CLOSING KEYNOTE:
MOBILIZING FOR GLOBAL PREVENTION AND EARLY DETECTION OF CERVICAL CANCER

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Cancer has gotten personal
The following talk is for mature audiences only. It may contain adult language and provocative statements, some (or many) with which you may disagree. It is intended to instigate open discussion and even disagreement in the hopes that we can accelerate progress and start saving (more) lives. This will NOT be a data-driven talk. This is a call to arms.
Global Cervical Cancer
“I’ll have an ounce of prevention.”
The Promise of Cervical Cancer Prevention

Vaccination

Screening

Schiffman & Castle, NEJM, 2005
1. Barriers to Vaccination: The Curious Case of Japan
2. Barriers to Screening: Don’t Let Perfection Be the Enemy of Good
3. The Big Picture
## Current HPV Vaccines

<table>
<thead>
<tr>
<th>HPV Types</th>
<th>Manufacturer</th>
<th>FDA Approval</th>
<th>Expected Preventive Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardasil</td>
<td>Merck</td>
<td>2007</td>
<td>70% Cervical Cancer, 90% Genital Warts</td>
</tr>
<tr>
<td>HPV16, HPV18, HPV6, HPV11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervarix</td>
<td>GSK</td>
<td>2009</td>
<td>70-80% Cervical Cancer</td>
</tr>
<tr>
<td>HPV16, HPV18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardasil 9</td>
<td>Merck</td>
<td>2015</td>
<td>90% Cervical Cancer, 90% Genital Warts</td>
</tr>
<tr>
<td>HPV16, HPV18, HPV6, HPV11, HPV31, HPV33, HPV45, HPV52, HPV58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Decline In Precancer Now Up To Age Of 30 Years

Rise in Cervical Cancer Incidence in Japanese Women under 50 Years Old

Motoki et al., Cancer Epidemiol, 2015
HPV Vaccination Coverage By Birth Cohort in Japan

Hanley et al., Lancet, 2015
World Health Organization’s Global Advisory Committee on Vaccine Safety (03/14/2014):

“…continue to affirm that its benefit-risk profile remains favorable…”

The European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (05/11/2015):

…the evidence does not support a causal link between the [HPV] vaccines and development of complex regional pain syndrome and postural orthostatic tachycardia syndrome…”
Organizations That Have Approved the Use of HPV Vaccination

- Food and Drug Administration (USA)
- World Health Organization/Pan-American Health Organization (List of Essential Medicines)
- Center for Disease Control and Prevention (USA)
- National Advisory Committee on Immunisation (Canada)
- Australian Technical Advisory Group on Immunisation
- National Health Service (UK)
- European Medicines Agency (European Union)
### Comparing Adverse Events

<table>
<thead>
<tr>
<th>HPV Vaccination</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope (Fainting)</td>
<td>Rare</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Neurogenic disease</td>
<td>Unproven</td>
</tr>
<tr>
<td>Immunological disease</td>
<td>Unproven</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>Unproven/Extremely rare</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cervical Cancer</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEATH</strong></td>
<td>Proven</td>
</tr>
<tr>
<td>Loss of Fertility</td>
<td>Proven</td>
</tr>
<tr>
<td>Surgically Induced Menopause</td>
<td>Proven</td>
</tr>
<tr>
<td>Bladder &amp; Bowel Complications</td>
<td>Proven</td>
</tr>
<tr>
<td>Radiation-Induced Cancer</td>
<td>Proven</td>
</tr>
</tbody>
</table>
Without HPV Vaccination:
310 Cervical Cancers &
90 Cervical Cancer-Related Deaths

With HPV Vaccination:
1 SAE?
Chronic Fatigue Syndrome 1 in 400
Suicide (10-24 y.o.) 1 in 3,900
Self-Inflicted Injuries (10-24 y.o.) 1 in 115
Fatal Accidental Injury (10-19 y.o.) 1 in 25,000
Teen Births (15-19 y.o.)* 1 in 250
HPV Vaccination SAE 1 in ≥50,000
History of Polio

• 1 in 200 infections leads to irreversible paralysis. Among those paralyzed, 5% to 10% die when their breathing muscles become immobilized.

• Polio cases have decreased by over 99% since 1988, from an estimated 350,000 cases then, to 74 reported cases in 2015. The reduction is the result of the global effort to eradicate the disease through vaccination.

• Poor sanitation led to early exposure in children and natural immunity. Improved sanitation increased the proportion of children and adults at risk of paralytic polio infection, by reducing childhood exposure and immunity to the disease (no protection from maternal antibodies and more severe immune responses).
## The Anti-HPV Vaccine Lobby

<table>
<thead>
<tr>
<th>Claims Against HPV Vaccinations</th>
<th>True or False</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV vaccines have not been shown to prevent cervical cancer</td>
<td>True</td>
<td>HOWEVER, HPV vaccines have been shown to prevent Pap-detected precancers, the same precancers that if detected and treated are supposedly the reason for Pap screening reduced cervical cancer incidence. Therefore, either both HPV vaccines and Paps work to prevent cervical cancer or they do not?</td>
</tr>
<tr>
<td>HPV vaccines cause serious adverse events</td>
<td>False</td>
<td>There is no epidemiological evidence or biological rationale for this to be true.</td>
</tr>
<tr>
<td>HPV vaccines encourage adolescents to have more and/or riskier sex</td>
<td>False</td>
<td>Many epidemiological studies have not been able to find a link between HPV vaccination and sexual behaviors.</td>
</tr>
</tbody>
</table>
Outline

1. Barriers to Vaccination: The Curious Case of Japan
2. Barriers to Screening: Don’t Let Perfection Be the Enemy of Good
3. The Big Picture
HPV Testing Reduces the Risk of Cervical Cancer Related Death (India)

Sankaranarayanan et al., NEJM, 2009
HPV vs. Pap: Pooled RCT Data on Cumulative Incidence of Cervical Cancer

All randomized women

Women with a negative test at entry

Ronco et al., Lancet, 2013
WHO recommendations for cervical cancer screening from http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf page XV 1. For those regions of the world currently without a program in place and with enough resources to provide a sequence of tests, like Rwanda, an HPV test followed by VIA is the preferred strategy.

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New WHO Guidelines

Decision-making flowchart for programme managers

- Do you have a screening programme in place?
  - Yes, VIA
  - No
    - Yes, cytology followed by colposcopy
    - No
      - Do you have enough resources to provide an HPV test?
        - Yes
          - Do you have enough resources to provide a sequence of tests (i.e. HPV test followed by another test)?
            - Yes
              - HPV test followed by VIA
            - No
              - HPV test alone
        - No
          - VIA alone
      - No
        - Does the programme meet quality indicators (e.g. training, coverage, and follow-up)?
          - Yes
            - Cytology or HPV test followed by colposcopy
          - No
            - Cryotherapy and/or LEEP must be part of a screen-and-treat programme

http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf
VIA: Success or Failure?

Cervical Cancer Incidence

Cervical Cancer Related-Death

Shastri et al., JNCI, 2014
Zambia

The Challenge of Screening Women Aged 30-49 Years

1. Screening women age 30-49 years represents ~20% of the female population and 10% of the total population. Therefore, for a small country of 10 million people (e.g., Rwanda), that is 1 million to be screened in a place that has never screened even 10% of the population. Plus, every year, another 0.5% reaches screening age.

2. Women aged 40-49 years are at the peak of cervical cancer incidence. Most LMICs do not have the capacity to manage all those screen-detected cancers.

3. Screening tests probably work best in younger women, whose cervical transformation zone is more visible and easier to sample.

4. Scaling up to screen 10% of the population will require a large but temporary workforce that later will be looking for jobs.
1. Restrict to 30-39, 30-34, 35-39 or even just 30 or 35 years of age.
2. Get good at screening these women who are the mostly likely to be benefit.
3. Try to get at least one high-quality screen in them and every subsequent 1-year age cohort. The first screen is the most effective and therefore cost effective.
4. Then if the resources are available, consider catch-up screening in the older age groups and/or more than once in a lifetime.
HPV Testing

HPV Negative

- Routine Screening Interval
  - Treatment {All}
    - VAT* Eligible?
      - Yes: Cryotherapy
      - No: Colposcopy and/or LEEP
  - Cryotherapy

HPV Positive

- Triage to Treatment
  - VIA, HPV16/18, methylation?
    - ≥CIN2: LEEP 6- to 18-Mo Follow-Up
    - <CIN2: 6- to 18-Mo Follow-Up
  - Triage+ 6- to 18-Mo Follow-Up
  - Triage- 6- to 18-Mo Follow-Up

- Colposcopy {All}
  - Triage+ 6- to 18-Mo Follow-Up
  - Triage- 6- to 18-Mo Follow-Up

- Triage to Colposcopy
  - Pap, HPV16/18, Biomarker

Sensitivity

Specificity ($)
Barriers to Care

Adesina et al., Lancet Oncol, 2013

Holmer et al., Lancet Global Health, 2015

Surgeons, Anesthesiologists, & Obstetricians

Access to Morphine Around the World

The World Health Organization considers morphine an essential medicine for the treatment of pain, but access to the drug depends largely on where you live.

High-income countries consume 93% of the world’s morphine supply, yet 70% of deaths from cancer occur in low- and middle-income nations.

Find out more about access to pain medication at theworld.org/cancer
Screen and Treat in South Africa

Denny et al., JNCI, 2010
1. Barriers to Vaccination: The Curious Case of Japan
2. Barriers to Screening: Don’t Let Perfection Be the Enemy of Good
3. The Big Picture
What Are the Barriers to Global Adoption of HPV-Targeted Cervical Cancer Prevention?

1. Misinformation/Vested Interested
2. Coordinated Procurement & Investment
3. Human Capital and Capacity
4. Health System Infrastructure & Logistics
5. Inertia

(to name a few)

{BE PRACTICAL}
2008: Gardasil "is a good vaccine and ... is generally safe,"

2009: "Gardasil has been associated with at least as many serious adverse events as there are deaths from cervical cancer developing each year."

2009: Harper stated to the Guardian "I fully support the HPV vaccines," she says. "I believe that in general they are safe in most women."[17]

In the December 2009 issue of *Current Opinion in Obstetrics and Gynecology*, Harper published an opinion piece regarding the potential risks of both Gardasil and Cervarix, and concluded that, given the various limitations and risks of the vaccines, the benefits and risks of HPV vaccination must be weighed with the benefits and risks of HPV screening (Pap smears) to reduce cervical cancer in a cost-effective manner.

2013: "Population health models show that if the HPV vaccine does not last for at least 15 years, no cancers will ever be prevented; women will just get the cancers at a later time in life after the vaccine has worn off"

2012: "[I]t's critical to note that more than 70 healthy young girls have died from a neurological reaction that occurred soon after getting Gardasil

2013: stated that newly developed pap screenings that combine HPV testing and cytology have a nearly 100% ability to detect pre-cancers and cancers; she noted that Gardasil doesn't last long enough to prevent cervical cancer and that there are some harms associated with it.

= 63 Citations
## MNCH vs. Cervical Cancer

<table>
<thead>
<tr>
<th>PREGNANCY-RELATED COMPLICATIONS (MATERNAL MORTALITY)</th>
<th>CERVICAL CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANNUAL DEATHS</strong></td>
<td></td>
</tr>
<tr>
<td>273,500 women</td>
<td>275,000 women</td>
</tr>
<tr>
<td>DIE ANNUALLY</td>
<td>DIE ANNUALLY</td>
</tr>
<tr>
<td><strong>MORTALITY TRENDS</strong></td>
<td></td>
</tr>
<tr>
<td>↓34% DECREASE IN MORTALITY</td>
<td>↑45% INCREASE IN MORTALITY</td>
</tr>
<tr>
<td>1990-2008</td>
<td>1990-2008</td>
</tr>
<tr>
<td><strong>PRIORITIZATION IN MILLENIUM DEVELOPMENT GOAL (MDG)?</strong></td>
<td></td>
</tr>
<tr>
<td>YES (MDG 5—IMPROVING MATERNAL HEALTH FROM PREGNANCY-RELATED COMPLICATIONS)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>CURRENT ANNUAL INVESTMENT IN DEVELOPING WORLD</strong></td>
<td></td>
</tr>
<tr>
<td>USD 12 billion</td>
<td>???</td>
</tr>
<tr>
<td>EXACT FIGURE UNKNOWN</td>
<td></td>
</tr>
</tbody>
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Global Alliance for Vaccination and Immunization (GAVI)
Roll-Out (?) of HPV Vaccination

<table>
<thead>
<tr>
<th>Income Level</th>
<th>Number of Women (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Income</td>
<td>14%</td>
</tr>
<tr>
<td>Upper Middle</td>
<td>30%</td>
</tr>
<tr>
<td>Lower Middle</td>
<td>40%</td>
</tr>
<tr>
<td>Low Income</td>
<td>16%</td>
</tr>
</tbody>
</table>

Bruni et al., Lancet Global Health, 2016
Integrated Healthcare Delivery

HIV

Estimated prevalence, 2009

TB

Estimated tuberculosis (TB) incidence rates, 2011

Malaria

Number of malaria reported confirmed cases, 2010

CxCa
“Knowing is not enough, we must apply. Willing is not enough, we must do”

-Goethe

GC3’s ONE Campaign: All women deserve at least one high-quality preventive or curative service against cervical cancer in their lifetime.
Scaled cervical cancer prevention and control