



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

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

Citation for published version:

Arbyn, M, Peeters, E, Benoy, I, Vanden Broeck, D, Bogers, J, De Sutter, P, Donders, G, Tjalma, W, Weyers, S, Cuschieri, K, Poljak, M, Bonde, J, Cocuzza, C, Zhao, FH, Van Keer, S & Vorsters, A 2018, 'VALHUDES: A protocol for validation of human papillomavirus assays and collection devices for HPV testing on self-samples and urine samples', *Journal of Clinical Virology*, vol. 107, pp. 52-56. <https://doi.org/10.1016/j.jcv.2018.08.006>

Digital Object Identifier (DOI):

[10.1016/j.jcv.2018.08.006](https://doi.org/10.1016/j.jcv.2018.08.006)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Journal of Clinical Virology

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



VALHUDES: a protocol for VALidation of HUman papillomavirus assays and collection DEvices for HPV testing on Self-samples and urine samples

M. Arbyn¹, E. Peeters¹, I. Benoy², D. Vanden Broeck^{2,3}, J. Bogers^{2,3}, P. De Sutter⁴, G. Donders⁵, W. Tjalma⁶, S. Weyers⁷, K. Cuschieri⁸, M. Poljak⁹, J. Bonde¹⁰, C. Cocuzza¹¹, FH Zhao¹², S. Van Keer¹³, A. Vorsters¹³

¹ Unit of Cancer Epidemiology, Belgian Cancer Centre, Sciensano, Brussels, Belgium

² Laboratory of Molecular Pathology, AML Sonic Healthcare, Antwerp; National Reference Centre for HPV, Brussels; AMBIOR, Laboratory for Cell Biology & Histology, University of Antwerp, Antwerp, Belgium

³ International Centre for Reproductive Health, Ghent University, Ghent, Belgium

⁴ UZ Brussel – VUB, dept Gynaecology-Oncology, Brussels, Belgium

⁵ Department of Obstetrics and Gynaecology of the General Regional Hospital Heilig Hart, Tienen, Belgium; Femicare vzw, Clinical Research for Women, Tienen, Department of Obstetrics and Gynaecology University Hospital Antwerpen, Antwerp, Belgium

⁶ Multidisciplinary Breast Clinic, Unit Gynaecologic Oncology, Department of Obstetrics and Gynaecology, Antwerp University Hospital (UZA), Edegem; Molecular Imaging, Pathology, Radiotherapy, Oncology (MIPRO), Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

⁷ Department of Obstetrics and Gynecology, Ghent University Hospital, Ghent, Belgium

⁸ Scottish HPV Reference Laboratory, Department of Laboratory Medicine, NHS Lothian, Royal Infirmary of Edinburgh

⁹ Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

¹⁰ Molecular Pathology Laboratory, Dept. Pathology, Copenhagen University Hospital, Hvidovre, Denmark

¹¹ Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

¹² Department of Epidemiology, Cancer Institute of Chinese Academy of Medical Sciences, Peking Union Medical College, Department of Gynaecology and Obstetrics, Beijing Tongren Hospital, Beijing, China

¹³ Centre for the Evaluation of Vaccination (CEV), Vaccine & Infectious Disease Institute (VAXINFECTIO), Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk (Antwerp), Belgium

Word count: 2538

Corresponding author:

Marc Arbyn, Unit of Cancer Epidemiology, Belgian Cancer Centre, Sciensano, J. Wytsmanstreet 14, B1050 Brussels, Belgium. marc.arbyn@sciensano.be; tel: +32 2 6425021

Keywords: cervical cancer, screening, diagnostic test accuracy, self-sampling, urine collection, test validation, VALHUDES.

ABSTRACT

Back ground

Systematic reviews have concluded that hrHPV DNA testing using target-amplification tests is as accurate on vaginal self-samples as on clinician-taken specimens for the detection of cervical precancer. However, insufficient evidence is available for specific HPV assay/self-sample device combinations.

Objectives

The VALHUDES protocol is designed as a diagnostic test accuracy study that aims to compare the clinical sensitivity and specificity of particular hrHPV assay(s) on vaginal self-samples and first-void-urine, collected in agreement with standardized protocols, with hrHPV testing on matched clinician-taken samples.

Study design

Five hundred enrolled women referred to a colposcopy clinic are invited to collect a first-void urine sample and one or more vaginal self-samples with particular devices before collection of a cervical sample by a clinician. Sample sets are subsequently analysed in a laboratory accredited for HPV testing. Disease verification for all enrolled patients is provided by colposcopy combined with histological assessment of biopsies.

Results

A first VALHUDES study has started in Belgium in December 2017 with enrolment from four colposcopy centres. The following assays are foreseen to be evaluated: RealTime High Risk

HPV assay (Abbott), cobas-4800 and -6800 (Roche), Onclarity (BD), Xpert HPV (Cepheid) and Anyplex II HPV HR (Seegene).

Conclusion

Given empirical evidence that the relative accuracy of HPV-testing on self- vs clinician-samples is robust across clinical settings, the VALHUDES protocol offers a framework for validation of HPV assay/self-sample device combinations that can be translated to a primary screening setting.

BACKGROUND

Offering devices which allow women to take a self-sample may increase uptake for cervical cancer screening among particularly those who do not participate in the regular programme. Several studies have shown that mailing a self-sampling kit to the women's home address generates a greater response compared to mailing of reminder letters recommending collection of a cervical sample by a health professional[1,2]. However, the magnitude of this response gain is very heterogeneous across studies, which suggests that the impact of self-sampling depends on local conditions, context and the design of the screening programme[2]. Implementation of strategies using self-sampling without knowledge of possible effects and influencing factors may result in small gains in population coverage but substantial costs for the health budget[3,4]. The opt-in approach where non-attending women are invited to order a self-sampling device is designed to reduce waste of self-sampling devices and thereby reduce cost of operations[5,6]. However, systematic reviews of randomised trials indicate that opt-in strategies generate lower participation rates compared with mail-to-all strategies[2,5,7]. Nevertheless, several demonstration studies using opt-in strategies were successful as well in mobilising women who did not respond to an invitation to have a Pap smear taken by a clinician overall generating a considerable prevention effect[6,8]. Whether a mail-to-all or opt-in approach is chosen, finding validated and safe procedures using devices which are affordable, easy to mail, acceptable, user-friendly, technically robust and compatible with used DNA extraction and detection methods are of paramount importance[9,10][11].

An increasing number of human papillomavirus (HPV) tests are now considered as acceptable for use in primary cervical cancer screening on clinician-collected cervical cell samples[12-14]. A recent meta-analysis demonstrated that high-risk (hr) HPV assays, based on a principle of signal-amplification were significantly less sensitive and specific for underlying high-grade cervical intra-epithelial neoplasia (CIN of grade 2 or worse [CIN2+]) on self-samples than on clinician-taken samples. However, testing with PCR-based hrHPV assays, already validated on clinician-taken samples[14], showed similar accuracy on vaginal self-samples compared to cervical samples taken by a health professional[15,16]. Sub-group meta-analysis did not reveal important self-sampling device effects, with the caveat that most studies directly compared the performance of (only) one particular self-sampling device with clinician-collected specimens, and as such no strong conclusions could be drawn regarding the impact or lack of impact of the choice of the self-samplers on the test accuracy.

Among methods for self-sampling, collection of urine samples is to be considered as well. Urine sampling is in some context more culturally and religiously acceptable than cervico-vaginal based self-sampling[17]. A recent review assessed the analytical sensitivity and

specificity of hrHPV testing in urine using presence of hrHPV in a clinician-collected cervical sample as endpoint[18]. The pooled sensitivity and specificity estimates were 77% (95% CI: 68-84%) and 88% (95% CI: 58-97%), respectively. Findings were however, very variable (high inter-study heterogeneity, and included a mixture of clinical settings [screening, follow-up, age ranges, random or first-void collection, procedures for sample handling, etc.]. In addition, very few data on clinical accuracy of hrHPV testing on urine specimens are available. The few studies which have assessed the clinical sensitivity for CIN2+ have shown lower clinical sensitivity of hrHPV testing in urine than in cervical samples[19,20]. In these studies, urine sample collection may have been suboptimal for the detection of HPV given recent evidence focusing on the capture of a first-void specimen as well as addition of preservation buffers which together has the potential to significantly enhance the sensitivity of hrHPV DNA detection in urine[21-25].

OBJECTIVES

The VALHUDES project aims to provide high quality comparative data on clinical performance of HPV testing on self-collected samples. The current protocol compares the clinical accuracy of hrHPV testing with defined, clinically validated PCR-based hrHPV assays on vaginal self-samples collected with various devices and on first-void urine, collected under standardised conditions, with hrHPV testing on matched clinician-taken samples.

STUDY DESIGN

Study questions

The main objective of VALHUDES is to assess whether HPV testing on vaginal self-samples or a first-void urine specimen, using a particular self-sampler, is as accurate as HPV testing on a cervical sample taken by a clinician to detect cervical precancer. Secondary objectives include the assessment of the absolute accuracy of each HPV test applied according to each sampling device, the proportion of adequate specimens as determined by amplification of an internal control (an ubiquitous human gene), the test positivity rate, relative and absolute predictive values. CIN2+ and CIN3 or cervical carcinoma *in situ* or worse (CIN3+) are the disease outcomes.

Study design

VALHUDES is designed as a diagnostic test accuracy study following the STARD guidelines[26], where all subjects are tested independently with an index and a comparator test and subsequently are submitted to a reference or gold standard. Collections of specimens used for testing and verification of disease status occur quasi simultaneously. The index tests are an HPV assay applied on a vaginal self-sample and on a first-void urine specimen, whereas the comparator test is the same HPV assay applied on a cervical liquid-based cytology sample collected by a trained clinician. Disease verification entails colposcopy applied to all women followed by colposcopy-directed biopsy. In case of multiple biopsy episodes, the worst histological outcome will be recorded. Negative colposcopy is accepted as providing sufficient ascertainment for absence of cervical precancer.

Study population and clinical setting

Women attending a colposcopy clinic referred due to previous cytological abnormalities, HPV infection or because of suspicious symptoms will be enrolled after obtaining informed consent. From a previous meta-analysis, it was concluded that the relative sensitivity and specificity of HPV testing on self-taken compared to clinician-collected samples were similar in screening and follow-up settings. For reasons of statistical power, it is more convenient to conduct a diagnostic trial in a colposcopy setting, where all women are referred for diagnostic evaluation

and where the application of the gold standard is required for clinical reasons (rather than a study-driven intervention). This minimises the requirement for additional interventions beyond standard of care and, additionally, biases induced by partial diagnostic verification are avoided. Exclusion criteria are: women younger than 25 or older than 64, hysterectomised women, women with known pregnancy at consultation and non-consenting women and inability to understand the patient materials and informed consent form.

Study size

The sample size was computed using a method for demonstrating non-inferiority in studies with matched design[27]. Expected probabilities (sensitivity or specificity of the standard test = hrHPV with validated PCR in follow-up settings) were derived from a recent meta-analysis[15]. Expected discordance (hrHPV positivity/negativity) of hrHPV PCR on self-samples taken with the new device vs Evalyn Brush (Rovers Medical Devices B.V., Oss, The Netherlands) were derived from a study conducted in Hannover[28]. We accepted $\alpha=0.05$, $\beta=0.20$, lower confidence interval for relative sensitivity and specificity (index/comparator)=0.90 and 0.95, respectively, which yielded a need to enrol 118 CIN2+ cases and $183 \leq$ CIN1 cases. The yearly number of referred patients, the proportion accepting enrolment in the study, the biopsy rate (proportion biopsied among women undergoing colposcopy), the expected prevalence of CIN2+ and \leq CIN1 have to be taken into account, to determine the required sample size in a specific colposcopy clinic. The non-inferiority in sensitivity for CIN2+ is expected to determine the study size, rather than the specificity. 118 CIN2 cases are expected to be retrievable among 353 participating colposcopy patients with biopsy. As a template we can put forward 500 included colposcopy patients, absorbing most assumptions and local statistics.

Evaluated tests and devices

In the first VALHUDES study, conducted in Belgium, the following collection procedures are foreseen: a) first-void urine collection using the Colli-Pee device (Novosanis NV, Wijnegem, Belgium) one day before the colposcopy visit; b) vaginal self-sampling with Multi-Collect Swab (Abbott Molecular, Inc., Des Plaines, IL, USA), c) vaginal self-sampling of half of the study population with Evalyn Brush and the other half with Qvintip (Aprox AB, Uppsala, Sweden) at the colposcopy centre and d) the collection of a cervical liquid-based cytology sample by a gynaecologist using the Cervex-Brush (Rovers Medical Devices) as recommended in the European guidelines for preparation of cervical liquid-based cytology samples[29]. After collecting cervical epithelial cells, the Cervex-Brush will be pressed vigorously against the bottom of a vial containing 20 mL PreservCyt (Hologic Inc., Bedford, MA, USA) to remove all the cellular material.

The dry self-sampling devices will be transferred after arrival in the laboratory into a storage medium: the Multi-Collect Swab into Abbott Cervi-Collect buffer and the Evalyn Brush or Qvintip into PreservCyt. Colli-Pee is a non-invasive self-sampling device for collection of the first 20 mL of urine (first-void) from women or men. The collector is prefilled with a solution of Urine Conservation Medium (UCM) buffer appropriate for molecular testing for detection of infectious agents such as HPV[22]. Detailed user instructions for the Colli-Pee, Multi-Collect Swab, Evalyn-Brush and Qvintip can be found in the Belgian VALHUDES protocol in the Supplementary Appendix.

The first assays that will be evaluated are the Abbott RealTime High Risk HPV assay (Abbott GmbH & Co. KG, Wiesbaden, Germany)[30-32], and the cobas 4800 and 6800 (Roche Molecular System, Pleasanton, CA, USA)[33,34] which identify DNA of the L1 gene of

HPV16 and HPV18 separately and the pool of 12 other hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). In addition, the RIATOL qPCR HPV genotyping assay[35] will be evaluated, which identifies DNA of the E6/E7 genes of the same 14 hrHPV types, separately, as well as HPV types 6, 11 and 53 and the L1 gene of HPV67. All these assays use the amplification of the beta-globin gene as a sample validity or process control.

Aliquotting and further testing of archived VALHUDES specimens

Residual material of all VALHUDES specimen will be aliquoted and stored, as explained in the Supplementary Appendix, following procedures and agreements with laboratories and manufactures as applied previously in the VALGENT framework, used for validation of HPV genotyping tests applied on clinician-taken samples[36].

Attitudes and acceptance by women

The attitudes and preferences of eligible women can be evaluated by questionnaires (see Supplementary Appendix). Response rates (proportion of approached women that accept to participate in the study) will be used to monitor the enrolment statistics.

Future VALHUDES studies

Other assays expected to be evaluated through the Belgian VALHUDES framework are: BD Onclarity HPV Assay (BD Diagnostics, Sparks, MD, USA)[37], Xpert HPV Assay (Cepheid, Sunnyvale, USA)[38], and Anyplex II HPV HR (Seegene, Seoul, Korea)[39,40]. Additional assays may be included as long as residual aliquots are available.

More VALHUDES studies will be conducted in other countries and will include other self-sample device/storage medium/HPV assay combinations. This will generate a uniquely rich database that will allow further meta-analytical pooling and form a framework for universal validation and comparison of HPV assays on self-samples (vaginal or urine).

RESULTS

The Belgian VALHUDES has started in December 2017 and will enrol women from four colposcopy centres (University Hospitals of Antwerp, Brussels and Ghent and Heilig-Hart Hospital of Tienen). The protocol was approved by the Ethical Boards of the respective study centres. Residual cervical and vaginal material will be archived in the AML laboratory whereas residual first-void urine samples will be archived in the Centre for the Evaluation of Vaccination (CEV) at the University of Antwerp. Colposcopy and biopsy results will be obtained from the four colposcopy centres and there affiliated histopathology laboratories. The Unit of Cancer Epidemiology of the Belgian Cancer Centre (Sciensano, Brussels) will coordinate the study and perform statistical analyses. An interim analysis after assessment of samples from 100 women and a final analysis after assessment of all 500 samples are foreseen in mid-2018 and early 2019, respectively.

DISCUSSION

The VALHUDES protocol aims to compare the clinical accuracy of HPV testing on vaginal self-samples and first-void urine specimens collected under standardised conditions, with HPV testing on matched clinician-taken samples.

Self-sampling is becoming increasingly important and applicable to supplement organised cervical screening program or as screening modality in areas without organised cervical screening. Consequently, diagnostic test accuracy studies should preferentially be conducted in the setting where it is intended to be used. However, empirical evidence indicates that the

relative accuracy of self- vs clinician-taken specimens is robust and translatable from referral to primary screening settings[15]. This finding offers the methodological basis for VALHUDES, which generates two major advantages: efficiency and avoidance of partial verification bias. Partial verification bias typically arises when unequal proportions of test-positive and test-negative subjects are submitted for verification of disease status with a valid reference standard[42,43]. More CIN2+ patients are found in a referral population such as a colposcopy centre than in a screening population, which increases the power to address sensitivity hypothesis. Moreover, in a colposcopy centre, it is straightforward to apply the verification of disease status to all enrolled patients, and consequently, the problem of verification is avoided. Partial verification and methods to control its impact by referring a random fraction of screen-negative subjects for disease verification by colposcopy/histology, imply major methodological and statistical challenges in screening studies[42,44-47].

Reflex cytology combined or not with genotyping for HPV16/18 are recommended in several guidelines for management of hrHPV-positive women[48]. Whereas HPV16/18 genotyping can be easily applied on self-samples (vaginal and first-void urine), cytology on self-samples is not recommended due to the substantially lower sensitivity compared to cytology on a clinician-taken specimen[49-51] and the higher rates of suboptimal sample adequacy[49]. Consequently, molecular rather than morphological triage approaches obviate the need for an additional clinic visit for women who are hrHPV-positive on their self-sample which is likely to compromise the efficiency of a strategy offering self-sampling kits to unscreened or under-screened women. Identifying molecular methods applicable to self-samples that serve as a triage of hrHPV-positive women is therefore considered a priority for future research. VALHUDES studies could be easily extended to incorporate a triage component, where aliquots of hrHPV-positive women are tested for promising markers such as methylation of certain viral or human genes or micro-RNA profiles which are associated with progressive HPV infection and neoplastic transformation[23,52,53].

Urine collection might be more socially and/or religiously acceptable or simply more comfortable for some women who are reluctant to perform vaginal self-sampling. Offering an appropriate kit for collection of a vaginal self-sample or a first-void urine sample might be particularly suited in settings when directly provided to patients, e.g. during a visit to a primary care service, who are identified as not screened. A small trial conducted in a group of general practices in Brussels reported a 78% response rate when a vaginal self-sampling kit was offered directly to women not screened since three year or more[54]. Large-scale trials should be set up to confirm these promising results. Offering a self-sampling instrument to eligible patients in contact with primary care services might simplify the logistics of mailing devices[55].

This VALHUDES study can easily be reproduced in other countries and settings and may assist in facilitating the generation of more comparative data sets for different combinations of defined self-sample device and HPV assay combinations. We invite researchers to conduct other VALHUDES-like studies which could then be pooled in individual-patient-data meta-analyses. The demonstration of similar sensitivity and specificity for CIN2+ of a given HPV assay on a (vaginal or first-void urine) self-sample taken with a particular device compared to a sample taken by a clinician could be a plausible validation principle under the condition that the HPV assay fulfils international requirements for use on clinician-taken cervical specimens[13].

Acknowledgements/conflict of interest:

The VALHUDES project is a researcher-induced study, where manufacturers of HPV assays and devices for vaginal self-collection of urine-collection can participate. For the first phase of VALHUDES support was received from Abbott Molecular, Inc. (Des Plaines, IL, USA), Novosanis NV (Wijnegem, Belgium), University of Antwerp (Antwerp, Belgium), Rovers Medical Devices B.V. (Oss, The Netherlands) and Aprovix AB (Uppsala, Sweden).

M. Arbyn, E. Peeters, and M. Poljak are supported by the COHEAHR Network funded by the 7th Framework Programme of DG Research and Innovation, European Commission, Brussels, Belgium (grant No. 603019). M. Arbyn, E. Peeters, K. Cuschieri M. Poljak, and C. Cocuzza are supported by the SME Instrument Grant GA 80551, funded by the Horizon 2020 programme of DG Research and Innovation, European Commission, Brussels, Belgium.

A. Vorsters is co-founder and board member of Novosanis NV a spin-off of the University of Antwerp.

I. Benoy, D. Vanden Broeck and J. Bogers are employed by AML, a commercial lab performing cervical cytology and HPV testing.

Registration:

The study was registered in ClinicalTrials.gov (identifier: NCT03064087).

Ethics approval:

Informed consent will be obtained from all individual participants enrolled in this study. The study was approved by the central Ethics Committee of University Hospital of Antwerp/University of Antwerp (B300201733869) and the local Ethics Committees of University Hospital of Brussels, University Hospital of Ghent and Hospital of Tienen.

Acknowledgements

The authors acknowledge J. Jonckheere (AML) who elaborated study agreements.

Reference List

- [1] Racey CS, Withrow DR, Gesink D. Self-collected HPV Testing Improves Participation in Cervical Cancer Screening: A Systematic Review and Meta-analysis. *Can J Public Health* 2013 Mar;104:e159-e166.
- [2] Verdoodt F, Jentschke M, Hillemanns P, Racey CS, Snijders PJF, Arbyn M. Reaching women who do not participate in the regular cervical cancer screening program by offering self-sampling kits: A systematic review and meta-analysis of randomised trials. *Eur J Cancer* 2015;51:2375-85.
- [3] Rozemeijer K, de Kok IM, Naber SK, et al. When Is It Effective to Offer Self-Sampling to Non-Attendees-Response. *Cancer Epidemiol Biomarkers Prev* 2015 Aug;24:1296.
- [4] Rozemeijer K, de Kok IM, Naber SK, et al. Offering self-sampling to non-attendees of organized primary HPV screening: When do harms outweigh the benefits? *Cancer Epidemiol Biomarkers Prev* 2015;24:773-82.
- [5] Giorgi-Rossi P, Fortunato C, Barbarino P, et al. Self-sampling to increase participation in cervical cancer screening: an RCT comparing home mailing, distribution in pharmacies, and recall letter. *Br J Cancer* 2015 Jan 29;112:667-75.
- [6] Lam JU, Rebolj M, Ejegod DM, et al. Human papillomavirus self-sampling for screening non-attenders: Opt-in pilot implementation with electronic communication platforms. *Int J Cancer* 2017 Feb 13;140:2212-9.

- [7] Giorgi-Rossi P, Marsili LM, Camilloni L, et al. The effect of self-sampled HPV testing on participation to cervical cancer screening in Italy: a randomised controlled trial (ISRCTN96071600). *Br J Cancer* 2011;104:248-54.
- [8] Lam JUH, Elfstrom KM, Ejegod DM, et al. High-grade cervical intraepithelial neoplasia in human papillomavirus self-sampling of screening non-attenders. *Br J Cancer* 2018;118:138-44.
- [9] Arrossi S, Paolino M, Thouyaret L, Laudi R, Campanera A. Evaluation of scaling-up of HPV self-collection offered by community health workers at home visits to increase screening among socially vulnerable under-screened women in Jujuy Province, Argentina. *Implement Sci* 2017 Feb 13;12:17.
- [10] Leinonen MK, Schee K, Jonassen CM, et al. Safety and acceptability of human papillomavirus testing of self-collected specimens: A methodologic study of the impact of collection devices and HPV assays on sensitivity for cervical cancer and high-grade lesions. *J Clin Virol* 2018;99:22-30.
- [11] Ejegod DM, Pedersen H, Alzua GP, Pedersen C, Bonde J. Time and temperature dependent analytical stability of dry-collected Evalyn HPV self-sampling brush for cervical cancer screening. *Papillomavirus Res* 2018 Apr 21;5:192-200.
- [12] Arbyn M, Ronco G, Anttila A, et al. Evidence regarding HPV testing in secondary prevention of cervical cancer. *Vaccine* 2012;30 Suppl 5:F88-F99.
- [13] Meijer CJLM, Castle PE, Hesselink AT, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer* 2009;124:516-20.
- [14] Arbyn M, Snijders PJ, Meijer CJLM, et al. Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening? *Clin Microbiol Infect* 2015 Apr 30;21:817-26.
- [15] Arbyn M, Verdoodt F, Snijders PJF, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* 2014;15:172-83.
- [16] Arbyn M, Castle P. Offering self-sampling kits for HPV testing to reach women who do not attend in the regular cervical cancer screening program. *Cancer Epidemiol Biomarkers Prev* 2015;24:769-72.
- [17] Sellors JW, Lorincz AT, Mahony JB, et al. Comparison of self-collected vaginal, vulvar and urine samples with physician-collected cervical samples for human papillomavirus testing to detect high-grade squamous intraepithelial lesions. *CMAJ* 2000;163:513-8.
- [18] Pathak N, Dodds J, Zamora J, Khan K. Accuracy of urinary human papillomavirus testing for presence of cervical HPV: systematic review and meta-analysis. *BMJ* 2014;349:g5264.

- [19] Sahasrabuddhe VV, Gravitt PE, Dunn ST, et al. Comparison of human papillomavirus detections in urine, vulvar, and cervical samples from women attending a colposcopy clinic. *J Clin Microbiol* 2014 Jan;52:187-92.
- [20] Stanczuk GA, Currie H, Baxter G, et al. Cobas 4800 HPV detection in the cervical, vaginal and urine samples of women with high-grade CIN before and after treatment. *J Clin Pathol* 2015 Apr 15;68:567-70.
- [21] Senkomago V, Des Marais AC, Rahangdale L, Vibat CR, Erlander MG, Smith JS. Comparison of urine specimen collection times and testing fractions for the detection of high-risk human papillomavirus and high-grade cervical precancer. *J Clin Virol* 2016 Jan;74:26-31.
- [22] Vorsters A, Van den Bergh J, Micalessi I, et al. Optimization of HPV DNA detection in urine by improving collection, storage, and extraction. *Eur J Clin Microbiol Infect Dis* 2014 Nov;33:2005-14.
- [23] Van Keer S, Pattyn J, Tjalma WAA, et al. First-void urine: A potential biomarker source for triage of high-risk human papillomavirus infected women. *Eur J Obstet Gynecol Reprod Biol* 2017 Jun 27;216:1-11.
- [24] Leeman A, del PM, Molijn A, et al. HPV testing in first-void urine provides sensitivity for CIN2+ detection comparable to a physician-taken smear or brush-based self-sample: cross-sectional data from a triage population. *BJOG* 2017 Apr 9;124:1356-63.
- [25] Cuzick J, Cadman L, Ahmad AS, et al. Performance and Diagnostic Accuracy of a Urine-Based Human Papillomavirus Assay in a Referral Population. *Cancer Epidemiol Biomarkers Prev* 2017 Feb 21;26:1053-9.
- [26] Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003 Jan 4;326:41-4.
- [27] Tang ML, Tang NS, Chan IS, Chan BP. Sample size determination for establishing equivalence/noninferiority via ratio of two proportions in matched-pair design. *Biometrics* 2002 Dec;58:957-63.
- [28] Jentschke M, Chen K, Arbyn M, et al. Direct comparison of two vaginal self-sampling devices for the detection of human papillomavirus infections. *J Clin Virol* 2016 Jun 28;82:46-50.
- [29] Arbyn M, Herbert A, Schenk U, et al. European guidelines for quality assurance in cervical cancer screening: recommendations for collecting samples for conventional and liquid-based cytology. *Cytopathology* 2007;18:133-9.
- [30] Carozzi FM, Burrioni E, Bisanzi S, et al. Comparison of Clinical Performance of Abbott RealTime High Risk HPV Test with That of Hybrid Capture 2 Assay in a Screening Setting. *J Clin Microbiol* 2011 Apr;49:1446-51.
- [31] Poljak M, Ostrbenk A, Seme K, et al. Comparison of Clinical and Analytical Performance of the Abbott RealTime High Risk HPV Test to the Performance of

- Hybrid Capture 2 in Population-Based Cervical Cancer Screening. *J Clin Microbiol* 2011 May;49:1721-9.
- [32] Hesselink AT, Meijer CJLM, Poljak M, et al. Clinical validation of the Abbott RealTime High Risk (HR) HPV assay according to the guidelines for HPV DNA test requirements for cervical screening. *J Clin Microbiol* 2013 May 1;51:2409-10.
- [33] Heideman DA, Hesselink AT, Berkhof J, et al. Clinical validation of the cobas(R)4800 HPV Test for cervical screening purposes. *J Clin Microbiol* 2011 Aug 31;49:3983-5.
- [34] Lloveras B, Gomez S, Alameda F, et al. HPV Testing by cobas HPV Test in a Population from Catalonia. *PLoS ONE* 2013;8:e58153.
- [35] Depuydt CE, Benoy IH, Beert JF, Criel AM, Bogers JJ, Arbyn M. Clinical validation of a type-specific real time quantitative human papillomavirus PCR to the performance of Hybrid Capture 2 for the purpose of cervical cancer screening. *J Clin Microbiol* 2012 Oct 10;50:4073-7.
- [36] Arbyn M, Depuydt C, Benoy I, et al. VALGENT: a protocol for clinical validation of human papillomavirus assays. *J Clin Virol* 2016;76 (Suppl 1):S14-S21.
- [37] Ejegod DM, Serrano I, Cuschieri K, et al. Clinical Validation of the BD Onclarity™ HPV Assay Using a Non-Inferiority Test. *J Med Microbiol Diagn* 2014;S3: 003:1-4.
- [38] Cuschieri K, Geraets D, Cuzick J, et al. Performance of a cartridge based assay for the detection of clinically significant HPV infection - lessons from VALGENT (Validation of HPV Genotyping Tests). *J Clin Microbiol* 2016 Jul 6;54:2337-47.
- [39] Hesselink AT, Sahli R, Berkhof J, et al. Clinical validation of Anyplex II HPV HR Detection according to the guidelines for HPV test requirements for cervical cancer screening. *J Clin Virol* 2016 Jan 15;76:36-9.
- [40] Jung S, Lee B, Lee KN, Kim Y, Oh EJ. Clinical Validation of Anyplex II HPV HR Detection Test for Cervical Cancer Screening in Korea. *Arch Pathol Lab Med* 2016 Mar;140:276-80.
- [41] Polman NJ, Ostrbenk A, Xu L, et al. Evaluation of the clinical performance of the HPV-Risk assay using the VALGENT-3 panel. *J Clin Microbiol* 2017;55:3544-51.
- [42] Arbyn M, Ronco G, Cuzick J, Wentzensen N, Castle PE. How to evaluate emerging technologies in cervical cancer screening? *Int J Cancer* 2009;125:2489-96.
- [43] Whiting P, Rutjes AW, Reitsma JB, Glas AS, Bossuyt PM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. *Ann Intern Med* 2004 Feb 3;140:189-202.
- [44] Begg CB, Greenes RA. Assessment of diagnostic tests when disease verification is subject to selection bias. *Biometrics* 1983;39:207-15.

- [45] Irwig L, Glasziou PP, Berry G, Chock C, Mock P, Simpson JM. Efficient Study Designs to Assess the Accuracy of Screening Tests. *Am J Epidemiol* 1994;140:759-69.
- [46] Schatzkin A, Connor RJ, Taylor PR, Bunnag B. Comparing new and old screening tests when a reference procedure cannot be performed on all screenees. Example of automated cytometry for early detection of cervical cancer. *Am J Epidemiol* 1987;125:672-8.
- [47] Zhou XH, Higgs RE. Assessing the relative accuracies of two screening tests in the presence of verification bias. *Stat Med* 2000 Jun 15;19:1697-705.
- [48] Wentzensen N, Schiffman M, Palmer T, Arbyn M. Triage of HPV positive women in cervical cancer screening. *J Clin Virol* 2016;76:S49-S55.
- [49] Garcia F, Barker B, Santos C, et al. Cross-sectional study of patient- and physician-collected cervical cytology and human papillomavirus. *Obstet Gynecol* 2003;102:266-72.
- [50] Nobbenhuis MA, Helmerhorst TJ, van den Brule AJ, et al. Primary screening for high risk HPV by home obtained cervicovaginal lavage is an alternative screening tool for unscreened women. *J Clin Pathol* 2002 Jun;55:435-9.
- [51] Brink AA, Meijer CJLM, Wiegnerink MA, et al. High concordance of results of testing for human papillomavirus in cervicovaginal samples collected by two methods, with comparison of a novel self-sampling device to a conventional endocervical brush. *J Clin Microbiol* 2006 Jul;44:2518-23.
- [52] Snellenberg S, De Strooper LM, Hesselink AT, et al. Development of a multiplex methylation-specific PCR as candidate triage test for women with an HPV-positive cervical scrape. *BMC Cancer* 2012;12:551-*
- [53] Wentzensen N, Sun C, Ghosh A, et al. Methylation of HPV18, HPV31, and HPV45 Genomes and Cervical Intraepithelial Neoplasia Grade 3. *J Natl Cancer Inst* 2012 Oct 23.
- [54] Cornet K. Kan de dekkingsgraad voor screening van baarmoederhalskanker verhoogd worden door gebruik te maken van een thuistest voor screening: een pilootstudie in een huisartsenpraktijk? Vrije Universiteit Brussel; 2015.
- [55] Lim AW, Hollingworth A, Kalwij S, Curran G, Sasieni P. Offering self-sampling to cervical screening non-attenders in primary care. *J Med Screen* 2017;24:43-9.