Leading the way for the prevention of cervical cancer and beyond

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FHS- AUB
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Points to be covered

- HPV: Epidemiology and burden
- Impact of HPV on disease progression and outcomes
- Vaccines and the public health challenge of primary prevention
- Recommendations

DISCLOSURE
1. Human papillomavirus

- HPV is a relatively small virus containing circular double-stranded DNA within a spherical shell (capsid)
- HPVs infect cutaneous epithelium (skin) and mucosal epithelium (e.g. cervical and other anogenital mucosae)

HPV infections of the genital tract

- The most common genital infection worldwide\(^1,2\)
- Sexually transmitted (non-sexual transmission is less frequent)\(^1\)
- Mostly clinically silent and self-limiting\(^1\)
- Some women remain persistent carriers of the viral infection and become at high risk of progression to precancer and cancer of the cervix, vulva, vagina and anal canal\(^1,3\)
- May cause cancers in the penis and anal canal\(^3\)
- Cancers at other sites\(^3\)

1. Trottier H & Franco EL. *Am J Manag Care* 2006; **12**:S462–472;
<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>10.4% (10.2-10.7)</td>
</tr>
<tr>
<td>Africa</td>
<td>22.1% (20.9-23.4)</td>
</tr>
<tr>
<td>Central and South America &amp; The Caribbean</td>
<td>13.0% (12.4-13.5)</td>
</tr>
<tr>
<td>Europe</td>
<td>8.1% (7.8-8.4)</td>
</tr>
<tr>
<td>Asia</td>
<td>7.9% (7.5-8.4)</td>
</tr>
</tbody>
</table>

2. Burden of the oncogenic and low-risk HPV types

- At least 30 HPV types target the genital mucosa\(^1\)
- At least 15 HPV types are classified as \textit{oncogenic} (high risk)\(^1\)
  - Globally, HPV types 16 and 18 together account for > 70\% of cervical cancer cases\(^1,2\)
  - The next most common oncogenic HPV types are 45, 31 and 33*\(^1,2\)

* In descending order of global prevalence in cervical cancer tissue.

2. Bosch FX \textit{et al.} \textit{Vaccine}. 2008; 26S:K1–K16;
Low risk HPV and burden of genital warts

- Non-oncogenic or ‘low-risk’ HPV types can cause benign condylomata acuminata, i.e. genital warts\(^1\)
- ‘Low-risk’ HPV types are rarely associated with severe cervical dysplasia or cervical carcinoma and commonly manifest as external genital warts\(^1\)
- Two low-risk HPV types, 6 and 11, are found in more than 90% of genital warts\(^1,2\)

Oncogenic HPV and burden of cervical cancer

- 500,000 women diagnosed per year\(^1\)
- Worldwide, every 2 minutes a woman dies of cervical cancer\(^1\)
  - 270,000 deaths (data from GLOBOCAN 2002)\(^1\)
  - In less-developed regions, cervical cancer remains the leading cause of cancer deaths in women
  - Projections indicate > 1 million new cases of cervical cancer each year by 2050\(^2\)
- Despite the impact of screening in a large number of countries, women continue to be at risk\(^3\)

3. Risk behavior
Determinants of risk of HPV infection

- HPV infections are very common
- The cumulative risk of acquiring cervical HPV infection in women with only one sexual partner is **46%** (3 years after first sexual encounter)\(^1\)
- The risk of oncogenic HPV infection is high even after first intercourse and continues throughout a woman’s sexually active lifetime\(^2-4\)

4. Impact on disease progression
HPV lifecycle in the cervix

Cervical canal

- Mature squamous layer
- Squamous layer
- Parabasal cells
- Basal (stem) cells

Basement membrane

Normal epithelium

Infected epithelium

- Virus particles are assembled and virus released
- Virus uses host cell to replicate viral DNA and express virally encoded proteins
- HPV infects basal layer of cervical epithelium

Disease progression

- For every 1 million women infected with HPV:
  - 100,000 will develop precancerous changes (cervical dysplasia)*
  - 8,000 will develop carcinoma in situ (CIS)*
  - 1,600 will develop invasive cervical cancer if dysplasia and CIS are not detected or treated*

- Cervical cancer is a **relatively rare** outcome of a common oncogenic HPV infection

- Over 80% of HPV infections are transient, asymptomatic and resolve spontaneously

* Highest estimate based on model without screening.

5. Leading the way to primary prevention?

- Vaccinate?
- OR
- Screen?
- OR
- Vaccinate and screen?
### Characteristics of Current HPV Vaccines

<table>
<thead>
<tr>
<th></th>
<th><strong>Quadrivalent</strong></th>
<th><strong>Bivalent</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Quadrivalent recombinant vaccine prepared from HPV L1 protein VLPs</td>
<td>Bivalent recombinant vaccine prepared from HPV L1 protein VLPs</td>
</tr>
<tr>
<td><strong>HPV types</strong></td>
<td>6, 11, 16, 18</td>
<td>16, 18</td>
</tr>
<tr>
<td><strong>Concentrations per dose (mcg)</strong></td>
<td>20/40/40/20</td>
<td>20/20</td>
</tr>
<tr>
<td><strong>VLP preparation</strong></td>
<td>Yeast Proprietary assembly/reassembly process increasing stability</td>
<td>Insect cell substrate</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>AAHS Amorphous aluminum hydroxyphosphate sulfate (Merck and Co., Inc.)</td>
<td>AS04 Aluminum hydroxide + 3-O-desacyl-4’-monophosphoryl lipid A (MPL, Corixa/GSK)</td>
</tr>
<tr>
<td><strong>Adjuvant dose</strong></td>
<td>225 mcg</td>
<td>500 mcg/50 mcg</td>
</tr>
</tbody>
</table>

VLP = virus-like particle.

QV: Cervical precancers and cancers, anogenital warts, vulvar and vaginal precancers and cancers

0, 2, 6 IM injections

BV: Cervical precancers and cancers

0, 1, 6 IM injections
The quadrivalent HPV vaccine has shown efficacy against HPV 6/11/16/18-related CIN and AIS (Phase III)

- Per-protocol population (protocols 007, 013 and 015):

<table>
<thead>
<tr>
<th>Endpoint*</th>
<th>Quadrivalent HPV vaccine cases (n = 9,075)</th>
<th>Placebo cases (n = 9,075)</th>
<th>Vaccine efficacy, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6-/11-/16-/18-related CIN or AIS</td>
<td>9</td>
<td>225</td>
<td>96</td>
<td>92–98</td>
</tr>
<tr>
<td>By type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 6-related</td>
<td>0</td>
<td>47</td>
<td>100</td>
<td>92–100</td>
</tr>
<tr>
<td>HPV 11-related</td>
<td>0</td>
<td>12</td>
<td>100</td>
<td>65–100</td>
</tr>
<tr>
<td>HPV 16-related</td>
<td>8</td>
<td>137</td>
<td>94</td>
<td>89–98</td>
</tr>
<tr>
<td>HPV 18-related</td>
<td>1</td>
<td>61</td>
<td>98</td>
<td>91–100</td>
</tr>
<tr>
<td>By disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN1</td>
<td>7</td>
<td>170</td>
<td>96</td>
<td>91–98</td>
</tr>
<tr>
<td>CIN2/3</td>
<td>2†</td>
<td>110</td>
<td>98</td>
<td>93–100</td>
</tr>
<tr>
<td>AIS</td>
<td>0</td>
<td>7</td>
<td>100</td>
<td>31–100</td>
</tr>
</tbody>
</table>

AIS = adenocarcinoma in situ.
Quadrivalent HPV vaccine efficacy (per-protocol susceptible population): Phase III trial (3.6 years)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine efficacy, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16/18 CIN2/3 or AIS</td>
<td><strong>98.2</strong> (93.5–99.8)</td>
</tr>
<tr>
<td>HPV 16/18 CIN3</td>
<td><strong>96.9</strong> (88.4–99.6)</td>
</tr>
<tr>
<td>HPV 16/18 AIS</td>
<td><strong>100</strong> (30.6–100.0)</td>
</tr>
</tbody>
</table>

Per-protocol susceptible population: women with no virological evidence of infection with HPV 16 or HPV 18 through 1 month after the third dose (Month 7), case counting started 30 days after third dose.

n = 8,493 (vaccine group); 8,464 (placebo).

Quadrivalent HPV vaccine Protocol 019:
24–45-year-old women (2.2 years’ mean follow-up)

- Combined incidence of infection (≥ 6 months) and disease (including CIN, VIN, VaIN; cervical, vulvar and vaginal cancer and genital warts)

<table>
<thead>
<tr>
<th>PPE population *</th>
<th>Quadrivalent HPV vaccine</th>
<th>Placebo</th>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Cases</td>
<td>n</td>
</tr>
<tr>
<td>HPV 16/18/6/11</td>
<td>1,615</td>
<td>4</td>
<td>1,607</td>
</tr>
<tr>
<td>HPV 16/18</td>
<td>1,601</td>
<td>4</td>
<td>1,579</td>
</tr>
<tr>
<td>HPV 6/11</td>
<td>1,329</td>
<td>0</td>
<td>1,323</td>
</tr>
</tbody>
</table>

* Per-protocol susceptible population: women with no virological evidence of infection with HPV 16 or HPV 18 through 1 month after the third dose (Month 7), case counting started 30 days after third dose.
VaIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia.
Proportion of new clients with Warts per quarter change

Vaccination program commences July 2007

-25.1, P=< 0.001
P for change<0.001

+1.8% P=0.03
+1.0% P = 0.43
-4.7% P=0.34

Women<28
Women ≥28
HSV
QV efficacy

- Combined analysis of phase II trial of the QV vaccine, 1 phase II trial of a monovalent HPV-16 vaccine and the 2 phase III trials of the QV vaccine ➔ an efficacy of 99% (95% CI, 93–100%) for the composite end-point of CIN2 or CIN3 or AIS after 3 years of FU among women naive to the relevant type at baseline who had received all 3 doses

  (Ault, Lancet, 07)
# Bivalent HPV vaccine: high efficacy confirmed up to 6.4 years against HPV 16/18 CIN2+ (Phase IIb, women aged 15–25 years)

<table>
<thead>
<tr>
<th></th>
<th>HPV 16/18-related CIN2+</th>
<th>Bivalent HPV vaccine</th>
<th>Control</th>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial efficacy study</strong></td>
<td>2.3 years(^1)</td>
<td>0</td>
<td>3</td>
<td>NA*</td>
</tr>
<tr>
<td><strong>Combined analysis of initial efficacy study and extended follow-up</strong></td>
<td>4.5 years(^2)</td>
<td>0</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>5.5 years(^3)</td>
<td>0</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>6.4 years(^4,5)</td>
<td>0</td>
<td>9</td>
<td>100</td>
</tr>
</tbody>
</table>

* The initial efficacy study was not powered to calculate vaccine efficacy against histopathologically confirmed CIN.

\(n = \) number of subjects reporting at least one event in each group. ITT analysis.

Bivalent HPV vaccine efficacy in TVC-naïve: final analysis of Phase III trial (39.4 months)

The TVC-naïve cohort approximates adolescent girls pre-exposure

Primary analysis (TVC-naïve)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>Vaccine Efficacy (96.1%CI)</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CIN2+ HPV-16/18</strong></td>
<td>HPV</td>
<td>5,449</td>
<td>1</td>
<td>98.4</td>
<td>98.4</td>
<td>90.4</td>
<td>100</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5,436</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CIN3+ HPV-16/18</strong></td>
<td>HPV</td>
<td>5,449</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>64.7</td>
<td>100</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5,436</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

vaccine cross-protection

- **BV**: High vaccine efficacy against combined non-vaccine HPV types substantiated by cross-protection against 31, 33 and 45 individually (TVC)
- 100% cross-protective efficacy against CIN2+ caused by non-vaccine HPV types 31/45 (TVC-naïve)

**QV**

- Cross-protection against CIN2+ or adenocarcinoma in situ:
  - naïve to 14 oncogenic HPV types
    - 70.0% cross-protective efficacy against HPV 31
- Overall efficacy was 42.7% against CIN2+ and 82.8% against genital warts irrespective of HPV type (RMITT-2 cohort)
- Clinical implication???
Rapid and Strong Anamnestic Response to Antigen Challenge

- **Anti-HPV 16**

  GMT = geometric mean titer.

  aSimilar response with the other 3 types of HPV within vaccine.

Safety: Vaccine Adverse Event Reporting System (VAERS)

- As of December 31, 2008
  - >23 million doses of QV distributed in the United States
  - 11,916 VAERS reports of adverse events following vaccination in the US
  - 94% were reports of events considered to be nonserious

- Bivalent vaccine had a clinically acceptable safety profile similar to that of other vaccines licensed and in general use

HPV = Human Papillomavirus; CDC=Centers for Disease Control and Prevention; FDA=Food and Drug Administration.
Screening prevention of cervical cancer

- Screening programmes vary widely between countries
- HPV DNA testing may be used to detect existing HPV infection
- BUT...Neither method offers 1ry prevention; HPV infection and cervical disease can still occur
  - Deaths from cervical cancer still occur in countries with established screening programmes
- Vaccination offers an important new management option in the primary prevention of cervical cancer

Is there a case for Lebanon?

- Screening: Opportunistic
- Burden is HPV: Sexual activity, Adolescents into adults
- Very good vaccine campaigns
- Utilization of services of RA women
- Quality and type of screening?
- Cost- effectiveness: Naïve, 70%, >10 years

<table>
<thead>
<tr>
<th>Country</th>
<th>Screening modality (1960s–1990s)</th>
<th>Decrease in cervical cancer mortality,1960s–1990s*, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>Organized</td>
<td>82</td>
</tr>
<tr>
<td>Swede n</td>
<td>Organized</td>
<td>65</td>
</tr>
<tr>
<td>Norway</td>
<td>Opportunistic</td>
<td>41</td>
</tr>
</tbody>
</table>
Lebanese recommendations

- Pre-adolescent 11- adult females 26
- Joint tasks (Intersociety + Government support)
- Two vaccines options
- Routine screening continues
- Clinic-based→ school-based
The way to primary prevention?

- Vaccinate?
- OR
- Screen?
- OR
- Vaccinate and screen?