HUMAN PAPILLOMAVIRUS (HPV) and RELATED BURDEN OF DISEASE IN LATIN AMERICA AND THE CARIBBEAN

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Cooperative Project of

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Suriname

VOLUME 1

HUMAN PAPILLOMAVIRUS INCIDENCE, PREVALENCE, AND RELATED BURDEN OF DISEASE IN LATIN AMERICA AND THE CARIBBEAN: A META-ANALYSIS:

Cooperative Project from

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Acronyms and Abbreviations

CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
LAC	Latin America and the Caribbean
ASCUS	Atypical squamous cells of undetermined significance
DALY	Disability-adjusted life years
CC	Cervical cancer
CDC	Centers for Disease Control and Prevention
95% CI	95% Confidence interval
CSW	Commercial sex workers
DNA	Deoxyribonucleic acid
HDNS	Health and Demography National Survey
STD	Sexually transmitted diseases
HC	Hybrid Capture assay
HSIL	High-grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
ICD-9	International Classification of Diseases, 9th revision
IF	Impact factor
GAVI	Global Alliance for Vaccines and Immunization
LSIL	Low-grade squamous intraepithelial lesion
CIN	Cervical intraepithelial neoplasia
PAHO	Pan American Health Organization
SVI	Sabin Vaccine Institute
HIV	Human Immunodeficiency Virus
HPV	Human papillomavirus
LR-HPV	Low oncogenic risk human papillomavirus
HR-HPV	High oncogenic risk human papillomavirus

VOLUME I

EXECUTIVE SUMMARY

Introduction

Epidemiologic studies have demonstrated that Human papillomavirus (HPV) infection causes cervical cancer (CC), particularly in persons at high risk for becoming infected with HPV. Although HPV infection is common and usually clears without treatment within two years, it is a necessary factor in the development of CC. However, studies have shown that other factors in addition to HPV infection contribute to the development of CC, including a high number of pregnancies, smoking, prolonged oral contraceptive use, nutritional deficiencies, genetic factors, and other sexually transmitted infections [1].

Each year in North, South, and Central America, and the Caribbean, more than 86,000 women will be diagnosed with CC and more than 38,000 will die from this cancer. These estimates result in an annual incidence rate of 18.8 cases per 100,000 women and 8.1 deaths per 100,000 (based on an estimated 336.5 million women). The burden of HPV disease across this region varies substantially and relates to lack of access to screening services and curative care. For example, the proportion of women with CC who die from this illness in the United States is 25%, whereas in Haiti, the proportion is 55% [2]. However, CC can be prevented if early lesions caused by HPV infection are detected and treated.

In Latin America and the Caribbean (LAC), CC is the fourth most common type of cancer and the second most common cancer in women of reproductive age (15–44 years of age). It is also the second most common cause of cancer deaths for women in Central and South America [3].

In LAC, the prevalence of HPV infection varies by country and population. Among women with normal Papanicolaou (Pap) cytology, the prevalence in several studies of HPV infection ranged from 10%-16.6% [3–8]. Depending on the population studied, among women with low-grade cervical lesions (LSIL or CIN-1), prevalence ranged from 2.3% to 99% [3,8–18]. Among women with high-grade lesions (HSIL or CIN II or CIN III), prevalence ranged from 13.6% to 100% [9,15,19–23]. Among women with CC, the proportion with detectable HPV infection is generally 100%. These prevalences represent data from selected populations and do not capture regional variability.

Objectives

The objectives of this report are to estimate the burden of HPV infection and HPV-related disease in LAC and to estimate the health and economic benefits of HPV screening and vaccination in selected LAC countries. Additionally, this study uses sensitivity analysis to evaluate the quality of the studies examined to assess the influence of the studies' design and methods on outcomes and to determine the appropriateness of the interpretation of results.

Results from this evaluation will inform national health authorities about the burden of HPV infection and HPV-related disease and about the economic value of implementing an HPV vaccination program in selected countries in this region and/or of introducing improved screening programs.

The final report consists of two volumes: the first is a meta-analysis of the burden of HPV infection and HPV-related disease in LAC; the second is a cost-effectiveness study of HPV vaccination and provides specific economic information for six selected countries in Latin America. Although epidemiologic estimates from both documents may differ because of the use of different methods, the reports are meant to be complementary.

Methods

Meta-analysis of the burden of HPV infection and HPV-related disease in LAC

To estimate the burden of HPV infection and HPV-related disease, investigators conducted a literature review of all published studies from 1990 through mid-2007, focusing on research describing HPV prevalence among men and women for specific anatomical sites. Because of advances in molecular biology and HPV diagnosis methods since 1990, articles published only after that year were selected. The literature review was complemented with additional information, including regional data obtained from subject-matter experts and pharmaceutical companies.

For the literature review, PubMed, LILACS, Scielo, CAB, EMBASE, ICNAHL, and Cochrane databases were searched with MeSH search terms, using library services at the U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, USA, and at the University of Chile, Santiago, Chile. Studies with original data on prevalence, incidence, costs, and cost-effectiveness of HPV vaccination in six selected countries in Latin America (Argentina, Brazil, Chile, Colombia, Mexico, and Peru) were abstracted if published after 1990 and if they included the following populations: women with normal cytology; women with abnormal cytology; women with lesions of the vulva, vagina, cervix or anus; and men with lesions of the penis or anus. Articles on prevalence of HPV infection in oropharyngeal lesions for both sexes were also analyzed. The minimum number of study participants was 30 for studies addressing cervical intraepithelial lesions and CC and 10 for studies about other types of cancer.

To calculate the incidence of genital HPV infection, data from two of three prospective cohort studies conducted in the region were used: the Ludwig-McGill Study in Brazil and the Bogotá Cohort Study in Colombia. The cohort from Guanacaste, Costa Rica, was not included because incidence data from this study are still under analysis. The Ludwig-McGill Study recruited 2,528 women 18–60 years of age, and the Bogotá Study recruited 1,610 women 13–85 years of age. An incident case was defined as the first detection of HPV infection during follow-up, and incidence was calculated using person-time denominators. Incidence rates by age, HPV type, HPV risk category (high and low oncogenic risk), and genotype group were calculated by using modern taxonomical classification based on recent epidemiologic and phylogenetic data from the scientific literature [24] with subsequent grouping based on biological and genetic relatedness among HPV species (Sabin Team, unpub. data).

To estimate the burden of cancer, we calculated the current number of HPV-related cancers in the region by using estimates from the International Agency for Research on Cancer (IARC). The proportion of CC cases attributable to HPV was assumed to be 100% [25]; for oropharyngeal cancer, we estimated the attributable risk (AR) from case-control studies by using the following formula:

$$AR = 1 - \sum_j \frac{p_j}{R_j}$$

In this formula, AR = attributable risk, $\mathbf{p_j}$ = proportion of cases in the jth exposure stratum, and $\mathbf{R_j}$ = relative risk or odds ratio in the jth exposure stratum. In the stratum j = 0 (unexposed), R takes the value of 1 [26].

From the studies analyzed, we selected for further analysis those with the largest number of cases, those published recently, or those with specific cancer definitions. It was not possible to calculate the attributable risk for oropharyngeal cancer, so we used the original estimate by Parkin et al. (50%)[27]. For vulvar, vaginal, penile, and anal cancers, the proportion caused by HPV infection was not estimated because information was unavailable at the level of individual countries; the etiologic fraction for these cancers attributed to HPV infection was also unavailable, mainly because studies of these cancers used serologic results from controls in case-control studies.

For the quality assessment of articles, two instruments were used. The first was the impact factor (IF) of the journal in which the study was published. For studies published in multiple journals, the journal with the highest IF was considered. Studies that appeared in publications with unknown IFs were excluded or received an IF value of zero in an alternative analysis. The second instrument was a six-item quality score that evaluated three study characteristics for validity and generalizability: population studied, HPV detection method, and classification of HPV-associated lesions. Two quality scores were calculated: one for studies of subjects without lesions (scale 0–8 points) and another for studies of subjects with HPV-associated lesions (scale 0–6 points). The relationship between IFs and quality scores was assessed by calculating Spearman’s rank correlation coefficients.

Data from articles, abstracts, and unpublished works were abstracted from three electronic databases: one for study-related variables, a second for prevalence-related variables, and the third for quality indicators. Epidemiologic variables extracted from each study included number of subjects, sex, age, behavioral risk factors, participants’ disease status, participants’ selection method, and study design. Extracted laboratory variables included HPV identification method (Hybrid Capture 2 [HC2] or polymerase chain reaction [PCR]), types of HPV identified, and number of persons with HPV types detected. Other captured laboratory data included whether beta globin was detected to ensure quality of specimens. HC2-based studies were included only for the analysis of HPV prevalence among women with normal cytology; prevalence estimates for women with lesions were based only on studies that used PCR. Study quality indicators such as characteristics of the population sampled and quality of laboratory methods were also recorded.

A descriptive analysis was performed to summarize all studies identified by subgroup (i.e., cytologically normal women by age group), using mean, median, or proportions as appropriate. The general HPV prevalence was estimated by using fixed effects; that is, each study was weighted by the inverse of its variance. Prevalence by age group was estimated by using mixed models. A meta-regression analysis was conducted to evaluate the influence of the following variables on prevalence estimates: specimen type (e.g., exfoliated cells, biopsy, surgical specimen), HPV detection method (i.e., HC2 or PCR), and study quality (continuous value).

Economic evaluation of HPV vaccination in selected Latin American countries

We synthesized available data to estimate the cost-effectiveness of vaccination for HPV 16 and HPV 18 (HPV 16+18) in six selected countries of Latin America (Argentina, Brazil, Chile, Colombia, Mexico, and Peru). A comprehensive literature review of epidemiologic data in countries of the region was conducted to locate information about age-specific CC incidence and mortality rates and distribution of incidence of HPV 16 and 18 among women with CC.

National treatment guidelines were used to learn about treatment practices for precancerous lesions and for CC in each country. To gather information about CC treatment by stage and cost, we conducted surveys in several countries of the region either in person, or by phone or e-mail. These surveys contained specific questions about screening for precancerous lesions and about CC diagnosis and treatment. Also, surveys collected information to evaluate costs of vaccinating preadolescents against HPV.

For an analysis of cost-effectiveness projections, we used an Excel-based model developed as a complementary model to a previously validated microsimulation model for HPV infection and CC. The Excel-based model relies on simplifed assumptions for exploring the costs and benefits of vaccination and is less data intensive than a comprehensive simulation model. This simplified model was used to generate broad qualitative insights into the potential benefits of HPV 16+18 vaccination of preadolescent girls in the six selected countries. Model outcomes included reduction in lifetime risk and in deaths due to CC as well as life years saved (LYS), disability-adjusted life years (DALY), and lifetime costs. DALYs reflect the disability weight and duration estimates for

CC, as provided by the Global Burden of Disease Study (not age-weighted) of the International Agency for Research on Cancer (IARC).

The economic analysis (Volume II of this report) describes the cost-effectiveness of implementing various vaccination strategies and uses incremental cost-effectiveness ratios, defined as the additional cost of a specific strategy divided by its additional benefit (per woman life-expectancy gain). Each cost-effectiveness ratio is compared with the next most costly strategy. Costs are presented in 2005 international dollars (ID) for comparison among countries and in local currency and U.S. dollars for local and regional decisions. We followed recommendations from several published guidelines for economic evaluations and adopted a modified social perspective in which future costs + life years were discounted by 3% annually.

To provide information that enables country-specific payors to differentiate cost-effectiveness results (i.e., long-term perspective of value for money) and affordability (i.e., short-term perspective of financial costs and budget limitations), we provided crude estimates of financial costs to vaccinate a single birth cohort at different coverage rates.

Results

Prevalence of HPV Infection

The literature search yielded 1,096 abstracts containing one or more of the MeSH search terms; abstracts were selected for full-text review. Of the 1,096 selected studies, 108 were unavailable, and 988 full-text articles were reviewed. Of those, 129 met inclusion criteria, 126 were included in the prevalence report, and an additional two contributed to incidence estimates.

Forty-five (36%) articles addressed HPV prevalence in Brazil, and 29 (23%) addressed prevalence in Mexico. Articles addressing other countries in the region accounted for the remaining 40%, including 15% on HPV prevalence in Argentina. The quality scores assigned by investigators to studies about cytologically normal women and women with CC correlated well ($p<0.01$) with the publication’s IF.

In 43 studies about cytologically normal women, overall HPV prevalence (based on PCR) was 18.7% (95% CI 15.4%–22.0%). Among women with cervical lesions, prevalences were 56.1% (95% CI 39.7%–72.4%) for those with atypical sqamous cells undetermined (ASCUS), 79.0% (95% CI 71.9%–86.1%) for those with LSIL, 96.8% (95% CI 93.5%–00%) for those with HSIL, and 94% (95% CI 89.4%–98.5%) for those with ICC. Seven studies related to healthy men; HPV prevalence for this group was 21.7% (95% CI 1.7%–41.6%).

Among women who were screened and among the general population, HPV prevalence by age followed the pattern observed in previous reports and publications: a high prevalence (20%–30%) for women 15–24 years of age, followed by decreases for women 25–50 years of age, followed again by increases up to approximately 20% in older women. Prevalences of high-risk HPV followed the pattern of general HPV prevalence, and was highest among women 15–24 years of age and those older than 50. Clinical populations (women seeking care in ambulatory settings) had higher prevalences at all ages.

Among cytologically normal women, the prevalence for HPV 16 was 2.6% (95% CI 1.8%–3.2%); prevalence of HPV 18 was 1.0% (95% CI 0.6%–1.3%). Among women with ICC, prevalence for HPV 16 was 49.3% (95% CI 45.5%–53.1%), and prevalence for HPV 18 was 10% (95% CI 7.6%–12.5%).

Incidence of HPV infection

The combined incidence of HPV infection in the two prospective cohorts was under 8% per year, although total risk was higher in Brazil (11.2%) than in Colombia (6.7%). As expected, incidence was highest among women under 25 years of age: 17.5/100 woman-years in Brazil and 14/100 woman-years in Colombia. Incidence was fewer than 10/100 woman-years among women 25–44 years of age or age 45 and older in both studies. The highest incidence was found for HPV 16: 1.7/100 woman-years for women younger than 25 years of age and 1.3/100 woman-years for women 25 and older. Table A shows incidence for combined data from the prospective studies for Colombia and Brazil.

TABLE A. HPV infection incidence and rates in women by HPV risk, taxonomic groups, and age group, combined data from Bogotá (Colombia) and Ludwig-McGill (Brazil) cohorts

HPV Risk Or Taxonomic Group	Woman-Years	Number Of Incident Cases	Incidence Rate (Per 100 Woman-Years)	95% CI
Under 25 years				

TABLE A. HPV infection incidence and rates in women by HPV risk, taxonomic groups, and age group, combined data from Bogotá (Colombia) and Ludwig-McGill (Brazil) cohorts					
HPV Risk Or Taxonomic Group	**Woman-Years**	**Number Of Incident Cases**	**Incidence Rate (Per 100 Woman-Years)**	**95% CI**	
Any HPV type	1723.4	276	16.01	14.18	18.02
High-risk HPV	2079.1	254	12.22	10.76	13.82
Low-risk HPV	2617.2	154	5.88	4.99	6.89
Species 1, 8, 10	3148.7	93	2.95	2.38	3.62
Species 5, 6, 7, 9, 11	1972.3	375	19.01	17.14	21.04
Species 3, 4, 15	3133.8	80	2.55	2.02	3.18
25–44 years					
Any HPV type	11003	830	7.54	7.04	8.07
High-risk HPV	12290.7	650	5.29	4.89	5.71
Low-risk HPV	13780.6	494	3.58	3.28	3.92
Species 1, 8, 10	15388.8	192	1.25	1.08	1.44
Species 5, 6, 7, 9, 11	11839.1	911	7.69	7.20	8.21
Species 3, 4, 15	15311.2	232	1.52	1.33	1.72
45 years or older					
Any HPV type	2351.3	136	5.78	4.85	6.84
High-risk HPV	2579.5	106	4.11	3.37	4.97
Low-risk HPV	2802.7	77	2.75	2.17	3.43
Species 1, 8, 10	3422.7	30	0.88	0.59	1.25
Species 5, 6, 7, 9, 11	2896.7	195	6.73	5.82	7.75
Species 3, 4, 15	3327.2	34	1.02	0.71	1.43

Woman years are the total number of women included in the stated cohort stratum multiplied by the average duration of follow up for women in that stratum. Low risk HPV includes types 2a, 6, 7, 11, 13, 27, 30, 32, 34, 40, 42, 43, 44, 54, 55, 57, 67, 71, 74, 69, 85, 90, 91. High risk HPV includes types 16, 18, 31, 33, 35, 45, 39, 51, 52, 56, 58, 59, 66, 68, 70, 73, 82. Types 26, 53, and 70 were defined as having a pending classification for risk. Species 1 includes types 32, 42; species 3 includes types 61, 62, 72, 81, 83, 84, 86, 87, 89; species 4 includes types 2a, 27, 57; species 5 includes types 51, 69, 82; species 6 includes types 63, 56, 66; species 7 includes types 18, 39, 45, 59, 68, 70, 85; species 8 includes types 7, 40, 43, 91; species 9 includes 16, 31, 33, 35, 52, 58, 67; species 10 includes types 6, 11, 13, 44, 55, 74; species 11 includes types 34, 73; species 15 includes types 71, 90.

Burden of cancer

According to IARC data, almost 100,000 new cases of HPV-associated cancer occur annually in the LAC, and 91.7% of these cases can be attributed to HPV. By far, the most important HPV-associated cancer is CC, which accounts for 79,000 cases annually (85.5%). The second most important HPV-associate cancer is oropharyngeal cancer, which accounts for 12,700 cases annually (6.5%). An estimated 11,300 HPV-associated cancer cases annually relate to anal, penile, vulvar, and vaginal cancers. Most cases of CC occur in Brazil, Mexico, Colombia, Peru, and Argentina, where a combined estimated 49,000 cases occur each year or 68% of all CC cases in the region (Table B).

TABLE B. Crude and age-adjusted incidence rates, incident cases, 1-year and 5-year prevalent cases, and deaths due to cervical cancer by country in Latin America and the Caribbean, 2002						
COUNTRY	Incidence Rate		Incident Cases	Prevalent Cases		Deaths
	Crude	Adjusted		1 Year	5 Years	
Haiti	64.7	87.3	2,774	2,328	8,098	1,484
Bolivia	42.0	55.0	1,831	1,538	5,330	987
Paraguay	39.5	53.2	1,131	950	3,297	513
Belize	34.5	52.4	40	34	114	16
Peru	40.5	48.2	5,400	4,535	15,548	2,663
Guyana	40.7	47.3	160	135	463	71
Nicaragua	30.2	47.2	809	679	2,363	354
El Salvador	36.6	45.6	1,213	1,020	3,491	609
Ecuador	30.4	38.7	1,978	1,649	5,513	1,064
Colombia	31.0	36.4	6,815	5,731	19,623	3,296
Venezuela	30.9	36.0	3,845	3,229	11,199	1,705
Jamaica	28.8	31.2	383	321	1,114	151
Dominican Republic	24.3	30.8	1,032	863	2,904	562
Guatemala	19.4	30.6	1,153	968	3,343	628
Honduras	19.9	30.6	664	559	1,927	361
Mexico	24.4	29.5	12,516	10,508	35,886	5,777
Panama	25.8	28.2	375	315	1,089	166
Trinidad y Tobago	28.4	27.1	186	156	530	73
Chile	27.5	25.8	2,163	1,818	6,236	931
Barbados	33.3	24.9	46	38	126	18
Brazil	22.2	23.4	19,603	16,457	56,418	8,286
Argentina	25.5	23.2	4,924	4,133	14,343	1,679
Costa Rica	19.0	21.6	392	330	1,132	210
Cuba	24.0	20.2	1,346	1,130	3,931	567
Uruguay	22.5	18.8	392	330	1,130	162
Bahamas	15.8	16.7	25	20	72	9
Puerto Rico	10.8	8.8	223	187	641	75
Total			71,419	59,961	205,861	32,417
Source: International Agency for Research on Cancer, 2002 and Globocan 2002.						

Quality assessment

In our analysis, for the selected studies published in journals for which an IF was available, we found that the mean IFs were 2.86, 2.23, 2.29, and 5.65 for studies of persons without lesions, with LSIL, with HSIL, and with ICC, respectively. The mean IFs for all studies were 1.63, 1.39, 1.49, and 4.33, respectively.

The mean (±SD) quality score was 3.41 (±1.31) for studies of persons without lesions and 3.68 (±1.01), 3.78 (±1.04), and 4.15 (±0.88) for studies of persons with LSIL, HSIL, and ICC, respectively. The correlation coefficient between IF and quality score was 0.36 ($p<0.0001$) overall, 0.47 ($p<0.0001$) for studies of persons without lesions, and 0.55

(p = 0.0001) for studies of persons with ICC. The correlation coefficient was not statistically significant for studies of persons with either HSIL or LSIL.

Meta-regression

Among cytologically normal women, the HPV prevalence was unrelated to the type of specimen (p = 0.8), the sample taker, or the manuscript quality score (p = 0.9). None of these factors was significant in the analysis of HPV prevalence by age. However, HPV detection method was significantly associated with prevalence. HPV detection using HC2 compared with PCR, underestimated prevalence by 57% (p = 0.001). This underestimation is expected because HC2 has lower molecular sensitivity and a more restricted range of detectable HPV genotypes than PCR.

Economic evaluation of HPV vaccination

Based on the available data for six countries, total screening direct medical cost per case ranged from $10 to $81 per woman and from $534 to $1,402 per woman for treatment of precancerous lesions. Higher screening costs were incurred in Argentina, and higher treatment costs for precancerous lesions occurred in Brazil. The majority of these costs were attributed to specialist consultation (for screening) and hospitalization (for precancerous lesions). The cost for CC treatment ranged from $3,745 per woman in Peru to $14,438 per woman in Argentina, with higher costs incurred at advanced stages of CC. The majority of this treatment cost was attributed to hospital stay and palliative care.

We used an Excel-based model to evaluate the clinical benefits of vaccination and assuming a 70% vaccination coverage of 12-year-olds, lifelong immunity, and 100% efficacy against HPV 16 and 18 in the six selected countries of the region. Given these assumptions, we found that HPV vaccination could reduce cancer incidence by approximately 40% in Mexico and Chile and up to 50% or more in Argentina. Almost 45,000 cancer deaths and 74,000 CC cases would be avoided over the lifetime of a single birth cohort, compared to outcomes with no intervention. The majority of potentially averted cases and deaths are for Brazil, where CC is more common than in other countries of the region. If we consider 10 birth cohorts and assume 70% coverage, we could expect to prevent nearly half a million deaths over the lifetime of vaccinated girls.

With lower cancer costs and a cost of $100 per vaccinated girl, using the Excel model to assess the cost-effectiveness ratio for preadolescent vaccination compared to no intervention (no screening or vaccination), the cost per LYS from a society perspective would range from $670 (Chile) to $1,500 (Mexico). At a lower cost of $75 per vaccinated girl ($20 per dose), the LYS cost would drop to between $420 (Chile) and $1,040 (Mexico). At a cost of $50 per vaccinated girl ($12 per dose), the LYS cost would drop to between $180 (Chile) and $580 (Mexico). If cost decreased to $25 per vaccinated girl ($5 per dose), the LYS cost per year would drop to between $10 (Brazil) and $160 (Peru). At $25 per vaccinated girl ($5 per dose), the model shows that vaccination would be cost-saving in Chile and Argentina.

These results were generated for vaccination only, so the incremental ratios appear more attractive than they would if the baseline for comparison had included screening. For example, if previously published independent models that included screening as well as vaccination were used, as the cost per vaccinated girl approximates $100, vaccination plus screening (at ages 35, 40, and 45) would improve outcomes more than vaccination alone, although the incremental cost-effectiveness ratio increases (i.e., becomes less attractive) with higher vaccine costs. For example, in Mexico, a two-visit HPV DNA testing strategy combined with vaccination and screening costing $75, $100, and $360 per girl results in costs of $1,530, I$1,78, and $7,070 per LYS, respectively.

Based on published data, at a vaccine price of $360 per girl (the approximate current U.S. vaccine price), screening, with or without vaccination, as the main CC prevention option in countries able to provide screening, was generally more cost-effective than vaccination alone. As the cost per vaccinated girl declines, preadolescent vaccination followed by screening three times per lifetime may be the most effective option in countries able to do both. In the poorest countries in this region, vaccination alone, if available for a markedly reduced price and if widespread coverage of young girls is achievable, may be the most feasible option to reduce CC.

However, vaccination still may not be affordable, even if it appears cost-effective according to the criterion that incremental cost-effectiveness ratios should be less than the per capita gross domestic product of a specific country. Even interventions that provide good value for invested resources may have prohibitive financial requirements that cannot be accommodated by some countries' health care systems. For the six countries studied, vaccinating five birth cohorts at 70% coverage for $25 per girl would cost $270 million (present value, discounted 3% annually). At $50 per vaccinated girl, vaccinating five birth cohorts at 70% coverage would cost nearly $600 million, and a cost per vaccinated girl of $360 (five cohorts at 70% coverage) would result in total costs of more than $4 billion. These projections highlight the important distinction between cost-effectiveness and affordability.

Study limitations

Limitations of this analysis include gaps in our understanding of HPV's natural history, uncertainties about the epidemiology and temporal trends of CC in many countries, lack of high-quality screening data, costs associated with HPV-related diseases, and CC treatment access and costs for many countries. We also lack data concerning the cost of initiating and maintaining a new adolescent vaccination program as well as data about the HPV vaccine's long-term efficacy (i.e., whether it provides life-long immunity). For countries with on-going screening, the cost-effectiveness of vaccination strategies, either alone or combined with screening, depends on assumptions about quality of screening and follow-up care, coverage, effectiveness, and screening costs. Data on these variables are critical for making evidence-based decisions about vaccines.

Conclusions

This meta-analysis and economic analysis provide a comprehensive summary of evidence available since 1990 on HPV infection prevalence, incidence, disease burden, illness, death, and cost-effectiveness of vaccination in LAC. For estimates of disease burden, we included a large variety of studies from 17 countries that used different methods and diverse populations. We found that the prevalence of HPV infection (18.7%) among women in LAC is within the range found in other parts of the world. Our study found age-specific differences in HPV infection prevalences among healthy women, with the highest prevalences occurring among women 15–24 years of age (29%) and those older than 65 (26%) and the highest incidence among women 15–24-years old (14–17 cases per 100 woman-years). We also found that the prevalence and distribution of high-

risk HPV, particularly types 16, 51, and 58, increase with higher grade cervical lesions. The largest proportion of HPV-related disease (85%) in the region is CC, with 80,000 new cases and 40,000 deaths annually, equating to 100,000 life-years lost annually. The highest rates of CC in the region occurred in Haiti, Bolivia, Paraguay, Belize, and Peru; Mexico, Brazil, and Colombia had the largest number of deaths due to CC. More research is needed to gain a better understanding of the following issues: distribution of HPV types in different countries by lesion type; incidence of rare HPV-related cancers such as penile, vulvar, and vaginal cancer in the region; and the risk attributable to HPV infection for these cancers. Differences in resources and the extent of existing screening programs in LAC countries highlight the challenges faced by each country in decisions about whether vaccination is affordable, even if it may be cost-effective.

Keywords : HPV infection, vaccines, cost-effectiveness, burden of disease.

CHAPTER 1. INTRODUCTION

1.1. Background

1.1.1. Infectious agent

Human Papillomavirus (HPV) particles consist of circular DNA molecules of approximately 8,000 base pairs surrounded by a protein cover formed by two molecules, L1 and L2. These proteins are codified by their respective late ("L") genes. Early genes, "E," are responsible for viral DNA replication control during the viral cycle as it progresses in synchrony with epithelial maturation. HPV is well adapted to the natural host, humans, and is transmitted by skin-to-skin contact. The infection takes place only at the epithelial layer of susceptible body areas, without the need for connective tissue invasion or regional or systemic dissemination. The etiologic role of HPV in cervical cancer (CC) has been biologically and epidemiologically established [28–30].

HPV infection commonly occurs through sexual transmission. Researchers have widely accepted that persistent infection by some HPV types constitutes the main cause of CC. The causal association between HPV infection and CC was proposed for the first time in the mid-80s and was afterwards confirmed by a large number of studies [29–35].

More than 110 different HPV types have been identified, and nearly 40 infect the anogenital tract. Depending on the technique used, HPV DNA can be found in almost all CC cases and in 90% of high-grade preinvasive lesions. A subgroup of HPV genotypes has been more frequently associated with high-grade preinvasive lesions and CC than other types. Those most commonly classified as being of high oncogenic risk are HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, 85, and IS39 (a subtype of HPV 82 that is frequently detected separately). Nevertheless, other types of the virus, such as HPV 6 or 11, which are responsible for genital condiloma development, are classified as low risk. Virus classification has been studied and widely debated for more than three decades. Viral taxonomy has been a dynamic field from the time when viruses were first detected by use of conventional methods until today, when detailed taxonomy is possible by use of molecular techniques, differentiation of genomic size, and nucleotide and amino acid sequences. The International Committee on the Taxonomy of Viruses provides updates of this subject [1,36–43].

HPV transmission is difficult to prevent. Barrier contraceptive methods are partially effective because HPV may be found to be inactive in genital tissues for years [33]. Although no curative treatment for HPV is available, in the majority of cases, the infection resolves spontaneously. Nevertheless, in some women HPV infection persists and progresses to preinvasive lesions known as cervical intraepithelial neoplasia (CIN).

HPV infection persistence and the integration of its genetic material inside the cellular DNA are the main factors contributing to oncogenesis. The transformation to malignancy has been traditionally described as a progressive phenomenon that gradually advances through the cervical epithelium (as progressive grades CIN I-III) until the neoplastic growth traverses the basal membrane finally invading the stroma. Although the progression process from CIN III to invasive cervical cancer (ICC) may take approximately two years, progression from CIN I can take 10 to 20 years or less time in some cases [44–50].

Only a small proportion of women who become infected with high-risk HPV genotypes eventually develop cancer, providing evidence that the presence of HPV infection alone is insufficient for malignant transformation, so other cofactors are important. Various endogenous and exogenous cofactors have been studied, and the most important are immunologic status, hormonal action, genital factors, exposure to oncogenic tobacco substances, genetic constitution, and infection from other sexually transmitted diseases (STDs).

1.1.2. Main risk factors associated with HPV infection and related cervical cancer

Initiation of sexual activity: Early sexual initiation is an important risk factor. Studies in Chile have shown that teenagers there begin their sexual life early [51].

Number of sex partners: Studies have demonstrated that HPV transmission occurs easily between sex partners. For example, in a Danish cohort, for women 20–29 years of age with two sex partners, the risk (odds) for HPV infection was twice that of women with only one sex partner throughout life (Odds Ratio, [OR] 2.00; 95% Confidence Intervals [CI] 1.29–3.10]). For women with 20 or more sex partners, the risk was 6.39 times higher (95% CI 4.34–9.31) than the risk for women with one sex partner throughout life [53].

Parity: High parity is associated with CC development.

Other factors related to HPV persistence and cancer:

Tobacco use. Users of tobacco have a risk for CIN II-III that is 1.6 (95% CI 1.48–1.73) times greater than the risk among never smokers [54].

Use of oral contraceptives for five to nine years. A meta-analysis of CC and hormonal contraceptives concluded that the risk for ICC increases for as long as the use of an oral contraceptive continues. Use of this contraceptive method for 10 years is related to twice the risk compared with women who have never used an oral contraceptive.

Other sexually transmitted diseases. Studies examining the relationship between HPV infection and other sexually transmitted diseases have found evidence of old or recent *Chlamydia trachomatis* infection in women with HPV infection and high-grade cervical lesions or ICC.

Cell-mediated immunological mechanisms. Evidence shows that cell-mediated immunological mechanisms are critical for virus elimination after an infection has been established.

Genetic factors. Some studies have observed that certain class II hystocompatibilty polymorphic antigens may increase risk for HPV infection and have demonstrated that DRB1*13 polymorphic antigen relates to the cumulative risk for oncogenic virus infection. This risk appears to be greater for HPV 16 than for other HPV genotypes [55,56]

Human Immunodeficiency Virus (HIV) infection. Studies published in 2002 and 2003 have reported high HPV infection persistence and intraepithelial squamous lesions in HIV-positive men and HIV-positive women [57–62].

1.1.3. Description of the problem at a regional level

In the United States, with a population of 336.5 million, an estimated 11,999 cases of CC were diagnosed in 2005, and 3924 deaths occurred. In the LAC region, the average age-standardized incidence rate of CC is 18.8 per 100,000 women, and the age-standardized mortality rate is 8.1 per 100,000 [3,63]. Incidence rates in Latin American and the Caribbean (LAC) have considerable variation (7.0 in Uruguay and up to 80 in Haiti). In North American countries, the relative importance of CC deaths (compared to total number of cancer deaths) is 2.5%, but in Haiti the relative importance is 49% [2].

CC ranks fourth in relative importance among all cancers in LAC and is the most common cancer among women 15–44 years of age in LAC [3].

Recent estimates reported by the World Health Organization and the Catalá Oncologic Institute for 2007 show that HPV infection prevalence in the general population varies among countries of the region. Among women with normal cytology, the prevalence of HPV ranges from 1.2%-22% [3–8], among women with LSIL the prevalence ranges from 2.3%-98% [3,8–18], and among women with HSIL HPV prevalence ranges from 2.3%-99% [9,15,19–23]. The prevalence in women with CC has been observed to be 90-100% (1,8–90). Published meta-analyses for different population groups indicate that HPV 16 and 18 are responsible for almost 70% of CC cases, with some variation among countries [10,21,23,52,64–75].

1.2. Justification

A lack of knowledge exists regarding HPV-related burden of disease at the LAC regional level, especially distribution of HPV genotypes by specific age groups. With better knowledge about this distribution, we could improve the model for cost-effective vaccines and other primary and secondary prevention strategies. At this time, two registered HPV vaccines are available for use in LAC countries, but we need to know HPV infection distribution by virus genotype and age to perform monitoring of genotype substitution that may result from the influence of vaccination on the virus ecology of a vaccinated human population. We must also increase knowledge of HPV infection related to specific genotypes in lesions and understand the extent to which the etiology of HPV infections is attributable to genotypes other than HPV 16 and 18. This knowledge will guide priorities for incorporating other genotypes into future vaccines.

Also, knowledge of the prevalence of HPV infection in healthy men as well as in men with penile cancer is needed. Knowing the extent of this problem in sites other than the cervix is important. Although the greatest burden of disease results from CC, ignoring the burden of disease originating from vulvar, vaginal, anal, penile, oral cavity, and oropharyngeal cancers will lead to misinformed projections for HPV-based preventive initiatives. We also need to know the importance of recurrent respiratory papillomatosis and condiloma acuminate (lesions associated with HPV genotypes 6 and 11) for LAC.

Through knowledge of HPV infection-related burden of disease, we can perhaps quantify health outcomes and determine what proportion of this burden may be avoided through interventions such as primary and secondary prevention.

Finally, we took into account the influence of the heterogeneity in laboratory methodology, diagnostic practices, patient samples, statistical analysis, and overall quality of published reports on the quality and quantity of the evidence for the burden of disease due to HPV infection in LAC countries. For this purpose, we graded the evidence according to indicators of study quality and validity to analyze their influence on the estimates of disease associated with HPV in the region..

CHAPTER 2. OBJECTIVES

2.1. General objectives

- Estimate the prevalence and incidence of HPV infection and HPV disease-related burden in LAC countries on the basis of an in-depth meta-analysis of published reports for the region.

- Using estimates from the meta-analysis, summarize the cost-effectiveness of HPV vaccines in the prevention of cancer and other nonmalignant diseases associated with HPV in LAC countries.

2.2. Specific objectives

- Estimate age-specific prevalence and HPV infection incidence, both overall and genotype specific, in healthy populations of both sexes.

- Estimate overall and type-specific HPV prevalence in cervical lesions of different grades and in vulvar, vaginal, penile, and oral cavity cancers.

- Estimate overall and type-specific HPV prevalence in condiloma acuminata.

- Estimate cancer and nonmalignant neoplasm incidence and mortality associated with HPV infection in LAC countries.

- Describe epidemiologic data quality and validity for HPV infection and related diseases in LAC countries and identify gaps in information that can be acquired through future surveys.

- Summarize the frequency of occurrence of risk factors for HPV infection and associated CC in LAC countries.

- Estimate disease costs related to HPV infection in LAC countries.

- Estimate the proportion of HPV-related disease that can be prevented by vaccines in LAC countries.

- Design cost-effectiveness models for different vaccination strategies, and design secondary prevention strategies for specific LAC countries.

CHAPTER 3. METHODS

- Determine inclusion and exclusion criteria for search studies and data extraction.
- Establish procedures and quality control.
- Analyze data and perform meta-regression for calculating HPV infection general prevalences according to specific virus types and specific age groups in healthy populations and in populations with different types of lesions.
- Calculate HPV infection incidence.
- Determine HPV–related burden of disease.
- Review risk factors for HPV infction.
- Conduct economic evaluation study (Details of this study are in Volume 2, which includes an explanation of theoretical models, data sources and countries included in the models, and the outcomes observed in a theoretical cohort of young women followed-up through a lifetime).

3.1. Types of studies included

We have included a systematic review of published scientific articles found in six databases as well as unpublished economic and epidemiologic data collected between 1990 and mid-2007 from LAC countries. We performed an economic analysis to establish direct and indirect costs or burden of disease from both the health services perspective and societal perspectives.

3.1.1. Inclusion and exclusion criteria

Only studies with information about residents of LAC countries were included. When the search found studies that included Latin American and non-Latin American countries, only data from LAC countries were considered.

Diseases and inclusion criteria for each epidemiologic indicator

a) To calculate prevalence, we included epidemiologic information about the diseases specified in Table 1.

Table 1. Cancer and other diseases associated with HPV that were considered in this report

HPV-associated neoplasm diseases
Cervical cancer
Cervical intraepithelial neoplasia, grades I, II, and III
Vulvar cancer and intraepithelial neoplasm
Vaginal cancer and intraepithelial neoplasm
Penile cancer and intraepithelial neoplasm
Anal cancer and intraepithelial neoplasm
Oropharyngeal neoplasms
Other diseases associated with HPV
HPV infection without lesions
Genital condiloma acuminata
Respiratory papillomatosis

b) To calculate incidence, we included HPV cervical infection.
c) To calculate burden of disease, we included information registered for cervical, vulvar, vaginal, anal, and oropharyngeal cancers.
d) We included information on the following risk factors: use of tobacco, age at initiation of sexual activity, and use of oral contraceptives.

Criteria for inclusion or exclusion of studies

Inclusion criteria

Study subject

A study must have included original data on HPV prevalence or incidence, based on either samples isolated from patients with lesions (Table 1) or samples from the same anatomical sites in healthy populations. This information must have been gathered from studies of LAC human populations.

Study design and sample size

Studies on the epidemiology of HPV in cervical lesions and on women with normal cervical or vaginal cytology were included if the sample size included 30 or more subjects.

Studies on the epidemiology of HPV in specific lesions or samples were included, even when the sample size had fewer than 30 subjects (with 10 being the lowest acceptable number).

Studies of HPV epidemiology in special populations (e.g., HIV-infected persons, commercial sex workers [CSW] were included, even when the sample size had fewer than 30 subjects (with 10 being the lowest acceptable number).

Regarding design of the studies, we examined all studies that provided data on incidence and prevalence, including all types of observational studies, such as cross-sectional, case-control, and cohort studies.

Study population

Studies for both general and special populations were selected.

Methods

A study was included only if HPV detection or typing was performed with molecular techniques for DNA amplification, such as polymerase chain reaction (PCR), line blot, hybrid capture, and reverse hybridization.

Studies related to HPV infection detected by performing Hybrid Capture 2 (HC2) in populations without lesions were included. This method can detect 13 high risk genotypes (and, in some reports, an additional 7 low risk genotypes) but cannot detect all virus types associated with CC, a limitation that affects results.

We included studies published between January 1990 and July 2007, without language restriction (e.g., English, French, Spanish, Portuguese). This time span was established because target or signal amplification molecular techniques for virus DNA detection have become well established since the 1990s. Before that time, non-amplified hybridization methods like Southern Blot were used.

Studies related to the cost of health services in screening programs, those related to cost of care for CC patients, and cost-effectiveness studies were also included.

Exclusion criteria

This stage was performed in two consecutive phases. The first phase omitted the following:

Studies without original data on HPV infection. Meta-analyses, systematic reviews, and letters to the editor were excluded. Nevertheless, those articles were used for identifying additional references and investigators within the region.

Articles published before 1990 using other virus DNA detection methods that were less developed than hybridization techniques with target or signal DNA amplification.

Studies that used virologic techniques without molecular amplification or nonmolecular techniques, including in situ hybridization, immunologic, and cyto-histopathologic techniques.

Studies related to detection of HPV in lesions and performed only with the HC2 technique. HPV prevalence in lesions is higher than in normal tissues, and this method detects only 13 genotypes thus underestimating the overall prevalence of HPV in lesional tissue.

In a second phase, after reviewing the journal databases, we added new exclusions and created an Excel database to which we added articles excluded from the analysis. Variables such as article identifier and reasons for elimination were collected. Reasons for elimination were classified as follows: studies published before 1990, studies not performed in LAC, studies with equivocal data or data irrelevant to this report, absence of original HPV data, articles duplicated in databases, studies of HPV-related CC infection with fewer than 30 subjects, and studies about HPV infection at other sites with fewer than 10 subjects (Appendix A).

3.2. Databases consulted and search strategies

The following databases were consulted: PubMed, LILACS, Scielo, CAB Health, EMBASE, ICNAHL and Cochrane Library (Appendix B).

3.2.1. Search strategies for published articles

Database search terms contained in Appendix A were used. These search terms were sent for review to CDC librarians who knew the purposes of the study. When the need to intensify search strategies increased, a research team member was available for questions.

A total of 1,096 summaries that fulfilled search terms were gathered and distributed to the investigators, who applied the inclusion criteria and selected the ones that had to be searched as full text.

3.2.2. Search strategies for unpublished literature or incomplete reports presented at congresses

Additional efforts were made to identify studies with unpublished results at the end of the bibliographic search time (July 2007). The search strategies (Appendix C) included the following:

- Contact with people in charge of cancer control programs through the Pan American Health Organization and the Ministries of Health in LAC countries.
- Identification of regional-level studies conducted with the support of government or pharmaceutical industries.
- Direct contact with 50 HPV investigators at the regional level.
- Direct contact with cancer registries through IARC.
- Information searches in countries with Health and Demography National Surveys, which are rarely published in related journals.
- Search of summaries from scientific conferences.

3.2.3. Selection procedures for full text summaries

The selected summaries by librarians at CDC and the University of Chile were distributed to investigators, who used the inclusion criteria to determine whether or not the full text for each article was to be reviewed. A selection of summaries was send to two investigators to evaluate their concordance with inclusion and exclusion criteria.

Once the list of summaries that required a full-text search was defined, it was distributed to the CDC and University of Chile librarians in charge of obtaining the texts in electronic format. The texts were sent to the investigators for analysis of the relevant data for the study or exclusion of the data according to the criteria previously defined.

3.2.4. Data extraction procedures

Investigators extracted the data from each selected study using questionnaires designed and validated using the EPIDATA software (version 3.02, by Jens Lawritsen and Michael Bruus).

One questionnaire gathered variables associated with study characteristics, matching the variables with corresponding identifiers, such as principal author´s name, journal characteristics, type of study population, population selection methods, and HPV detection methods used. Investigators also assigned each study a value for its level of evidence, which was determined by previously established quality criteria.

A second questionnaire collected each study's virologic and epidemiologic results, such as HPV prevalence stratified by age, type of lesion, and virus type.

Appendices E and F show the structure of the questionnaires used to extract information about each article's general characteristics and HPV epidemiologic variables, respectively.

In the general population studies, the HC2 method was used to identify virus DNA in normal cytology subjects, whereas information regarding lesions was included only when virus identification was completed by PCR.

Special efforts were made to ensure that the virologic information for the analyzed studies was complete. For example, if specific data by HPV type were gathered but not published, the authors were contacted by e-mail or airmail to obtain the additional information. The same procedure was followed to obtain additional information about age and type of lesion. In some cases, an article lacked original prevalence information, so the study author was contacted to obtain these data. Rates of authors' responses following the study team's requests were also recorded.

3.3. Criteria and procedures for quality control

3.3.1. Case definition

Normal cytology: No abnormal cervical cells observed on cytologic examination [3,76,77].

Low-grade cervical lesions (LSIL/ICIN-1): Lesions defined by early changes in the size, form, and number of abnormal cells at the cervical surface; can be denominated as mild dysplasia [3,76,77].

High-grade cervical lesions (HSIL/CIN-2/CIN-3): Lesions defined by a high number of precancerous, abnormal cells at the cervical surface and having the potential to develop into malignancy and to invade deep cervical tissues; can be denominated as moderate to severe dysplasia or in situ cervical carcinoma.

Cervical carcinoma-in situ (CIS): Carcinoma confined to the cervix, without dissemination to the rest of the body. In classifications of CIN, CIS is included as CIN3.

Invasive cervical cancer (ICC): Invasion of deep cervical tissues or other organs and tissues by cancerous cells [3,76,77].

3.3.2. Quality of the review

For establishing the quality of articles, three topics were evaluated:

Reader's concordance: A subgroup of summaries was sent to the investigators to evaluate each study's concordance with selection and exclusion criteria. Concordance was evaluated using the Kappa Index for more than two observers.

Quality evaluation: A six-item simplified quality score was designed for this analysis (Appendix D) [78,79] The six items evaluated three main study characteristics to determine the validity and generalizability of the studies: study population, HPV-infection diagnosis, and classification of HPV-related lesions.

Two readers assigned the quality score through an independent review process for data collection. Every study was assigned values for each HPV type of lesion addressed in the study (including without lesion; that is, the study of HPV infection in healthy women). Scores can therefore be directly compared only if they come from studies related to the same type of lesion. Variables from this type of scoring were developed to use as restrictive criteria in the sensitivity analysis and to verify the impact of the studies' quality on reported HPV prevalence and burden of disease**.**

Distribution of quality scores for the studies is presented in the results section.

Impact Factor: The impact factor (IF) of the journal in which each study was published was recorded. When results of a study were published in multiple articles, the journal with the highest IF for each study was chosen. In contrast with the quality score, only one IF was recorded for each study, even if multiple HPV-associated lesions were investigated. The IF was obtained using the *Journal Citation Reports*® (JCR) [80], without relying on each article´s publication date. A journal's IF score is well correlated with its manuscript rejection rate and thus can serve as an indicator of the article's perceived priority in a given specialty. The IF description and its correlation with the quality score are presented in the results section.

3.4. Data analysis

3.4.1. Prevalence estimates

The characteristics of the studies were described with frequency tables. The general continuous variables for each study were summarized by using the mean and standard deviation and then weighted by reported sample sizes. Crude prevalences reported in each study for women with normal cytology by age group were represented in a scatter plot.

Prevalences and their 95% CIs were estimated by fixed effects; that is, the general prevalence corresponds to the weighted mean of the prevalences obtained from each study, the weight corresponding to the inverse of the respective variance. This weight measures the accuracy of each study relative to its prevalence determination.

To determine age-related prevalences, we used mixed models to capture variability within each study and among studies. For age-related prevalence, we included only studies with information about prevalences for at least three age groups. We report these prevalences with their respective 95% CI.

Age-specific prevalences were estimated for HPV infection among healthy women. Also, prevalences were estimated separately for low- and high-risk HPV types by using oncogenicity information based on the classification presented in Appendix G, Table 8.

A meta-regression was conducted to estimate study characteristics that might explain the variability of general prevalences reported in each study. Variables examined in this meta-regression were type of samples (i.e., exfoliated cells, biopsies, or surgical samples) and method of virus typing (i.e., measured by either HC2 or PCR) [81,82]. Also, a meta-regression was performed to quantify each study´s quality (expressed through a discrete score of 1–6) indicator regarding its influence on the magnitude of the HPV prevalence estimates.

The data reported in each article was registered in EPIDATA (version 3.02 by Jens M. Lawritsen and Michael Bruus) and analyzed by STATA (release 10.0 [College Station, Texas 77845, USA, 800-StataPC; http://www.stata.com]).

Genotype-specific prevalence: Prevalences were expressed as percentages of all persons tested for HPV infection with an adequate specimen. If a person was positive for more than one genotype, each genotype was recorded separately. Table 2 shows the internationally accepted classifications for HPV genotypes as well as past designations for types that did not have official taxonomic entries. Virus types are sometimes incorrectly designated as subtypes, but, for practical reasons, whenever virus types were expressed in past subtype nomenclature, we classified them with the official type designation. For example, if a study showed separate prevalences for IS39 (a subtype of HPV 82) and HPV82, the values were added and considered to be one prevalence for HPV82.

The heterogeneity of HPV type classifications that aim to group types by oncogenic potential led to the creation of a new classification derived from a review of previously existing reports and expert opinions (shown at Appendix G, Table 8). Type designation followed that of standard taxonomic nomenclature [24].

Table 2. Past and current international classification of HPV types

Past HPV type designations (used as synonyms)	Official HPV type designations
HPV 46	HPV 20 (a subtype)
HPV 64	HPV 34 (a subtype)
HPV 55	HPV 44 (a subtype)
CP141	HPV 70
LVX160	HPV 70
CP8061	HPV 71
CP4173	HPV 72
LVX100	HPV 72
MM9	HPV 73
PAP238A	HPV 73
CP8304	HPV 81
W13B	HPV 82
MM4	HPV 82
IS39	HPV 82 (a subtype)
AE2	HPV 82 (a subtype)
PAP291	HPV 83
MM7	HPV 83
LVX82	HPV 83
PAP155	HPV 84
MM8	HPV 84
HLT7474	HPV 85 (candidate) [a]
CP6108	HPV 89
AE6	HPV 89
X06 or X08	HPV 89
AE11	HPV 90 (candidate) [a]
Han831 or han1353	HPV 90 (candidate) [a]
AE13	HPV 91 (candidate) [a]
JC9813	HPV 91 (candidate) [a]

[a] Taxonomic denomination awaiting final approval by systematic consensus at the time of this report.

3.4.2. Incidence studies

At the beginning of the 1990s, three cohort studies were initiated in different regions of Latin America: Brazil, Costa Rica, and Colombia. To estimate incidence data at the regional level, we contacted the institutions and principal investigators of those studies and obtained unpublished incidence data from two (Brazil and Colombia). Table 3 shows general baseline characteristics of these studies.

Table 3. Principal characteristics of cohort studies at baseline

Place	Population	n	Median Age (IQR [a])	Type of PCR	Follow-up
Bogotá, Colombia	Screening program participants	1,610	32.3 (26.5–39.2)	GP5+/GP6+	Every six months
	Four low-income zones. Bogotá			37 genital types identified by post-amplification hybridization	
	Recruitment from 1993 through 1995				
	13–85 years of age				
Sao Paulo, Brazil	Public health program participants	2,528	33.3 (26.0–39.0)	MY09/11	Every four months in first year; every six months in future years
	Low-income zone in the north of the city			40 genital types identified by post-amplification hybridization	
	Recruitment from 1993 through 1997				
	18–60 years of age				

[a] Interquartile range.

Both the Brazil and Colombia cohorts are similar in age, number, and income of participants and in methods used at follow-up and for infection identification.

For analysis, two different age classifications were used, one of which provided more detail than the other. The detailed classification had the following age groups: younger than 25 years of age, 25–34, 35–44, 45–54, and 55 and older. The less detailed classification had three age groups: younger than 25 years of age, 25–44, and 45 and older.

For incidence calculation, the following definitions were used for all HPV genotypes:

- Incident case: A case counted during the entire period of observation from first incorporation into the cohort until first visit during which positivity for a given genotype was detected for the first time in that woman.

- Person-Time: The time in months between a visit (either initial or follow-up) until detection of positivity for a specific HPV genotype. Exact time between visits was recorded, but measurement between visits was interrupted after the first detection of infection with any genotype, but only for that genotype. For example, if a woman was found at a visit to be positive for genotype 6, from that time, she no longer contributed to the person-time observation for that genotype but still contributed to the person-time data for other genotypes (Figure 1).

Woman without infection - - - - - - contributes to counts with 30 months of follow-up

Months of observation ---→ contributes to denominator of incidence rates : 0 6 12 18 24 30 months for all genotypes

Woman who is HPV 16+ - - + - - - contributes to counts with 12 months of follow-up

Months of observation ---→ contribute to the denominator of incidence rates: 0 6 12 18 24 30 months for HPV 16 and 30 months of follow-up for all other genotypes.

Woman who is HPV 16/18 (+) - - +16 +18 - - contributes to counts with 12 months of follow-up

Months of observation --→ contribute to denominator of incidence rates: 0 6 12 18 24 30 months for HPV 16, 18 months for incidence rate of HPV 18, and 30 months of follow-up for incidence rate of all other genotypes.

Figure 1. Criteria for quantification of follow-up time for calculating three sample incidence rates.

For women without infection of any genotype, the exact period of observation until the last visit was calculated.

Incidence rates for each specific genotype were calculated by dividing the number of positive cases for each genotype by the total number of person-time observations and were expressed per 100 woman–years. In addition, rates were expressed with 95% CI using the Poisson method.

Age-specific global and specific rates were calculated for the following categories:

a) Oncogenic risk:

i. High Risk: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 82.
ii. Low Risk: All other genotypes, except unknown and undetermined types.

b) Alphapapillomavirus species, combined with the phylogenetic classification (based on the homologous DNA composition and amino acids combination) proposed by Schiffman et al. [42]:
   i. Group 1: Species 1, 8, and 10
   ii. Group 2: Species 5–7, 9, and 11
   iii. Group 3: Species 2–4 and 15

c) HPV overall positivity, independent of virus type.

In addition to incidence rates calculated as above, 5-year cumulative incidence rates were calculated using the Kaplan-Meier actuarial method.

3.5. Risks and projections for HPV-associated cancer in LAC

3.5.1. Methods

The number of cases of HPV-associated cancer at the regional level was estimated; number of cases of CC and oropharyngeal cancer was calculated for each country individually. Both incidence and prevalence of other types of cancer were estimated for the region.

3.5.2. Population estimation

Population estimates for Latin America were obtained from projections performed by the Demography Latin America Center (CELADE) ("Population Estimations and Projections, 1950–2050. Demographic Paper of January 2004, Santiago–Chile").

3.5.3. Calculating number of actual cases

For CC and oropharyngeal cancer, IARC estimates for 2002 were used. We assumed that changes in population size would be small and that the incidence rates would be relatively constant for a short period of time. Because IARC estimates do not cover all cancer anatomic sites, for vaginal, vulvar, anal, and penile cancers, we used 2008 population estimates and projected adjusted rates for those neoplasms reported by Latin American cancer registries. Using the average disease duration, we estimated the number of prevalent cases for a year. Table 4 shows the calculated incidences for vaginal, vulvar, anal, and penile cancers. Table 4 also shows each cancer's median incidence and medians calculated at the 25th and 75th percentile.

Table 4. Estimated crude and adjusted incidence rates for anal, penile, vulvar, and vaginal cancers, Latin American cancer registries, 2008[a]

	Anal cancer				Penile cancer		Vulvar cancer		Vaginal cancer	
	Men		Women							
Country/city	**Crude**	**AIR**	**Crude**	**AIR**	**Crude**	**AIR**	**Crude**	**AIR**	**Crude**	**AIR**
Argentina, Bahía Blanca	0.3	0.2	1.4	0.8	1.5	1.1	0.8	0.5	1.2	1.0
Brazil, Brasilia	0.5	0.9	0.9	1.4	2.1	3.7	0.8	1.4	0.9	1.5
Brazil, Cuiaba	0.4	0.6	0.5	0.8	1.4	2.3	0.5	0.8	0.6	0.8
Brazil	0.1	0.1	0.6	0.6	1.8	2.6	1.3	1.5	0.5	0.6
Brasil, Sao Paulo	0.7	0.8	1.2	1.1	1.3	1.5	1.7	1.6	0.9	0.9
Chile, Valdivia	0.4	0.5	0.1	0.1	0.7	0.7	0.6	0.5	0.4	0.4
Colombia, Cali	0.4	0.6	1.2	1.4	1.5	1.8	0.9	0.9	0.8	0.7
Costa Rica	0.2	0.3	0.5	0.6	1.0	1.3	0.6	0.7	0.3	0.3
Ecuador, Quito	0.2	0.2	0.6	0.7	0.6	0.8	0.3	0.3	0.3	0.3
France, La Martinique	0.6	0.4	1.5	0.9	1.0	0.7	1.0	0.6	1.3	0.9
Perú, Trujillo	0.3	0.5	0.8	1.2	1.1	1.8	1.3	2	0.1	0.2
Median	0.4	0.5	0.8	0.8	1.3	1.5	0.8	0.8	0.6	0.7
25th percentile	0.3	0.3	0.6	0.7	1.0	1.0	0.6	0.6	0.4	0.4
75th percentile	0.5	0.6	1.2	1.2	1.5	2.1	1.2	1.5	0.9	0.9

[a] Rates per 100,000 population; AIR, age-adjusted incidence rate using the 1960 world population as standard. Source: International Agency for Research on Cancer.

3.5.4. Calculating the HPV-associated risk for noncervical cancers

For HPV-associated cancer, we also calculated actual observed values and the expected number of cancer cases within a hypothetical cohort. For CC, the proportion causally attributable to HPV infection was established as 100%. The proportion of oropharyngeal cancer associated with HPV was estimated by using information gathered from all available case-control studies in the literature that explored the relationship between HPV and other cancers and that examined the presence of HPV in situ in the control groups. We then calculated the proportion of HPV-associated oropharyngeal cancers by using the following formula [25,83–94]:

$$RA = 1 - \sum_j \frac{p_j}{R_j}$$

In this formula, *RA* = attributable risk; P_j = proportion of cases in stratum $_j$. R_j = relative risk or OR at the $_j$ stratum. When the $_j$ stratum = 0 (no exposure), *R* takes the value of 1 [87].

3.6. HPV-associated risk factors

We extracted available data in the studies obtained by systematic review, realizing that most of the studies were conducted in nonprobabilistic samples, so some results cannot be extrapolated, including median age for first sexual relation and average number of sex partners. Prevalences for tobacco use and sexually transmitted diseases (STDs) were obtained from national surveys of reproductive health and lifestyles available from websites of various national health ministries and from CDC in Atlanta.

3.7. Ethical Aspects

This investigation is based on the review of secondary information from both published articles and cancer registries; there was no involvement of any human subjects who may have been patients studied in the individual articles or whose information had been recorded in the various public databases. The data in the original articles that were abstracted or in the databases used to derive complementary information contained no personal identifiers.

3.8. Financial aspects

This investigation was financed by the Albert Sabin Institute. The authors provide their conflicts of interest in section 6.1.

CHAPTER 4. RESULTS

4.1. Search results

Outcomes of studies selected for review

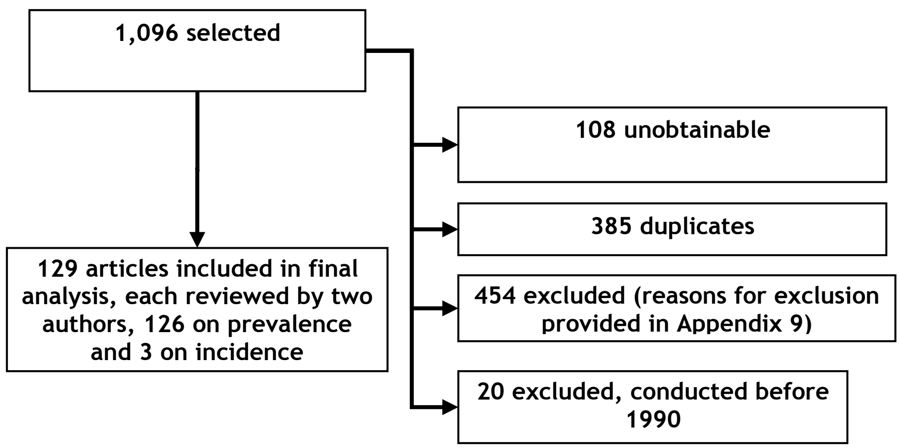

Figure 2. Diagram showing outcome of selected studies and criteria for inclusion in the systematic review

4.2. Quality evaluation results

The quality score distribution for studies addressing CC and normal cytology is described in Table 5. Table 6 shows a general summary of the quality scores for studies addressing CC and normal cytology by country.

Table 7 summarizes the distribution of IFs for the studies published in journals classified by the Journal Citation Reports (JCR) for 2006. Table 8 shows the distribution of IFs for all studies evaluated by pairs of investigators, including those for which a value of 0 was assigned if a study was published in a journal not rated by JCR 2006 or in journals not indexed. Figure 3 shows the correlation between the quality score and the IF for studies included in Table 5, and Figure 4 shows the correlation between the quality score and the IF for all studies, as indicated in Table 6. Table 9 shows in detail the correlation between the quality score and the IF for each HPV-associated type of lesion investigated (considering all the studies). Figure 5 shows this correlation for studies related to HPV infection in persons with normal cytology.

Table 5. Mean quality score distribution for all studies by type of lesion or cytology status, Latin America and the Caribbean

Type of lesion/cytology status	No. studies	Average score[a]	SD
Normal	73	3.41	1.31
LSIL	38	3.68	1.01
HSIL	47	3.78	1.04
CC	47	4.15	0.88
All studies	249	3.60	1.21

[a] Range of scores: 1–6.
SD, standard deviation; LSIL, low-grade lesions; HSIL high-grade lesions; CC, cervical cancer.

Table 6. Mean quality score distribution for all studies by country, Latin America and the Caribbean

Country	No. studies	Average score[a]	SD
ARGENTINA	59	3.4	1.07
BARBADOS	1	3.0	-
BOLIVIA	1	4	-
BRASIL	75	3.4	1.4
CHILE	8	4.4	1.4
COLOMBIA	7	5.1	0.4
COSTARICA	5	5.2	0.5
CUBA	1	5	-
ECUADOR	4	3.5	1
HONDURAS	7	3.7	1.9
JAMAICA	4	4	0.8
MEXICO	54	3.7	1.1
NICARAGUA	6	3.5	0.6
PANAMA	1	5	-
PARAGUAY	3	4	1
PERU	5	4.2	0.8
SURINAM	3	3	1.7
VENEZUELA	5	2.6	0.6

[a] Range of scores, 1-6.
SD, standard deviation.

Table 7. Impact factor distribution for studies rated by JCR (2006) by whether studies addressed no or low-grade lesions, Latin America and the Caribbean[a]

Lesion status	No. studies	Impact factor	SD
Without lesion	42	2.86	2.47
LSIL	24	2.23	1.55

[a] JCR, Journal Citation Reports; SD, standard deviation; LSIL, low-grade lesions.

Table 8. Impact factor distribution for all studies by type of lesion or cytology status, Latin America and the Caribbean[a]

Type of lesion/cytology status	No. studies	Impact factor	SD
Without lesion	73	1.63	2.34
LSIL	38	1.39	1.62
HSIL	41	1.49	1.74
Cervical cancer	47	4.33	5. 91
All studies	245	2.10	3.30

[a] Includes studies published in journals rated by Journal Citation Report (JCR) for 2006 and those not rated in JCR; a zero value was assigned to those not published in JCR-rated journals.
SD, Standard deviation; LSIL, low-grade lesions; HSIL high-grade lesions.

Table 9. Correlation between impact factors and quality scores for all studies by type of lesion or cytology status, Latin America and the Caribbean

Type of lesion/cytology status	No. Studies	*p*[a]	*P* value
Without lesion	73	0.47	<0.0001
LSIL	38	0.19	NS
HSIL	41	0.24	NS
Cervical cancer	47	0.55	0.0001
All studies	245	0.36	<0.0001

[a] P, Spearmans correlation coefficient, LSIL, low-grade lesions; NS, not significant, HSIL, high-grade lesions.

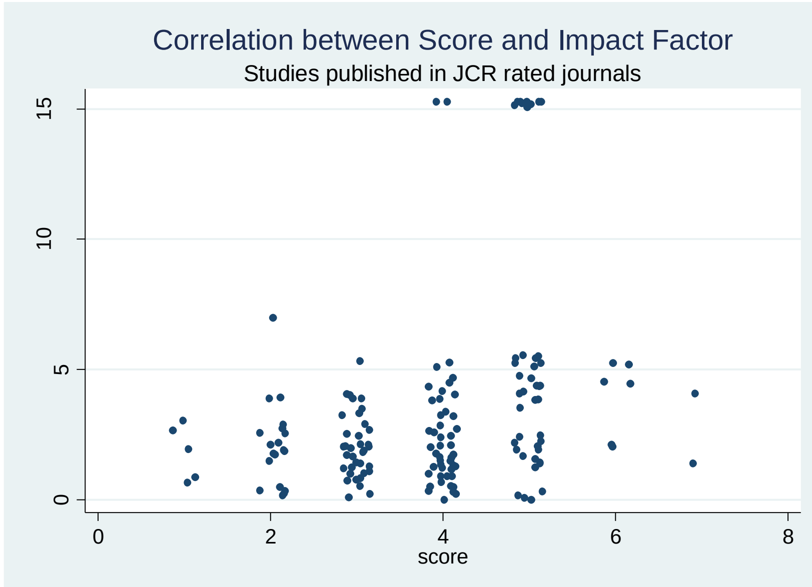

Figure 3. Correlation of quality scores and impact factors for studies published in journals rated by Journal Citation Reports (2006) , Latin America and the Caribbean

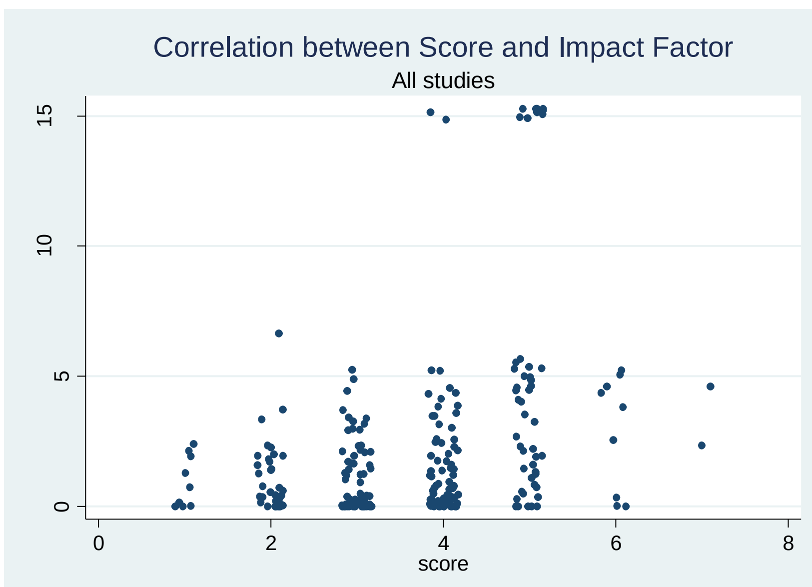

Figure 4. Correlation between quality scores and impact factors for all studies, Latin America and the Caribbean. A zero value was assigned to those studies published in journals not registered in Journal Citation Reports (JCR) (2006) and to studies published in journals not indexed by JCR.

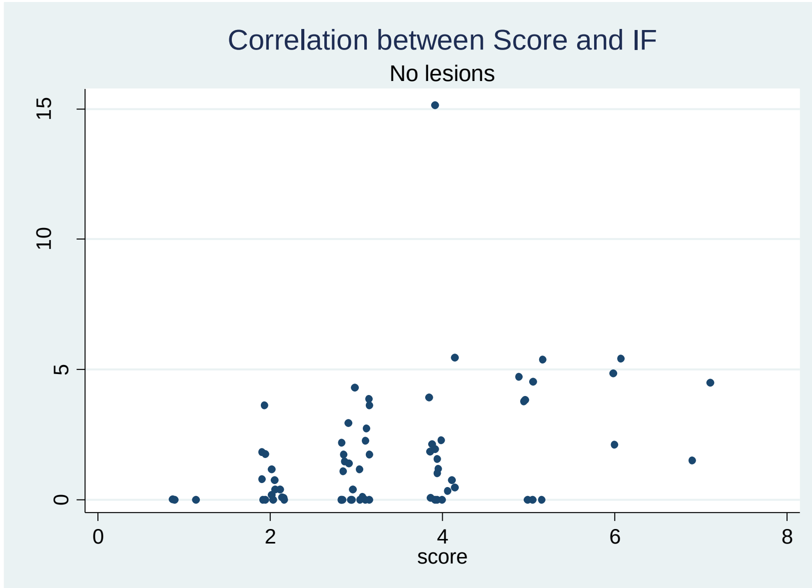

Figure 5. Correlation between quality scores and impact factors for studies related to HPV infection in subjects with normal cytology, Latin America and the Caribbean.

4.3. Prevalence results

Table 10 shows the breakdown by country of the 126 articles reviewed to calculate HPV prevalence. The 126 articles addressed 16 countries in Latin America and the Caribbean. The majority (74%) were publications from Brazil, Mexico, and Argentina.

Table 10. Number of studies by country used to determine HPV prevalence

Country	No. of studies	Percentage
ARGENTINA	19	15.1
BARBADOS	1	0.8
BOLIVIA	1	0.8
BRAZIL	45	35.7
CHILE	3	2.4
COLOMBIA	6	4.8
COSTA RICA	1	0.8
ECUADOR	1	0.8
HONDURAS	3	2.4
JAMAICA	1	0.8
MEXICO	29	23.0
MULTIPLE	2	1.6
NICARAGUA	2	1.6
PARAGUAY	1	0.8
PERU	4	3.2
SURINAM	2	1.6

VENEZUELA	5	4.0
TOTAL	126	100.00

Argentina was represented by studies from 10 provinces; Brazil by studies from 18 states; and Mexico by studies from 10 states. The largest number of useful studies for calculating HPV prevalence addressed women; Table 11 describes these studies.

Table 11. Number of studies and size of study populations used to calculate HPV prevalence by type of lesion and cytology status[a]

Type of lesion/cytology status	No. studies	No. women
Normal cytology	52	38,471
ASCUS	11	294
LSIL	27	1,773
HSIL	32	1,339
CC	38	2,227

[a] ASCUS, atypical squamous cells undetermined; LSIL, low-grade lesions; HSIL, high-grade lesions; CC, cervical cancer.

Few studies were about men, and sample sizes for healthy men (n = 3,183) and for men with penile cancer (n = 71) were low. Studies addressing the prevalence of HPV infection in such localized sites as the vulva, vagina, anus, or oropharynx lacked sufficient size to be useful.

Table 12 shows HPV infection prevalence in different populations by viral DNA detection method used. HPV infection prevalence in healthy women, determined by PCR and observed in genotype-specific studies that also used PCR, was larger than the prevalence detected by HC2 (18.7% and 11.1%, respectively). The same difference was observed for healthy men, who were studied by using exfoliated cells and, more rarely, urethral and skin samples. Prevalence determined by PCR was 21.7%, compared to prevalence observed by HC2 of 18.3%, a statistically significant difference. Results by HC2 correspond only to high-risk viral infections, PCR-determined prevalences are not directly comparable because they include all types, regardless of oncogenic risk.

Table 12. HPV infection prevalence in healthy men and women by type of lesion or cytology status and viral detection method, Latin America and the Caribbean[a]

Population by type of lesion/cytology status	PCR			HC2		
	No. studies	No. subjects	% (95% CI)	No. studies	No. subjects	% (95% CI)
Women						
Normal cytology	43	21,586	18.7 (15.4–22.0)	9	16,885	11.1 (7.4 –14.8)
ASCUS	11	294	56,1 (39.7 –72.4)	NA	NA	NA
LSIL	27	1,773	79.0 (71.9 –86.1)	NA	NA	NA
HSIL	32	1,399	96.8 (93.5 –100)	NA	NA	NA
ICC	38	2,227	94.0 (89.4 –98.5)	NA	NA	NA
Squamous and unspecified cervical cancer	28	1,795	88.0 (80.6 –95.4)	NA	NA	NA
Cervix adenocarcinoma	3	277	85.2 (63.0 –100)	NA	NA	NA
Men						
Normal cytology	7	2,003	21.7 (1.7 –41.6)	1	1,180	18.3
Penile cancer	2	71	67.8 (31.4 –100)	NA	NA	NA
Men and women						
Anal cancer	-	-	--	NA	NA	NA
Oropharynx cancer	-	-	--	-	-	--
Condiloma acuminata	2	158	81.5 (0.0 –100)	-	-	--
Respiratory papillomatosis	1	15	53.3	-	-	--
Normal oral mucosa	2	43	9.3 (1.1 –17.5)	-	-	--
HIV +	7	1,082	79.5 (72.1 –87.0)	-	-	--

[a] Some confidence intervals were not calculated due to insufficient number of studies. Blank combinations represent absence of studies related to the subject.
HC2, Hybrid Capture 2 assay; ASCUS, Atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; ICC, invasive cervical cancer; NA: not applicable.

Table 12 reports only studies that enabled calculation of HPV infection prevalence. For respiratory papillomatosis, four studies were found with a total of 93 subjects; three of these studies addressed only HPV-positive populations, and one contributed to the general prevalence calculation. Results of this study showed that the most reported HPV types were HPV 16 (83%), 33 (55%), 11 (38%), and 6 (32%) (Bello de Alford [Mexico 2001]). This is the only study that identified different virus genotypes; however, the virus distribution data suggest contamination because of the preponderance of HPVs 16 and 33, types not known to cause these lesions. Therefore, the results of this study should be viewed with caution.

Figure 6 shows the years in which the studies began accruing subjects; 43.4% started between 1998 and 2001.

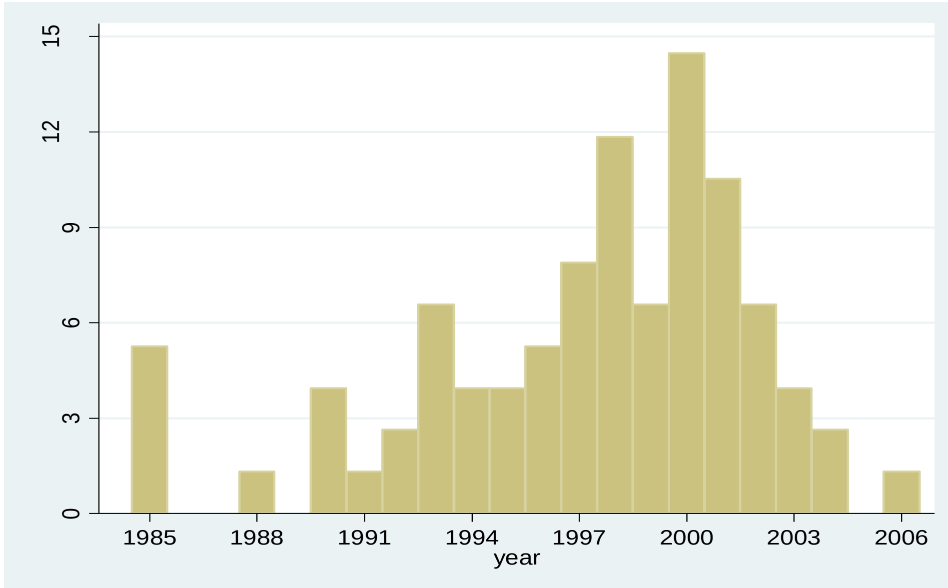

Figure 6. Initial years of HPV prevalence studies, Latin America and the Caribbean

Subjects for the studies were obtained or recruited in different ways: 105 studies were conducted at ambulatory health centers, and 18 were conducted in the community. The other six studies were based on retrospective reviews of laboratory samples. Samples for 13 studies used statistical sampling, 110 were did not use sampling, and three included data using both convenience samples and statistical sampling.

Data on the person obtaining the samples for viral DNA detection were reported in 95 studies; 93.7% of the studies reported that samples were obtained by health teams; only 6.3% of studies reported that study subjects obtained the samples themselves.

Data on type of samples collected were reported by 114 (90.5%) studies. Of those studies, 71 (62.3%) used exfoliated cells; 19 (16.7%) used liquid-based collection of exfoliated cells; nine (7.9%) used fresh biopsies; 27 (23.4%) used fixed biopsies; and three (2%) used fixed surgical samples.

Information for sample type by population group is shown in Appendix G, Table 1.

The most frequently used viral DNA detection method was PCR MY09/11 (39.2%), followed by GP5+/6+ (16.5%) and GP5/6 (an early version of GP5+/6+) (9.3%). Of 172 studies that used PCR, 107 (62%) reported testing for β globin, an important indicator of specimen adequacy and thus of study quality.

4.3.1. HPV infection prevalence results

Figure 7 shows prevalences reported for each study by population (clinical sample studies versus general screening population studies) and by age group. In the Figure, each dot represents a study, and the circled area represents the population sample size. The median prevalence reported by population studies is shown by a discontinuous line between consecutive age groups to better reflect the prevalences' bimodal tendencies; that is, higher values are observed at age extremes. The figure shows that prevalence results obtained from clinic-based studies are generally higher than in studies which are population-based. In the age group 15–25 years of age, population studies report a prevalence of 22%, and in clinic-based studies, prevalence reaches 50%. Also, in clinic populations, a higher prevalence is observed especially in women 45–54 years of age compared with that age group of women in the general population. These disparities may occur because women in clinic-based studies are generally of higher risk than those in studies of asymptomatic women being screened in opportunistic settings, despite being labeled as cytology negative. Likewise, a higher proportion of women 45–54 years of age are screened than in other age groups.

Figure 8 shows median prevalence for high-risk HPV infections determined by PCR. A bimodal curve is observed, and, as in Table 7, median prevalence is higher for women 15–24 years of age and those older than 65.

Figure 9 shows median prevalence for low-risk HPV infections determined by PCR; this prevalence remained constant at almost 3% for nearly all age groups. Only in women older than age 70 does the median prevalence rise to 6%. Women 45–54 years of age also have a higher prevalence of low-risk HPV infections.

Table 13 and Figures 10, 11, and 12 show estimated prevalences for all HPV types by age group and corresponding 95% CI for women with normal cytology. Estimates were obtained with the mixed effects model by PCR. Figure 10 shows differences between estimated HPV prevalences in women with normal cytology in the general population and in clinic populations. Estimated prevalence for women 45–54 years of age is much lower than expected, as suggested in Figure 7 and estimated by the mixed effects model (Figure 10).

Women 15–24 years of age had the highest prevalence for any HPV type (29.4%), but prevalence decreased gradually with age, reaching the lowest prevalence at ages 55–64 (14.2%), and then increased gradually to 26.2% in the highest age group (65 and older). The estimated prevalence for high-risk HPV infection ranged from 15.6% among women in the oldest age group to 5.6% in women 45–54 years of age. Prevalences for high-risk infection by age group are similar to the prevalences for all HPV infections. Estimated prevalences for low-risk HPV infections ranged from 8.2% for the oldest age group to 2.1% in women 35–44 years old. (The same data obtained by HC2 is found in Appendix G.)

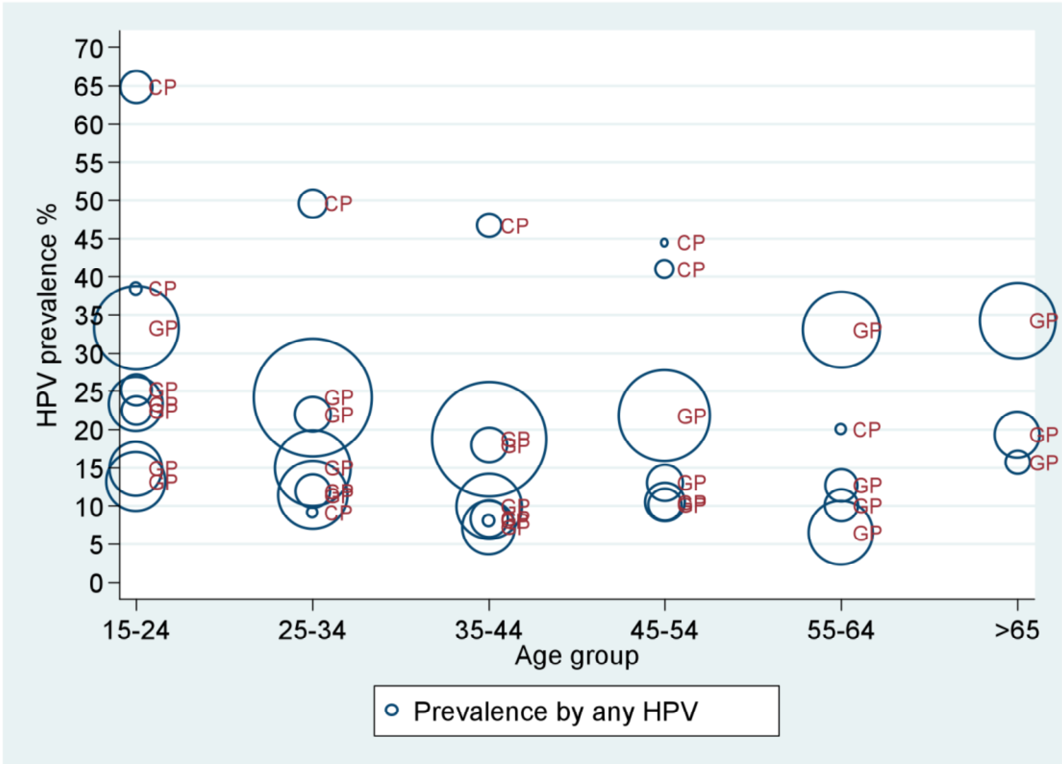

Figure 7. HPV prevalence rates and median rates by age for women with normal cytology, Latin America and the Caribbean. PCR method used. GP, population studies; CP, clinic-based studies. N studies = 36.

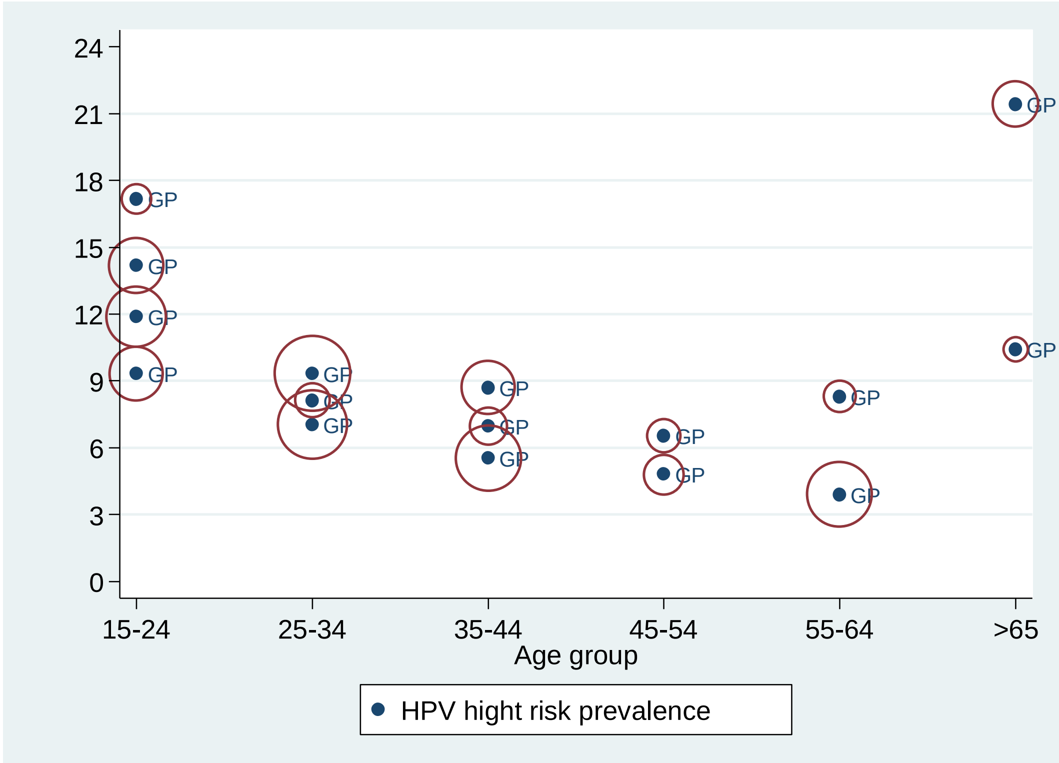

Figure 8. High-risk HPV prevalences by age for women with normal cytology, Latin America and the Caribbean. PCR method used. GP, population studies. PCR method. N studies = 16.

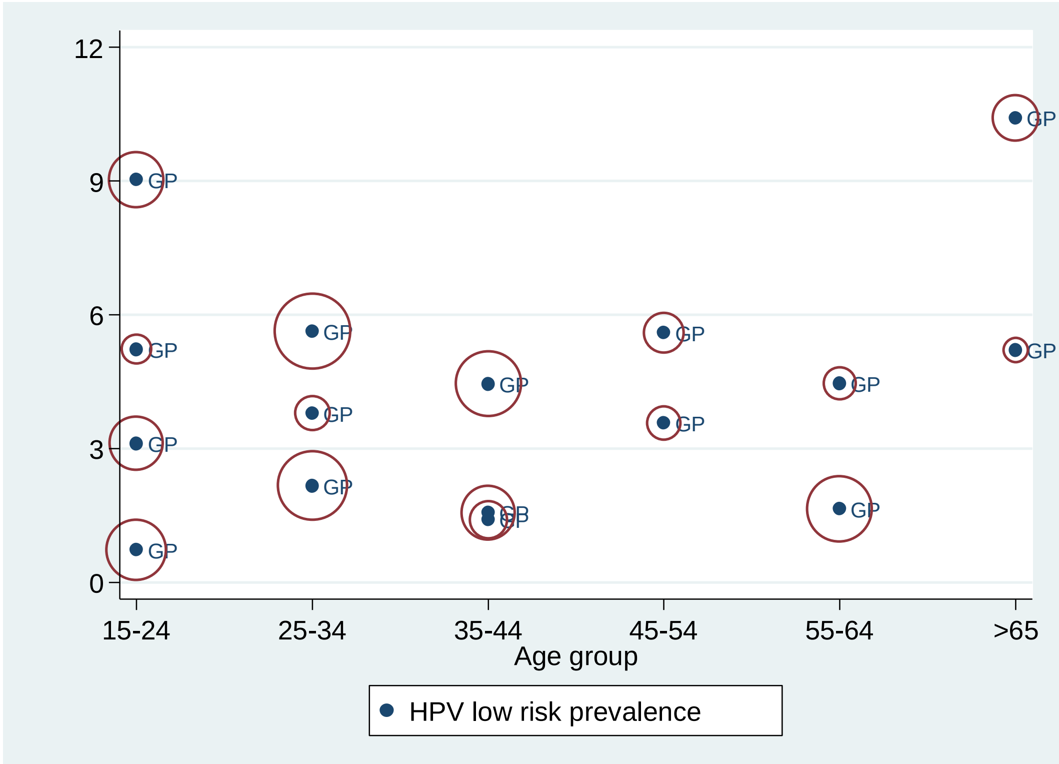

Figure 9. Low-risk HPV prevalence by age group for women with normal cytology, Latin America and the Caribbean. PCR method used. GP, population studies. N studies = 16.

Table 13. High- and low-risk HPV prevalence by age group for women with normal cytology in population and clinic-based studies using PCR[a]

Age groups	HPV all types N = 8	High risk N = 4	Low risk N = 4
	% (95% CI)	% (95% CI)	% (95% CI)
15–24[†]	29.4 (19.6–39.2)	13.1 (9.8–16.5)	4.5 (0.0–2.4)
25–34	19.2 (9.0–29.3)	8,3 (4.5–12.2)	3.7 (0.8–6.6)
35–44	15.5 (5.3–25.6)	6,9 (3.0–10.7)	2.1 (0.0–5.0)
45–54	20.6 (10.0–31.2)	5.6 (0.9–19.3)	3.9 (0.4–7.3)
55–64	14.2 (3.1–25.3)	6.3 (1.6–11.0)	3.7 (0.3–7.2)
≥65	26.2 (13.1–39.3)	15.6 (10.9 –20.3)	8.2 (4.7–11.7)

[a] Using mixed effects model; N = Number of studies.
[†] Reference group.

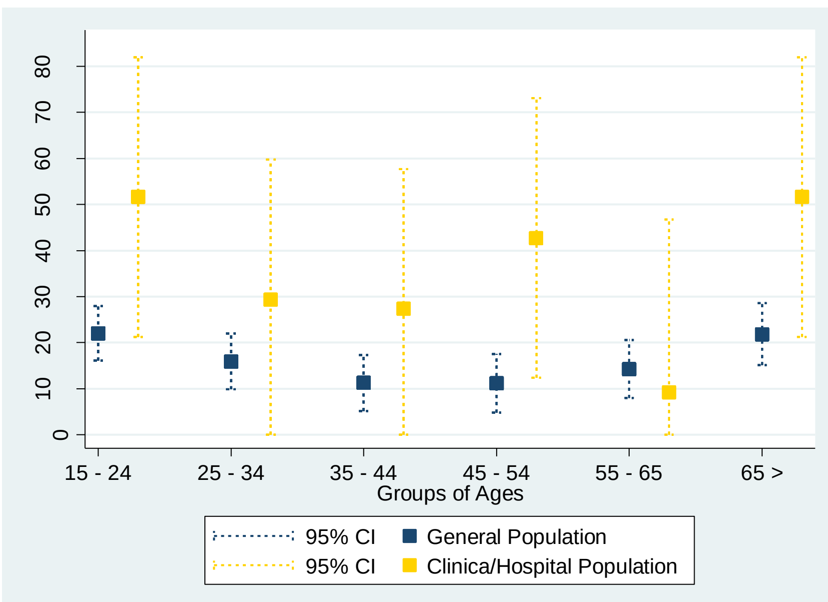

Figure 10. HPV prevalence estimates (all types) and 95% confidence intervals by age group and type of population for women with normal cytology, Latin America and the Caribbean. Calculations used mixed effects model. PCR method used. N studies = 8.

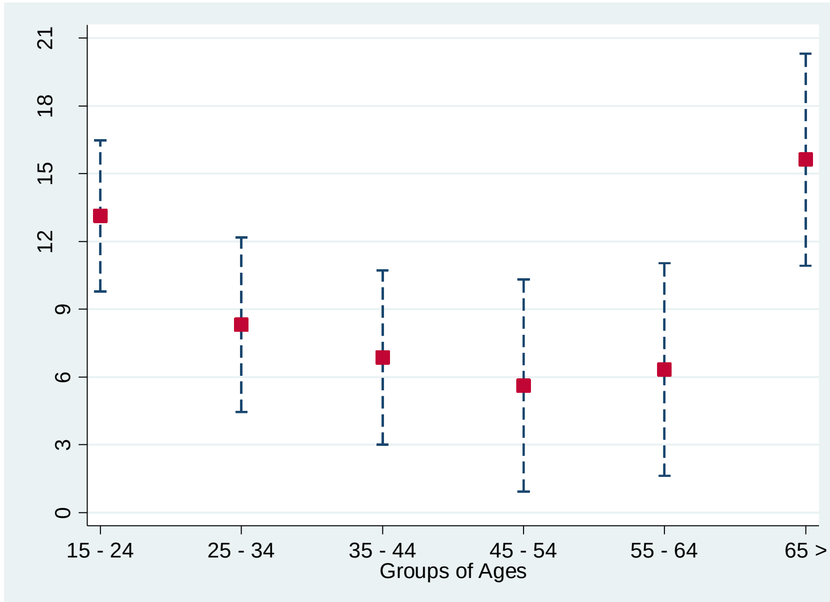

Figure 11. High-risk HPV prevalence estimates and 95% confidence intervals by age group and type of population for women with normal cytology, Latin America and the Caribbean. PCR method used. N studies = 4.

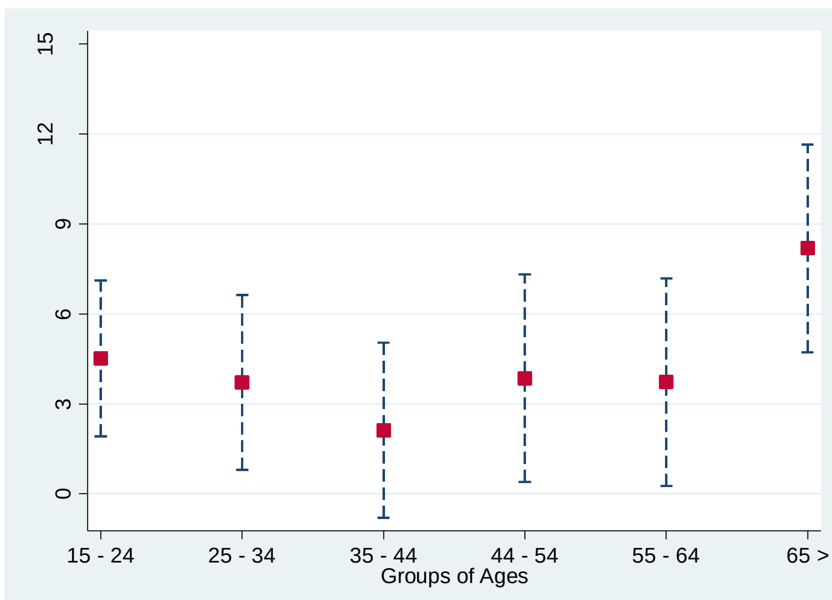

Figure 12. Low-risk HPV prevalence estimates and 95% confidence intervals by age group and type of population for women with normal cytology, Latin America and the Caribbean. PCR method used. N studies = 4

4.3.2. HPV prevalences by population group and HPV genotype

Table 14 shows HPV infection prevalences in different types of populations for low- and high-risk virus-associated lesions. High-risk HPV prevalences vary from 10.8% in healthy female populations to 62.4% in those with HSIL. The highest low-risk HPV prevalence was observed in women with atypical squamous cells of undetermined significance (ASCUS).

Table 15 shows important differences between healthy populations and populations with CC by prevalence of specific HPV infection type. The total number of healthy women included in the analysis ranged from 7,001 for HPV type 82 to 22,609 for type 16. Among healthy populations, the most frequently occurring types were 16, 18, 58, 31, 51, and 52 with prevalences of 2.6%, 1.0%, 1.0%, 0.9%, 0.8%, and 0.6%, respectively. Infection prevalences among both healthy men and women were similar; types 6, 11, 39, 40, 51, 52, 58, and 59 had the highest prevalences. Among men, type 59 (3.6%) was most prevalent.

In women with CC, the most prevalent types were 16, 18, 45, 31, and 33, with prevalences of 49.3%, 10.0%, 4.3%, 4.2% and 3.6%, respectively. Types 16 and 18 are highly oncogenic, which is confirmed by the low prevalences of these types among women with normal cytology and their high prevalences among women with CC. Prevalences for HPV 16 and 18 in populations with cancer are 19 times and 10 times more prevalent, respectively, than prevalences for these HPV types among healthy populations.

Table 16 and Figure 12 show specific types of HPV infection prevalences among healthy women by age group. For HPV 16, the highest prevalences were observed among women 15–24 and 25–34 years of age as well as among older age groups 55–64 years of age and 65 and older. The second most prevalent HPV type among the youngest age group (15–24) and the oldest age group (65 and older) was HPV 58, with prevalences for these age groups of 1.5% and 1.6%, respectively.

Table 17 shows the same information for healthy men. In young men, the most prevalent HPV types were 6, 16, 58, 52, and 59. In order of importance, HPV 52, 59, and 16 had higher prevalences than other HPV types.

Infection was rare among men older than age 45, except for HPV 16, 31, and 45, but this information must be viewed with caution because of the small number of subjects.

Table 18 shows prevalences for specific HPV types in populations of specific cytological categories: ASCUS, LSIL, and HSIL. The most prevalent types were 16, 58, 52, 6, and 18 with prevalences of 9.7%, 4.8%, 4.0%, 3.7% and 3.1%, respectively.

In women with LSIL, the most prevalent virus types were 16, 6, 58, 56, and 31, with prevalences of 15.8%, 7.9%, 6.1%, 4.9% and 4.4%, respectively.

In women with HSIL, the most prevalent types were 16, 58, 18, 52, 31, and 33, with prevalences of 27.9%, 9.3%, 4.8%, 4.1% and 4%, respectively.

HPV 16 prevalence increased proportionally with severity of lesion; HPV 16 prevalence was 2.6% in healthy populations, 9.7% in those with ASCUS, and 49.3% in populations with cancer. Prevalence for HPV 18 increased moderately with the severity of lesion. HPV 18 prevalence was 1% in healthy populations, 4.8% in those with HSIL, and 10% in populations with cancer. Table 19 shows prevalences of specific HPV types by age group in women with ASCUS. Little information is available regarding these types in healthy women. The age group 25–34 years of age was the largest age group of women with ASCUS, with almost 150 women. For the youngest age group (ages 15–24), the sum of prevalences for HPV 16, 58, 52, 51, and 31 was 56.4% with a wide 95% CI for each type (Table 19). For ages 25– 44, the proportion of women having types 16, 58, 39, 56, and 18 was 32.8%, with a smaller 95% CI for each type. For ages 45–54, the combined prevalence for types 59, 16, 51, 35, and 18 was 28.6%. In older ages (55 and older), the most prevalent types were 16 and 18. Among women with ASCUS, HPV types 16, 18, and 58 were present among all age groups.

Table 20 shows the prevalences by virus type by age group among women with HSIL, and Table 21 shows the prevalences by virus type by age group among women with LSIL and among women with both LSIL and HSIL, respectively. Among younger women with lesions, HPV 16 and 6 were the most prevalent HPV types. Among young women with LSIL, HPV 16 was the most frequent type (22.0%), but this type decreased among women 45–54 years of age (12.1%); other prevalent HPV types among women with LSIL were 51 (10.2%), 58 (17.1%), 52 (10.,4%) and 6 (10.9%). Prevalence of HPV 6 increased with age, peaking at 74.1% among women 35–44 years of old. In women with HSIL, the most prevalent viruses were 16 (42.7%), 58 (21.7%), 18 (12.8), 51 (12.5%), and 52 (12.1%).

In contrast with women with LSIL, prevalences for HPV 16, 18, 58, and 52 were high in older women with HSIL. Also, HPV 16 prevalence in the youngest age group of women with HSIL was twice that for women in the same age group with LSIL, and the HPV 18 prevalence was 5 times higher.

Table 14. Prevalences for high- and low-risk HPV in women and men by type of lesion or cytology status and viral detection method used (PCR vs. HC2)[a]

Study population	High risk		Low risk	
	n (%)	95% CI	n (%)	95% CI
PCR				
Women				
Healthy / normal cytology	18,229 (10.8)	7.5–14.1	16.529 (6.2)	3.1–9.4
ASCUS	541 (35.7)	0.0–72.1	491 (16.1)	14.9–17.2
LSIL	661 (54.2)	40.4–68.1	532 (4.5)	0.0–9.9
HSIL	561 (62.4)	33.4–91.3	392 (3.9)	0.1–7.6
ICC	-	--	83 (15,7)	--
Vulvar cancer	-	--	-	--
Men				
Healthy	2,044 (16.5)	0.0–76.9	2,044 (6.7)	0.0–26.6
Penile cancer	-	--	-	--
Men and women				
Anal cancer	-	--	-	--
Oropharynx cancer	-	--	-	--
Condiloma Acuminata	-	--	-	--
Respiratory Papillomatosis	-	--	-	--
Normal oral mucosa				
HIV+[b]	108 (39.6)	0.0 – 95.7	83 (15.7)	--
HC2[c]				
Healthy women / normal cytology	2,253 (11.8)	9.5 -14.2	-	--
Healthy men	1,284 (18.0)	14.4–21.6	-	--

[a] Some confidence intervals were not calculated because of insufficient precision in some categories. Blank spaces represent absence of studies related to the combination.
[b] Corresponds to women in clinic-based studies.
[c] Hybrid Capture 2 (HC2) was used only in studies of women with normal cytology.
ASCUS, Atypical squamous cells undetermined; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions, ICC, invasive cervical cancer.

Table 15. HPV prevalences by HPV type in healthy women with normal cytology and in women with invasive cervical cancer, Latin America and the Caribbean[a]

Virus type	NORMAL CYTOLOGY				INVASIVE CERVICAL CANCER	
	WOMEN		MEN			
	N (%)	95% CI	n (%)	95% CI	n (%)	95% CI
6	17,425 (0.3)	0.0–0.5	2,669 (2.3)	0.0–6.3	229 (4.4)	0.4–8.3
11	17,425 (0.3)	0.1–0.5	2,669 (1.1)	0.0–4.1	148 (1.1)	0.0–8.2
16	22,609 (2.6)	1.8–3.2	2,910 (2.1)	0.0–5.2	2,713 (49.3)	45.5–53.1
18	21,176 (1,0)	0.6–1.3	2,591 (1.3)	0.0–3.5	2,497 (10.0)	7.6–12.5
31	20,202 (0.9)	0.6–1.2	2,811 (0.4)	0.0–1.4	1,757 (4.2)	3.0–5.5
33	18,844 (0.5)	0.3–0.7	2,032 (0.9)	0.0–1.7	1,057 (3.6)	2.1–5.0
35	17,603 (0.2)	0.1–0.3	2,626 (0.3)	0.0–1.0	693 (2.2)	1.1–3.3
39	17,538 (0.3)	0.1– 0.5	2,385 (1.3)	0.0–6.2	496 (1.5)	0.0–3.0
40	1,646 (0.3)	0.0–0.7	681 (1.8)	0.0–7.6	-	--
45	18,752 (0.5)	0.3–0.6	2,626 (0.7)	0.0–2.5	1,395 (4.3)	3.1–5.6
51	18,701 (0.8)	0.4–1.2	2,811 (2.1)	0.0–4.7	628 (1.2)	0.0–2.6
52	19,769 (0.6)	0.4–0.9	2,385 (1.4)	0.0–7.4	706 (1.9)	0.3–3.4
56	18,291 (0.4)	0.2–0.6	2,385 (0.4)	0.0–2.4	502 (1.0)	0.1–1.9
58	18,997 (1.0)	0.7–1.3	2,626 (1.6)	0.0–4.6	874 (3.2)	2.0–4.5
59	18,540 (0.2)	0.0–0.4	2,385 (3.6)	0.0–13.5	739 (1.1)	0.2–1.9
68	16,796 (0.2)	0.1–0.4	2,385 (0.4)	0.0–2.0	218 (1.0)	0.0–2.9
73	14,597 (0.3)	0.0–0.4	2,385 (0.6)	0.0–2.7	113 (2.7)	--
82	7,001 (0.1)	0.0–0.3	1,606 (0.8)	0.0–5.4	69 (1.5)	--
Others	20,629 (5.4)	3.4–7.5	2,931 (6.9)	0.0–14.3	1,446 (4.1)	2.1–6.1

[a] Some confidence intervals were not calculated because of insufficient study precision in some categories. Blank spaces represent absence of studies related with the combination. PCR used for virus detection.

Table 16. Specific type virus prevalence by age groups in women with normal cytology, PCR.

Type of virus	15-24		25-34		35-44		45-54		55-64		65>	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
6	1,720	0.7l (0.1-1.3)	2,901	0.2 (0.0-0.8)	2,042	0.6 (0.0-3.9)	1,324	0.2 (0.0-3.0)	919	0.3	1,220	0.4 (0.0-1.6)
11	1,614	0.2 (0.0-0.8)	2,893	0.3 (0.2-0.3)	2,479	0.2 (0.0-1.1)	1,324	0.2 (0.0-0.3)	1,587	0.2 (0.0-6.1)	1,220	0.1 (0.0-4.5)
16	2,672	3,0 (2,2-3.8)	3,946	2.4 (1.5-3.3)	3,289	1.1 (0.2-2,1)	1,683	1.3 (0.3-2.2)	1,618	2,0 (1.6-2.5)	1,220	2.2 (1.2-3.2)
18	2,606	1,4 (0.1-2.7)	3,782	0.7 (0.4-1.0)	3,142	0.6 (0.2-0.9)	1,567	0.6 (0.0-1.7)	919	1,0	1,220	1.4 (0.7-2,1)
31	2,580	1,3 (0.0-2.8)	3,782	0.6 (0.0-1.9)	3,131	0.4 (0.0-0.9)	1,326	0.8 (0.0-4.0)	1,587	0.3 (0.0-3.0)	1,220	1.0 (0.0-5.1)
33	2,606	0.5 (0.0-1.1)	3,782	0.3 (0.1-0.5)	3,131	0.3 (0.0-0.8)	1,576	0.6 (0.0-1.2)	1,587	0.3 (0.0-3.0)	1,220	0.9 (0.0-2.9)
35	2,130	0.3 (0.0-0.5)	3,041	0.3 (0.0-1.2)	2,708	0.1 (0.0-0.3)	1,326	0.3 (0.0-2,0)	919	0.2	884	0.3
39	2,580	0.5 (0.0-8.9)	3,782	0.3 (0.0-0.9)	2,479	0.3 (0.0-2,6)	1,317	0.4	1,587	0.2 (0.0-1.3)	884	0.6
40	2,024	0.2 (0.0-0.7)	3,782	0.1 (0.0-0.2)	-	--	1,567	0.1 (0.0-0.1)	668	0.1	884	0.1
45	2,580	0.6 (0.2-0.9)	3,782	0.4 (0.0-1.1)	3,131	0.3 (0.0-0.8)	1,527	0.5 (0.0-1.1)	919	0.7	884	0.5
51	2,580	0.5 (0.0-1.8)	3,782	1.0 (0.0-2,5)	3,131	0.8 (0.0-1.5)	1,527	1.2 (0.0-4,3)	1,587	0.8 (0.0-7.5)	1,220	1.4 (0.0-6.8)
52	2,580	0.5 (0.0-1.6)	3,782	0.8 (0.0-2,1)	3,131	0.6 (0.1-1.1)	1,527	0.7 (0.0-3,2)	1,587	0.5 (0.0-6.5)	884	1.0
56	2,024	1.1 (0.1-1.4)	3,782	0.4 (0.3-0.5)	3,131	0.2 (0.0-0.4)	1,317	0.17	1,587	0.4 (0.0-1.9)	884	0.3
58	2,580	1.5 (0.0-3.6)	3,782	1.0 (0.3-1.7)	3,131	0.6 (0.0-1.3)	1,317	0.5 (0.0-1.2)	1,587	0.7 (0.0-5.8)	884	1.6
59	1,574	0.4 (0.0-3.6)	3,782	0.3 (0.0-0.7)	2,683	0.1 (0.0-1.3)	1,317	0.1	919	0.2	-	--
68	2,130	0.5 (0.0-1.6)	1,630	0.4 (0.0-2.8)	3,131	0.1 (0.0-0.4)	1,567	0.2 (0.0-0.1)	919	0.1	884	0.1
73	1,574	0.4 (0.0-2.4)	3,041	0.1 (0.0-1.3)	3,131	0.2 (0.1-0.3)	1,567	0.3 (0.0-1.9)	919	0.4	884	0.3
82	465	0.4	741	0.1	1,100	0.2 (0.0-0.6)	-	--	-	--	-	--
Other	2,635	6,7 (0.0-13,7)	3,804	6.4 (0.0-14.7)	3,156	7.2 (0.1-13.7)	1,567	10.7 (0.0-56.9)	1,587	3.6 (0.0-81.7)	1,220	14.2 (0.0-100)

Some confidence intervals were not calculated because of the unsufficient precision in some categories
Blank spaces represent absence of studies related to the combination

Figure 13 shows trends in prevalences of specific HPV types by age group among women with normal cytology. The most prevalent virus type for all age groups was HPV 16.

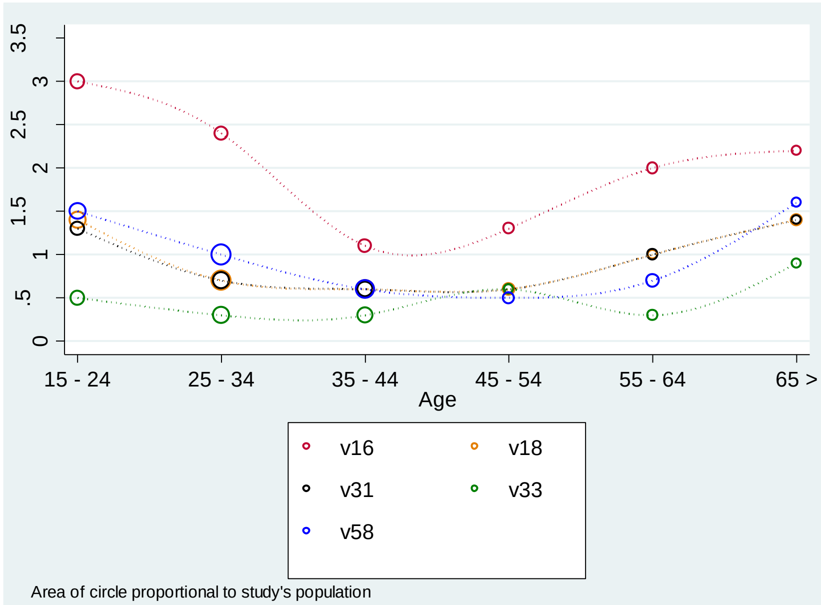

Figure 13. Estimated prevalences for specific HPV types by age group among women with normal cytology, Latin America and the Caribbean. PCR used for virus detection.

Table 17. HPV prevalences by HPV type and age group among healthy men, Latin America and the Caribbean[a]

Virus type	15–24		25–34		35–44		45–54		55–64		≥65	
	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)
6	671	4.3 (0.0–10.3)	301	5.0 (3,7–6,3)	-	--	-	--	-	-	-	--
11	671	3.7 (0.0–10.5)	301	2.7 (0.7–4.7)	52	1.9	-	--	-	--	-	--
16	671	6.2 (0.0–28.7)	358	4.9 (2.4–7.4)	115	3.4 (0.0–35.9)	53	1.9	-	--	27	3.7
18	671	3.6 (2.6–4.5)	301	3.5 (0.0–14.1)	52	3.8	-	--	-	--	-	--
31	671	1.8 (0.0–7.8)	301	2.2 (0.0–15.0)	115	1.7 (0.0–3.8)	-	--	37	2.7	27	3.7
33	671	0.9 (0.0–4.9)	-	--	63	1.6	-	--	-	--	27	3.7
35	671	0.8 (0.0–3.5)	218	0.5	-	--	-	--	37	2.7	-	--
39	671	3.9 (0.0–22.4)	301	3.9 (0.0–20.5)	52	3.8	-	--	-	--	-	--
40	497	1.2	301	2.0	-	--	-	--	-	--	-	--
45	671	4.0 (0.0–8.1)	301	2.6 (0.6–4.7)	-	--	-	--	-	--	27	3.7
51	671	6.5 (0.0–16.9)	358	2.8 (0.0–8.2)	52	1.9	-	--	-	--	-	--
52	671	6.1 (4.5–7.7)	301	5.3 (0.0–22.8)	52	5.8	-	--	-	--	-	--
56	671	1,9 (0.0–4,5)	301	2.2 (0.0–15.0)	-	--	-	--	-	--	-	--
58	675	4.7 (0.0–9.7)	358	2.3 (0.0–6.4)	52	1.9	-	--	-	--	-	--
59	671	10.0 (0.0–23.8)	301	7.2 (0.0–17.8)	52	1.9	-	--	-	--	-	--
68	671	3.7 (1.6–5.9)	301	1.0 (0.0–2.5)	-	--	-	--	-	--	-	--
73	671	1.5 (0.0–4.2)	301	1.6 (0.0–5.5)	-	--	-	--	-	--	-	--
82	--	0.5 (0.0–5.0)	218	0.5	-	--	-	--	-	--	-	--
Other	671	16.6 (0.0–34.7)	358	15.3 (8.0–22.6)	115	13.6 (0.0–41.1)	53	13.2	37	13.5	27	18.5

[a] Some confidence intervals were not calculated because of an insufficient precision in some categories. Blank spaces represent absence of studies related with the combination. PCR used for virus detection.

Table 18. HPV prevalences by specific HPV type and type of lesion among women with lesions, Latin America and the Caribbean[a]

Virus type	ASCUS		LSIL		HSIL	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
6	533 (3.7)	0.0–12.9	1,110 (7.9)	1.9–13.9	590 (3.6)	0.0–8.7
11	501 (0.3)	0.0–13.5	1,110 (3.8)	2.1–7.5	631 (3.3)	1.1–5.5
16	649 (9.7)	6.4–12.9	1,840 (15.8)	10.9–20.9	1,552 (27.9)	20.1–35.6
18	542 (3.1)	1.6–4.5	1,606 (4.0)	2.5–5.5	1,158 (4.8)	2.8–6.9
31	616 (2.6)	1.2–3.9	1,141 (4.4)	2.6–6.3	1,129 (4.0)	2.5–5.4
33	575 (1.3)	0.3–2.3	1,280 (3.7)	2.5–4.9	1,055 (4.0)	2.7–5.2
35	427 (1.9)	0.0–9.1	828 (2.9)	1.8–3.9	674 (2.1)	1.2–3.2
39	522 (2.9)	0.6–5.2	543 (3.1)	0.6–5.6	358 (3.6)	1.7–5.6
40	-	--	70 (2.9)	--	-	--
45	532 (2.9)	1.9–3.9	763 (2.9)	1.6–4.1	565 (3.7)	2.3–5.1
51	606 (3.0)	0.5–5.5	978 (1.6)	0.0–3.3	536 (7.7)	5.6–9.9
52	522 (4.0)	2.7–5.2	741 (2.9)	0.5–5.3	489 (4.1)	0.9–7.3
56	417 (3.9)	--	592 (4.9)	3.1–6.8	506 (1.7)	1.0–2.5
58	522 (4.8)	0.0–14.1	817 (6.1)	4.6–7.5	608 (9.3)	5.8–12.8
59	522 (0.8)	0.0–2.4	531 (2.7)	1.5–3.9	275 (2.2)	0.0–7.1
68	522 (2.1)	0.4–3.9	269 (1.3)	0.0–12.1	234 (1.2)	0.0–17.7
73	458 (2.2)	1.2–3.1	291 (2.6)	0.0–5.9	211 (2.6)	0.1–5.1
82	-	- -	103 (1.9)	0.0–19.9	24 (4.2)	--
Others	533 (3.7)	0.0–12.9	630 (5.5)	1.2–9.7	1,023 (7.2)	2.7–11.7

[a] Some confidence intervals were not calculated because of insufficient precision in some categories. Blank spaces represent absence of studies related with the combination. PCR used for virus detection.
ASCUS, Atypical squamous cells undetermined; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions

Figure 14 shows a summary of virus type prevalences for healthy women and for those with CC. Prevalences by type of lesion or cytology status show an increasing gradient for different virus types. Prevalence of HPV 16 among healthy women with normal cytology is 2.6% and increases to 49.3% among women with CC. Other prevalent types of HPV in women with CC are 18, 45, 31, 33, 58, and 51.

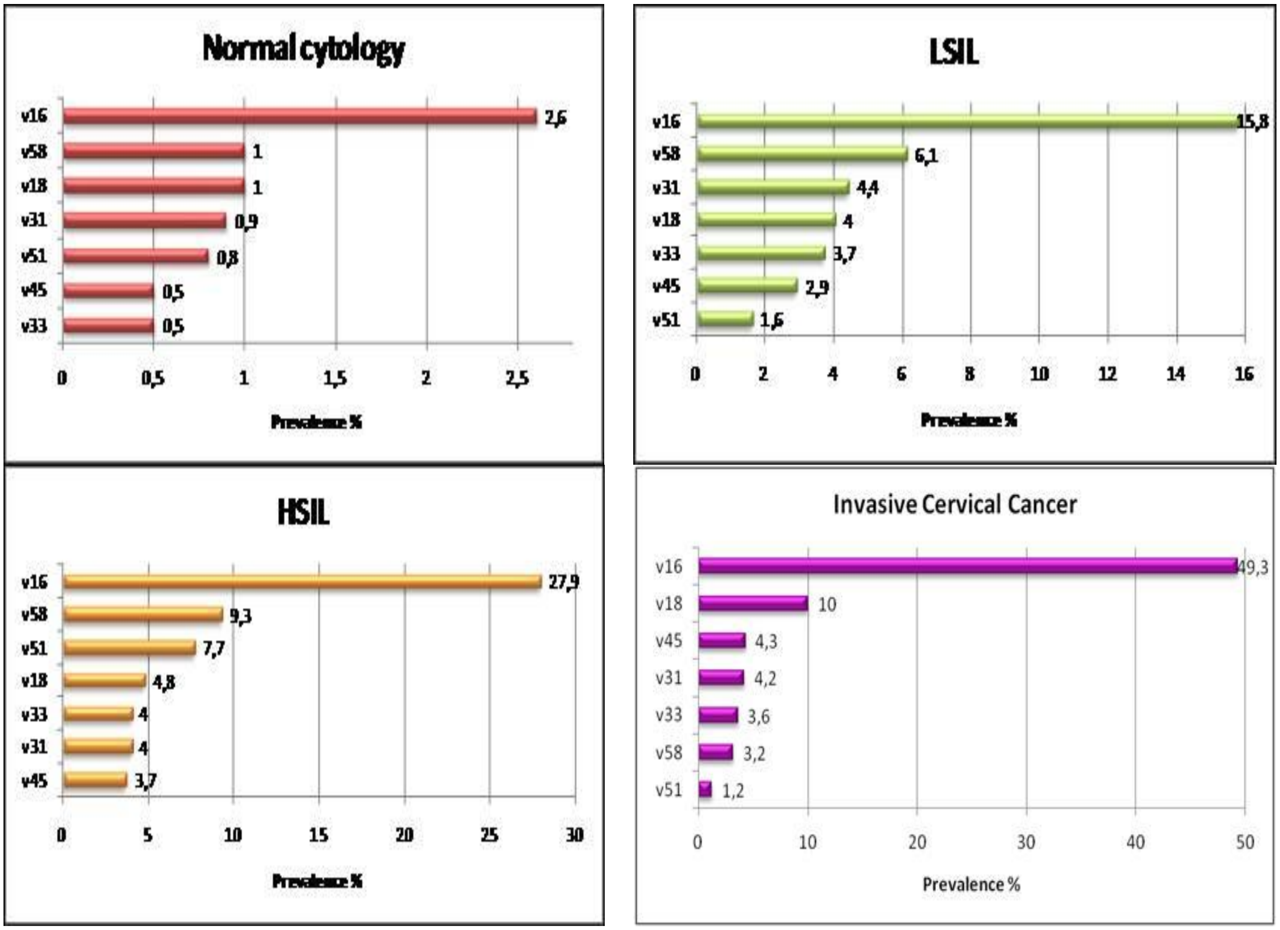

Figure 14. Distribution of prevalences of specific HPV types by type of lesion or cytology status among women in Latin America and the Caribbean. LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions.

Table 19. Prevalences of specific HPV types by age group among women with ASCUS, Latin America and the Caribbean[a]

Virus type	15–24		25–34		35–44		45–54		55–64		≥65	
	n	% (95% CI)	N	% (95% CI)	n	% (95% CI)	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)
6	70	4.3	140	0.8 (0.0–32.1)	99	2.1 (0.0–27.2)	51	5.9	-	-	28	7.1
11	70	1.4	-	--	-	--	-	--	-	--	-	--
16	84	14.1 (0.0-72.1)	152	9.7 (0.0–20.1)	99	5.4 (0.0–41.5)	57	10.0 (0.0–72.6)	37	2.7	28	17.8
18	84	1.6 (0.0-15.9)	134	4.3 (0.0–20.9)	106	3.9	51	8.1	-	-	-	--
31	84	6.6 (0.0-54.1)	134	1.5	97	1.0	51	2.0	37	5.4	28	3.5
33	70	1.4	134	2.2	-	--	-	--	-	--	28	3.5
35	70	1.4	134	0.7	97	4.1	-	--	-	--	28	7.1
39	70	5.7	146	6.1 (0.0-13.3)	97	1.0	51	2.0	-	--	-	--
40	-	--	134	2.2	-	--	-	--	-	--	-	--
45	84	4.6 (0.0-15.9)	134	2.2	97	3.1	51	2.0	37	--	28	3.7
51	84	8.3 (0.6-1.0)	146	2.3 (0.0-14.4)	97	4.1	51	2.0	37	5.4	28	3.8
52	84	12.4 (0.0-52.7)	134	2.2	-	--	57	4.3 (0.0-32.3)	-	--	28	10.7
56	70	2.9	134	4.5	97	2.1	51	2.0	37	5.4	28	--
58	84	15.0 (0.0-82.5)	134	8.2	97	3.1	51	7.8	-	--	28	7.1
59	84	1.6 (0.0-15.9)	134	1.5	97	11.1	-	--	-	--	-	--
68	84	4.9 (0.0- 5.8)	134	2.2	97	1.0	-	--	37	5.4	-	--
73	84	3.2 (0.0-17.7)	134	3.0	‘’	1.0	51	2.0	-	--	28	3.5
82	-	--	-	--	-	--	-	--	-	--	-	--
Other	84	67.4	146	39.0 (16.5-61.6)	106	28.1 (3.2-53.1)	-	--	-	--	-	--

[a] Some confidence intervals were not calculated because of insufficient precision in some categories. Blank spaces represent absence of studies related with the combination. PCR used for virus detection. ASCUS, Atypical squamous cells undetermined.

Table 20. Prevalences of specific HPV types by age group among women with LSIL, Latin America and the Caribbean[a]

Virus type	15–24		25–34		35–44		45–54		55–64		≥65	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
6	102	10.9 (0.0-41.9)	32	43.8	67	74.1 (0.0-41.8)	21	13.0	-	--	-	--
11	102	5.6 (0.0-14.2)	58	1.7	8	12.5	7	28.6	-	--	-	--
16	125	22.0 (9.1-34.9)	158	16.1 (4.8-27.4)	73	13.5 (5.5-21.6)	31	12.1 (0.0-35.6)	-	--	-	--
18	102	2.3 (0.0-11.5)	111	5.2 (0.0-12.9)	69	6.0 (0.0-14.9)	7	14.3	3	33.3	-	--
31	66	7.6	122	10.1 (2.3-17.8)	71	2.6 (0.0-11.7)	10	20.0	3	33.3	4	25.0
33	102	5.6 (1.5-9.7)	138	3.0 (0.0-6.7)	45	4.4	7	14.3	-	--	-	--
35	78	3.3 (0.0-20.0)	106	3.8 (0.0-9.7)	49	2.4 (0.0-31.4)	-	--	-	--	4	25.0
39	89	7.9 (6.4-9.4)	105	5.1 (0.0-10.5)	71	6.1 (0.0-38.0)	14	7.1	3	33.3	“	25.0
40	66	1.5	58	1.7	45	2.2	-	--	-	--	-	--
45	78	3.5 (0.0-36.1)	75	7.6 (0.0-29.9)	45	4.4	-	--	-	--	-	--
51	114	10.2 (0.0-22.4)	105	5.6 (0.0-13.2)	71	11.5 (0.0-61.7)	14	7.1	-	--	-	--
52	77	10.4 (3.3-17.4)	122	6.7 (0.4-13.0)	75	14.3	14	7.1	-	--	4	50.0
56	100	8.4 (4.0-12.9)	89	7.7 (0.0-21.1)	45	11.1	-	--	3	33.3	4	50.0
58	77	17.1 (0.0-74.9)	105	7.3 (2.1-12.4)	71	3.0 (0.0-27.9)	10	10.0	-	--	-	--
59	66	1.5	47	3.9 (0.0-19.7)	71	5.3 (0.0-23.4)	-	--	3	33.3	4	25.0
68	78	1.7 (0.0-17.5)	31	6.5	-	--	14	7.1	-	--	-	--
73	66	3.0	74	2.0 (0.0-17.1)	45	4.4	-	--	-	--	4	50.0
82	-	--	-	--	-	--	-	--	-	--	-	--
Other	100	44.9 (4.4-84.8)	105	36.6 (0.0-91.5)	97	16.2 (7.2-25.2)	24	19.1	-	--	-	--

[a] Some confidence intervals were not calculated because of insufficient precision in some categories. Blank spaces represent absence of studies related with the combination. PCR used for virus detection. LSIL, low-grade squamous intraepithelial lesions.

Table 21. Prevalences of specific HPV types by age group among women with HSIL, Latin America and the Caribbean[a]

Virus type	15–24		25–34		35–44		45–54		55–64		≥65	
	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
6	18	16.7	28	32.1	51	5.3 (0.0-71.8)	7	14.3	-	--	17	5.8
11	-	--	79	5.4 (0.0-51.7)	-	--	7	14.3	-	--	-	--
16	46	42.7 (0.0-94.3)	130	47.7 (38-57.4)	92	31.8 (0.0-65.7)	39	22.9 (0.0-57.0)	10	39.5	17	17.7
18	46	12.8 (0.0-30.9)	81	10.5 (0.0-22.1)	92	6.3 (0.0-19.0)	37	11.5 (0.0-28.5)	-	--	17	5.8
31	46	8.1 (0.0-23.9)	130	9.1 (0.0-19.4)	54	8.5 (0.0-71.7)	37	7.2 (0.0-15.4)	6	16.7	-	--
33	46	7.5 (0.0-17.1)	90	3.8 (0.0-24.3)	63	5.0 (0.0-38.7)	25	7.6	-	--	-	--
35	14	7.1	90	2.2 (0.0-5.7)	63	4.3 (0.0-21.4)	-	--	-	--	17	5.8
39	28	19.7	51	3.9	33	6.1	18	5.5	-	--	-	--
40	-	--	-	--	-	--	-	--	-	--	-	--
45	14	7.1	90	4.3 (0.0-11.9)	63	4.3 (0.0-21.4)	12	8.3	6	16.7	-	--
51	46	12.5 (0.0-40.8)	118	4.9 (0.0-14.3)	84	4.1 (0.0-15.8)	12	8.3	-	--	17	17.7
52	31	12.1 (0.0-35.7)	102	3.2 (0.0-10.5)	63	12.7 (5.2-20.1)	18	16.7	-	--	17	11.8
56	-	--	39	5.1	-	--	12	8.3	-	--	17	11.7
58	28	21.7	102	10.6 (0.0-22.1)	63	15.9 (6.1-25.7)	30	9.8 (0.0-27.6)	4	25.0	17	11.8
59	28	14.3	39	2.6	-	--	-	--	-	--	-	--
68	14	14.3	39	7.7	30	3.3	-	--	-	--	-	--
73	14	7.1	51	3.9	-	--	-	--	-	--	17	5.9
82	-	--	-	--	-	--	-	--	-	--	-	--
Other	31	38.9	102	11.8 (0.0-46.3)	71	15.4 (0.0-49.3)	30	57.6	-	--	17	70.5

[a] Some confidence intervals were not calculated because of insufficient study number. Blank spaces represent absence of studies related to the subject. PCR used for virus detection. HSIL, high-grade squamous intraepithelial lesions.

4.3.3. Infection prevalences by groups of countries

Analysis of HPV infection prevalences by groups of countries is difficult because not all LAC countries have representative studies providing information. The Pan American Health Organization proposes a regionalization among six groups of countries (clusters). Appendix Table 3 shows HPV infection prevalences in healthy female populations with normal cytology for the following groups:

- Cluster 1–Southern Cone: Argentina, Chile, and Paraguay
- Cluster 2–Southern Cone: Brazil
- Cluster 3–Andean countries: Bolivia, Colombia, Ecuador, Peru, and Venezuela
- Cluster 4: Barbados, Cuba, Jamaica, and Surinam
- Cluster 5–Central America: Costa Rica, Honduras, Nicaragua, and Panama
- Cluster 6: Mexico

The two countries with the largest number of women included in the studies we examined were Brazil and Mexico. The highest prevalences were found among populations in countries of Cluster 5, which had similar prevalences to those in Caribbean countries (Appendix G, Table 4).

4.4. Meta-regression results

We performed meta-regression analyses to determine the influence of selected variables on the overall prevalence of HPV among healthy women. Rates estimated in PCR-based studies were not significantly affected by the type of genital sample (exfoliated cells, biopsy, or surgical samples) or by the way samples were obtained (self obtained vs. obtained by health worker). The proportion of studies that used self-obtained samples was low, so the meta-regression was unable to determine the effects that self-obtained samples might have had on HPV infection prevalence.

A second meta-regression was performed that compared virus detection methods (PCR and HC2) and found that HC2 underestimates the general prevalence by approximately 57% (p = 0.001).

The general HPV prevalence was not significantly affected by the quality impact score (p =0.963). Analysis of the influence of sampling methodology on general HPV prevalence showed that sampling method was not statistically significant. Analysis of prevalence by age groups and adjusted by sample method also failed to show that any sampling method was statistically significant. (Table 22).

Table 22. Results of meta–regression analysis of effects of studies' quality score and type of samples on HPV general prevalence, Latin America and the Caribbean

	Coefficient	95 % CI	P value
Quality score[a]			
Quality score	-0.0001	-0.04–0.04	0.936
Type of sample[b]			
Exfoliated cells	-6.72	-40.32–26.87	0.695
With B-globin	2.37	-23.15–27.90	0.855
Without B-globin	-9.62	-41.78–22.53	0.558
Type of sample adjusted for age group			
Exfoliated cells	-3.88	-35.91–28.14	0.812
With B-globin	2.44	-22.19–27.06	0.846
Without B-globin	-9.21	-40.25–21.83	0.561

[a] Simple linear regression model adjusted by the inverse of the variance of each study.
[b] Multivariate generalized estimating equations model.

4.5. Incidence studies

For LAC, although many publications addressing multiple prevalences were available, including the Guanacaste cohort study (Costa Rica) that sampled a large number of women, data were available from only two incidence studies useful for this analysis. Results from the Ludwig-McGill cohort study (Brazil) and the Cancer Institute study (Colombia) are shown, but data from Guanacaste were unavailable.

According to the combined analysis of these two cohorts, annual risk for acquiring HPV infection was more than 8%, although the risk was greater in the Brazilian cohort, which shows an incidence that is almost double that of the Colombian cohort (11.18 and 6.7, respectively, per 100 woman-years). Incidence of high-risk HPV was similar in both cohorts, although the Colombian cohort contributed more to the total incidence, in contrast to the Brazilian cohort, in which incidences for high- and low-risk HPV were similar. The greatest difference occurred for the HPV low-risk infection rate: the Brazilian cohort almost tripled the risk of the Colombian cohort (7.15 and 2.48, respectively, per 100 woman-years).

Tables 23 to 26 show HPV infection incidence for the Ludwig-McGill cohort (Brazil) and the Bogotá cohort (Colombia) and shows HPV incidence for both cohorts combined (by age group and groups of viruses. Tables 27 and 28 show HPV infection incidence by specific type of virus for the separate cohorts and the cohorts combined.

In the three age groups of the Ludwig-McGill cohort, the HPV infection incidence rate for all virus types was higher than for Bogotá. This difference was even greater for persons older than age 25; for this group, the rate almost doubled, principally for low-risk HPV infections.

The highest HPV 16 infection incidence rate was observed in Brazil, where the rate was almost double that of the Bogotá rate (2.07 and 1.34, respectively, per 100 woman-years). However, HPV 18 had similar rates for both countries (0.53 and 0.58 , respectively, per 100 woman-years). Infection rates by other HPV types in both cohorts was similar, with the most prevalent types in order of importance being HPV 31, 35, 45, 58, 18, and 81. HPV incidence was distributed among more virus types in Bogotá than in Brazil.

Table 23. HPV infection incidence rates in the Ludwig-McGill cohort (Brazil) by HPV type/group and age group,

HPV type/group	Person-time in years	Number of incident Cases	Incidence rate (per 100 woman--years)	95% CI	
Younger than 25 years of age					
All HPV	988.4	173	17.50	15.08	20.32
High-risk HPV	1,269.1	153	12.06	10.29	14.13
Low-risk HPV	1,535.2	113	7.36	6.12	8.85
Species 1, 8, 10	1,870.7	57	3.05	2.35	3.95
Species 5, 6, 7, 9, 11	1,176.3	158	13.43	11.49	15.70
Species 3, 4, 15	1,869.8	65	3.48	2.73	4.43
25–44 years of age					
All HPV	4,936.0	499	10.11	9.26	11.04
High-risk HPV	5,842.7	365	6.25	5.64	6.92
Low-risk HPV	6,146.6	335	5.45	4.90	6.07
Species 1, 8, 10	7,231.8	109	1.51	1.25	1.82
Species 5, 6, 7, 9, 11	5,601.1	399	7.12	6.46	7.86
Species 3, 4, 15	6,988.2	168	2.40	2.07	2.80
45 years of age and older					
All HPV	647.3	63	9.73	7.60	12.46
High-risk HPV	768.5	46	5.99	4.48	7.99
Low-risk HPV	758.7	43	5.67	4.20	7.64
Species 1, 8, 10	910.7	14	1.54	0.91	2.60
Species 5, 6, 7, 9, 11	738.7	52	7.04	5.36	9.24
Species 3, 4, 15	880.2	19	2.16	1.38	3.4

Table 24. HPV infection incidence rates in the Bogotá (Colombia) cohort by HPV type/group and age group

HPV type/group	Person-Time in years	Number of incident Cases	Incidence rate (per 100 woman-years)	95% CI	
Younger than 25 years of age					
All HPV	735	103	14.01	11.44	17.00
High-risk HPV	810	101	12.47	10.16	15.15
Low-risk HPV	1,082	41	3.79	2.72	5.14
Species 1, 8, 10	1,278	36	2.82	1.57	3.90
Species 5, 6, 7, 9, 11	7,960	217	27.26	23.75	31.14
Species 3, 4, 15	1,264	15	1.19	0.66	1.96
25–44 years of age					
All HPV	6,067	331	5.46	4.88	6.08
High-risk HPV	6,448	285	4.42	3.92	4.96
Low-risk HPV	7,634	159	2.08	1.77	2.43
Species 1, 8, 10	8,157	83	1.02	0.81	1.26
Species 5, 6, 7, 9, 11	6,238	512	8.21	7.51	8.95
Species 3, 4, 15	8,323	64	0.77	0.59	0.98
45 years of age and older					
All HPV	1,704	73	4.28	3.36	5.39
High-risk HPV	1,811	60	3.31	2.53	4.26
Low-risk HPV	2,044	34	1.66	1.15	2.32
Species 1, 8, 10	2,512	16	0.64	0.36	1.03
Species 5, 6, 7, 9, 11	2,158	143	6.63	1.44	2.68
Species 3, 4, 15	2,447	15	0.61	0.34	1. 01

Table 25. HPV infection incidence rates in women from the combined Ludwig-McGill (Brazil) and Bogotá (Colombia) cohorts by HPV type/group and age group

HPV type/group	Person-Time in years	Number of incident cases	Incidence rate (per 100 woman-years)	95% CI	
Younger than 25 years of age					
All HPV	1,723.4	276	16.01	14.18	18.02
High-risk HPV	2,079.1	254	12.22	10.76	13.82
Low-risk HPV	2,617.2	154	5.88	4.99	6.89
Species 1, 8, 10	3,148.7	93	2.95	2.38	3.62
Species 5, 6, 7, 9, 11	1,972.3	375	19.01	17.14	21.04
Species 3, 4, 15	3,133.8	80	2.55	2.02	3.18
25–44 years of age	11,003.0	830	7.54	7.04	8.07
All HPV	12,290.7	650	5.29	4.89	5.71
High-risk HPV	13,780.6	494	3.58	3.28	3.92
Low-risk HPV	15,.388.8	192	1.25	1.08	1.44
Species 1, 8, 10	11,839.1	911	7.69	7.20	8.21
Species 5, 6, 7, 9, 11	15,311.2	232	1.52	1.33	1.72
Species 3, 4, 15					
45 years of age and older					
All HPV	2,351.3	136	5.78	4.85	6.84
High-risk HPV	2,579.5	106	4.11	3.37	4.97
Low-risk HPV	2,802.7	77	2.75	2.17	3.43
Species 1, 8, 10	3,422.7	30	0.88	0.59	1.25
Species 5, 6, 7, 9, 11	2,896.7	195	6.73	5.82	7.75
Species 3,4,15	3,327.2	34	1.02	0.71	1.43

Table 26. HPV infection incidence rates in women from the combined Ludwig-McGill (Brazil) and Bogotá (Colombia) cohorts by specific HPV type/group

HPV type/group	Person-Time in years	Number of incident cases	Incidence rate (per 100 woman-years)	95% CI	
6/11	20,784.2	107	0.51	0.42	0.62
16	19,712.9	337	1.71	1.53	1.90
18	20,601.2	116	0.56	0.47	0.68
26	21,076.5	37	0.18	0.12	0.24
31	20,621.0	145	0.70	0.59	0.83
32	10,682.4	9	0.08	0.04	0.16
33	20,806.3	67	0.32	0.25	0.41
34	21,135.0	7	0.03	0.01	0.07
35	20,793.2	109	0.52	0.43	0.63
39	20,928.0	73	0.35	0.27	0.44
40	20,942.9	68	0.32	0.25	0.41
42	20,934.6	68	0.32	0.25	0.41
43	10,344.5	36	0.35	0.22	0.44
44	20,921.1	84	0.40	0.32	0.50
45	20,662.2	126	0.61	0.51	0.73
51	20,540.8	145	0.71	0.60	0.83
52	20,706.6	137	0.66	0.56	0.78
53	20,570.4	149	0.72	0.61	0.85
54	20,912.7	68	0.33	0.25	0.41
55	20,954.7	80	0.38	0.30	0.48
56	20,819.8	99	0.48	0.39	0.58
57	10,688.4	6	0.06	0.03	0.13
58	20,450.6	145	0.71	0.60	0.83
59	20,874.9	75	0.36	0.28	0.45
61	20,958.3	45	0.21	0.16	0.29
62	10,561.9	48	0.45	0.34	0.60
64	10,701.0	1	0.01	0.00	0.07
66	20,920.9	78	0.37	0.29	0.47
67	10,674.6	7	0.07	0.03	0.14
68	20,912.9	63	0.30	0.23	0.39
69	10,689.5	6	0.06	0.03	0.12
70	20,947.3	54	0.26	0.19	0.34
71	21,107.3	29	0.14	0.09	0.20
72	21,105.3	12	0.06	0.03	0.10
73	20,946.4	59	0.28	0.21	0.36
81	20,842.4	72	0.35	0.27	0.44
82	21,026.4	33	0.16	0.11	0.22
83	20,991.9	59	0.28	0.21	0.36
84	20,850.4	103	0.49	0.40	0.60
89	10,645.6	21	0.20	0.13	0.30
All HPV	14,138.4	1,242	8.78	8.30	9.29
High-risk HPV	15,914.9	1,010	6.35	5.96	6.75
Low-risk HPV	17,849.2	725	4.06	3.77	4.37
Species 1, 8, 10	20,96.1	343	1.70	1.52	1.89
Species 5, 6, 7, 9, 11	17,674.7	1,439	8.14	7.73	8.57
Species 3,4,15	19,762.4	346	1.75	1.57	1.95

Table 27. HPV infection incidence rates in women from the Bogotá (Colombia) cohort by specific HPV type/group

HPV type/group	Person-Time in years	Number of incident cases	Incidence rate (per 100 woman-years)	95% CI	
6/11	10,400.6	39	0.37	0.27	0.51
16	9,819.8	132	1.34	1.02	1.45
18	10,184.0	60	0.59	0.41	0.69
26	10,431.5	22	0.21	0.12	0.29
31	10,195.9	78	0.77	0.55	0.86
32					
33	10,260.2	35	0.34	0.21	0.43
34	10,446.8	6	0.06	0.02	0.11
35	10,298.2	38	0.37	0.24	0.46
39	10,320.0	35	0.34	0.21	0.43
40	10,364.0	32	0.31	0.19	0.39
42	10,286.2	41	0.40	0.26	0.49
43	10,344.5	36	0.35	0.22	0.44
44	10,446.1	8	0.08	0.03	0.14
45	10,155.7	70	0.69	0.49	0.79
51	10,317.8	30	0.29	0.18	0.37
52	10,280.4	55	0.54	0.36	0.63
53	10,417.2	24	0.23	0.13	0.31
54	10,420.4	13	0.12	0.06	0.19
55	10,456.7	7	0.07	0.02	0.12
56	10,284.3	50	0.49	0.33	0.58
57					
58	10,077.8	69	0.68	0.48	0.78
59	10,368.8	25	0.24	0.14	0.32
61	10,466.5	5	0.05	0.01	0.10
62					
64					
66	10,349.6	40	0.39	0.25	0.48
67					
68	10,413.5	13	0.12	0.06	0.19
69					
70	10,368.2	27	0.26	0.15	0.34
71	10,478.9	2	0.02	0.00	0.06
72	10,454.4	6	0.06	0.02	0.11
73	10,452.9	10	0.10	0.04	0.16
81	10,262.1	45	0.44	0.29	0.53
82	10,425.8	11	0.11	0.05	0.17
83	10,414.8	19	0.18	0.10	0.26
84	10,413.1	17	0.16	0.09	0.24
89					
All HPV	7,566.7	507	6.70	5.67	6.76
High-risk HPV	8,034.6	446	5.55	4.65	5.61
Low-risk HPV	9,408.7	234	2.49	1.98	2.57
Species 1, 8, 10	10,182.9	163	1.60	1.38	1.81
Species 5, 6, 7, 9, 11	10,158.6	830	8.17	7.51	8.68
Species 3,4,15	10,024.2	94	0.94	0.68	1.18

Table 28. HPV infection incidence rates in the Ludwig-McGill (Brazil) cohort by specific HPV type/group

HPV type/group	Person-Time in years	Number of incident cases	Incidence rate (per 100 woman-years)	95% CI	
6/11	10,383.6	68	0.65	0.52	0.83
16	9,893.2	205	2.07	1.81	2.38
18	10,417.2	56	0.54	0.41	0.7
26	10,645	15	0.14	0.09	0.23
31	10,425.1	67	0.64	0.51	0.82
32	10,682.4	9	0.08	0.04	0.16
33	10,546.1	32	0.30	0.21	0.43
34	10,688.2	1	0.01	0	0.07
35	10,495.0	71	0.68	0.54	0.85
39	10,608.0	38	0.36	0.26	0.49
40	10,578.9	36	0.34	0.25	0.47
42	10,648.4	27	0.25	0.17	0.37
43		0			
44	10,475	76	0.73	0.58	0.91
45	10,506.5	56	0.53	0.41	0.69
51	10,223.0	115	11.25	0.94	13.51
52	10,426.2	82	0.79	0.63	0.98
53	10,153.2	125	1.23	1.03	14.67
54	10,492.3	55	0.52	0.4	0.68
55	10,498.0	73	0.7	0.55	0.87
56	10,535.5	49	0.47	0.35	0.62
57	10,688.4	6	0.06	0.03	0.13
58	10,372.8	76	0.73	0.59	0.92
59	10,506.1	50	0.48	0.36	0.63
61	10,491.8	40	0.38	0.28	0.52
62	10,561.9	48	0.45	0.34	0.6
64	10,701.0	1	0.01	0	0.07
66	10,571.3	38	0.36	0.26	0.49
67	10,674.6	7	0.07	0.03	0.14
68	10,499.4	50	0.48	0.36	0.63
69	10,689.5	6	0.06	0.03	0.12
70	10,579.1	27	0.26	0.18	0.37
71	10,628.4	27	0.25	0.17	0.37
72	10,650.9	6	0.06	0.03	0.13
73	10,493.5	49	0.47	0.35	0.62
81	10,580.3	27	0.26	0.18	0.37
82	10,600.6	22	0.21	0.14	0.32
83	10,577.1	40	0.38	0.28	0.52
84	10,437.3	86	0.82	0.67	1.02
89	10,645.6	21	0.20	0.13	0.3
All HPV	6,571.7	735	11.18	10.4	12.02
High-risk HPV	7,880.3	564	7.16	6.59	7.77
Low-risk HPV	8,440.5	491	5.82	5.32	6.36
Species 1, 8, 10	10,013.2	180	1.80	1.55	2.08
Species 5, 6, 7, 9, 11	7,516.1	609	8.10	7.48	8.77
Species 3,4,15	9,738.2	252	2.59	2.29	2.93

4.6. Results of study of burden of disease

For Latin America and the Caribbean during 2008, an estimated 79,000 new cases of CC occurred. The number of prevalent cases in a year was approximately 66,000. and in five years with follow-up, prevalence reached approximately 230.000 cases. The countries that mostly contribute to this number are Brazil, followed by Mexico, Colombia, Peru, and Argentina. The 75th percentile for the distribution of the adjusted rates for this cancer was 46.4 per 100.000 women; the countries with rates above this percentile were Haiti, Bolivia, Paraguay, Belice, Peru, Guyana, and Nicaragua. These countries account for approximately 17% of all cases in the region.

Table 29. Estimated incidence, prevalence, and annual deaths from cervical cancer, Latin America and the Caribbean, 2008

Country	Population 2008[a]	Incidence		Prevalence (Cases)		No. Deaths
		Crude rate[b]	No. Cases	1 year	5 years	
Argentina	20,679,482	25.5	5,273	4,426	15,360	1,798
Bahamas	167,560	15.8	26	21	76	10
Barbados	140,639	33.3	47	39	128	18
Belice	139,103	34.5	48	41	137	19
Bolivia	5,026,078	42.0	2,111	1,773	6,145	1,138
Brazil	98,805,750	22.2	21,935	18,415	63,129	9,272
Chile	8,465,654	27.5	2,328	1,957	6,712	1,002
Colombia	24,366,925	31.0	7,554	6,352	21,750	3,653
Costa Rica	2,235,033	19.0	425	357	1,226	227
Cuba	5,729,456	24.0	1,375	1,154	4,016	579
Ecuador	6,888,039	30.4	2,094	1,746	5,836	1,126
El Salvador	3,664,686	36.6	1,341	1,128	3,860	673
Guatemala	7,017,827	19.4	1,361	1,143	3,947	742
Guyana	395,612	40.7	161	136	466	71
Haití	4,883,520	64.7	3,160	2,652	9,224	1,690
Honduras	3,899,629	19.9	776	653	2,252	422
Jamaica	1,405,837	28.8	405	339	1,178	160
Mexico	55,817,239	24.4	13,619	11,434	39,050	6,286
Nicaragua	2,911,357	30.2	879	738	2,568	385
Panama	1,683,036	25.8	434	365	1,261	192
Paraguay	3,306,335	39.5	1,306	1,097	3,807	592
Peru	14,503,368	40.5	5,874	4,933	16,912	2,897
Puerto Rico	2,066,582	10.8	223	187	642	75
Dominican Republic	4,684,905	24.3	1,138	952	3,203	620
Trinidad and Tobago	670,805	28.4	191	160	543	75
Uruguay	1,808,979	22.5	407	343	1,173	168
Venezuela	13,918,411	30.9	4,301	3,612	12,527	1,907
Total			78,793	66,153	227,129	35,799

[a] Source of female population estimates: El Centro Latinoamericano y Caribeño de Demografía
[b] Source: Globocan 2002

Around 35,000 deaths from CC occurred in LAC in 2008; more than half of these deaths occurred in Brazil, Mexico, and Colombia. Peru, Venezuela, and Argentina also contributed significantly to these deaths (Table 29).

An estimated 25,000 new cases of oropharynx cancer occurred during 2008, 66% of which were among men. The one-year prevalence for men was 13,000. and the five-year prevalence was 43,000 cases. For women, the prevalence was 4,500 for one year and 7,000 over five years. The countries with the most cases were Brazil, Mexico, Argentina, Colombia, and Cuba. The countries with rates above the 75th percentile of the adjusted rate for men (5.9 per 100.000) were Puerto Rico, Brazil, Belice, Bolivia, Bahamas, Cuba, and Uruguay. In women, the 75th percentile of the adjusted rate was 2.3 per 100.000; the countries with rates above that percentile were Bolivia, Cuba, Panama, Colombia, Puerto Rico, Belice, and Jamaica.

If we assume that approximately 50% of oropharynx cancer cases were due to HPV infection [27], HPV would be responsible for an estimated 12,500 new cases of this cancer annually and 8,750–25,000 prevalent cases in a year (Tables 30 and 31).

Table 30. Estimated incidence, prevalence, and number of annual deaths due to oropharynx cancer in women, Latin America and the Caribbean, 2008

Country	Population 2008	Incidence			Prevalence (cases)		No. deaths
		Crude rate		Cases	1 year	5 years	
		Oral cancer	Pharynx cancer				
Argentina	20,679,482	1.7	0.3	414	294	969	196
Bahamas	167,560	1.3	0.0	2	2	2	1
Barbados	140,639	2.2	0.0	3	2	1	1
Belice	139,103	1.7	0.0	2	1	1	1
Bolivia	5,026,078	2.6	0.3	146	104	230	77
Brazil	98,805,750	1.6	0.7	2,273	1,608	1,142	1,182
Chile	8,465,654	1.0	0.2	102	70	74	52
Colombia	24,366,925	2.1	0.8	707	497	1,188	323
Costa Rica	2,235,033	1.5	0.3	40	29	66	17
Cuba	5,729,456	3.8	0.8	264	184	254	117
Ecuador	6,888,039	1.1	0.4	103	73	189	53
El Salvador	3,664,686	0.1	1.2	48	32	38	25
Guatemala	7,017,827	0.9	0.3	84	58	110	47
Guyana	395,612	0.5	0.0	2	2	2	3
Haití	4,883,520	0.6	0.3	44	30	43	26
Honduras	3,899,629	0.9	0.3	47	32	63	29
Jamaica	1,405,837	2.0	0.5	35	28	47	19
Mexico	55,817,239	1.3	0.4	949	679	1,342	346
Nicaragua	2,911,357	0.2	0.6	23	15	20	9
Panama	1,683,036	2.7	0.7	57	41	94	21
Paraguay	3,306,335	0.5	0.1	20	14	7	11
Peru	14,503,368	1.9	0.3	319	229	711	130
Puerto Rico	2,066,582	3.6	1.3	101	72	63	38
Dominican Republic	4,684,905	1.5	3.0	211	139	213	116
Trinidad and Tobago	670,805	2.4	0.8	21	16	20	8
Uruguay	1,808,979	2.1	0.4	45	31	22	23
Venezuela	13,918,411	1.7	0.4	292	207	438	126
Total				6,354	4,490	7,348	2,998

Table 31. Estimated incidence, prevalence, and number of annual deaths due to oropharynx cancer in men, Latin America and the Caribbean, 2008

Country	Population 2008	Incidence			Prevalence (Cases)		No. deaths
		Crude rate		Cases	1 year	5 years	
		Oral cancer	Pharynx cancer				
Argentina	20,679,482	5.6	2.0	1,514	1,055	3,417	657
Bahamas	167,560	4.6	5.2	16	12	38	7
Barbados	140,639	5.4	6.1	15	12	35	8
Belice	139,103	4.2	3.4	11	7	20	5
Bolivia	5,026,078	4.1	0.5	230	167	564	125
Brazil	98,805,750	6.8	4.2	10,587	7,421	24,476	4,995
Chile	8,465,654	2.4	1.4	315	214	676	150
Colombia	24,366,925	2.7	1.4	978	688	2,253	414
Costa Rica	2,235,033	1.6	1.1	62	43	147	38
Cuba	5,729,456	7.8	3.0	618	431	1,381	357
Ecuador	6,888,039	1.1	0.9	138	95	303	80
El Salvador	3,664,686	0.3	3.3	128	84	258	60
Guatemala	7,017,827	1.4	0.9	154	106	361	95
Guyana	395,612	1.6	1.1	3	2	6	1
Haití	4,883,520	1.4	1.1	119	85	277	76
Honduras	3,899,629	1.5	0.9	95	65	223	58
Jamaica	1,405,837	3.2	1.5	65	44	141	30
Mexico	55,817,239	2.0	1.0	1,631	1,156	3,874	655
Nicaragua	2,911,357	0.8	1.1	55	39	121	22
Panama	1,683,036	3.2	1.9	87	60	190	36
Paraguay	3,306,335	2.7	1.1	128	88	289	93
Peru	14,503,368	2.0	0.5	366	262	897	154
Puerto Rico	2,066,582	12.2	7.3	369	252	801	135
Dominican Republic	4,684,905	2.1	6.4	411	273	823	221
Trinidad and Tobago	670,805	3.9	48.0	338	210	635	139
Uruguay	1,808,979	7.6	5.2	219	148	453	105
Venezuela	13,918,411	2.3	1.1	476	337	1,121	209
Total				19,131	13,357	43,782	8,926

For anal, penile, vulvar, and vaginal cancers, no specific data were available by country, so total incidence for the region was calculated. Estimated annual incidence for the region was 3,500 (2,500–4,500) new cases of anal cancer, 3,800 (2,900–4,300) new cases of penile cancer, and 4,000 (2,800–6,000) new cases of vulvar and vaginal cancer. Estimated prevalence for anal cancer was 3,000 in one year and 12,000 over five years of follow-up; for vulvar and vaginal cancers, estimated prevalence for one year and five years were 3,375 and 13,500. respectively; and for penile cancer, estimated prevalence for one year and five years were 2,250 and 9,000 cases. Total estimated prevalence for these cancers together were 8,700 for one year and 35,000 over five years.

For these cancers, proportion of HPV-related cases were not estimated because case-control studies for these cancer sites calculate infection frequency in controls by using serologic methods, which do not enable correct estimates of HPV prevalence, thus compromising attributable risk calculation validity (Table 32).

Table 32. Estimated median and estimates at the 25th and 75th percentiles for annual cases of penile, vulvar, vaginal, and anal cancers, Latin America and the Caribbean

	Anal		Penile	Vulvar	Vaginal
	Men	Women			
Median	1,162	2,369	3,777	2,369	1,777
25th percentile	726	1,629	2,905	1,777	1,036
75th percentile	1,307	3,553	4,358	3,405	2,665

4.7. Risk factors

Many factors contribute to rates of CC and other diseases related to HPV in LAC. CC risk factor prevalences, such as early initiation of sexual activity, tobacco use, fertility rates, and coverage of cytology screening vary among and within countries. Data published on socioeconomic and demographic characteristics, reproductive health, education, and screening for CC may reflect only part of a country´s population, or information may be unavailable for some countries in the region. Our risk factor data published here are limited and are based on assumptions about the region.

The Gross Domestic Product (GDP) per capita in international dollars (ID) varies greatly in LAC: Argentina, Chile, Mexico, and Costa Rica have the highest GDP per capita, with each more than ID $10.000 per year [83]. In contrast, Haiti has a GDP of ID $1,660. Some countries with low GDP, such as Bolivia, Guatemala, Paraguay, and Honduras, have high population growth rates. In these countries, the population growth rate exceeds 1.5% annually, a growth rate similar to that of Belice and French Guyana.

The literacy level of women from Guatemala, Honduras, El Salvador, Nicaragua, and Bolivia is not more than 80%.[95]. Other countries in the region with available information have literacy rates that exceed 80%.

The educational level in LAC differs in each country, but generally is lower in rural zones than in urban areas. For example, in Colombia, urban women and men over 15 years of age have completed an average of 8.5 years of education, but in rural areas, this average decreases to 4.9 years [95].

Tobacco constitutes another risk factor for CC. In America, 15% of teenagers 13–15 years of age smoked cigarettes at least once during the month before they were surveyed, and 6.8% had used tobacco products other than cigarettes the month before [96]. In LAC, the percentage of adolescent women who smoke tobacco is high in some cities: 39.2% in Santiago, Chile; 33.4% in Bogotá, Colombia; 27.1% in Mexico City; and 26.8% in Buenos Aires, Argentina. Among adult women, smoking occurs in various LAC countries at the following rates: 39.2% in Venezuela, 34.0% in Argentina, 29.3% in Brazil, and 26.3% at Cuba [97].

We found limited data on reproductive health and screening programs. The median age for initiation of sexual activity in Guatemala and El Salvador was 16–18 years of age, although data were available suggesting an earlier initiation in some locations [98]. The age at which sexual activity was initiated increased as educational level increased. For example, in Colombia, the median age for initiation of sexual activity in women without education was 15.8 years of age, but in women with higher education levels (more than secondary school), the average was 20 years of age [95].

The use of condoms appears to be limited in the majority of LAC countries (2%–12%). A study performed at El Salvador demonstrated that the use of condoms was higher in urban areas (7.0%) than in rural zones (3.8%) [98].

Some LAC countries have national screening programs for CC, but even those countries with screening have limited screening processes. In Colombia, 85% of women 18–69 years of age have had a vaginal cytology at least once in their lives, but only 13% have had a Papanicolaou test. Many barriers to prevention and effective control of CC exist in the region, including insufficient extension of screening programs and women's limited knowledge about CC and the importance of its early detection. Also, in many countries, screening is associated with reproductive heath and preborn care programs, so younger women (in their second and third decades) constitute most of the screening population. For older women who have no reason to attend a family planning center or preborn care program, access to CC screening is much lower than access for younger women [2].

CHAPTER 5. DISCUSSION

HPV infection generates a large burden of disease for LAC countries. Each year, 79,000 new cases of CC arise in the region, all related to HPV, and 40,000 deaths are related to HPV infection. Additionally, 12,500 new cases of oropharynx cancer related to HPV occur each year as well as 3,000–5,000 new cases of anal, penile, vulvar, and vaginal cancer.

According to LAC cancer registries, a woman's estimated risk for acquiring HPV-related CC during her lifetime is 2.1%–2.4% until age 64 [63]. In a cohort of five million women, among 13-year-olds with a life expectancy of 74 years, 120,000 cases of HPV-related cancer occur, including genital and nongenital neoplasms. In populations younger than 75 years of age, the risk among men (0.09%–0.25%) is four to 12 times lower than among women. Based on this level of risk among men, about 10,000 cases of genital and nongenital cancer occur in a cohort of five million men followed to age 75.

Calculated risk values from different cancer registries showed an important variation in lifetime CC risk (0.9%–4%), suggesting that the median for this range of values and the 25th and 75th percentiles are good approximations of the average risk value for the region.

Strengths of this study include that it incorporated databases from all the identifiable and informative published HPV studies in LAC countries from 1990 to mid-2007 and included at least 17 countries from the region.

In addition, the methods used for information extraction and data analysis were standardized with preestablished criteria and evaluation of readers' concordance. Also, assessment of the quality of the different studies was attempted through a score created by the investigators. This score was based on six characteristics: type of population, sample size, HPV detection techniques, type of sample studied for virus detection, and type of diagnosis. Each study's precision, based on sample size and characteristics of the population studied, was evaluated. Besides the quality of the studies, clearly defined inclusion and exclusion criteria, our study methods considered other indicators, including general prevalence for different populations, from healthy subjects to subjects with lesions.

This report was comprehensive because it considered HPV infection prevalences not only in healthy female populations, but also in those with different degrees of lesions and with CC. It also considered prevalence information for other populations, including men, populations at risk, and those with other types of lesions possibly explained by HPV infection. Prevalences were estimated for different age groups, taking into consideration variations in study characteristics such as population size, HPV detection methods, and type of population (clinic-based or population-based). We also examined HPV infection incidence through two cohort studies in the region: Ludwig-McGill in Brazil and the Cancer Institute study in Colombia. In addition, we calculated attributable risk to determine the HPV-related burden of disease.

For prevalences, a meta-analysis with meta-regression was performed. The study results enabled us to show HPV prevalences by age group and specific genotypes, instead of grouping them only by low- and high-risk HPV infections. We were also able to obtain prevalences for HPV-specific genotype by type of lesion.

General prevalences in healthy women and in those with lesions were similar to results obtained in previously published meta-analyses. Our study considers the largest number of women studied as of mid-2007, resulting in an overall prevalence of 18.7%, which is higher than estimates from previous overviews [35,64,96,98,99]. In agreement with results from the Guanacaste study, the prevalence in healthy female populations for different age groups shows a bimodal curve, with high prevalence in the youngest population (15–24 years of age), decreased prevalence for ages 25–44, and increased prevalences in older age groups [23]. Although our study was able to estimate HPV infection prevalence in men, these results must be analyzed with caution due to lack of standardized methods for sample collection and virus detection.

The mixed effects model contributed to control for the variability of results among and within the different studies. Nevertheless, observational studies have other variabilities due to their inherent biases. In contrast to randomized clinical trials, which are designed to reduce biases as much as possible, biases in observational studies cannot be controlled.

Another contribution of this study was the analysis of prevalences according to the study population. This stratified analysis explains why overestimation of HPV prevalence may occur in clinic-based studies compared with the prevalence in population-based studies. We could verify the underestimation of general prevalence in healthy populations when the HC2 virus detection method was used.

Of all the variables analyzed by the meta-regression, the only one with a statistically significant effect on the results was the virus identification method used by each study. Neither the study quality nor the sample size affected prevalence.

Few studies have been conducted in our region on incidence of HPV infection Nonetheless, two important cohorts contributed to knowledge of incidence, which is estimated as 8% annually. Incidence was higher in the age group younger than 25 years of age (16/100 person-years). Incidence of high-risk HPV infection was higher than for low-risk HPV (8.8 vs. 4.1/100 person-years).

The burden of disease expressed by the number of new cases and by prevalent cases in one year and during five years was also estimated for CC and oropharynx cancer by country in the region. However, these estimates could not be produced for other HPV-related cancers. Either no information was available or control studies were not performed by HPV virus detection in situ.

At this time, evidence about HPV attributable risk in CC and oropharynx cancer is solid; however, an attributable risk could not be calculated for other cancers because case-control studies at this time measure the exposure to HPV by using serologic tests among controls. Calculation of attributable risk in these studies would underestimate the role of HPV in the etiology of these cancers because only some virus types produce an antibody response that can be measured serologically. The alternative is using the proportion of HPV-positive cancer cases as an attributable fraction, but this method overestimates the proportion of cases related to HPV. Serologic studies have demonstrated that some persons can be infected but never develop the disease, although their infections are at the same anatomical sites as persons who develop the disease. This potential for overestimation does not impact the disease total because the most frequent cancers, CC and oropharynx cancer, have an accepted attributable risk value. CC represents more than 90% of all the burden of disease for HPV-related neoplasms in the region; thus, we believe that the influence of other cancers, independent of the frequency of HPV as a pathogen, does not affect the interpretation of the information presented here.

Information about cofactors related to HPV infection and the prognosis of cervical lesions' evolution to CC was not obtained directly from the studies examined because this was usually not provided or, if available, it would have limited external validity. This information was obtained from surveys related to reproduction and lifestyles through population databases available at CDC in Atlanta and on websites from national health ministries. According to this information, prevalence of risk factors in the studies does not differ from what is known about age of initiation of sexual activity, number of sexual partners, number of pregnancies, tobacco use, and prolonged use of contraceptives for the region.

5.1. Main results

We conclude that the overall HPV infection prevalence in healthy women is 18.7%. The prevalence in higher in younger women, lower in middle-aged women, and increases again for ages 45 and older. We demonstrated how the prevalence changes based on the population studied and test used, PCR or HC2, and changed based on how the subjects were recruited into the study, clinic or community-based.

In 2,227 cancer cases reported by 28 studies, the largest sample analyzed to date, a relation with cancer was established for HPV 16 in 49.3% of cases and with HPV 18 in 10% of cases. The quadrivalent vaccine would cover 60% of the causes of invasive cervical cancer, a lower proportion than the one reported in a meta-analysis recently published by Smith [100].

The other prevalent genotypes related to cancer in LAC countries are, in decreasing order, 45, 31, 33, and 58, which together account for an additional 15.3% of cancer cases. These HPV genotypes are present worldwide. This finding is important for future vaccine formulations, which will need to consider these genotypes for CC prevention.

5.2. Epidemiological information limitations

In LAC countries, few population-based studies are available. Instead, the majority are nonrepresentative population studies, which may not be representative of the population as a whole. Although heterogeneity is mostly controlled, the inclusion of studies with different designs may be a relevant limitation to determining genotype-specific prevalence. A meta-analysis performed with observational studies has greater heterogeneity than a meta-analysis performed with clinical trials. The social, population, cultural, and economic variables related to HPV infection cannot be controlled.

Also, few HPV infection incidence studies for LAC countries exist. In two geographically close countries like Brazil and Colombia, the age at which infection was acquired varied, being earlier in Brazil. HPV 16 infection was also higher at Brazil than in Colombia, but the Colombian cohort showed greater diversity among virus types responsible for HPV infection.

CHAPTER 6. Conclusions

This meta-analysis and economic analysis provide a comprehensive summary of evidence available from 1990 through mid-2007 on HPV prevalence, incidence, disease burden, morbidity, mortality, and cost-effectiveness of vaccination in LAC. For disease burden estimates, we included a large variety of studies from 17 countries that used different methods among diverse populations. We found that the prevalence of HPV (18.7%) among women in LAC is similar to that found in other parts of the world, including some of the following trends: age-specific changes in HPV prevalence among healthy women; highest prevalences among women 15–24 years of age (29%) and those older than 65 years of age (26%); highest incidence among women 15–24 years of age (14–17 cases per 100 woman-years); and increased prevalence and distribution of high-risk HPV, particularly types 16, 51, and 58, with higher-grade cervical lesions. The largest proportion of HPV-related disease (85%) in the region is CC among women, with 80,000 new cases and 40,000 deaths annually, generating 100000 life-years lost each year. The highest rates of CC in the region occurred in Haiti, Bolivia, Paraguay, Belize, and Peru; Mexico, Brazil, and Colombia had the largest number of deaths. Continuing research needs to address the distribution of HPV types in different countries by lesion type; incidence of rare HPV-related cancers such as penile, vulvar, and vaginal cancers in the region; and the risk attributable to HPV for these cancers. Differences in resources and in the extent to which each country has existing screening programs highlight the challenges faced by each country in deciding whether vaccination is affordable, even if it may be cost-effective.

6.1. Conflicts of Interest

The investigators report the following relationships entities that may have an interest in the content of this document:

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Appendix A. Exclusion criteria for articles accepted for meta-analysis, Latin America and the Caribbean, 1990–mid-2007

Reader	Reference	ID
	Reason for exclusion	
☐	The study has been published before 1990.	
☐	The study does not include original data on HPV prevalence or incidence.	
☐	The study was not conducted in Latin America and The Caribbean countries.	
☐	The study included **30** subjects or fewer (for studies on HPV epidemiology in cervical lesions or cervico-vaginal samples).	
☐	The HPV identification/typization has not been conducted with molecular techniques using target or signal amplification.	

Appendix B. Consulted databases

- **PubMed:** A U.S. National Library of Medicine service that includes approximately 17 million MEDLINE citations and other life–sciences-related journals or biomedical articles published since 1950.
- **LILACS:** A database that includes health sciences literature published in LAC countries.
- **CAB Health:** A database specializing in public health publications and containing more than 1 million quotes since 1973.
- **EMBASE:** A database of pharmacology and biomedical sciences publications; it contains more than 11 million registries since 1974 and more than 5,000 journals from 70 countries.
- **CINAHL:** A literature Index related to nursing and allied health subjects and containing articles from 2,000 journals.
- **The Cochrane Library:** A research collection about evidence-based medicine; it contains a database of systematic reviews.

Appendix C. Search terms

- **Disease-related search terms**

“Uterine Cervical Neoplasms” [MeSH]. OR “Cervical Intraepithelial Neoplasia” [MeSH]. OR “Squamous Intraepithelial Neoplasia” [MeSH]. OR “Uterine Cervical Dysplasia” [MeSH]. OR “Vulvar Neoplasms” [MeSH]. OR “Vaginal Neoplasms” [MeSH]. OR “Penile Neoplasms” [MeSH]. OR “Anus Neoplasms” [MeSH]. OR “Oro-pharyngeal Neoplasms”[MeSH]. OR “Genital wart” [MeSH]. OR “Condyloma Acuminata”[MeSH]. OR “Recurrent respiratory papillomatosis”[MeSH]. HPV-related Search Terms: “Papillomavirus,Human” [MeSH]. OR “Papillomavirus Infections” [MeSH]. OR “VPH” [MeSH]. OR “Human papillomavirus 6” [MeSH]. OR “Human papillomavirus 11” [MeSH]. OR “Human papillomavirus 16” [MeSH]. OR “Human papillomavirus 18” [MeSH]. OR “Cervix Uteri” [MeSH]. OR “Genitalia, Female” [MeSH].

- **Economic search terms**

OR“Costs” [MeSH]. OR “Effectiveness” [MeSH]. OR “Efficacy” [MeSH]. OR “Cost Minimization Analysis” [MeSH]. OR “Cost Effectiveness Analysis” [MeSH]. OR “Cost Benefits Analysis” [MeSH]. OR “Cost Utility Analysis” [MeSH]. OR “Burden of Disease” [MeSH]. OR “QALY” [MeSH]. OR “DALYS” [MeSH].

- **Epidemiologic search terms**

AND “Prevalence” [MeSH]. OR “Incidence” [MeSH]. OR “Cross Sectional Studies” [MeSH]. OR “Cohort Studies” [MeSH]. OR “Case-Control Studies” [MeSH]. OR “Epidemiology” [MeSH]. OR “Data collection” [MeSH].

- **Geographic search terms**

AND “Latin America” [MeSH]. OR “The Caribbean”[MeSH].

The search results produced articles in Spanish, English, Portuguese, and French; articles were considered for the study if they fulfilled inclusion criteria.

The following terms were also used:

“Uterine Cervical Neoplasms,“ “Cervical Intraepithelial Neoplasia,” “Squamous Intraepithelial Neoplasia,” “Uterine Cervical Dysplasia,” “Vulvar Neoplasms,” “Vaginal Neoplasms,” “Penile Neoplasms,” “Anus Neoplasms,” “Oro-pharyngeal Neoplasms,” “Genital wart,” “Condyloma Acuminata,” “Recurrent respiratory papillomatosis,” “Papillomavirus, Human,” “Papillomavirus Infections,” “VPH,” “Human papillomavirus 6,” “Human papillomavirus 11,” “Human papillomavirus 16,” “Human papillomavirus 18,” “Cervix Uteri,” “Genitalia, Female,” “Latin America,” “The Caribbean,” “Prevalence,” “Incidence,” “Cross Sectional Studies,” “Cohort Studies,” “Case-Control Studies,” “Epidemiology,” “Data collection,” “Costs,” “Effectiveness,” “Efficacy,” “Cost Minimization Analysis,” “Cost Effectiveness Analysis,” “Cost Benefits Analysis,” “Cost Utility Analysis,” “Burden of Disease,” “QALY,” “DALYS.”

Appendix D. Quality evaluation criteria

a) Is it a population study (probabilistic)? (only for normal subjects)

Yes = 2
No / without information = 0

b) Is it a multicentric study? (only for normal subjects)

Yes = 1
No / without information = 0

c) Sample size

- For normal subjects
  - <100 = 0
  - 100–1000 = 1
  - >1000 = 2
- For any lesion
  - <30 = 0
  - 30–300 = 1
  - >300 = 2

d) Molecular detection technique

Hybrid capture = 0
PCR without betaglobin = 1
PCR with betaglobin = 2

e) Specimen

Fresh or Fixed, but used GP5/6 ó SPF10 = 1
Fixed = 0

f) Hystologic diagnosis? (only for lesions)

Yes = 1
No = 0

Appendix E. Standardized procedure used to capture study characteristics

Id	**Assigned paper identification number**	Variable codification
Lector	**Name of the reader**	
Tituloarti	**Title of the paper**	
Autor	Authors	
Anopulicac	Year of publication	
Revista	Journal	
Volumen	Volume	
Pagina	First page	
Poblacion Objetivo	**Target population**	
Poblacion	General population	0: no 1: yes
Vih	HIV positive	0: no 1: yes
Inmunocomp	Other immunocompromised	0: no 1: yes
Its	STD clinic attendees	0: no 1: yes
Tamizaje	Screening attendees	0: no 1: yes
Homosexual	Homosexual/bisexual	0: no 1: yes
Trabajo	Occupational setting	0: no 1: yes
Otra	Other	Specify
Año	**Year**	
Anoinicio	Year the study begun	
Anotermino	Year the study was completed	
Mesessegui	Months of follow up	
Edad	**Age**	
Edadminima	Minimum age of participants	
Edadmaxima	Maximum age of participants	
Edadpromed	Mean age of participants	
Desvesteda	Age of study participants: standard deviation	
Edad25	Age of study participants: 25th percentile	
Edad50	Age of study participants median	
Edad75	Age of study participants: 75th percentile	
Pais	**Country**	
Region	Region	
Areageogra	Does the study area cover the entire country or part of it?	1: Total 2: Partial
Estudios	**Studies**	
Tipodestud	Type of study (Descriptive statistic used)	Prevalence incidence Prevalence + incidence
Tipodiseno	Study design	Transversal Cohort (prospective) Retrospective Case-controls Clinical trial Case series
Subject of the investigation question (HPV disease investigated in the study: a single study can investigate HPV in multiple conditions**)**		
Normales	Subject with no lesions	0: no 1: yes
ASCUS	ASCUS	0: no 1: yes

CIN1	Cervical intraepithelial neoplasia, grade I	0: no	1: yes
CIN2	Cervical intraepithelial neoplasia, grade II	0: no	1: yes
CIN3	Cervical intraepithelial neoplasia, grade III	0: no	1: yes
Cacuellout	Cervical cancer, unspecified stages	0: no	1: yes
Estadiocu1	Cervical cancer, stage 1	0: no	1: yes
Estadiocu2	Cervical cancer, stage 2	0: no	1: yes
Estadiocu3	Cervical cancer, stage 3	0: no	1: yes
Estadiocu4	Cervical cancer, stage 4	0: no	1: yes
Cavulva	Vulvar cancer, unspecified stages	0: no	1: yes
Estadiovu1	Vulvar cancer, stage 1	0: no	1: yes
Estadiovu2	Vulvar cancer, stage 2	0: no	1: yes
Estadiovu3	Vulvar cancer, stage 3	0: no	1: yes
Estadiovu4	Vulvar cancer, stage 4	0: no	1: yes
CaVagina	Vaginal cancer, unspecified stages	0: no	1: yes
Estadiova1	Vaginal cancer, stage 1	0: no	1: yes
Estadiova2	Vaginal cancer, stage 2	0: no	1: yes
Estadiova3	Vaginal cancer, stage 3	0: no	1: yes
Estadiova4	Vaginal cancer, stage 4	0: no	1: yes
CaPene	Penile cancer, unspecified stages	0: no	1: yes
Estadiope1	Penile cancer, stage 1	0: no	1: yes
Estadiope2	Penile cancer, stage 2	0: no	1: yes
Estadiope3	Penile cancer, stage 3	0: no	1: yes
Estadiope4	Penile cancer, stage 4	0: no	1: yes
CaAnal	Anal cancer, unspecified stages	0: no	1: yes
Estadioan1	Anal cancer, stage 1	0: no	1: yes
Estadioan2	Anal cancer, stage 2	0: no	1: yes
Estadioan3	Anal cancer, stage 3	0: no	1: yes
Estadioan4	Anal cancer, stage 4	0: no	1: yes
CaOrofarin	Oropharyngeal cancer, unspecified stages	0: no	1: yes
Estadioor1	Oropharyngeal cancer, stage 1	0: no	1: yes
Estadioor2	Oropharyngeal cancer, stage 2	0: no	1: yes
Estadioor3	Oropharyngeal cancer, stage 3	0: no	1: yes
Estadioor4	Oropharyngeal cancer, stage 4	0: no	1: yes
CaCavOral	Vaginal cancer, unspecified stages	0: no	1: yes
Estadiocavoral1	Oral cavity cancer, stage 1	0: no	1: yes
Estadiocavoral2	Oral cavity cancer, stage 2	0: no	1: yes
Estadiocavoral3	Oral cavity cancer, stage 3	0: no	1: yes
Estadiocavoral4	Oral cavity cancer, stage 4	0: no	1: yes
CaCabezaCu	Head and neck cancer, unspecified stages	0: no	1: yes
Estadiocabezacu1	Head and neck cancer, stage 1	0: no	1: yes
Estadiocabezacu2	Head and neck cancer, stage 2	0: no	1: yes
Estadiocabezacu3	Head and neck cancer, stage 3	0: no	1: yes
Estadiocabezacu4	Head and neck cancer, stage 4	0: no	1: yes
VerrugasGe	Anogenital warts	0: no	1: yes
Papilomato	Respiratory papillomatosis	0: no	1: yes

Porcentaje de tipo de ITS	**STD type and percentage**	
Hiv	Prevalence of HIV	
Otro	Prevalence of other STD	
Tamanomues	Study sample size	
Lugar Reclutamiento (Source population)		
Ambulatori	Clinic	0: no 1: yes
Hospitaliz	Hospital	0: no 1: yes
Comunidad	Community	
Caracterst	Probabilistic nature of the sample	Random Convenience
Sexo	Gender of the subjects	Males Famales Both
Estudiomul	Multicentric study	0: no 1: yes
Quien	Who collects the sample?	0: study personnel 1: subject (self sampling)
Tipo De Muestra	**Sample type**	
Celulasexf	Exfoliated cells	0: no 1: yes
Celexfolli	Exfoliated cells, liquid	0: no 1: yes
Biopsiafre	Fresh biopsy	0: no 1: yes
Biopsiafij	Fixed biopsy	0: no 1: yes
Pquirurgic	Fresh surgical specimen	0: no 1: yes
Pquirurgi1	Fixed surgical specimen	0: no 1: yes
Otro	Other	Specify
Metodo Deteccion VPH	**HPV detection method**	
MY09/11	PCR, primers MY09/11, primers MY09/11+HM BO1	0:no 1:yes
PGMY	PCR, primers PGMY, line blot assay, primers PGMY	
GP56	PCR, primers GP5/6	
GP57	PCR, primers GP5+/6+	
SPF10	Reverse hybridization (INNO-LIPA)	
Tipconbet	PCR type specific primers, with betaglobin control	
Tipsinbet	PCR type specific primers, without betaglobin control	
Captura	Hybrid Capture assay	
Clasificación del Tipo De lesión	**Lesion type classification**	
Histol	Hystologic	
Citol	Cytologic	
Otra	Other	Specify
Tipodecanc	Hystologic type	Squamous cell Ca AdenoCa Other (specify)
Sesgos Posibles (BIASES)	**Possible bias**	
Seleccion	Selection bias	Low risk of bias Bias probable Bias evident
Clasificac	Misclassification (validity of diagnostic methods; see also HPV detection method)	
Control	Control for confounders in association studies	0:no 1: yes 2: not specified
Observacio	Comments of the reader on bias	

Nivelevide	Overall evidence level (use the dedicated quality assessment tool)	Strong Sufficient Limited No evidence

Appendix F. Standardized procedure used to capture virus epidemiology

Id	Assigned paper ID: pivot field	
Sex		0: men 1: women
Type of lesion		1 No lesion 2 ASCUS 3 LSIL 4 HSIL 5 Squamous cell Cancer 6 AdenoCancer 7 Cervical Cancer unspecified 8 Vulvar Cancer 9 Penile Cancer 10 Anal Cancer 11 Oropharyngeal Cancer 12 Anogenital Warts 13 Respiratory Papillomatosis 14 HPV infection, other
Number of cases	Absolute number of cases (Denominator for global and overall prevalence)	
Mettipvir #	Diagnostic Methods	1: PCR 2: Hybrid capture I 3: Hybrid capture II 4: Other(specify)
Number of isolated virus	Number of genotypes detected or identified by molecular techniques in above row Use the fields below only when neither age-specific nor type-specific data are available, even after contacting the authors	
VirusVPHA	Global HPV prevalence. Insert percentage	
VirusVPHALR	Global low-risk HPV types prevalence. Insert percentage	
VirusVPHAHR	Global high-risk HPV types prevalence. Insert percentage	
Genotypified HPV percentage	Overall type-specific HPV prevalence (Use when data analyzed by age are not available from the authors). Insert percentage	
Virus6 Virus11 Virus16 Virus18 Virus31 Virus33 Virus35 Virus39 Virus45 Virus51 Virus52		

Virus56			
Virus58			
Virus59			
Virus66			
Virus68			
Virus70			
Virus73			
Virus82			
Prevalence or incidence by age group for NORMAL, ASCUS, LSIL, HSIL, or CANCER			
Age group		Insert lower and upper limits for non-overlapping age groups when provided. When an interval is open ended, use minimum or maximum age in the study population	
ei1	es1		
ei2	es2		
ei3	es3		
ei4	es4		
ei5	es5		
ei6	es6		
ei7	es7		
		Insert absolute frequencies (number of cases)	
f1			
f2			
f3			
f4			
f5			
f6			
f7			
Prevalence by age group of virus type PrevInc			1: prevalence
Virus in general (HPV General Infection)		Insert absolute frequencies (number of cases) Use the fields below only when age-specific data are available, but type-specific data are unavailable, even after contacting the authors (e.g Hybrid Capture)	
Vgen1			
Vgen2			
Vgen3			
Vgen4			
Vgen5			
Vgen6			
Vgen7			
		Type-specific/age-specific HPV prevalence data Insert absolute frequencies (number of cases)	
Virus6			
V6e1			
V6e2			
V6e3			
V6e4			

V6e5
V6e6
V6e7

analogous fields for VPH 6,11,13,16,18,31,33,35,39,40.41,43,45,51,52,56,58,59,68,73,82

VIRUSOTRO <A> Prevalence of other HPV types not specified in the above list
Insert absolute frequencies (number of cases)

Votroe1
Votroe2
Votroe3
Votroe4
Votroe5
Votroe6
Votroe7

Use the fields below only when age-specific data are available, but type-specific data are not, even after contacting the authors, while a stratification by high- and low-risk types is given (e.g Hybrid Capture)

High-risk virus
Varie1
Varie2
Varie3
Varie4
Varie5
Varie6

Low-risk virus
Vbrie1
Vbrie2
Vbrie3
Vbrie4
Vbrie5
Vbrie6
Vbrie7

Appendix G. Tables and annex figures

Table 1. Number of healthy women and of populations with lesions by sample type studied[a]

	Exfoliated cells No./%	Liquid exfoliated cells No./%	Fresh biopsy No./%	Fixed biopsy No./%	Fresh surgical piece No./%	Fixed surgical piece No./%
Healthy women	35,673/89.6	7,048/17.7	526/1.3	6,465/16.2	--	--
ASCUS	585/75.8	126/16.3	--	37/4.8	--	11/1.4
LSIL	1,310/61.0	696/32.4	268/12.5	601/28.0		
HSIL	1,062/65.9	323/20.1	230/14.3	701/43.5		
ICC	964/46.5	108/5.2	453/21.9	1.430/69.0	--	--
Penile cancer	--	--	--	71/100.0	--	--

[a] The relative importance of each sample type total 100% but some lesions were studied by more than one method.
ASCUS, Atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; ICC, invasive cervical cancer.

Table 2. High-risk HPV prevalence by age group in women with normal cytology, population- and clinic-based studies (HC2)[a]

Age groups	High-risk N = 4		Low-risk N = 4	
	% (95% CI)	*P value*	% (95% CI)	*P value*
15– 24[b]	26.3 (18.4–32.8)	-	NA	NA
25– 34	20.1 (12.2–28.1)	0.211	NA	NA
35– 44	15.4 (7.1 –23.7)	0.032	NA	NA
45– 54	15.3 (6.3–24.2)	0.039	NA	NA
55– 64	7.6 (0.0–18.2)	0.002	NA	NA
≥65	10.8 (0.0–25.0)	0.052	NA	NA

[a] Mixed effects model; N = Number of studies.
[b] Referent group.

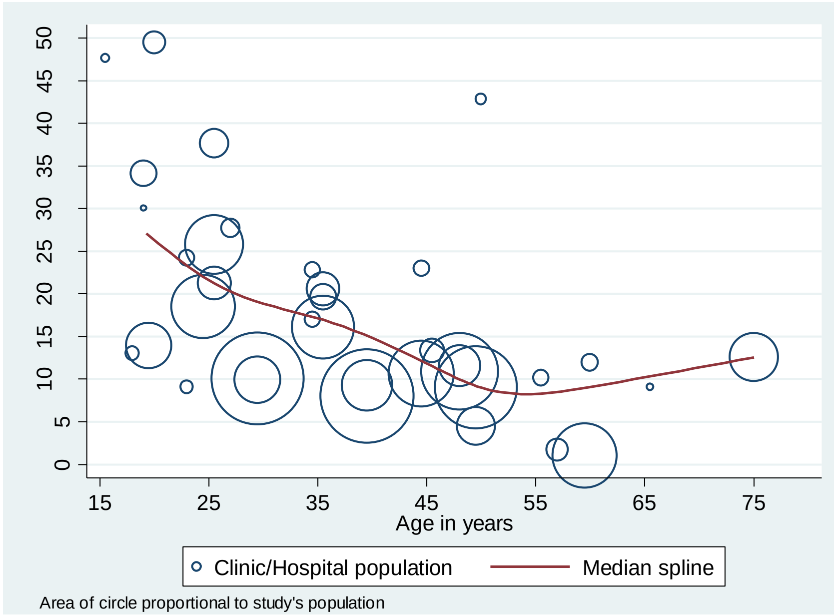

Figure 1. High-risk HPV prevalence by age in women with normal cytology, population- and clinic-based studies. HC2 method used for detection. N studies = 36.

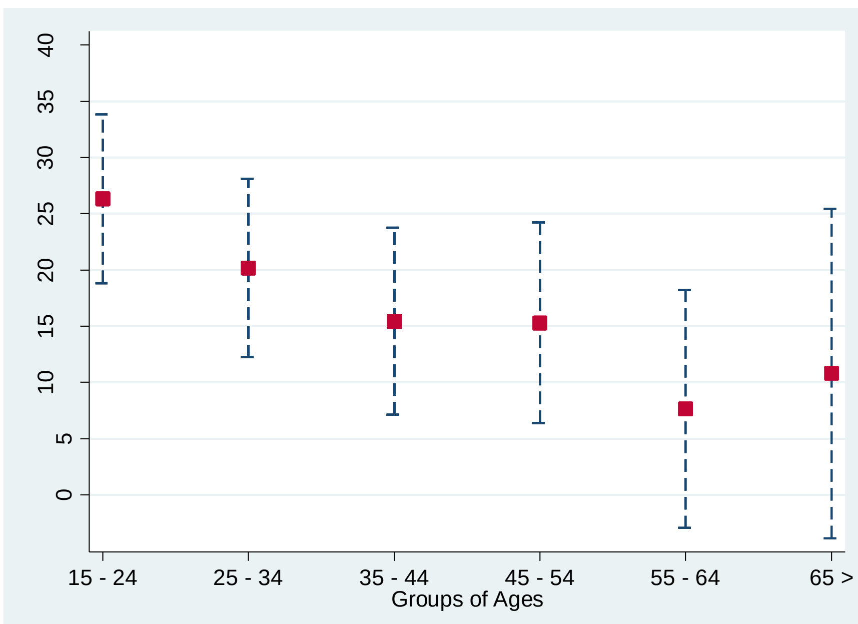

Figure 2. HPV general prevalence and 95% confidence intervals by age groups in women with normal cytology. HC2 method used for detection. Mixed effects model.

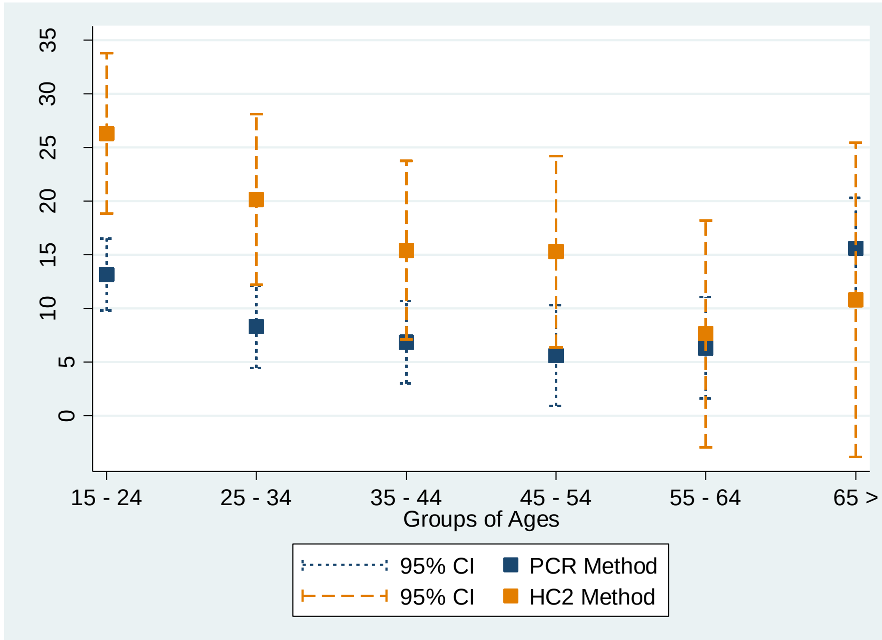

Figure 3. Prevalence and 95% confidence intervals for high-risk HPV infection by age group among women with normal cytology. HC2 and PCR methods used for detection.

Table 3. HPV prevalences in women without lesions by clusters of countries and type of populations[a]

Groups of countries	All HPV		High risk		Low risk	
	General population	Clinic population	General population	Clinic population	General population	Clinic population
	no. (%) 95% CI	no. (%) 95% CI	no. (%) 95% CI	no. (%) 95% CI	no. (%) 95% IC	no. (%) 95% CI
CLUSTER 1						
Argentina Chile Paraguay	1,882 (14.8) 0.0–44.3	1,297 (41.7) 30.5–52.6	1,882 (10.7) 0.0–34.0	511 (21.7) 0.0–100	955 (3.7)	458 (16.2)
CLUSTER 2						
Brazil	2,756 (16.6) 0.0–84.1	914 (11.7) 4.1–19.2	2,256 (8.7)	2,259 (8.7)	2,756 (6.0)	112 (16.4)
CLUSTER 3						
Bolivia Ecuador Colombia Peru Venezuela	2,009 (10.2) 1.2–19.2	426 (14.7) 3.4–26.0	1,859 (6.6)		1,859 (2.2)	
CLUSTER 4						
Barbados Cuba Jamaica Surinam		36 (25.0)		100 (80.0)		
CLUSTER 5						
Costa Rica Honduras Nicaragua Panama	8,412 (25.7) [b]	538 (36.5) 0.0–92.7	8,412 (9.9) *	538 (28,4) 0.0–100	8,412 (12.5) *	438 (3.9)
CLUSTER 5						
Mexico	1,340 (12.7)	1,688 (15.2) 0.0–37.8	1,340 (13.2)	1,544 (13.2) 13.1–13.3	1,340 (3.4)	463 (8,7) 0.0–100

[a] Some confidence intervals were not calculated due to insufficient study number; blank spaces represent absence of related studies; PCR method used for detection.
[b] Corresponds to the confidence interval of the cohort of Guanacaste.

Table 4. Type-specific HPV prevalence in healthy populations for selected countries, Latin America and the Caribbean[a]

HPV genotype	Prevalence % (95% CI)				
	Argentina no. = 5,503	**Colombia** no. = 2,601	**Costa Rica** no. = 9,184	**Brazil** no. = 19,531	**Mexico** no. = 17,899
6	1.7 (0.0–59.3)	0.05	0.4	0	0.5
11	1.7 (0–48.4)	0.2	0.2		0.9
16	7.8 (0–89.0)	2.4	2.2	1.9	1.9
18	1.5 (0–12.2)	0.4	1	1.1	1
31	1.2	0.3	1	0.8	1.4
33	3.7	0.2	0.5	0.4	1.2
35	2.4		0.2	0.3	0.07
39		0.3	0.4	0.09	0.7
40		0.3	0.06	0.3	
45	1.2	0.2	0.5	0.5	0.6
51		0.4	1.4	1.1	0.8
52		0.3	1.1	0.6	0.5
56		0.5	0.5	0.5	0.1
58		0.9	1.4	0.9	0.5
59		0.05	0.2	0.4	
68		0.1	0.2	0.6	0.3
73			0.3	0.4	0.07
82		0.05		0.1	0.07

[a] Some confidence intervals were not calculated because of an insufficient precision in some categories. Blank spaces represent absence of studies related with the combination. PCR used for virus detection..

Table 5. Type-specific HPV prevalence in women with LSIL for selected countries, Latin America and the Caribbean[a]

HPV genotype	Prevalence % (95% CI)				
	Argentina no. = 5,503	Costa Rica no. = 9,184	Brazil no. = 19,531	Mexico no. = 17,899	Nicaragua no. = 274
6	23.2 (0–26.3)	4.2			
11	6.8 (0–16.9)	2.1			
16	25.5 (0–99.9)	15.3	22.6	28.6	7.6
18	12.8 (0–31.8)	3.1		28.6	
31	2.7	7.4	12.9		7.6
33	3.9 (0–18.9)	3.7	3.2		2.5
35	5.4	3.1	3.2		2.5
39	2.7	8.4	3.2		3.8
40		1.6			
45	5.4	4.2			2.5
51	12.6	12.1	12.9		6.3
52	2.7	10.3	9.7		10.1
56	2.7	9.4	6.5		3.8
58		9.5	9.7		6.3
59		3.2	3.2		2.5
68		1			3.8
73		3.7	3.2		
82					

[a] Some confidence intervals were not calculated because of an insufficient precision in some categories. Blank spaces represent absence of studies related with the combination. PCR used for virus detection.; LSIL, low-grade squamous intraepithelial lesion.

Table 6. Type-specific HPV prevalence in women with HSIL for selected countries, Latin America and the Caribbean[a]

HPV genotype	Prevalence % (95% CI)				
	Argentina no. = 5,503	Costa Rica no. = 9,184	Brasil no. = 19,531	México no. = 17.899	Nicaragua no. = 274
6	22.7	1.5			
11	6.7	1.5			
16	51.1 (0-99.9)	43.1	47.6	33.3	27.9
18	19.7 (7.9-31.5)	6.9	4.8		6.7
31	5.3	9.2	9.5		12.5
33	4	4.6			5.8
35		3.1			2.9
39		4.6			4.8
40					
45		4.6			3.8
51	12	7.7			6.7
52	16.7	7.7	4.8		10.6
56		2.3			1.9
58		13.1	9.5		15.4
59		1.5			2.9
68		0.8			4.8
73		3.1			
82					

[a] Some confidence intervals were not calculated because of an insufficient precision in some categories. Blank spaces represent absence of studies related with the combination. PCR used for virus detection.; HSIL, high-grade squamous intraepithelial lesion

Table 7. Summary of meta-analysis published in the literature

Study population (n)	Total no. studies	No. examined women	HPV (+) women	HPV crude prevalence (%)	Adjusted HPV prevalence (95% CI)
Population with normal cytology [9]	Central America:4	10,232	2,097	20.5	20.4 (19.3–21.4)
	South America: 7	4,345	623	14.3	12.3 (11.2–13.4)
Low-grade cervical lesions [101]	Central and South America:13	1,279	874	68.3	
High-grade cervical lesions [102]	Central and South America: 10	967	815	84.3	
Invasive cervical cancer [99]	Central and South America: 12	1,460 Squamous/ adeno: 1,407/53		89.3	

Table 8. HPV classification by oncogenic risk

Group	Species	Type	Schiffman 2005	Muñoz 2003	Hiller 2006	Cogliano 2005	Hybrid Capture II (Nindl et al. 1998)	GP5/6+ Jacobs et al. 1997	Sabin Group 2007
Group 1	10	6	Low	Low	Low	Pos. Carcin			Low
		11	Low	Low	Low	Pos. Carcin			Low
		13							Low
		74							Low
		44	Low	Low	Low				Low
		55							Low
	8	91							Low
		7							Low
		43		Low					Low
		40	Low	Low					Low
	1	32							Low
		42	Low	Low					Low
	13	54	Low	Low	Low				Low
Group 2	9	52	High	High	High	Carcinog	High	High	High
		67							Low
		33	High	High	High	Carcinog	High	High	High
		58	High	High	High	Carcinog	High	High	High
		16	High	High	High	Carcinog	High	High	High
		31	High	High		Carcinog	High	High	High
		35	High	High	High	Carcinog	High	High	High
	11	34							Low
		73	High	High					High
	7	59	High	High		Carcinog	High	High	High
		18	High	High	High	Carcinog	High	High	High
		45	High	High	High	Carcinog	High	High	High
		70	?Low	Low	High				Pending
		39	High	High	High	Carcinog	High	High	High
		68	High	High			High	High	High
		85							Low
	5	26	?High	?High					Pending
		69							Low
		51	High	High	High	Carcinog	High	High	High
		82	High	High	High				High
	6	30							Low
		53	?High	?High	High				Pending
		56	High	High	High	Carcinog	High	High	High
		66	?High	?High	High	Carcinog		High	High
Group 3	4	57							Low
		2a							Low
		27							Low
	15	71							Low

		90				Low
	3	61	Low	Low	Low	Low
		72	Low	Low		Low
		62				Low
		81	Low	Low		Low
		83				Low
		89	Low			Low
		84				Low
		86				Low
		87				Low
	2	28				Low
		3				Low
		10				Low
		29				Low
		77				Low

Notes: HPV 55 = HPV 44; HPV 64 = HPV 34; HPV 46 = HPV 20
HPV 46, HPV 64, and HPV 55 are blank to avoid confusion.

References: [1, 24, 41–43, 103, 104]

Appendix H. Descriptions of studies included in meta-analysis, Latin America and the Caribbean, 1990–mid-2007

No.	Principal author	Title	Journal	Year	Country
1	ABBA MC	DISTRIBUCION DE LOS GENOTIPOS DEL VIRUS PAPILOMA HUMANO EN I	REVISTA ARGENTINA DE MICROBIOLOGIA	2003	ARGENTINA
2	ABBA MC	THE C-MYC ACTIVATION IN CERVICAL CARCINOMAS AND HPV 16 INFEC	MUTATION RESEARCH	2004	ARGENTINA
3	AEDO S	DETECCION Y TIPIFICACION DE VIRUS PAPILOMA HUMANO EN LESIONE	REV MED CHILE	2007	CHILE
4	AGUILAR LV	HUMAN PAPILLOMAVIRUS IN MEN: COMPARISON OF DIFFERENT	SEX TRANSM INFECT	2006	MEXICO
5	ALONIO LV	MUTACIONES EN GENES HA-RAS Y P53 DETECTADAS MEDIANTE PCR-SSC	MEDICINA (BUENOS AIRES)	2000	ARGENTINA
6	ANSCHAU F	ANALISE DA PREVALENCIA DO PAPILOMAVIRUS HUMANO EM RELACAO AO	SCIENTIA MEDICA. PORTO ALEGRE	2004	BRASIL
7	BALDWIN S	COMPARISON OF TYPE-SPECIFIC HUMAN PAPILLOMAVIRUS DATA FROM SELF AND CLINICIAN DIRECTED SAMPLING		2005	MEXICO
8	BELLO DE ALFORD M	TIPIFICACION DEL VIRUS DEL PAPILOMA HUMANO EN PAPILOMATOSIS LARINGEA RECURRENTE JUVENIL	Revista de la Facultad de Medicina. CARACAS	2001	VENEZUELA
9	BERUMEN J	ASIAN-AMERICAN VARIANTS OF HUMAN PAPILLOMAVIRUS 16	JOURNAL OF THE NATIONAL CANCER INSTITUTE	2001	MEXICO
10	BOON ME	PRESENCE OF PROLIFERATING (MIB-1-POSITIVE) CELLS IN CERVICAL	DIAGN CYTOPATHOL	2001	BRASIL
11	BOSCH FX	HUMAN PAPILLOMAVIRUS AND CERVICAL INTRAEPITHELIAL NEOPLASIA	CANCER EPIDEMIOLOGY. BIOMARKERS AND PREVENTION	1993	COLOMBIA

No.	Principal author	Title	Journal	Year	Country
12	BOSCH FX	PREVALENCE OF HUMAN PAPILLOMAVIRUS IN CERVICAL CANCER	JOURNAL OF THE NATIONAL CANCER INSTITUTE	1995	MULTIPLE
13	BRAVO MM	INFECCION POR VIRUS DEL PAPILOMA HUMANO EN UNA MUESTRA DE MUJERES JOVENES CON CITOLOGIA NORMAL	REVISTA COLOMBIANA DE CANCEROLOGIA	2004	COLOMBIA
14	BRITO EB	HUMAN PAPILLOMAVIRUSES IN AMERINDIAN WOMEN FROM BRAZILIAN AM	EPIDEMIOL INFECT	2002	BRASIL
15	CAMBRUZZI E	EXPRESSION OF KI-67 AND SQUAMOUS INTRAEPITHELIAL LESIONS	PATHOLOGY ONCOLOGY RESEARCH	2005	BRASIL
16	CAMPOS RR	PREVALENCIA DO PAPILOMAVIRUS HUMANO E SEUS GENOTIPOS EM MULH	REV BRAS GINECOL OBSTET	2005	BRASIL
17	CARESTIATO FN	PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN THE GENITAL	BRAZILIAN JOURNAL OF INFECTIOUS DISEASES	2006	BRASIL
18	CARESTIATO FN	ANALYSIS OF MOLECULAR BIOLOGY TECHNIQUES FOR THE DIAGNOSIS O	REV SOC BRAS MED TROP	2006	BRASIL
19	CARRILLO A	UTILIDAD DE LA COMBINACION DE OLIGONUCLEOTIDOS UNIVERSALES	SALUD PUBLICA DE MEXICO	2004	MEXICO
20	CARVALHO MOO	HUMAN PAPILLOMAVIRUS INFECTION IN RIO DE JANEIRO BRAZIL	BRAZILIAN JOURNAL OF INFECTIOUS DIS	2005	BRASIL
21	CARVALHO MOO	DETECCAO DE PAPILOMAVIRUS HUMANOS PELA TECNICA DE	J BRAS DOENCAS SEX TRANSM	2001	BRASIL
22	CASTELLSAGUE X	PREVALENCE OF PENILE HUMAN PAPILLOMAVIRUS DNA IN HUSBANDS OF	THE JOURNAL OF INFECTIOUS DISEASES	1997	COLOMBIA
23	CERQUEIRA DM	HIGH HPV GENETIC DIVERSITY IN WOMEN INFECTED WITH HIV-1	ARCHIVES OF VIROLOGY	2007	BRASIL
24	CHOUHY D	DEVELOPMENT AND EVALUATION OF A COLORIMETRIC PCR SYSTEM	INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE	2006	ARGENTINA

No.	Principal author	Title	Journal	Year	Country
25	CLAEYS P	PREVALENCE AND RISK FACTORS OF SEXUALLY TRANSMITTED INFECTIO	SEX TRANSM INFECT	2002	NICARAGUA
26	CORRENTI M	DETECCION DE VIRUS PAPILOMA HUMANO (VPH) MEDIANTE BIOLOGIA MOLEC	REVISTA VENEZOLANA DE ONCOLOGIA	1997	VENEZUELA
27	DELUCA GD	INFECCION POR CHLAMYDIA TRACHOMATIS Y PAPILOMAVIRUS EN MUJER	MEDICINA (BUENOS AIRES)	2006	ARGENTINA
28	DELUCA GD	HUMAN PAPILLOMAVIRUS GENOTYPES IN WOMEN WITH CERVICAL CYTOLO	REV INST MED TROP S PAULO	2004	ARGENTINA
29	DERCHAIN S	ASSOCIATION OF ONCOGENIC HUMAN PAPILLOMAVIRUS DNA WITH HIGH GRADE	SEX TRANSM INF	1999	BRASIL
30	DO SACRAMENTO PR	THE PREVALENCE OF HUMAN PAPILLOMAVIRUS IN THE OROPHARYNX IN	JOURNAL OF MEDICAL VIROLOGY	2006	BRASIL
31	FERRECCIO C	POPULATION-BASED PREVALENCE AND AGE DISTRIBUTION OF	CANCER EPIDEMIOLOGY. BIOMARKERS AND PREVENTION	2004	CHILE
32	FERRERA A	HUMAN PAPILLOMAVIRUS INFECTION. CERVICAL DYSPLASIA	INTERNATIONAL JOURNAL OF CANCER	1999	HONDURAS
33	FERRERA A	ASSOCIATION OF INFECTIONS WITH HUMAN IMMUNODEFICIENCY VIRUS	AM J TROP MED HYG	1997	HONDURAS
34	FRANCO E	DESIGN AND METHODS OF THE LUDWIG-MCGILL LONGITUDINAL STU	REV PANAMERICANA SALUD PÚBLICA	1999	BRASIL
35	FUESSEL HAWS AL	HUMAN PAPILLOMAVIRUS INFECTION AND P53 CODON 72 GEN	JOURNAL OF MEDICAL VIROLOGY	2005	MEXICO
36	FURRER VE	BIOPSY VS. SUPERFICIAL SCRAPING: DETECTION OF HUMAN	J ORAL PATHOL MED	2006	ARGENTINA
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