HPV Vaccination to prevent HPV-associated cancers

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Demystifying Medicine
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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 potential off-label uses of the EMA/FDA-approved vaccines: protecting against HPV-positive oropharyx cancer and fewer vaccine doses

• Licensees of other NIH technologies of which I am an inventor: GlaxoSmithKline, Sanofi, Shanta Biotech, Cytos Biotech, Aura Biosciences, Etna Biotech, Acambis, PanVax
More than 40% of men & women 18-59 have genital HPV infection

McQuillan et al, NCHS Databrief 280, 2017
IARC’s Globocan 2012 projection: Cervical cancer mortality rates continue to increase in Low- & Middle-income countries (LMIC’s)

- In LMIC’s, cervical cancer represents ~90% of HPV-associated cancer

*Projections developed from Globocan 2012*
USA: HPV-associated cancers affect both sexes

Cancers Attributable to HPV infection

- **MEN**
  - Penile
  - Anal
  - Oropharyngeal

- **WOMEN**
  - Cervical
  - Vulvar/Vaginal

% HPV positive

- Cervical: ~100%
- Non-cervical cancers:
  - Penile: 63%
  - Anal: 70%
  - Vulvar/Vaginal: 91%
  - Oropharyngeal: 70%

Annual number of cases

- Total number of HPV-positive cancers = ~31,000. 65% women; 35% men
- HPV16/18: Accounts for 70% of cervical cancers, 90% of non-cervical cancers
- Pap screening has reduced cervical cancer incidence by ~80%
- Incidence of HPV-positive oropharynx cancer 1988-2004 increased >3-fold

*Adapted from Viens, et al., MMWR, 2016*
First Generation
HPV Vaccines
Many Collaborators: If you want to go quickly, go alone; If you want to go far, go together

Laboratory of Cellular Oncology, CCR, NCI

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Choosing an appropriate molecular target for a preventive HPV vaccine

• Licensed vaccines: mainly preventive, induce neutralizing antibodies

• HPVs contain viral oncogenes (E5, E6, E7); need subunit vaccine lacking oncogenes.

• Two HPV proteins can induce neutralizing antibodies: capsid proteins L1 and L2.
  – L1 contains the most immunogenic neutralization epitopes; conformational

• OUR HYPOTHESIS: L1 self-assembles, makes empty particles with correct conformation, induce high levels of neutralizing antibodies.
Prophylactic HPV Vaccines Are L1 Virus-Like Particles (VLPs)

Insert L1 in Baculovirus expression vector

Produce L1 in insect cells

L1 spontaneously assembles into VLPs

L1 VLP vaccination Induces high titers of neutralizing antibodies

Shown first for BPV-1, then for HPV16

Non-infectious, Non-oncogenic

First generation HPV vaccines: Composed of Multiple Types of HPV L1 VLPs

Gardasil (quadrivalent, Merck)

HPV16

70% of Cervix Cancer

>90% of Non-cervix Cancer

HPV18

HPV6

90% of Genital Warts

HPV11

Cervarix (bivalent, GlaxoSmithKline)

Three intramuscular injections over 6 months
• Prospective post-licensure assessment of 600,558 doses (Gardasil) from 7 managed care organizations

• **No excessive vaccine-related increased risk to prespecified outcomes:** Guillan-Barré syndrome, stroke, venous thromboembolism, appendicitis, seizure, **allergic reactions**
  – Prespecified outcomes derived from CDC analysis from VAERS (Vaccine Adverse Events Reporting System): Slade et al, JAMA 2009

• **Rate of anaphylaxis (1 case, 26 y.o.) similar to other vaccines**

• Rate of fainting similar to that of other adolescent vaccines

• Similar conclusions in recent review: Gee et al, Hum Vaccin Immunother 2016
Short-term Population-wide Impact of HPV Vaccination
Goals of HPV Vaccination

- Directly reduce risk of infection and disease in vaccinees
- Indirectly reduce risk by reducing prevalence of “HPV vaccine types” in general population (herd immunity)
Age-dependent decrease in genital warts in Australian women after HPV Vaccine Implementation in 2007

Herd Immunity: Decreased incidence of genital warts in heterosexual Australian men following female HPV vaccine implementation in 2007

Herd immunity: Decreased prevalence of HPV6/11/16/18 in heterosexual Australian men following female HPV vaccine implementation in 2007

Chow et al, Lancet Infect Dis 17:68-77, 2017
**Trends in U.S. Vaccination Rates: Ages 13-17 Years**

MMWR Vol. 66, #33, August 25, 2017

![Graph showing vaccination rates](image-url)
Parents’ Top 5 Reasons for not vaccinating their Children with the HPV Vaccine (CDC, 2013)

<table>
<thead>
<tr>
<th>Reason</th>
<th>%</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents of girls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of knowledge</td>
<td>15.5</td>
<td>(13.0–18.5)</td>
</tr>
<tr>
<td>Not needed or necessary</td>
<td>14.7</td>
<td>(12.5–17.3)</td>
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<tr>
<td>Safety concern/Side effects</td>
<td>14.2</td>
<td>(11.8–16.8)</td>
</tr>
<tr>
<td>Not recommended</td>
<td>13.0</td>
<td>(10.8–15.5)</td>
</tr>
<tr>
<td>Not sexually active</td>
<td>11.3</td>
<td>(9.1–13.9)</td>
</tr>
<tr>
<td>Parents of boys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not recommended</td>
<td>22.8</td>
<td>(20.6–25.0)</td>
</tr>
<tr>
<td>Not needed or necessary</td>
<td>17.9</td>
<td>(15.9–20.1)</td>
</tr>
<tr>
<td>Lack of knowledge</td>
<td>15.5</td>
<td>(13.7–17.6)</td>
</tr>
<tr>
<td>Not sexually active</td>
<td>7.7</td>
<td>(6.4–9.2)</td>
</tr>
<tr>
<td>Safety concern/Side effects</td>
<td>6.9</td>
<td>(5.6–8.5)</td>
</tr>
</tbody>
</table>

Stokley et al, MMWR 63:620-4, July 25, 2014
Decreased prevalence of HPV16/18 in the US despite limited HPV vaccine uptake: 14-19 year old girls (51% received 1 or more doses)

Adapted from Markowitz et al, Pediatrics 2016
High Efficacy of VLP Vaccine

- Repetitive structure of VLP intrinsically immunogenic
- Tissue-associated neutralizing antibodies exudated at potential sites of infection
  - Levels of exudated antibodies high, similar to serum levels, not lower levels of non-disrupted genital tract
- HPV highly susceptible to neutralizing antibodies
- For further discussion: see Schiller & Lowy, Vaccine 2018
Neutralizing L1 Antibodies (in red) Bound to Papillomavirus Particle
Second generation vaccine: Protecting against more HPV types
Further reduction in cervical cancer by adding more HPV Types to L1 VLP Vaccine

Adapted from Munoz et al, Int J Cancer 111: 278-85, 2004
Increasing HPV vaccine uptake: Safely reducing the number of doses
Moving to two vaccine doses for young adolescents

- Immune response in girls and boys <15 years old stronger than older teenagers
- Young adolescents: 2 doses separated by 6 months produce an immune response even greater than the efficacy trials
  - Immunogenicity of 9-valent vaccine: Iverson et al., JAMA. 316: 2411-21, 2016
- **October 2016: FDA approves and ACIP recommends 2 doses for 9-valent vaccine for adolescent girls and boys 9-14**
Might a single HPV vaccine dose confer years of protection?
A challenge: Projected limited impact on worldwide cervical cancer from current global HPV vaccination rates

- Only ~3% of eligible women in Low- and Middle-income countries (LMICs) have been vaccinated
  - ~33% of eligible women in industrialized world have been vaccinated
- Women in LMICs account for ~90% of worldwide cervical cancer mortality; ~8% of worldwide female cancer mortality
- Widespread global uptake of HPV vaccine may require decreased costs & simplified logistics
- Possible solutions: Producing biosimilar vaccines and protecting vaccinees with a single dose
1, 2, or 3 doses of bivalent vaccine confer at least 7 years of protection against incident HPV 16/18 infection: Post-hoc analysis

Safaeian et al, J Natl Cancer Inst, published August 28, 2017

- Similar shorter term results in GSK PATRICIA trial: Kreimer et al, Lancet Oncol 2015
- Similar shorter term Gardasil results in IARC India trial, Sandaranarayanan et al, Lancet Oncol 2016
Stable HPV16/18 serum antibodies after bivalent HPV vaccination: Costa Rica Vaccine Trial

Safaeian M et al, JNCI, published August 28, 2017
Randomized controlled efficacy trial in Costa Rica to test efficacy of 1 dose vs. 2 doses (NCI & Gates Foundation)

- A 4-arm non-inferiority trial in 12-16 year old girls: compare protection from 1 dose and 2 doses of bivalent vaccine (Cervarix, GSK) and 9-valent vaccine (Gardasil9, Merck)
  - Unethical to have a placebo arm; measure current HPV prevalence in young women in same area
- Main hypothesis: Protection induced by 1 dose is not inferior to 2 doses
- Second hypothesis: Protection will be similar for 1 dose of either vaccine (evaluates possible role of adjuvant; Merck uses alum, GSK uses AS04)
- For more information:
  - For 1 dose trial concept, see Kreimer et al, J Natl Cancer Inst, 2015; Kreimer et al, Vaccine, in press
  - See clinicaltrials.gov: Identifier NCT03180034
Potential impact of demonstrating 1 dose can confer strong protection

- Could establish a new minimum serum antibody titer needed for high level protection
- Could provide a strong rationale for considering a repetitive structure for future vaccines against other agents
- 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
Henrietta Lacks (HeLa cells) had Cervical Adenocarcinoma

- Pap smear screening: more sensitive for squamous cell carcinoma than adenocarcinoma
- ~90% of cervical adenocarcinoma caused by HPV16 or HPV18
- Henrietta Lacks: HPV 18 cervical adenocarcinoma not detected by cytology
- Her cancer should now be preventable by HPV vaccination or by HPV-based screening
A longer-term goal: “Rapid” reduction in worldwide cervical cancer by Vaccinating multiple birth cohorts of younger women & screening older women

Bosch et al, HPV Faster, Nature Rev Clin Oncol, 2016; modified by Mark Schiffman
Summary and Conclusions

• Basic research led to identification of HPV as the cause of several cancers and to development of the HPV vaccine

• The HPV vaccine is highly effective in preventing new infection and disease caused by the HPV types targeted by the vaccine
  – The HPV vaccine can induce strong herd immunity
  – It may be possible to induce long-term protection with even a single dose

• Control of HPV-associated cancer as a worldwide public health problem may soon be feasible