Burden of Human Papillomavirus (HPV) Infection and HPV-Related Disease in Latin America and the Caribbean, and Health and Economic Outcomes of HPV Vaccination in Selected Countries in Latin America

Executive Summary

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A collaborative project of:

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Executive summary

Introduction

Epidemiologic and microbiologic studies have demonstrated that human papillomavirus (HPV) infection, particularly with the high risk types of HPV, is a necessary but not sufficient cause of cervical cancer. Because HPV infection is very common and most infections are cleared within two years, studies have shown that other factors are likely to contribute to HPV persistence and the development of cancer. Co-factors that may be involved include parity, smoking, prolonged oral contraceptive use, nutritional deficiencies, genetic factors, and other sexually transmitted infections.

It is estimated that in the Americas, among the over 336.5 million women over the age of 15, more than 86,000 will be diagnosed with cervical cancer and over 38,000 will die of the disease annually. This translates into an annual incidence of 18.8 per 100,000 and a mortality of 8.1 per 100,000. Substantial variation of the burden of HPV disease in the region, related to access to screening services and curative care exists, because cervical cancer can be prevented if early lesions are treated. For example, the proportion of cancer deaths caused by cervical cancer in women in the U.S.A. is 2.5%, whereas in Haiti it is 49%.

In Latin America and the Caribbean, cervical cancer is the fourth most common cause of cancer, the second most common cause of cancer among women aged 15-44, and it is the second most common cause of death due to cancer among women in Central and South America.

In Latin America and the Caribbean, the prevalence of HPV infection varies by country and population. Among women with normal Papanicolaou (Pap) cytology, the average prevalence has been estimated as 16% (95% confidence interval [CI] 15.2%-16.9%). Among a group of 3,600 women with low grade cervical lesions (LSIL), the prevalence was 75.6% (95% CI 74.4%-77.2%), and among a group of 1900 women with high grade lesions (HSIL) it was 83.9% (95% CI 82.1%-85.5%). Among women with cervical cancer the proportion with detectable HPV approaches 100%, as would be expected. However, these prevalences represent data from selected populations and do not capture the variability in the region.

Study Objectives

The objectives of this report are twofold: 1 - to estimate the burden of HPV and HPV-related disease in Latin America and the Caribbean and 2 - to provide estimates of the health and economic outcomes of HPV vaccination and screening in selected countries in Latin America. Ancillary to these objectives was an evaluation of the quality of the studies that were included in the meta-analysis to assess the influence of exclusion criteria of study design, methodology, and appropriateness of interpretation via sensitivity analysis.

The findings will be used to inform national health authorities about the burden of HPV and HPV-related disease and the economic value of implementing an HPV vaccination program in selected countries of the region or/and introducing improving screening programs.

The final report will have two volumes, the first one containing the meta-analysis of the burden of HPV and HPV-related disease in Latin America and the Caribbean, and the second part containing the cost-effectiveness study of HPV vaccination. It provides specific economic information for six selected countries in Latin America. Although some of the epidemiological estimates from the two documents may differ due to differences in methodology, the reports should be viewed as complementary.

Methods

Meta-analysis of the burden of HPV and HPV-related disease in Latin America and the Caribbean

To estimate the burden of HPV and HPV-related disease, a literature review of all published studies since 1990 was performed, focusing on research that described prevalence of HPV in different patient subsets. Because of advancements in molecular biology and HPV diagnostic methods since 1990, articles published after that year were selected. The literature review was augmented by contacting subject-matter experts and pharmaceutical companies with data from the region for additional information.

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, Department of Health and Human Services, and the University of Chile. Studies with original data on prevalence, incidence, cost, or cost-effectiveness of HPV vaccination in six selected countries in Latin America (Argentina, Brazil, Chile, Colombia, Mexico and Peru) were abstracted if they were published after 1990, and if they included cytologically normal women, cytologically abnormal women, or women with lesions of the vulva, vagina, cervix, or anus, or men with lesions of the penis or anus. For both sexes, articles on the prevalence of HPV in lesions of the oropharynx were also abstracted. The minimum number of study participants was 30 for studies of cervical intraepithelial lesions and cervical cancer, and 10 for studies of other kinds of cancer.

To calculate the incidence of HPV, data from two prospective cohort studies conducted in the region were used: the Ludwig-McGill study in Brazil and the Colombia study in Bogotá. The cohort from Guanacaste, Costa Rica was not included because the incidence data from this study are still being analyzed. The Ludwig-McGill study recruited 2,528 women between the ages of 18 and 60 years and the Bogotá study recruited 1,610 women between the ages of 13 and 85 years. The first time HPV was detected during follow up was defined as an incident case, and incidence was calculated in person-time. Incidences by age, by type, by risk-type, and by genotype group were calculated using modern taxonomical classification based on recent epidemiologic and phylogenetic data from the scientific literature (Sabin Team).

For the calculations of the burden of cancer, we calculated the current number of HPV-related cancers in the region using estimates from the International Agency for Research on Cancer (IARC). The proportion of cervical cancer attributable to HPV was assumed to be 100% [1]

[1] . Parkin M, Bray F. The burden of HPV related cancers. Vaccine 2006; 24 (S3): S3/11-S3/25.

while for other cancers we estimated the attributable risk (AR) from case control studies using the following expression:

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

Where AR= attributable risk, $\mathbf{p_j}$=proportion of cases in the jth exposure stratum, $\mathbf{R_j}$= relative risk or odds ratio in the jth exposure stratum. Note that in the stratum j=0 (unexposed) R will take the value of 1.[2]

We estimated the attributable risk using the formula shown above for vulvar, vaginal, penile, anal, and oropharyngeal cancer using case control studies that reported the proportion of those cancers with HPV. From the studies retrieved we selected those with the largest number of cases, published more recently, or those where cancer definitions were clearer. The AR was 54% for HPV 16 in oropharyngeal cancer[3], 40% for HPV 16 and 18 in penile cancer[4], 52% for HPV 16 and 18 in anal cancer among women, 42% for HPV 16 in anal cancer among men[5], and 46% for HPV 16 and 18 in vulvar and vaginal cancer[6].

For the quality assessment, two instruments were used: the first was the Impact Factor (IF) of the journal where the study was published. In the case of studies published in multiple journals, the highest IF was used. The studies that appeared in publications for which an impact factor was not available were excluded, or assigned the 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, method of HPV detection, and how HPV-associated lesions were classified. Two quality scores were calculated, one for studies of subjects without lesions (scale 0 to 8 points), and another one for studies of subjects with HPV-associated lesions (scale 0 to 6 points). The relationship between IFs and quality scores was assessed by calculating Spearman's rank correlation coefficient.

Data from articles, abstracts, and from unpublished works were abstracted into 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, disease status of participants, method of selection of participants and study design. The laboratory variables included the method of identifying HPV (Hybrid Capture 2 [HC2] or polymerase chain reaction [PCR]), types of HPV identified, and number of person(s) with HPV types detected, and whether beta-globin was detected. HC2 was only used for estimating prevalence among women with normal cytology;

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[2] Bruzzi P, Green S, Byar D, Brinton L, and Schairer C. Estimating the population attributable risk for multiple risk factors using case control data. American Journal of Epidemiology 1985; 122 (5):904-14.

[3] D'Souza G, Kreimer A, Viscidi R, et al. Case control study of human papillomavirus and oropharyngeal cancer. N Eng J Med 2007; 356: 1944-56

[4] Heideman DA, Paulita M, Diemen PD, Nindl L, Leijte J, et al. Human papillomavirus type 16 is the predominant type etiologically involved in penile squamous cell carcinoma. Journal of Clinical Oncology 2007; 25:4550-6

[5] Carter J, Shera K, Schwartz SM, Cushing Haugen KL, Wipf GC, et al. Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites. Cancer Research 2001; 61:1934-40

[6] Daling J, Madeleine M, Schwartz S, Shera K, Carter JJ, McKnight B, et al. A population-based study of squamous cell vaginal cancer: HPV and cofactors. Gynecol Oncol 2002;84:263-70.

among women with lesions, only data based on PCR was used. Study quality indicators, such as the nature of the population sampled and the quality of the laboratory methods were also abstracted.

A descriptive analysis was performed summarizing all of the studies identified, by subgroup (i.e. cytologically normal women, by age group), using mean, median, or proportions as appropriate. The general prevalence of HPV was estimated using fixed effects, that is, each study was weighted by the inverse of its variance. Prevalence by age group was estimated using mixed models. The independent variable was age, with the referent group being those aged 15 to 24. In order to model the variability in prevalence, metaregression was used with the following variables: specimen type (exfoliated cells, biopsy, surgical specimen), HPV detection method (HC2 or PCR), and study quality (as a continuous value).

Economic evaluation of HPV vaccination in selected countries in Latin America
We synthesized the available data to estimate the cost-effectiveness of HPV 16+18 vaccination in six selected countries in Latin America (Argentina, Brazil, Chile, Colombia, Mexico and Peru). A comprehensive literature review of epidemiologic data in countries of the region was conducted to inform age-specific cervical cancer incidence and mortality rates, and the distribution of HPV 16 and HPV 18 in cervical cancer.

National treatment guidelines were used to learn about treatment practices of precancerous lesions and cervical cancer in each country. To further determine cervical cancer treatment by stage and cost of care, we conducted surveys in several countries of the region in person and by phone or e-mail. These surveys contained specific questions about screening for precancerous lesions and diagnosis and treatment of cervical cancer. In addition, surveys were conducted to derive assumptions about the costs required to vaccinate pre-adolescents against HPV.

To conduct the cost-effectiveness projections we used an excel-based model that was developed as a companion model to a previously validated micro-simulation model of HPV infection and cervical cancer. This model relies on simplifying assumptions to explore the costs and benefits of vaccination and is less data intensive than a comprehensive simulation model; as such, its use is restricted to generating broad qualitative insight into the potential benefits of HPV 16+18 vaccination of pre-adolescent girls in the six selected countries. Model outcomes include reduction in the lifetime risk of cervical cancer and averted cases and deaths from cervical cancer, as well as years of life saved (YLS), disability-adjusted life years (DALYs), and lifetime costs. DALYs calculated reflect the disability weight and duration estimates for cervical cancer as provided in the Global Burden of Disease study, although are not age-weighted.

The performance of vaccination strategies is described using incremental cost-effectiveness ratios, defined as the additional cost of a specific strategy, divided by its additional benefit (per-woman life expectancy gain), and compared with the next most costly strategy**.** Costs are presented in international dollars (2005) for purposes of broad comparison across countries, but also in local currency and U.S. dollars for local and regional decision makers. We followed the recommendations made in several published guidelines for economic evaluations, adopted a modified societal perspective and discounted future costs and life years by 3% annually.

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

Results

1. Prevalence of HPV Infection

The literature search yielded 9710 abstracts with one or more of the MeSH search terms. Upon review, 1085 were selected for full text review. There were 279 articles that could not be located. Of the 806 full text articles that were reviewed, 116 met the inclusion criteria and are included in the prevalence report. There are two studies that contribute to the incidence estimates.

There were 42 (36%) articles on prevalence in Brazil and 27 (23%) on prevalence in Mexico, the other countries in the region accounted for the remaining 40%, with only Argentina contributing more than 10%. The quality score given during abstraction correlated well ($p<0.01$) with the impact factor of the journal of publication for cytologically normal women and for women with cancer.

There were 41 studies among cytologically normal women; the overall prevalence of HPV by PCR was 18.6% (95% CI 15.3-22.0%). Among women with ASCUS prevalence was 56.1% (95% CI 39.7%-72.4%), among women with LSIL it was 79.0% (95% CI 71.9%-86.1%), among women with HSIL it was 96.8% (95% CI 93.5%-100%), and among women with invasive cancer it was 94% (95% CI 89.4%-98.5%). There were 7 studies among healthy men; HPV prevalence was 21.7% (95% CI 1.7%-41.6%) (Table 1).

TABLE 1. PREVALENCE OF HPV IN WOMEN AND MEN, BY LESION TYPE AND HPV DETECTION METHOD						
POPULATION BY LESION TYPE	**PCR**			**HC2**		
	No. studies	**No. Subjects**	**% (95% CI)**	**No. studies**	**No. Subjects**	**% (95% CI)**
WOMEN						
Normal Cytology	41	21.298	18,6 (15,3-22,0)	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 & Unspecified cervical cancer	28	1795	88,0 (80,6-95,4)	NA	NA	NA
Adenocarcinoma of the cervix	3	277	85,2 (63,0-100)	NA	NA	NA
MEN						
Normal	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
Oropharyngeal Cancer	-	-	--	-	-	-
Genital Warts	2	158	81,5 (0,0-100)	-	-	-
Respiratory Papillomatosis	-	-	--	-	-	-
Normal Oral Mucosa	3	43	9,3 (1,1-17.5)	-	-	-
HIV +	7	1.082	79,5 (72,1-87.0)			

*Some CI were not calculated because of insufficient numbers of studies.
Missing spaces indicate that no studies were found for this HPV detection method and lesion type
NA: This method of HPV detection (HC2) was not included for HPV prevalence calculations for this lesion type

In the general population, HPV prevalence by age followed the pattern seen in previous reports and publications; prevalence was high (20-30%) among women aged 15-24, prevalence decreased with age through age 50, then prevalence increased again up to ~20%. Prevalence of high-risk HPV followed the pattern of general HPV prevalence, being highest among women aged 15-24 and those aged >50 years. Clinic populations (women seeking care in ambulatory settings) had higher prevalences at all ages.

Among cytologically normal women, the prevalence of HPV-16 was 2.6% (95% CI 1.8-3.2) and of HPV-18 was 1.0 (95% CI 0.6-1.3). Among women with invasive cervical cancer,

prevalence of HPV-16 was 49.3% (95% CI 45.5%-53.1%) and HPV-18 was 10% (95% CI 7.6%-12.5%) (Table 2).

TABLE 2. HPV TYPE-SPECIFIC PREVALENCE IN WOMEN AND MEN AND IN ICC, BY PCR.

	WOMEN- NORMAL CYTOLOGY		HEALTHY MEN		INVASIVE CERVICAL CANCER (ICC)	
	n (Prev %)	95% CI	n (Prev %)	95% CI	n (Prev%)	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,)	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	1446 (4,1)	2,1 - 6,1

Some CI were not calculated because of insufficient numbers of studies.
Missing spaces represent no studies or insufficient numbers to calculate a confidence interval
n= the number of women studied for each HPV type

2. Incidence of HPV infection

The combined incidence of HPV in the prospective cohorts was 8% per year, although the total risk was higher in Brazil (11.2%) than in Colombia (6.7%). As expected, it was highest among women aged less than 25 years, 17.5/100 woman years in Brazil and 14/100 woman years in Colombia. It was 10/100 woman years or less among women 25-44 or older than 44 in both studies. The type with the highest incidence was HPV 16, at 1.7 and 1.3/100 woman-years (Table 3).

TABLE 3. HPV INCIDENCE IN WOMEN. BOGOTÁ (COLOMBIA) AND LUDWIG-MCGILL (BRAZIL), BY HPV RISK AND TAXONOMIC GROUPS, AND AGE GROUP					
HPV RISK OR TAXONOMIC GROUP	**PERSON-YEARS**	**NUMBER OF INCIDENT CASES**	**INCIDENCE RATE (per 100 women-years)**	**95% CI**	
UNDER 25 YEARS OLD					
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					
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 OR MORE					
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

3. Burden of cancer

Using IARC rates and the estimates of attributable risk as described, it is estimated that there are 85,000 HPV-related cancers in Latin America and the Caribbean annually. These are mostly cases of cervical cancer (85%), followed by oropharyngeal cancer (8%), anal (2.5%), penile (2%) and vaginal/vulvar (2.5%). Most cases of cervical cancer occur in Brazil, Mexico, Colombia, Peru and Argentina where 49,000 cases are estimated to occur every year, or 68% of the total cases in the region (Table 4).

TABLE 4. ESTIMATES OF INCIDENCE RATES, CASES AND DEATHS DUE TO CERVICAL CANCER FOR LATIN AMERICA AND THE CARIBBEAN FOR 2002, ORDERED BY AGE-ADJUSTED INCIDENCE RATE.

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: IARC 2002. Globocan.

4. Quality assessment
When considering studies published in journals for which an impact factor was available, the mean IF were 2.86, 2.23, 2.29 and 5.65, for studies of subjects without lesions, with LSIL, HSIL, and ICC respectively. When considering all studies, the mean IF were 1.63, 1.39, 1.49, and 4.33, respectively.

The mean (± SD) quality score was 3.41 (±1.31) for studies of subjects without lesions, and 3.68 (±1.01), 3.78 (±1.04), 4.15 (±0.88), for studies of subjects with LSIL, HSIL, and ICC, respectively. The coefficient of correlation between IF and quality score was 0.36 ($p<0.0001$) overall, and in particular 0.47 ($p <0.0001$) for studies on subjects without lesions and 0.55 ($p= 0.0001$), for studies on subjects with ICC, while there was no significant correlation for studies of high or low risk intraepithelial lesions.

5. Meta-regression
Meta-regression analysis indicated that, among cytologically normal women, the prevalence of HPV was not related to the type of specimen ($p=0.8$), who took the specimen, or the quality score of the manuscript ($p=0.9$). None of these factors was significant in the analysis of HPV prevalence by age. However, the method of detection was significantly associated with prevalence, in that HC2, compared to PCR, underestimated prevalence by 57% in relative terms ($p=0.001$).

6. Economic evaluation of HPV vaccination
Based on the available data of six countries, the total direct medical cost per case for screening and treatment of precancerous lesions ranged from I$10 to I$81 per woman and from I$534 to I$1,402 per woman, respectively. These costs were generally attributed to the cost of specialist consultation (in the case of screening) and hospital stay (in the case of treating precancerous lesions). The cost of cervical cancer treatment was much higher and ranged from I$6,004 (Colombia) to I$14,517 (Argentina) per woman, with higher costs in the more advanced stages of cervical cancer. The majority of these treatment cost was attributed to the cost of hospital stay and the cost of palliative care.

Assuming 70% vaccination coverage by 12 years of age and 100% efficacy against types 16, 18, in the six selected countries of the region we found that almost 45,000 cancer deaths and 74,000 cervical cancer cases would be averted over the lifetime of a single birth cohort. The majority of the cases and deaths averted occur in Brazil where cervical cancer is more common than in other countries of the region. When 10 birth cohorts of 12-year-olds for the six countries are considered (n = 27,924,000), assuming a 70% coverage, we would expect to prevent half a million deaths over the lifetime of the vaccinated girls.

At the U.S. vaccine price of I$360 per vaccinated girl (I$120 per dose), the cost per life saved from a societal perspective would range from I$640 (Argentina) to I$1,980 (Mexico) and would not be cost-effective in Peru. At lower costs of I$75 per vaccinated girl (I$20 per dose), I$50 per vaccinated girl (I$12 per dose), I$25 per vaccinated girl (I$5 per dose), the cost per year of life saved would drop to I$424 and I$1,038, I$178 and I$578, I$7 and I$162, respectively. At I$15 per vaccinated girl (I$5 per dose), vaccination was cost-saving in Chile.

This analysis assumes all women with detected invasive cervical cancer are treated and the costs are derived indirectly. It also assumes vaccine coverage of 70% for a single birth cohort of pre-adolescent girls (i.e., 12 year-olds) in 2007 with a 100% effective vaccine.

Based on published data and a vaccine cost of $360 per vaccinated girl, in countries able to perform screening, screening was generally more cost-effective than vaccination as the main cervical cancer prevention option. As the cost per vaccinated girl declines however, pre-adolescent 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 is achievable in young girls, may be the most feasible option to reduce cancer.

It is important to emphasize that even if vaccination can be cost-effective in that the incremental cost-effectiveness ratio is less than the per capita GDP of a specific country, it may have significant financial implications to the health care systems of the countries studied. For all six countries studied, the financial costs to vaccinate over a five year period at 70% coverage when the cost per vaccinated girl is I$25 results in I$290 million annually. When the cost per vaccinated girl increased to I$360, the cost would be over 15 times this amount. This highlights the important difference between cost-effectiveness and affordability. While interventions may be “very cost-effective”, they may turn out to cost hundreds of millions of dollars a year.

Conclusions

This meta-analysis is the largest to date on the effect of HPV in Latin America and the Caribbean. It describes the prevalence of HPV among healthy men (21.7%) and women (18.6%), among those with lesions, and the proportion of non-cervical cancers that are HPV-related. The prevalence among women with ASCUS, LSIL, HSIL, and invasive cancer was 18.6%, 56.1%, 79.0%, 96.8%, and 94.0%. HPV-16 and HPV-18 were detected in 59.4% of cervical cancer.

HPV affects women and men in Latin America and the Caribbean as it does in other parts of the world. Prevalence and incidence are highest among those who have recently become sexually active. The proportion of cervical cancer that is due to HPV 16 and 18 is less (~60%) than is assumed for the U.S.A. (~70%). There are variations by country and region. For example, healthy women in Costa Rica have a HPV prevalence of 25.7%, and women in Mexico have a prevalence of 12.7%. However, no population is unaffected.

This analysis also describes the incidence, in 100 woman-years, of HPV among women. By age, incidence was 16/100 person-years among women aged <25, and by risk type, incidence of high-risk types was higher than low risk types (8.8 vs 4.1/100 person/years). We found that among all studies, the method of viral detection and location of the study population were significantly associated with the prevalence of infection.

Finally, the quality scores we developed correlate with IFs, especially for investigations on normal subjects, (which represent the majority of cohort studies, population based studies, and natural history studies) and cancer. This indicates that the characteristics that affect study quality are important to reviewers and editors of the journals in which these study are published.

This report presents new evidence that vaccinations that are almost 100 percent effective against two high-risk types of HPV could dramatically reduce cervical cancer deaths in the region. This study found that over 10 birth cohorts of 12-year-olds, vaccinating at a coverage rate of 70 percent could eventually prevent half a million deaths over the lifetime of the vaccinated girls in these countries alone. However, the study found that the cost of the vaccine—which now sells for $360 for the required three-dose regimen—would need to come down considerably to be affordable. At its current price, it would cost the six countries over $4.7 billion annually to vaccinate over a five-year period. Even if costs came down to $25 per vaccinated girl, while the vaccine would certainly be very cost-effective in the countries studied compared to other control methods, it would still have significant financial implications for health care systems, costing $290 million annually.

Limitations of this analysis include, but are not limited to, gaps in our understanding of the natural history of HPV, uncertainties around the epidemiology and temporal trends of cervical cancer in many countries, lack of high-quality data on screening, costs associated with HPV-related diseases, and access to, and costs of, cervical cancer treatment for many countries. There is also an absence of data for the cost of initiating, scaling up, and maintaining a new adolescent vaccination program.