.0–13.6)	10.9 (10.7–11.2)
HC2	812,677	46,441	5.7 (5.7–5.8)	5.1 (5.0–5.1)
Sample origin				
Population based	133,629	15,311	11.5 (11.3–11.6)	9.8 (9.6–10.0)
Screening	775,775	42,164	5.4 (5.4–5.5)	4.9 (4.8–4.9)
Controls (case-control studies)	46,610	3896	8.4 (8.1–8.6)	6.2 (6.0–6.4)
Other	60,705	11,647	19.2 (18.9–19.5)	15.5 (15.3–15.8)

NOTE. CI, confidence interval; HC2, Hybrid Capture 2; PCR, polymerase chain reaction.

[a] Model adjusted by geographical subregion, mean age of women, ending year of the study, HPV testing method, proportion of high-risk HPV types tested, proportion of low-risk HPV types tested, and cluster (analysis of mixtures).

DISCUSSION

In the last 15 years, major efforts have been made worldwide to generate epidemiological data on the carriage of cervical HPV DNA. The meta-analysis presented here combines 194 studies from 59 countries published since 1995 and comprises 1,016,719 women with normal cytological findings tested for cervical HPV infection with PCR techniques or HC2. It is the largest meta-analysis conducted to date, including studies selected on the basis of their quality and aiming to produce standardized results across populations. The findings show that at a given point in time 11.7% of women with normal cervical cytological findings had a detectable cervical HPV infection. The estimate varies by geography and age. African and Latin American regions showed higher average HPV prevalence estimates than European, Northern American, and Asian regions. Country-specific adjusted HPV prevalences ranged from 1.6% to 41.9%. The age distribution of cervical HPV infection showed a bimodal curve in half of the regions, with a first peak at younger ages (just after sexual debut), a lower prevalence plateau at middle ages, and a variable rebound at older ages (⩾45 years). Vaccine-targeted types 16 and 18 were the most frequent types worldwide, with HPV-16 being the most common type everywhere. HPV-18 and other oncogenic types, such as types 52, 31, 58, 39, 56, and 51, shared similar prevalences and were among the most common HPV types after HPV-16. HPV-31 was very common in Europe and Latin America but was much less common in Northern America or Asia, where it was surpassed by HPV-52. HPV-18 ranked in the top positions in most regions.

Chiefly, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59—classified as group 1, "carcinogenic to humans," in the last review of human carcinogens by the International Agency for Research on Cancer (IARC) [17]—were found to be the most common types in the general female population worldwide, accounting for 70% of HPV infections in the presence of normal cytological findings. Although these most fre-

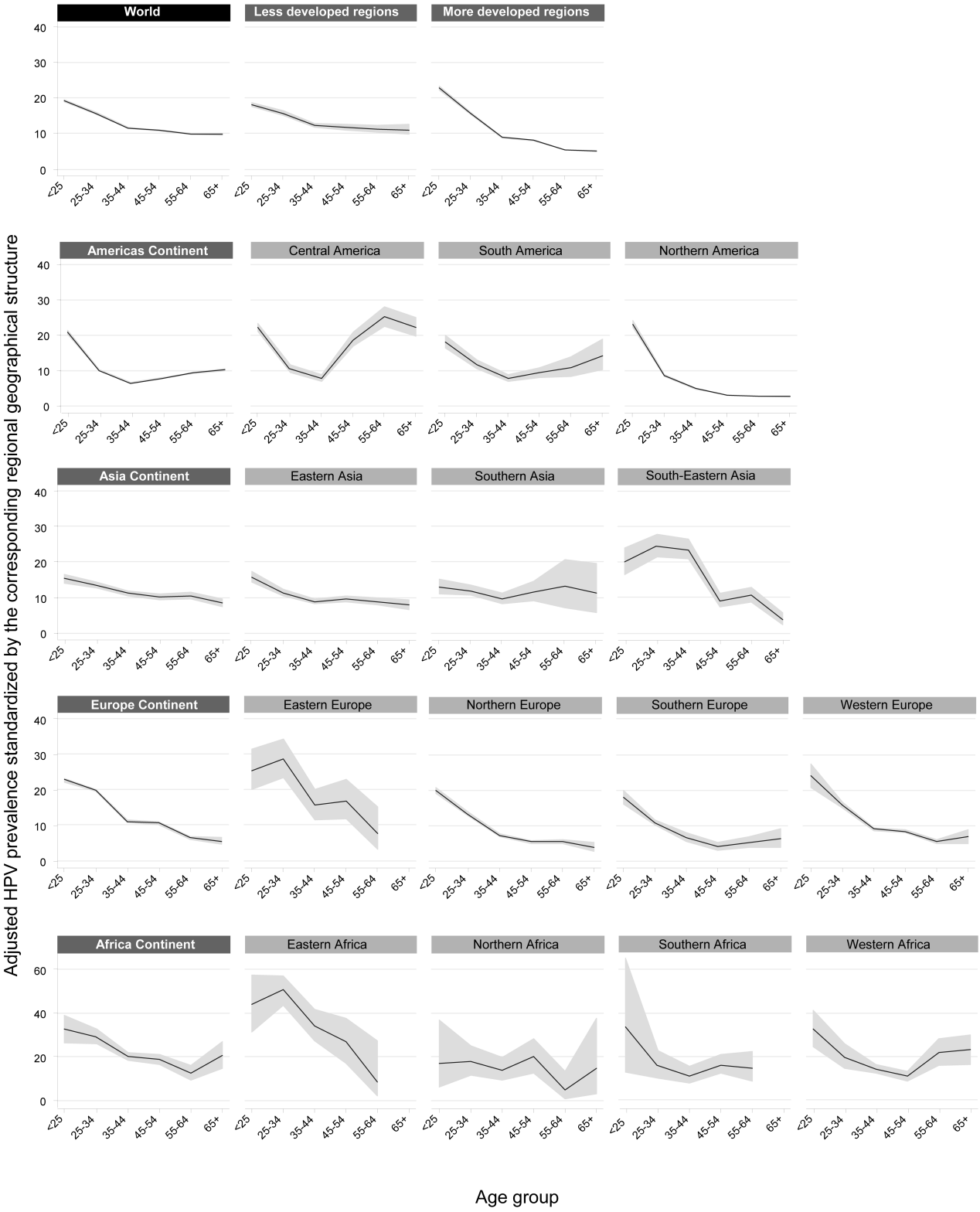

Figure 2. Human papillomavirus (HPV) prevalence and 95% confidence intervals (*shaded areas*) by region and age. See Table 1 for contributing studies.

Table 4. Adjusted Human Papillomavirus (HPV) Prevalence by Region and Age Group

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quent types (Figure 3) happened to be those most often tested for, the general distribution is consistent with previous IARC surveys that used the same protocols and wide-spectrum HPV testing methods [9]. HPV-16 was not only the most prevalent type but also had a high relative contribution compared with other types. Among HPV-positive women, HPV-16 accounted for >22% of HPV infections. Interestingly, this contribution correlated inversely with the overall HPV prevalence, with the result that the regions with higher HPV prevalences had the lowest relative contributions of HPV-16. This pattern is explained by a higher prevalence of other HPV types in areas where HPV is extremely common (ie, Africa), and the increase is not explained by the contribution of any other single type. This variability in the contribution of HPV-16 may translate into a difference in the fraction of cervical squamous cell carcinoma attributable to HPV-16 in the corresponding regions.

International correlation between the prevalence of high-risk HPV infection in the general population and its cervical cancer burden has been shown, mostly at elderly ages [18]. This correspondence is also present in our results; the regions with high HPV prevalences are the ones with the highest cervical cancer incidences, and the regions with lower prevalences had the lowest incidences. However, 2 regions did not follow this pattern: Southern Asia and Eastern Europe. Studies from Southern Asia, mostly from India, presented a relatively high incidence rate of cervical cancer (age-standardized incidence rate [ASIR], 25.0 new cases per 100,000 women per year) [19] but low HPV prevalence estimates, with an overall adjusted prevalence of 7.1% (Table 2 and Figure 1). Eastern Europe was the opposite, presenting a high HPV prevalence (21.4%) (Table 2) but a relatively low incidence (ASIR, 14.5 new cases per 100,000 women per year [below the worldwide ASIR of 15.2]) [19].

Age-specific HPV distribution presents as either a bimodal curve or a unimodal distribution skewed to the left (Figure 2). The reasons behind these 2 different patterns are still controversial. The detection of HPV infection in women has been found to start consistently with a peak just after the onset of sexual relations, usually from 15 years of age [20], reaching prevalences up to 80% in some populations [16], mostly at the expense of transient infections that clear rapidly [21]. The first mode of HPV infection observed in women <25 years old (Figure 2) reflects this pattern, although the present meta-analysis was blind to the beginning, attainment, and exact age at the maximum of this peak. Figure 2 shows how after this first peak the prevalence of infection gradually declined to a plateau in middle-aged women.

In some populations a less steep second peak in older women has also been observed [7, 22, 23], and in 2 large Central American studies this second peak was even equal to the first peak [24, 25]. It has been hypothesized that immunosenescence, changes in sexual behavior during middle age (both for men and women), or a cohort effect may play a role [7]. Other scientists have suggested that this perimenopausal increase may be mostly due to higher rates of HPV persistence at older ages rather than new HPV acquisition, partly at the expense of infection with low-risk types [26]. In contrast, no association between age and duration of incident HPV infections was observed in other similar large Latin American cohort studies [27, 28]. The Colombian cohort study presented a bimodal age-specific curve for incident HPV infections, showing a second peak of high-risk HPV infections around menopause [29]. Another factor to consider is cytological screening. Screening not only reduces the burden of precancerous lesions and related persistent HPV infections, but removal of lesions may have a direct antigen-presenting effect that could protect against subsequent HPV infections [30]. Regions with effective screening in age groups <40 years may therefore have this second peak attenuated, as consistently observed in Europe and Northern America (Figure 2). Supporting the latter possibility, the Costa Rica study presented a clear U-shaped curve of age-specific HPV prevalence at enrollment, but at follow-up, when this population was effectively screened, the curve proved much less pronounced [26]. Other studies have shown that HPV prevalence was independently associated with perimenopausal status [31], thus implying some hormonal interaction with the HPV life cycle. Althoff et al [31] suggested that geographical variability in this second peak may be partially explained by indirect indicators of menopausal hormonal patterns, such as body mass index and ethnicity, and not only age. The second peak of HPV prevalence might be multifactorial and result from the interplay of sexual behavior [32], viral characteristics such as HPV type and variants [33], host susceptibility, and previous individual screening practices.

One of the difficulties in the interpretation of meta-analyses is to properly accommodate the heterogeneity of the studies. In our analysis, heterogeneity regarding methods of HPV detection and the selection and representativeness of the populations were the most influential variables (Figure 1).

To limit heterogeneity related to HPV detection methods, only those studies using PCR-based methods or HC2 were included. However, sensitivity and specificity within PCR-based methods vary largely, aside from built-in changes due to the development of techniques over time. Women from the same underlying population tested with different techniques may double or even triple the estimated HPV prevalence. For instance, a sample of 196 Mozambican women with normal cytological findings showed HPV prevalences as diverse as 32.1%

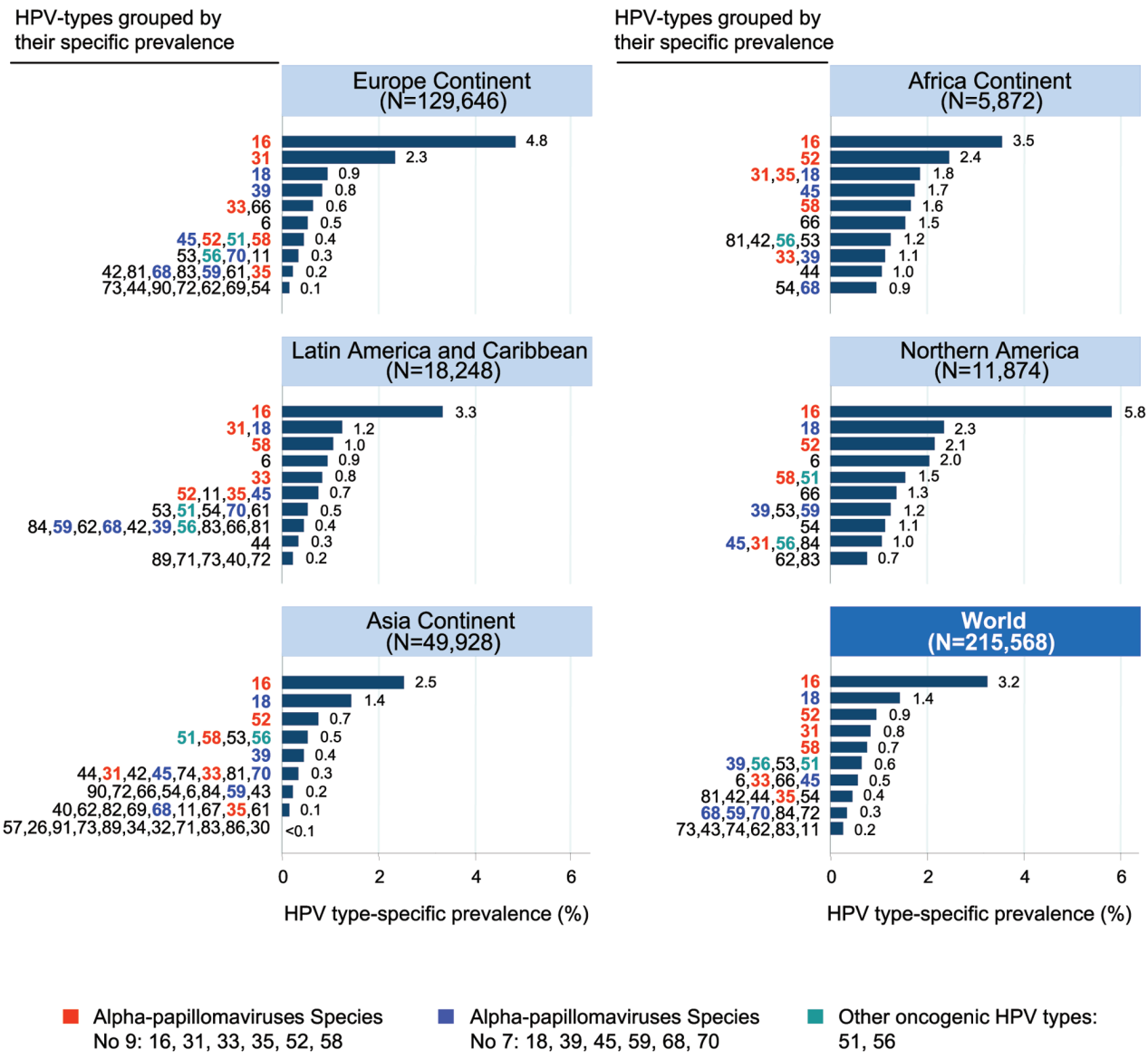

Figure 3. Type-specific human papillomavirus (HPV) prevalence for most frequent HPV types by geographical region. Type-specific HPV prevalence is weighted by study size and standardized by the world's geographical structure. See Table 1 for contributing studies.

and 76.0% by PCR with PGMY09/11 and SPF10, respectively [34, 35]. A large number of comparative studies have presented HC2 as the HPV detection method with the lowest analytical sensitivities but with a validated clinical value for screening. PCR with GP5+/6+ and PGMY09/11 showed intermediate analytical sensitivity, and PCR with SPF10 showed the highest sensitivity [36, 37], particularly at very low concentrations of HPV, which is common in normal cytological findings [38]. Another source of variability is the differential sensitivity of PCR primers sets to specific HPV types [39], especially with the less frequent types. Although type-specific prevalences have been estimated only for the corresponding targeted types in each study, certain types may be underestimated in some regions relative to others where more sensitive techniques were used. The type-specific performance of the assays depends not only on the technique but also on the laboratory and the processing of the specimen [37]. The standardization of protocols and techniques in population-based genotyping characterizations is crucial for HPV vaccine surveillance and international comparisons [40].

Women included in most of the studies were participants in cervical screening programs or, to a lesser extent, were from population-based surveys. The rationale behind the strict inclusion of women with normal cytological findings was to minimize the selection bias in studies recruiting women from colposcopic clinics or from clinical settings with a higher proportion

of women with cytological abnormalities—and thus HPV infection—than in the general population. Cytology, however, is a subjective and poorly reproducible test with limited sensitivity that requires regular repetitions to achieve the desired efficacy [41]. Even when an analysis is restricted to women considered to be cytologically normal, false-negative rates may differ between settings and affect HPV prevalence estimates. However, considering that interobserver variability is low in women with normal cytological findings, we propose that HPV in such women is a robust conservative estimate of the HPV prevalence in the general population, allowing comparisons across populations.

Geographical representation of the studies included in the meta-analysis differed from the real-world distribution of population. European and Northern American studies contributed the most (22.6% and 63.4%, respectively) while accounting for only 19.6% of the worldwide population. To overcome the studies' lack of geographical representativeness and to generate a global summary estimate, all HPV prevalence estimates were standardized by the world's population structure, and countries with greater populations were given more weight, irrespective of the number of studies or the number of women studied from these countries.

In summary, HPV prevalence and type distribution restricted to women with normal cytological findings may be the indicator of choice when population-based sampling is not available or feasible. It allows interpretation and comparisons based on a large number of reports from screening studies and generates slightly conservative estimates less influenced by interobserver variability in cytological readings. This meta-analysis confirms the high prevalence of HPV infection in cross-sectional measurements among women with normal cytological findings worldwide, although findings are highly variable depending on the population, and it further indicates that the vast majority of detected HPV infections include high-risk types.

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References

1. Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **2007**; 56:1–24.
2. European Cervical Cancer Association. HPV vaccination across Europe. http://www.ecca.info/fileadmin/user_upload/HPV_Vaccination/ECCA_HPV_Vaccination_April_2009.pdf. Published **2009**. Accessed 31 May 2009.
3. Jagu S, Karanam B, Gambhira R, et al. Concatenated multitype L2 fusion proteins as candidate prophylactic pan-human papillomavirus vaccines. J Natl Cancer Inst **2009**; 101:782–792.
4. Merck. Broad spectrum HPV (human papillomavirus) vaccine study in 16-to 26-year-old women (V503–001). http://clinicaltrials.gov/show/NCT00543543. Accessed 2 November 2009.
5. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med **2009**; 360:1385–1394.
6. Muñoz N, Franco EL, Herrero R, et al. Recommendations for cervical cancer prevention in Latin America and the Caribbean. Vaccine **2008**; 26(suppl 11):L96–L107.
7. de Sanjose S, Diaz M, Castellsague X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis **2007**;7: 453–459.
8. World Health Organization and Institut Català d'Oncologia (ICO). WHO/ICO Information Centre on HPV and Cervical Cancer. http://www.who.int/hpvcentre/en/. Accessed 16 March 2009.
9. Clifford GM, Gallus S, Herrero R, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet **2005**; 366:991–998.
10. Womack SD, Chirenje ZM, Gaffikin L, et al. HPV-based cervical cancer screening in a population at high risk for HIV infection. Int J Cancer **2000**; 85:206–210.
11. Bohning D, Dietz E, Schlattmann P. Recent developments in computer-assisted analysis of mixtures. Biometrics **1998**; 54:525–536.
12. United Nations Statistics Division. Standard country and area codes classifications (M49). http://unstats.un.org/unsd/methods/m49/m49regin.htm. Accessed 16 March 2009.
13. Population Division, Department of Economic and Social Affairs, United Nations Secretariat. World population prospects: the 2005 revision. New York, NY: United Nations. **2005**.
14. Castle PE, Fetterman B, Poitras N, Lorey T, Shaber R, Kinney W. Five-year experience of human papillomavirus DNA and Papanicolaou test cotesting. Obstet Gynecol **2009**; 113:595–600.
15. Zhao C, Elishaev E, Yuan KH, Yu J, Marshall Austin R. Very low human papillomavirus DNA prevalence in mature women with negative computer-imaged liquid-based Pap tests. Cancer **2007**; 111:292–297.
16. Moscicki AB, Hills N, Shiboski S, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. JAMA **2001**; 285:2995–3002.
17. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens. B. Biological agents. Lancet Oncol **2009**; 10:321–322.
18. Maucort-Boulch D, Franceschi S, Plummer M; IARC HPV Prevalence Surveys Study Group. International correlation between human papillomavirus prevalence and cervical cancer incidence. Cancer Epidemiol Biomarkers Prev **2008**; 17:717–720.
19. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, cancer incidence and mortality worldwide: IARC CancerBase no. 10 [Internet]. Lyon, France: International Agency for Research on Cancer, **2010**. http://globocan.iarc.fr. Accessed 15 June 2010.
20. Wellings K, Collumbien M, Slaymaker E, et al. Sexual behaviour in context: a global perspective. Lancet **2006**; 368:1706–1728.
21. Rodriguez AC, Schiffman M, Herrero R, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst **2008**; 100:513–517.
22. Franceschi S, Herrero R, Clifford GM, et al. Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. Int J Cancer **2006**; 119:2677–2684.
23. Smith JS, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of infection with human papillomavirus in females: a global review. J Adolesc Health **2008**; 43:S5–S25.
24. Herrero R, Castle PE, Schiffman M, et al. Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica. J Infect Dis **2005**; 191:1796–1807.
25. Lazcano-Ponce E, Herrero R, Muñoz N, et al. Epidemiology of HPV

infection among Mexican women with normal cervical cytology. Int J Cancer **2001**; 91:412–420.
26. Castle PE, Schiffman M, Herrero R, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. J Infect Dis **2005**; 191:1808–1816.
27. Trottier H, Mahmud S, Prado JC, et al. Type-specific duration of human papillomavirus infection: implications for human papillomavirus screening and vaccination. J Infect Dis **2008**; 197:1436–1447.
28. Muñoz N, Hernandez-Suarez G, Mendez F, et al. Persistence of HPV infection and risk of high-grade cervical intraepithelial neoplasia in a cohort of Colombian women. Br J Cancer **2009**; 100:1184–1190.
29. Muñoz N, Mendez F, Posso H, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. J Infect Dis **2004**; 190:2077–2087.
30. Passmore JA, Morroni C, Shapiro S, Williamson AL, Hoffman M. Papanicolaou smears and cervical inflammatory cytokine responses. J Inflamm (Lond) **2007**; 4:8.
31. Althoff KN, Paul P, Burke AE, Viscidi R, Sangaramoorthy M, Gravitt PE. Correlates of cervicovaginal human papillomavirus detection in perimenopausal women. J Womens Health (Larchmt) **2009**; 18:1341–1346.
32. Bosch FX, Burchell AN, Schiffman M, et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine **2008**; 26(suppl 10):K1–K16.
33. Sichero L, Ferreira S, Trottier H, et al. High grade cervical lesions are caused preferentially by non-European variants of HPVs 16 and 18. Int J Cancer **2007**; 120:1763–1768.
34. Castellsague X, Klaustermeier J, Carrilho C, et al. Vaccine-related HPV genotypes in women with and without cervical cancer in Mozambique: burden and potential for prevention. Int J Cancer **2008**; 122:1901–1904.
35. Castellsague X, Menendez C, Loscertales MP, et al. Human papillomavirus genotypes in rural Mozambique. Lancet **2001**; 358:1429–1430.
36. Snijders PJ, van den Brule AJ, Meijer CJ. The clinical relevance of human papillomavirus testing: relationship between analytical and clinical sensitivity. J Pathol **2003**; 201:1–6.
37. Gravitt PE, Coutlee F, Iftner T, Sellors JW, Quint WG, Wheeler CM. New technologies in cervical cancer screening. Vaccine **2008**; 26(suppl 10):K42–K52.
38. Kleter B, van Doorn LJ, Schrauwen L, et al. Development and clinical evaluation of a highly sensitive PCR-reverse hybridization line probe assay for detection and identification of anogenital human papillomavirus. J Clin Microbiol **1999**; 37:2508–2517.
39. Qu W, Jiang G, Cruz Y, et al. PCR detection of human papillomavirus: comparison between MY09/MY11 and GP5+/GP6+ primer systems. J Clin Microbiol **1997**; 35:1304–1310.
40. World Health Organization. WHO HPV Laboratory Network. http://www.who.int/biologicals/areas/vaccines/hpv_labnet/en/index.html. Accessed 25 November 2009.
41. Kitchener HC, Castle PE, Cox JT. Chapter 7: Achievements and limitations of cervical cytology screening. Vaccine **2006**; 24(suppl 3):S63–S70.