

# Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis



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We set out to estimate the age and genotype-specific prevalence of cervical human papillomavirus (HPV) DNA in women with normal cervical cytology worldwide by meta-analysis of a systematic literature review. Reports on HPV prevalence published between January, 1995, and January, 2005, were retrieved. To be included, studies required information on cervical cytology, plus detailed descriptions of study populations, methods used to collect cervical samples, and assays used for HPV DNA detection and typing. Final analyses included 78 studies that could be separated into women with normal cytology, and of which subsets of 44 and 48 studies had data on age and type-specific HPV prevalence, respectively. Overall HPV prevalence in 157 879 women with normal cervical cytology was estimated to be 10.4% (95% CI 10.2–10.7). Corresponding estimates by region were Africa 22.1% (20.9–23.4), Central America and Mexico 20.4% (19.3–21.4), northern America 11.3% (10.6–12.1), Europe 8.1% (7.8–8.4), and Asia 8.0% (7.5–8.4). In all world regions, HPV prevalence was highest in women younger than 35 years of age, decreasing in women of older age. In Africa, the Americas, and Europe, a clear second peak of HPV prevalence was observed in women aged 45 years or older. On the basis of these estimates, around 291 million women worldwide are carriers of HPV DNA, of whom 32% are infected with HPV16 or HPV18, or both. The HPV types most commonly detected are similar to those most commonly described in pre-neoplastic and cancer cases, although the relative contribution of HPV16 and HPV18 is substantially lower in cytologically normal women.

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## Introduction

Infection by certain types of human papillomavirus (HPV) is recognised as a causal and necessary factor for cervical cancer.<sup>1–3</sup> Cervical cancer represents the second most common malignancy in women around the world and contributes to 9.8% of all female cancers.<sup>4</sup> Other tumours related to HPV, such as anal, vaginal, vulvar, penile, and oropharyngeal, represent an additional 0.7% of all cancer sites in both men and women, so that HPV is estimated to be responsible for 5.2% of all cancers worldwide.<sup>5</sup> A cross-sectional evaluation of the HPV DNA prevalence in 13 countries estimated that 6.6% of women in the age-range 15–74 years with normal cytology are carriers of HPV DNA, with marked variation within and between world regions (range 1.4–25.6%).<sup>6</sup> Therefore, HPV can be considered as the most common known sexually transmitted agent worldwide.

To allow further comparisons of prevalence, type, and age-distribution of HPV across world regions, published data from female populations participating in screening programmes or epidemiological studies were retrieved and pooled. Statistical models were built to adjust for confounding variables and to standardise results to allow comparability of HPV prevalence estimates worldwide.

## Methods

### Identification and eligibility of relevant studies

A systematic Medline search was done to identify all reports on HPV prevalence published from January, 1995, to January, 2005, using combinations of the following index terms: “Papovaviridae”, “Papillomavirus (human)”, “Cervix neoplasms (epidemiology OR virology OR prevention and control)”, “epidemiology”, “prevalence”, “DNA probes

(HPV)”, “polymerase chain reaction”, “enzyme-linked immunosorbent assay”, “women/female”, and “population”. Relevant additional references cited in retrieved articles were also evaluated for inclusion together with the review of abstract books from relevant scientific meetings, the Cochrane library, and Lilacs database. Only papers published in English, French, and Spanish were reviewed.

Included studies had to meet all the following criteria: (1) the possibility to separate HPV prevalence data for women with normal cytology only; (2) use of PCR-based or high-risk Hybrid Capture 2 (HC2) technology to detect HPV DNA; (3) inclusion of at least 100 women with cytology results; and (4) detailed methodological description of cervical sampling techniques, cell transport medium, and details of the different PCR HPV DNA assays and HPV typing used.

### Data extraction

Data were extracted by two independent investigators (MD, SS, or RV) with discrepancies resolved by forced consensus. The following information was abstracted from each included study: first author; journal name and year of publication; country of study population; study period; study sample type (population-based [random sample of the population and population-based screening programmes] or convenient [mainly including family planning clinics and colposcopic clinics]); study design (derived from case-control or other cross-sectional studies); age range; sample size; number of HPV-positive, HPV-negative, and inadequate test results; type-specific HPV prevalence, when available; distribution of women and HPV prevalence by age-group, when available; cervical cell collection media (phosphate-buffered saline or other);

sample collection device (spatula, cytobrush, cervical or vaginal washing, and other); HPV testing method (PCR or HC2; all the studies selected that used HC2 did the high-risk probe B and only one also used the low risk probe<sup>7</sup>); if PCR was used, PCR primers (MY09/11 [including HMBO1], GP5+/6+ and GP5/6, SPF-10, CPI-CPIIG, and L1C1/L1C2); HPV typing method (dot blot hybridisation, Southern blot hybridisation, reverse line, RFLP, PCR with type-specific probes, direct sequencing, and other), when available.

When HPV prevalence was assessed by both HC2 and PCR, only the prevalence obtained using PCR was included. Furthermore, when key information was not available in the published paper, missing data were requested from the authors or principal investigators. We contacted over 70 authors that published their reports up to January, 2005, and we received additional information for 47 studies.

The units of geographical evaluation were continent, region (when smaller than continents), and country. All studies were grouped into geographical regions based on Globocan, a project of the International Agency for Research on Cancer (IARC) that presents incidence, prevalence, and mortality estimates of 27 cancers for all countries in the world.<sup>4</sup> The geographical areas included four regions in Africa (eastern, northern, western, and southern Africa), three regions in the Americas (northern America [includes Greenland], Central America [includes Mexico], and South America, and four regions in Europe

(northern, southern, western, and eastern Europe), four regions in Asia (eastern Asia, southeastern Asia, south-central Asia, and Japan and Taiwan). No studies were available from the Caribbean, central Africa, western Asia, the Pacific islands, or Australia and New Zealand. Countries were also classified as less or more developed according to Globocan.<sup>4</sup> For studies including women from different countries or regions, data were extracted separately for each country/region.

In total, more than 312 papers were evaluated from which 78 studies were included in final analyses. Analyses were restricted to women with normal cytology to obtain the best comparable prevalence estimates across studies, and to avoid an over-representation of women with abnormal cytology from convenient samples. The webtable lists all the included studies and some key study variables.

### Statistical analyses

#### HPV prevalence by regions

HPV prevalence was estimated through logistic regression models for grouped data by stepwise introduction of different study characteristics. The final model included geographical region, study sample type (population based, convenient), study design (cross-sectional, derived from case-control studies), limits of the age-range of enrolled women, publication year, sampling collection device, cell storage medium, HPV assay, primers used, and

See Online for webtable

Contributing studies (number)		Number of studies	Number of women tested	Number of women HPV-positive	Crude HPV prevalence (%)	Adjusted HPV prevalence* (95% CI)
<b>Global estimate</b>		<b>78</b>	<b>157 879</b>	<b>15 764</b>	<b>10.0</b>	<b>10.4 (10.2-10.7)</b>
<b>Africa</b>		<b>8</b>	<b>6 226</b>	<b>1 429</b>	<b>22.9</b>	<b>22.1 (20.9-23.4)</b>
Eastern Africa	Kenya (1), Mozambique (1), Zimbabwe (1)	3	2 144	759	35.4	31.6 (29.5-33.8)
Northern Africa	Morocco (1)	1	172	37	21.5	21.5 (16.0-28.9)
Southern Africa	South Africa (1)	1	1 269	197	15.5	15.5 (13.6-17.6)
Western Africa	Nigeria (1), Senegal (2)	3	2 641	436	16.5	17.0 (15.5-18.5)
<b>The Americas</b>		<b>24</b>	<b>40 399</b>	<b>6 291</b>	<b>15.6</b>	<b>13.0 (12.4-13.5)</b>
Central America	Costa Rica (1), Honduras (1), Mexico (2)	4	10 232	2 097	20.5	20.4 (19.3-21.4)
South America	Argentina (1), Brazil (1), Chile (1), Colombia (2), Paraguay (1), Peru (1)	7	4 354	623	14.3	12.3 (11.2-13.4)
Northern America	Canada (2), USA (10), Greenland (1)	13	25 813	3 571	13.8	11.3 (10.6-12.1)
<b>Europe</b>		<b>27</b>	<b>70 129</b>	<b>4 649</b>	<b>6.6</b>	<b>8.1 (7.8-8.4)</b>
Eastern Europe	Russia (1)	1	309	90	29.1	29.1 (24.3-34.4)
Northern Europe	Denmark (3), Sweden (1), UK (4)	8	16 235	1 291	8.0	7.9 (7.4-8.4)
Southern Europe	Greece (2), Italy (3), Spain (2)	7	4 884	276	5.7	6.8 (5.7-7.2)
Western Europe	Belgium (1), France (4), Germany (2), Netherlands (4)	11	48 701	2 992	6.1	8.4 (8.0-8.8)
<b>Asia</b>		<b>19</b>	<b>41 125</b>	<b>3 395</b>	<b>8.3</b>	<b>8.0 (7.5-8.4)</b>
Eastern Asia	China (1), South Korea (4)	5	4 908	910	18.5	13.6 (12.5-14.9)
Japan and Taiwan	Taiwan-China (1), Japan (5)	6	12 859	965	7.5	7.0 (6.3-7.7)
Southeastern Asia	Philippines (1), Thailand (3), Vietnam (2)	6	4 194	259	6.2	6.2 (5.5-7.0)
South-central Asia	India (2)	2	19 164	1 261	6.6	7.5 (7.0-8.0)

\*Prevalence estimates are adjusted for region, study type, study design, publication year, sampling collection device, cell storage medium, HPV assay, primer used, study youngest age included, and study oldest age included in each study.

**Table: Meta-analysis of HPV prevalence in 78 studies including 157 879 women with normal cytology, by world region**

HPV typing method. To control for residual heterogeneity between studies, an analysis of mixtures using the computer package C.A.MAN (computer-assisted analysis of mixtures) was done. This approach resulted in the identification of a set of clusters of prevalence estimates from the different studies that were also added to the logistic model.<sup>8</sup> All the variables included in the final model contributed in a significant manner to a better fit of the overall model. Prevalence estimates are presented with 95% CIs and unless specified, are always fully adjusted.

#### Age-specific prevalence

Studies not reporting age-specific HPV prevalence were excluded from age-specific estimates, leaving 44 studies for analysis (see webtable for contributing studies). HPV prevalence was estimated within five broad age-groups (25 years and less, 25–34 years, 35–44 years, 45–54 years, and more than 54 years) to minimise the impact of outliers and incorporate study-to-study fluctuations in the reporting of age-specific HPV prevalence, using multivariate logistic regression models, with adjustment as above. The age-groups were selected to best fit the available data extracted from the literature because not all the authors contributed to row data.

Prevalence estimates weighted by the age structure of each region were computed for the world and for the summary of the regions defined as developed and developing.<sup>4</sup>

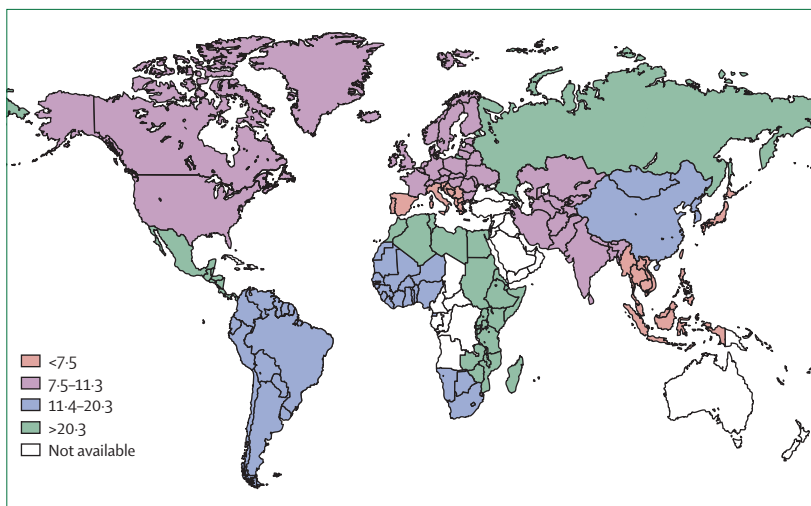
#### HPV type-specific and multiple types estimates

Each HPV type was evaluated independently of others. 48 studies provided HPV type-specific prevalence data in women with normal cytology (see webtable for contributing studies). All 48 studies provided information on HPV16 and HPV18, but for other genotypes, prevalence was estimated only in those studies testing for the HPV genotype in question. Type-specific prevalence includes the presence of a given type either as a single type or combined with the presence of other concomitant types. Type-specific HPV prevalence is expressed as a proportion of all women tested for the given HPV type. HPV type-specific prevalences are always provided as crude estimates and are weighted by the number of women tested.

## Results

The table shows crude and adjusted HPV prevalence estimates in 157 879 women with normal cytology, stratified by 15 world regions. The largest sample consisted of European studies (44.4% of all study women), followed by studies from the Americas (16.3% and 9.2% for northern and Central/South America, respectively). Studies from Asia contributed 26.0% of all study participants, of whom half were from south-central Asia (Indian subcontinent). African studies contributed 3.9% of all study women.

The worldwide crude HPV prevalence estimate among women with normal cytology was 10.0%. The corresponding adjusted prevalence estimate was 10.4%, 95% CI 10.2–10.7



**Figure 1: Estimated HPV DNA prevalence in the world regions**

Estimates are based on a meta-analysis of 78 studies including 157 879 women with normal cytology. Colours represent the adjusted prevalence in the region and denote the quartile distribution of all the estimates.

Africa, in particular eastern Africa, registered the highest adjusted HPV prevalence (31.6%, 29.5–33.8). Asia, in particular southeastern Asia, had the lowest adjusted HPV prevalence (6.2%, 5.5–7.0), followed by southern Europe (6.8%, 5.7–7.2). The adjustment of HPV prevalence estimates resulted in minor changes from the crude estimates. Figure 1 shows the estimates of the adjusted HPV prevalence for the different world regions, by quartiles of HPV prevalence.

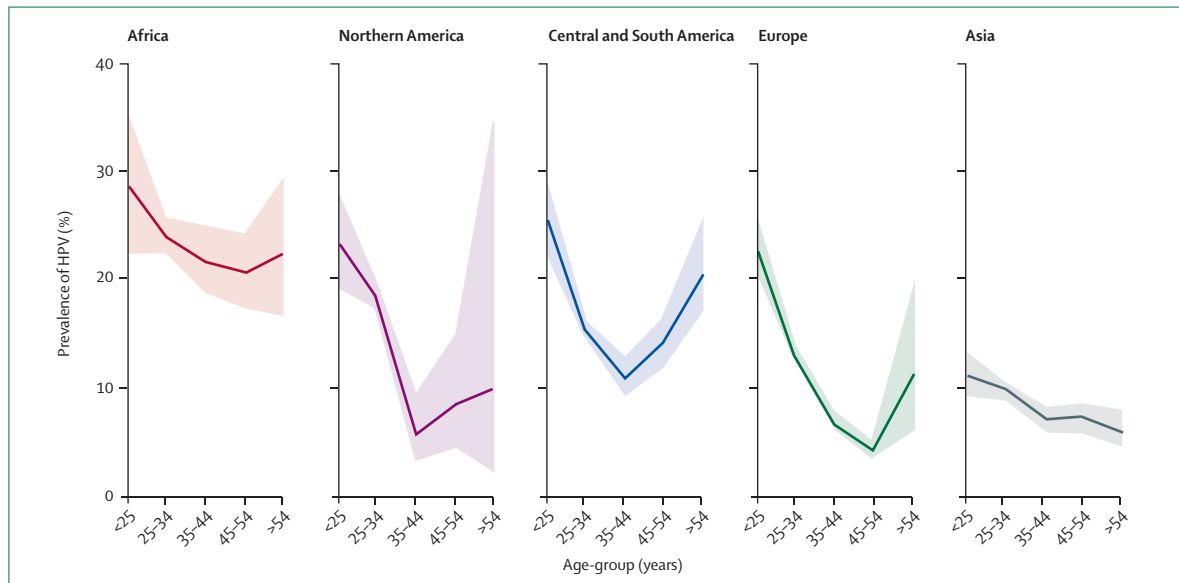
#### Age-specific HPV prevalence

Figure 2 shows HPV prevalence estimates for 44 studies including women with normal cytology, stratified by region. For all major world regions, HPV prevalence estimates were highest in women younger than 34 years and prevalence decreased in the 35–44 year-group. An increase was observed in the older age-groups (45–54 years and more than 54 years) in all regions, with the exception of Asia where rates continued to decrease.

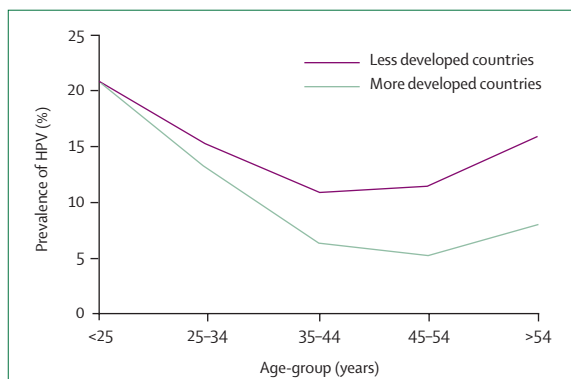
Figure 3 shows age-specific HPV prevalence estimates for the world separated into developed and less developed countries. Estimates are weighted by the age structure of the female population in the corresponding regions. After the age of 25 years, HPV prevalence was higher in less developed than more developed countries, but both sets of countries showed a continuous decline with increasing age until the age-group 45–54 years, when estimates increased in both regions. The overall HPV prevalence was estimated to be 15.5% in less developed world regions and 10.0% in more developed regions.

#### HPV type distribution in women with normal cytology

From the 48 studies that provided type-specific information in cytologically normal women, the five most common HPV types were HPV16 (2.5%), HPV18 (0.9%), HPV31 (0.7%), HPV58 (0.6%), and HPV52 (0.6%). Figure 4



**Figure 2: Age-specific HPV prevalence among women with normal cytology, by world region**  
Shaded areas represent 95% CIs.



**Figure 3: World estimates of the age-specific HPV prevalence by country-specific development status**  
Age-specific HPV prevalence estimates derived from the meta-analysis are applied to the female population within each 10-year age-group by development area. Countries were classified as less or more developed according to Globocan.<sup>4</sup>

shows the prevalence of the five most common HPV types in each region. HPV16 was the most common type in all regions with the exception of eastern Africa, and Japan and Taiwan where the most common type was HPV52. However, the degree to which HPV16 predominated over other types varied by region. The second most common types were HPV18 in the pooled estimate, the individual regions of eastern Asia (without Japan), northern Africa and northern and western Europe, HPV58 in western Africa and South America, HPV31 in Central America and eastern Europe, HPV66 in southern Europe, and finally HPV53 in northern America.

HPV16, HPV18, and HPV31 were consistently the first, second, and third most common types in studies using MY09/11, GP5+6+, and other PCR primers, respectively.

#### Effect of potential modifiers in prevalence estimates

Women from population-based and case-control studies tended to yield lower HPV prevalence estimates than women from convenient study sampling or from cross-sectional design ( $p < 0.001$ ). Out of the 78 studies, 67 reported to have used PCR and of these 15 used MY09/11, 28 used GP5+/6+, and 24 used a variety of other assays. 40% of the 67 studies reported to have used more than one primer. The adjusted HPV prevalence was slightly higher in studies that used HC2 (13.1%, 12.7–13.5) compared with all PCR techniques (10.0%, 9.8–10.3). The correlation between HPV prevalence measured by HC2 and PCR was linear across the geographical regions, but studies using PCR provided higher estimates compared with HC2 in western Europe, and in Japan and Taiwan. In all other regions estimates were higher with HC2 than with PCR.

#### Burden of HPV infection

To quantify the overall burden of HPV infection, the age-specific adjusted prevalence in cytologically normal women in each continent was applied to the age structure of the world female population of over 15 years old (2250462452 women). At a given point in time, around 291 million women were estimated to have an HPV infection, of whom 23.3% were estimated to be infected with HPV16 and 8.5% with HPV18.

#### Discussion

This large meta-analysis of 157879 women with normal cytology derived from 78 published studies worldwide allowed us to produce the most precise, comprehensive, and comparable estimates of HPV prevalence to date. The results estimate that at any given point in time, 10.4% of women worldwide were positive for cervical HPV DNA.

Prevalence of HPV was higher in less developed countries (15.5%) than more developed countries (10.0%), and was highest in women younger than 25 years old (16.9%), decreasing with age thereafter. Our analysis showed a distinct geographical pattern in women over 44 years of age, with a second peak of HPV prevalence in all the continents except Asia. Among infected women, one-third of infections were caused by HPV16 or HPV18, or both.

### Regional variations

African women had the highest prevalence of HPV (22.1%, 20.9–23.4), and estimates were consistently high across all African studies. Compared with women from other world regions, women in Africa were least likely to be screened for cervical cancer and had the greatest risk of invasive cervical cancer. The early age at first marriage, marriage with older men or with men that have several concomitant partners, and poor hygienic conditions are probably some of the key factors that explain the high prevalence in this region.<sup>9</sup> We were unable to evaluate whether the high prevalence of HPV observed in Africa might be caused in part by concomitant HIV infection, a risk factor for increased HPV prevalence, because the majority of the studies included in this meta-analysis did not test for HIV.

Regions in the Americas showed similar age-specific HPV prevalence patterns, with a peak in HPV prevalence in women aged 45 years and older. The overall estimate was higher for Central America (20.4%, 19.3–21.4) and South America (12.3%, 11.2–13.4) than northern America (11.3%, 10.6–12.1). These estimates were roughly in agreement with the observed cervical cancer incidence rates in these regions (age-standardised incidence rates 30.6 per 100 000 population in Central America, 28.6 per 100 000 in South America, and 7.7 per 100 000 for northern America).<sup>4</sup> Assuming that the studies included were a good representation of the respective populations, this suggests an important differential effect of cervical screening programmes and management of cervical lesions between northern America and other regions in the Americas.

Our pooled estimate of the HPV prevalence in Asia was potentially the least representative of all regions. Southeastern Asia showed the lowest prevalence worldwide (6.2%, 5.5–7.0) whereas HPV in eastern Asia (which includes China without Taiwan; 13.6%, 12.5–14.9) was as high as that observed in the Americas, and higher than that of south-central Asia (India) where HPV prevalence was only intermediate (7.5%, 7.0–8.0). These HPV prevalence estimates were not in agreement with historical cervical cancer incidence data that show that China has low, and India very high, rates of cervical cancer.<sup>10</sup> However, these discrepancies might partly represent a new epidemic of HPV infection in eastern Asia following more liberal sexual behaviour patterns in recent decades.<sup>11</sup> This finding would predict a rising cervical cancer epidemic in a region with poor cervical cytology (Pap) screening<sup>12</sup> and one of the fastest growing HIV epidemics in the world.<sup>13</sup> The

unexpectedly low estimate of HPV prevalence for India was based on two studies, one of which included more than 17 000 women in several parts of India using the high-risk probe HC2.<sup>14</sup> Although HPV prevalence across study regions varied from 7.8% to 4.8% in this large study, the other study from India was a more recent report based on 1799 women with normal cytology that identified an HPV

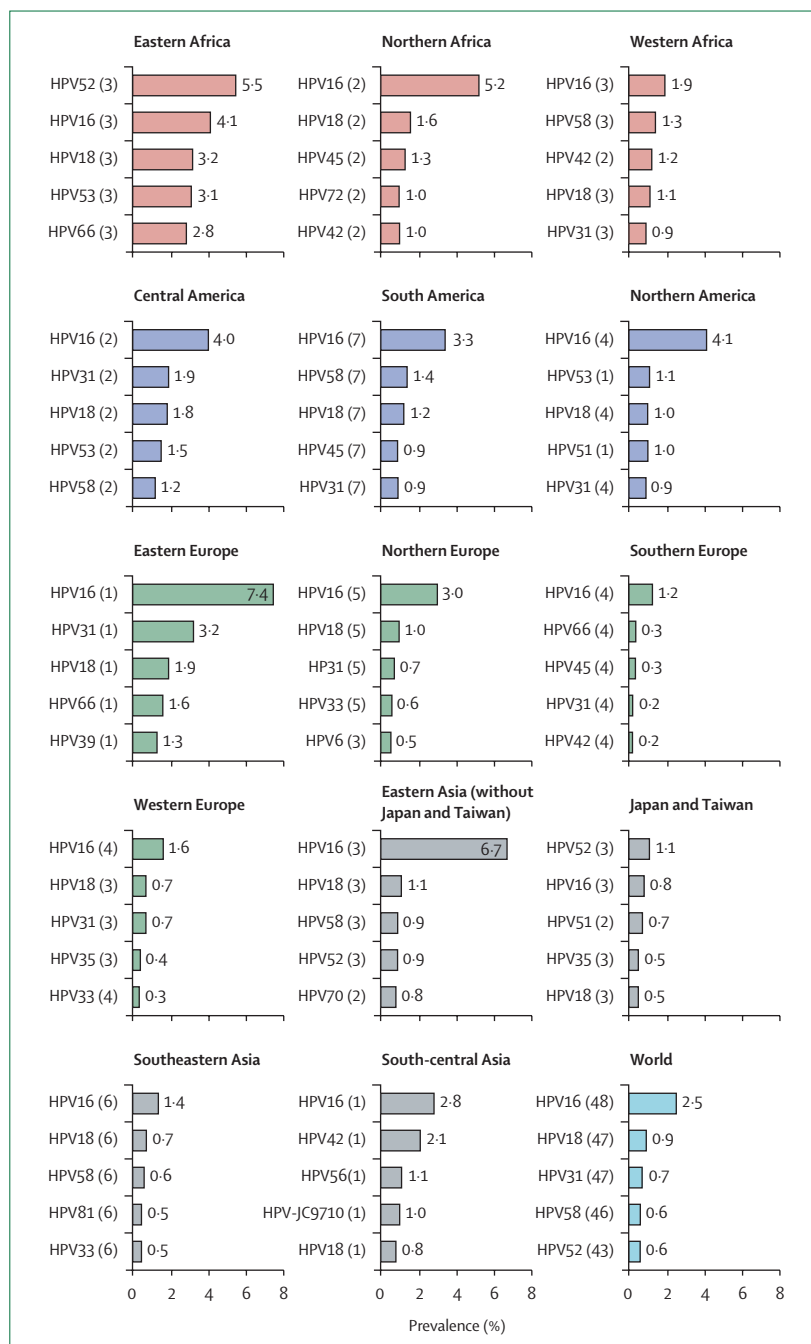


Figure 4: Ranking of the five most common HPV types among women with normal cytology within world regions and in the world

Data are based on meta-analysis of 48 studies. Each estimate has been weighted by the number of women tested for each HPV type. Number of studies included in brackets.

prevalence of 14.0%, of which 9.6% were found to be high-risk types using a PCR-based HPV assay.<sup>15,16</sup> These observations indicate that even if the prevalence of the main risk factor for cervical cancer is low, poor cervical screening programmes and management of cervical lesions may lead to very high rates of invasive disease.

Europe was well represented in the meta-analysis, and showed low HPV prevalence in three out of four regions. A north/south pattern was evident, with HPV prevalence decreasing with decreasing latitude. Eastern Europe, a region with high rates of cervical cancer (age-standardised incidence rates for the region 14.5 per 100 000 population<sup>4</sup>) was represented by only one Russian study<sup>17</sup> and showed the highest crude estimate of HPV infection (29.1%, 24.3–34.4) of all European studies.

The lack of studies in the general population for the Oceania region that complied with our inclusion criteria was surprising and calls for attention.

### Age-related prevalence

This meta-analysis confirms that HPV infection is most common in women younger than 25 years of age. However, a second peak of HPV prevalence is seen in women aged 45 years or older in all regions with the exception of Asia. The pattern was not consistent, however, because the turning point from a downward trend to an upward trend was observed after 54 years of age in Africa and Europe, but after 44 years of age in estimates from the Americas. This age-specific phenomenon observed in older women is compatible with at least three potential underlying causes. A first hypothesis is that impaired immune response as a result of hormonal changes at menopause somehow induces reactivation of existing, perhaps latent, HPV infections that were replicating at a very low, undetectable rate. If this was the principal mechanism of age-related HPV patterns, however, it should be observed in post-menopausal women in all world regions at similar ages. A second interpretation attributes the second peak to changes in the sexual behaviour of women and their partners in middle age. Among the three IARC HPV surveys among South American populations (Chile, Colombia, and Argentina), more than 95% of all women reported that their husbands had extramarital relationships.<sup>15</sup> However, this was also the case in Ho Chi Minh, Vietnam, and Nigeria, where no second peaks of HPV prevalence were observed. Finally, the age-variation in HPV prevalence could be the reflection of population-specific period/cohort effects. This could explain why the age-curves are not always consistent in the second peak or across world regions. Sexual attitudes are closely related to social changes and are likely to affect the transmission of HPV.

The Asian continent showed the flattest age-shape of all regions, and this finding has been replicated in more recent studies from the region.<sup>11</sup> It should also be noted that the worldwide age-specific prevalence calculated from

this meta-analysis is heavily influenced by the estimated age-specific HPV prevalence in Asia, because of its large population weighting.

The fact that HPV prevalence increases around the age of, or after, the menopause should probably be considered in the evaluation of the age at which women should stop having regular screening exams. New infections at 50 years of age may result in an invasive cervical cancer far beyond the screening target groups.

### HPV type-specific distributions

The five most common HPV types in HPV-positive women worldwide were HPV16, HPV18, HPV31, HPV58, and HPV52, representing 50% of all HPV infections. The most common HPV type was HPV16 with a prevalence of 2.5% followed by HPV18 (0.9%). However, there was variation in the ranking of the prevalence estimates of these types by region. In Japan and Taiwan and eastern Africa, HPV52 was the most common type. HPV18 was one of the most common HPV types in all regions apart from southern Europe, and HPV53 was among the five most common HPV types detected in eastern Africa and Central and northern America. The differences in HPV type-specific prevalence might be related to a geographical tendency to use HPV assays with a particular sensitivity to detect a specific HPV type, as previously described.<sup>18</sup> The known discrepancies in the ability of primers to amplify certain types (eg, GP5+/6+ and HPV53), was taken into consideration when possible, but do not fully account for the observed geographical differences.

HPV16 and HPV18 remain under-represented in women with normal cytology (32% of all infections) by comparison with their importance in severe cervical lesions. HPV16 and/or HPV18 contribute to more than 50% of the infections detected in high-grade squamous intraepithelial lesions, 70% of infections in invasive cervical cancer, and 81.5% of infections detected in adenocarcinomas.<sup>19–21</sup> This observation is concordant with prospective studies showing that HPV16 and HPV18 have an advantage for persistence and progression to cervical lesions compared with other high-risk types.<sup>22</sup> Although much rarer, HPV45 may also have this biological advantage since it ranked only 11th among HPV-positive women with normal cytology (0.4%), but is consistently identified among the five most common types in invasive cervical cancer. The most common low-risk HPV type identified was HPV42 when using GP5+/6+, and HPV53 when MY09/11 was the method used. HPV6 and HPV11 ranked 15th and 18th, respectively.

### Strengths and limitations

We attempted to correct previous estimates of the global prevalence of HPV<sup>23</sup> by accounting for variation in study design and detection assays used. Our estimates are in general concordance with the ones reported in a previous multicentric study,<sup>6</sup> but provide more robust estimates from an increased number of studies. Nevertheless, the caveat is increased variability in epidemiological study

design, cervical sampling methods, and HPV assays. Restricting analyses to women with normal cytology, however, was expected to reduce selection bias afforded to women identified at colposcopy clinics and other referral centres.

The full statistical analysis identified that the HPV prevalence was higher for the studies using HC2 (13.1%) compared with those using PCR assays (10.0%), even after adjustment of age inclusion or study design characteristics. Although the difference in HPV prevalence between both methods was of statistical significance ( $p < 0.01$ ), the relative difference between both techniques was not of clinical relevance for the purpose of this evaluation and the estimates of both methods were reported combined. This observation also applies to all other variables that were included in the fully adjusted model. The analysis of the point estimate of HPV prevalence controlled for the effect of the vaginal/cervical sampling and indicated that the prevalence using cervicovaginal washing was 12.5% (12.0–13.0) compared with 10.46% (10.1–10.8) using detection of cervix with spatula. However, these differences should be interpreted with caution because studies did not always clearly specify how samples were collected. Further studies that derived from case-control studies included women with more advanced age and therefore their HPV prevalence was slightly lower than cross-sectional studies (9.1% and 10.6%, respectively). The difference in prevalence might be explained by the older age of women included in case-control studies because they are selected to match the age of the case women.

Finally, the strong effect of age on HPV prevalence could affect the relative estimates of HPV prevalence by region because the different studies/regions included different age-ranges. To control for this potential bias, models were always adjusted for the age-range of the study population. Nevertheless, because of the nature of the meta-analysis approach, a more refined adjustment by age was not possible.

In summary, when we applied the age and region-specific results of this meta-analysis to the world population, it was estimated that about 291 million women had HPV DNA at a given point in time and that around 23% of these infections were related to HPV16 and 8.5% to HPV18. Both HPV types are potentially preventable by existing prophylactic HPV vaccines.

#### Conflicts of interest

NM is a consultant of Merck and Co Inc. FXB is a consultant for GlaxoSmithKline and Merck and Co Inc and has research projects partly sponsored by these companies. XC has received research grants from Merck and Co Inc, GlaxoSmithKline, and Digene Corporation companies. SS has received research grants from GlaxoSmithKline and travel grants from Digene Corporation companies. LB, MD, and GC declare that they have no conflicts of interest.

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#### Search strategy and selection criteria

These are described in detail in the Methods section on page 453.