Cancer prevention through HPV vaccination in developing countries

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Introduction

- Childhood vaccination programmes have had a dramatic impact on child morbidity and mortality worldwide.
- 1974 WHO established Expanded Program on Immunization (EPI) which included:
  - Diphtheria-Tetanus-Pertussis (DTP)
  - Measles Containing Vaccine (MCV)
  - Polio vaccine (Pol3)
  - BCG
- Later other vaccines added:
  - Haemophilus influenzae type b (Hib 3)
  - Yellow fever (YF)
  - Hepatitis B vaccine (HepB3)
- New vaccines:
  - Rotavirus
  - Pneumococcal conjugate vaccine
Introduction

- Value of vaccination lies in preventing disease
  - Estimated to save 3 million lives per year
  - Preventative medicine
  - High acceptability in developing countries
  - Reduction in cost of health care borne by public sector and private individuals due to prevention of disease
  - Reduction in lost days of work due to sickness or caring for a sick patient
  - Increased lifetime productivity due to better health which improves cognition, educational attainment and physical strength
  - Economic improvements due to increased survival of children
Vaccination

• Global immunisation effort emerged following the success of the Smallpox Eradication Program – an unprecedented public health achievement
• By 1990s the global immunization program reached 75% of target population, except in India and SSA where it was less than 65%
• During 1990s the Polio Eradication program reached 90% world’s children
• 2000 GAVI Alliance was formed and raised billions of dollars for introduction of new and underutilized vaccines
• In first 10 years GAVI has prevented 5 million future deaths caused by Hep B, Hib, measles, pertussis, pneumococcal disease, polio, rotavirus and yellow fever
• Due to GAVI funding an additional 288 million children were immunized in period 2000 - 2010
HPV Vaccination

• GAVI agreed in principle to support HPV vaccination in 2008 but only had resources for funding in 2011
• Funding was conditional on
  • Successful negotiations for an affordable vaccine
  • Development of plans to reach pre-adolescent girls
  • Support pilot programs prior to national scale-up
• Negotiated price of $4.50 per dose with commercial companies
• So why is HPV vaccination relevant in developing countries??
Overview of HPV associated Cancer - Globocan 2008*

- Of 12.7 million new cases of cancer in 2008 globally
  - 700 000 occurred in HPV-associated cancer sites
- 610 000 cancers were attributable to HPV infection
  - 4.8% of total cancer burden world wide
- 530 000 (86.9%) were cancers of the cervix

*Forman et al. Vaccine 2012;30S:F12 – F23
Overview of HPV associated Cancer - Globocan 2008*

- Cervical cancer **third** most common cancer in women worldwide, second to breast and colo-rectal cancer
- And 4\textsuperscript{th} most common cancer cause of death (275,000) after breast, lung and colorectal
- Cause of 7.8 million years of life lost (YLL), third after breast and lung cancer
- Strong association between cervical cancer incidence and level of development
  - 88% of deaths occur in less developed regions
  - Incidence and mortality at least 4 x higher in poor countries (mostly in sub-Saharan Africa)

*Forman et al. 2012
New cases of cancer in 2008 attributable to HPV by anatomic site globally*

<table>
<thead>
<tr>
<th>HPV Cancer Site</th>
<th>New cases 2008</th>
<th>Attributable to HPV</th>
<th>Attributable Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>530 000</td>
<td>530 000</td>
<td>100 %</td>
</tr>
<tr>
<td>Vulva</td>
<td>27 000</td>
<td>12 000</td>
<td>43.0 %</td>
</tr>
<tr>
<td>Anus</td>
<td>27 000</td>
<td>24 000</td>
<td>88.0 %</td>
</tr>
<tr>
<td>Penis</td>
<td>22 000</td>
<td>11 000</td>
<td>50.0 %</td>
</tr>
<tr>
<td>Vagina</td>
<td>13 000</td>
<td>9 000</td>
<td>70.0 %</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>85 000</td>
<td>22 000</td>
<td>25.6 %</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>700 000</strong></td>
<td><strong>610 000</strong></td>
<td><strong>86.3 %</strong></td>
</tr>
</tbody>
</table>

*Forman et al. 2012
Key issues on HPV natural history

- Sexually transmitted through skin to skin contact
- Highly transmittable
- Prevalence of HPV is highest among women initiating sexual activity and decreases with increasing age
- Usually asymptomatic, majority of infections transient and are cleared within 1 – 2 years
- Persistent infection with high risk types, notably HPV 16 and 18 is associated with development of dysplasia and cervical cancer
- HPV 16/18 associated with 70% of cancers and 50% of HSIL
- HPV 6/11 associated with 90% of genital warts
# HPV Vaccines

<table>
<thead>
<tr>
<th>MSD</th>
<th>GSK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Types 6, 11, 16, 18</strong></td>
<td><strong>Types 16, 18</strong></td>
</tr>
<tr>
<td>• VLP L1 of four HPV types</td>
<td>• VLP L1 of two HPV types</td>
</tr>
<tr>
<td>• Yeast expressed</td>
<td>• Baculovirus expressed in insect cells</td>
</tr>
<tr>
<td>• Adjuvant aluminum</td>
<td>• ASO4 adjuvant</td>
</tr>
<tr>
<td>• First licensed in 2006 to over 100 countries</td>
<td>• Aluminum salts and monophosphoryl lipid A</td>
</tr>
<tr>
<td>• Prequalified by WHO 2009</td>
<td>• First licensed in 2007 in over 90 Countries</td>
</tr>
<tr>
<td>• Age 9 – 26</td>
<td>• Prequalified 2009</td>
</tr>
<tr>
<td><strong>3 doses</strong></td>
<td>• Age 10 – 26</td>
</tr>
<tr>
<td><strong>Intramuscular injection</strong></td>
<td><strong>3 doses</strong></td>
</tr>
<tr>
<td><strong>Cold chain required</strong></td>
<td><strong>Intramuscular injection</strong></td>
</tr>
<tr>
<td>• Safe, immunogenic and effective</td>
<td>• Cold chain required</td>
</tr>
<tr>
<td></td>
<td>• Safe, immunogenic and effective</td>
</tr>
</tbody>
</table>
Safety and immunogenicity in HIV positive people*

- Cape Town randomised 120 HIV positive women, aged 18 – 25 years to receive bivalent vaccine or placebo and 30 HIV negative women.
- Safety and reactogenicity profile of the HPV 16/18 vaccine was comparable in HIV positive and HIV negative women.
- All women who received the vaccine were seropositive for up to 12 months and the antibody titres remained substantially above levels associated with natural infection.

Denny L et al Vaccine 2013;31:5745 - 5753
Comparison of immunogenicity and Reactogenicity of Cervarix and Gardasil in HIV infected adults*

- 92 participants randomized
- No difference in antibody titres in women against HPV 16 between two vaccines
- Overall Cervarix was more immunogenic than Gardasil, particularly in terms of antibody to HPV 18, but whether this translates into enhanced or prolonged protection against cervical cancer is unknown

One, two or three doses?

• Girls (aged 9 – 13) randomized to receive quadrivalent vaccine*
  • 0, 2 and 6 months (n = 261) or
  • 0 and 6 months (n = 259)
  • And young women aged 16 – 26 years (n= 310) received 3 doses
• Antibody levels measured at 0, 7, 18, 24 and 36 months
• Primary outcome was noninferiority of GMT ratios for HPV 16 and 18 in girls given 2 vs 3 doses compared to young women

• Key findings
  • GMT ratios were noninferior for girls who received 2 compared to 3 doses of vaccine and compared to young women who received three doses
  • This remained true to 36 months
  • However antibody responses in girls after 2 vs 3 doses, were inferior for HPV 18 at month 24 and HPV 6 at month 36
  • More data needed before reduced does schedules can be recommended

*Dobson S et al JAMA 2013;309(17): 1793-1802
One dose?*

- Costa Rica HPV 16/18 Vaccine trial
- Four year efficacy against 12 month HPV 16/18 persistent infection similar in women who received one (n = 78), two doses separated by one month (n = 140), two doses separated by 6 months (n = 52) or three doses (n = 120) of bivalent vaccine
- At four years, 100% of women in all groups remained HPV 16/18 seropositive
- GMTs among extended two dose group were non-inferior to three dose group
- Compared to natural infection, HPV 16/18 GMTs were 25 –14 times higher among two dose group and 9 and 5 times higher among one-dose vaccinees
- Antibody levels following one dose remained stable form month 6 tp month 48

Vaccine programs in developing countries*

- Gardasil Access Program (GAP) through Axios Healthcare Development
- Free vaccine (3 doses provided)
- Countries responsible for covering costs
  - Importation
  - Transportation
  - Storage
  - Distribution
  - Community outreach
  - Management of the program
  - Data collection
- Follow WHO guidelines in terms of target population (girls 9 – 13 yrs) and safe administration of vaccine
- Effectiveness of program determined by
  - Vaccine coverage
  - Vaccine adherence

Vaccine programs in developing countries

- Eight programs in seven countries
  - Bhutan, Bolivia, Cambodia, Cameroon, Haiti, Lesotho and Nepal
- Eight programs targeted 87,580 girls, of which 76,983 received full 3 doses = coverage of 87.8%
- 3 vaccine delivery models
  - Health facility based – lowest coverage at 77%
  - Mixed School and health facility – 94%
  - School based – 93%
- Lessons learned
  - Clear understandable messaging
  - Strong community involvement
  - Small financial contributions
  - Rewards for vaccinated girls
  - Careful collaboration of all stakeholders
GAP projects in Africa

- Cameroon
- Ghana
- Kenya
- Lesotho
- Mali
- Tanzania
- Uganda
- Zambia

- South Africa planned roll-out 2014
Demonstration project in KwaZulu-Natal, South Africa*

- Co-ordinated by Departments of Health and Education
- Location: Rural District of Zululand characterised by poverty, high HIV incidence and poor access to basic services and facilities
- Prior situational analysis of area in terms of schools, clinics and distances to and from
- 1000 female learners aged 9 – 12 years (or grades 4-5) from 31 schools targeted for vaccination
- Donation of 3000 doses from MSD

*Moodley I et al. SAMJ 2013;103(%):318 - 321
Demonstration project in KwaZulu-Natal, South Africa

- Working group established to prepare community
  - DOH and DOE
  - School principals, teachers, school governing bodies, parents, community and religious leaders, traditional leaders and healers, school health teams, hospital nurses and doctors and private practitioners
- Signed informed consent from parent or caregiver
- School health teams administered vaccine
  - 4 staff members (all nurses)
    - Gen examination performed
    - Height, weight and mid-arm circumference
- Other linkages desired were:
  - Vitamin A supplementation, deworming, booster doses of Dpt vaccine
  - Each child to bring in 5 women in their lives over the age of 30 for cervical cancer screening
Demonstration project in KwaZulu-Natal, South Africa

• Cold chain reviewed prior to implementation
  • MSD purchased refrigerators and freezers and donated to two local district hospitals
  • Vaccine in cooler boxes with accompanying ice-packs were prepared by pharmacy and collected by school health teams on day of vaccination
• Vaccination commenced March 2011, second dose May 2011 and third dose October 2011
• 963 girls aged 7 – 14 participated
• Linkages and screening did not work
Coverage of targeted population of girls in the two districts

<table>
<thead>
<tr>
<th>District</th>
<th>First Dose</th>
<th>Second Dose</th>
<th>Third Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceza (n = 423)</td>
<td>423</td>
<td>416</td>
<td>411</td>
</tr>
<tr>
<td>Nongoma (n = 540)</td>
<td>537</td>
<td>527</td>
<td>527</td>
</tr>
<tr>
<td>Total</td>
<td>960</td>
<td>943</td>
<td>938</td>
</tr>
</tbody>
</table>
PATH Projects*

- 2006 – 2010
- India, Peru, Uganda and Vietnam
- Formative research
  - Sociocultural environment
  - Capacity of health system
  - Policy pathways
- Demonstration projects based on results of formative research
- Vaccine delivery
  - School based
  - Health centre based
  - Vaccine combined with other interventions
  - Girls selected according to grade or age
- All programs used existing EPI infrastructure

*D Scott LaMontagne et al. Bull world Health Organ 2011;89:821 – 830
PATH Projects*

• WHO guidelines for introduction of new vaccines were followed
  • Comprehensive training on cervical cancer, HPV vaccines and program logistics for health workers, teachers, community mobilizers
  • Information, education and communication materials for girls, parents and wider community
  • Prevaccination assessment of cold storage and transport
  • Mechanisms for monitoring adverse events
  • Supportive supervision
Key findings

• Coverage
  • School based programs
    • Peru 83%
    • Uganda 89%
    • Viet Nam 83 – 96%
    • India 77 – 88%

• Survey of parents: Reasons for vaccinating
  • 2/3’s: To prevent Ca Cx
  • Prevent disease in general
  • Vaccines are good for health
  • Following advice of others
  • Vaccine free of charge
  • Government was providing the vaccine
Key findings

- Reasons *for not* vaccinating daughters
  - HPV vaccine was ‘experimental’ (26%)
  - Allergic to vaccines (23%)
  - Following advice of others (20%)
  - Concerns regarding safety (7%)
  - Impact on fertility (1%)
  - Fear of injections (8%)
  - Vaccine encourages early sexual activity (0%)
Rwanda

- April 2011
  - 93,888 girls received first dose of vaccine (donated by MSD)
  - 98,792 were eligible
  - 4,651 not vaccinated

- Coverage
  - Dose 2  94%
  - Dose 3  93%

- Success attributed to creation of Technical Working Group on Vaccinations consisting of:
  - Ministry of Education
  - Ministry of Gender and Family Promotion
  - Center for Treatment and Research on AIDS, Tuberculosis, Malaria and other Epidemics
  - Cancer care health workers
  - Nationwide population sensitization campaign prior to vaccination
  - Intensive situational analysis
Rights violation found in HPV vaccine studies in India

The Indian parliament's Standing Committee on Health, which, in April, 2010, began probing the use of HPV vaccines in two states after the reported deaths of seven girls, has concluded that "safety and rights of children were highly compromised and violated". In view of the report's finding of violation of human rights and clinical trial rules, the committee has recommended legal action against non-profit organisation Programme for Appropriate Technology in Health (PATH), which initiated the HPV project with the Indian Council of Medical Research (ICMR) in 2007, a year before marketing approval for HPV vaccines was given in India.

PATH and the ICMR, the committee notes, did a full-scale clinical trial in vulnerable population groups, such as tribal girls, without mandatory permission from the Drug Controller General of India or the Indian National Technical Advisory Group on Immunization (NTAGI). The trial's purpose was to prepare ground for inclusion of the HPV vaccine in the Universal Immunization Programme (UIP). The report noted that "PATH resorted to an element of substitution by calling the clinical trial as 'observational studies' or 'demonstration project'". PATH, the committee reported, was not even a registered legal entity when it began working with the ICMR.

"Not all studies of health topics (even when they involve humans and licensed pharmaceuticals) are clinical trials. Yet we took all approved steps to ensure that participants knew what the study was about and that participation was voluntary", said Vivien Davis Tsu, of PATH, Seattle.

Chandra M Gulhati, Editor of the Monthly Index of Medical Specialties, New Delhi, said: "The fact that four out of five outcome measures pertaining to determination of adverse reactions makes it a Phase IV clinical trial. In all such projects existing regulatory steps including payment of compensation in case of injury or death must be observed."

Amar Jesani, Editor of the Indian Journal of Medical Ethics, Mumbai, said: "For a vaccine claiming to be a candidate for the UIP, the ICMR should have insisted on preliminary assessment by NTAGI to see if it was immediately needed, affordable, and sustainable for use in UIP."

Slamming state agencies including the Drug Controller General of India for dereliction of duty, the committee recommended further investigation into the PATH trial and marketing approvals given for HPV vaccines.

Dinesh C Sharma
An Indian parliamentary committee has recommended legal action against a major US-based NGO that it accuses of violating ethical standards and national law during a study to assess the possibility of launching a cervical cancer vaccination programme in the country.
Hindustan Times

‘…………..Report points to a serious dereliction of duty by many of the institutions involved………….’
A trial done by PATH with HPV vaccines on 24,000 girls in Andhra Pradesh and Gujarat has been termed a “sordid incident” by the Parliamentary Standing Committee for Health and Family Welfare that found the entire matter “very intriguing and fishy”. This trial has left in its trail at least 1,200 girls in the two states with chronic health problems.....
AHA! The sure sign of promiscuity!!
"This new mandatory STD vaccine shouldn't hurt a bit."
Cervical Cancer Burden In GAVI eligible countries

* 56 GAVI-eligible countries identified using list provided at: www.gavialliance.org/support/who/eligible/index.php

Note: GLOBOCAN database does not include information for Gambia or Sao Tome y Principe.
GAVI ALLIANCE TACKLES CERVICAL CANCER

Every year, 275,000 women die of cervical cancer. Over 85% of those deaths are in developing countries.

CHANGING THE BALANCE

High-income countries

Low-income countries

GAVI’s support for HPV vaccines will help redress the inequity, delivering vaccines to countries with the highest burden.

ABOUT HPV VACCINE

Safe and effective, human papillomavirus (HPV) vaccines protect against 70% of cervical cancer.

LOWERING THE PRICE

Cervix smear

USA

The new low price of US$4.50 per dose marks a two-thirds reduction on the current lowest public sector price.

DRAMATIC ACCELERATION

By 2020, over 30 million girls in more than 40 countries will be vaccinated against HPV.

The first GAVI-supported HPV vaccines will be delivered in May 2013.
Way forward

• Political awareness
• Understanding burden of disease associated with HPV and the possibilities for prevention
• Develop culturally appropriate and sensitive messaging
• Evaluate one versus two versus three dose regimes for efficacy over time
• Use school based platforms – ideal opportunity to develop adolescent health programs
• Integrated implementation with all stakeholders working together
• Community buy-in essential
• Manage adverse events promptly and transparently
Way forward

- Worse than doing nothing is doing it badly!
- Careful pre-implementation planning is critical to success
- Phased introduction more likely to be successful than attempting mass roll-out
- Well prepared communities and public health sector key starting point
- Do it, but do it well!
never give up