HPV immunity studies in different age groups

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Content

- VLP-based Multiplex assay
- Population based seroprevalence study
- Immunological studies
  - Monitoring high-risk group population
  - Monitoring three-dose vaccination schedule
  - HPV one-dose study
  - EVI study: early vaccine immunization
- Dutch Health council: Advice June 2019

- Conclusions
HPV serology; Multiplex Immuno assay

- Multi-Analyte Profiling technology (xMAP)
  - Measuring antibodies against multiple HPV types simultaneously
- High throughput
- Low sample volume required

- MIA has good correlation with GST-L1 assay (Pawlita) and cLIA
Luminex® xMAP technology
Multiplex Immuno assay (MIA)

- Analyte (antigen) coupled beads + diluted sample in a 96-well plate layout
- Specific (human) antibody binds to bead coupled antigen
- R-PE conjugated anti-human IgG binds to specific antibody
- International standard included
Introduction - Population serosurvey

- Monitoring protection against (future) infectious diseases
- Changes in HPV-seroprevalence over 20-year period in the Netherlands
- Impact of introduction of a girls-only vaccination program on HPV seroprevalence in the Netherlands
### Prevalence difference between the 2016-17 and 2006-07 survey after pooling both surveys

|                | All
<table>
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<td></td>
<td>N= 5194</td>
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<tr>
<td></td>
<td>Men</td>
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<tr>
<td></td>
<td>N= 2308</td>
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<tr>
<td></td>
<td>Women</td>
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<tr>
<td></td>
<td>N= 2886</td>
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<tr>
<td>HPV seropositive n (%)</td>
<td>aPR (95% CI)</td>
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<tr>
<td>2006-2007</td>
<td>546 (24.1) Ref</td>
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<tr>
<td>2016-2017</td>
<td>778 (26.6) aPR (0.9-1.2)</td>
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<tr>
<td>HPV16</td>
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<td>2006-2007</td>
<td>276 (12.2) Ref</td>
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<tr>
<td>2016-2017</td>
<td>394 (13.5) aPR (0.9-1.2)</td>
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<tr>
<td>HPV18</td>
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<tr>
<td>2006-2007</td>
<td>151 (6.7) Ref</td>
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<tr>
<td>2016-2017</td>
<td>280 (9.6) aPR (1.1-1.7)</td>
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|                | Women
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<tbody>
<tr>
<td>HPV seropositive n (%)</td>
<td>aPR (95% CI)</td>
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<tr>
<td>2006-2007</td>
<td>208 (21.2) Ref</td>
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<tr>
<td>2016-2017</td>
<td>245 (18.5) 0.9 (0.7-1.1)</td>
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<tr>
<td>2006-2007</td>
<td>111 (11.3) Ref</td>
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<tr>
<td>2016-2017</td>
<td>102 (7.7) 0.7 (0.5-0.9)</td>
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<td>2006-2007</td>
<td>338 (26.3) Ref</td>
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<td>2016-2017</td>
<td>533 (33.3) 1.2 (1.0-1.3)</td>
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<td>2006-2007</td>
<td>165 (12.8) Ref</td>
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<tr>
<td>2016-2017</td>
<td>292 (18.2) 1.3 (1.0-1.6)</td>
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<tr>
<td>2006-2007</td>
<td>78 (6.1) Ref</td>
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<tr>
<td>2016-2017</td>
<td>181 (11.3) 1.8 (1.3-2.3)</td>
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Confidential
Conclusion – population serosurvey

- In a 10-year period in HPV seroprevalence
  - Increase seroprevalence in women
  - Decrease seroprevalence in men (HPV16)

- Still, a large part of the population is seronegative
  > Eligible for vaccination?

- Note:
  - In The Netherlands vaccination with bivalent HPV vaccine since 2010
(Un)adjusted VE against incident and persistent infections

Donken et al., 2018 JID
Bivalent vaccine effectiveness

Evidence for cross-protection

High-risk group

Woestenberg et al., 2018 JID
High-risk group

No evidence for cross-protection of bivalent vaccine against HPV6/11

A) HPV-6/11

B) Anogenital warts

Woestenberg et al., 2017 Journal of Infection
Monitoring three-dose schedule

GMCs over time: vaccinated vs. non-vaccinated

Hoes, Pasmans et al., submitted
Mucosal antibodies

- HPV specific antibodies are present in cervical secretion

Scherpenisse et al 2012, Human Vaccines and Immunotherapeutics
HPV16 and HPV18 IgG levels

→ One 2vHPV-vaccine dose results in less seropositivity and lower antibody levels than two- or three-doses.

Pasmans et al., 2019 Vaccine
Avidity similar for 1, 2 or 3 dose schedules
Similar sub class response

Quantitatively lower cellular responses to HPV in individuals that received only one 2vHPV-dose compared with two and three-doses
- memory B- and T-cell responses

Pasmans et al., 2019 Vaccine
Ongoing study: Early Vaccine Immunisation (EVI)

**AIM**
Early differences in the immune responses between the bivalent and nonavalent HPV vaccines
→ does this explain the differences seen on the long term, i.e. antibody levels
*HPV-type specific

**Women (23-46 years of age) are seronegative for HPV16, 18, 31, 33, 45, 52 and 58. Women vaccinated with either bivalent or nonavalent HPV vaccine
Euroflow method

APS 1

cMo subsets

iMo

ncMo subsets

myDC CD1c+
pDC
Basophils
Eosinophils
Neutrophils
myDC CD141+

APS 4

Naïve

Central memory

Transition memory

Effector memory

APS 5

Naïve

Early effector

Terminal effector

APS 1

Effector memory

Terminal Effector

Naive

Central memory

Transitional memory

APC2

PC1

Immature

Plasma cells

Naive CD5+

Memory Swt

Memory Non-Switched
Dutch Health Council – June 2019

Advice

● Implement a sex-neutral vaccination program
● Vaccinate at a age of 9 years (currently 13 years of age)
● Implement additional vaccination program for people until 26 years of age.

● No advice was given for a particular vaccine.
Overall conclusions and considerations

- In adolescents and young adults;
  - Cross-protection against 31, 35, 45 and 52 but not for 6 & 11
  - Ongoing monitoring
    › After a three (and two) dose schedule antibodies remain high up to nine year post-vaccination both for HPV16/18 but also others types

- Adults;
  - Considerable part of adult population is HPV seronegative
    › Opportunity to vaccinate; no preexisting antibodies
    › Role of antibodies? Correlate of Protection?
    › Clearance and/or no systemic immune reaction
  - Await results EVI study – correlate antibody levels to cellular response

*Do early immune responses predict longterm antibody levels?*
Acknowledgements

Hella Pasmans
Annemarie Buisman, PhD
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Joske Hoes
Petra Woestenberg
Tessa Schurink-van ‘t Klooster

Prof. Jacques van Dongen, PhD
Magda Berkowska, PhD
Follow-up study: girls vaccinated with a two-dose schedule with the bivalent vaccine.
Additional slides
Prevalence difference between the **male population from 15-39 years of age** of the 2016-17 and 2006-07 after pooling both surveys: adjustment of demographic characteristics and sexual risk factors.

<table>
<thead>
<tr>
<th></th>
<th>Any HPV type</th>
<th>HPV16</th>
<th>HPV18</th>
</tr>
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<tbody>
<tr>
<td><strong>2006-07</strong></td>
<td>60 (15.8)</td>
<td>34 (8.9)</td>
<td>22 (5.8)</td>
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<tr>
<td><strong>2016-17</strong></td>
<td>76 (14.5)</td>
<td>38 (7.3)</td>
<td>27 (5.2)</td>
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<tr>
<td><strong>N= 904</strong></td>
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<td><strong>N= 904</strong></td>
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**HPV seropositive n (%) aPR (95% CI)**
HPV16 cellular response

- Th2 cytokines: IL-13 and IL-5 higher in two- and three dose vaccinated individuals
- IL-13/IL-5 correlated with IgG levels (R=0.66***)
- Memory B cells correlated with IgG levels (R=0.66***)