Brazilian Experience on Translational Medicine:
The successful case of HPV prophylactic vaccines

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Declaration of potential conflict of interest:

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## Diseases attributed to HPV types 6, 11, 16, 18

<table>
<thead>
<tr>
<th>Type 18</th>
<th>Cervical cancer</th>
<th>Clinical endpoints</th>
<th>70 %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIN-2/3</td>
<td></td>
<td>50 %</td>
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<tr>
<td></td>
<td>CIN-1 / ASCUS</td>
<td></td>
<td>30 %</td>
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<tr>
<td></td>
<td>Anal Cancer</td>
<td></td>
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<td></td>
<td>Ca. Vulva / Vagina / Penis</td>
<td></td>
<td>~40 %</td>
</tr>
<tr>
<td></td>
<td>Ca. oropharynx</td>
<td></td>
<td>~3-12 %</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 16</th>
<th>CIN-1 / ASCUS</th>
<th>10 %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genital warts / condylomas</td>
<td>90 %</td>
</tr>
<tr>
<td></td>
<td>Recurrent Respiratory Papillomatosis (RRP)</td>
<td>90 %</td>
</tr>
</tbody>
</table>

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**Attributable fraction**

- Cervical cancer: 70%
- CIN-2/3: 50%
- CIN-1 / ASCUS: 30%
- Anal Cancer: ~70%
- Ca. Vulva / Vagina / Penis: ~40%
- Ca. oropharynx: ~3-12%
- Genital warts / condylomas: 90%
- Recurrent Respiratory Papillomatosis (RRP): 90%
A Common Cancer Among Women in Latin America

Approximately 86,000 women were diagnosed with cervical cancer in 2002 and an estimated 38,000 women died from the disease.
The Seven Most Frequent Cancers in Women

Central & South America

**Incidence**

- Breast: 40.3
- Cervix: 29.2
- Colon/Rectum: 13.2
- Stomach: 11.4
- Lung: 7.6
- Ovary: 7.3
- Corpus: 6.4

**Mortality**

- Breast: 13.9
- Cervix: 13.6
- Stomach: 8.7
- Lung: 7.4
- Colon/Rectum: 7.0
- Liver: 5.1
- Pancreas: 4.2
Prevention of Cervical Cancer

• Screening regularly with Pap tests
  • Programs vary in their effectiveness and coverage and in some areas are non-existent
    • Few relatively well-organised screening programs are primarily located in large urban centers

• Primary prophylaxis - HPV vaccines have provided new and innovative means to help prevent cervical cancer
How Does The HPV Vaccine Work?

- Each injection contains HPV types e.g., 6/11/16/18 (VLPs)
- Recombinant - does not contain live virus
- Intramuscular, 3 injections
Antibody titers generated by L1 VLP vaccine are much higher than observed in natural HPV infections

*Quadrivalent HPV vaccine*

**GMTs comparable between population groups (noninferior; P<0.001)***

- **Females 10–15 years of age**: N = 510
- **Males 10–15 years of age**: N = 506
- **Females 16–23 years of age**: N = 513

* A P value <0.025 supports a conclusion that the specific type anti-HPV response in 10- to 15-year-old adolescents was noninferior to the response in 16- to 23-year-old females.


GARDASIL is a trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.
Safety Profile of HPV Vaccines

- Common adverse reactions include fever, nausea and dizziness; and local injection site reactions

- Serious adverse events were less common and until the date have not been related to vaccine

- The vaccine is not for women who are pregnant

- The vaccine is not therapeutic, and will not protect against diseases caused by other HPV types; important to continue regular cervical cancer screenings
HPV Vaccines Trial Results in Women

• Both the Bivalent (Cervarix, GSK) and the Quadrivalent (Gardasil, MSD) vaccines show a good safety profile and so far have sustained durability (up to 9 years), possibly by generating immune memory.

• Immune responses are potent, observed similarly in different ages and both genders.

• Both vaccines have shown high efficacy rates to prevent the immediate precursors of cervical cancer caused by HPV 16 and 18.

• In addition, the quadrivalent vaccine was shown to be efficaceous against HPV 16 and 18 related vulvar and vaginal premalignant lesions, and to prevent genital warts caused by HPV 6 and 11.
Quadrivalent HPV Vaccine Trials in Latin American Women

- ~6,000 females aged 9 to 24 years old from Brazil, Mexico, Colombia, Costa Rica, Guatemala and Peru participated in the international clinical trial program for the quadrivalent HPV vaccine
Quadrivalent HPV Vaccine Trials results in Latin American Women

- **92.8%** (95% CI: 77.6 to 98.6) efficacy against CIN1 or worse related to HPV types 6, 11, 16 and 18

- **95.3%** (95% CI: 71.0 to 99.9) efficacy against CIN2 or worse related to HPV types 6, 11, 16 and 18

- **100%** (95% CI: 93.3 to 100) efficacy against external genital lesions (VIN, VaIN, Condyloma) related to HPV types 6, 11, 16 and 18

Perez G et al., *Int J Cancer* 122: 1311, 2008
Quadrivalent HPV vaccine in Men

- Randomized (1:1), placebo-controlled
- 3 doses of GARDASIL™ or placebo at 0, 2, and 6 months
- 36 months follow-up

- Heterosexual men (HM) n= 3,400
  - 16-23 year old
- Men having sex with men (MSM) n= 600
  - 16-26 year old

J. Palefski, A. Giuliano, EUROGIN, Montecarlo, Feb 2010
Number of subjects enrolled by country

HM = heterosexual men; MSM = men having sex with men.
GARDASIL in Men: Efficacy Against HPV 6/11/16/18-Related External Genital Lesions

Per-Protocol Efficacy Population

![Graph showing efficacy results](chart)

- **90.4% Reduction (69, 98)**
- **3 Related Cases**
- **31 Placebo Related Cases**

**HPV 6-, 11-, 16-, or 18-Related External Genital Lesions**

n=1397  n=1408

Quadrivalent HPV Vaccine approved in 117 countries (includes 27 GAVI-eligible) and recommended by numerous local and global physician associations.
Vaccine Introduction aspects

- Competing priorities for immunization resources
- Cost of the vaccine
- The “affordability” of the vaccine to the country
- The behavior of other countries in the region and the world;
- The strength of internal advocacy for introduction of the vaccine into the public sector;
- Influence of global and local vaccine producers
Quadrivalent HPV Vaccine Indications in Latin America

- **Brazil**
  - Females: 9 - 26
  - Males: N/A

- **Ecuador**
  - Females: 9 - 45
  - Males: 9 - 26

- **Argentina**
  - Females: 16 - 26
  - Males: 9 - 15

- **Peru**
  - Females: 9 - 26
  - Males: N/A

- **Chile**
  - Females: 9 – 45
  - Males: N/A

- **Guatemala and Honduras**
  - Females: 9 - 45
  - Males: N/A

- **El Salvador, Costa Rica, Panama and Nicaragua**
  - Females: 9 - 26
  - Males: N/A

- **Mexico**
  - Females: 9-45
  - Males: 9-26

- **Colombia**
  - Females: 18 - 26
  - Males: 9 - 17
HPV Vaccine Implementation in Latin America

- HPV vaccine delivery varies by country according to the existing infrastructure and competing health priorities.

- Panama has a national program to vaccinate 11-12 yrs old girls. Mexico has recently launched public immunization for girls between 11 and 13 yrs at 0, 2 and 60 months.

- Brazil has not issued recommendations and as for several other Latinamerican countries the HPV vaccine is available only in the private sector.
Potential impact of HPV Vaccine Introduction in Developing Countries

- Most women in the developing world are never screened and do not receive effective treatment when they present with disease. Therefore, cervical cancer continues to be #1 cause of cancer death in women in most of the developing world.

- Introduction of HPV prophylactic vaccines could change this scenario, but may be more difficult to introduce than in developed countries.

- Primary problem will be economic: current vaccines at $10/child are seen to be a problem.
Vaccine Introduction: facilitators

- Local epidemiology and burden of disease
- Successful demo projects in country/region
- Economic modeling of cost effectiveness and impact
- Level of knowledge about the disease and the vaccine in the medical community, the public and the media
- Global and regional WHO recommendations*
Primary and Secondary Prevention of Cervical Cancer: WHO Recommendations

- WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and recommends that routine HPV vaccination should be included in national immunization programs.

- HPV vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer and other HPV-related diseases.

- Opportunities to link introduction of vaccine to other programs targeting young people should be sought.

Primary and Secondary Prevention of Cervical Cancer: **WHO Recommendations**

- Introduction of vaccine should not undermine or divert funding from effective screening programs.

- HPV vaccination should not be deferred if at least 1 of these interventions cannot be implemented at the time that vaccination could be introduced.

The Solution: Comprehensive Cervical Cancer Control

Growing Evidence of HPV in Non-Cervical Diseases

• Vulvar cancer and precancerous or dysplastic lesions

• Vaginal cancer and precancerous or dysplastic lesions

• Genital warts (condyloma acuminata)
Conclusions

- Recommendations and funding actions demonstrate international support for vaccination of girls and young women against HPV.
  - Vaccinate before sexual debut, but benefit to vaccinating girls/women after sexual debut (9-26 year old girls/women).
  - HPV test not required prior to vaccination; Vaccinate regardless of previous HPV infection or abnormal Pap test.
  - Continue cervical cancer screening after vaccination.

In the absence of an immune correlate for protection, sustained efficacy can only be determined by disease endpoints.

Durability of vaccine protection will only be known in years.
“Scientific data is essential but it is not enough. Without political support, these large-scale public health programmes will not be implemented.”