Sabin Vaccine Institute Project

MT Valenzuela, U de los Andes, Chile
F de la Hoz, U Nacional, Colombia
E Koumans, CDC, USA
G Cavada, U de Chile y de los Andes, Chile
MN Labó, NCI Frederick, USA
C Koss, CDC, USA
H Posso, U Militar Nueva Granada, Colombia
D Constenla, Denver, CO, USA
S Goldie, Harvard School of Public Health
N Alvis, U Cartagena, Colombia
M O’Shea, Harvard School of Public Health
S Sweet, Harvard School of Public Health
C Urquidi, U de los Andes Chile
Backgrounds

• The available vaccines, against HVP only include two HR genotypes and two LR genotypes
• LAC didn’t have (2006) a comprehensive and detailed analysis about the proportion of different types of HPV related to general population and with lesions.
• This information is absolutely neccesary to take decisions regarding the possibility to incorporate the vaccines to the EPI in the Región.
Objectives:

- To estimate the burden of disease in LAC:
  - Infection
  - Disease
- To provide the cost effectiveness of vaccines and screening in 6 selected countries, in the prevention of cancer
- To evaluate the quality of the studies included in the Metaanalysis.

Source: Sabin Vaccine Institute Project
Specific Objectives

- To estimate the specific prevalence by type specific virus in normal population and with HPV related lesions.
- In general population Type specific and age specific groups
- To estimate the incidence of HPV infections by types and age-group
- To estimate the proportion of Cancer attributable to HPV
- To summarize the prevalence of some risk factor associated to HPV infection and disease

Source: Sabin Vaccine Institute Project
Method

Systematic Review and Data Extraction

Others Sources of Information
“Grey” Literature
Unpublished Reports

Summary of the Epidemiological Virological Quality Data
(3 electronic databases)

Prevalence: Metaanalysis and Metaregression
Incidence
Burden of Disease
Cost effectiveness of interventions

Source: Sabin Vaccine Institute Project
Prevalence

• General Prevalence was estimated using fixed effects: each study was weighted by the inverse of the variance of the reported prevalence
• Prevalence by Age Group was estimated using mixed models
• Metaregression was applied to estimate the impact on the prevalence of: sampling methods, type of specimens, quality score of papers and detection methods (HC2 and PCR).
Inclusion Criteria

- Healthy Population-HPV
- CIN 1,2,3-HPV, = or > 30 cases

- Cervical Cancer –HPV, = or >30 cases

- Vulvar Cancer, vagina, penis, anal, oropharynx, = or >10 cases

- Genital Warts, = or > 10 cases

- Recurrent Respiratory Papillomatosis, = or > 10 cases

- Cost and Cost- Effectiveness

Type of Studies:

- Case series,
- Cohort,
- Case-Control,
- Cross-sectional,
- Intervention Studies,
- Clinical Trials,
- Systematic Reviews

Limits:

- Years: 1990- June 2007
- Languages and Ages: without restriction
- Both genders

Source: Sabin Vaccine Institute Project
Exclusion Criteria

First Step:
- Studies not including data from Latin American or Caribbean countries
- Articles published before 1990
- Studies without original data
- Studies from which data could not be extracted

Second Step:
- Studies that used non-molecular techniques for HPV identification
- Studies developed in the same populations

For Lesions:
- All studies that use Hybrid Capture 2 (HC2)

For Analysis
- For age specific group:
  - All studies without at least 3 groups of age

Source: Sabin Vaccine Institute Project
Assessment of study quality

Quality score

A six-items quality score was developed, that evaluated three areas we considered critical for study validity and generalizability, that is:

• Population studied
  ß  Is the study population-based?*
  ß  Is it a multicentric study?*
  ß  What is the sample size?

• Diagnosis of HPV infection
  ß  Which molecular detection technique has been utilized?
  ß  Which type of specimen has been collected?

• Classification of HPV associated lesions**
  ß  Was it confirmed histologically?

Impact Factor

The Impact Factor of the journal where each study was published, was derived from JCR 2006

• first, the quality evaluation was restricted to studies published in indexed journals

• then, all studies were included, and the value zero was assigned to those for which an IF was not available.

*For studies of subject without HPV associated lesions
**For studies of subject with HPV associated lesions
Incidence Data

• Update on HPV type specific incidence from two Latin American cohort studies (Brazil* and Colombia**). Raw data from Guanacaste’s cohort was not available.

• Age groups for analysis: <25, 25-44, 45+.
• Follow up until 8 years in Colombia and 9 years in Brazil
• Type-specific (from taxonomic and epidemiological classifications of HPV types based on Muñoz et al, NEJM 2003 and IARC Monograph 2007).

*Franco Villa, ** Muñoz Posso
Criteria to calculate person-time during the follow-up

<table>
<thead>
<tr>
<th>Woman HPV-DNA (-)</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>Contributes 30 months of follow-up to the denominator of incidence rates on all types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months)</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Woman HPV 16 (+)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Contributes 12 months of follow-up to the denominator of the incidence rate of HPV 16 and 30 months to the incidence rate for the rest of types</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Woman HPV 16/18 (+)</td>
<td>-</td>
<td>-</td>
<td>+16</td>
<td>+18</td>
<td>-</td>
<td>-</td>
<td>Contributes 12 months of follow-up to the denominator of the incidence rate of HPV 16, 18 months to the incidence rate of HPV 18 and 30 months to the incidence rate for the rest of types</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Source: Sabin Vaccine Institute Project
Proportion of Cancer Atributable to HPV

• The current number of HPV related cancers, we estimates from the International Agency for Research on Cancer (IARC).

• The proportion of cervical cancer attributable to HPV was assumed to be 100%. For other cancers we estimated the attributable risk (AR) from case control studies, with this expression:

\[ AR = 1 - \sum_j \frac{p_j}{R_j} \]

• AR= attributable risk, \( p_j \)=proportion of cases in the jth exposure stratum, \( R_j \)= 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.

Burden of HPV in LAC. Methods

- **Number of cases and deaths by Cervical and oropharyngeal cancer:** Incidence rates estimated by the IARC for every country.

- **Number of cases and deaths by anus, penis, vulva/vagina cancer:** No country specific estimate available. Median of the crude incidence rates estimated in the cancer registries across the region (8 countries*) projected over the LAC population for 2005.

*Argentina, Brazil, Colombia, Ecuador, Martinique, C Rica, Peru, Chile.*
Burden of HPV in LAC.

- HPV AR for cervical, anal, pene and vulva/vagina: Parkin and Bray estimates.*
  - Cervical 100%
  - Pene 40%
  - Ano 90%
  - Vulva 40%
  - Vagina ~ Ano

* Vaccine 2006; 24 (Suppl 3)
Burden of HPV in LAC.

• **HPV AR for oropharyngeal cancer:** Estimated using data from Kraimer et al* and D’Souza et al**:

  – 36%.


Results
Flow Diagram of Literature Review- 1

1085 full text requested

→ 279 not retrievable in study timeframe

→ 298 Excluded (reasons specified)

→ 385 Duplicated

123 studies included in database

\[\{\]

120 prevalence studies

3 incidence studies

\[\}]

Source: Sabin Vaccine Institute Project
Prevalence of HPV in Latin America & the Caribbean by Type of Study

N = 123 studies

Source: Sabin Vaccine Institute Project
Prevalence of HPV in LA & tC
According to Sample Characteristics

Source: Sabin Vaccine Institute Project
Prevalence of HPV in LA & tC
According to Sex

- Women: 81%
- Both Sexes: 11%
- Men: 8%

N = 120

Source: Sabin Vaccine Institute Project
Prevalence of HPV in LA & tC
According to Who Took the Sample

Self-sample 8%

Health Worker 92%

N = 119

Source: Sabin Vaccine Institute Project
## Assessment of study quality

### Distribution of Quality Scores, by study population

<table>
<thead>
<tr>
<th>Lesion</th>
<th>No. Studies</th>
<th>Mean Score</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>73</td>
<td>3.41</td>
<td>1.31</td>
</tr>
<tr>
<td>LSIL</td>
<td>38</td>
<td>3.68</td>
<td>1.01</td>
</tr>
<tr>
<td>HSIL</td>
<td>41</td>
<td>3.78</td>
<td>1.04</td>
</tr>
<tr>
<td>CIC</td>
<td>47</td>
<td>4.15</td>
<td>0.88</td>
</tr>
<tr>
<td>All studies</td>
<td>249</td>
<td>3.60</td>
<td>1.21</td>
</tr>
</tbody>
</table>

### Distribution of Impact Factors, by HPV lesion, all studies included.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>No. Studies</th>
<th>Mean FI</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>73</td>
<td>1.63</td>
<td>2.34</td>
</tr>
<tr>
<td>LSIL</td>
<td>38</td>
<td>1.39</td>
<td>1.62</td>
</tr>
<tr>
<td>HSIL</td>
<td>41</td>
<td>1.49</td>
<td>1.74</td>
</tr>
<tr>
<td>CIC</td>
<td>47</td>
<td>4.33</td>
<td>5.91</td>
</tr>
<tr>
<td>All studies</td>
<td>245</td>
<td>2.10</td>
<td>3.30</td>
</tr>
</tbody>
</table>
Prevalence in different type of population
# Prevalence of HPV in Latin America & the Caribbean

According to the Research Question of the Author

<table>
<thead>
<tr>
<th>Study Population</th>
<th># of Studies</th>
<th># of Subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Women</td>
<td>50</td>
<td>38.183</td>
<td>18.6-11.1</td>
</tr>
<tr>
<td>ASCUS</td>
<td>11</td>
<td>294</td>
<td>56.1</td>
</tr>
<tr>
<td>LSIL</td>
<td>27</td>
<td>1.773</td>
<td>79.0</td>
</tr>
<tr>
<td>HSIL</td>
<td>32</td>
<td>1.399</td>
<td>96.8</td>
</tr>
<tr>
<td>ICC</td>
<td>38</td>
<td>2.227</td>
<td>94.0</td>
</tr>
<tr>
<td>Squamous &amp; Unspecified CC</td>
<td>28</td>
<td>1.795</td>
<td>88.0</td>
</tr>
</tbody>
</table>

Source: Sabin Vaccine Institute Project

<table>
<thead>
<tr>
<th>Study Population</th>
<th># of Studies</th>
<th># of Subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>3</td>
<td>277</td>
<td>85.2</td>
</tr>
<tr>
<td>Hombres sanos</td>
<td>7</td>
<td>2.003</td>
<td>21.7</td>
</tr>
<tr>
<td>Ca Pene</td>
<td>2</td>
<td>71</td>
<td>67.8</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>2</td>
<td>158</td>
<td>81.5</td>
</tr>
<tr>
<td>Recurrent Respiratory Papillomatosis</td>
<td>4</td>
<td>93</td>
<td>92.4</td>
</tr>
<tr>
<td>Normal Oral Mucosa</td>
<td>3</td>
<td>43</td>
<td>9.3</td>
</tr>
</tbody>
</table>
Prevalence of HPV Infection in Healthy Women with normal and abnormal cytology

<table>
<thead>
<tr>
<th></th>
<th>Normal Cytology</th>
<th>ASCUS</th>
<th>LSIL</th>
<th>HSIL</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>41</td>
<td>11</td>
<td>27</td>
<td>32</td>
<td>1399</td>
</tr>
<tr>
<td>Women</td>
<td>21.298</td>
<td>294</td>
<td>1.773</td>
<td>38</td>
<td>2227</td>
</tr>
</tbody>
</table>

Source: Sabin Vaccine Institute Project
Median and HPV Prevalence by Age-group in Women with normal citology, Population based (GP) and in clinics (CP). PCR, N = 36
Age-specific HPV prevalence among women with normal cytology

Source: Sabin Vaccine Institute Project
Type-specific HPV Prevalence by age-group in women with normal citology: by PCR
Prevalence of High and Low risk HPV Infection in Healthy Women and According to Type of Lesion. PCR Method

![Graph showing percentages of HPV High Risk and Low Risk in different cytology categories: Normal cytology, ASCUS, LSIL, HSIL. Percentages are: Normal cytology: 10.7% HPV High Risk, 6.1% HPV Low Risk; ASCUS: 35.7% HPV High Risk, 16.1% HPV Low Risk; LSIL: 54.2% HPV High Risk, 4.5% HPV Low Risk; HSIL: 62.4% HPV High Risk, 3.9% HPV Low Risk.]
Prevalence of High and Low risk HPV Infection in Healthy Women and According to Type of Lessions. PCR Method

<table>
<thead>
<tr>
<th></th>
<th>Normal cytology</th>
<th>ASCUS</th>
<th>LSIL</th>
<th>HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td></td>
<td></td>
<td>16.1</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>6.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>35.7</td>
<td></td>
<td>54.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62.4</td>
</tr>
</tbody>
</table>

%
Age-specific Prevalence of High and Low risk HPV among women with normal cytology
Type-specific HPV Prevalence in normal women and with lesions: by PCR

**Normal cytology**

- **v16**: 2.6%
- **v58**: 1.1%
- **v18**: 0.9%
- **v31**: 0.8%
- **v51**: 0.5%
- **v45**: 0.5%
- **v33**: 0.5%

**LSIL**

- **v16**: 5.8%
- **v58**: 6.1%
- **v31**: 4.4%
- **v18**: 3.4%
- **v33**: 3.7%
- **v45**: 2.9%
- **v51**: 1.6%

**HSIL**

- **v16**: 27.9%
- **v58**: 9.3%
- **v31**: 7.7%
- **v18**: 4.8%
- **v33**: 3.4%
- **v31**: 3.4%
- **v45**: 3.7%

**Invasive Cervical Cancer**

- **v16**: 49.3%
- **v18**: 10%
- **v45**: 4.3%
- **v31**: 4.2%
- **v33**: 3.6%
- **v58**: 3.2%
- **v51**: 1.2%
Incidence of HPV infection by age groups per 100 women-year. Combined analysis of J.A. Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Under 25 yr</th>
<th>25-44</th>
<th>45 +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any HPV</td>
<td>16.0</td>
<td>7.5</td>
<td>5.8</td>
</tr>
<tr>
<td>High risk</td>
<td>12.2</td>
<td>5.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Low risk</td>
<td>3.9</td>
<td>2.5</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Source: Sabin Vaccine Institute Project
Incidence of Any HPV infection by age groups.
LA Cohort Studies

Source: Sabin Vaccine Institute Project
Others HPV related cancer. Total number and HPV related proportion.
Discussion

• HPV is related to as much as 85,000 cases of cancer across the region each year.
• Vaccine preventable high risks types account for between 60 to 70% of those cancers.
• A significant proportion of healthy men (22%) are infected with HPV. Its role in containing infection should be considered.
Discussion

• Considerable gaps in the knowledge of HPV epidemiology existed in the region, especially among some high incidence countries.

• However, we are already filling these gaps, thus helping to accelerate the introduction of HPV vaccines.
Acknowledgements

- **Permanent Advisor:** Dr. Eduardo Franco
- **Technical Advisory Team:**
  - Drs. N Muñoz, J Andrus, M Lewis, L Markowitz, X Bosch, C de Quadros
- A large list of Scientific Researches, mainly Dra. L Villa
- **Instituto Nacional de Cancerología, Colombia**
- Ana Carvalho, N Wolff