Introducing HPV vaccines in adolescent populations: Update on PATH's HPV Vaccine Project

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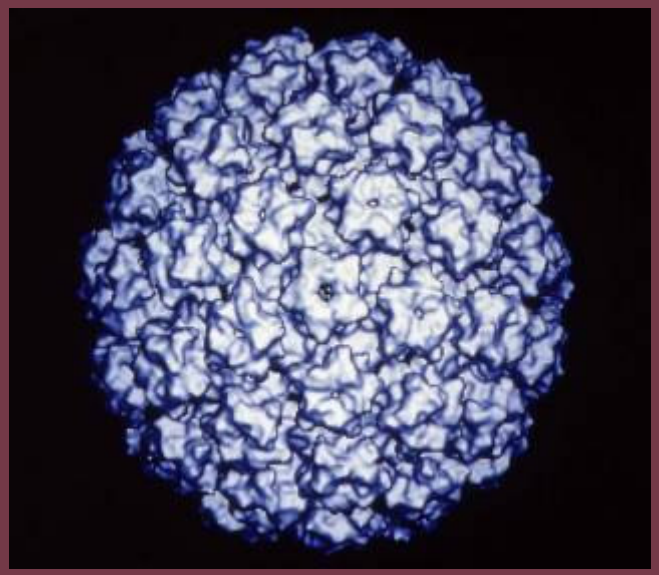

PATH
A catalyst for global health

Presentation

- *Key issues related to HPV vaccine acceptance*
- *BMGF grants awarded*
- *Recap on vaccine candidates*
- *PATH HPV Vaccine Project*
- *Socio-cultural research and demonstration projects in 4 countries*

Preparing for introduction of HPV vaccines: Opportunities and challenges

- ***HPV vaccines provide a unique opportunity to implement widespread primary prevention of cervical cancer and other HPV-related diseases through immunization***
- ***Multiple challenges to widespread vaccination:***
  - ***Poor knowledge/understanding: HPV, link to cancer***
  - ***Sociocultural barriers: issues surrounding "STI vaccine"***
  - ***Programmatic issues: lack of established vaccination programs for pre-adolescents and adolescents, cost, requirement for three doses, cold chain implications***

Broutet et al., WHO, 2006

Industrialized countries: Health care provider knowledge and attitudes

- *Knowledge about HPV among health care providers is poor*
  - *< 50% understand link between HPV and cancer*
- *However, ~75% of health care providers would recommend HPV vaccines*
- *Factors driving provider recommendations:*
  - *Demand among clients*
  - *Few perceived societal and parental barriers*
  - *Clinical experience with young adolescents*
  - *Endorsement by influential organizations*
  - *Perception of early age of sexual debut, proportion of clients likely to be sexually active*

Kahn 2005, Riedesel 2005

Industrialized countries: Parental knowledge and attitudes

- *Knowledge about HPV is poor*
- *67-83% of parents would agree to vaccinate daughters*
- *Minority of parents concerned about:*
  - *Increase in risky sexual behaviors*
  - *Sending message that they condone premarital sex*
- *Factors driving parental decisions:*
  - *Desire to protect child from cancer*
  - *Beliefs about HPV: serious, child is susceptible*
  - *Attitudes about HPV vaccines: safe, effective*
  - *Personal experience with STIs, abnormal Pap, genital warts*
  - *Health care provider recommendation*

Kahn 2003, Davis 2004, Dempsey 2006, Brabin 2006

Developing countries: Issues regarding HPV vaccine acceptance and delivery differ

- ***Research on HPV vaccine acceptability has been conducted largely in more developed regions, based on theories of individual health behavior***
- ***Context is a critical determinant of vaccine acceptance, delivery and use in developing countries***
- ***Conceptual models have been developed to understand determinants of vaccine acceptance and delivery in developing countries***
- ***Conclusion: Research specific to HPV vaccines urgently needed in developing countries***

Streefland 1999, Kaljee 2004

Four Gates Foundation HPV Vaccine Grants:
A coordinated strategy for exploring how to make HPV vaccines available, acceptable, and affordable to those most in need

Harvard University (2005-2008)

- ***Decision models for vaccine cost-effectiveness and potential population impact of vaccine introduction***

IARC (2005-2010)

- ***Epidemiological data collection and analysis in low-resource settings in Asia, Africa, Eastern Europe***

WHO Initiative for Vaccine Research (2005-2010)

- ***Quality standards for HPV Laboratory Network***
- ***Guidelines for vaccine introduction***
- ***Information Centre for HPV and Cervical Cancer (ICO, Barcelona)***

PATH (2005-2011)

- ***Planning grant to promote and accelerate evidence-based introduction (2005-2006)***
- ***HPV Vaccine Project (2006-2011)***

Two HPV vaccines currently entering market - 1

	Gardasil®	Cervarix®
Manufacturer	Merck & Co., Inc.	GlaxoSmithKline (GSK) Biologicals
Vaccine	L1 VLP vaccine based on recombinant yeast technology	L1 VLP vaccine based on recombinant baculovirus technology
HPV strains	6, 11, 16, and 18 -- protects against cervical cancer and genital warts	16 and 18 -- protects against cervical cancer
Presentation	Liquid, injectable, IM, monodose	Liquid, injectable, IM, monodose
Adjuvant	Alum (aluminium salt)	AS04 (alum plus proprietary adjuvant MPL)
Schedules	3 injections at months 0, 2, and 6	3 injections at months 0, 1, and 6
Target popn.	Pre-/Adolescent girls and boys	Pre-/Adolescent girls
Cold chain	+2°C to +8°C; liquid, cannot be frozen	+2°C to +8°C; liquid, cannot be frozen
Clinical trials	✓ Efficacy studies of about 25,000 women 15-26 years in 33 countries ✓ Adolescent immunogenicity and tolerability study of 4,800 boys and girls 9-15 years ✓ Efficacy and tolerability study of women 24-45 years ✓ Efficacy study of men 16-26 years	✓ Efficacy study of 18,000 women 15-25 years in 14 countries ✓ Efficacy study of 7,467 women 18-25 years in Costa Rica ✓ Adolescent safety and immunogenicity study of girls as young as 10 years ✓ Efficacy study of women 26-55 years

Two HPV vaccines currently entering market - 2

	Interim results of phase II Clinical Trial of Gardasil®	Results of Phase IIb Clinical Trial and Other Studies of Cervarix®
Safety	✓ No serious adverse effects from vaccine ✓ Most common adverse effects are local discomfort at injection site and headache	✓ No serious adverse effects from vaccine ✓ Most common adverse effects are local discomfort at injection site, headache
Immunogenicity	✓ 100% of women develop antibodies to all four HPV types ✓ Antibody levels remain higher than in natural HPV infections at 36 months ✓ Antibody response is stronger in girls and boys age 10-15 than women age 16-23	✓ 100% of women develop antibodies to HPV-16 and 18 ✓ Antibody levels remain higher than in natural HPV infections at 18 months ✓ Antibody response is stronger in girls age 10-14 than women aged 15-25 ✓ Antibody levels rise faster, higher, and last longer when vaccine is formulated with AS04 than alum alone
Efficacy	✓ 100% efficacy against CIN 2/3 and AIS associated with HPV-16/18 in per protocol analysis ✓ 97% efficacy against CIN 2/3 and AIS associated with HPV-16/18 in intention-to-treat analysis ✓ 100% efficacy against genital warts, vaginal dysplasia, and vulvar dysplasia in per protocol analysis ✓ 95% efficacy against genital warts, vaginal dysplasia, and vulvar dysplasia in intention-to-treat analysis	✓ 96% efficacy against persistent infection with HPV-16/18 in per protocol analysis and 94.4% in intention-to-treat analysis ✓ 100% efficacy against CIN 1/2/3 and invasive cell carcinoma associated with HPV-16/18 in combined initial and extended follow-up analysis ✓ Evidence of cross-protection: 94% efficacy against incident infection with HPV-45 and 55% efficacy against incident infection with HPV-31

Status of HPV vaccine licensure, as of November 2006

Merck Gardasil™ licensure (42 countries):

WHO Region	*Countries that have licensed Gardasil™*	
Americas	*6*	*Argentina, Brazil, Canada, Mexico, Perú, USA*
Africa	*2*	*Chad, Togo*
Europe	*27*	*Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Serbia, Slovakia, Slovenia, Spain, Sweden, UK*
Middle East	*1*	*UAEmirates*
Southeast Asia	*0*	
Western Pacific	*6*	*Australia, Hong Kong, Macau, Malaysia, New Zealand, Taiwan*

GSK Cervarix® not licensed in any countries yet.

HPV Vaccine Project 2006-2011

Objective:

To strengthen the capability of developing countries to prevent cervical cancer through generating and providing necessary evidence about public-sector introduction of HPV vaccines.

HPV Vaccine Project Objectives

Objective 1: ***Generate critical data and experience for evidence-based decision making, strengthening essential health system capabilities, and creating a supportive social and political environment for national readiness in 4 countries****

Objective 2: ***Leverage country experience to inform and promote favorable global HPV vaccine policy, regional HPV vaccine strategies, and government introduction plans***

Objective 3: ***Develop strategic forecasts, investment cases, and decision-making tools to inform and influence industry supply and pricing decisions, international agency financing decisions, and government introduction plans***

****India, Peru, Uganda, Vietnam***

India: what is the best age for community-based delivery?

- ***Objective:*** ***To select a target age that maximizes acceptability and operational feasibility in a community outreach vaccination strategy***
- ***Primary outcome:*** ***3-dose vaccine coverage rate in each age group***
- ***Secondary outcomes:*** ***partially vaccinated subjects, resource use & costs, acceptability, inputs for cost-effectiveness analyses***

Peru: what is the best strategy for a school-based delivery strategy: girls only or girls+boys?

- ***Objective:*** ***To compare a school-based vaccination strategy that targets boys and girls to one that targets girls only***
- ***Primary outcome:*** ***3-dose vaccination coverage rates among 11 or 12-year-old boys and girls***
- ***Secondary outcomes:*** ***partially vaccinated subjects, vaccinated boys, resource use & costs, acceptability, inputs for cost-effectiveness analyses***

Vietnam: what is the best delivery strategy for reaching 14 year-old girls in Vietnam?

- *Objective:* ***To compare a school-based strategy for reaching lower secondary school ages (14 year-old girls) to (1) a facility-based strategy and (2) a school+facility strategy.***
- *Primary outcome:* ***3-dose vaccine coverage rate among 14 year-old girls***
- *Secondary outcomes:* ***partially vaccinated subjects, resource use & costs, acceptability, and inputs for cost-effectiveness analyses***

Uganda: feasibility of delivering HPV vaccine through school-based strategy

- ***Research objectives:***
  1. ***To conduct socio-cultural research to ascertain KAP among pre-adolescent girls, their parents or guardians, teachers, health workers and community leaders related to sexuality, reproductive health, cervical cancer, 1^{ary} and 2^{ary} prevention, and attitudes on vaccinating pre-adolescent girls***
  2. ***To assess feasibility of different vaccine delivery options***
  3. ***To cost vaccine delivery options***
- ***Methods:*** ***mix of interview surveys, focus group work and other social science methods as appropriate, institutional mapping, costing studies***
- ***Primary outcome:*** ***in-depth analysis of socio-cultural and behavioral factors that will influence societal response to the prospect of HPV vaccine introduction***

Uganda: feasibility of delivering HPV vaccine through school-based strategy

- ***Rough timeline:***
  - ***Research institutions identified, RFP disseminated October 2006***
  - ***Bids received November 2006***
  - ***Selection process concluded December 2006***
  - ***HSPC and local clearance by end-February 2007***
  - ***Research initiated March 2007, completed November 2007***
- ***Study sites:*** ***representative communities in culturally distinct regions***

Demonstration project: feasibility of delivering HPV vaccine through school-based strategy

- *Objective:* ***To assess feasibility of school-based strategy for reaching girls in school aged 10-12 years, plus additional strategy for reaching girls out of school, possibly synchronized with semi-annual Child Health Days***
- *Primary outcome:* ***3-dose vaccination coverage in each group***
- *Secondary outcomes:*
  - ***1- and 2-dose vaccination coverage***
  - ***Vaccination drop-out rate***
  - ***Cost of each strategy***
  - ***Data for cost-effectiveness estimates***
  - ***Acceptability (KAP) among recipients, families***

Demonstration project: feasibility of delivering HPV vaccine through school-based strategy

- *Research institutions and possible study sites identified*
- *Rough timeline:*
  - *RFP ready November 2007*
  - *Bids due January 2008*
  - *Selection process concluded Feb 2008*
  - *HSPC and local clearance by May 2008*
  - *Research initiated July 2008, completed June 2009*

Uganda and Vietnam: pre-licensure studies

- *Objective:* ***to assess immunogenicity of alternative dose schedules, for example 0, 6, 12 months, to facilitate delivery strategies***
- *Vaccines:* ***different vaccine candidate in Uganda and Vietnam***
- *Sample size:* ***800 subjects per site***
- *Timetable:* ***2007-08***

HPV Vaccine Project *optimal* global timeline

- ***Late 2007:* PATH submits investment case to GAVI Board, to include HPV vaccine in the GAVI portfolio of subsidized vaccines**
- ***Early 2008:* WHO pre-qualifies HPV vaccine for international procurement**
- ***Early 2008:* WHO SAGE recommends HPV vaccine use**
- ***Late 2008:* PAHO Revolving Fund and UNICEF SD negotiate with manufacturers on HPV vaccine supply**
- ***Late 2008:* GAVI sets co-pay vaccine price, invites eligible countries to apply for vaccine**
- ***Late 2009* : Vaccine delivery implemented**

THANK YOU

www.path.org/cervicalcancer
www.aim-e-learning.stanford.edu/

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