Global HPV Disease Burden: Rationale for Vaccine

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Muscat, September 2011
Presentation Outline

- HPV Disease Burden
  - Global
  - Regional
- What do we have against HPV Related Cancers?
- Recommendations.
- Gardasil study results:
  - 9-26 CC
  - GW & Other Cancers
  - 26-45 Efficacy
  - Male Efficacy
- Real-Life Impact
- Summary
- Discussion:
  - Cross – Protection
  - Duration of Protection
HPV Causes More Than Cervical Cancer

Global HPV Prevalence in Females With Normal Cytology: A Meta-Analysis

- HPV infects ~660 million individuals worldwide.

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2008 Cervical Cancer Incidence and Mortality Estimates by Region

Worldwide incidence = 530,232
More developed countries = 76,701—Less developed countries = 453,531

*Incidences for Melanesia (724), Micronesia (24), and Polynesia (48) not shown on maps. More developed countries defined as North America, Japan, Europe, and Australia/New Zealand.
Estimated Cervical Cancer Incidence - 2008

GLOBOCAN 2008 (IARC)
Worldwide Prevalence of HPV Types in Cervical Cancer*.

* A pooled analysis and multicenter case control study (N = 3607)

HPV Causes Multiple Cancers in Men and Women

- Penile Cancer: 1000
- Vulvar & Vaginal Cancer: 3,700
- Anal Cancer: 1,600 (males), 2,800 (females)
- H&N Cancer: 11,600 (males), 2,300 (females)
- Cervical Cancer: 23,000 (males), 292,000 (females)
- Genital warts: 329,000 (males), 292,000 (females)

Annual new cancers and genital warts cases related to HPV 6,11,16 and/or 18 in Males and Females in Europe

Annual number of new cancer cases calculated based on crude incidence rates from IARC database (1998-2002) and population estimate Eurostat 2008; estimate Globocan 2008 for cervical cancer; published HPV prevalence rates were applied (for Europe, when available) Genital warts estimates based on incidence rates in UK, HPA 2007
HPV and Anogenital Warts

- HPV 6 and 11 responsible for >90% of anogenital warts.\(^1\)
- Clinically apparent in \(\sim\)1% of sexually active US adult population.\(^2\)
- Estimated lifetime risk of developing genital warts \(\sim\)10%.\(^3\),\(^4\)
- >75% of sexual partners develop warts when exposed.\(^5\)
- Topical and surgical therapies available for genital warts.\(^6\)
  - Treatment can be painful and embarrassing.\(^7\)
  - Recurrence rates vary greatly.\(^6\)
    - As low as 5% with podofilox or laser treatment
    - As high as 65% with other treatments
  - Negative impact on quality of life.\(^8\)

• The tools to help fighting against HPV Related cancers are available today.¹

The Solution: Comprehensive Cancer Control

**Primary Prevention**
Education, behavior modification, and HPV vaccination.\(^1\) HPV Vaccination offers the opportunity to help prevent cervical dysplasia and cancer caused by HPV types 6, 11, 16, and 18.\(^2\)

**Secondary Prevention/Screening**
Cervical cancer screening is important for the detection of cervical disease and appropriate disease management.\(^1\)

**Treatment**
Women with cervical precancers can be treated with relatively simple procedures to prevent cancer; women with invasive cancer often require surgery, radiation, or chemotherapy.\(^1\)

**Palliative Care**
Women with advanced cervical cancer suffer from pain and other morbidity; palliative care can reduce suffering by providing symptomatic relief and compassionate support.\(^1\)

*Improving awareness and education about HPV infection and cervical cancer can reduce high-risk sexual behaviors. Implementation of local strategies can change behavior and decrease risk.*\(^1\)

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WHO Recommendation

- Identification of a viral agent such as HPV as a major cause of diseases implies that prophylactic vaccines or interventions against the viral agent should prevent the disease(s) it causes.

- This is the first WHO position paper on vaccines against diseases caused by human papillomaviruses (HPVs).
- Diseases caused by HPVs include cancers of the cervix, vagina, vulva, penis and anus; a subset of head and neck cancers; anogenital warts; and recurrent respiratory papillomatosis.
- 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 programmes….
15 years ago in Cairo for the landmark Int. Conf. on Population and Development (ICPD). Sexual and reproductive health was embraced as a basic human right.¹

Cervical cancer is the 2nd most common cancer in women worldwide. Over 80% of the deaths from cervical cancer occur in the developing world where access to cytology-based screening programs is minimal or absent.¹

The development of these vaccines is among the great recent accomplishments in preventive medicine……¹

Education of both health professionals and communities about prevention of cervical cancer through both vaccination and screening strategies is an obligation of health professionals…..²

The development and maintenance of screening strategies must be addressed for women regardless of vaccination strategy, due to the ongoing risk for unvaccinated women, women who were exposed prior to vaccination, or those with an uncovered oncogenic HPV subtype……²

Development of community/national/NGO/WHO partnerships is needed to create affordability for vaccination and screening programs to prevent cervical cancer.²

Obstetrician/Gynecologists have an obligation to advocate for vaccination and screening and to assist in the creation of coalitions to address prevention of cervical cancer.²

¹.http://www.figo.org/publications/hpv_supplement
## Summary of Organizational Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>ACOG</th>
<th>AAFP</th>
<th>SAM</th>
<th>AAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine vaccination in females 11-12 years old &amp; catch-up vaccination in 13-26 year olds</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Females 9-10 years old may be vaccinated</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Vaccinate regardless of previous HPV infection or abnormal Pap test results</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Continue Pap testing after vaccination</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

ACOG : American College of Obstetricians and Gynecologists  
AAFP : American Academy of Family Physicians  
SAM : Society for Adolescent Medicine  
AAP : American academy of Ped.
GARDASIL™ [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

GARDASIL: FUTURE I/II End-of-Study Efficacy Against HPV 6/11/16/18-Related CIN 2/3 or AIS

Per-Protocol Efficacy Population

- **Total**
  - GARDASIL: 110
  - Placebo: 120

- **HPV 6/11/16/18 Related**
  - GARDASIL: 2
  - Placebo: 8

- **HPV 16 Related**
  - GARDASIL: 81
  - Placebo: 81

- **HPV 18 Related**
  - GARDASIL: 0
  - Placebo: 29

Women 16–26 years of age followed up through 3–4 years

- One case was a coinfection with HPV 52; the other was a coinfection with HPV 51 and 56.
- AIS = adenocarcinoma in situ; CIN = cervical intraepithelial neoplasia.
GARDASIL™ [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

GARDASIL: FUTURE I/II End-of-Study Results
Efficacy Against HPV 6/11/16/18-Related External Genital Lesions¹-³

Per-Protocol Efficacy Population

- **Total**
  - GARDASIL: 227
  - Placebo: 190

- **HPV 6/11/16/18-Related EGL**
  - GARDASIL: 2
  - Placebo: 2
  - 99% Reduction (97, 100)
  - n = 7,900

- **Genital Warts**
  - GARDASIL: 2
  - Placebo: 28
  - 99% Reduction (96, 100)
  - n = 7,665

- **VIN 1, ValN 1**
  - GARDASIL: 0
  - Placebo: 28
  - 100% Reduction (86, 100)
  - n = 7,665

- **VIN 2/3, ValN 2/3**
  - GARDASIL: 0
  - Placebo: 23
  - 100% Reduction (83, 100)
  - n = 7,900

Women 16–26 years of age followed up through 3–4 years

EGL = external genital lesion; ValN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia.
WORLDWIDE AGE-SPECIFIC HPV PREVALENCE
WOMEN FROM GENERAL POPULATION

No HPV free decade / Lasting protection is essential

DE SANJOSÉ, DIAZ, CASTELLSAGUE ET AL. Lancet ID, 2007
GARDASIL™ [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

GARDASIL: Adult Women Efficacy Study

Combined Incidence of HPV 6/11/16/18-Related Persistent Infection or Cervical/Vulvar/Vaginal Disease¹

Per-Protocol Efficacy Population—a – Primary Endpoint

Mean Follow-Up: 3.8 Years

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total</th>
<th>GARDASIL Reduction (78, 95)</th>
<th>Placebo Reduction (58, 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24- to 45-Year-Olds</td>
<td>10</td>
<td>89%</td>
<td>84%</td>
</tr>
<tr>
<td>24- to 34-Year-Olds</td>
<td>5</td>
<td>91%</td>
<td>84%</td>
</tr>
<tr>
<td>35- to 45-Year-Olds</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Efficacy after 3 doses in women 24–45 years of age naïve to the relevant type at baseline.

GARDASIL in Males: Efficacy Against HPV 6/11/16/18-Related External Genital Lesions

Per-Protocol Efficacy Population

90.6% Reduction (70, 98)

32

3

n=1,394  n=1,404
HPV 6-, 11-, 16-, or 18-Related External Genital Lesions

### Effectiveness Against HPV 16/18-Related CIN 2 or Worse

**Per-protocol population, women followed for up to 7 years**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Cohort 1 (N=2,650)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>HPV 16/18-Related CIN 2 or Worse</td>
<td>1,080</td>
</tr>
<tr>
<td>By HPV Type</td>
<td></td>
</tr>
<tr>
<td>HPV 16-Related CIN 2 or Worse</td>
<td>921</td>
</tr>
<tr>
<td>HPV 18-Related CIN 2 or Worse</td>
<td>1,032</td>
</tr>
<tr>
<td>By Lesion Type</td>
<td></td>
</tr>
<tr>
<td>CIN 2</td>
<td>1,080</td>
</tr>
<tr>
<td>CIN 3 or Worse</td>
<td>1,080</td>
</tr>
<tr>
<td>CIN 3</td>
<td>1,080</td>
</tr>
<tr>
<td>AIS</td>
<td>1,080</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>1,080</td>
</tr>
</tbody>
</table>

†Vaccine effectiveness measures the relative reduction of the disease incidence in vaccine recipients compared to the baseline incidence rate of 0.0287 per 100 person-years established from the incidence rate in an unvaccinated cohort and under the assumption vaccine efficacy is 90%.

Not enough follow-up time was accrued in any time interval since Day 1 to draw conclusions from the results of the analysis.

Adolescent Long-Term Follow-Up: Study Design

Gardasil

Base Study
1,184 boys and girls aged 9 to 15 randomized to Gardasil

Long-term Follow-up Study
Early Vaccination Group
N = 1,179

Base Study
597 boys and girls aged 9 to 15 randomized to Placebo

Long-term Follow-up Study
Catch up Vaccination Group
N = 482

First interim analysis for effectiveness
1.8 years follow-up post Month 42
Vaccine Effectiveness for HPV6/11/16/18-related Infection and Disease (all Subjects with Follow-up)¹

Per-protocol population, followed for 6 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Early Vaccination Group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Persistent Infection</td>
<td>157</td>
</tr>
<tr>
<td>HPV 6</td>
<td>157</td>
</tr>
<tr>
<td>HPV 11</td>
<td>157</td>
</tr>
<tr>
<td>HPV 16</td>
<td>157</td>
</tr>
<tr>
<td>HPV 18</td>
<td>157</td>
</tr>
<tr>
<td>CIN (any grade)</td>
<td>158</td>
</tr>
<tr>
<td>GW, VIN, VaIN</td>
<td>208</td>
</tr>
</tbody>
</table>

n = number of subjects who have at least one effectiveness follow-up visit after Month 42.

*EVG represents 6 years post-vaccination of Gardasil

GARDASIL™ [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

GARDASIL: Protects Against Diseases Caused by HPV Types 6/11/16/18

- **In young adult women**, high efficacious in preventing HPV 6/11/16/18-related
  - Cervical cancer (CIN 2/3 and AIS)
  - Vulvar and vaginal cancer (VIN 2/3, VaIN 2/3)
  - Genital warts

- **In women age 24-45 years**, highly efficacious in preventing persistent infection, cervical, vulvar, and vaginal disease caused by HPV 6/11/16/18

- **In young adult men**, highly efficacious in preventing anal cancer, AIN and genital warts caused by HPV types 6/11/16/18 in young adult men

- **Sustained efficacy for up to 7 years**

AIS = adenocarcinoma in situ; CIN = cervical intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia.
Objective: Assess safety and immune response in adolescents.

Methods: 1781 boys and girls randomized 2:1 to vaccine or saline placebo.

Conclusions: Vaccination well tolerated and results in robust immune response. *PIDJ, 2007*
Postlicensure Safety Profile Review of GARDASIL

Based on a CDC-FDA report analyzing adverse events following administration of GARDASIL from June 2006 through December 2008.

“The findings were generally not that different from what is seen in the safety reviews of other vaccines recommended for a similar age group, 9 to 26 years old (meningitis and Tdap).

Based on the review of available information by FDA and CDC, the HPV vaccine continues to be safe and effective, and its benefits continue to outweigh its risks.”

CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration.
Australia National Quadrivalent HPV Vaccination Program

- From April 2007:
  - school-based 12-13yo girls – ongoing.

- From July 2007:
  - community-based 18-26yo women – to end 2009.
Australia: Impact of GARDASIL on Genital Warts: Analysis of National Sentinel Surveillance Data

• Methods
  – new patients attending eight sexual health services in Australia between January 2004, & December 2009
  – Obtained data for demographic factors, frequency of genital warts, HPV vaccination status and sexual behavior
  – Used $\chi^2$ analysis to identify significant trends in proportions of patients diagnosed with warts in periods before and after vaccination began
  – Primary group of interest was female Australian residents who were eligible for free vaccination (12yrs – 26 yrs)

Donavan et. al. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. www.thelancet.com/infection Published online November 9, 2010 DOI:10.1016/S1473-3099(10)70225-5
Proportion of women of free vaccine eligible age with genital warts, by resident status, 2004-2010

High grade cervical abnormalities in young Victorian women, by age group, 2003-2009

Red lines = Lowess smoothing
Quadrivalent HPV Vaccine

- Broad Indications:
  - Cervical,
  - Vulvar
  - Vaginal Cancer
  - Genital Warts

- Proven long term efficacy: at least 7 years

- The only vaccine with real-world data available.
  (73% reduction in genital warts)
GARDASIL™ [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

GARDASIL Approved in 124 Countries (Includes 31 GAVI-Eligible Countries)

Caribbean & Central America:
- Costa Rica
- Puerto Rico
- Guatemala
- Curacao
- Bermuda
- Bahamas
- Barbados
- Jamaica
- Trinidad & Tobago
- El Salvador
- Honduras
- Nicaragua
- Panama
- Cayman Islands
- Aruba
- Dominican Republic

North America:
- USA
- Canada
- Mexico

Europe:
- Germany
- France
- UK
- Spain
- Italy
- Austria
- Belgium
- Bulgaria
- Portugal
- Slovenia
- Montenegro
- Bosnia
- Croatia
- Herzegovina
- Czech Republic
- Denmark
- Estonia
- Finland
- Greece
- Iceland
- Romania
- Sweden
- Switzerland
- Turkey
- Macedonia
- Montenegro

Asia Pacific:
- Kyrgyzstan
- Uzbekistan
- Kazakhstan
- Australia
- Indonesia
- Korea
- Taiwan
- Hong Kong
- Singapore
- New Zealand
- Macau
- Malaysia
- Philippines
- Thailand
- India
- Vietnam
- Fiji
- Bhutan
- Georgia
- Japan

GAVI – Eligible Registration Approvals (31): Bolivia, Burkina Faso, Cameroon, Central African Republic, Chad, Congo (Brazzaville), Congo (DR), Cote d’Ivoire, Ethiopia, Georgia, Guinea (Conakry), Honduras, India, Indonesia, Kenya, Malawi, Mauritania, Nicaragua, Pakistan, Togo, Uganda, Ukraine, Vietnam, Bhutan, Kyrgyzstan, Mali, Nigeria, Tanzania, Uzbekistan, Rwanda, Zambia

Middle East & Africa:
- Gabon
- Israel
- Morocco
- Kenya
- Mauritania
- Guinea Eq.
- Uganda
- Malawi
- Jordan
- Cote d’Ivoire
- Chad
- South Africa
- Pakistan
- Guinea Conakry
- Namibia
- C.A.R.
- Mauritius
- Kuwait
- UAE
- Ethiopia
- Togo
- Congo Brazzaville
- Egypt
- Botswana
- Bahrain
- Tanzania
- Cameroon
- Tunisia
- Saudi Arabia
- Rwanda
THANK YOU
Clinical efficacy and duration of protection:

Since the immunological correlates of vaccine protection are unknown and the development of cervical cancer may occur decades after HPV infection, regulatory authorities have accepted the use of CIN grade 2 or 3 (CIN2–3) and AIS as clinical end-points in vaccine efficacy trials……
Correlation Between Antibodies and Efficacy: WHO Statement

World Health Organization

GUIDELINES TO ASSURE THE QUALITY, SAFETY AND EFFICACY OF RECOMBINANT HUMAN PAPILLOMAVIRUS VIRUS-LIKE PARTICLE VACCINES

- No serologic correlate of short-term or long-term protection has been established for any HPV VLP type.\(^1,2\)
- Therefore, no known minimal level of HPV antibodies that confers protection from HPV\(^1,3\)

C.1 Immune responses to the vaccine

- Induction of immune memory should be assessed by means of evaluating immune responses to additional doses of vaccine administered at planned intervals following completion of the primary series;
Assessment of Population Impact and Cross-Protection
Key Questions

• What are the drivers of population impact efficacy estimates with prophylactic HPV vaccines?

• What is the contribution of non-vaccine and vaccine HPV types to population impact estimates?

• What is the evidence for duration of cross-protection?
What is “Population Impact”?

- The impact of vaccination on the prevention of disease due to any HPV type
  - Efficacy against CIN 2+ due to any HPV type

### Disease Due to ANY HPV Type

<table>
<thead>
<tr>
<th>Endpoints Caused by Vaccine or Non-vaccine HPV Types</th>
<th>Analysis</th>
<th>GARDASIL</th>
<th>AAHS Control</th>
<th>% Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 2/3 or AIS</td>
<td>Prophylactic Efficacy*</td>
<td>4616 cases</td>
<td>4680 cases</td>
<td>136 cases</td>
</tr>
<tr>
<td></td>
<td>Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types**</td>
<td>8559 cases</td>
<td>8592 cases</td>
<td>516 cases</td>
</tr>
</tbody>
</table>

*Includes all individuals who received at least 1 vaccination and who had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 and were naive to 14 common HPV types at Day 1. Case counting started at 1 month postdose 1.

**Includes all individuals who received at least 1 vaccination (regardless of baseline HPV status or Pap test result at Day 1). Case counting started at 1 month postdose 1.

Table 7. Efficacy of CERVARIX in Prevention of CIN or AIS Irrespective of Any HPV Type in Females 15 Through 25 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine Types (Study 2)

<table>
<thead>
<tr>
<th>CIN2/3 or AIS</th>
<th>Prophylactic Efficacy</th>
<th>5,449</th>
<th>33</th>
<th>5,436</th>
<th>110</th>
<th>70.2 (54.7, 80.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irrespective of HPV DNA at Baseline</td>
<td>8,667</td>
<td>224</td>
<td>8,682</td>
<td>322</td>
<td>30.4 (16.4, 42.1)</td>
<td></td>
</tr>
</tbody>
</table>
## Cross-Protection or Another Factor?

| Observed Prophylactic Efficacy vs. CIN 2+ due to ANY HPV type | 70.2% CERVARIX | 42.7% GARDASIL |

Expected % of CIN2 due to ~50% HPV 16 and HPV 18

Expected % of CIN 3 due to ~70% HPV 16 and HPV 18
Impact of HPV 16/18 Co-Infection on Efficacy Against Disease Due to Any HPV Type

Prevalence of Different HPV Types
Contributions to CIN2+ Positive to Any HPV Type

• Over the follow-up period, subjects may become:

  – Cases related to HPV 16/18 only; OR
  – Cases related to non-vaccine types only; OR
  – Cases related to both 16/18 and a non-vaccine type
CIN2+ Positive to Any HPV Type: Placebo Group Cases¹⁻³

# GARDASIL Analysis

**Prevention of (CIN 2/3 or AIS) Due to HPV types Not in the Vaccine = Cross Protection**

## Generally HPV naïve population†

<table>
<thead>
<tr>
<th>CIN 2/3 or AIS</th>
<th>Cases (Vaccine)</th>
<th>Cases (Placebo)</th>
<th>Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>31/45</td>
<td>11</td>
<td>27</td>
<td>58.7%</td>
<td>(14.1, 81.5)</td>
</tr>
<tr>
<td>31/33/45/52/58</td>
<td>44</td>
<td>66</td>
<td>32.5%</td>
<td>(-0.3, 55.0)</td>
</tr>
<tr>
<td>10 non-vaccine oncogenic HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59</td>
<td>62</td>
<td>93</td>
<td>33%</td>
<td>(6, 52)</td>
</tr>
<tr>
<td>HPV 31</td>
<td>8</td>
<td>27</td>
<td>70%</td>
<td>(32.88)</td>
</tr>
</tbody>
</table>

†Seronegative to 6/11/16 and 18 and PCR negative to 6/11/16/18 plus 10 other high-risk types at day 1. Had normal cytology at day 1.

Adapted from Brown, JID 2009
## Cervarix Analysis

### Vaccine Efficacy Against Non-Vaccine Types (Phase III PATRICIA – TVC-Naïve)\(^1,2\)

<table>
<thead>
<tr>
<th>HPV Types</th>
<th>TVC-Naive</th>
<th>6-months persistent infection</th>
<th>CIN2+ (including HPV 16/18 co-infections)</th>
<th>CIN2+ (excluding HPV 16/18 co-infections)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vacc/Contr # cases</td>
<td>VE % (95% CI)</td>
<td>Vacc/Contr # cases</td>
</tr>
<tr>
<td>12 Non-vaccine HPV Types*</td>
<td>907/1087</td>
<td>19.0 (11.5, 25.9)</td>
<td>45/102</td>
<td>56.2 (36.2, 69.9)</td>
</tr>
<tr>
<td>Any Oncogenic type**</td>
<td>925/1307</td>
<td>33.1 (27.1, 38.5)</td>
<td>46/151</td>
<td>69.8 (57.8, 78.8)</td>
</tr>
</tbody>
</table>

TVC-Naive = total vaccinated cohort-naïve; CI = confidence interval; CIN = cervical intraepithelial neoplasia; Contr = control; Vacc = vaccine (Cervarix); VE = vaccine efficacy.


* HPV 31/33/35/39/45/51/52/56/58/59/66/68
** HPV16/18/31/33/35/39/45/51/52/56/58/59/66/68
## Duration of Cross-Protection

Individual Non-Vaccine Type Efficacy: 6-Month Persistent Infection Endpoint\(^1\) Up to 8-Year Follow-Up In A Phase II Study of Cervarix\(^\text{TM}\) (Protocol 023)

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Phase III (Study 008)(^1) Follow-Up: 48 Months TVC-N*</th>
<th>Phase II (Study 007)(^2) Follow-Up: Up to 6.4 Years ATP-E**</th>
<th>Phase II (Study 023)(^3) Follow-Up: Up to 8 Years ATP-E**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vacc</td>
<td>Contr</td>
<td>VE % (95% CI)</td>
</tr>
<tr>
<td>HPV 16/18</td>
<td>5</td>
<td>97</td>
<td>95 (88, 98)</td>
</tr>
<tr>
<td>HPV 16</td>
<td>2</td>
<td>81</td>
<td>98 (91, 100)</td>
</tr>
<tr>
<td>HPV 18</td>
<td>3</td>
<td>23</td>
<td>87 (57, 98)</td>
</tr>
<tr>
<td>HPV 31</td>
<td>38</td>
<td>163</td>
<td>77 (67, 84)</td>
</tr>
<tr>
<td>HPV 33</td>
<td>53</td>
<td>92</td>
<td>43 (19, 60)</td>
</tr>
<tr>
<td>HPV 45</td>
<td>13</td>
<td>61</td>
<td>79 (61, 89)</td>
</tr>
</tbody>
</table>

ATP-E=according to protocol for efficacy; TVC-N=total vaccinated cohort-naïve; Contr = control; Vacc = vaccine; CI = confidence interval; VE = vaccine efficacy.

*TVN-N = included subjects who were given at least 1 vaccine dose, were evaluable for efficacy and at baseline had normal cytology, were DNA (-) for all 14 oncogenic HPV types investigated, and were sero (-) for HPV 16 and 18; cases were counted after Day 1; in Protocol 008, the efficacy analyses for HPV 16 and/or 18 were performed in the ATP-E population.

**ATP-E = included subjects who met all eligibility criteria, complied with study procedures, and had data available for the efficacy measure considered; TVC-N in Protocol 008 and ATP-E in Protocol 007/023 are equivalent since subjects in 007/023 were only enrolled if they were PCR (-) to the 14 HPV types tested, sero (-) to HPV 16 and 18, and had a normal Pap test at screening.

Important Observations Regarding Cross-Protection Conferred by HPV Vaccines

• Cross-protective efficacy is less robust and less consistent than that observed for vaccine HPV types\(^1,2\)

• High degree of co-infection with vaccine and non-vaccine HPV types confounds disease case ascertainment\(^3,4\)
  
  — “Population Impact” is driven by HPV 16/18 efficacy

• The duration of cross-protective efficacy is unknown
  
  — Data suggest efficacy is of short duration

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WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer

WHO/ICO (Institut Català d'Oncologia) Information Centre on HPV and Cervical Cancer

The WHO/ICO Information Centre on HPV and Cervical Cancer is developed to accelerate the development and introduction of prophylactic human papillomavirus (HPV) vaccines in countries with the highest burden of cervical cancer and reduce the incidence of this disease and related lesions among women.

Our new 2010 edition of the WHO/ICO HPV Information Centre website provides data on:

- The burden of HPV-related cancers using new data from Globocan 2008: cervix, anus, vulva, vagina, penis, oral cavity, and pharynx
- HPV prevalence and type distribution in women with normal cytology, precancerous cervical lesions and invasive cervical cancer up to 2009
- HPV in cancer of the anus, vulva, vagina, and penis
- HPV in men
- Statistics on factors that contribute to cervical cancer
- Preventative practices: screening and HPV vaccination
- Prevalence of male circumcision and condom use
- HPV vaccine licensure and introduction
- Data on immunization coverage and practices
- Socio-demographic characteristics

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