Deep Sea, Deep Science

Douglas R. Lowy
National Cancer Institute, National Institutes of Health

ACS National HPV Vaccine Roundtable Meeting
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The views expressed are my own and do not necessarily reflect those of NCI/NIH
Disclosures

• National Institutes of Health (NIH) has patents on papillomavirus L1 virus-like particle (VLP) vaccine technology. I am an inventor.

• NIH has licensed L1 VLP technology to Merck and GlaxoSmithKline, the two companies with commercial versions of the vaccine.

• *I will discuss a potential off-label use of the FDA-approved vaccines: protecting with a single vaccine dose*

• Licensees of other NIH technologies of which I am an inventor: GlaxoSmithKline, Sanofi, Shanta Biotech, Cytos Biotech, Aura Biosciences, Etna Biotech, Acambis, PanVax
Topics for this evening

• A "fish story"

• HPV vaccination, reducing disparities in the US and globally
  – Cervical cancer screening can reduce disease burden faster than vaccination

• A single vaccine dose: a future possibility?

• A 2025 goal
The closest I could get to a fish story


A “papillomavirus” whose genome is 5,748 bp. No lesions attributable to it have been described.
The closest I could get to a fish story

Lopez-Bueno et al, Concurrence of Iridovirus, Polyomavirus, and a unique member of a new group of fish papillomaviruses in lymphocytosis disease-affected gilthead seabream. J Virol 90: 8768-79, 2016. A “papillomavirus” whose genome is 5,748 bp. No lesions attributable to it have been described.

Bossart et al, Viral papillomatosis in Florida manatees (Trichechus manatus latirostris). Exp Mol Pathol 72: 37-48, 2002. “In 1997, seven captive Florida manatees developed multiple, cutaneous, pedunculated papillomas over a period of 6 months. Approximately 3 years later, four of the seven manatees developed multiple, cutaneous, sessile papillomas topically and clinically distinct from the initial lesions, some of which are still present.”
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Herman Melville, Chapter 32, Cetology, Moby-Dick, 1851. “The whale is a fish.”
Cervical cancer in the USA: Incidence in black women is now similar to white women; mortality disparity remains.

Current mortality rates
ASR* 2012-2016
Black women: 3.5
White women: 2.2

*ASR=Annual Standardized Rate
Cervical cancer screening can reduce cancer faster than vaccination.

Natural history is universal: Same in high- and low-resource settings.

Wentzensen and Schiffman Lancet Public Health 2017
Collaborators

Laboratory of Cellular Oncology, CCR, NCI

John Schiller

- Patricia Day
- Nicolas Cuburu
- Rhonda Kines
- Susana Pang
- Cynthia Thompson
- Alessandra Handisurya
- Lukas Bialkowski
- Alex Bell

- Chris Buck, Diana Pastrana
  - LCO, CCR, NCI, Bethesda
- Aimee Kreimer, Allan Hildesheim, Mark Schiffman, Mahboobeh Safaeian, Ligia Pinto
  - DCEG, NCI, Bethesda
- Peter Choyke, Marcelino Bernardo
  - Molecular Imaging, CCR, NCI, Bethesda
- Jeffrey Roberts – FDA, Rockville
- Rolando Herrero – IARC, Lyon, France
- Bryce Chackerian – University of New Mexico
- Reinhard Kirnbauer – University of Vienna, Austria
Neutralizing L1 Antibodies (in red) Bound to Papillomavirus Particle
Disease prevention goals of HPV vaccination: in less developed countries vs. more developed countries

- **Less developed countries:** mainly to protect against cervical cancer
  - Female vaccination most cost-effective

- **More developed countries:** to protect both males and females against a range of HPV-associated cancers
  - Female vaccination with high uptake is most cost-effective, but adding male vaccination can confer even greater protection for vaccinees than can herd immunity alone
  - Male vaccination is the fastest way to reduce HPV prevalence in MSM
Impact of bivalent HPV vaccine on young women in Scotland: herd immunity and reductions in cervical precancer and cervical cancer

HPV16/18 prevalence

Cervical Precancer

Cervical Cancer

From Scotland cancer statistics web site: https://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Female-Genital-Organ/#cervix

Kavanaugh et al, Lancet Infect Dis 17:1293-1302, 2017
In Black and Hispanic women, 9-valent HPV vaccine may be especially useful for preventing more precancers

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
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<tbody>
<tr>
<td><strong>Cervical cancer</strong></td>
<td></td>
<td></td>
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<tr>
<td>HPV16/18</td>
<td>67%</td>
<td>68%</td>
<td>64%</td>
</tr>
<tr>
<td>HPV31/33/45/52/58</td>
<td>12%</td>
<td>15%</td>
<td>18%</td>
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<tr>
<td>Total</td>
<td>79%</td>
<td>83%</td>
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<tr>
<td><strong>In situ cervical cancer</strong></td>
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</tr>
<tr>
<td>HPV16/18</td>
<td>67%</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>HPV31/33/45/52/58</td>
<td>16%</td>
<td>37%</td>
<td>26%</td>
</tr>
<tr>
<td>Total</td>
<td>83%</td>
<td>64%</td>
<td>76%</td>
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*From Saraiya et al, JNCI, 2015*
Lower HPV vaccine uptake in many states with higher incidence of HPV-associated cancer

Incidence of HPV-associated cancers

Percentage of adolescents who are up to date on HPV vaccination

Source: MMWR August 28, 2015

www.cdc.gov/hpv
### 2017 HPV and Meningococcal Vaccination Rates for 13-17 year olds

<table>
<thead>
<tr>
<th></th>
<th>HPV vaccine (≥1 dose)</th>
<th>Meningococcal vaccine (≥1 dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>65%</td>
<td>85%</td>
</tr>
<tr>
<td>Below poverty</td>
<td>73%</td>
<td>86%</td>
</tr>
<tr>
<td>At or above poverty</td>
<td>63%</td>
<td>85%</td>
</tr>
<tr>
<td>Illinois</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicago</td>
<td>82%</td>
<td>91%</td>
</tr>
<tr>
<td>Rest of state</td>
<td>63%</td>
<td>89%</td>
</tr>
<tr>
<td>Indiana</td>
<td>59%</td>
<td>93%</td>
</tr>
</tbody>
</table>

*From MMWR August 24, 2018*
One more complication: A worldwide HPV vaccine shortage

- In 2018, UNICEF and the World Health Organization called attention to a worldwide shortage of the HPV vaccine.
  - https://www.unicef.org/supply/files/HPV_2_Status_Update.pdf
- Secondary to increased vaccine demand
- The shortage is projected to last several years.

**Question:** During this period, should there be policy implications in the industrialized world when considering **adding** gender-neutral vaccination or **increasing** the age range for recommending vaccination?
The challenge to global HPV vaccination

*107 million girls 10-14 years old have received at least one dose of the HPV vaccine (2006-2017)*

• However, <5% of eligible girls have been vaccinated in Low- and Middle-Income Countries (LMICs), where ~90% of cervical cancer deaths occur

• Worldwide >60 million girls are now born annually

To control of cervical cancer worldwide, should vaccinate 40-50 million girls in each birth cohort
Might a single HPV vaccine dose confer years of protection?
One dose is not inferior to three doses (post-hoc analysis)

The Costa Rica Vaccine Trial: Prevalent HPV infection 11 years after bivalent HPV vaccination:

- HPV 16/18
- HPV 31/33/35
- Other HPV
Stable HPV16 serum antibodies 11 years after one dose of the bivalent HPV vaccine (post-hoc analysis)

100% of 1 dose recipients remain seropositive at 11 years.
Randomized controlled trial in Costa Rica to test efficacy of 1 dose vs. 2 doses (NCI & Gates Foundation)

- 4-arm: 1 vs. 2 dose Cervarix
  1 vs. 2 dose Gardasil9
- 5000 12-16 year old females per arm
- Survey of HPV prevalence in region
- 4 year primary trial, longer term follow-up

For more information
  - clinicaltrials.gov: Identifier NCT03180034
  - Aimee Kreimer et al, Vaccine 2018
Potential impact of demonstrating 1 dose can confer strong protection

- Could change standard of care in US & globally
  - Could save US > $300 million each year in vaccine costs
- Could make it feasible to control the worldwide public health problem of cervical cancer and other HPV-associated cancers
A 2025 Goal: HPV16 will replace the bald eagle on the endangered species list!