Cervical Cancer Prevention in Low-resource Countries: Is a Comprehensive Approach Possible?

Vivien Tsu, PhD, MPH
PATH, Seattle

VIDI Symposium, FHCRC, Seattle
January 14, 2008
Overview

1. Background on cervical cancer
2. New opportunities: vaccine and non-vaccine
3. Challenges and benefits of a comprehensive approach
1. **Background on cervical cancer: A global problem**

- Over 270,000 deaths each year*
- Almost 500,000 new cases per year, 85% in the developing world*
- Most common cause of cancer death in developing world

*Sankaranarayanan & Ferlay (2006)*
Estimated number of cases and incidence of cervical cancer, 2002

- Central and South America: 71,862
- North America: 14,670
- Europe: 59,931
- Africa: 78,897
- Asia: 265,884
Age-specific cervical cancer mortality rates per 100,000 women

The HPV-cervical cancer link

• Human papillomavirus (HPV) is a very common STI (more than 50% of adults get it).

• 99.7% of cervical cancer cases are associated with HPV.

• About 5% of HPV-positive women will develop cervical cancer (if their precancerous lesions are untreated).

• Progression from HPV infection to cancer usually takes 20–30 years.
How cervical cancer develops

Long latent period allows screening to detect precancer

Why hasn’t cytologic screening (Pap testing) worked for low-income areas?

- Low sensitivity and limited reproducibility
- Requires frequent visits and high coverage
- Requires quality controls and regular training
- Global costs of programs are very high
What does a comprehensive cervical cancer program entail?

- **Primary prevention:**
  - HPV vaccine
  - Promote condoms and fewer partners—limited effect?

- **Secondary prevention:**
  - Screening (Pap, HPV test, visual inspection)
  - Treatment of pre-cancer (cryotherapy, LEEP)

- **Cancer treatment:**
  - Surgery
  - Radiotherapy

- **Palliative care**

- **Community education:**
  - Raises awareness about cervical cancer
  - Reduces stigma
  - Increases acceptance of both vaccine and screening
2. **New opportunities: vaccine and non-vaccine**

New era of cervical cancer prevention with new options and approaches for both primary and secondary prevention.
HPV and the new vaccines

- >100 types of HPV
- ~15 are high-risk for genital cancers
- L1 protein of virus is antigen in vaccine
- Virus-like particles (VLP)—but with no viral DNA
Vaccine opportunity: Focus on key high-risk HPV types*

- Types 16 and 18 alone cause ~70% of the world’s cervical cancer cases.*
- 16 & 18 account for at least 65% in every region, even with regional and country variation in the distribution of HPV types.*
- Protection might be 80–85% for cancer cases due to cross-protection for related types.**

## Prophylactic HPV VLP Vaccines

<table>
<thead>
<tr>
<th>Brand names</th>
<th>Quadrivalent (Merck)</th>
<th>Bivalent (GSK)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Gardasil</strong>, <strong>Silgard</strong></td>
<td><strong>Cervarix</strong></td>
</tr>
<tr>
<td>Vaccine Type</td>
<td>HPV 6/11/16/18</td>
<td>HPV 16/18</td>
</tr>
<tr>
<td>Licensure status</td>
<td>Licensed in &gt; 80 countries</td>
<td>Licensed in &gt;30 countries</td>
</tr>
<tr>
<td>Licensed groups</td>
<td>Girls/Women age 9–26 (age varies by country)</td>
<td>Girls/Women age 10–55</td>
</tr>
<tr>
<td></td>
<td>Boys 9–15 (Europe, Australia, Mexico, others)</td>
<td></td>
</tr>
<tr>
<td>Schedule</td>
<td>0, 2, 6 months</td>
<td>0, 1, 6 months</td>
</tr>
</tbody>
</table>
## Clinical trial populations

<table>
<thead>
<tr>
<th></th>
<th><strong>Gardasil (Merck)</strong></th>
<th><strong>Cervarix (GSK)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Females 16–26</td>
<td>Females 15–25</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Boys/girls 9–15</td>
<td>Females 10–14, 26–55</td>
</tr>
<tr>
<td><strong>Pending efficacy</strong></td>
<td>Males 16–26?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females 24–45</td>
<td></td>
</tr>
<tr>
<td><strong>Regions</strong></td>
<td>North/South America, Europe, Asia-Pacific</td>
<td>North/South America, Europe, Asia-Pacific</td>
</tr>
<tr>
<td><strong>Total number</strong></td>
<td>~21,000</td>
<td>~27,000</td>
</tr>
</tbody>
</table>
Vaccine: Safe and effective

- VLPs are non-infectious, reducing potential risks
  - ACIP did not advise HIV testing or pregnancy testing before vaccination
  - Well-tolerated with minor local side effects (pain, redness), some fainting; GACVS reviewed in June 2007 and concluded safe

- Efficacy is high in women naïve to a given HPV type (16 or 18) before vaccination
  - >90% against persistent infection due to relevant HPV type
  - >95% against 16-/18-related CIN 2 (bivalent) or CIN 2/3/AIS (quadrivalent)

- Efficacy is much lower in "intent-to-treat" population of sexually experienced women 15–26 (NEJM 2007)
  - 44% against vaccine-related HPV CIN 2/3 or AIS
  - 17% against CIN 2/3 or AIS of any HPV type

- No therapeutic efficacy for women infected before vaccination

- Both vaccines show preliminary evidence of cross protection against 2–3 oncogenic non-vaccine types (45,31,52)
Duration of protection at least 5 years: Anti-HPV 16 GMTs, quadrivalent vaccine

Merck, unpublished data, Presented at ACIP meeting, June 2006

* (Sero (+) and PCR (-) to HPV 16 at Day 1)
Remaining clinical questions

• Duration of protection
• Immunogenicity and safety in HIV+ and other subpopulations
• Efficacy in males
• Cross protection
• Immunogenicity of different dosing schedules and of 2-dose regimen
Challenges for vaccine introduction

- Establishing vaccine availability, affordability, and sustainable financing.
- Identifying new strategies to reach young adolescent girls with health services.
- Addressing potential community concerns about vaccine safety and association with sexually transmitted infection.
- Coordinating with screening services for older women.
- Estimating timing and extent of long-term impact.
- Competing with other new vaccines and health needs.
### PATH’s HPV vaccine project, 2006–2011

**Goal:**
Generate and disseminate evidence for informed public-sector introduction of HPV vaccines*

**4 Focus countries:**
- India
- Peru
- Uganda
- Vietnam

**Primary project components:**
- Country demonstration projects
- Vaccine forecasting and financing
- Policy and advocacy initiatives
- Modest support for secondary prevention

---

*In collaboration with key partners—WHO, IARC, Harvard University, ICO, IAVI, vaccine manufacturers, and others*
Do we know how to deliver the vaccines in low-income countries?

- What target group?
- How to reach them?
- What have we learned so far?
Who to vaccinate? Girls aged 10–13 years

- No efficacy data for males yet.
- Modeling suggests incremental value of vaccinating boys is small, as long as adequate coverage is achieved for girls.
- Before sexual debut and HPV exposure—for highest impact.
- At age when girls are easier to reach efficiently.
- Older adolescents and young women (“catch-up”) less cost-effective and logistically more difficult; gives earlier result but with much lower “net” benefit.
Leading service delivery options

- School-based programs
- Child Health Days (CHDs) and Vaccination Weeks
- Mixed model: school-based supplemented by community outreach for missed girls
- Health facility-based in special settings
Schools offer promising venue in most regions

- Completion of primary school by girls is high in many regions and increasing rapidly.

- Schoolgirls can also be a channel for reaching out-of-school girls (e.g., Peru, Uganda).
Another option…Child Health Days

- Child Health Days and Vaccination Weeks occur annually or semi-annually in many countries and include young adolescents
  - Approximately 60 countries in Africa and Asia conducted Child Health Days, 2005\(^1\)
  - 17 countries in Latin America conducted Vaccination Weeks, 2006\(^2\)

- As primary strategy or for “mop-up”

\(^1\)Source: 24 Jan 07 Vitamin A Coverage Database
\(^2\)Source: 4 May 06 PAHO presentation at MNT meeting at UNICEF, NY
Potential acceptability issues

- Lack of awareness of cervical cancer burden
  - More public education, good both for vaccine and screening
- Rumors about possible fertility effects of vaccine
  - Work with opinion leaders to counter misinformation
- Association with STIs, fear of stigma
  - Share data on widespread nature of HPV to reduce stigma
- Fear of promoting unsafe sex or promiscuity
  - Share data on absence of negative consequences of other interventions related to sex (sex education, condom promotion, emergency contraception)
**Health system capacity: EPI already has most components to deliver vaccine**

<table>
<thead>
<tr>
<th>Have:</th>
<th>Will need:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Cold chain</td>
<td>• Training on:</td>
</tr>
<tr>
<td>✓ Staff with IM injection skills</td>
<td>- Who is eligible</td>
</tr>
<tr>
<td>✓ Injection supplies and medical waste disposal</td>
<td>- How to explain HPV</td>
</tr>
<tr>
<td>✓ Vaccine storage and transport</td>
<td>- How to handle the vaccine</td>
</tr>
<tr>
<td></td>
<td>- Advice on future screening, if available</td>
</tr>
<tr>
<td></td>
<td>• Record systems for individual (3 doses) and program monitoring</td>
</tr>
</tbody>
</table>
Synergy of HPV vaccine with other health interventions for children and young adolescents

- **Other vaccines**—TT or Td, rubella, hepatitis B, measles catch-up; eventually HIV
- **Other medications**—deworming, malaria IPT, schistosomiasis, filariasis, trachoma, iron and/or iodine supplementation
- **Health education/promotion messages**—bednets, handwashing, puberty, tobacco and other harmful substances, STI/pregnancy prevention
Even with vaccine, screening is still needed

- For **non-vaccinated** women already exposed to HPV.
- For **vaccinated** women to protect them from the 30% of cancers due to types other than HPV-16 and -18.
- To monitor the impact of the vaccine and other control efforts.
Exciting new options in screening and precancer treatment (secondary prevention)

- New screening methods
- New algorithms for delivering secondary prevention
- New evidence that mid-level providers can manage most screening and precancer treatment
Potential cervical cancer screening methods in low-resource settings

- Visual inspection with acetic acid (VIA)
- Visual inspection with Lugol’s iodine (VILI)
- FastHPV (QIAGEN)
- Conventional pap
- Hybrid Capture® 2 (hc2, QIAGEN)
VIA and VILI: alternatives to Pap

VIA-positive:
After vinegar application, a large acetowhite area.

VILI-positive:
After Lugol’s iodine application, the lesion is iodine negative.
FastHPV kit and reagents
### FastHPV compared with standard HPV Hybrid Capture 2 (Gaithersburg, MD)

<table>
<thead>
<tr>
<th></th>
<th>QIAGEN Hybrid Capture 2</th>
<th>QIAGEN FastHPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test format</strong></td>
<td>Batch</td>
<td>Rapid-batch</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>7 hours</td>
<td>Less than 2.5 hours</td>
</tr>
<tr>
<td><strong>Detects</strong></td>
<td>HPV-DNA</td>
<td>HPV-DNA</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Lab</td>
<td>Static or mobile clinic</td>
</tr>
<tr>
<td></td>
<td>Refrigeration needed</td>
<td>No refrigeration needed</td>
</tr>
<tr>
<td><strong>Number of samples</strong></td>
<td>96 well batch</td>
<td>24 or 48 well batch</td>
</tr>
<tr>
<td><strong>Number of HPV types</strong></td>
<td>13</td>
<td>All 13 + type 66</td>
</tr>
<tr>
<td><strong>Target price per specimen</strong></td>
<td>Substantially more than US$5</td>
<td>Less than US$5</td>
</tr>
</tbody>
</table>
Highly variable estimates of screening test accuracy in developing countries

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>31–78%</td>
<td>91–99%</td>
</tr>
<tr>
<td>HPV HC2</td>
<td>61–90%</td>
<td>62–94%</td>
</tr>
<tr>
<td>VIA</td>
<td>50–96%</td>
<td>44–97%</td>
</tr>
<tr>
<td>VILI</td>
<td>44–93%</td>
<td>75–85%</td>
</tr>
</tbody>
</table>

Cryotherapy: Simple treatment

- Metal probe applied to the cervix to freeze (-50° C) the abnormal area for total of 6 minutes.
- 80–90% effective in destroying high-grade precancerous lesions (CIN 2 or 3).
- Ideal for nurses to perform at district hospitals and maybe even in health centers.
- Does not require electricity; uses low-cost CO₂ or N₂O gas.
- Appropriate for most lesions, except very large ones and those involving the cervical canal.
ACCP: screening and treatment evidence from many settings (2000–2007)
The most efficient and effective strategy for secondary prevention of cervical cancer in low-resource settings is to

- screen using either HPV DNA testing or VIA (visual inspection)
- then treat using cryotherapy.

With VIA, this is optimally achieved in a single visit.
Programmatic requirements for new secondary prevention strategies

- Build political support.
- Train mid-level providers in clinical procedures and client interaction.
- Invest in basic equipment and supplies.
- Establish referral system for complex cases.
- Mobilize women and their communities.
3. Challenges and benefits of a comprehensive approach to prevention

Challenges:

• Involves different health sectors: immunization, reproductive health, cancer.

• Involves different beneficiaries: young adolescents, women in 30s and 40s.

• Requires different investments and has different time frames for payoff.

• Screening and vaccine sometimes seen as competitive with each other.
Synergy of comprehensive approach

- Combining interventions may reduce cost of each by sharing key resources like staff and transport.
- Both vaccine and screening will benefit from heightened community awareness of cervical cancer.
- Vaccine will eventually reduce the costs of screening by reducing numbers that need treatment for precancer.
- Providing both assures current and future benefits.
Promise of comprehensive approaches: vaccine and screening

Cervical Cancer Prevention Options and Reduction in Lifetime Risk of Cancer, Brazil

*Assumes coverage 70%, VE 100%; Goldie et al. Vaccine, 2007.
Conclusions

- Cervical cancer is a major women’s health problem in developing countries.
- New secondary prevention approaches can dramatically reduce morbidity and mortality from cervical cancer in low-resource settings in the near term.
- Feasible HPV vaccine delivery strategies exist and are being tested.
- HPV vaccine—combined with secondary prevention—offers great promise for eliminating the inequitable burden of cervical cancer.
Cervical cancer library

- General cervical cancer resources
- Vaccination
- Screening and treatment
- Advocacy, policy, and financing
- Adults, teens, and communities
- Training
- Cervical cancer organizations
- Multimedia

Copyright 1997-2007, PATH. All rights reserved.

www.rho.org

Cervical cancer prevention

Cervical cancer, although easily preventable, affects more than 493,000 women each year and leads to more than 270,000 deaths worldwide. PATH has been active in cervical cancer control for many years—through alliances that increase women’s access to screening and treatment, through vaccine development and introduction, and through global dissemination of information and ideas.

A vaccine for women’s health
Preparing the way for another tool in the fight against cervical cancer

START project
Developing biochemical tests for cervical cancer

www.path.org/cervicalcancer
Thank You

Vivien Tsu, PhD, MPH
Senior Program Advisor
vtsu@path.org

www.path.org/cervicalcancer

PATH, Nguyen Thi Kiem