HPV and cervical cancer control
Epidemiological modeling

Barriers in HPV vaccination & cervical screening programmes
Antwerp, Belgium, 27-28 June 2016

International Agency for Research on Cancer
Lyon, France
“Cancer research for cancer prevention”

Iacopo Baussano
Outline

• Mathematical models of HPV transmission
  – HPV transmission
  – HPV progression (not presented)

• Epidemiological modeling (projections & empirical)
  – Impact of catch-up in High-income countries
  – Impact of catch-up in Middle/Low-income countries

• Effect of Herd Immunity
  – HPV prevalence heterogeneity across populations
  – HPV prevalence heterogeneity within populations
  – Finnish community randomized vaccination trial
HPV transmission model

Calibration against empirical data from several countries

Cross-validation against independent sets of data from the same countries

Source: NTCC trial, Ronco et al 2010

Rates dependent on age only
Rates dependent on age and time elapsed since infection

* all causes mortality rate
Catch-up in Sweden: faster & resilient

Alternative vaccination strategies

~5 to 7 years faster

Routine (age 11)

Routine (age 11) and catch-up (age 12-18)

Routine (age 11) and catch-up (age 12-26)

Coverage: routine, 70%; catch-up, 50%; extended catch-up, 70%
*Reduction attributable to vaccination, among 15-34 year-old women

Evidence of Early Impact: Catch-up

- Model-based projections
  - IARC HPV-transmission model
  - Replicates HPV prevalence
  - Simulated vaccination introduction with realistic coverage
  - Adapted sexual behavior of young birth cohorts

- Chlamydia screening in Sweden
  - Genital swabs or urine samples; PCR with genotyping.
  - Most samples were from women 18 to 23 years of age.
  - Vaccination coverage available for each birth cohort.
  - HPV6/11/16/18 prevalence decline, only among women below 23 years of age (high vaccination coverage)

Sources: Soderlund-Strand A et al. 2014, CEPB & Elfstrom KM et al. 2015, JID
Monitoring HPV vaccination in Rwanda

- **Surveys.**
  - *Cytology:* general population, n. 2,508, aged 18–69, 20% HIV positive.
  - *Urine:* school-based, n. 912, aged 17-22

Rwanda, 2011 (Gardasil; MoH MSD)

Cumulative human papillomavirus vaccination coverage, by vaccination round

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls vaccinated in school, no.</td>
<td>91,752</td>
<td>89,704</td>
<td>88,927</td>
</tr>
<tr>
<td>Girls vaccinated outside school, no.</td>
<td>2,136</td>
<td>3,066</td>
<td>3,180</td>
</tr>
<tr>
<td>Total no. of girls vaccinated</td>
<td>93,888</td>
<td>92,770</td>
<td>92,107</td>
</tr>
<tr>
<td>Cumulative coverage (%)</td>
<td>95.04</td>
<td>93.90</td>
<td>93.23</td>
</tr>
</tbody>
</table>

**Prevalence**
- Any HPV = 34%
- HR-HPV = 22%
- HPV16/18 = 7%

Adapted from Ngabo et al BMC Infect Dis, 2016 & Binagwaho et al. Bull World Health Organ 2012
## Urine survey: effect of vaccination

### Choice of test for HPV prevalence monitoring from urine sensitivity versus specificity

<table>
<thead>
<tr>
<th>Vaccinated</th>
<th>N</th>
<th>HPV6/11/16/18-pos</th>
<th>Adjusted(^1) PR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bhutan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP5+/6+</td>
<td>973</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77</td>
<td>2 (2.6)</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>896</td>
<td>6 (0.7)</td>
<td>0.32 (0.06-1.64)</td>
</tr>
<tr>
<td><strong>E7-MPG (IARC)</strong></td>
<td>973</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77</td>
<td>1 (1.3)</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>896</td>
<td>11 (1.2)</td>
<td>0.86 (0.11-6.77)</td>
</tr>
<tr>
<td><strong>Rwanda</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP5+/6+</td>
<td>912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>519</td>
<td>21 (4.1)</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>393</td>
<td>2 (0.5)</td>
<td>0.12 (0.03-0.51)</td>
</tr>
<tr>
<td><strong>E7-MPG (IARC)</strong></td>
<td>912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>519</td>
<td>33 (6.4)</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>393</td>
<td>11 (2.8)</td>
<td>0.45 (0.23-0.90)</td>
</tr>
</tbody>
</table>

\(^1\)Adjusted for age and sexual behavior
HPV Prevalence* heterogeneity

Mostly attributable to different sexual activity patterns (i.e. ≠ incidence)

Median prevalence = 4.2%
10th to 90th centiles = 0.6% to 10.8%

Age-adjusted prevalence of cervical HPV in sexually active women aged 15–69 years

*Pre-vaccination prevalence, source: IARC Multi-centre HPV Prevalence Surveys, 1995-2016
HPV prevalence across populations

- Assuming same vaccination coverage & efficacy
  - ≠ HPV16 prevalence (i.e. 1% vs. 5%).
  - Women ≤ 35 years of age.
  - For any level of coverage impact of vaccination is larger in population 1% prevalence.
  - Same direct effect across populations, different herd immunity effect.
  - Larger HI in populations with lower prev.

- HPV control thresholds
  - Same vaccination coverage are likely to meet ≠ prevalence reduction targets according to the pre-vaccination prevalence.
  - Crucial difference with most vaccine-preventable infections, elimination threshold ($P_c$) assumed as constant across populations.
  - HPV R$_0$ range $\sim$1.8 to 5.0 $\rightarrow$ $P_c$= to 45% to 80%
≠ HPV prevalence within populations

- HPV16 vs. HPV45
  - Share the transmission network
  - Prevalence determined by their ≠ biology (in particular Infection Duration)
  - Infection duration is inversely related to $R_0$ → directly related to $P_c$

- Implications to project the impact of HPV vaccination against types other than HPV16/18
  - HI estimated for HPV16 is a conservative estimate of the HI expected for other types
  - Impact of vaccination is proportional to the fraction of cancer attributable to each HPV type

For any level of coverage impact of vaccination is larger for HPV45
Arm A communities (n.11): 90% of participating girls and boys were assigned to receive HPV-16/18 vaccine.

Arm B communities (n.11): 90% of girls were assigned to receive HPV-16/18 vaccine, boys were assigned to receive hepatitis B-virus (HBV) vaccine.

Arm C communities (n.11): all were assigned to receive HBV-vaccine.

Notably, sample size calculations allowed for herd immunity effect and were obtained using an HPV transmission model.

Lehtinen M. et al, Vaccine 2015
HPV vaccination in Finland

<table>
<thead>
<tr>
<th>Birth cohort/Calendar year</th>
<th>ICL/IARC model(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine coverage</strong></td>
<td></td>
</tr>
<tr>
<td>(\phi) 45.5% (Arm B)</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>n.a.</td>
</tr>
<tr>
<td>Reduction</td>
<td>n.a.</td>
</tr>
<tr>
<td>(\phi) 47.5%/(\phi) 19.8% (Arm A)</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>n.a.</td>
</tr>
<tr>
<td>Reduction</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Lehtinen M. et al, Vaccine 2015
Conclusions – Future developments

• Catch-up
  – Accelerate direct protection against HPV (and consequently cervical cancer) among cohort of sexually active women at vaccination.
  – Accelerate indirect protection against HPV (and consequently cervical cancer) among unvaccinated and sexually active women.
  – Modeling and empirical results are consistent

• Herd immunity effect
  – Is not constant across populations and HPV types
  – Is directly dependent from HPV prevalence in absence of vaccination
  – Populations with different HPV prevalence need different coverage to reach the same HPV control threshold
  – In the same population vaccination coverage may generate ≠ HI vs. ≠ HPV types
  – Finnish trial will provide empirical data to test the model-based findings
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IARC
– Infection and Cancer section
– Cancer Surveillance section

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