Informing HPV vaccination strategy about target groups: girls-only, gender-neutral, catch-up and selective adult vaccination

Johannes A Bogaards, PhD

National Institute for Public Health and the Environment, The Netherlands
VU University Medical Centre, Amsterdam, The Netherlands
## Disclosure belangen spreker

<table>
<thead>
<tr>
<th>(potentiële) belangenverstrengeling</th>
<th>Geen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voor bijeenkomst mogelijk relevante relaties met bedrijven</td>
<td>Niet van toepassing</td>
</tr>
<tr>
<td>• Sponsoring of onderzoeksgeld</td>
<td>•</td>
</tr>
<tr>
<td>• Honorarium of andere (financiële) vergoeding</td>
<td>•</td>
</tr>
<tr>
<td>• Aandeelhouder</td>
<td>•</td>
</tr>
<tr>
<td>• Andere relatie, namelijk ...</td>
<td>•</td>
</tr>
</tbody>
</table>
Outline

1. Some HPV background
2. Girls-only vaccination revisited
3. Improving HPV prevention?
4. Current outlook

RVP research day | November 10, 2017
Human papillomavirus (HPV)

- Papillomaviridae: small skin viruses
  - ~8 kbp ds DNA circular genome

- Cutaneous vs mucosal tropism
  - Virus ≠ host-species phylogeny

- High diversity in mammalian hosts
  - >170 HPV types identified

- alpha-genus oncogenic in humans
  - 15 HPV types “high-risk”
  - Transmitted through sexual contact

IG Bravo et al. (2010), *Trends in Microbiology*
HPV induced processes: infectious virion producing pathway in non-dividing cells and the clonal transforming pathway in dividing cells

Depuydt et al. (2016), *Facts Views Vis Obgyn*
Molecular events leading to HPV-induced (high-grade) neoplasia, i.e. the abnormal proliferation of benign or malignant cells

Wilting & Steenbergen (2016), *Papillomavirus Res*
Vink et al. (2013), *Am J Epidemiol*
Cervical screening relies on diagnosis and treatment of high-grade CIN

Restructured HPV-based screening program
HPV vaccines

- HPV-VLP vaccines available since 2006
  - >95% efficacy if given before sexual debut

- Three vaccines; all target HPV16 and -18
  - associated with majority of (cervical) cancers
  - bi- (Cervarix), quadri- (Gardasil) and nonavalent

- Since 2014, the bi- and quadrivalent vaccines are licensed in a reduced two-dose schedule

- Strong cross-protection reported for Cervarix

A VLP (virus-like particle) looks exactly like the virus but contains no viral DNA
A decade since the first national introduction of HPV vaccination in Australia, we have seen vaccine introductions in over 50 countries...

Donken et al. (2016), *Hum Vaccin Immunother*
... but introduction in settings with highest burden is lagging behind

Estimated no. of HPV16/18-related cervical cancers per 100 000 girls

Jit et al. (2014), *Lancet Global Health*
Of 14 million new cancer cases worldwide in 2012, 640 thousand (4.6%) were attributable to HPV, of which 570 thousand (89%) in women.
### Disease burden of HPV infection in the Netherlands, 2011-2014:
approximately 60% due to cervical disease, 25% in males

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>Est. average annual burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV (2011-2014)</td>
<td>13,795</td>
</tr>
<tr>
<td>Pneumococcal disease</td>
<td>9,444</td>
</tr>
<tr>
<td>Influenza*</td>
<td>8,670</td>
</tr>
<tr>
<td>HIV*</td>
<td>6,987</td>
</tr>
<tr>
<td>HPV excl. cervix</td>
<td>5,627</td>
</tr>
<tr>
<td>Legionellosis*</td>
<td>4,283</td>
</tr>
<tr>
<td>Toxoplasmosis*</td>
<td>3,593</td>
</tr>
<tr>
<td>Chlamydia*</td>
<td>3,551</td>
</tr>
<tr>
<td>HPV excl. females</td>
<td>3,345</td>
</tr>
</tbody>
</table>

* est. average annual burden 2007-2011

---

Van Lier et al. (2016), *PLoS One*
McDonald et al. (2017), *Cancer Causes Control*
Cost-effectiveness of cervical cancer prevention by vaccination @ 12y

‘He who seeks for gain, must be at some expense’
Back to the future: introducing girls-only programs in EU, North America
Seto et al. (2012), Drugs [Systematic Review, studies published 2007-2010]
Girls-only vaccination in the Netherlands; the benefit of hindsight pt. 1
Anticipated and realized participation (and projected impact) of HPV vaccination

Impact van HPV vaccinatie

Anticipated HPV vaccine uptake
Realized HPV vaccine uptake

Cost reduction
Impact reduction

Some HPV background
Girls-only vaccination revisited
Improving HPV prevention?
Current outlook

RVP research day | November 10, 2017
Indirect effects of HPV vaccination on cervical cancer prevention: at current vaccine uptake in girls, 1 in 4 cases averted is in non-vaccinated women.

Bogaards et al. (2011), *Epidemiology*
Some HPV background
Girls-only vaccination revisited
Improving HPV prevention?
Current outlook

Girls-only vaccination in the Netherlands; the benefit of hindsight pt. 2
Input to Coupé et al. (2009), Int J Cancer; De Kok et al. (2009), J Natl Cancer Inst
Trends in HPV-related disease burden in the Netherlands, 1989-2014: the gap between females and males is diminishing

McDonald et al. (2017), Cancer Causes Control
Girls-only vaccination in the Netherlands; the benefit of hindsight pt. 3
Long-term impact on HPV16/18-related cancer burden in males

Bogaards et al. (2015), BMJ
Including non-cervical diseases in economic evaluations of HPV vaccination makes girls-only vaccination about 3 times more favorable

Suijkerbuijk et al. (2017), *Expert Rev Vaccines*
Girls-only vaccination in the Netherlands; the benefit of hindsight pt. 4
Qendri et al., Vaccine price development in EU tender-based settings (EUROGIN)
Some HPV background
Girls-only vaccination revisited
Improving HPV prevention?
Current outlook

The combined benefit of hindsight: Revised health and economic impact of HPV16/18 vaccination in the Netherlands

ICER of girls-only vaccination (3% discount rate)

Coupé et al. (2009) ~40,000 euro/QALY
Qendri et al. (2017) ~ 2,000 euro/LY

Qendri et al. (2017), J Infect Dis
Girls-only vaccination in the Netherlands; combined benefit of hindsight
Revised ICER about 20-fold lower than conventional cost-effectiveness threshold!
Considerable scope for improved HPV prevention through vaccination

- Girls-only vaccination with 60% coverage will confer a 64% reduction in the life-years lost due to HPV16/18 infections
  - 71% reduction in women; 37% in men

- Scope for improvement; even more so when considering the total HPV-related burden

- Vaccinating 2 boys leads to a similar further reduction in HPV16/18-related cancer burden as vaccinating 1 ‘additional’ girl

- Differential impact due to gender disparity in burden + asymmetry in transmission dynamics

Qendri et al. (2017), *J Infect Dis*
Factors affecting heterosexual transmission dynamics of mucosal HPV infection: sex-specific reproduction numbers

Factors increasing $R_{01}$
- Greater number of partners ($c$)
- HIV ($d$, $S_{01}$)
- Herpes simplex virus 2 ($d$)
- Chlamydia trachomatis ($d$)
- Smoking* ($d$)
- HLA* ($d$)
- Increasing viral load* ($p$)

Factors decreasing $R_{01}$
- Condom use* ($c$)

Factors with unknown direction of effect on $R_{02}$
- Oral contraceptive use ($d$)
- HIV ($p$)
- Concurrent sexually transmitted infections ($p$)
- Male circumcision ($S_{02}$)

Factors increasing $R_{02}$
- Greater number of partners ($c$)
- HIV ($d$, $S_{01}$)
- Increasing viral load* ($p$)

Factors decreasing $R_{02}$
- Condom use* ($c$)
- Vaccination ($S_{02}$)

Factors with unknown direction of effect on $R_{02}$
- Male circumcision ($d$, $p$)
- Bacterial vaginosis ($S_{01}$)
- Oral contraceptive use ($S_{01}$)
- Vaginal practices ($S_{03}$)
- HIV ($p$)

$R_0 = c \times d \times p$

Veldhuijzen et al. (2010), *Lancet Infect Dis*
Effectiveness of vaccinating boys on the transmission of HPV: analysis of the basic reproduction number $R_0$

**Objectives**
In many countries, universal vaccination of girls against infection with human papillomavirus was recently introduced or will be introduced soon. The decision of whether or not to include boys in the national immunization programmes depends on the strength of indirect effects of vaccinating boys on the incidence in girls and the resulting incremental cost-effectiveness. Our aim was to assess the contributions of males and females, respectively, to the transmission dynamics of HPV using the concept of the basic reproduction number.

**Methods**
Based on a model stratified by age and sexual activity, we derived a formula for the basic reproduction number $R_0$ for HPV. The reproduction number is a geometric mean of two factors describing the average number of secondary cases in men by one infected woman and vice versa. Women and men differ in terms of their normal history of infection and their transmission probabilities (Figure 1). Where possible, we based our choices of parameters on available literature data, and otherwise chose plausible values. We assumed that the infectiousness in different stages in women is determined by the viral load, which has been shown to vary between infections with and without lesions of Kesseli et al. (2005). We investigated how the reproduction number depends on transmission probabilities, the duration of the infection period, and on vaccination coverage of men and women.

The basic reproduction number $R_0$ is composed of

$R_0 = \sqrt{R_{mf} \cdot R_{fm}}$

**Results**
Assuming that persistent infections contribute substantially to transmission, women produce many more secondary infections than vice versa. The exact ratio depends on the duration of infectiousness during transient infections, and on the transmission probabilities per partnership. Even with a substantially higher transmission probability from males to females, the transmission chain is driven by female to male transmission (Figure 2).

$R_0 = \sqrt{R_{mf} \cdot R_{fm}}$

**Conclusions**
If vaccination coverage among women is above a critical threshold, vaccination of men does not add anything to effectiveness. If both women and men are vaccinated at the same level of coverage, the fraction of the total population needs to be vaccinated for elimination is higher than when vaccinating women only (Figure 2). It might be very effective to target intervention to highly sexually active women.

**References**

“women produce many more secondary infections in men than vice versa”

Because of an increased prevalence in women!

“If both women and men are vaccinated (…), the fraction of the total population that needs to be vaccinated for elimination is higher than when vaccinating women only”

Also true for men only!

Kretzschmar & Franco, 18th ISSTDR 2009
Differential impact of sex-specific immunization on the reproduction number and on the heterosexual prevalence of HPV infection

Bogaards et al. (2011), PLoS Medicine
Gender-neutral vaccination: neither required nor sufficient for elimination from heterosexual population

HPV vaccination in boys, girls

Among 13- to 17-year-olds, the vaccination rate for human papillomavirus for boys lags that of girls. Recent vaccination rates, and what parents said their vaccination intentions were for their sons and daughters in the next year:

<table>
<thead>
<tr>
<th>STATUS/INTENTION</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOYS</td>
<td>1.4%</td>
<td>8.3%</td>
</tr>
<tr>
<td>GIRLS</td>
<td>48.7%</td>
<td>53%</td>
</tr>
<tr>
<td>Somewhat/very likely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOYS</td>
<td>27.4%</td>
<td>31.2%</td>
</tr>
<tr>
<td>GIRLS</td>
<td>16.7%</td>
<td>16.9%</td>
</tr>
<tr>
<td>Not likely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOYS</td>
<td>59.2%</td>
<td>51.5%</td>
</tr>
<tr>
<td>GIRLS</td>
<td>27.9%</td>
<td>25%</td>
</tr>
<tr>
<td>Unsure/unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOYS</td>
<td>11.9%</td>
<td>9.1%</td>
</tr>
<tr>
<td>GIRLS</td>
<td>6.7%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Sources: Immunization Services Division, Centers for Disease Control and Prevention

Elimination requires changing attitudes towards HPV vaccination, even more so for boys than for girls
Population-level impact of HPV16 vaccination: meta-analytic predictions

Predictions of 16 transmission-dynamic models
Girls-only vaccination, Vaccine duration=Life-long, Vaccine efficacy=100%

40% coverage

Girls-only

80% coverage

Relative reduction (%), HPV-16 prevalence

NOTE: Corresponding author, 16 of 19 Transmission models published in 2009-2014, identified through systematic review

Brisson et al. (2016), Lancet Public Health
Population-level impact of HPV16 vaccination: meta-analytic predictions

Predictions of 16 transmission-dynamic models
Girls-only and Girls & Boys vaccination, Vaccine duration=Lifelong, Vaccine efficacy=100%

40% coverage

Girls-only

Girls&Boys

53% (46%;68%) 74% (64%;93%) 80% coverage

93% (90%;100%) 100% (97%;100%)

NOTE: Corresponding author, 16 of 19 Transmission models published in 2009-2014, identified through systematic review

Brisson et al. (2016), Lancet Public Health
Incremental effectiveness of vaccinating boys along with girls

Predictions of 16 transmission-dynamic models
Girls-only and Girls & Boys vaccination, Vaccine duration=Lifelong, Vaccine efficacy=100%

40% coverage

80% coverage

Note 1. Incremental effectiveness decreases at high coverage among girls
Note 2. Relative uncertainty increases at high coverage among girls

Brisson et al. (2016), *Lancet Public Health*
Vaccinating boys along with girls is cost-effective in the Netherlands... if the anticipated cost for vaccinating boys were the same as for girls

ICER of extending eligibility to boys (40% boys - 60% girls)

Qendri et al. (2009) ~9000 euro/LY

Qendri et al. (2017), *J Infect Dis*
... and would remain cost-effective at increased coverage among girls (provided that uptake among girls will not exceed 90%)

ICER of extending eligibility to boys (40% boys - 90% girls)

Qendri et al. (2009) ~36000 euro/LY

Qendri et al. (2017), *J Infect Dis*
Generalizability to other national immunization programs?
Qendri et al. (FC 13-2), Cost-effectiveness in six EU tender-based settings
Who will benefit from extending vaccine eligibility to preadolescent boys?

Gain in LYs for women, heterosexual and homosexual men from vaccinating 40% of boys along with girls
Until which age should (wo)men be eligible for HPV vaccination?
> Or: how can modelling help improve existing prevention efforts?

- Topical in settings where HPV vaccination still needs to be introduced
  - Effectiveness of catch-up campaigns function of individuals’ past as much as future
  - Key drivers of uncertainty: accurate modelling of sexual activity, immunity, latency

- Also topical in settings where uptake among (pre)adolescents is suboptimal
  - Expanding vaccine eligibility as a means to improve HPV prevention efforts

- Opportunities to combine vaccination with (HPV-based) cervical screening
  - Catch-up vaccination at (first?) screening visits to align future cancer risks
  - ‘One size fits all’ vs. personalized approach to screening (privacy, equity?)
  - Feasibility and acceptability of modelled strategies need to be considered
Projected trends in HPV16 incidence under overtly optimistic scenarios

STI consultations: *all* STI clinic visitors <30y are offered and accept HPV vaccine

Screening: *all* screening attenders aged 30y are offered and accept HPV vaccine

Matthijssse et al. (2016), *J Infect Dis*
Should men who have sex with men be targeted for HPV vaccination?
> Or: what is the (temporal) benefit compared to vaccinating boys?

- Modelling MSM vaccination is more involved than preadolescent vaccination
  - Distinct transmission dynamics (one sex, multiple anatomic locations)
  - Selective vaccination of MSM can only be realistically achieved after sexual debut
  - Likewise requires accurate modelling of sexual activity, natural immunity, latency, etc.

- Large amount of uncertainty around extent and mode of prophylactic efficacy
  - Distinction between ‘leaky’ vs. ‘all-or-nothing’ efficacy becomes important
  - Effect of previous or current infections on efficacy against future infections?

- Models of selective MSM vaccination should consider the route by which vaccines can be delivered to this group, and implications in terms of vaccine coverage
  - Explore analogies to selective MSM vaccination against HepB
Projected trends in HPV16 prevalence under optimistic efficacy scenario
Selective MSM vaccination assuming HepB uptake rates vs. 40% boys’ uptake @ 12y
**Take home message**

The current girls-only program is projected to be very cost-effective!

**The case for gender-neutral vaccination**

- Cervical disease remains the predominant source of HPV burden, at least until the effects of vaccination become apparent
  - Even so, burden in males is considerable by any standard
  - Moreover, the gender disparity in HPV burden is diminishing

- Extending vaccine eligibility to preadolescent boys is only modestly less efficient than increasing vaccine uptake among girls
  - Moreover, it may be easier to include boys than to increase uptake in girls
  - Gender-neutral vaccination is cost-effective at realistic tender prices
How can modelling guide future vaccination policy and implementation?

Opportunities to combine vaccination with cervical screening
- Further development of combined vaccination + screening modalities
  - Prior definition of feasibility to manage computational complexity

Adding boys likely has strong impact on HPV-related diseases in MSM
- But will not protect currently active MSM, who have high risk for anal cancer
  - Targeting interventions to MSM may lead to a reduced acceptability in boys

Feasibility and impact of selective vaccination of MSM is still uncertain
- Unknowns in natural history of infection, prophylactic efficacy, mode of delivery
  - Multi-modelling approach needed to deal with many structural uncertainties
Informing public health strategy by mathematical modelling...

Very impressive, colleague...

But will it work in theory?
Acknowledgements

- Hans Berkhof
- Venetia Qendri
- Scott McDonald
- Marc Brisson (slides 25, 26)

- VWS
- FP7 project www.coheahr.eu