Towards the Elimination of HPV-Related Disease: Starting with Cervical Cancer

Anna R Giuliano, PhD
Center for Infection Research in Cancer
Moffitt Cancer Center
Conflicts of Interest

• Dr. Giuliano reports the following:
  – Institutional research grants from Merck & Co, Inc., Kenilworth, NJ, USA
  – Member of the v503 scientific advisory board for Merck & Co, Inc., Kenilworth, NJ, USA
  – Member of the Global Advisory Board for Merck & Co, Inc., Kenilworth, NJ, USA
We have the tools to eliminate cervical cancer

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

-Goethe
Infection/Disease Control to Extinction

• Control
  – Reduction of disease incidence, prevalence, morbidity, and mortality to acceptable levels

• Elimination of Disease
  – Reduction to zero, or near zero, incidence of disease in a defined geographic area

• Elimination of Infection
  – Reduction to zero, or near zero, incidence of infection caused by a specific agent in a defined geographic area

• Eradication
  – Permanent reduction to zero worldwide incidence of infection caused by a specific agent

• Extinction
  – The specific agent no longer exists in nature or the laboratory

Dahlem, Workshop on Eradication of Infectious Diseases, 1997
HPV and Cervical Cancer Satisfy Necessary Pre-Conditions for Elimination

1. No animal reservoir for the virus is known or suspected
2. Sensitive and specific tools are available for diagnosis and surveillance (and treatment)
3. Transmission from one individual to another can be interrupted

4. Non-lethal infection or vaccination confers life long immunity
5. The burden of disease is important to international public health
6. Political commitment to elimination efforts exist

Dahlem, *Workshop on Eradication of Infectious Diseases, 1997*
HPV Vaccination Interrupts Transmission

Australian Heterosexual Males

Genital Wart diagnoses (%)

- <21 years
- 21-30 years
- >30 years

Ali H et al. *BMJ* 2013 (extended data)
HPV and Cervical Cancer Satisfy Necessary Pre-Conditions for Elimination

1. No animal reservoir for the virus is known or suspected
2. Sensitive and specific tools are available for diagnosis and surveillance (and treatment)
3. Transmission from one individual to another can be interrupted
4. Non-lethal infection or vaccination confers life long immunity
5. The burden of disease is important to international public health
6. Political commitment to elimination efforts exist

Dahlem, Workshop on Eradication of Infectious Diseases, 1997
Programmatic Interventions to Prevent HPV Infection, Cervical Cancer, and Mortality

**PRIMARY PREVENTION**

Girls and Boys 9-14 years
- HPV vaccination
- Girls and boys, as appropriate
  - Health information and warnings about tobacco use*
  - Sexuality education tailored to age & culture
  - Condom promotion/provision for those engaged in sexual activity
  - Male circumcision

**SECONDARY PREVENTION**

Women >30 years of age
- Screening and treatment as needed
  - “Screen and treat” with low cost technology VIA followed by cryotherapy
  - HPV testing for high risk HPV types (e.g. types 16, 18 and others)

**TERTIARY PREVENTION**

All women as needed
- Treatment of invasive cancer at any age
  - Ablative surgery
  - Radiotherapy
  - Chemotherapy

WHO Guide to Introducing HPV Vaccine into National Immunization Programmes, 2016
Cervical Cancer Control

Screening + Treatment
Sensitive and Specific Tools For Hg CIN Diagnosis and Surveillance

- Cytology-based (Pap test)
  - Widespread use; requires good health care and laboratory infrastructure
- HPV DNA testing (preferred method)
  - HPV + Pap co-testing
  - Primary HPV test followed by triage test
- Visual inspection with acetic acid (VIA)
  - Screen-and-treat approach

Self-sampling methods hold the promise of overcoming cultural and access barriers

Ogilvie et al Int J Gynecol Obstet 2017
Image from Johns Hopkins - http://apps.pathology.jhu.edu/blogs/pathology/tag/pap-smear
Availability of Effective Cervical Intraepithelial Lesion Treatments

• Surgical
  – Cold knife conization
  – Large loop excision procedure (LLETZ or LEEP)

• Ablative
  – Cryotherapy
  – Thermal coagulation

Castle et al *In J Gynecol Obstet* 2017
Cervical Cancer Incidence Declines with Screening in the US, 1975-2014

![Graph showing the decline in cervical cancer incidence rates from 1975 to 2014, categorized by race/ethnicity.](image-url)
Cervical Cancer Elimination

Vaccination + Screening + Treatment
HPV Prevention Vaccines

- Nearly 100% efficacy against 7 oncogenic HPV types
- Safe
- Enduring protection
- Since 2013, heavily subsidized through GAVI and PAHO Revolving fund
- Feasible to reach >70% in LMICs as well as high resource countries

Joura et al NEJM 2015; Huh et al Lancet 2017; LaMontagne et al Int J Gynecol Obstet 2017
HPV Vaccination Reduces Genital HPV Infection, Genital Warts, and High-Grade CIN

- Australia
- Denmark
- The Netherlands
- Scotland
- Sweden
- United States
- Etc.

Effectiveness of HPV Vaccination Programs

Results from a Meta-Analysis

72% Lower HPV 16/18 Infection Prevalence Following HPV Vaccination in Girls 13-19 Years

- **Overall**: $P_{trend} = 0.005$
- **qHPV**
- **Low Coverage**
- **High Coverage**

-aData from 20 studies in 9 countries (United States, Australia, England, Scotland, New Zealand, Sweden, Denmark, Canada, and Germany).
-bCompared to pre-vaccination period.
-cIncludes both quadrivalent and bivalent HPV vaccines.

Vaccine-Type HPV Prevalence Significantly Declined Following qHPV Vaccination Program

- Significantly lower vaccine-type HPV prevalence was seen in the vaccine era (2007 to 2010) compared with the prevaccine era (2003 to 2006).

Vaccine HPV-Type Prevalence in Females 14 to 19 Years of Age, Before and After HPV Vaccine Introduction in the United States

-56% (P<0.001)
-50% (P<0.001)

Markowitz LE et al., J Infect Dis. 2013:208:385-393
Decline in Prevalence of 4vHPV Vaccine Types in Australian Females in Post-vaccine Period

Crude HPV prevalence among Australian females aged 18–24 years attending for routine cervical cytology screening according to study period

<table>
<thead>
<tr>
<th></th>
<th>2005-2007 (n=88)</th>
<th>2010-2012 (n=688)</th>
<th>2015 (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6, 11, 16, 18</td>
<td>22.7</td>
<td>7.3</td>
<td>1.5</td>
</tr>
<tr>
<td>HPV 31, 33, 45, 52, 58</td>
<td>14.8</td>
<td>19</td>
<td>15.5</td>
</tr>
<tr>
<td>HR-HPV types excluding 16&amp;18</td>
<td>33</td>
<td>36.5</td>
<td>p=0.80</td>
</tr>
<tr>
<td>Any HR-HPV types</td>
<td>40.9</td>
<td>39.1</td>
<td>p=0.80</td>
</tr>
<tr>
<td>Any HPV types</td>
<td>53.4</td>
<td>51.6</td>
<td>38</td>
</tr>
</tbody>
</table>

p<0.001  p=0.80  p=0.80  p=0.05  p=0.005

Dorothy A Machalek et al. Downloaded from https://academic.oup.com/jid/advance-article-abstract/doi/10.1093/infdis/jiy075/4841780
Cancer Incidence Among Vaccinated and Non-Vaccinated Finnish Females

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>HPV Vaccinated Women (65,565 person-years)</th>
<th>Non-Vaccinated Women (124,245 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate (95% CI)</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Vulva</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Other HPV cancers*</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>All HPV assoc. cancers</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>3.0 (0.8, 12)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>1.5 (0.2, 11)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
<td>4.6 (1.5, 14)</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>2</td>
<td>3.0 (0.8, 12)</td>
</tr>
</tbody>
</table>

* Vaginal carcinoma, anal carcinoma

Luostarinen et al, IJC, 2017
Relative Contribution of 7 and 2 HPV Types to HPV positive Cervical Cancer and Precancerous Lesions

![Graph showing the relative contribution of 7 HPV types and HPV 16/18 to different cervical lesions.]

- **Cervical Cancer**: 7 HPV types (20%) vs. HPV 16/18 (20%-30%)
- **CIN 3**: 7 HPV types (20%) vs. HPV 16/18 (50%)
- **CIN 2**: 7 HPV types (50%)
- **CIN 1**: 7 HPV types (25%) vs. HPV 16/18 (25%)

**References**


**Notes**

- **Overall contribution**:
  - CIN 1: 73%
  - CIN 2: 86%
  - CIN 3: 93%
  - Cervical cancer: 100%

a. HPV 6/11/16/18/31/33/45/52/58
Elimination of HPV 16, Cervical Cancer in Countries without Screening, and Non-Cervical HPV-Related Cancers

Vaccination
HPV 16 is Eliminated in Females When 80% of Both Boys + Girls are Vaccinated

HPV Elimination: What HPV Transmission Models Tell Us

- HPV 16 elimination requires:
  - ~40 years with girls + boys vaccination at 80% coverage, or
  - ~70 years with girls only sustained vaccination at 100% coverage
- Complete elimination including men who have sex with men (MSM) requires girls + boys vaccination
- Gender neutral HPV vaccine programs add resiliency to fluctuations in vaccine coverage over time

Brisson et al Lancet, 2016; Baussano et al JID 2017; Elfdtrom et al JID 2016
Political Will - Yes

• WHO – Global Action Plans
  • Global Vaccine Action Plan (GVAP)
  • Global Action Plan for the Prevention and Control of non-Communicable Diseases

• PAHO
• International and National non-Governmental Organizations
• Donors (e.g., Bill and Melinda Gates Foundation)
• Union for International Cancer Control
• International Federation of Gynecology and Obstetrics (FIGO)
• First Ladies Initiative (Pink Ribbon/Red Ribbon)
• Individual countries (e.g., Australia, Canada, etc.)
We have the tools to eliminate cervical cancer

Advocating for *elimination* will increase awareness and galvanize political will.
Participating Agencies

WHO
IAEA
IARC
UNAIDS
UNFPA
UNICEF
UNWomen
IPVS Statement

Moving Towards Elimination of Cervical Cancer as a Public Health Problem

IPVS is releasing a Call to Action to health authorities to adhere to international standards developed by WHO to develop national, regional and local plans to ultimately achieve the goal of cervical cancer elimination as a public health problem. A markedly reduced incidence of cervical cancer is possible in the near term, with elimination thereafter, if high rates of HPV vaccination and cervical screening are achieved.

Today we are poised to markedly reduce the incidence of cervical cancer, with the vision of eventually eliminating it as a public health problem, using the combination of sustained high coverage HPV vaccination and sustained high coverage screening with treatment.

Jan 2018

We should endorse and embark on a *Cervical Cancer Elimination* strategy with enthusiasm and without delay.

Kane M and Giuliano AR, *HPV World* 2018
Today I am calling for coordinated action globally to eliminate #CervicalCancer, one of the greatest threats to women’s health. We have the tools and, crucially, the political commitment to achieve it. Let’s beat cervical #cancer, let’s #BeatNCDs.

May 19, 2018
The End of Cervical Cancer is in sight

Aranda et al In J Gynecol Obstet 2017
HPV Vaccine Coverage:
13-17 year old (males and females combined)
National Indian Health Service

Data source: National Immunization Reporting System (NIRS):
https://www.ihs.gov/NonMedicalPrograms/ihipes/immunizations/index.cfm?module=immunizations&option=home
Cancers caused by the HPV are a significant public health problem. The NCI-designated cancer centers fully endorse the goal of eliminating cancers caused by HPV through gender-neutral HPV vaccination and evidence-based cancer screening. These practices offer a rare opportunity to prevent 12,000 cervical cancers and nearly 40,000 other HPV-related cancers among men and women annually in the United States.

June 7, 2018
A World Without HPV-Related Diseases

Eliminate Cervical Cancer as early as **2030** in some geographic regions

Eliminate HPV 16 **2060**
THANK YOU!