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Collection devices to reduce contamination in urine samples provided for diagnosis of uncomplicated urinary tract infection: a single blind randomised controlled trial

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Abstract

Background: Urine collection devices (UCD) are being marketed and used in clinical settings to reduce urine sample contamination, despite inadequate supporting evidence.

Aim: To determine whether UCDs, compared to standardised instructions for urine sample collection, reduce the proportion of contaminated samples.

Design, Setting: Single blind randomised controlled trial in UK Primary care

Method: Women aged ≥ 18 years presenting to with symptoms attributable to urinary tract infection (UTI) were randomised (1:1:1) to use either a Peezy UCD, a Whizaway Midstream UCD, or standardised verbal instructions (SVI) for midstream sample collection. The primary outcome was the proportion of urine samples reported as contaminated by microbiology laboratory analysis.

Results: 1264 women (Peezy $n=424$; Whizaway $n=421$; SVI $n=419$) were randomised between 5/10/16 and 20/8/18. 90 women were excluded from the primary analysis due to ineligibility or lack of primary outcome data, leaving 1174 ($n=381$; $n=390$; $n=403$) for intention-to-treat analysis. The proportion of contaminated samples was 26.5% with the Peezy, 28.2% Whizaway, and 29% SVI (relative risk (RR) Peezy v SVI 0.91 [95% Confidence Interval (CI) 0.76 to 1.09] ($P = 0.32$); Whizaway v SVI 0.98 [95% CI 0.97 to 1.20] ($P = 0.82$)). There were 100 (25.3%) device failures with Peezy and 35 (8.8%) with Whizaway UCDs; the proportion of contaminated samples was similar after device failure samples were excluded.

Conclusion: Neither Peezy nor Whizaway UCDs reduced sample contamination when used by women presenting to primary care with suspected UTI. Their use cannot be recommended for this purpose in this setting.

Keywords: UTI, diagnosis

How this fits in:

This trial is the first to evaluate the effectiveness of urine collection devices in the population of most relevance: women with symptoms of UTI presenting to primary care. Neither the Peezy nor Whizaway UCDs reduced sample contamination when used by women presenting to primary care with symptoms attributable to uncomplicated UTI. Since there are no other studies in this population, their use cannot be recommended for this purpose in this setting.

INTRODUCTION

Urinary tract infection (UTI) is one of the commonest bacterial infections managed in general practice and is the reason for 1-3% of all GP consultations¹. UTI is more common in women, for whom the lifetime risk is 50% and annual incidence is over 10%¹. Urine culture, a test which can take up to 3 days to provide a result, is commonly requested by primary care clinicians to confirm a suspected diagnosis of UTI and to understand antibiotic sensitivities. In the UK, some laboratories perform urine culture on all urine samples, whereas others use the concentration of white cells, determined using flow cytometry, to identify samples which will proceed to urine culture in certain cases.

Uniquely amongst medical tests, GPs will not receive a clinically useful result from the urine culture in up to 30% of cases because these samples are contaminated by bacteria from the host's faeces, skin and vaginal secretions². Such samples are often reported as contaminated or as 'mixed growth', and this result neither rules in nor rules out bacterial infection. Repeat samples are often required in order to guide care, with implications for patients, as they may have to wait longer for appropriately targeted antibiotic therapy, and for health services, as repeated culture tests are costly and time consuming.

Few solutions have been proposed for this wide-scale problem. Patients have been advised to discard the first part of the urine stream, as this may contain the majority of the contaminants, and capture only the mid-stream for the sample.^{3,4} However, this procedure is often challenging to explain and implement, with two small low quality randomised trials finding no clear evidence of benefit⁵

Another solution, which is already being implemented in healthcare settings, is the use of a urine collection device (UCD). The Whizaway Midstream (Whiz, Oxford, UK)⁶ uses a pressure valve system to allow the early urine stream to flow into the toilet and the midstream sample then flows into a sample bottle. The Peezy (Forte Medical Ltd, London, UK)⁷ device channels the early stream into a sponge, collecting the sample by back pressure. However, of three published studies evaluating the impact of UCD use on urine culture contamination,⁸⁻¹⁰ only one, using the Whizaway device in antenatal women with no UTI symptoms⁸, found evidence of small benefit. No randomised trial has been conducted in the population with greatest potential for widespread benefit, namely women presenting to primary care with uncomplicated UTI. We performed a randomised controlled trial of the effectiveness of UCDs in reducing the proportion of urine samples from women with suspected uncomplicated UTI that are contaminated on laboratory culture.

METHODS

We conducted a three arm, single blind, individually randomised controlled trial (RCT). Ethical approval was granted by East of England - Cambridge East Research Ethics Committee ref 16/EE/0200. The trial was registered (ISRCTN68511881).

Participants

Women aged 18 years and over presenting to UK general practice were eligible for inclusion if they had symptoms attributable to uncomplicated urinary tract infection (UTI), including at least one of dysuria, haematuria or frequency of urination, and were able to give informed consent. Exclusion criteria were current or recent (< 7 days) antibiotic use, indwelling catheter or intermittent self-catheterisation, previous recruitment to this trial or current involvement in a clinical trial of an investigational medicinal product, participant unable to provide a sample during their index consultation or to understand and complete trial materials in English.

Interventions

Participants were randomised to obtain a urine sample using one of the following approaches:

- 1) Standardised verbal instructions (SVI) for collecting a mid-stream urine (i.e. without a UCD) as follows: 'Please pass the first portion of your urine into the toilet and collect the next portion in this sample pot'
- 2) Peezy UCD with instructions for its use on the device packaging.
- 3) Whizaway midstream UCD with instructions for its use on the device packaging.

Devices were purchased using usual purchasing routes. Manufacturers did not provide any funding towards the study and had no role in its design, conduct or analysis.

Study procedures

After eligibility assessment and written informed consent, baseline questionnaires and CRFs were completed. Participants who were unable to pass urine during their baseline appointment were deemed ineligible post randomisation. If the participant was able to pass urine, and attempted to collect a sample using a device, but was unable to do so (a device failure), they continued in the study, and were offered a standard collection pot to attempt to produce a second sample. This pragmatic approach was taken following discussion with our Patient and Public Involvement (PPI)

group, and because participants were generally unwilling to attempt to use a device for a second time. If used in routine care, this approach would probably be implemented in practice. Since device failures had not been anticipated to be frequent based on previous studies,^{8,9} sites were initially trained to report device failures through direct telephone or email contact with the study team. From 19/5/2017 the baseline CRF allowed documentation of device failure.

Participants were contacted by telephone or text message at 14 days to collect symptom duration, EQ-5D-5L and healthcare usage. Primary care record review at 14 days documented antibiotic prescriptions and healthcare contacts.

To assess the proportion of participants approached who enrolled in the study, recruiting practices were requested to provide detailed data over a two week 'snapshot' period on the number of participants approached, eligible and recruited. Continuous screening logs have historically been very poorly completed.

Randomisation and Blinding

Participants were randomised (1:1:1) using Sortition, an online randomisation system developed and managed by the University of Oxford Primary Care and Vaccines Clinical Trials Unit. The laboratory staff reporting the primary outcome and the trial team entering participant data were blinded to intervention allocation, but the patient and recruiting clinician were not. Patient follow up data were collected by trial administrators trained to avoid being informed of the participant's allocation as far as possible. Trial statisticians were blind to group allocation.

Outcome measures

The primary outcome was the proportion of contaminated urine samples, defined as those reported as a mixed growth according to NHS laboratory national standard operating procedures. Secondary outcomes were the proportion of samples reported as a pure or predominant growth of a known urinary pathogen according to national standard reporting procedures (the actionable information of most importance to clinicians), the presence and number of white cells (often elevated in urinary tract infection) and epithelial cells (skin cells, which can also indicate sample contamination) on urine microscopy, the diagnostic accuracy of dipstick urinalysis for a pure or predominant growth of a known urinary pathogen on urine culture, healthcare resource use, duration of symptoms, and health utility measured with the EQ-5D-5L (to be reported separately, as will tertiary microbiological outcomes). Hospitalisations related to UTI within 14 days of baseline assessment were recorded.

Sample Handling

The recruiting clinician performed a dipstick urinalysis and sent the sample to a Central study laboratory. If the responsible GP required a culture result for clinical care the sample was split into two. The study sample was cultured and reported using standard NHS laboratory procedures and definitions. Where sufficient volumes of urine were available, flow cytometry (SediMAX Automated Urine Microscopy Analyser) was used to identify and quantify epithelial cells and white cells.

Sample size calculation

Allowing for a 5% loss of samples, we estimated that a sample size of 1191 participants would provide 90% power to detect an absolute reduction of contaminated samples of 10.8%. Although the proportion of urine samples reported as contaminated from primary care nationally is not known, the proportion in our local tertiary care hospital microbiology laboratory averaged 26% between 2008 and 2018.¹¹ A reduction of less than 10% was not felt to be clinically meaningful.

Statistical Analyses

The primary analysis population was defined as all participants for whom data were available and were analysed according to the groups they were randomly allocated to, regardless of device failures and deviation from protocol. For the primary outcome, and other binary outcomes (reporting of samples, presence of white blood and epithelial cells, requiring one or more further urine cultures, requiring a repeat consultation with GP or hospital admission), a generalised linear mixed-effects model analysed included all data available, adjusting for intervention arm as a fixed effect, and GP surgery as a random effect. An ordinal logistic mixed effects regression model analysed the concentration of white blood and epithelial cells. Duration of symptoms was analysed by survival analysis in a mixed effects Cox proportional hazards model, censoring on whether symptoms resolved or not. Sensitivities and specificities of the dipstick urinalysis (assuming a pure growth of a known urinary pathogen from urine culture as reference standard) were evaluated using a decision rule as follows: A positive dipstick result (indicating presence of urinary tract infection) was indicated by the dipstick result showing nitrite (positive), or both leucocytes (+, ++, +++) and blood (haemolysis trace or greater¹²). A second analysis used only the presence of leucocytes to indicate infection. Sensitivities and specificities were compared by means of a Fisher's exact test.

The primary outcome was obtained from the reporting of the urine culture from the Central Laboratory. Where the primary outcome was not available from the Central Laboratory, but the GP had split the sample in order to receive a result to guide clinical care, this NHS laboratory result was available from medical notes review and used as the primary outcome. A sensitivity analysis analysed only the culture results from the research sample provided for the study. Since NHS laboratories can use different procedures, a post-hoc sensitivity analysis was performed using only the trial samples or split NHS samples that were analysed in the Central Laboratory.

A per-protocol sensitivity analysis was performed on the primary outcome on only those women who provided a sample with the allocated device. All women who reported experiencing a device failure were excluded from the per-protocol analysis.

Planned subgroup analyses were performed for women who were post-menopausal, pregnant, or had a history of recurrent UTI. These groups are suggested to have physiological changes in the urinary tract¹³⁻¹⁵ which might have the potential to alter either the proportion of samples which are contaminated or device performance. We compared samples received ≤ 48 hours and > 48 hours after provision to explore the potential impact of duration of storage and transport on our findings.

Patient and Public Involvement (PPI)

Four women who had suffered from UTI supported this project from inception to dissemination, providing feedback on study design and materials. They advised on processes for participants and recruitment, and dissemination of findings. One PPI participant served on the trial steering committee.

RESULTS

From October 2016 to August 2018 we randomised 1264 women from 61 general practices in England and Wales. 424 participants were randomised to Peezy UCD, 421 to Whizaway midstream and 419 to standardised verbal instructions (SVI). Figure 1 details participant screening, recruitment and follow-up and reasons for ineligibility after randomisation. We found 29 (Peezy), 23 (Whizaway) and 14 (SVI) participants to be ineligible subsequent to randomisation, of whom 16 participants in the Peezy arm and 8 in the Whizaway arm were ineligible as they were unable to pass urine; no patients in the SVI arm were excluded for this reason. Device failures, for example due to urine failing to enter the specimen tube, urine failing to enter the device as a whole or parts of the device falling to the toilet, were reported by 100/395 (25.3%) of participants using a Peezy and 35/398 (8.8%) of participants using a Whizaway. Five participants (3 Peezy, 2 Whizaway) experienced a device failure and were unable to provide a second urine specimen in a standard container. 775 samples (253 Peezy, 206 Whizaway, 316 SVI) were of sufficient volume to allow flow cytometry analysis.

The majority of baseline characteristics were similar in the three study groups, including symptom severity, age and dipstick results (Supplementary Table 1). Less samples were cloudy in the Peezy arm (38.6%) compared to the SVI arm (52.7%), and Whizaway arm (43.2%), and more participants had a sample additionally sent for routine care in the standardised instructions arm (SVI 52.1%, Peezy 39.3%, Whizaway 44.0%).

Primary Outcome

The proportion of samples reported as contaminated by standard NHS laboratory procedures was not significantly different when comparing either UCD to SVI (Table 1). The relative risk of contamination with the Peezy compared to SVI was 0.91 [95% Confidence Interval (CI) 0.76 to 1.09] ($P = 0.32$) and for Whizaway was 0.98 [95% CI 0.97 to 1.20] ($P = 0.82$). Findings were similar in a per protocol analysis including only those participants who provided a sample using the allocated approach (Peezy RR 0.91 (95% CI 0.73 to 1.14) $P = 0.41$; Whizaway RR 1.01 (95% CI 0.82 to 1.24) $P = 0.96$). Findings were also similar in pre-specified sensitivity analyses that assumed all missing outcomes were mixed growth, using multiple imputation to replace missing primary outcomes, and including only participant samples which were analysed at the main study laboratory (Supplementary Table 2). There was no difference in the proportion of contaminated samples when subgroups of participants who were pre / post-menopausal, pregnant, or had a history of recurrent UTI were examined separately for each UCD versus SVI. Subdividing samples into those received less than or

equal to 48 hours after provision and greater than 48 hours after provision gave similar results (Supplementary figures 1 and 2).

Secondary Outcomes

The proportion of samples reported as a pure or predominant growth of uropathogen did not differ significantly between either UCD and SVI groups (Peezy 55.0% v SVI 54.4% RR 1.01 [95% CI 0.86 to 1.18] $P = 0.90$), (Whizaway 52.8% v SVI 54.4% RR 0.97 [95% CI 0.88 to 1.07] $P = 0.56$) (Table 2).

Use of either UCD did not affect the proportion of urine samples containing white cells (Table 2), although a reduced concentration of white cells was evident with both UCDs compared to SVI (Supplementary table 3). Significantly fewer samples with epithelial cells were produced in the Peezy arm (RR 0.82 [95% CI 0.70 to 0.95] $P = 0.010$) and the concentration of epithelial cells was lower (adjusted OR 0.61 [95% CI: 0.45 to 0.83]; $P = 0.001$ (Supplementary Table 3) compared to the SVI group.

There was no significant difference between either UCD and the SVI arm in the diagnostic accuracy of dipstick urinalysis using a decision rule based on presence of blood, leucocytes and nitrites with a positive culture result as a reference standard¹² (Table 2). A decision rule using only presence of leucocytes demonstrated greater sensitivity but not specificity for UTI in the SVI arm than the Peezy arm (Peezy sensitivity 68.04% [95% CI 60.98% to 74.54%], SVI 78.70% [95% CI 72.64% to 83.97%] $P = 0.018$) (full details in Supplementary Table 4).

For those participants where the GP chose to receive a culture result, and therefore this result could have influenced onward care, there was no difference between either UCD and SVI in repeat urine cultures, or healthcare contacts for symptoms or complications of UTI. The duration of symptoms was also similar between arms (Table 3). When data from study participants whose GP did not request a culture result were included in the analysis, findings were similar. (Supplementary Table 5). Five serious adverse events were noted (2 SVI, 2 Whizaway, 1 Peezy), all were hospital admissions with suspected pyelonephritis which fully resolved after treatment and were deemed unrelated to the intervention.

DISCUSSION

Summary of main findings

UCDs did not reduce the proportion of urine samples from women presenting to primary care with symptoms of uncomplicated UTI that were reported as contaminated on laboratory culture. Furthermore, a quarter of women allocated to the Peezy arm and nearly one in ten allocated to the Whizaway arm were unable to collect a urine sample successfully using the UCD. UCD use did not improve the diagnostic accuracy of dipstick urinalysis for infection and did not alter the proportion of urine samples with white cells present or reported as positive for infection on urine culture. Although samples produced using the Peezy device had lower levels of epithelial cells, which have also been seen as a marker of contamination, this has little clinical significance, and indeed recent studies have questioned the link with contamination¹⁶.

Strengths and weaknesses of the study

This is the only adequately powered trial of urine collection devices, and the only one conducted in the symptomatic primary care population where the problem of urine contamination is most prevalent. This pragmatic study used standard NHS transport and laboratory analysis processes.

However, there are several limitations. First, there were more device failures than we expected, where participants could not successfully capture their urine using the device. About a quarter of Peezy devices failed, and this may have impacted our intention to treat analysis. However, with nearly 300 women in the Peezy arm per protocol analysis, this trial remains the largest to examine this question.

Second, as would be the case in everyday care, we could not control the time taken for sample transport and laboratory analysis. This means that the proportion of contaminated samples could have been higher because of bacterial growth during any delay. However, we found no difference in contamination in samples analysed up to 48 hours and beyond 48 hours after provision, and a recent trial in an Emergency Department found no benefit of the Peezy device, despite much shorter times between obtaining the sample and analysis.¹⁰

Finally, it is possible that many patients do not receive explicit instructions for midstream urine collection. We cannot be certain what the impact on our findings would have been had our control arm participants been issued with no instructions.

Comparison with existing literature

Previous studies evaluating the impact of UCDs on urine culture contamination found either small or no beneficial effects. In the only randomised controlled trial⁵ of the Whizaway midstream UCD, in 2182 asymptomatic pregnant women, a 5% reduction in mixed growth was demonstrated compared to the control group receiving usual care⁴. The only published randomised controlled trial of the Peezy UCD,⁷ recruiting 1374 adults, (27% men) in an Emergency Department, found no significant difference in contamination compared to using a simple collection pot, and higher failure rates in those using Peezy (5% unable to use the device and 20% producing insufficient urine). A non-randomised study of the Peezy device in renal transplant patients using historical controls also demonstrated no difference in the proportion of contaminated samples⁹.

Implications for research or practice

In comparison to standardised instructions for midstream urine collection, we found no significant benefit of using either Peezy or Whizaway midstream UCDs on the proportion of contaminated samples in symptomatic women presenting to primary care. The use of UCDs cannot be recommended for this purpose. Although UCDs did not improve care in our study, further evaluation in patient groups where physical limitations may make standard instructions for midstream urine collection harder to accomplish, may be warranted.

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DECLARATION OF INTERESTS: No conflicts of interest to declare

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Practice, Eynsham Medical Group, Fakenham Medical Practice, Gladstone Road Surgery, Gosford Hill Medical Centre, Hucclecote Surgery, Hughenden Valley Surgery, Kier Hardy PCT 3, Lancaster Medical Practice, Mann Cottage Surgery, Milman Road Surgery, Oakenhurst Medical Practice, Pont Newydd Medical Centre, Prices Mill Surgery, Queens Square Medical Practice, Railway Medical Group, Rendcomb Surgery, Ridge Green Medical Practice, River Brook Medical Centre, Rolle Medical Partnership, South Oxford Health Centre, St Chads Surgery, Staploe Medical Centre, Stow Surgery, Summertown Health Centre, Teign Estuary Medical Group, The Abingdon Surgery, The Ashgrove Surgery, The Boat House Surgery, The Downland Practice, The Key Medical Practice, The Portland Practice, Wellington House Surgery, West Bar Surgery, Whaddon Medical Centre, White Horse Medical Practice, Winchcombe Medical Centre, Windrush Medical Practice, Wokingham Medical Centre, Yorkley Health Centre.

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	Peezy UCD	Whizaway Midstream UCD	Standardised Verbal Instructions
ITT analysis Lab culture urine result	(n=395)	(N=398)	(N=405)
Mixed growth, n(%)	101 (26.5%)	110 (28.2%)	117 (29.0%)
Not 'mixed growth', n(%)	280 (73.5%)	280 (71.8%)	286 (71.0%)
<i>Missing</i>	14	8	2
Per protocol Lab urine culture result	(N=295)	(N=363)	(N=405)
Mixed growth, n(%)	77 (26.3%)	104 (29.1%)	117 (29.0%)
Not 'mixed growth', n(%)	216 (73.7%)	254 (70.9%)	286 (71.0%)
<i>Missing</i>	2	5	2

Table 1: Number and proportion of contaminated samples in the 3 trial arms in the primary intention to treat analysis and per protocol analysis.

	Peezy UCD (N=395)	Whizaway Midstream UCD (N=398)	Standardised Verbal Instructions (N=405)
Urine Culture results			
Pure or predominant growth, n(%)	194 (55.0%)	197 (52.8%)	216 (54.4%)
No predominant growth, n(%)	159 (45.0%)	176 (47.2%)	181 (45.6%)
Missing	42	25	8
Diagnostic accuracy of dipstick urinalysis*#			
Sensitivity (95% CI)	59.79% [52.53% to 66.75%]	63.45% [56.31% to 70.18%]	65.28% [58.52% to 71.61%]
Specificity(95% CI)	62.89% [54.88% to 70.41%]	63.07% [55.48% to 70.21%]	60.77% [53.26% to 67.93%]
Presence of cells in Urine samples detected using Flow cytometry			
Epithelial cells	114 (45.1%)	117 (56.8%)	174 (55.1%)
White cells	142 (56.1%)	114 (55.3%)	203 (64.2%)
Missing	142	192	89

Table 2: For Peezy and Whizaway UCDs and SVI: The proportion of samples taken with showing a pure or predominant growth of a uropathogen, the proportion with white cells or epithelial cells present and the diagnostic accuracy (sensitivity and specificity) of urine dipstick analysis.

* Pure or predominant growth ($10^4 - 10^5$ or $>10^5$) of uropathogen on urine culture as reference standard.

Decision rule for urine dipstick: A positive dipstick result (indicating presence of urinary tract infection) was indicated by the dipstick result showing nitrite (positive), or both leucocytes (+, ++, +++) and blood (haemolysis trace or greater)¹².

All fisher's exact tests statistics $p > 0.2$

	<i>Peezy UCD</i>	<i>Whizaway</i> <i>Midstream UCD</i>	<i>Standardised</i> <i>Verbal</i> <i>Instructions</i>
	(N=154)	(N=172)	(N=210)
<i>Requiring a repeat consultation from any source for symptoms or complications of UTI within 14 days</i>			
<i>Yes, n(%)</i>	50 (32.5%)	54 (31.4%)	70 (33.3%)
<i>No, n(%)</i>	104 (67.5%)	118 (68.6%)	140 (66.7%)
<i>Missing</i>	0	0	0
<i>Duration of symptoms in days</i>			
<i>Mean (sd)</i>	5.10 (3.88)	5.57 (3.72)	5.19 (3.09)
<i>Median (IQR)</i>	4.00 (3.00 to 7.00)	4.50 (3.00 to 7.00)	4.00 (3.00 to 7.00)
<i>[range]</i>	[0 to 28]	[1 to 21]	[1 to 15]
<i>Missing</i>	52	58	64
<i>Repeat urine culture requested within 14 days</i>			
<i>Yes, n(%)</i>	18 (12.8%)	14 (8.5%)	19 (9.3%)
<i>No, n(%)</i>	123 (87.2%)	151 (91.5%)	185 (90.7%)
<i>Missing</i>	13	7	6

Table 3: Health outcomes for participants where the GP received the culture results by group allocation

FIGURE LEGENDS

Figure 1: Consort flow diagram

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*A 2 week snapshot screening log suggested that 63.9% of patients approached were eligible and 39.6% of those approached consented to participant (63.6% of those eligible)