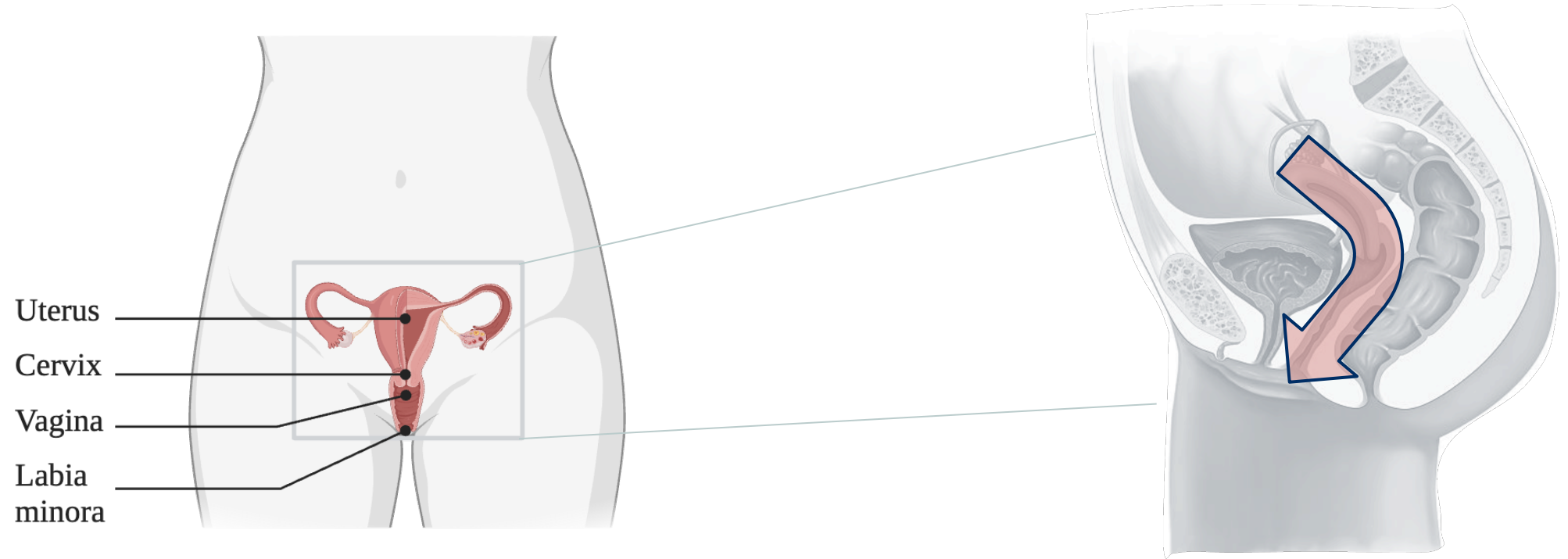


Understanding local HPV-related immunity using First-Void Urine (FVU)

Presenter: Laura Téblick, PhD

Team: Margo Bell, Ricardo Burdier, Annemie De Smet, Marijana Lipovac, Laura Téblick, Anne Van Caesbroeck, Eef van den Borst, prof. Severien Van Keer, prof. Alex Vorsters, Nayab Waheed

Why are we using first-void urine?

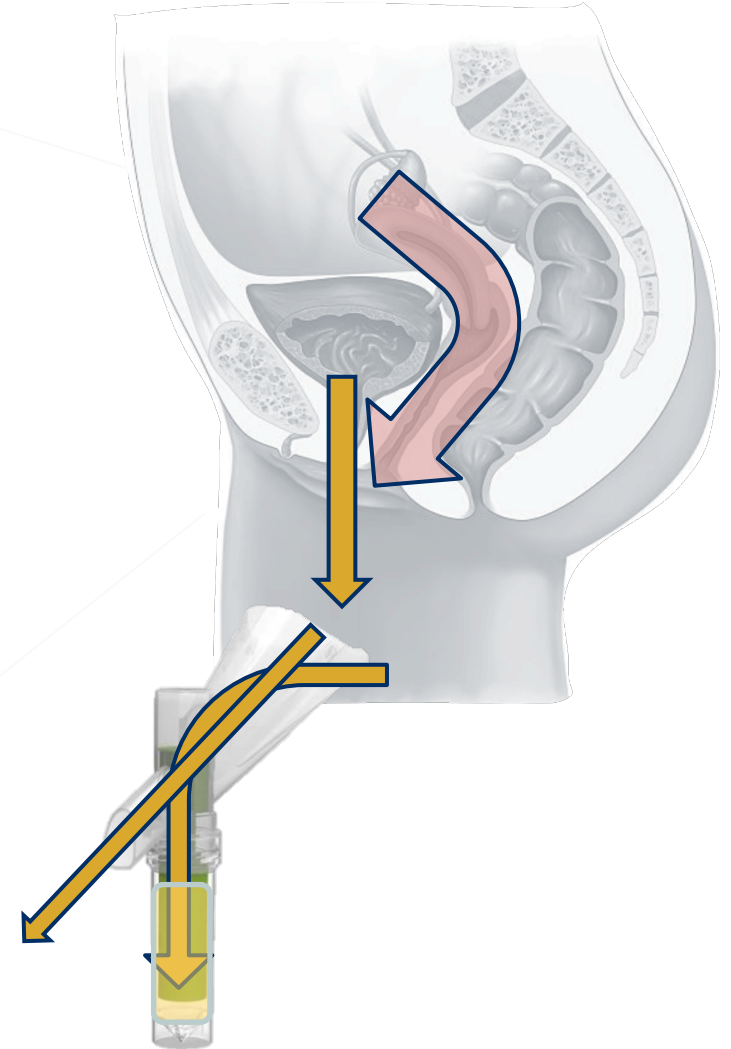


Why are we using first-void urine?

Uterine epithelium

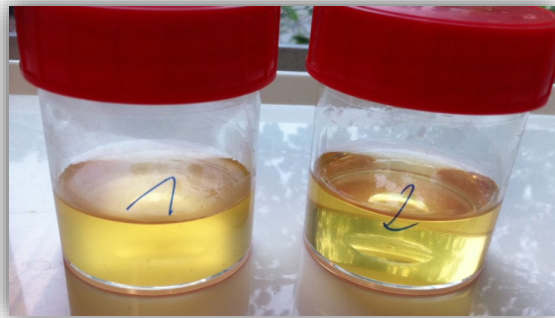
Cervical epithelium

Vaginal epithelium



Why are we using first-void urine?

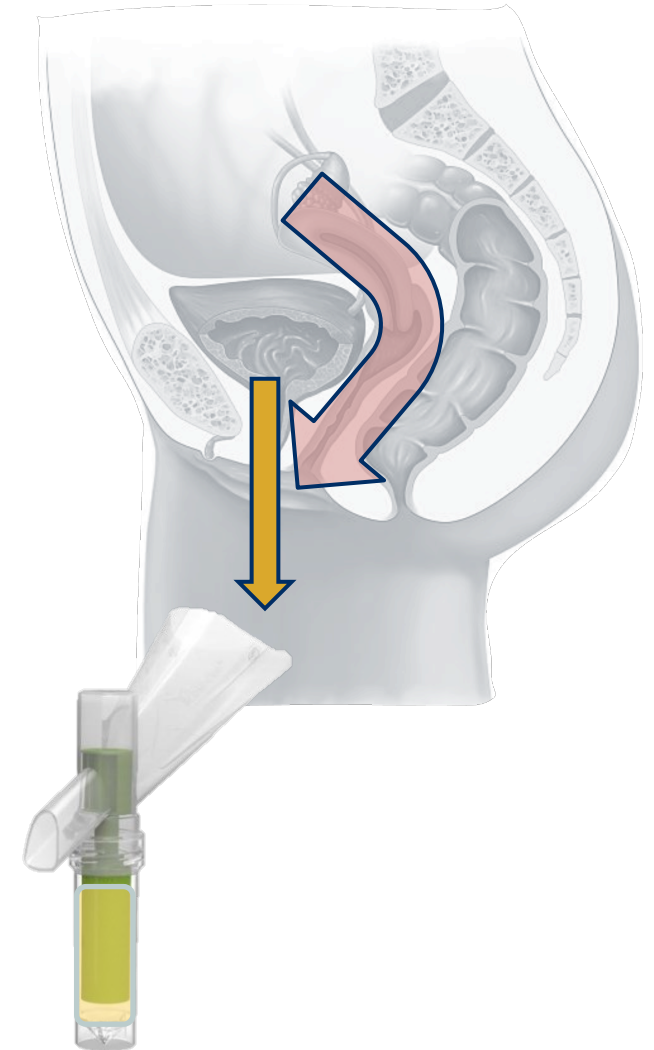
Easy-to-collect and reliable biological samples are critical to advance life sciences and public/personal health.



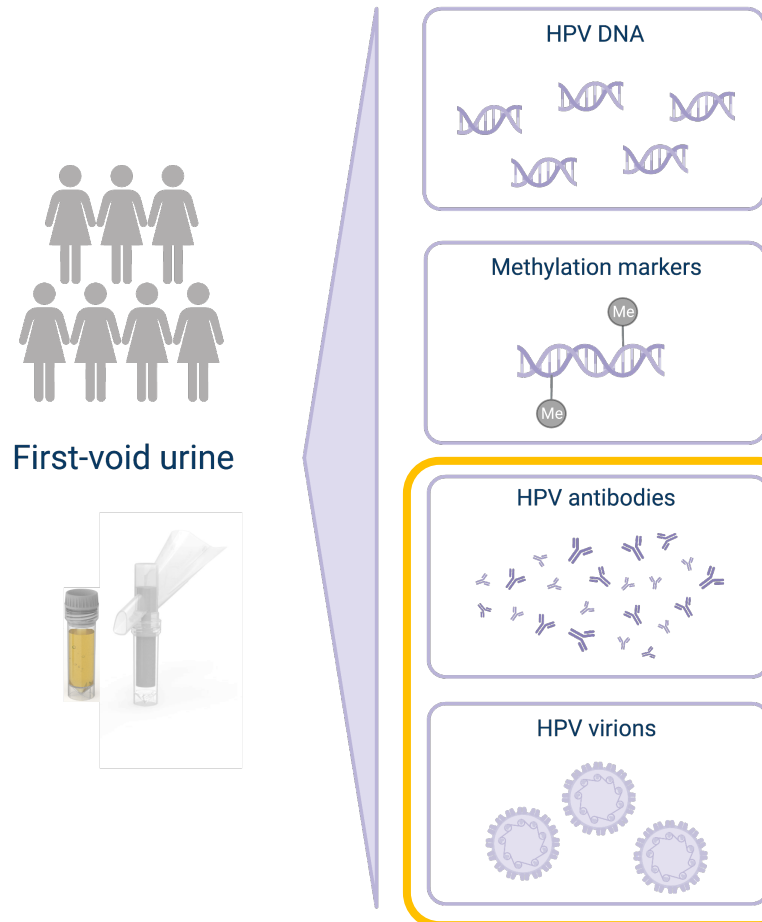
First-void urine

Midstream urine

We capture virological, immunological and diagnostic information from the infection site itself



FVU is potentially the ideal sample to study infection, immune response, and the interaction between pathogen and immune defense



What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

European Journal of Clinical Microbiology & Infectious Diseases (2018) 37:859–869
<https://doi.org/10.1007/s10096-017-3179-1>

ORIGINAL ARTICLE

Human papillomavirus genotype and viral load agreement between paired first-void urine and clinician-collected cervical samples

Severien Van Keer^a · Wiebren A. A. Tjalma^{a,b} · Jade Pattyn^a · Samantha Biesmans^a · Zoë Pieters^{a,b} · Xaveer Van Ostade^a · Margareta Ieven^a · Pierre Van Damme^a · Alex Vorsters^a



VALHUDES: A protocol for validation of human papillomavirus assays and collection devices for HPV testing on self-samples and urine samples

M. Arbyn^{a,b}, E. Peeters^a, I. Benoy^{a,c,d}, D. Vanden Broeck^{a,e,f}, J. Bogers^{a,g,h,i}, P. De Sutter^a, G. Donders^{a,b,j}, W. Tjalma^{a,b}, S. Weyers^a, K. Cuschieri^a, M. Poljak^a, J. Bonde^a, C. Cocuzza^a, F.H. Zhao^a, S. Van Keer^a, A. Vorsters^a

HPV DNA detection in urine samples of women: 'an efficacious and accurate alternative to cervical samples?'

Jade Pattyn, Severien Van Keer, Laura Téblick, Pierre Van Damme & Alex Vorsters

Optimization of HPV DNA detection in urine by improving collection, storage, and extraction

A. Vorsters · J. Van den Bergh · I. Micalessi · S. Biesmans · J. Bogers · A. Hens · I. De Coster · M. Ieven · P. Van Damme

Urine testing to monitor the impact of HPV vaccination in Bhutan and Rwanda

Silvia Franceschi¹, M. Chantal Umulisa², Ugyen Tshomo³, Tarik Gheit¹, Iacopo Baussano¹, Vanessa Tenet¹, Tshokey Tshokey⁴, Maurice Gatera², Fidele Ngabo², Pierre Van Damme¹, Peter J.F. Snijders⁵, Massimo Tommasino¹, Alex Vorsters² and Gary M. Clifford¹

Impact of Human Papillomavirus Vaccination, Rwanda and Bhutan

Iacopo Baussano, Felix Sayinzoga, Ugyen Tshomo, Vanessa Tenet, Alex Vorsters, Daniëlle A.M. Heideman, Tarik Gheit, Massimo Tommasino, Marie Chantal Umulisa, Silvia Franceschi, Gary M. Clifford



Clinical and analytical evaluation of the RealTime High Risk HPV assay in Colli-Pee collected first-void urine using the VALHUDES protocol

Severien Van Keer^{a,*}, Eliana Peeters^b, Davy Vanden Broeck^{c,d,e,f}, Philippe De Sutter^g, Gilbert Donders^{h,i,j}, Jean Doyen^k, Wiebren A.A. Tjalma^{l,m}, Steven Weyersⁿ, Alex Vorsters^a, Marc Arbyn^b



Human papillomavirus detection in urine: Effect of a first-void urine collection device and timing of collection

Jade Pattyn^{a,*}, Severien Van Keer^a, Samantha Biesmans^a, Margareta Ieven^{a,b}, Charlotte Vanderborght^a, Koen Beyers^a, Vanessa Vankerckhoven^{a,b}, Robin Bruyndonckx^{a,d}, Pierre Van Damme^a, Alex Vorsters^a

Urine testing for HPV: rationale for using first void

Alex Vorsters^{researcher¹}, Pierre Van Damme^{professor¹}, Gary Clifford^{cancer epidemiologist²}

¹Faculty of Medicine and Health Sciences, Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, University of Antwerp, 2610 Antwerpen (Wijk), Belgium; ²Infectious and Cancer Epidemiology Group, International Agency for Research on Cancer, Lyon, Cedex 08, France

Article

Long-Term Follow-up of HPV Infection Using Urine and Cervical Quantitative HPV DNA Testing

Alex Vorsters^{1,*}, Severien Van Keer¹, Samantha Biesmans¹, Annick Hens¹, Ilse De Coster¹, Herman Goossens^{2,3}, Margareta Ieven^{2,3} and Pierre Van Damme¹

Impact of Collection Volume and DNA Extraction Method on the Detection of Biomarkers and HPV DNA in First-Void Urine

Laura Téblick^{1,*}, Severien Van Keer¹, Annemie De Smet¹, Pierre Van Damme¹, Michelle Laerebans², Alejandra Rios Cortes², Koen Beyers², Vanessa Vankerckhoven^{1,2}, Veerle Matheussen^{3,4,5}, Renee Mandersloot⁶, Arno Floore⁶, Chris J. L. M. Meijer^{6,7}, Renske D. M. Steenbergen⁷ and Alex Vorsters¹

RESEARCH

Open Access

Concentration strategies for spiked and naturally present biomarkers in non-invasively collected first-void urine

Laura Téblick^{1,*}, Marijana Lipovac¹, F. Ricardo Burdier¹, Annemie De Smet¹, Margo Bell¹, Eef van den Borst^{1,2}, Veerle Matheussen^{3,4,5} and Alex Vorsters¹

OPEN

Triage of human papillomavirus infected women by methylation analysis in first-void urine

Severien Van Keer^{a,b}, Annina P. van Splunter^a, Jade Pattyn^a, Annemie De Smet^a, Sereina A. Herzog^a, Xaveer Van Ostade^a, Wiebren A. A. Tjalma^{a,b}, Margareta Ieven^a, Pierre Van Damme^a, Renske D. M. Steenbergen^a and Alex Vorsters^a

Analytical and clinical performance of extended HPV genotyping with BD Onclarity HPV Assay in home-collected first-void urine: A diagnostic test accuracy study

Severien Van Keer^{a,*}, Ardeshel Latourzhiaia^b, Davy Vanden Broeck^{c,d,e,f}, Philippe De Sutter^g, Gilbert Donders^{h,i,j}, Jean Doyen^k, Wiebren A.A. Tjalma^{l,m}, Steven Weyersⁿ, Marc Arbyn^{b,o}, Alex Vorsters^a

Testing for Human Papillomaviruses in Urine, Blood, and Oral Specimens: an Update for the Laboratory

● Mario Poljak^a ● Kate Cuschieri^b ● Laia Alemany^{c,d} ● Alex Vorsters^a

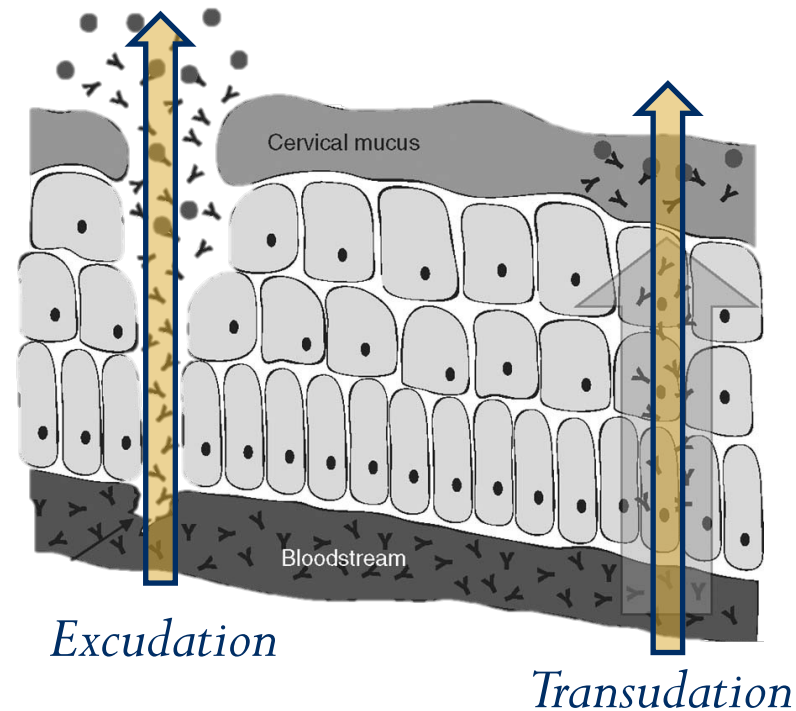
What have we done thus far using first-void urine

*Detection of HPV DNA and
methylation markers*

*Detection of HPV-specific
total antibodies*

How do the antibodies end up in first-void urine?

**Transudation &
excudation to female
genital tract**



What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

Detection of HPV-specific total antibodies



First-void urine as a non-invasive liquid biopsy source to detect vaccine-induced human papillomavirus antibodies originating from cervicovaginal secretions

Severien Van Keer^{a,*}, Martina Willhauck-Fleckenstein^b, Jade Pattyn^a, Julia Butt^b, Wiebren A.A. Tjalma^{c,d}, Xaveer Van Ostade^e, Niel Hens^{f,g}, Pierre Van Damme^a, Tim Waterboer^b, Alex Vorsters^a

Comparison of a VLP-based and GST-L1-based multiplex immunoassay to detect vaccine-induced HPV-specific antibodies in first-void urine

Jade Pattyn¹ | Gitika Panicker² | Martina Willhauck-Fleckenstein³ | Severien Van Keer¹ | Laura Téblick¹ | Zoë Pieters^{4,5} | Wiebren A. A. Tjalma^{6,7} | Veerle Matheeußen^{8,9,10} | Pierre Van Damme¹ | Tim Waterboer³ | Elizabeth R. Unger² | Alex Vorsters¹



Infection and vaccine-induced HPV-specific antibodies in cervicovaginal secretions. A review of the literature

Jade Pattyn^{a,*}, Severien Van Keer^a, Wiebren Tjalma^b, Veerle Matheeußen^c, Pierre Van Damme^a, Alex Vorsters^a

Non-invasive Assessment of Vaccine-Induced HPV Antibodies via First-Void Urine

Jade Pattyn^{*}, Severien Van Keer, Laura Téblick, Pierre Van Damme and Alex Vorsters

Faculty of Medicine and Health Sciences, Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Follow-up of humoral immune response after HPV vaccination using first-void urine: A longitudinal cohort study

Laura Téblick¹ | Jade Pattyn¹ | Severien Van Keer¹ | Annemie De Smet¹ | Ilse De Coster¹ | Wiebren A. A. Tjalma² | Ira Rajbhandari³ | Gitika Panicker³ | Elizabeth R. Unger³ | Alex Vorsters¹

What have we done thus far using first-void urine

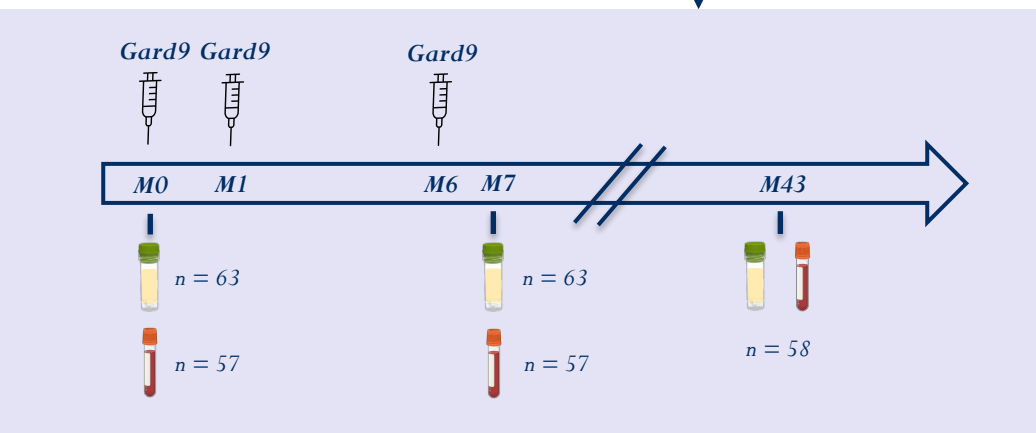
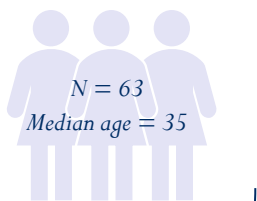
Detection of HPV DNA and methylation markers

Detection of HPV-specific total antibodies

Phase III vaccine trial in adult women with Gardasil9 vaccine

Substudy

AB-SOP follow-up



RESEARCH ARTICLE

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Follow-up of humoral immune response after HPV vaccination using first-void urine: A longitudinal cohort study

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Elizabeth R. Unger³ | Alex Vorsters¹

**First-void
urine
samples**

HPV DNA

- Roche Cobas 6800: all samples
- Riatol qPCR: Cobas 6800 positive samples

**Paired
samples**

Immunology

- **HPV 9-Plex VLP-based IgG ELISA (M9ELISA)**
- Bio-Rad Bioplex Total IgG Luminex assay

What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

Detection of HPV-specific total antibodies

Type	Months	First-void urine		Serum	
		Antibody detection	Antibody concentration (AU-IU/ml or µg/ml)	Antibody detection	Antibody concentration (AU-IU/mL or µg/mL)
HPV6	0	9/58 (16%)	0.000 (0.000–0.000)	21/57 (37%)	0.000 (0.000–0.380)
	7	57/58 (98%)	0.057 (0.022–0.203)	57/57 (100%)	92.60 (56.30–137.00)
	43	57/58 (98%)	0.006 (0.002–0.013)	58/58 (100%)	10.01 (4.89–18.13)
HPV11	0	4/58 (7%)	0.000 (0.000–0.000)	7/57 (12%)	0.000 (0.000–0.000)
	7	58/58 (100%)	0.058 (0.029–0.199)	57/57 (100%)	106.0 (56.60–158.0)
	43	57/58 (98%)	0.007 (0.003–0.016)	58/58 (100%)	10.72 (5.24–17.93)
HPV16	0	7/58 (12%)	0.000 (0.000–0.000)	10/57 (18%)	0.000 (0.000–0.000)
	7	58/58 (100%)	0.184 (0.077–0.552)	57/57 (100%)	291.0 (178.0–468.0)
	43	58/58 (100%)	0.019 (0.008–0.045)	58/58 (100%)	32.17 (13.32–64.67)
HPV18	0	6/58 (10%)	0.000 (0.000–0.000)	21/57 (37%)	0.000 (0.000–0.440)
	7	56/58 (97%)	0.058 (0.031–0.274)	57/57 (100%)	102.0 (44.00–210.0)
	43	52/58 (90%)	0.005 (0.002–0.015)	58/58 (100%)	6.54 (2.07–17.35)
HPV31	0	4/58 (7%)	0.000 (0.000–0.000)	8/57 (14%)	0.000 (0.000–0.000)
	7	58/58 (100%)	0.145 (0.050–0.573)	57/57 (100%)	195.0 (118.0–541.0)
	43	55/58 (95%)	0.016 (0.004–0.036)	58/58 (100%)	21.28 (10.48–49.17)
HPV33	0	3/58 (5%)	0.000 (0.000–0.000)	5/57 (9%)	0.000 (0.000–0.000)
	7	58/58 (100%)	0.238 (0.078–0.573)	57/57 (100%)	322.0 (197.0–677.0)
	43	56/58 (97%)	0.020 (0.004–0.051)	58/58 (100%)	31.92 (13.36–69.07)
HPV45	0	2/58 (3%)	0.000 (0.000–0.000)	7/57 (12%)	0.000 (0.000–0.000)
	7	55/58 (95%)	0.202 (0.061–0.586)	57/57 (100%)	336.0 (140.0–562.0)
	43	52/58 (90%)	0.016 (0.003–0.050)	58/58 (100%)	16.37 (8.63–63.59)
HPV52	0	0/58 (0%)	0.000 (0.000–0.000)	11/57 (12%)	0.000 (0.000–0.000)
	7	57/58 (98%)	0.110 (0.035–0.507)	57/57 (100%)	297.0 (151.0–600.0)
	43	49/58 (84%)	0.017 (0.003–0.046)	57/58 (98%)	28.27 (11.45–65.31)
HPV58	0	4/58 (7%)	0.000 (0.000–0.000)	9/57 (16%)	0.000 (0.000–0.000)
	7	58/58 (100%)	0.359 (0.079–0.849)	57/57 (100%)	365.0 (222.0–790.0)
	43	53/58 (91%)	0.026 (0.010–0.078)	58/58 (100%)	39.81 (15.65–97.34)

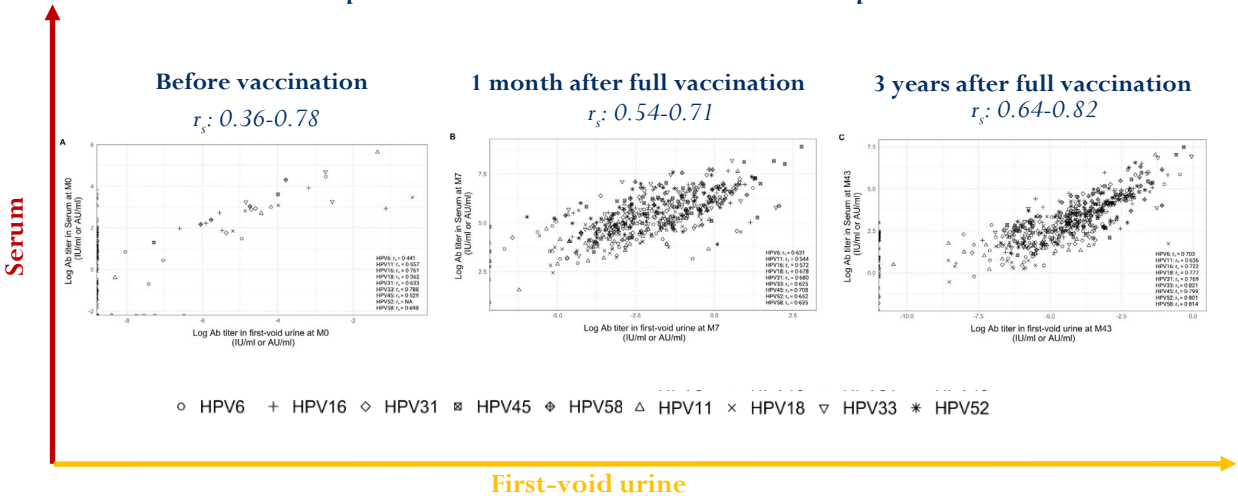
RESEARCH ARTICLE

JOURNAL OF
MEDICAL VIROLOGY
WILEY

Follow-up of humoral immune response after HPV vaccination using first-void urine: A longitudinal cohort study

Laura Téblick¹ | Jade Pattyn¹ | Severien Van Keer¹ | Annemie De Smet¹ |
Ilse De Coster¹ | Wiebren A. A. Tjalma² | Ira Rajbhandari³ | Gitika Panicker³ |
Elizabeth R. Unger³ | Alex Vorsters¹

Spearman Rank correlations at three timepoints



What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

Detection of HPV-specific total antibodies

Detection of HPV-specific neutralizing antibodies


By using first-void urine, we investigate the immune response at the site of infection

- *Are these antibodies still neutralizing the pseudovirions and thus functional?*

RESEARCH ARTICLE

 OPEN ACCESS  Check for updates

HPV-specific antibodies in female genital tract secretions captured via first-void urine retain their neutralizing capacity

Laura Téblick ^a, Marijana Lipovac^a, Freya Molenberghs^b, Peter Delputte^c, Winnok H. De Vos^{b,d,e}, and Alex Vorsters^a

^aCentre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium; ^bLaboratory of Cell Biology and Histology, University of Antwerp, Antwerp, Belgium; ^cLaboratory for Microbiology, Parasitology and Hygiene, University of Antwerp, Antwerp, Belgium; ^dAntwerp Centre for Advanced Microscopy, University of Antwerp, Antwerp, Belgium; ^eμNEURO Centre of Research Excellence, University of Antwerp, Antwerp, Belgium

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RESEARCH ARTICLE

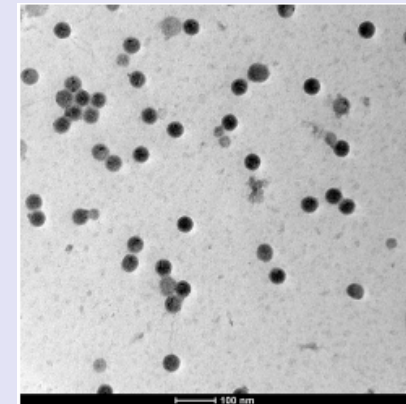
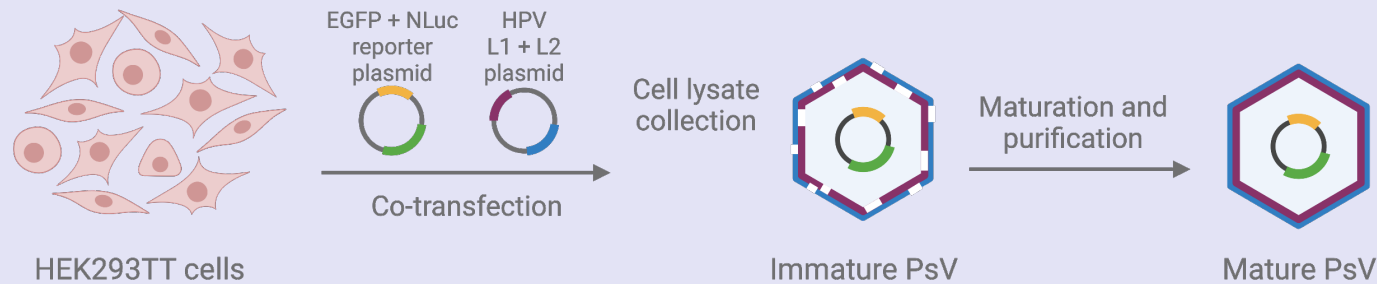
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HPV-specific antibodies in female genital tract secretions captured via first-void urine retain their neutralizing capacity

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Production of HPV PsV in-house (CDC protocol)



What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

Detection of HPV-specific total antibodies

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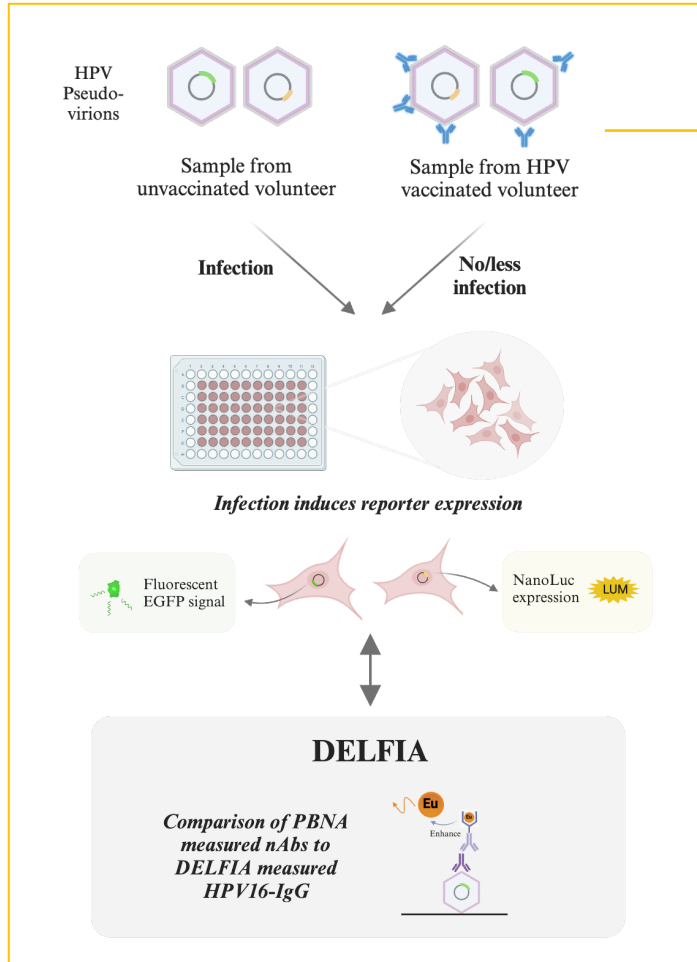
RESEARCH ARTICLE

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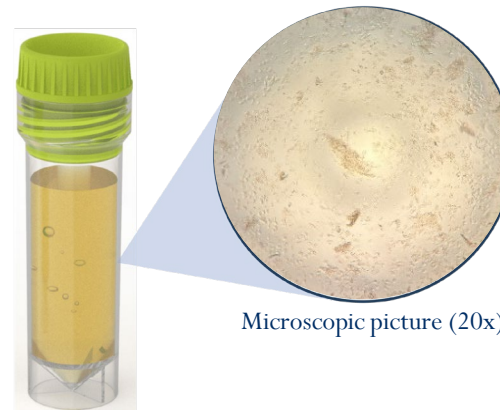
HPV-specific antibodies in female genital tract secretions captured via first-void urine retain their neutralizing capacity

Laura Téblick¹, Marijana Lipovac², Freya Molenberghs³, Peter Delpitte⁴, Winnok H. De Vos^{5,6,7}, and Alex Vorsters⁸

¹Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium; ²Laboratory of Cell Biology and Histology, University of Antwerp, Antwerp, Belgium; ³Laboratory for Microbiology, Parasitology and Hygiene, University of Antwerp, Antwerp, Belgium; ⁴Antwerp Centre for Advanced Microscopy, University of Antwerp, Antwerp, Belgium; ⁵µNEURO Centre of Research Excellence, University of Antwerp, Antwerp, Belgium



First-void urine



Sample purification required

Final selected 'purification' method:

Amicon filtration



retentate of 500 µl in dPBS centrifuged at 1000g for 10 minutes



supernatant on cells

What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

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Results from 25 HPV vaccinated and 25 unvaccinated female volunteers

Assay	Outcome	Total			Unvaccinated		Vaccinated	
		FVU	Serum	Ratio FVU/serum % (IQR)	FVU	Serum	FVU	Serum
DELFI	Positive (%)	31/50 (62%)	29/50 (58%)		6/25 (24%)	4/25 (16%)	25/25 (100%)	25/25 (100%)
	HPV16-IgG (IU/ml)	0.012 (0.000–0.046)	19.6 (0.0–86.1)	0.07 (0.04–0.12)	0.000 (0.000–0.000)	0.0 (0.0–0.0)	0.047 (0.025–0.104)	86.45 (47.2–167.9)
EGFP PBNA	Positive (%)	10/50 (20%)	27/50 (54%)		2/25 (8%)	2/25 (8%)	8/25 (32%)	25/25 (100%)
	HPV16-nAbs EC ₅₀	0.00 (0.00–0.00)	197 (0.00–1457)	0.22 (0.09–0.33)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–6.04)	1573 (774–4887)
Nluc PBNA	Positive (%)	19/50 (38%)	28/50 (56%)		1/25 (4%)	3/25 (12%)	18/25 (72%)	25/25 (100%)
	HPV16-Abs EC ₅₀	0.00 (0.00–6.65)	211 (0.00–2030)	0.34 (0.15–0.51)	0.00 (0.00–0.00)	0.000 (0.00–0.00)	5.69 (0.00–18.69)	1616 (520–6981)

! Protocol optimization for FVU samples is required !

What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

Detection of HPV-specific total antibodies

Detection of HPV-specific neutralizing antibodies

Investigating the virion-antibody interaction

By using first-void urine, we investigate the immune response at the site of infection

- *Are these antibodies still neutralizing the wild-type virions and thus functional?*

Perspective

HPV vaccination: Are we overlooking additional opportunities to control HPV infection and transmission?



Alex Vorsters^{a,*}, Pierre Van Damme^a, F. Xavier Bosch^{b,c}

^a Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, Faculty of Medicine, University of Antwerp, Universiteitsplein 1, 2610 Antwerp, Belgium

^b Cancer Epidemiology Research Programme (CERP), Catalan Institute of Oncology (ICO- IDIBELL), Avinguda de la Granvia de l'Hospitalet 199-203, 08908 L'Hospitalet de Llobregat, Barcelona, Spain

^c Open University of Catalonia (UOC), Barcelona, Spain

RESEARCH

Open Access

Concentration strategies for spiked and naturally present biomarkers in non-invasively collected first-void urine



Laura Téblick^{1*}, Marijana Lipovac¹, F. Ricardo Burdier¹, Annemie De Smet¹, Margo Bell¹, Eef van den Borst^{1,2}, Veerle Matheeußen^{3,4,5} and Alex Vorsters¹

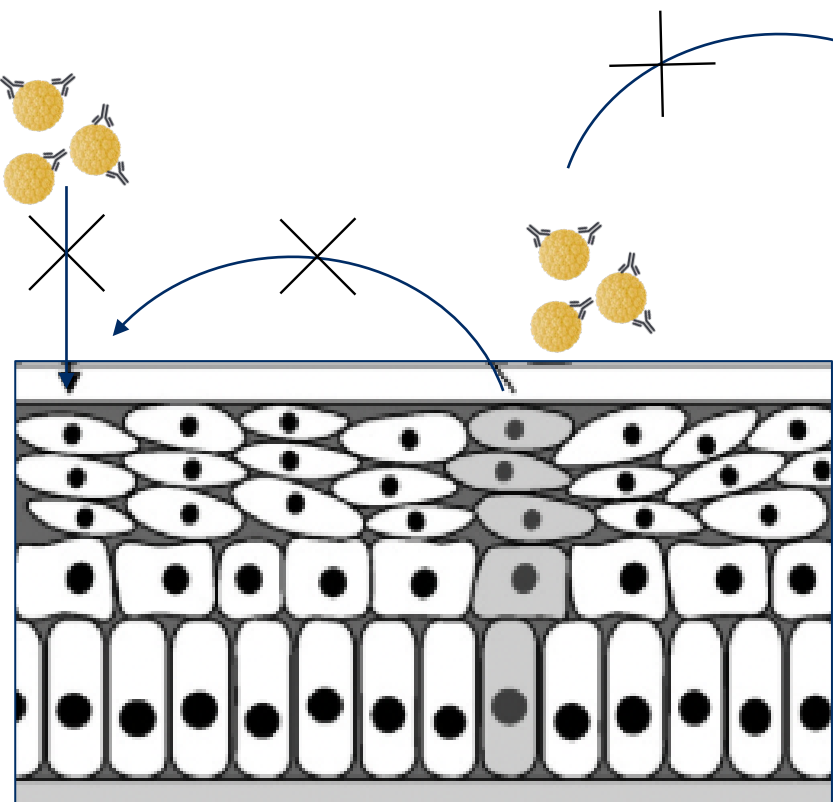
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Prevent new infection

Prevent infection from reaching other site (autoinnoculation)

Prevent transmission to sexual partner

What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

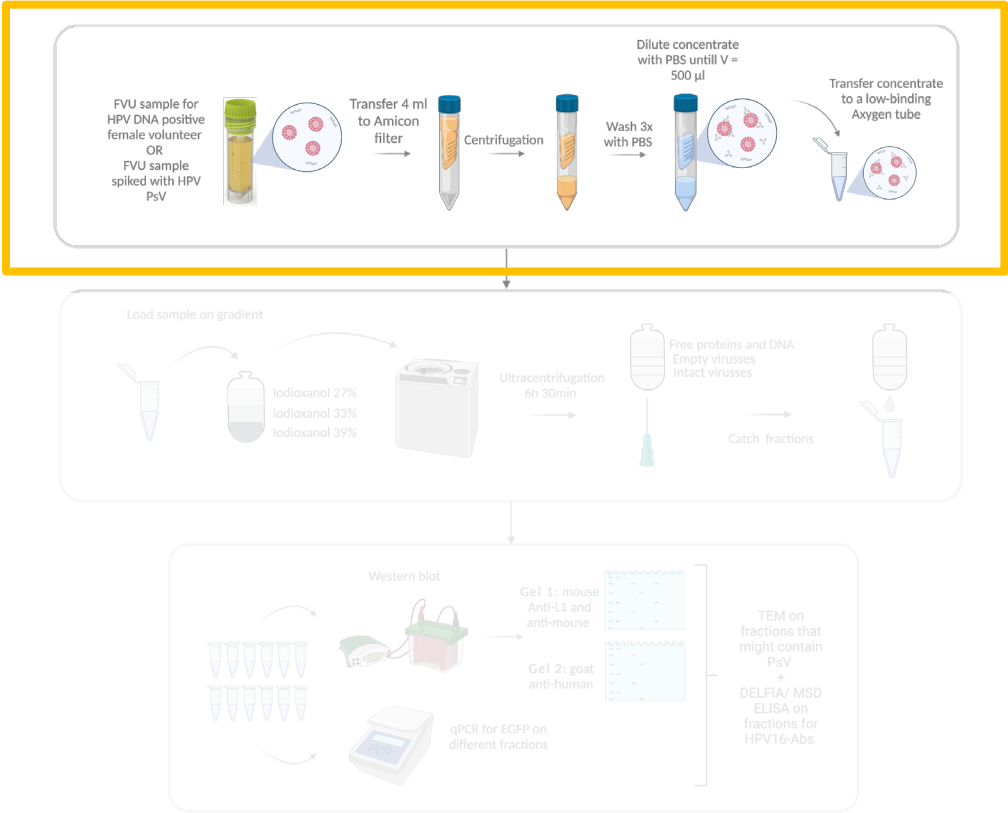
Detection of HPV-specific total antibodies

Detection of HPV-specific neutralizing antibodies

Investigating the virion-antibody interaction

Isolation of viral particles from FVU

1. Concentration



RESEARCH

Open Access

Concentration strategies for spiked and naturally present biomarkers in non-invasively collected first-void urine

Laura Téblick^{1*}, Marijana Lipovac¹, F. Ricardo Burdier¹, Annemie De Smet¹, Margo Bell¹, Eef van den Borst^{1,2}, Veerle Matheeußen^{3,4,5} and Alex Vorsters¹

- Pseudovirions are pelleted
- Pelleting is enhanced by adding precipitating agent
- Urine matrix has an effect

What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

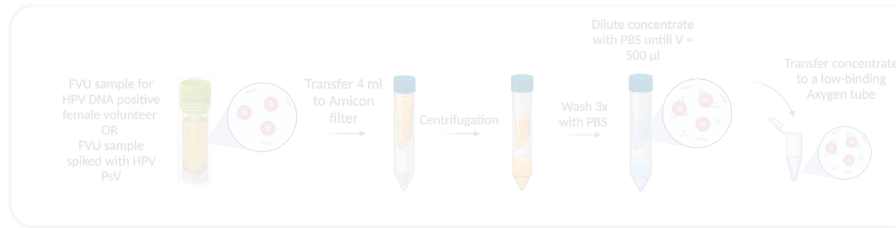
Detection of HPV-specific total antibodies

Detection of HPV-specific neutralizing antibodies

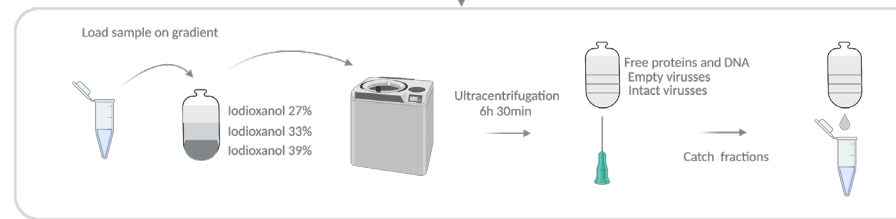
Investigating the virion-antibody interaction

Isolation of viral particles from FVU

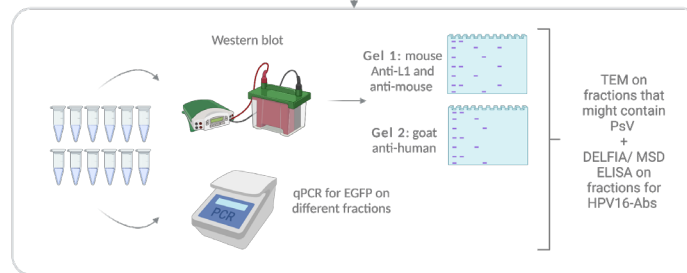
1. Concentration



2. Purification



3. Quantification /detection



Spiking of first-void urine samples from vaccinated/unvaccinated female volunteers with **HPV16 PsV** as a 'model'

Western blot on fractions for L1

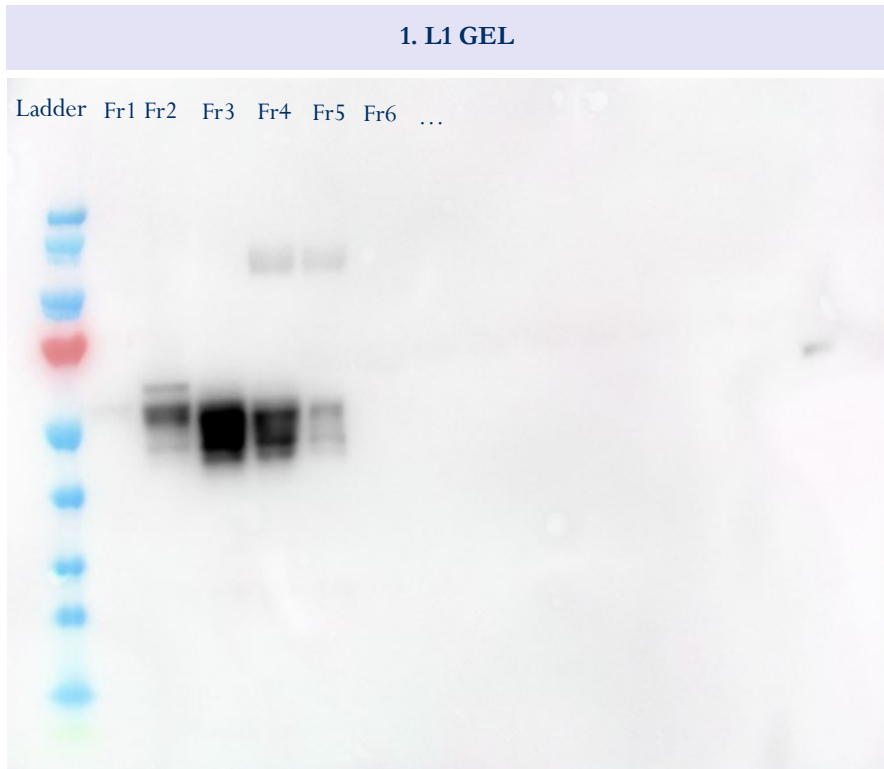
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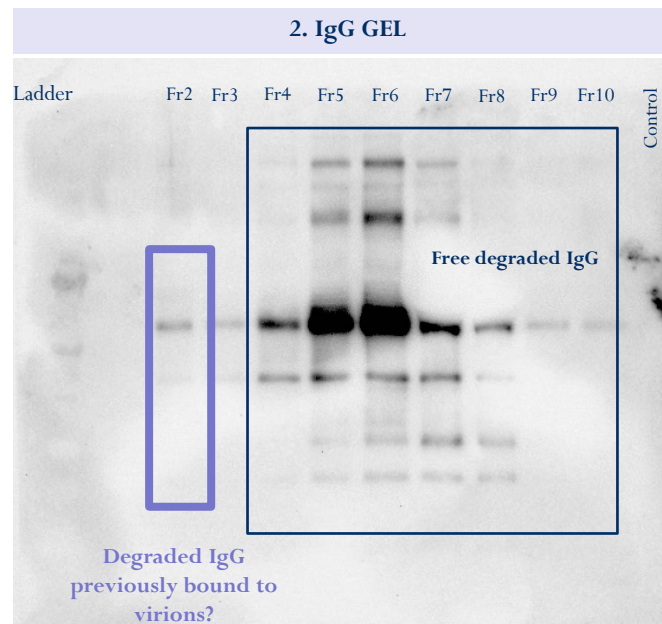
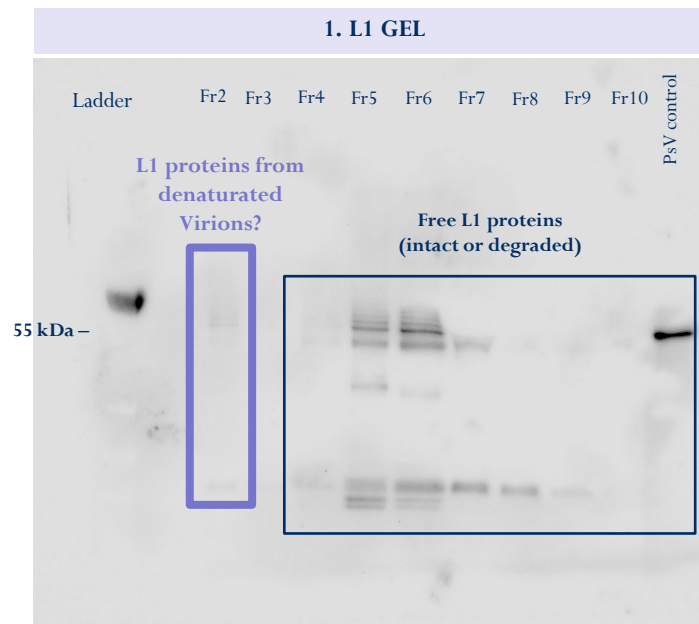
What have we done thus far using first-void urine

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Investigating the virion-antibody interaction



First experiment using a first-void urine sample from **HPV16 infected – vaccinated volunteer**

Western blot for IgG and L1

Further experiments using spiking and later wild-type virions are ongoing

What have we done thus far using first-void urine

Detection of HPV DNA and methylation markers

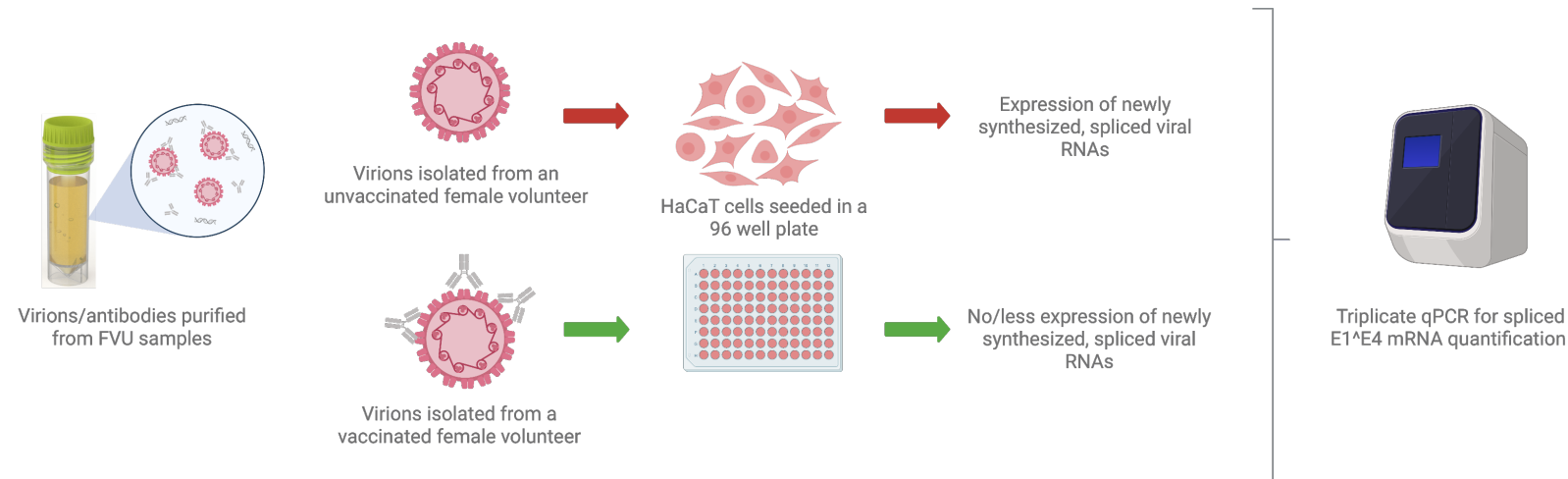
Detection of HPV-specific total antibodies

Detection of HPV-specific neutralizing antibodies

Investigating the virion-antibody interaction

By using first-void urine, we investigate the immune response at the site of infection

- Are these antibodies still neutralizing the wild-type virions and thus functional?



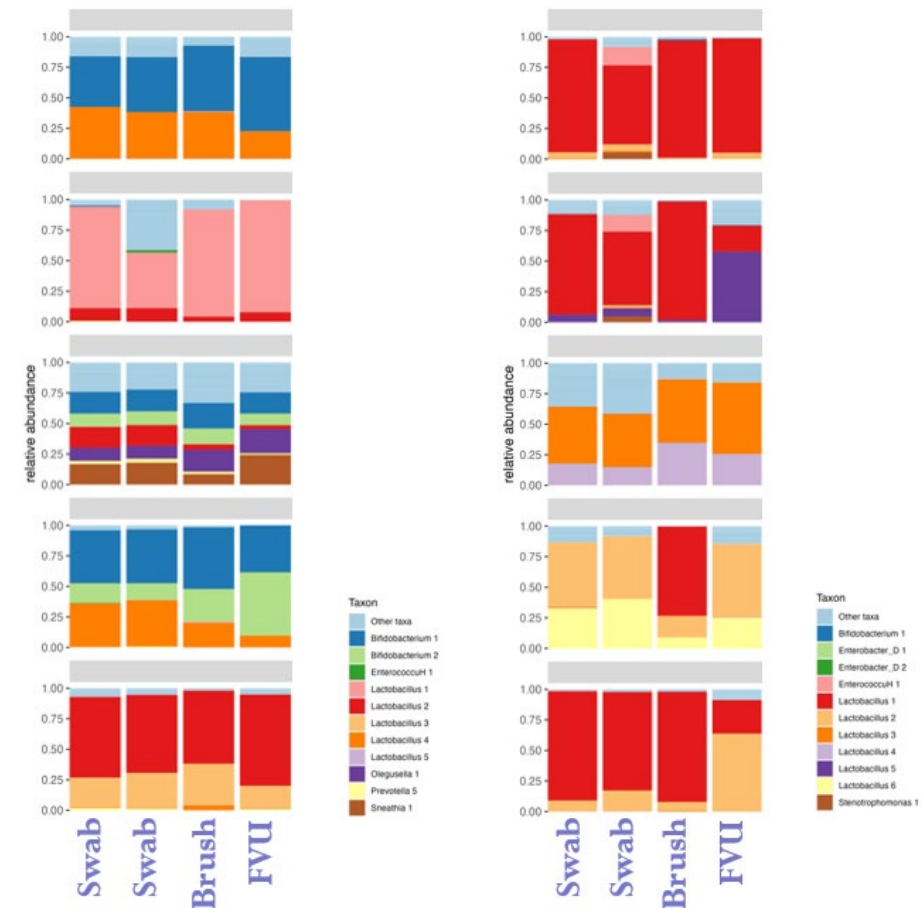
→ Will be evaluated in a FVU based HPV infection model

What else can we do using first-void urine

Confidential slides – do not copy or redistribute

Vaginal microbiome research

- Compare microbiome in FVU to cervical/vaginal samples
- Investigate the influence of the microbiome on HPV infection and vice-versa using first-void urine



What else can we do using first-void urine

Confidential slides – do not copy or redistribute

Vaginal microbiome research

*Chlamydia trachomatis
research*

*And more unexplored
research fields...*



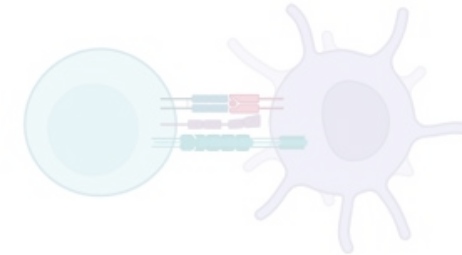
WP1: Systematic review

Humoral and cellular immune responses
Male & female genital secretions
Ct infection



WP2: *Ct*-antibodies in FVU

Selecting commercial antigens
Producing EBs
Setting up a multiplex immunoassay
Neutralization assay
Phagocytic activity assay



WP3: *Ct*-specific cellular immune responses in FVU

IFN- γ ELISPOT assay
ARTE
Phenotypic characterization
Lymphoproliferation
Intracellular staining

*Cellular immune
response towards
HPV will also be
investigated*

Understanding local HPV-related immunity using First-Void Urine (FVU)

Presenter: Laura Téblick, PhD

Team: Margo Bell, Ricardo Burdier, Annemie De Smet, Marijana Lipovac, Laura Téblick, Anne Van Caesbroeck, Eef van den Borst, prof. Severien Van Keer, prof. Alex Vorsters, Nayab Waheed