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ABSTRACT:

Objectives: Pre-exposure prophylaxis (PrEP) users are screened bi-annual for Sexually Transmitted Infections (STIs). A novel device, called the Colli-Pee™, collects first-void urine in a standardized way and the collector tube can be easily delivered by regular post to a certified laboratory. The aim of the study was a one-to-one comparison between the STI test results obtained with the urine collected in the clinic, versus urine collected at home in a real-life setting by Men who have Sex with Men (MSM) in Belgium. The usability and acceptability of the Colli-Pee™ device by the users was also evaluated.

Design: A single-site nested sub-study in a prospective PrEP demonstration project (Be-PrEP-ared) among MSM in Belgium.

Participants: A total of 473 home-based samples from 213 MSM were received with a mean age of 38.5 years.

Interventions: Participants were requested to collect a urine sample at home using the Colli-Pee™ device and to send it to the laboratory via regular mail.

Primary and secondary outcome measures: The presence of *Chlamydia trachomatis* (CT)*, Neisseria gonorrhoeae* (NG)*, Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV) was determined using molecular amplification assays. Agreement between test results of samples collected at the clinic and collected at home were evaluated using Cohen's kappa statistic.

Results: Trichomonas vaginalis was not detected. A very good to almost perfect agreement was found for CT, NG and MG of κ=0.75; 0.87 and 0.85, respectively. Using the Colli-Pee™ device only one low positive CT and two MG infections were missed, however, three additional CT, two NG and six MG infections were detected.

Conclusions: The Colli-Pee™ device is a feasible and convenient way to collect urine at home for STI testing. This may be particularly relevant for populations that need frequent STI testing, such as PrEP users, and patients who prefer home-sampling.

Trial registration: Clinicaltrials.gov database: NCT02552914

ARTICLE SUMMARY

Strengths and limitations of this study

- The study was designed as such to provide real-world experience concerning home-based sampling for STI detection including shipment by post among PrEP users.
- Home-based and clinic-based samples were processed and analyzed using the same procedures and laboratory staff was blinded for the results of the matching sample.
- A total of 49 samples was found to be positive for an STI on 471 samples, resulting in a high prevalence of STIs: 10.4%.
- Our main limitation is that home-based samples were not taken on the same day as clinic-based sampling and participants could have become positive during that window period.
- Views and perception concerning the usability and acceptability of the device during the study were captured but not yet analyzed.

INTRODUCTION:

According to the World Health Organisation's Global Health Sector Strategy on Sexually Transmitted Infections (STIs) 2016-2021, early diagnosis and linkage to treatment are one of the key elements for preventing further transmission of STIs.[1] Currently, first-void urine is still favoured as the sample of choice for the detection of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) in men, using nucleic acid amplification tests (NAATs).[2–4] In general, a regular urine container is used to collect the first-void urine sample, but the collected volume of urine is not standardized. Furthermore, this type of container is less convenient for postal delivery to the laboratory. Another sponged-based device (UriSWAB, Copan Diagnostics, Brescia, Italy) has been suggested as an alternative for postal delivery of urine. However, this device only holds 2 mL of urine and does not guarantee that only first-void urine is collected.[4,5] The CE-IVD labelled Colli-Pee™ device

(Novosanis, Belgium), provides a clean and standardized solution to the above-mentioned issues as it efficiently captures first-void urine (20 mL) without interruption of the urine flow and allows the samples to be sent by post. (Fig 1) The Colli-Pee™ device is currently used for the detection of Human Papilloma Virus (HPV) and several urological cancers for which collection of first-void urine is essential .[6,7] In the field of STIs, a standardized first-void urine study reported that the organism load of *C. trachomatis* is maximal in the first 4-5 mL and that the performance of diagnostic tests improved when using only first-void urine.[8,9]

Although pre-exposure prophylaxis (PrEP) is becoming crucial in HIV prevention, recent reviews of real-world PrEP demonstration studies showed that PrEP is associated with increased diagnoses of STIs in Men who have Sex with Men (MSM).[10,11] Consequently, current guidelines recommend a bi-annual screening of STIs in PrEP users because of their high risk behaviour.[12,13]

In order to facilitate the patient flow during follow-up visits by PrEP users, and prompt treatment of STIs, home-based collection of first-void urine could be sent to the laboratory by regular mail for STI detection before the scheduled visit. STI results may then be available at the time of the physician consultation and in the case of a detected STI also immediately treated, limiting the risk of further transmission.

The objectives of this study were to compare the results of the molecular detection of several STIs using the Colli-Pee™ device versus a sample obtained in the clinic, the use and acceptability of the Colli-Pee™ device and its convenience for shipment by regular mail. To assess these objectives, a nested sub-study was performed among MSM who participated in a Belgian PrEP demonstration cohort. [14]

METHODS:

The evaluation was undertaken as a sub-study of Be-PrEP-ared, a PrEP demonstration study among MSM at high risk for HIV in Belgium.

The main study

The Be-PrEP-ared project (EudraCTn°: 5015-00005437) was a phase 3, single-site, open-label prospective cohort study where 200 MSM at high risk of acquiring HIV were asked to participate in the project and to take PrEP daily or event-driven. Detailed study methods are described elsewhere.[14] Participants were tested for *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV) at baseline and every three months. Detection of these STIs was performed at the three biological sites: urethra, anorectum and pharynx. During each study visit, participants collected urine in two urine containers at the clinic as per the following instructions: urinate in the first container up to the marked line at approximately 20 mL, afterwards complete the second cup with no restrictions. Urine in the first container (hereafter the clinic-based sample) was stored refrigerated until analysis that took place within a maximum of 48h. Urine in the second container was used to detect proteinuria.

The main study was approved by the Institutional Review Board of the Institute of Tropical Medicine and the Ethics Committee of the Antwerp University Hospital. All participants signed an informed consent form.

Laboratory procedures

In the first instance, CT/NG detection was performed using the Abbott Real Time (RT) CT/NG assay (DNA extraction and sample preparation using Abbott m2000sp and the Abbott m2000rt system for amplification and detection of CT/NG (Abbott Molecular Inc. Des Plaines, Illinois, USA)) according to manufacturer's instructions. The remainder of the urine and DNA extracts were stored at -80 °C. In the case of positivity, the same DNA extracts were tested by in-house real time-PCR (RT-PCR) assays

for CT and/or NG, both based on previously published primer sets.[15,16]. A sample was considered positive when positive in both the Abbott and the in-house RT-PCR. An initial positive Abbott assay result followed by a negative confirmatory NAAT result was defined as 'not confirmed'. Inhibition of the NAAT according to the Abbott assay was defined as 'inhibition'.

The same DNA extracts were used for further testing. MG was detected and reported using an accredited in-house RT-PCR that targets the pdhD-gene [17] and in addition the DiaMGTV multiplex kit that detects MG and TV simultaneously was used for TV detection. No further confirmation of TV took place.

The Colli-Pee™ sub-study

At the baseline visit of the Be-PrEP-ared study, participants were asked consent to participate in this sub-study. After signing the informed consent form, they received a Colli-Pee™ device and a prepaid envelope. They were instructed to collect first-void urine the next day at home using the Colli-Pee™ device (the home-based sample), to document the date and time of collection and to send the collector tube filled with urine back to the laboratory by regular post, using the prepaid envelope. Upon receipt in the laboratory, the urine was stored refrigerated (2-8°C) and CT, NG, MG, TV was detected using the same NAATs within 48 hours. The urine and DNA extracts' remnants were stored at -80°C. The quantity of human cells was measured at baseline using a human Endogenous Retrovirus-3 (ERV-3) quantitative PCR on the paired clinic- and home-based samples.[18]

The lab technicians were blinded for the results obtained for the clinic-based sample. In addition, the result of the home-based sample was not disclosed to the physician or participant.

During the next visit, which took place within 14 days after baseline, participants were asked to complete a small survey (five questions only) on the usability and willingness to use the Colli-Pee™ device (acceptability). Two questions documenting their opinion (likes-dislikes) of the Colli-Pee™ device were open-ended.

At follow-up month 6 and month 18 of the study, Colli-Pee™ devices were again distributed to those who agreed to participate and the survey was repeated at month 18 (results unreported).

The sub-study was approved by the Institutional Review Board of the Institute of Tropical Medicine (Ref:1027/15) and has been registered in the clinicaltrials.gov database (NCT02552914).

Patient and Public Involvement

Patients were not involved in the colli-pee™ substudy. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Statistical analysis

The agreement of the results of the molecular assays using each of the two sampling methods was assessed by the use of Cohen's kappa statistic. Samples that were not confirmed were coded as negative samples for the calculation of the agreement. The agreement of concentration of human DNA in both sampling methods was assessed by using a t-test. A p-value of <0.05 was considered statistically significant. Both analyses were performed using STATA version 15.0 (StataCorp LP, College Station, TX, USA).

A descriptive analysis was made of the results of the self-administered questionnaire on the usability of the Colli-Pee™ device.

RESULTS

Demographics

The main study took place at the Institute of Tropical Medicine, Antwerp, Belgium from Sep 2015 until May 2018. Of the 219 participants who were screened for eligibility into the main study, six participants did not consent to the Colli-Pee™ sub-study. All participants who consented to the sub-

study were MSM and three identified themselves as transwomen.[19] The mean age of the participants was 38.5 years (Interquartile Range 32-44). A total of 473 home-based samples from 213 participants were received. Two home-based samples could not be linked to the corresponding clinic-based sample and were therefore excluded, bringing the total number to 471. As shown in Table 1, the number of home-based samples received at the laboratory declined over time.

Kind Of Visit	**Clinic based**	**Home Based (% home-based samples received)**
Screening	218	187 (85.8%)
Month 6	191	152 (79.6%)
Month 18	179	132 (73.7%)

Table 1: Number of clinic and home-based samples received during the study

Although the participants were instructed to report the urine collection date and hour on the collection device, only 72.8% (343/471) were labelled with collection date. Most of the home-based samples (79.6%) were taken within two days after the clinic-based sample and 3.8% were taken after 20 days (13/343) (median one day; min-max: 0-70 days). The median time between the collection of the home-based sample and its reception at the laboratory after postal return was five days (min-max: 0-27 days) and 69.6% arrived at the laboratory within those five days.

Comparison of weight and concentration of human material between both sampling methods.

A total of 455 home-based and 423 clinic-based samples were weighed. The mean net weight of the home-based sample was 19.68g $\pm$ 2.14g (95%CI: 19.5g-19.9g and min-max: 6.81g-39.47g) vs 22.87g $\pm$ 13.64g (95%CI: 21.6g-24.2g and min-max: 2.88g - 86.23g) for the clinic-based sample.

The quantity of human cells was analysed at baseline only (n=187). In a total of five home-based and one clinic-based sample ERV could not be detected and these samples were considered as lacking human material. After removal of the paired samples lacking ERV or containing inhibitors, 182 observations could be paired. The mean quantity of the clinic-based sample was 11.3*10³ cells/PCR (95%CI: 7.4 - 15.2*10³) and for the home-based sample 14.2*10³ cells/PCR (95% CI: 6.8-21.5*10³) (p>0.05).

STI results and agreement

Of the 471 home-based samples with a matching visit, six home-based and one clinic-based sample gave inhibition and were excluded from the analysis (n=464). The results are shown in Table 2.

STI	**Home-based urine result**	**Clinic-based urine results**		
		Negative	**Positive**	**Total**
Chlamydia trachomatis (non-LGV)	**Negative**	454*	**1**	455
	Positive	**3**	6	9
	Total	457	7	464
Neisseria gonorrhoeae	**Negative**	455	**0**	455
	Positive	**2**	7	9
	Total	457	7	464
Mycoplasma genitalium	**Negative**	431	**2**	433
	Positive	**6**	25	31
	Total	437	27	464
Trichomonas vaginalis	**Negative**	464	0	464
	Positive	0	0	0
	Total	464	0	464

Table 2: STI results of the home-based and clinic-based urine samples

** Two result were not-confirmed in the clinic-based sample*

Trichomonas vaginalis was not detected. Cohen's kappa-agreement for CT/NG/MG is 0.75; 0.87 and 0.85, respectively, which indicates substantial agreement for *Chlamydia trachomatis* and almost perfect agreement for the other two STIs.

Tables 3 and 4 show the discordant results. For some of the home-based samples the date of collection was unknown so the time between the clinic visit and time of reception at the laboratory is depicted here. A delta-cycle (DC) value of the Abbott assay of less than two indicates a low positive infection.

STI	DC value CT/NG Abbott assay	Ct value in-house RT-PCR for CT or NG*	Ct-value S-DiagMGTV RT-PCR	Days between collection	Days of transport
CT	1.49	33.19	NA	0	2
MG	NA	32.20	Neg	3	4
MG	NA	32.04	37.44	0	8

Table 3: STI infections that were not detected in home-based urine samples

**: a different in-house RT-PCR assay was used for CT and NG*

DC = delta cycle; Ct = Cycle threshold; NA = not applicable; Max = days between clinic visit and reception of the home-based sample at the laboratory

STI	DC value CT/NG Abbott assay	Ct value in-house RT-PCR for CT or NG*	Ct-value S-DiagMGTV RT-PCR	Days between collection	Days of transport
CT	3.99	34.26	NA	1	2
CT	2.68	35.31	NA	1	6
CT	0.27	36.06	NA	6	4

STI	DC value CT/NG Abbott assay	Ct value in-house RT-PCR for CT or NG*	Ct-value S-DiagMGTV RT-PCR	Days between collection	Days of transport
NG	2.93	37.58	NA	8	4
NG	10.08	25.26	NA	2	6
MG	NA	31.28	Neg	Max 6	Max 6
MG	NA	31.96	40.51	1	2
MG	NA	28.66	34.67	Max 3	Max 3
MG	NA	34.58	38.50	9	4
MG	NA	34.23	Neg	1	5
MG	NA	32.04	38.14	Max 3	Max 3

Table 4: STI infections that were additionally detected in home-based urine samples

**: a different in-house RT-PCR assay was used for CT and NG*

DC = delta cycle; Ct = Cycle threshold; NA = not applicable; Max = days between clinic visit and reception of the home-based sample at the laboratory

Acceptability and usability of the Colli-Pee™ device

A total of 164 participants provided feedback regarding the use of the Colli-Pee™ device at baseline. On a scale of one to five, 87.8% found that the Colli-Pee™ device was easy to very easy to use. Instructions on how to send the Colli-Pee™ device were found to be easy by 90.2% of the participants. Four participants found the Colli-Pee™ difficult to use (2.4%) and four other participants found it difficult to follow the instructions (2.4%). Likes from participants were: the ease of use (54.9%), no interruption of the urine flow (15.9%), hygienic (11.6%) and privacy of the home-based sample collection (11.0%); the dislikes were: nothing (47.0%), not being recyclable (14.6%), not hygienic (10.4%) and being too large (6.1%).

To the question of whether they would order an online STI test, 89.0% answered positively (146/164) and 91.1% (133/146) of those individuals would use the Colli-Pee™ device in that case. Six

participants (4.1%) would not want to use the Colli-Pee™ device when ordering an online STI test. Participants were also asked how much they would pay for an online STI test with self-sampling. Price indications ranged from 0€ (10 participants) to 60€. Most of the participants (89/164) were willing to pay 10-20€.

DISCUSSION

Many studies have reported on male self-collected urine versus urethra clinician-collected sampling for STI screening , but 'real-world' studies, including sending of home-based urine samples for STI detection in men by post, are sparse.[4,5,20,21] In this study, we showed that the Colli-Pee™ collection device is a valuable and reliable method for collecting first-void urine for STI detection in MSM in Belgium, and that the collector can be shipped by regular post. Compared to the clinic-based sample, a total of three STIs (one CT and two MG infections) were not detected in the home-based sample. However, 11 additional infections were found in home-based samples collected with the Colli-Pee™ device (3 CT, 2 NG and 6 MG infections). This high number of additional STIs could be explained by the fact that first-void urine contains more DNA/RNA than mid-stream and, as a consequence, should still be used for STI detection.[9] However, the fact that participants could become positive during the time in between sampling points is one of our main limitations and cannot be ignored. Nevertheless, the most important observation is that only one Chlamydia positive result was missed. The DC value of the Abbott assay performed on that clinic-based sample highlighted the low bacterial load of that infection; in addition, transportation at room temperature for two days could have induced DNA degradation.

The World Health Organisation (WHO) underlines the importance of integrating point-of-care assays (POCTs) including innovative delivery options such as self-testing. [22] Unfortunately, to our knowledge, current commercial POCTs for the most important STIs such as *Chlamydia trachomatis*

and *Neisseria gonorrhoeae* are still of sub-optimal quality and do not meet the ASSURED criteria that were developed by the WHO STI Diagnostics Initiative.[22–25] A solution to the unavailability of qualitative POCTs could be internet-accessed STI testing (e-STI testing) which is increasingly available as an alternative to clinic testing all over the world.[26] E-STI testing includes postal self-sampling test kits that are sent to a certified laboratory and web-based delivery of test results. Swab2Know, an online HIV testing project confirmed that e-HIV testing is acceptable and feasible among MSM in Belgium. [27] Commercial online self-sampling services for STIs are now emerging over the internet, but evaluation of these services is lacking.

The present study is, however, subject to several limitations. Firstly, we could only enrol Be-PrEP-ared participants and the participation level seriously declined during the study. As a result, our number of CT/NG positives is quite low, which precludes firm conclusions. Secondly, as mentioned above, home-based samples were not taken on the same day as clinic-based sampling and participants could have become positive during that window period. We also do not know whether participants had urinated one hour prior to collection. However, recent data show that the time between micturitions is not crucial for the detection of Chlamydia in men.[28] Finally, reporting bias is also not to be excluded. Not all participants who used a Colli-Pee™ device completed the survey, the additional questions were included at the end of the lengthy main questionnaire of the Be-PrEP-ared study.

Besides PrEP users, e-STI testing has the potential to reach those who are most in need and a recent study showed that some higher-risk groups, such as MSM, were more likely to use online services [26,29]. Many studies have shown that home-based sampling is well accepted and, in fact, is the preferred approach in these groups for STIs. Reasons for choosing home-based sampling were shorter waiting times for results, convenience and less embarrassment. [30] Participants views regarding ordering an online STI test in this study were very positive, 89% would like to order such a kit. The Colli-Pee™ device was also found to be easy (90.2%) and although hygiene was one of the

likes, it also appeared in the dislikes, probably because the need to detach the collector manually can cause leakage of urine. Participants were also concerned regarding possible ecological consequences, although the plastic material is recyclable and can be incinerated into energy.

We demonstrated that postal delivery of home-based collected urine does not influence STI detection and can be used among PrEP users. Subsequently, PrEP users will be able to send first-void urine to the laboratory with the Colli-Pee™ device one to two weeks before their routine PrEP follow up visit. Results can then be discussed during the physician consultation and followed by treatment and future antimicrobial testing if applicable, decreasing the number of physician visits. Decreasing the number of face-to-face visits will lower the burden on staff workload and healthcare resources. However, future economic evaluations will need to be conducted to prove this statement. E-STI testing could be a promising approach in Belgium to reach patients in hard-to-reach populations and research on this topic should be stimulated. Therefore, future studies to study the acceptability and impact of postal shipment of home-collected material on the performance of STI assays requires additional assessment.

Figure legend: Fig 1: The Colli-Pee™ device instructions for use.

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COMPETING INTERESTS STATEMENT

The authors have no competing interests to declare.

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This work was supported by Novosanis who provided the Colli-Pee™ devices and partially paid for the analyses performed on the home-based samples. In addition, a grant was obtained from the Flemish Agency for Innovation and Entrepreneurship to conduct the Be-PrEP-ared study.

DATASHARING STATEMENT

The data will be made publicly available except for the use and acceptability data as these will be retained at the Institute of Tropical Medicine (ITM), Antwerp due to ethical and privacy concerns. According to the ITM research data sharing policy, only fully anonymised data can be shared publicly. The data can however be made available after approval of a motivated and written request to the ITM at ITMresearchdataaccess@itg.be. The ITM data access committee will verify if the dataset is suitable for obtaining the study objective and assure that confidentiality and ethical requirements are in place.

CONTRIBUTORSHIP STATEMENT

IDB, TC, and BV designed the study. TR designed the acceptability survey. IDB performed the statistical analysis and wrote the first draft of the manuscript. HS, BDD, VC, SA performed testing. All authors read the final version of the manuscript and provided comments.

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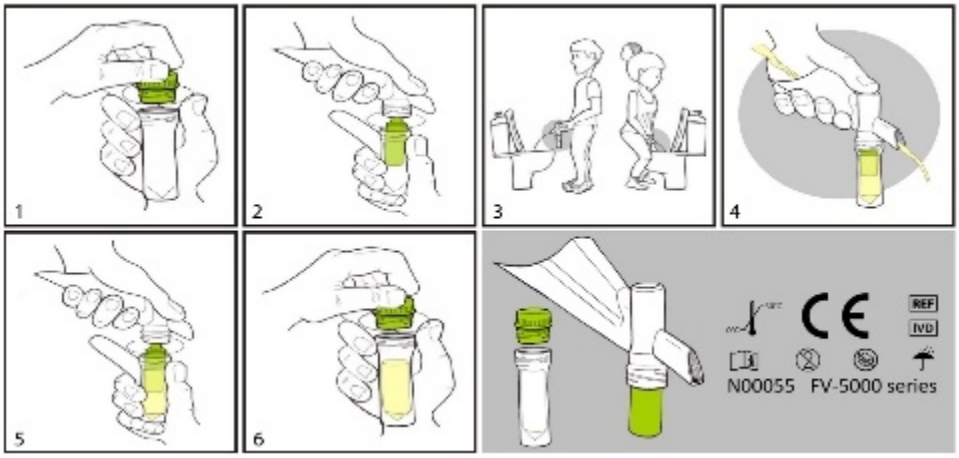

55x26mm (220 x 220 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2 (agreement was used as this is not a diagnostic study)
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	3-4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5-6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5-6
Test methods	**10a**	Index test, in sufficient detail to allow replication	Not applicable same assay was used on both samples (but different kind of sample)
	10b	Reference standard, in sufficient detail to allow replication	Not applicable same assay was used on both samples (but different kind of sample)
	11	Rationale for choosing the reference standard (if alternatives exist)	Not applicable same assay was used on both samples (but different kind of sample)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5-6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	5-6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	6
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	6
	16	How missing data on the index test and reference standard were handled	Not applicable
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not applicable
	18	Intended sample size and how it was determined	Not applicable
RESULTS			
Participants	**19**	Flow of participants, using a diagram	We did not include of flow of participants, however this has been discussed in the text p7-8

	20	Baseline demographic and clinical characteristics of participants	7-8
	21a	Distribution of severity of disease in those with the target condition	Not applicable
	21b	Distribution of alternative diagnoses in those without the target condition	Not applicable
	22	Time interval and any clinical interventions between index test and reference standard	8
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	8
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Cohen's kappa agreement was used p9
	25	Any adverse events from performing the index test or the reference standard	Not applicable
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	13
	27	Implications for practice, including the intended use and clinical role of the index test	13-14
OTHER INFORMATION			
	28	Registration number and name of registry	6
	29	Where the full study protocol can be accessed	Will be added as appendix
	30	Sources of funding and other support; role of funders	15

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

EVALUATION OF THE "COLLI-PEE™," A FIRST-VOID URINE COLLECTION DEVICE FOR SELF-SAMPLING AT HOME FOR THE DETECTION OF SEXUALLY TRANSMITTED INFECTIONS, VERSUS A ROUTINE CLINIC BASED URINE COLLECTION IN A ONE-TO-ONE COMPARISON STUDY DESIGN: EFFICACY AND ACCEPTABILITY AMONG MSM IN BELGIUM

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EVALUATION OF THE "COLLI-PEE™", A FIRST-VOID URINE COLLECTION DEVICE FOR SELF-SAMPLING AT HOME FOR THE DETECTION OF SEXUALLY TRANSMITTED INFECTIONS, VERSUS A ROUTINE CLINIC BASED URINE COLLECTION IN A ONE-TO-ONE COMPARISON STUDY DESIGN: EFFICACY AND ACCEPTABILITY AMONG MSM IN BELGIUM

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ABSTRACT:

Objectives: Pre-exposure prophylaxis (PrEP) users are screened bi-annual for Sexually Transmitted Infections (STIs). A novel device, called the Colli-Pee™, collects first-void urine in a standardized way and the collector tube can be easily delivered by regular post to a certified laboratory. The aim of the study was a one-to-one comparison between the STI test results obtained with the urine collected in the clinic, versus urine collected at home in a real-life setting by Men who have Sex with Men (MSM) in Belgium. The user-friendliness and acceptability of the Colli-Pee™ device by the users was also evaluated.

Design: A single-site nested sub-study in a prospective PrEP demonstration project (Be-PrEP-ared) among MSM in Belgium.

Participants: A total of 473 home-based samples from 213 MSM were received with a mean age of 38.5 years.

Interventions: Participants were requested to collect a urine sample at home using the Colli-Pee™ device and to send it to the laboratory via regular mail.

Primary and secondary outcome measures: The presence of *Chlamydia trachomatis* (CT)*, Neisseria gonorrhoeae* (NG)*, Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV) was determined using molecular amplification assays. Agreement between test results of samples collected at the clinic and collected at home were evaluated using Cohen's kappa statistic. Results: Trichomonas vaginalis was not detected. A very good to almost perfect agreement was found for CT, NG and MG of κ=0.75; 0.87 and 0.85, respectively. Using the Colli-Pee™ device only one low positive CT and two MG infections were missed, however, three additional CT, two NG and six MG infections were detected.

Conclusions: The Colli-Pee™ device is a feasible and convenient way to collect urine at home for STI testing. This may be particularly relevant for populations that need frequent STI testing, such as PrEP users, and patients who prefer home-sampling.

Trial registration: Clinicaltrials.gov database: NCT02552914

ARTICLE SUMMARY

Strengths and limitations of this study

- The study was designed as such to provide real-world experience concerning home-based sampling for STI detection including shipment by post among PrEP users.
- Home-based and clinic-based samples were processed and analyzed using the same procedures and laboratory staff was blinded for the results of the matching sample.
- A total of 49 samples was found to be positive for an STI on 471 samples, resulting in a high prevalence of STIs: 10.4%.
- Our main limitation is that home-based samples were not taken on the same day as clinic-based sampling and participants could have become positive during that window period.
- Another limitation of the study is that the temperature during transportation of home-based samples to the clinic was not monitored. Large temperature variations could have an impact on the quality of the samples.

INTRODUCTION:

According to the World Health Organisation's Global Health Sector Strategy on Sexually Transmitted Infections (STIs) 2016-2021, early diagnosis and linkage to treatment are one of the key elements for preventing further transmission of STIs.[1] Currently, first-void urine is still favoured as the sample of choice for the detection of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) in men, using nucleic acid amplification tests (NAATs).[2–4] In general, a regular urine container is used to collect

the first-void urine sample, but the collected volume of urine is not standardized. Furthermore, this type of container is less convenient for postal delivery to the laboratory. Another sponged-based device (UriSWAB, Copan Diagnostics, Brescia, Italy) has been suggested as an alternative for postal delivery of urine. However, this device only holds 2 mL of urine and does not guarantee that only first-void urine is collected.[4,5] The CE-IVD labelled Colli-Pee™ device (Novosanis, Belgium), provides a clean and standardized solution to the above-mentioned issues as it efficiently captures first-void urine (20 mL) without interruption of the urine flow and allows the samples to be sent by post. (Fig 1) The Colli-Pee™ device is currently used for the detection of Human Papilloma Virus (HPV) and several urological cancers for which collection of first-void urine is essential.[6,7] In the field of STIs, a standardized first-void urine study reported that the organism load of *C. trachomatis* is maximal in the first 4-5 mL and that the performance of diagnostic tests improved when using only first-void urine.[8,9]

Although pre-exposure prophylaxis (PrEP) is becoming crucial in HIV prevention, recent reviews of real-world PrEP demonstration studies showed that PrEP is associated with increased diagnoses of STIs in Men who have Sex with Men (MSM).[10,11] Consequently, current guidelines recommend a bi-annual screening of STIs in PrEP users because of their high risk behaviour.[12,13]

In order to facilitate the patient flow during follow-up visits by PrEP users, and prompt treatment of STIs, home-based collection of first-void urine could be sent to the laboratory by regular mail for STI detection before the scheduled visit. STI results may then be available at the time of the physician consultation and in the case of a detected STI also immediately treated, limiting the risk of further transmission.

The objectives of this study were to compare the results of the molecular detection of several STIs using the Colli-Pee™ device versus a sample obtained in the clinic, the use and acceptability of the Colli-Pee™ device and its convenience for shipment by regular mail. To assess these objectives, a

nested sub-study was performed among MSM who participated in a Belgian PrEP demonstration cohort. [14]

METHODS:

The evaluation was undertaken as a sub-study of Be-PrEP-ared, a PrEP demonstration study among MSM at high risk for HIV in Belgium.

The main study

The Be-PrEP-ared project (EudraCTn°: 5015-00005437) was a phase 3, single-site, open-label prospective cohort study where 200 MSM at high risk of acquiring HIV were asked to participate in the project and to take PrEP daily or event-driven. Detailed study methods are described elsewhere.[14] Participants were tested for *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV) at baseline and every three months. Detection of these STIs was performed at the three biological sites: urethra, anorectum and pharynx. During each study visit, participants collected urine in two urine containers at the clinic as per the following instructions: urinate in the first container up to the marked line at approximately 20 mL, afterwards complete the second cup with no restrictions. Urine in the first container (hereafter the clinic-based sample) was weighed and thereafter stored refrigerated until analysis that took place within 48h. Urine in the second container was used to detect proteinuria.

Laboratory procedures

In the first instance, CT/NG detection was performed using the Abbott Real Time (RT) CT/NG assay (DNA extraction and sample preparation using Abbott m2000sp and the Abbott m2000rt system for

amplification and detection of CT/NG (Abbott Molecular Inc. Des Plaines, Illinois, USA)) according to manufacturer's instructions. The remainder of the urine and DNA extracts were stored at -80 °C. In the case of positivity, the same DNA extracts were tested by in-house real time-PCR (RT-PCR) assays for CT and/or NG, both based on previously published primer sets.[15,16]. A sample was considered positive when positive in both the Abbott and the in-house RT-PCR. An initial positive Abbott assay result followed by a negative confirmatory NAAT result was defined as 'not confirmed'. Inhibition of the NAAT according to the Abbott assay was defined as 'inhibition'.

The same DNA extracts were used for further testing. MG was detected and reported using an accredited in-house RT-PCR that targets the pdhD-gene [17] and in addition the DiaMGTV multiplex kit (Diagenode diagnostics,Seraing, Belgium) that detects MG and TV simultaneously was used for TV detection. The results for MG of the DiaMGTV multiplex kit were not used for reporting purposes and are only provided for information only. No further confirmation of TV took place.

The Colli-Pee™ sub-study

At the baseline visit of the Be-PrEP-ared study, participants were asked consent to participate in this sub-study. After signing the informed consent form, they received a Colli-Pee™ device and a prepaid envelope. They were instructed to collect first-void urine the next day at home using the Colli-Pee™ device (the home-based sample), to document the date and time of collection and to send the collector tube filled with urine back to the laboratory by regular post, using the prepaid envelope. Upon receipt in the laboratory, the urine was weighed, stored refrigerated (2-8°C) and CT, NG, MG, TV was detected using the same NAATs within 48 hours. The urine and DNA extracts' remnants were stored at -80°C. The quantity of human cells was measured at baseline using a human Endogenous Retrovirus-3 (ERV-3) quantitative PCR on the paired clinic- and home-based samples.[18]

The lab technicians were blinded for the results obtained for the clinic-based sample. In addition, the result of the home-based sample was not disclosed to the physician or participant.

During the next visit, which took place within 14 days after baseline, participants were asked to complete a small survey (five questions only) on the user-friendliness and willingness to use the Colli-Pee™ device (acceptability). Two questions documenting their opinion (likes-dislikes) of the Colli-Pee™ device were open-ended.

At follow-up month 6 and month 18 of the study, Colli-Pee™ devices were again distributed to those who agreed to participate and the survey was repeated at month 18 (results unreported).

The main study was approved by the Institutional Review Board of the Institute of Tropical Medicine and the Ethics Committee of the Antwerp University Hospital. In addition, a separate approval for this sub-study was obtained by the Institutional Review Board of the Institute of Tropical Medicine (Ref:1027/15) and this sub-study is also registered in the clinicaltrials.gov database (NCT02552914).

Patient and Public Involvement

Patients were not involved in the Colli-Pee™ substudy. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Statistical analysis

The agreement of the results of the molecular assays using each of the two sampling methods was assessed by the use of Cohen's kappa statistic and percent agreement. Samples that were not confirmed were coded as negative samples for the calculation of the agreement. The agreement of volume of urine collected and the agreement of concentration of human DNA in both sampling methods was assessed by using a t-test. A p-value of <0.05 was considered statistically significant. Both analyses were performed using STATA version 15.0 (StataCorp LP, College Station, TX, USA).

A descriptive analysis was made of the results of the self-administered questionnaire on the acceptability and user-friendliness of the Colli-Pee™ device.

RESULTS

Demographics

The main study took place at the Institute of Tropical Medicine, Antwerp, Belgium from Sep 2015 until May 2018. Of the 219 participants who were screened for eligibility into the main study, six participants did not consent to the Colli-Pee™ sub-study. All participants who consented to the sub-study were MSM and three identified themselves as transwomen.[19] The mean age of the participants was 38.5 years (Interquartile Range 32-44). A total of 473 home-based samples from 213 participants were received. Two home-based samples could not be linked to the corresponding clinic-based sample and were therefore excluded, bringing the total number to 471. As shown in Table 1, the number of home-based samples received at the laboratory declined over time.

Kind Of Visit	Clinic based	Home Based (% home-based samples received)
Screening	218	187 (85.8%)
Month 6	191	152 (79.6%)
Month 18	179	132 (73.7%)

Table 1: Number of clinic and home-based samples received during the study

Although the participants were instructed to report the urine collection date and hour on the collection device, only 72.8% (343/471) were labelled with collection date. Most of the home-based samples (79.6%) were taken within two days after the clinic-based sample and 3.8% were taken after 20 days (13/343) (median one day; min-max: 0-70 days). The median time between the collection of the home-based sample and its reception at the laboratory after postal return was five days (min-max:

0-27 days), 72.9% arrived at the laboratory within those five days, an additional 25.7% within 10 days and five samples were received after 10 days (11, 13, 15, 17 and 27 days respectively).

Comparison of weight and concentration of human material between both sampling methods.

A total of 455 home-based and 423 clinic-based samples were weighed. The mean net weight of the home-based sample was 19.68g ± 2.14g (95%CI: 19.5g-19.9g and min-max: 6.81g-39.47g) vs 22.87g ± 13.64g (95%CI: 21.6g-24.2g and min-max: 2.88g - 86.23g) for the clinic-based sample ($p<0.001$).

The quantity of human cells was analysed at baseline only (n=187). In a total of five home-based and one clinic-based sample ERV could not be detected and these samples were considered as lacking human material. After removal of the paired samples lacking ERV or containing inhibitors, 182 observations could be paired. The mean quantity of the clinic-based sample was $11.3*10^3$ cells/PCR (95%CI: 7.4 - $15.2*10^3$) and for the home-based sample $14.2*10^3$ cells/PCR (95% CI: 6.8-$21.5*10^3$) ($p>0.05$).

STI results and agreement

Of the 471 home-based samples with a matching visit, six home-based and one clinic-based sample gave inhibition and were excluded from the analysis (n=464). The results are shown in Table 2.

STI	**Home-based urine result**	**Clinic-based urine results**		
		Negative	**Positive**	**Total**
Chlamydia trachomatis	**Negative**	454*	**1**	455
	Positive	**3**	6	9

STI	Home-based urine result	Clinic-based urine results		
		Negative	Positive	Total
(non-LGV)	**Total**	457	7	464
Neisseria gonorrhoeae	**Negative**	455	**0**	455
	Positive	**2**	7	9
	Total	457	7	464
Mycoplasma genitalium	**Negative**	431	**2**	433
	Positive	**6**	25	31
	Total	437	27	464
Trichomonas vaginalis	**Negative**	464	0	464
	Positive	0	0	0
	Total	464	0	464

Table 2: STI results of the home-based and clinic-based urine samples

** Two result were not-confirmed in the clinic-based sample*

Trichomonas vaginalis was not detected. Percent agreement (Cohen's kappa coefficient) for CT/NG/MG is 99.1% (0.75); 99.6% (0.87) and 98.3% (0.85), respectively, which indicates substantial agreement for *Chlamydia trachomatis* and almost perfect agreement for the other two STIs.

Tables 3 and 4 show the discordant results. For some of the home-based samples the date of collection was unknown so the time between the clinic visit and time of reception at the laboratory is depicted here. A delta-cycle (DC) value of the Abbott assay of less than two indicates a low positive infection.

STI	DC value CT/NG Abbott assay	Ct value in-house RT-PCR for CT, NG or MG*	Ct-value S-DiagMGTV RT-PCR (for information only)	Days between collection	Days of transport
CT	1.49	33.19	NA	0	2

MG	NA	32.20	Neg	3	4
MG	NA	32.04	37.44	0	8

Table 3: STI infections that were not detected in home-based urine samples

**: a different in-house RT-PCR assay was used for CT, NG or MG*

DC = delta cycle; Ct = Cycle threshold; NA = not applicable; Max = days between clinic visit and reception of the home-based sample at the laboratory

STI	**DC value CT/NG Abbott assay**	**Ct value in-house RT-PCR for CT, NG or MG***	**Ct-value S-DiagMGTV RT-PCR (for information only)**	**Days between collection**	**Days of transport**
CT	3.99	34.26	NA	1	2
CT	2.68	35.31	NA	1	6
CT	0.27	36.06	NA	6	4
NG	2.93	37.58	NA	8	4
NG	10.08	25.26	NA	2	6
MG	NA	31.28	Neg	Max 6	Max 6
MG	NA	31.96	40.51	1	2
MG	NA	28.66	34.67	Max 3	Max 3
MG	NA	34.58	38.50	9	4
MG	NA	34.23	Neg	1	5
MG	NA	32.04	38.14	Max 3	Max 3

Table 4: STI infections that were additionally detected in home-based urine samples

**: a different in-house RT-PCR assay was used for CT, NG or MG*

DC = delta cycle; Ct = Cycle threshold; NA = not applicable; Max = days between clinic visit and reception of the home-based sample at the laboratory

Acceptability and user-friendliness of the Colli-Pee™ device

A total of 164 participants provided feedback regarding the use of the Colli-Pee™ device at baseline. On a scale of one to five, 87.8% found that the Colli-Pee™ device was easy to very easy to use. Instructions on how to send the Colli-Pee™ device were found to be easy by 90.2% of the participants. Four participants found the Colli-Pee™ difficult to use (2.4%) and four other participants found it difficult to follow the instructions (2.4%). Likes from participants were: the ease of use (54.9%), no interruption of the urine flow (15.9%), hygienic (11.6%) and privacy of the home-based sample collection (11.0%); the dislikes were: nothing (47.0%), not being recyclable (14.6%), not hygienic (10.4%) and being too large (6.1%).

To the question of whether they would order an online STI test, 89.0% answered positively (146/164) and 91.1% (133/146) of those individuals would use the Colli-Pee™ device in that case. Six participants (4.1%) would not want to use the Colli-Pee™ device when ordering an online STI test. Participants were also asked how much they would pay for an online STI test with self-sampling. Price indications ranged from 0€ (10 participants) to 60€. Most of the participants (89/164) were willing to pay 10-20€.

DISCUSSION

Many studies have reported on male self-collected urine versus urethra clinician-collected sampling for STI screening , but 'real-world' studies, including sending of home-based urine samples for STI detection in men by post, are sparse.[4,5,20,21] In this study, we showed that the Colli-Pee™ collection device is a valuable and reliable method for collecting first-void urine for STI detection in MSM in Belgium, and that the collector can be shipped by regular post. Compared to the clinic-based sample, a total of three STIs (one CT and two MG infections) were not detected in the home-based sample. However, 11 additional infections were found in home-based samples collected with the Colli-

Pee™ device (3 CT, 2 NG and 6 MG infections). This high number of additional STIs could be explained by the fact that first-void urine contains more DNA/RNA than mid-stream and, as a consequence, should still be used for STI detection.[9] Indeed, we showed that using the Colli-Pee™ device first-void urine was collected in a more standardized way compared to the clinic-based samples ($p<0.001$) . Also, more human cells were collected in the home-based samples, however statistical significance was lacking. The fact that participants could become positive during the time in between sampling points is one of our main limitations and cannot be ignored. Preliminary data of the Be-PrEP-ared study showed high incidence estimates after twelve months of the main Be-PrEP-ared study for urethral CT/NG and MG: 11.5, 5.1 and 6.9 incidence rate per 100 person-years respectively.

Nevertheless, the most important observation is that only one Chlamydia positive result was missed. The DC value of the Abbott assay performed on that clinic-based sample highlighted the low bacterial load of that infection; in addition, transportation at room temperature for two days could have induced DNA degradation.

The World Health Organisation (WHO) underlines the importance of integrating point-of-care assays (POCTs) including innovative delivery options such as self-testing. [22] Unfortunately, to our knowledge, current commercial POCTs for the most important STIs such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are still of sub-optimal quality and do not meet the ASSURED criteria that were developed by the WHO STI Diagnostics Initiative.[22–25] A solution to the unavailability of qualitative POCTs could be internet-accessed STI testing (e-STI testing) which is increasingly available as an alternative to clinic testing all over the world.[26] E-STI testing includes postal self-sampling test kits that are sent to a certified laboratory and web-based delivery of test results. Swab2Know, an online HIV testing project confirmed that e-HIV testing is acceptable and feasible among MSM in Belgium. [27] Commercial online self-sampling services for STIs are now emerging over the internet, but evaluation of these services is lacking.

The present study is, however, subject to several limitations. Firstly, we only enrolled Be-PrEP-ared participants and the participation level seriously declined during the study. As a result, our number of CT/NG positives is quite low, which precludes firm conclusions. Secondly, as mentioned above, home-based samples were not taken on the same day as clinic-based sampling and participants could have become positive during that window period. We also do not know whether participants had urinated one hour prior to collection. However, recent data show that the time between micturition is not crucial for the detection of Chlamydia in men.[28] Thirdly, we did not monitor the temperature of the transport of home-based samples which could also have an impact on the quality of the samples, however, outside temperature between Oct 2015 and May 2018 varied between -10°C to 33°C with an average of 11°C.

Fourthly, we cannot exclude specimen contamination, however, participants were instructed how to correctly collect the clinic-based and home-based sample. Finally, reporting bias is also not to be excluded. Not all participants who used a Colli-Pee™ device completed the survey, the additional questions were included at the end of the lengthy main questionnaire of the Be-PrEP-ared study.

Besides PrEP users, e-STI testing has the potential to reach those who are most in need and a recent study showed that some higher-risk groups, such as MSM, were more likely to use online services [26,29]. Many studies have shown that home-based sampling is well accepted and, in fact, is the preferred approach in these groups for STIs. Reasons for choosing home-based sampling were shorter waiting times for results, convenience and less embarrassment. [30] Participants views regarding ordering an online STI test in this study were very positive, 89% would like to order such a kit. The Colli-Pee™ device was also found to be easy (90.2%) and although hygiene was one of the likes, it also appeared in the dislikes, probably because the need to detach the collector manually can cause leakage of urine. Participants were also concerned regarding possible ecological consequences, although the plastic material is recyclable and can be incinerated into energy.

We demonstrated that postal delivery of home-based collected urine does not influence STI detection and can be used among PrEP users. Subsequently, PrEP users will be able to send first-void urine to the laboratory with the Colli-Pee™ device one to two weeks before their routine PrEP follow up visit. Results can then be discussed during the physician consultation and followed by treatment and future antimicrobial testing if applicable, decreasing the number of physician visits. Decreasing the number of face-to-face visits will lower the burden on staff workload and healthcare resources. However, future economic evaluations will need to be conducted to prove this statement. E-STI testing could be a promising approach in Belgium to reach patients in hard-to-reach populations and research on this topic should be stimulated. Therefore, future studies to study the acceptability and impact of postal shipment of home-collected material on the performance of STI assays requires additional assessment.

Figure legend: Fig 1: The Colli-Pee™ device instructions for use.

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COMPETING INTERESTS STATEMENT

The authors have no competing interests to declare.

FUNDING STATEMENT

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DATASHARING STATEMENT

The data will be made publicly available except for the use and acceptability data as these will be retained at the Institute of Tropical Medicine (ITM), Antwerp due to ethical and privacy concerns. According to the ITM research data sharing policy, only fully anonymised data can be shared publicly. The data can however be made available after approval of a motivated and written request to the ITM at ITMresearchdataaccess@itg.be. The ITM data access committee will verify if the dataset is suitable for obtaining the study objective and assure that confidentiality and ethical requirements are in place.

CONTRIBUTORSHIP STATEMENT

IDB, TC, and BV designed the study. TR designed the acceptability survey. IDB performed the statistical analysis and wrote the first draft of the manuscript. HS, BDD, VC, SA performed testing. All authors read the final version of the manuscript and provided comments.

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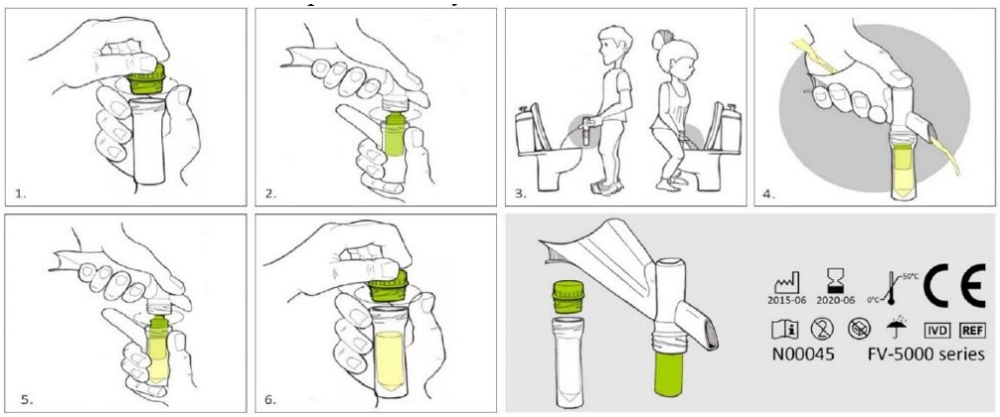

Fig 1: The Colli-PeeTM device instructions for use.

268x110mm (95 x 95 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2 (agreement was used as this is not a diagnostic study)
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	3-4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5-6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5-6
Test methods	**10a**	Index test, in sufficient detail to allow replication	Not applicable same assay was used on both samples (but different kind of sample)
	10b	Reference standard, in sufficient detail to allow replication	Not applicable same assay was used on both samples (but different kind of sample)
	11	Rationale for choosing the reference standard (if alternatives exist)	Not applicable same assay was used on both samples (but different kind of sample)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5-6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	5-6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	6
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	6
	16	How missing data on the index test and reference standard were handled	Not applicable
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not applicable
	18	Intended sample size and how it was determined	Not applicable
RESULTS			
Participants	**19**	Flow of participants, using a diagram	We did not include of flow of participants, however this has been discussed in the text p7-8

	20	Baseline demographic and clinical characteristics of participants	7-8
	21a	Distribution of severity of disease in those with the target condition	Not applicable
	21b	Distribution of alternative diagnoses in those without the target condition	Not applicable
	22	Time interval and any clinical interventions between index test and reference standard	8
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	8
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Cohen's kappa agreement was used p9
	25	Any adverse events from performing the index test or the reference standard	Not applicable
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	13
	27	Implications for practice, including the intended use and clinical role of the index test	13-14
OTHER INFORMATION			
	28	Registration number and name of registry	6
	29	Where the full study protocol can be accessed	Will be added as appendix
	30	Sources of funding and other support; role of funders	15

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

EVALUATION OF THE "COLLI-PEETM", A FIRST-VOID URINE COLLECTION DEVICE FOR SELF-SAMPLING AT HOME FOR THE DETECTION OF SEXUALLY TRANSMITTED INFECTIONS, VERSUS A ROUTINE CLINIC BASED URINE COLLECTION IN A ONE-TO-ONE COMPARISON STUDY DESIGN: EFFICACY AND ACCEPTABILITY AMONG MSM IN BELGIUM

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EVALUATION OF THE "COLLI-PEE™", A FIRST-VOID URINE COLLECTION DEVICE FOR SELF-SAMPLING AT HOME FOR THE DETECTION OF SEXUALLY TRANSMITTED INFECTIONS, VERSUS A ROUTINE CLINIC BASED URINE COLLECTION IN A ONE-TO-ONE COMPARISON STUDY DESIGN: EFFICACY AND ACCEPTABILITY AMONG MSM IN BELGIUM

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ABSTRACT:

Objectives: Pre-exposure prophylaxis (PrEP) users are screened bi-annual for Sexually Transmitted Infections (STIs). A novel device, called the Colli-Pee™, collects first-void urine in a standardized way and the collector tube can be easily delivered by regular post to a certified laboratory. The aim of the study was a one-to-one comparison between the STI test results obtained with the urine collected in the clinic, versus urine collected at home in a real-life setting by Men who have Sex with Men (MSM) in Belgium. The user-friendliness and acceptability of the Colli-Pee™ device by the users was also evaluated.

Design: A single-site nested sub-study in a prospective PrEP demonstration project (Be-PrEP-ared) among MSM in Belgium.

Participants: A total of 473 home-based samples from 213 MSM were received with a mean age of 38.5 years.

Interventions: Participants were requested to collect a urine sample at home using the Colli-Pee™ device and to send it to the laboratory via regular mail.

Primary and secondary outcome measures: The presence of *Chlamydia trachomatis* (CT)*, Neisseria gonorrhoeae* (NG)*, Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV) was determined using molecular amplification assays. Agreement between test results of samples collected at the clinic and collected at home were evaluated using Cohen's kappa statistic. Results: Trichomonas vaginalis was not detected. A very good to almost perfect agreement was found for CT, NG and MG of κ=0.75; 0.87 and 0.85, respectively. Using the Colli-Pee™ device only one low positive CT and two MG infections were missed, however, three additional CT, two NG and six MG infections were detected.

Conclusions: The Colli-Pee™ device is a feasible and convenient way to collect urine at home for STI testing. This may be particularly relevant for populations that need frequent STI testing, such as PrEP users, and patients who prefer home-sampling.

Trial registration: Clinicaltrials.gov database: NCT02552914

ARTICLE SUMMARY

Strengths and limitations of this study

- The study was designed as such to provide real-world experience concerning home-based sampling for STI detection including shipment by post among PrEP users.
- Home-based and clinic-based samples were processed and analyzed using the same procedures and laboratory staff was blinded for the results of the matching sample.
- The study was performed among MSM PrEP users who have a high prevalence of STIs.
- Our main limitation is that home-based samples were not taken on the same day as clinic-based sampling and participants could have become positive during that window period.
- Another limitation of the study is that the temperature during transportation of home-based samples to the clinic was not monitored.

INTRODUCTION:

According to the World Health Organisation's Global Health Sector Strategy on Sexually Transmitted Infections (STIs) 2016-2021, early diagnosis and linkage to treatment are one of the key elements for preventing further transmission of STIs.[1] Currently, first-void urine is still favoured as the sample of choice for the detection of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) in men, using nucleic acid amplification tests (NAATs).[2–4] In general, a regular urine container is used to collect the first-void urine sample, but the collected volume of urine is not standardized. Furthermore, this type of container is less convenient for postal delivery to the laboratory. Another sponged-based

device (UriSWAB, Copan Diagnostics, Brescia, Italy) has been suggested as an alternative for postal delivery of urine. However, this device only holds 2 mL of urine and does not guarantee that only first-void urine is collected.[4,5] The CE-IVD labelled Colli-Pee™ device (Novosanis, Belgium), provides a clean and standardized solution to the above-mentioned issues as it efficiently captures first-void urine (20 mL) without interruption of the urine flow and allows the samples to be sent by post. (Fig 1) The Colli-Pee™ device is currently used for the detection of Human Papilloma Virus (HPV) and several urological cancers for which collection of first-void urine is essential.[6,7] In the field of STIs, a standardized first-void urine study reported that the organism load of *C. trachomatis* is maximal in the first 4-5 mL and that the performance of diagnostic tests improved when using only first-void urine.[8,9]

Although pre-exposure prophylaxis (PrEP) is becoming crucial in HIV prevention, recent reviews of real-world PrEP demonstration studies showed that PrEP is associated with increased diagnoses of STIs in Men who have Sex with Men (MSM).[10,11] Consequently, current guidelines recommend a bi-annual screening of STIs in PrEP users because of their high risk behaviour.[12,13]

In order to facilitate the patient flow during follow-up visits by PrEP users, and prompt treatment of STIs, home-based collection of first-void urine could be sent to the laboratory by regular mail for STI detection before the scheduled visit. STI results may then be available at the time of the physician consultation and in the case of a detected STI also immediately treated, limiting the risk of further transmission.

The objectives of this study were to compare the results of the molecular detection of several STIs using the Colli-Pee™ device versus a sample obtained in the clinic, the use and acceptability of the Colli-Pee™ device and its convenience for shipment by regular mail. To assess these objectives, a nested sub-study was performed among MSM who participated in a Belgian PrEP demonstration cohort. [14]

METHODS:

The evaluation was undertaken as a sub-study of Be-PrEP-ared, a PrEP demonstration study among MSM at high risk for HIV in Belgium.

The main study

The Be-PrEP-ared project (EudraCTn°: 5015-00005437) was a phase 3, single-site, open-label prospective cohort study where 200 MSM at high risk of acquiring HIV were asked to participate in the project and to take PrEP daily or event-driven. Detailed study methods are described elsewhere.[14] Participants were tested for *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV) at baseline and every three months. Detection of these STIs was performed at the three biological sites: urethra, anorectum and pharynx. During each study visit, participants collected urine in two urine containers at the clinic as per the following instructions: urinate in the first container up to the marked line at approximately 20 mL, afterwards complete the second cup with no restrictions. Urine in the first container (hereafter the clinic-based sample) was weighed and thereafter stored refrigerated until analysis that took place within 48h. Urine in the second container was used to detect proteinuria.

Laboratory procedures

In the first instance, CT/NG detection was performed using the Abbott Real Time (RT) CT/NG assay (DNA extraction and sample preparation using Abbott m2000sp and the Abbott m2000rt system for amplification and detection of CT/NG (Abbott Molecular Inc. Des Plaines, Illinois, USA)) according to manufacturer's instructions. The remainder of the urine and DNA extracts were stored at -80 °C. In

the case of positivity, the same DNA extracts were tested by in-house real time-PCR (RT-PCR) assays for CT and/or NG, both based on previously published primer sets.[15,16]. A sample was considered positive when positive in both the Abbott and the in-house RT-PCR. An initial positive Abbott assay result followed by a negative confirmatory NAAT result was defined as 'not confirmed'. Inhibition of the NAAT according to the Abbott assay was defined as 'inhibition'.

The same DNA extracts were used for further testing. MG was detected and reported using an accredited in-house RT-PCR that targets the pdhD-gene [17] and in addition the DiaMGTV multiplex kit (Diagenode diagnostics,Seraing, Belgium) that detects MG and TV simultaneously was used for TV detection. The results for MG of the DiaMGTV multiplex kit were not used for reporting purposes and are only provided for information only. No further confirmation of TV took place.

The Colli-Pee™ sub-study

At the baseline visit of the Be-PrEP-ared study, participants were asked consent to participate in this sub-study. After signing the informed consent form, they received a Colli-Pee™ device and a prepaid envelope. They were instructed to collect first-void urine the next day at home using the Colli-Pee™ device (the home-based sample), to document the date and time of collection and to send the collector tube filled with urine back to the laboratory by regular post, using the prepaid envelope. Upon receipt in the laboratory, the urine was weighed, stored refrigerated (2-8°C) and CT, NG, MG, TV was detected using the same NAATs within 48 hours. The urine and DNA extracts' remnants were stored at -80°C. The quantity of human cells was measured at baseline using a human Endogenous Retrovirus-3 (ERV-3) quantitative PCR on the paired clinic- and home-based samples.[18]

The lab technicians were blinded for the results obtained for the clinic-based sample. In addition, the result of the home-based sample was not disclosed to the physician or participant.

During the next visit, which took place within 14 days after baseline, participants were asked to complete a small survey (five questions only) on the user-friendliness and willingness to use the Colli-

Pee™ device (acceptability). Two questions documenting their opinion (likes-dislikes) of the Colli-Pee™ device were open-ended.

At follow-up month 6 and month 18 of the study, Colli-Pee™ devices were again distributed to those who agreed to participate and the survey was repeated at month 18 (results unreported).

The main study was approved by the Institutional Review Board of the Institute of Tropical Medicine and the Ethics Committee of the Antwerp University Hospital. In addition, a separate approval for this sub-study was obtained by the Institutional Review Board of the Institute of Tropical Medicine (Ref:1027/15) and this sub-study is also registered in the clinicaltrials.gov database (NCT02552914).

Patient and Public Involvement

Patients were not involved in the Colli-Pee™ substudy. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Statistical analysis

The agreement of the results of the molecular assays using each of the two sampling methods was assessed by the use of Cohen's kappa statistic and percent agreement. Samples that were not confirmed were coded as negative samples for the calculation of the agreement. The agreement of volume of urine collected and the agreement of concentration of human DNA in both sampling methods was assessed by using a t-test. A p-value of <0.05 was considered statistically significant. Both analyses were performed using STATA version 15.0 (StataCorp LP, College Station, TX, USA).

A descriptive analysis was made of the results of the self-administered questionnaire on the acceptability and user-friendliness of the Colli-Pee™ device.

RESULTS

Demographics

The main study took place at the Institute of Tropical Medicine, Antwerp, Belgium from Sep 2015 until May 2018. Of the 219 participants who were screened for eligibility into the main study, six participants did not consent to the Colli-Pee™ sub-study. All participants who consented to the sub-study were MSM and three identified themselves as transwomen.[19] The mean age of the participants was 38.5 years (Interquartile Range 32-44). A total of 473 home-based samples from 213 participants were received. Two home-based samples could not be linked to the corresponding clinic-based sample and were therefore excluded, bringing the total number to 471. As shown in Table 1, the number of home-based samples received at the laboratory declined over time.

Kind Of Visit	Clinic based	Home Based (% home-based samples received)
Screening	218	187 (85.8%)
Month 6	191	152 (79.6%)
Month 18	179	132 (73.7%)

Table 1: Number of clinic and home-based samples received during the study

Although the participants were instructed to report the urine collection date and hour on the collection device, only 72.8% (343/471) were labelled with collection date. Most of the home-based samples (79.6%) were taken within two days after the clinic-based sample and 3.8% were taken after 20 days (13/343) (median one day; min-max: 0-70 days). The median time between the collection of the home-based sample and its reception at the laboratory after postal return was five days (min-max: 0-27 days), 72.9% arrived at the laboratory within those five days, an additional 25.7% within 10 days and five samples were received after 10 days (11, 13, 15, 17 and 27 days respectively).

Comparison of weight and concentration of human material between both sampling methods.

A total of 455 home-based and 423 clinic-based samples were weighed. The mean net weight of the home-based sample was 19.68g ± 2.14g (95%CI: 19.5g-19.9g and min-max: 6.81g-39.47g) vs 22.87g ± 13.64g (95%CI: 21.6g-24.2g and min-max: 2.88g - 86.23g) for the clinic-based sample (p<0.001).

The quantity of human cells was analysed at baseline only (n=187). In a total of five home-based and one clinic-based sample ERV could not be detected and these samples were considered as lacking human material. After removal of the paired samples lacking ERV or containing inhibitors, 182 observations could be paired. The mean quantity of the clinic-based sample was $11.3*10^3$ cells/PCR (95%CI: 7.4 - $15.2*10^3$) and for the home-based sample $14.2*10^3$ cells/PCR (95% CI: 6.8-$21.5*10^3$) (p>0.05).

STI results and agreement

Of the 471 home-based samples with a matching visit, six home-based and one clinic-based sample gave inhibition and were excluded from the analysis (n=464). The results are shown in Table 2.

STI	**Home-based urine result**	**Clinic-based urine results**		
		Negative	**Positive**	**Total**
Chlamydia trachomatis (non-LGV)	**Negative**	454*	**1**	455
	Positive	**3**	6	9
	Total	457	7	464
Neisseria	**Negative**	455	**0**	455

STI	Home-based urine result	Clinic-based urine results		
		Negative	Positive	Total
gonorrhoeae	**Positive**	**2**	7	9
	Total	457	7	464
Mycoplasma genitalium	**Negative**	431	**2**	433
	Positive	**6**	25	31
	Total	437	27	464
Trichomonas vaginalis	**Negative**	464	0	464
	Positive	0	0	0
	Total	464	0	464

Table 2: STI results of the home-based and clinic-based urine samples

** Two result were not-confirmed in the clinic-based sample*

Trichomonas vaginalis was not detected. Percent agreement (Cohen's kappa coefficient) for CT/NG/MG is 99.1% (0.75); 99.6% (0.87) and 98.3% (0.85), respectively, which indicates substantial agreement for *Chlamydia trachomatis* and almost perfect agreement for the other two STIs.

Tables 3 and 4 show the discordant results. For some of the home-based samples the date of collection was unknown so the time between the clinic visit and time of reception at the laboratory is depicted here. A delta-cycle (DC) value of the Abbott assay of less than two indicates a low positive infection.

STI	DC value CT/NG Abbott assay	Ct value in-house RT-PCR for CT, NG or MG*	Ct-value S-DiagMGTV RT-PCR (for information only)	Days between collection	Days of transport
CT	1.49	33.19	NA	0	2
MG	NA	32.20	Neg	3	4
MG	NA	32.04	37.44	0	8

Table 3: STI infections that were not detected in home-based urine samples

**: a different in-house RT-PCR assay was used for CT, NG or MG*

DC = delta cycle; Ct = Cycle threshold; NA = not applicable; Max = days between clinic visit and reception of the home-based sample at the laboratory

STI	DC value CT/NG Abbott assay	Ct value in-house RT-PCR for CT, NG or MG*	Ct-value S-DiagMGTV RT-PCR (for information only)	Days between collection	Days of transport
CT	3.99	34.26	NA	1	2
CT	2.68	35.31	NA	1	6
CT	0.27	36.06	NA	6	4
NG	2.93	37.58	NA	8	4
NG	10.08	25.26	NA	2	6
MG	NA	31.28	Neg	Max 6	Max 6
MG	NA	31.96	40.51	1	2
MG	NA	28.66	34.67	Max 3	Max 3
MG	NA	34.58	38.50	9	4
MG	NA	34.23	Neg	1	5
MG	NA	32.04	38.14	Max 3	Max 3

Table 4: STI infections that were additionally detected in home-based urine samples

**: a different in-house RT-PCR assay was used for CT, NG or MG*

DC = delta cycle; Ct = Cycle threshold; NA = not applicable; Max = days between clinic visit and reception of the home-based sample at the laboratory

Acceptability and user-friendliness of the Colli-Pee™ device

A total of 164 participants provided feedback regarding the use of the Colli-Pee™ device at baseline. On a scale of one to five, 87.8% found that the Colli-Pee™ device was easy to very easy to use. Instructions on how to send the Colli-Pee™ device were found to be easy by 90.2% of the participants. Four participants found the Colli-Pee™ difficult to use (2.4%) and four other participants found it difficult to follow the instructions (2.4%). Likes from participants were: the ease of use (54.9%), no interruption of the urine flow (15.9%), hygienic (11.6%) and privacy of the home-based sample collection (11.0%); the dislikes were: nothing (47.0%), not being recyclable (14.6%), not hygienic (10.4%) and being too large (6.1%).

To the question of whether they would order an online STI test, 89.0% answered positively (146/164) and 91.1% (133/146) of those individuals would use the Colli-Pee™ device in that case. Six participants (4.1%) would not want to use the Colli-Pee™ device when ordering an online STI test. Participants were also asked how much they would pay for an online STI test with self-sampling. Price indications ranged from 0€ (10 participants) to 60€. Most of the participants (89/164) were willing to pay 10-20€.

DISCUSSION

Many studies have reported on male self-collected urine versus urethra clinician-collected sampling for STI screening , but 'real-world' studies, including sending of home-based urine samples for STI detection in men by post, are sparse.[4,5,20,21] In this study, we showed that the Colli-Pee™ collection device is a valuable and reliable method for collecting first-void urine for STI detection in MSM in Belgium, and that the collector can be shipped by regular post. Compared to the clinic-based sample, a total of three STIs (one CT and two MG infections) were not detected in the home-based sample. However, 11 additional infections were found in home-based samples collected with the Colli-

Pee™ device (3 CT, 2 NG and 6 MG infections). This high number of additional STIs could be explained by the fact that first-void urine contains more DNA/RNA than mid-stream and, as a consequence, should still be used for STI detection.[9] Indeed, we showed that using the Colli-Pee™ device first-void urine was collected in a more standardized way compared to the clinic-based samples ($p<0.001$) . Also, more human cells were collected in the home-based samples, however statistical significance was lacking. The fact that participants could become positive during the time in between sampling points is one of our main limitations and cannot be ignored. Preliminary data of the Be-PrEP-ared study showed high incidence estimates after twelve months of the main Be-PrEP-ared study for urethral CT/NG and MG: 11.5, 5.1 and 6.9 incidence rate per 100 person-years respectively.

Nevertheless, the most important observation is that only one Chlamydia positive result was missed. The DC value of the Abbott assay performed on that clinic-based sample highlighted the low bacterial load of that infection; in addition, transportation at room temperature for two days could have induced DNA degradation.

The World Health Organisation (WHO) underlines the importance of integrating point-of-care assays (POCTs) including innovative delivery options such as self-testing. [22] Unfortunately, to our knowledge, current commercial POCTs for the most important STIs such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are still of sub-optimal quality and do not meet the ASSURED criteria that were developed by the WHO STI Diagnostics Initiative.[22–25] A solution to the unavailability of qualitative POCTs could be internet-accessed STI testing (e-STI testing) which is increasingly available as an alternative to clinic testing all over the world.[26] E-STI testing includes postal self-sampling test kits that are sent to a certified laboratory and web-based delivery of test results. Swab2Know, an online HIV testing project confirmed that e-HIV testing is acceptable and feasible among MSM in Belgium. [27] Commercial online self-sampling services for STIs are now emerging over the internet, but evaluation of these services is lacking.

The present study is, however, subject to several limitations. Firstly, we only enrolled Be-PrEP-ared participants and the participation level seriously declined during the study. As a result, our number of CT/NG positives is quite low, which precludes firm conclusions. Secondly, as mentioned above, home-based samples were not taken on the same day as clinic-based sampling and participants could have become positive during that window period. We also do not know whether participants had urinated one hour prior to collection. However, recent data show that the time between micturition is not crucial for the detection of Chlamydia in men.[28] Thirdly, we did not monitor the temperature of the transport of home-based samples which could also have an impact on the quality of the samples, however, outside temperature between Oct 2015 and May 2018 varied between -10°C to 33°C with an average of 11°C.

Fourthly, we cannot exclude specimen contamination, however, participants were instructed how to correctly collect the clinic-based and home-based sample. Finally, reporting bias is also not to be excluded. Not all participants who used a Colli-Pee™ device completed the survey, the additional questions were included at the end of the lengthy main questionnaire of the Be-PrEP-ared study.

Besides PrEP users, e-STI testing has the potential to reach those who are most in need and a recent study showed that some higher-risk groups, such as MSM, were more likely to use online services [26,29]. Many studies have shown that home-based sampling is well accepted and, in fact, is the preferred approach in these groups for STIs. Reasons for choosing home-based sampling were shorter waiting times for results, convenience and less embarrassment. [30] Participants views regarding ordering an online STI test in this study were very positive, 89% would like to order such a kit. The Colli-Pee™ device was also found to be easy (90.2%) and although hygiene was one of the likes, it also appeared in the dislikes, probably because the need to detach the collector manually can cause leakage of urine. Participants were also concerned regarding possible ecological consequences, although the plastic material is recyclable and can be incinerated into energy.

We demonstrated that postal delivery of home-based collected urine does not influence STI detection and can be used among PrEP users. Subsequently, PrEP users will be able to send first-void urine to the laboratory with the Colli-Pee™ device one to two weeks before their routine PrEP follow up visit. Results can then be discussed during the physician consultation and followed by treatment and future antimicrobial testing if applicable, decreasing the number of physician visits. Decreasing the number of face-to-face visits will lower the burden on staff workload and healthcare resources. However, future economic evaluations will need to be conducted to prove this statement. E-STI testing could be a promising approach in Belgium to reach patients in hard-to-reach populations and research on this topic should be stimulated. Therefore, future studies to study the acceptability and impact of postal shipment of home-collected material on the performance of STI assays requires additional assessment.

Figure legend: Fig 1: The Colli-Pee™ device instructions for use.

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COMPETING INTERESTS STATEMENT

The authors have no competing interests to declare.

FUNDING STATEMENT

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DATASHARING STATEMENT

The data will be made publicly available except for the use and acceptability data as these will be retained at the Institute of Tropical Medicine (ITM), Antwerp due to ethical and privacy concerns. According to the ITM research data sharing policy, only fully anonymised data can be shared publicly. The data can however be made available after approval of a motivated and written request to the ITM at ITMresearchdataaccess@itg.be. The ITM data access committee will verify if the dataset is suitable for obtaining the study objective and assure that confidentiality and ethical requirements are in place.

CONTRIBUTORSHIP STATEMENT

IDB, TC, and BV designed the study. TR designed the acceptability survey. IDB performed the statistical analysis and wrote the first draft of the manuscript. HS, BDD, VC, SA performed testing. All authors read the final version of the manuscript and provided comments.

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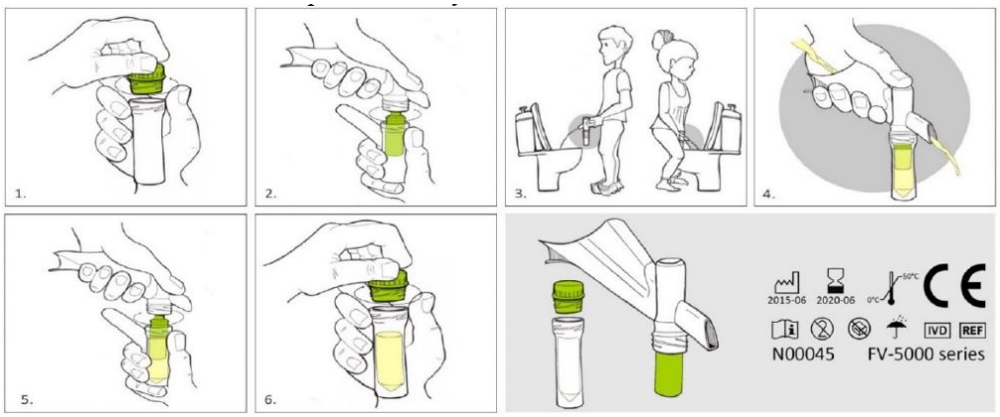

Fig 1: The Colli-PeeTM device instructions for use.

268x110mm (95 x 95 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2 (agreement was used as this is not a diagnostic study)
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	3-4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5-6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5-6
Test methods	**10a**	Index test, in sufficient detail to allow replication	Not applicable same assay was used on both samples (but different kind of sample)
	10b	Reference standard, in sufficient detail to allow replication	Not applicable same assay was used on both samples (but different kind of sample)
	11	Rationale for choosing the reference standard (if alternatives exist)	Not applicable same assay was used on both samples (but different kind of sample)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5-6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	5-6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	6
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	6
	16	How missing data on the index test and reference standard were handled	Not applicable
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not applicable
	18	Intended sample size and how it was determined	Not applicable
RESULTS			
Participants	**19**	Flow of participants, using a diagram	We did not include of flow of participants, however this has been discussed in the text p7-8

	20	Baseline demographic and clinical characteristics of participants	7-8
	21a	Distribution of severity of disease in those with the target condition	Not applicable
	21b	Distribution of alternative diagnoses in those without the target condition	Not applicable
	22	Time interval and any clinical interventions between index test and reference standard	8
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	8
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Cohen's kappa agreement was used p9
	25	Any adverse events from performing the index test or the reference standard	Not applicable
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	13
	27	Implications for practice, including the intended use and clinical role of the index test	13-14
OTHER INFORMATION			
	28	Registration number and name of registry	6
	29	Where the full study protocol can be accessed	Will be added as appendix
	30	Sources of funding and other support; role of funders	15

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.