The Estimated Impact and Cost-effectiveness of Nonavalent HPV Vaccination in the United States

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Human papillomaviruses
- Family of non-enveloped DNA viruses
- >150 types found in humans
- Tropism for mucosa or keratinized skin
- ~40 mucosal types
  - "Low risk" - non-oncogenic types
  - "High risk" - oncogenic types

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Diseases associated with human papillomavirus (HPV)
- Oncogenic types (16, 18, 31, 33, 45, 52, 58, others)
  - Cervical cancers
  - Other cancers
    - Oropharyngeal cancers
    - Anal cancers
    - Vaginal cancers
    - Vulvar cancers
    - Penile cancers
    - High grade intraepithelial neoplasias
- Non-oncogenic types (6, 11, others)
  - Anogenital warts
  - Recurrent respiratory papillomatosis (RRP)
  - Low grade intraepithelial neoplasias

Available HPV vaccines

<table>
<thead>
<tr>
<th></th>
<th>Bivalent (Cervarix)</th>
<th>Quadrivalent (Gardasil)</th>
<th>9-valent (Gardasil 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 VLP types</td>
<td>16, 18</td>
<td>6, 11, 16, 18</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, 58</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>GlaxoSmithKline</td>
<td>Merck &amp; Co.</td>
<td>Merck &amp; Co.</td>
</tr>
<tr>
<td>First licensure in US</td>
<td>2009</td>
<td>2006</td>
<td>2014</td>
</tr>
</tbody>
</table>

~99% of HPV vaccine administered in US through 2014 has been quadrivalent vaccine

L1: Main capsid protein; VLP: virus-like particle
Marked in June 2015 ACIP
Disease burden associated with HPV types in the US

- **HPV 16/18** (targeted by bivalent, quadrivalent, 9-valent)
  - Account for 64% of invasive HPV-associated cancers
  - 65% female, 63% male, ~21,300 cases annually
  - 66% of cervical cancers, 50% of ≥CIN2

- **HPV 6/11** (targeted by quadrivalent and 9-valent)
  - Account for 90% of anogenital warts and most RRP

- **HPV 31,33,45,52,58** (targeted by 9-valent)
  - Account for 10% of invasive HPV-associated cancers
  - 14% female, 4% males, ~3,400 cases annually
  - 15% of cervical cancers, 25% of ≥CIN2

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Mathematical models critical to predict impact and cost-effectiveness of HPV vaccine strategies

- Long term benefits of HPV vaccination will not be realized for decades
  - Many adverse health outcomes
- Indirect effects (“herd effects”) of HPV vaccination

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Overview of study

<table>
<thead>
<tr>
<th>Study feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model structure</td>
<td>Simplified deterministic, dynamic, population-based model</td>
</tr>
<tr>
<td>Perspective</td>
<td>Societal</td>
</tr>
<tr>
<td>Time frame</td>
<td>100 years</td>
</tr>
<tr>
<td>Analytic horizon</td>
<td>100 years + lifetime costs averted and lifetime QALYs averted over 100-year period</td>
</tr>
<tr>
<td>Cervical cancer screening</td>
<td>Assumed to occur but not explicitly modeled</td>
</tr>
<tr>
<td>Study question</td>
<td>What is the cost-effectiveness of a 9-valent HPV vaccination program for both sexes in the US, compared to a quadrivalent HPV vaccination program for both sexes?</td>
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Selected model assumptions

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<tbody>
<tr>
<td>Ages vaccinated</td>
<td>12-26 years (female) 12-21 years (male)</td>
</tr>
<tr>
<td>Vaccine efficacy (quadrivalent &amp; 9-valent)</td>
<td>95%</td>
</tr>
<tr>
<td>Quadrivalent cross-protection efficacy against additional high-risk HPV types*</td>
<td>In some scenarios: HPV 52: 45.2%, HPV 33: 38.7%, HPV 58: 32.8%, HPV 70: 18.4%, HPV 31: 3.5%</td>
</tr>
<tr>
<td>Duration of vaccine protection</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Vaccine cost per dose including $15 per dose administration</td>
<td>$145 quadrivalent, $158 9-valent</td>
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Selected model assumptions

Cumulative vaccination coverage

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Lower coverage scenario</th>
<th>Base case coverage scenario</th>
<th>Higher coverage scenario</th>
</tr>
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<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>13 to 17</td>
<td>37.9%</td>
<td>14.0%</td>
<td>45.5%</td>
</tr>
<tr>
<td>17</td>
<td>48.0%</td>
<td>19.5%</td>
<td>56.4%</td>
</tr>
<tr>
<td>26</td>
<td>55.2%</td>
<td>22.8%</td>
<td>63.9%</td>
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BASE CASE RESULTS

Reduction in incidence of cervical intraepithelial neoplasia 2/3

Cost-effectiveness of 9-valent (both sexes) vs quadrivalent (both sexes)

<table>
<thead>
<tr>
<th>Incremental cost per quality-adjusted life year (QALY) gained</th>
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<td>No quadrivalent cross-protection</td>
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Reduction in cervical cancer incidence

Incremental cost per quality-adjusted life year (QALY) gained

| No quadrivalent cross-protection                              |
| With quadrivalent cross-protection                            |
| <$0 (cost-saving)                                             |
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SENSITIVITY ANALYSES

Cost-effectiveness of 9-valent (both sexes) vs quadrivalent (both sexes)

Sensitivity analysis: No cross protection for quadrivalent

- In one-way sensitivity analyses, 9-valent vs. quadrivalent for both sexes was cost-saving, except
  - Higher cost per 9-valent vaccine series ($513): $16,700 per QALY
  - Higher vaccine coverage scenario: $3,900 per QALY
  - Lower medical costs per HPV outcome: $6,700 per QALY
  - Lower incidence rates of HPV outcomes: $3,900 per QALY
  - Lower % of disease caused by HPV vaccine types: $10,900 per QALY
- In multi-way sensitivity analyses, cost-per QALY ranged from < $0 (cost-saving) to $12,800 in 90% of simulations

Summary

- We found favorable cost-effectiveness ratios for 9-valent HPV vaccine across a wide range of assumptions
  - Vaccine characteristics: coverage, efficacy, cost
  - Burden of HPV-associated health outcomes
    - Medical costs, quality of life impacts, and incidence
    - Percent of health outcomes attributable to vaccine types
- Results consistent with other, more complex models
- Providing 9-valent vaccine to females accounted for most of the medical costs averted and QALYs gained by 9-valent vaccination of both sexes (vs. quadrivalent for both sexes)

Limitations

- Our model incorporates several simplifying features
  - Does not explicitly account for cervical cancer screening
  - Does not explicitly model natural history of HPV
    - Reduction in disease burden of a given HPV type assumed proportional to reduction in cumulative exposure to the HPV type
  - Simple model of transmission dynamics
    - Does not classify the population according to sexual activity level
    - Does not explicitly model mixing of sex partners
- Uncertainty in model parameters
  - Quality of life impacts of cervical cancer precursors
  - Vaccine duration of protection
  - Model unable to account for less than lifetime duration

Conclusions

- At current vaccine costs, 9-valent vaccination is likely cost-saving compared to quadrivalent vaccination
  - Medical costs averted by preventing outcomes related to HPV 31, 33, 45, 52, 58 exceed additional cost of 9-valent vaccine in most scenarios
- Results consistent over wide range of sensitivity analyses
  - Cost per QALY < $0 in most scenarios, < $20,000 in all scenarios
- Results consistent with other models
  - Consistency across 3 distinct models will likely be reassuring to decision makers
Acknowledgments:

Modeling team:
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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

Thank you
HChesson@cdc.gov

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