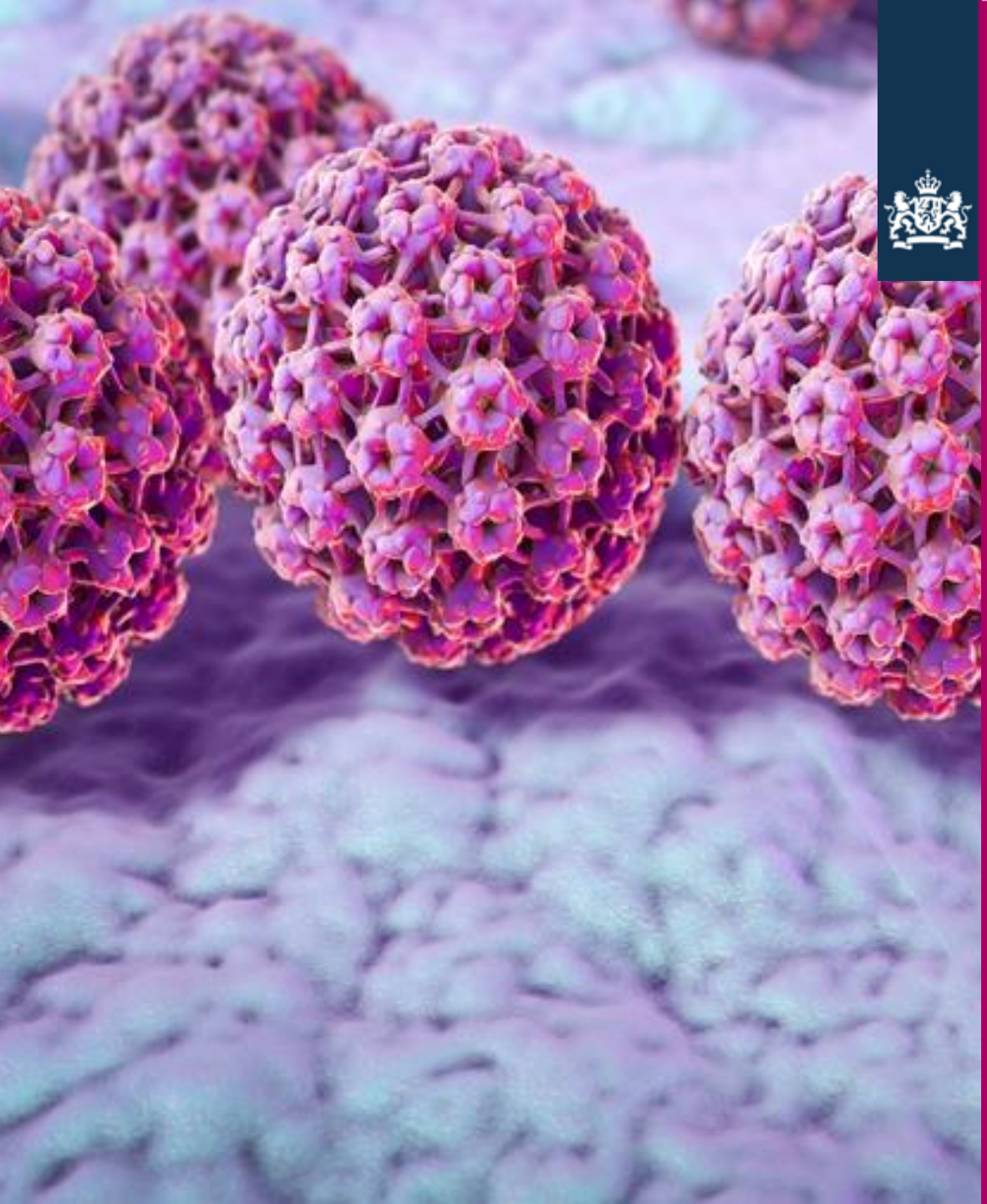


Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

HPV immunity

studies in different age groups

Fiona van der Klis, PhD
Dutch Institute for Public Health, the Netherlands

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

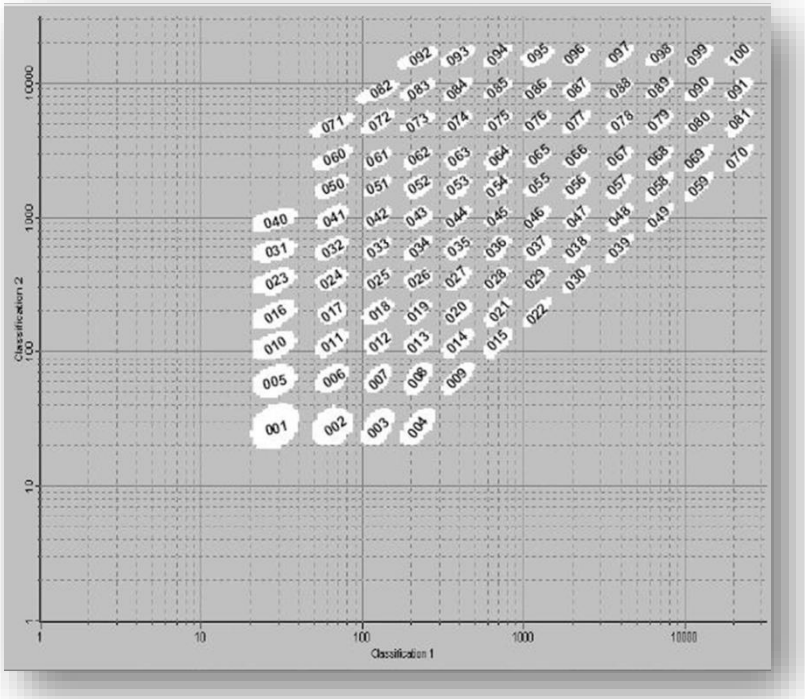
- Conclusions

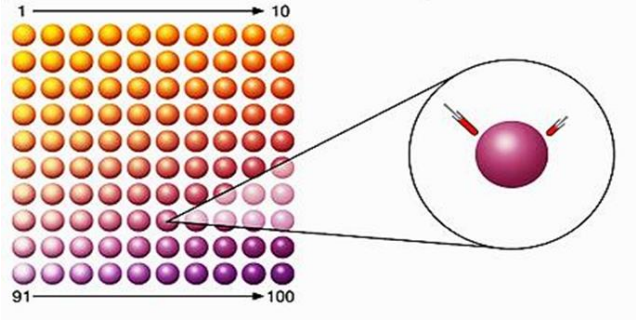
HPV serology; Multiplex Immuno assay

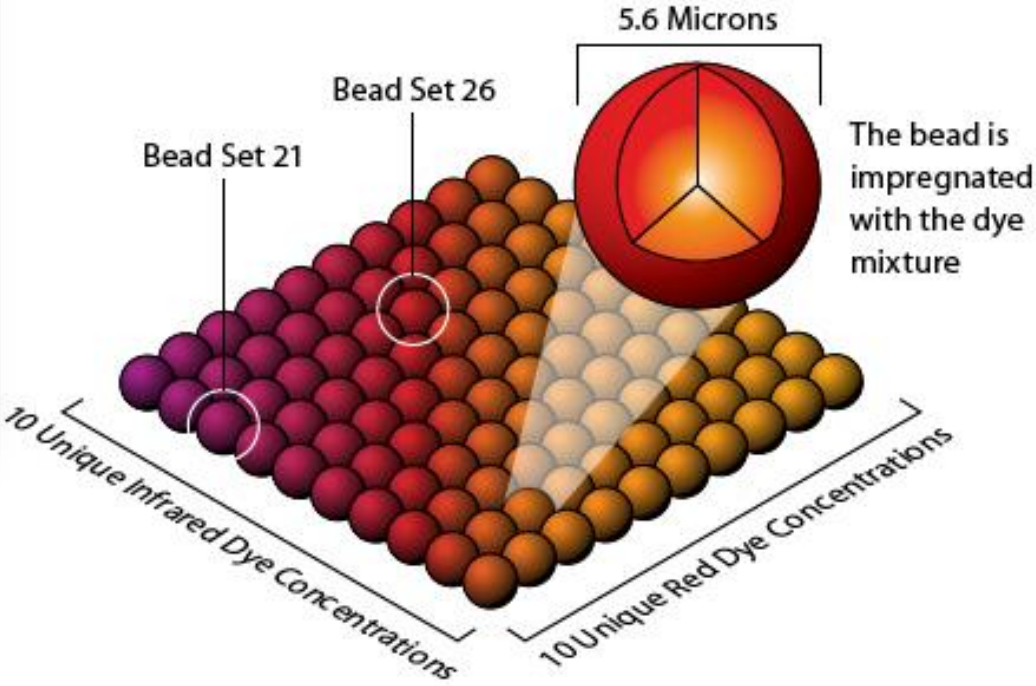
- Multi-Analyte Profiling technology (xMAP)
  - Measuring antibodies against multiple HPV types simultaneously
- High throughput
- Low sample volume required

- MIA has good correlation with GST-L1 assay (Pawlita) and cLIA

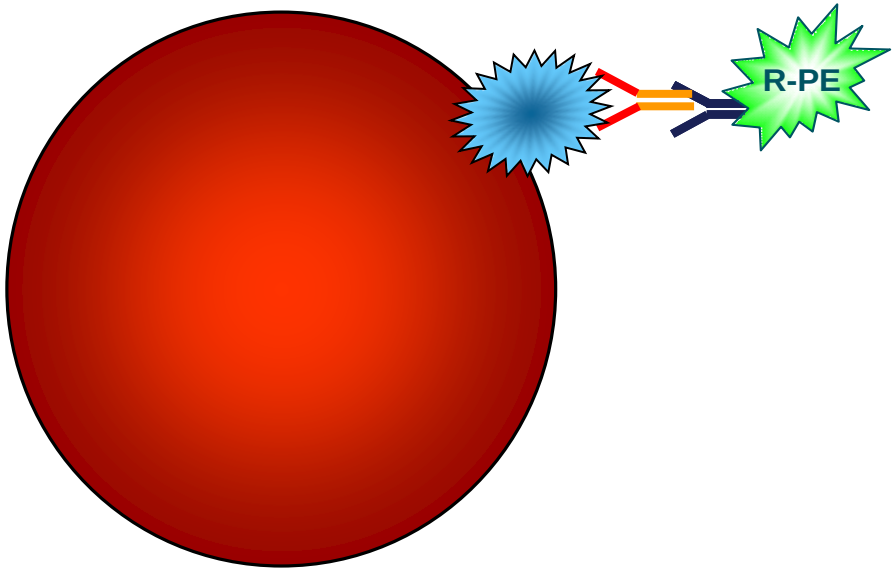
Luminex® xMAP technology







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 N= 5194		Men N= 2308		Women N= 2886	
	HPV seropositive n (%)	aPR (95% CI)	HPV seropositive n (%)	aPR (95% CI)	HPV seropositive n (%)	aPR (95% CI)
Any HPV type						
2006-2007	546 (24.1)	Ref	208 (21.2)	Ref	338 (26.3)	**Ref**
2016-2017	778 (26.6)	1.0 (0.9-1.2)	245 (18.5)	0.9 (0.7-1.1)	533 (33.3)	**1.2 (1.0-1.3)**
HPV16						
2006-2007	276 (12.2)	Ref	111 (11.3)	**Ref**	165 (12.8)	**Ref**
2016-2017	394 (13.5)	1.0 (0.9-1.2)	102 (7.7)	**0.7 (0.5-0.9)**	292 (18.2)	**1.3 (1.0-1.6)**
HPV18						
2006-2007	151 (6.7)	**Ref**	73 (7.4)	Ref	78 (6.1)	**Ref**
2016-2017	280 (9.6)	**1.4 (1.1-1.7)**	99 (7.5)	1.0 (0.7-1.4)	181 (11.3)	**1.8 (1.3-2.3)**

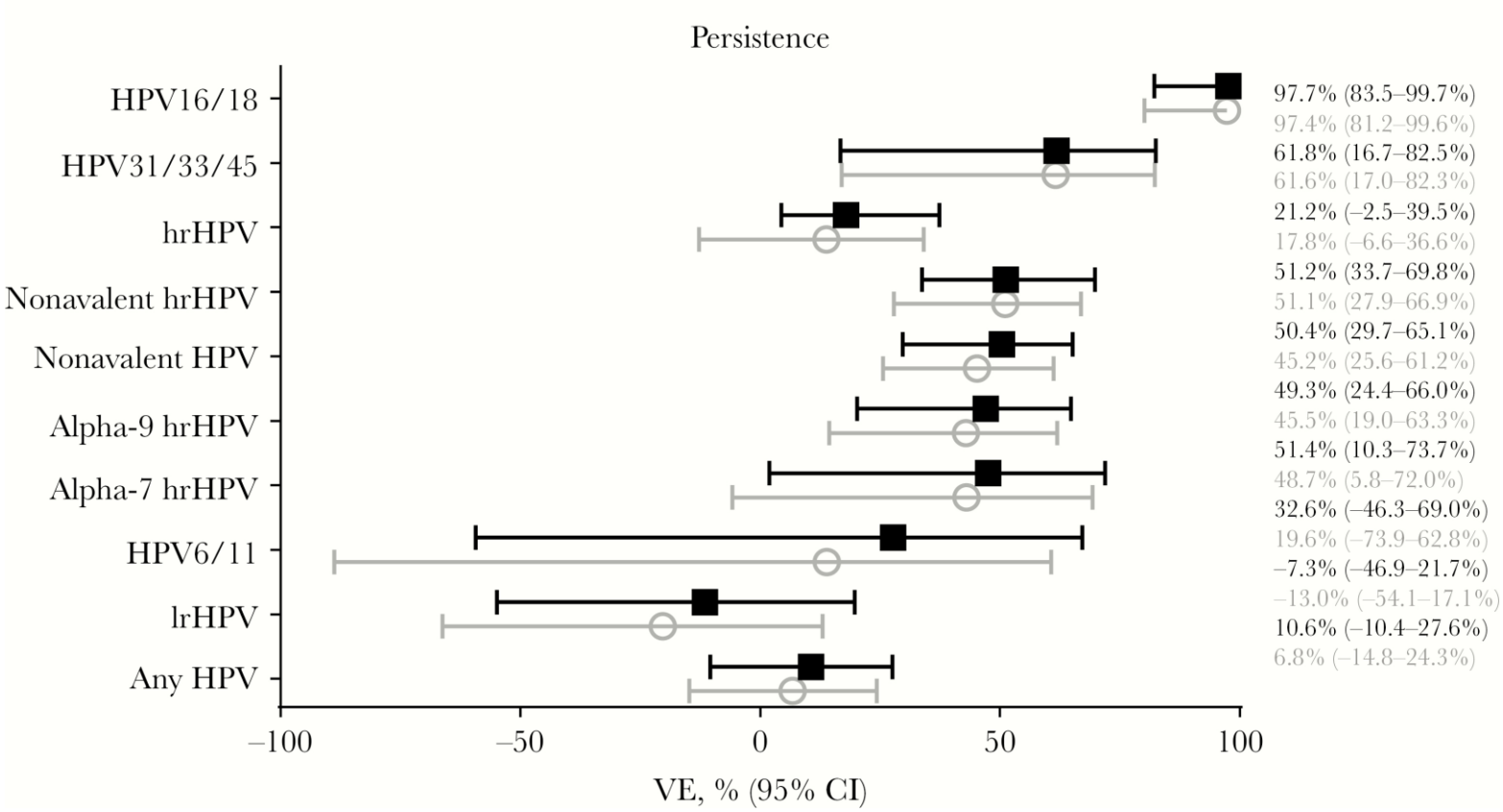
Conclusion – population serosurvey

- 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

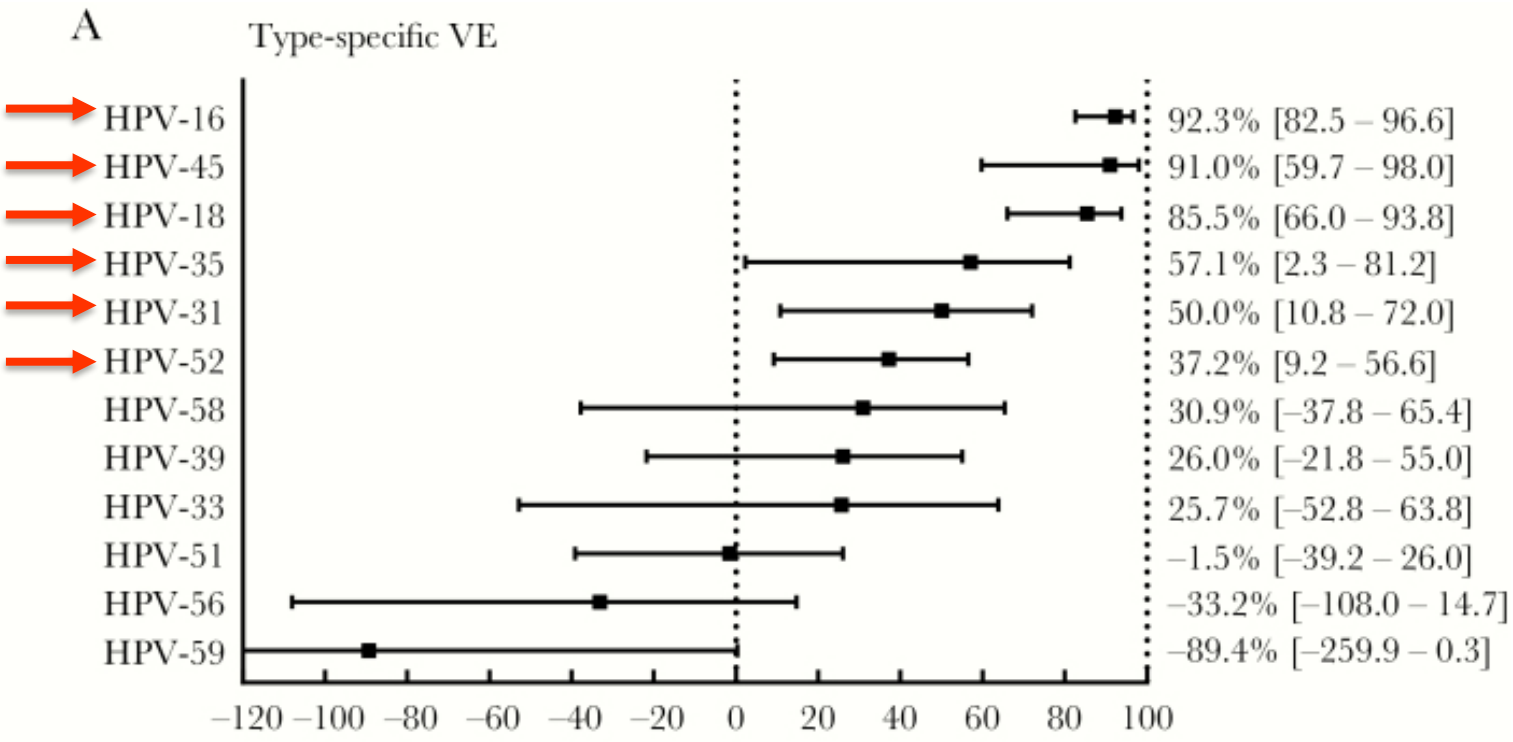
(Un)adjusted VE against incident and persistent infections



Donken et al., 2018 JID

High-risk group

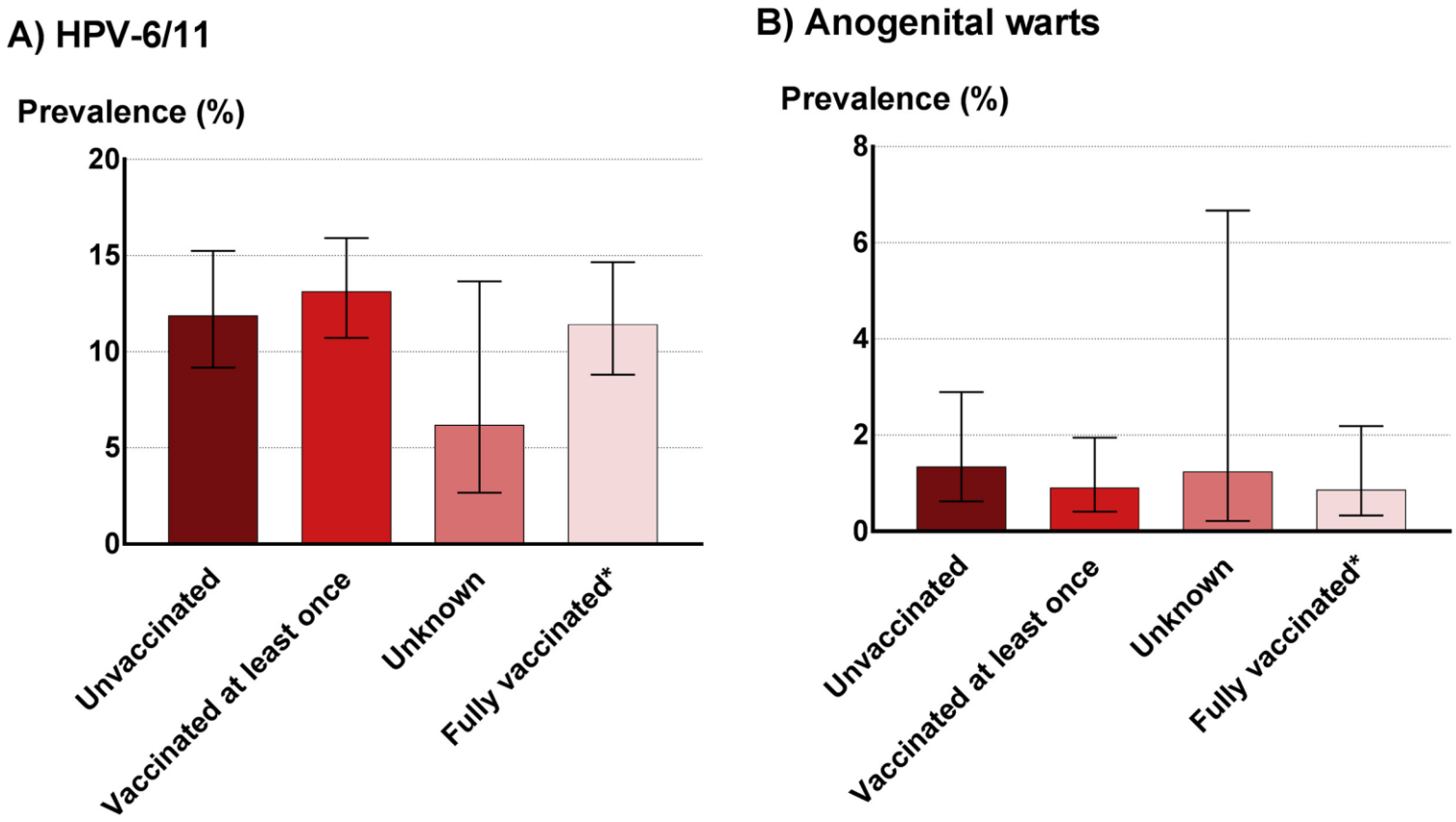
Bivalent vaccine effectiveness
Evidence for cross-protection



Woestenberg et al., 2018 JID

High-risk group

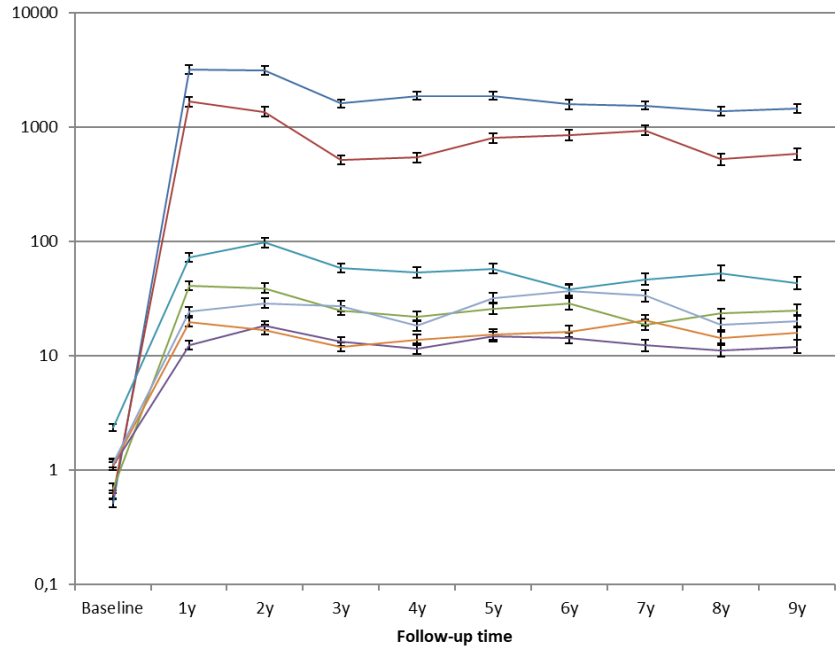
No evidence for cross-protection of bivalent vaccine against HPV6/11

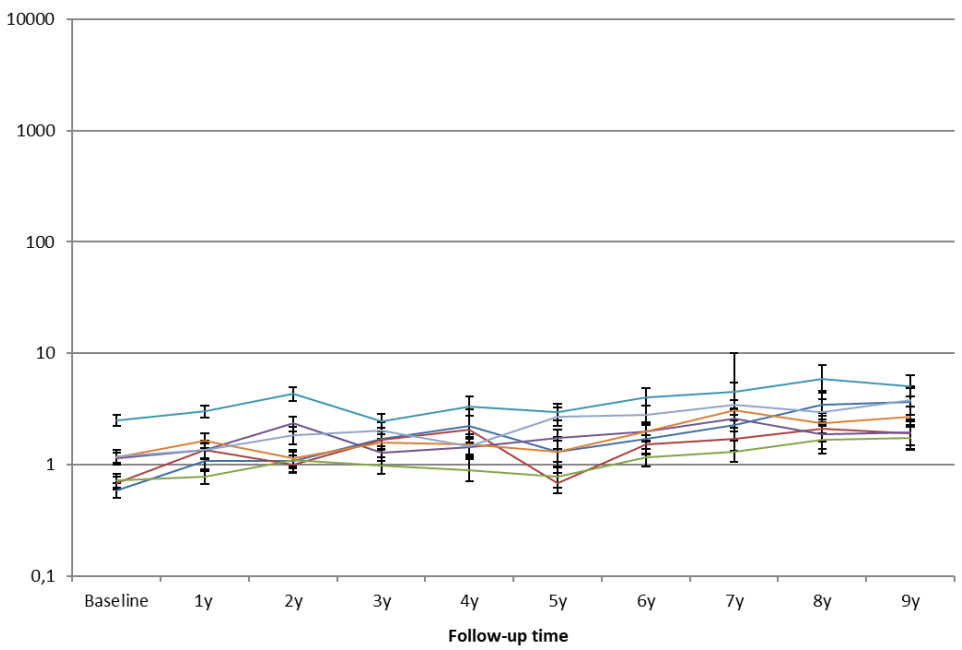


Woestenberg et al., 2017 Journal of Infection

Monitoring three-dose schedule

GMCs over time: vaccinated vs. non-vaccinated



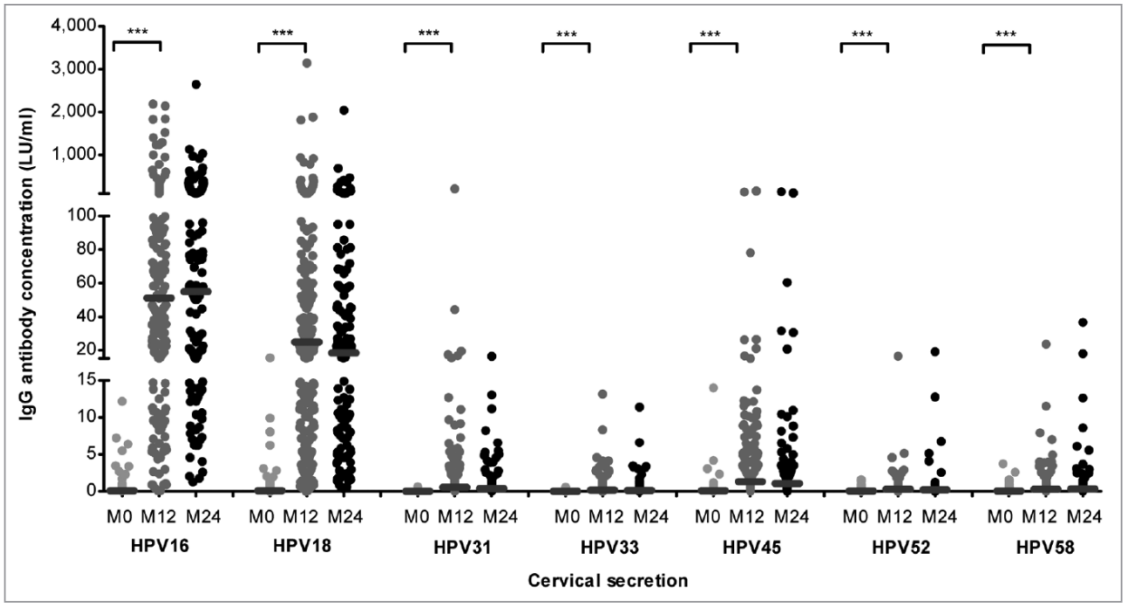


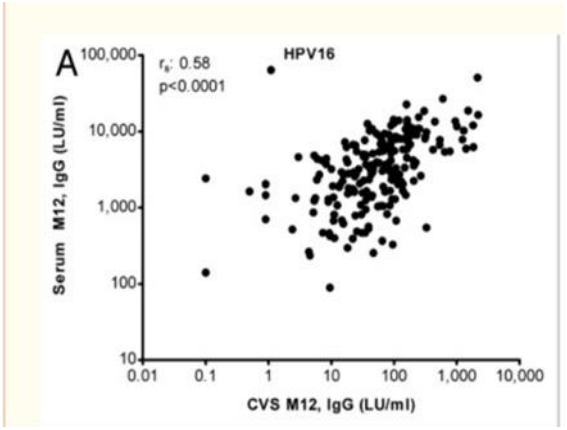
HPV16 HPV33 HPV58
HPV18 HPV45
HPV31 HPV52

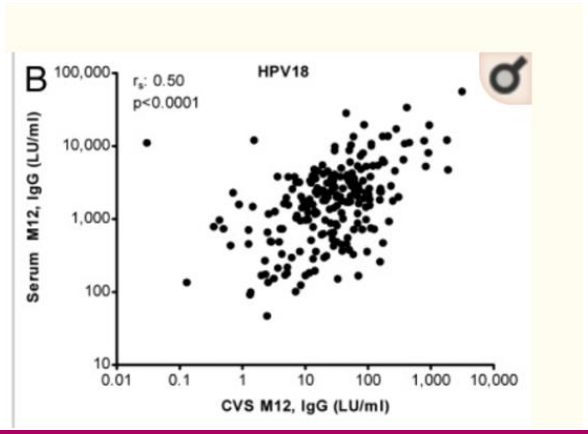
Hoes, Pasmans et al., submitted

Mucosal antibodies

- HPV specific antibodies are present in cervical secretion



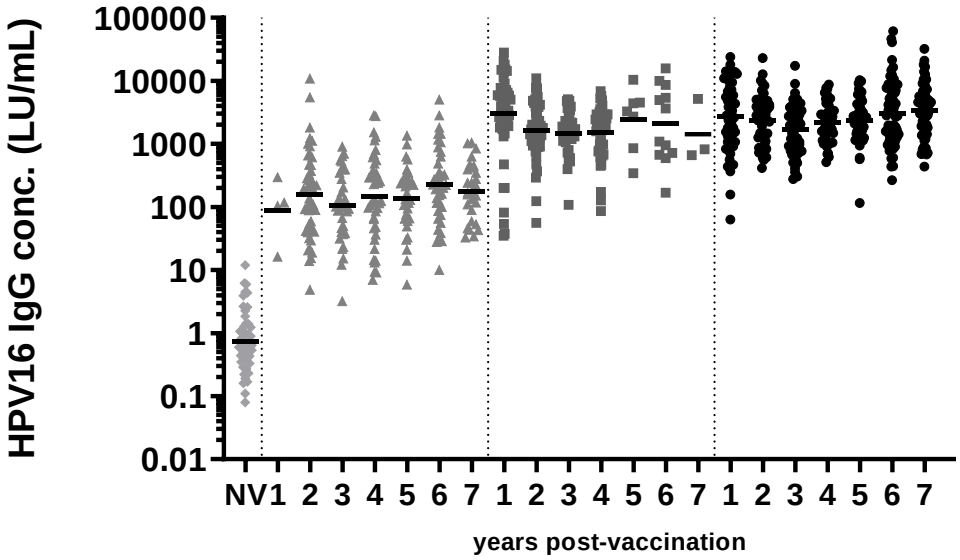


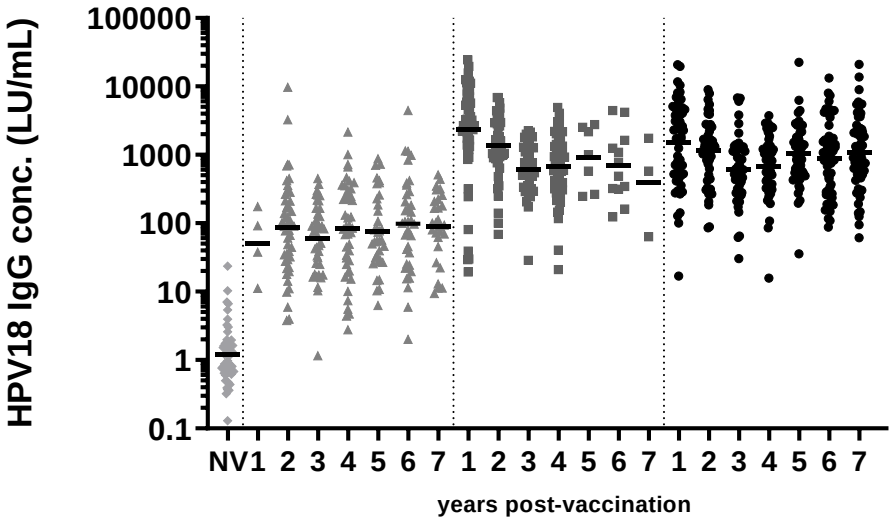


Scherpenisse et al 2012, Human Vaccines and Immunotherapeutics

HPV1D study

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

HPV1D study

- 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

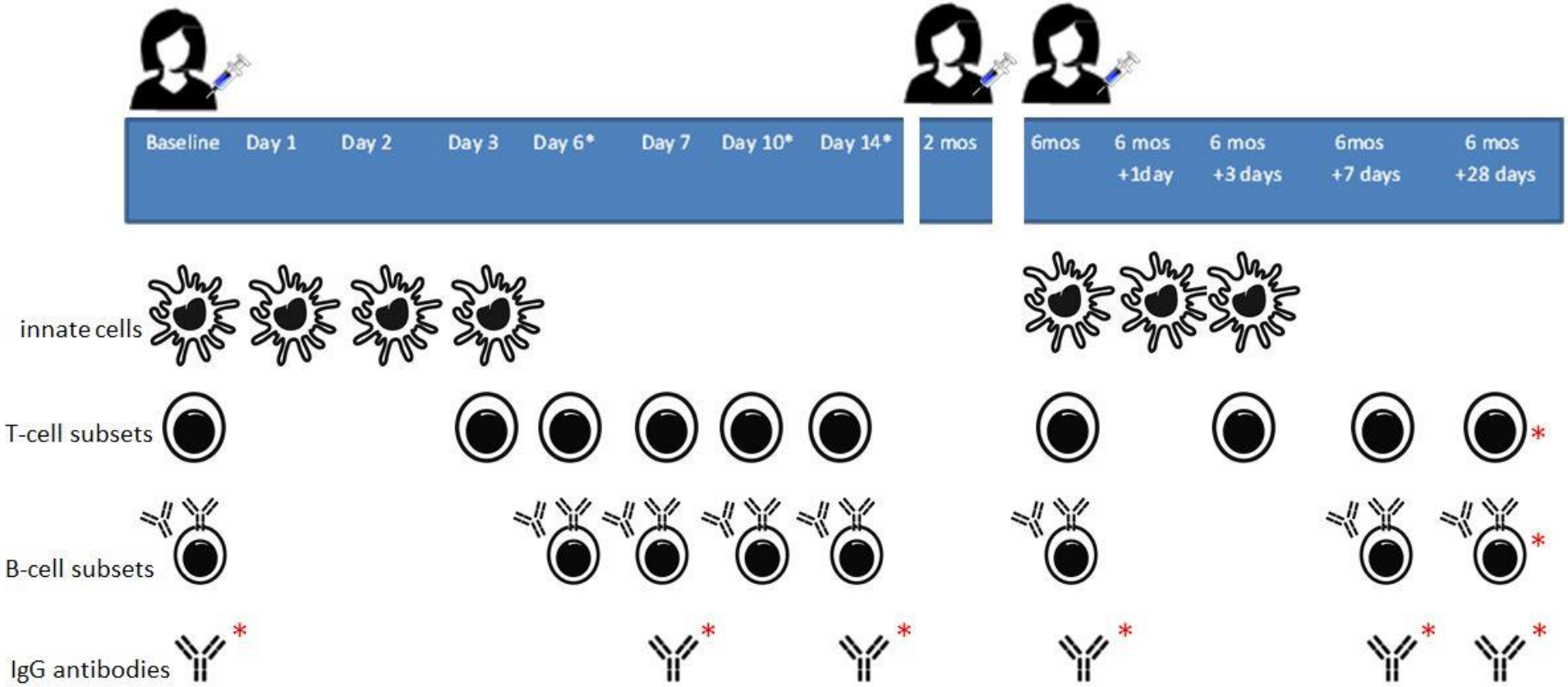
Pasmans et al., 2019 Vaccine

Ongoing study: **E**arly **V**accine **I**mmunisation (EVI)

AIM

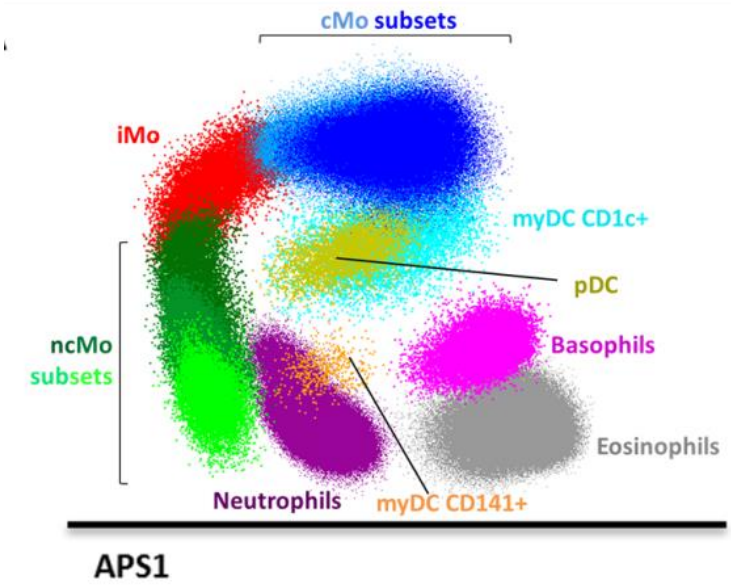
Early differences in the immune responses between the bivalent and nonavalent HPV vaccines

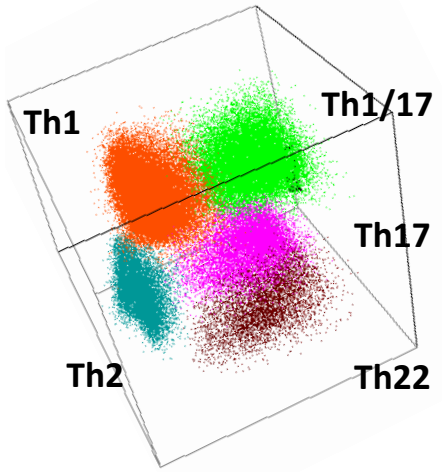
→ does this explain the differences seen on the long term, i.e. antibody levels

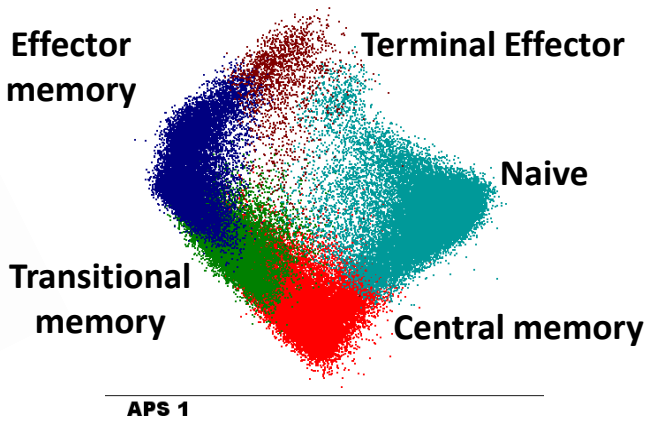


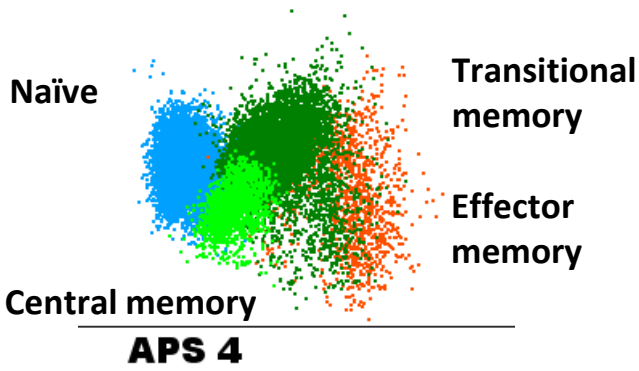
*HPV-type specific
**Women (23-46 years of age) are seronegative for HPV16, 18, 31, 33, 45, 52 and 58.
Women vaccinated with either bivalent or nonavalent HPV vaccine

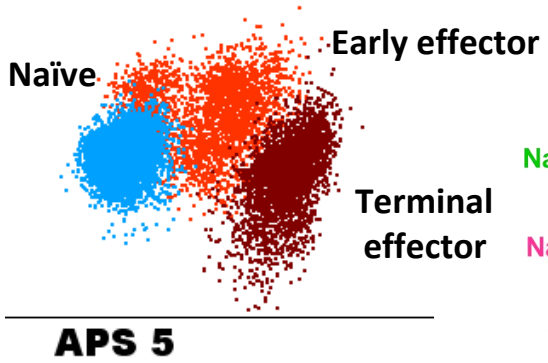
Euroflow method

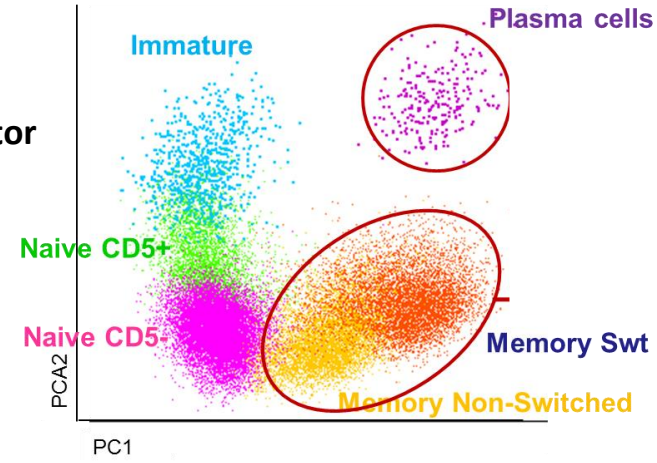












Dutch Health Council – June 2019

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
Hester de Melker, PhD
Joske Hoes
Petra Woestenberg
Tessa Schurink-van ‘t Klooster

Prof. Jacques van Dongen, PhD
Magda Berkowska, PhD

Rijksinstituut voor Volksgezondheid en Milieu
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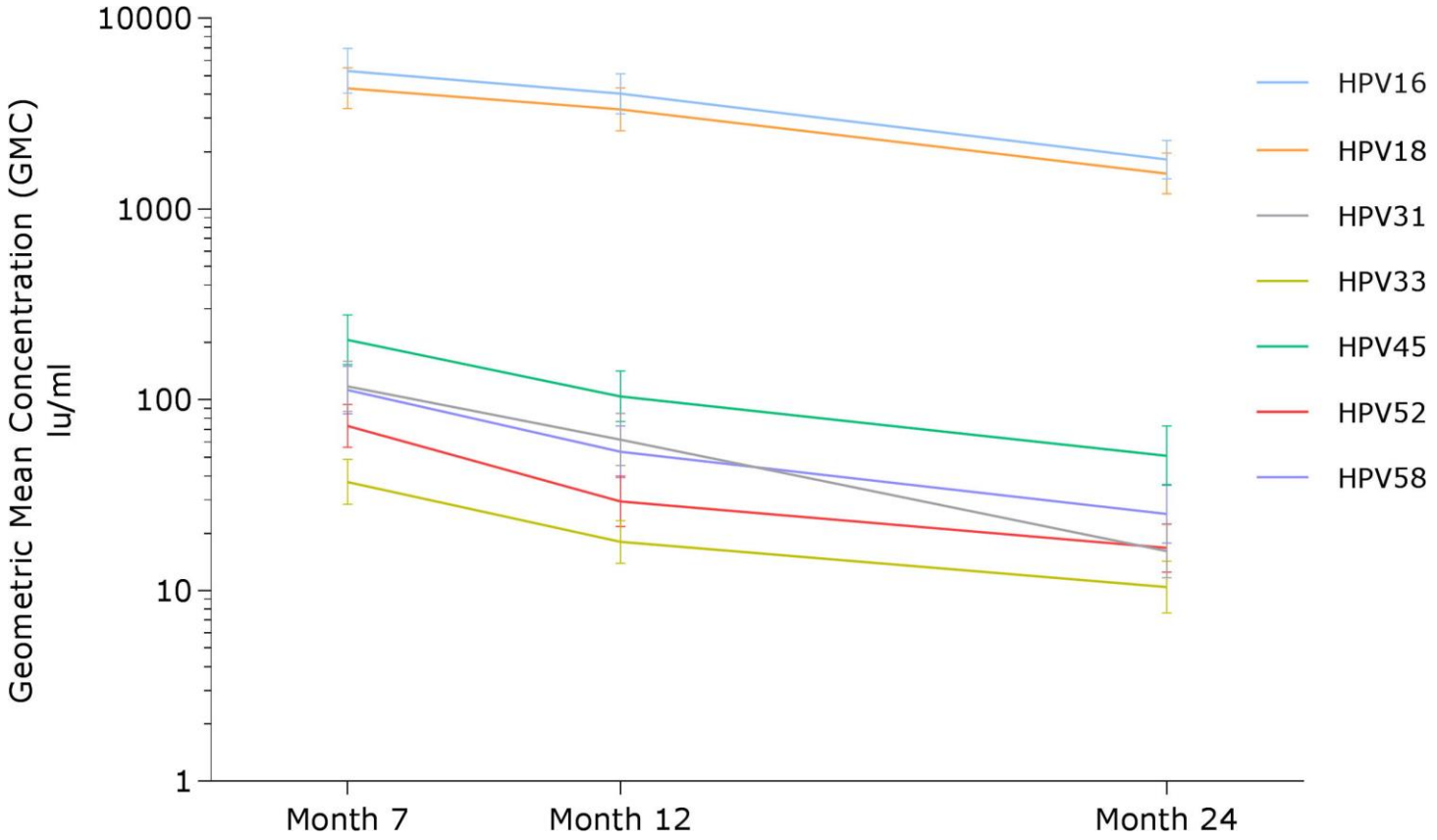
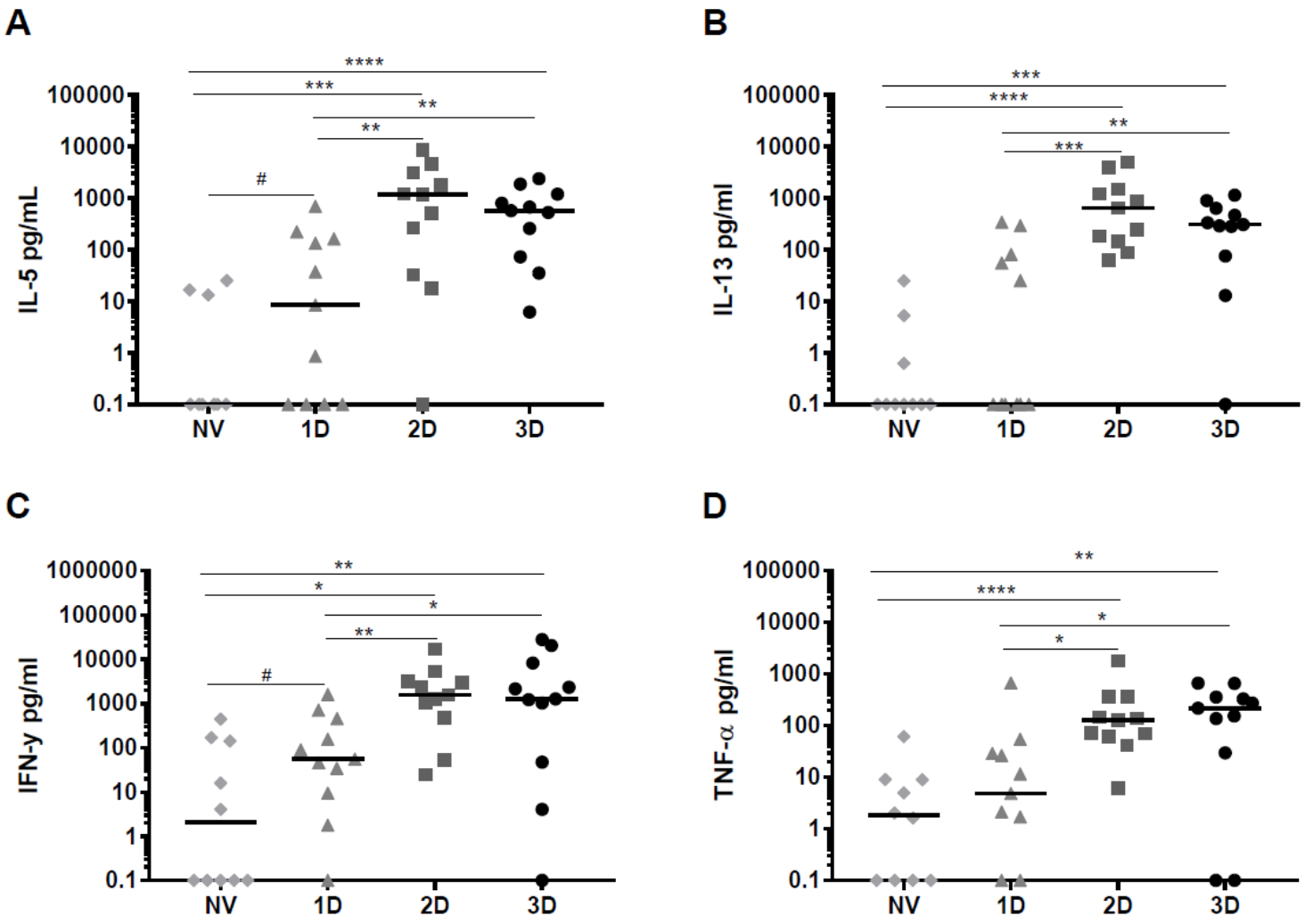
Leids Universitair Medisch Centrum

HPV2D-study

Follow-up study: girls vaccinated with a two-dose schedule with the bivalent vaccine.



Schurink et al., 2018 Vaccine


A
IL-5 pg/mL
100000
10000
1000
100
10
1
0.1
NV
1D
2D
3D
****
***
**
**
#
B
IL-13 pg/ml
100000
10000
1000
100
10
1
0.1
NV
1D
2D
3D
***
****
**
***
C
IFN-y pg/ml
1000000
100000
10000
1000
100
10
1
0.1
NV
1D
2D
3D
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D
TNF-α pg/ml
100000
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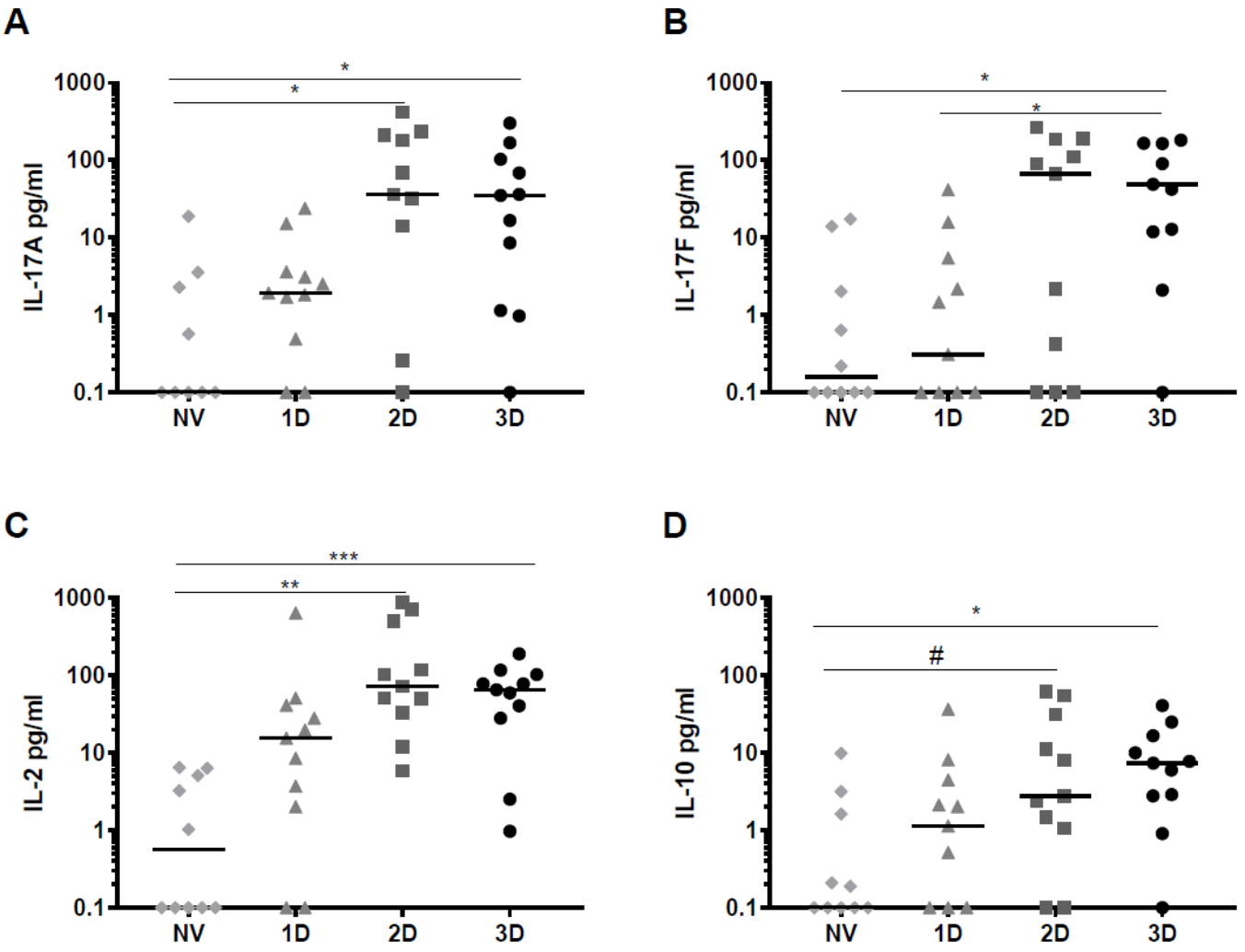
A
IL-17A pg/ml
1000
100
10
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1D
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3D
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1
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NV
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C
IL-2 pg/ml
1000
100
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1
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***
**
NV
1D
2D
3D
D
IL-10 pg/ml
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10
1
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*
#
NV
1D
2D
3D

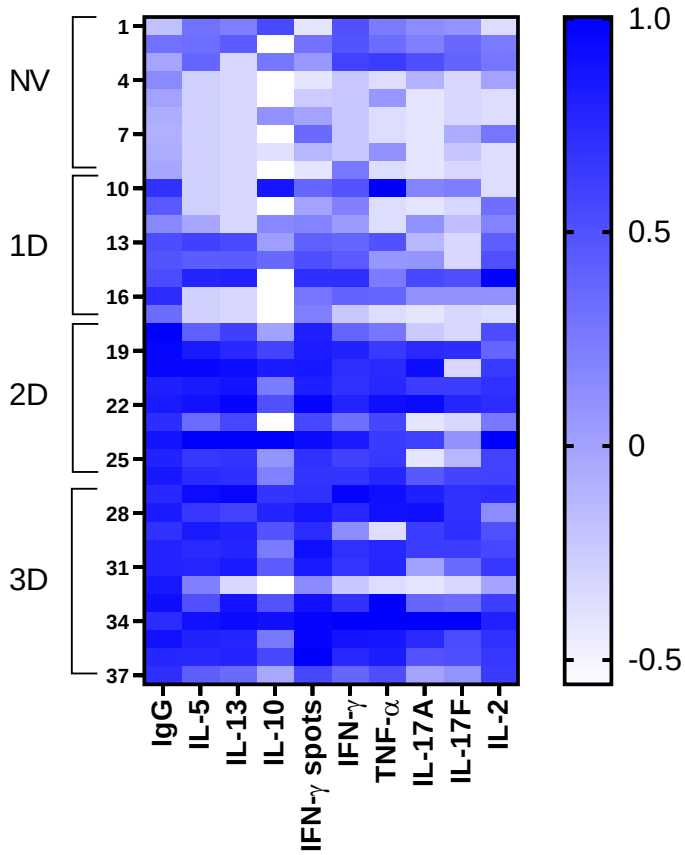
Additional slides

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.

b	Men 15-39 years of age N= 904	
	HPV seropositive n (%)	aPR (95% CI)
Any HPV type		
2006-07	60 (15.8)	Ref
2016-17	76 (14.5)	0.98 (0.7-1.4)
HPV16		
2006-07	34 (8.9)	Ref
2016-17	38 (7.3)	0.87 (0.5-1.4)
HPV18		
2006-07	22 (5.8)	Ref
2016-17	27 (5.2)	0.90 (0.5-1.6)

HPV1D study

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***)