Sexually transmitted infections and prior antibiotic use as important causes for negative urine cultures among adults presenting with urinary tract infection symptoms to primary care clinics in Zimbabwe: a cross-sectional study

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ABSTRACT

Objective Urinary tract infections (UTIs) are common in primary care. The yield of urine cultures in patients with UTI symptoms can be considerably different between high-income and low-income settings. This study aimed to explore possible causes of negative urine cultures in patients presenting with symptoms of UTI to primary health clinics in Harare.

Design Cross-sectional study.

Setting Nine primary health clinics in Harare, Zimbabwe.

Participants Adults presenting with symptoms of UTIs between March and July 2020.

Primary outcome measures Urine samples underwent dipstick testing, microscopy, culture, and testing for sexually transmitted infections (STIs) using GeneXpert and for the presence of antibiotic residues using an antibiotic bioassay. The primary outcomes were the number and proportion of participants with evidence of STIs, prior antibiotic exposure, leucocyturia and UTIs.

Results The study included 425 participants with a median age of 37.3 years, of whom 275 (64.7%) were women. Leucocyturia was detected in 130 (30.6%, 95% CI 26.2% to 35.2%) participants, and 96 (22.6%, 95% CI 18.7% to 26.9%) had a positive urine culture for a uropathogen. Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis were detected in 43/425 (10.1%, 95% CI 7.4% to 13.4%), 37/425 (8.7%, 95% CI 6.2% to 11.8%) and 14/175 (8.0%, 95% CI 4.4% to 13.1%) participants, respectively. Overall, 89 (20.9%, 95% CI 17.2% to 25.1%) participants reported either having taken prior antibiotics or having had a positive urine bioassay. In 170 (40.0%, 95% CI 35.3% to 44.8%) participants, all of the tests that were performed were negative.

Conclusions This study found a high prevalence of STIs and evidence of prior antimicrobial use as possible explanations for the low proportion of positive urine cultures.

INTRODUCTION

Urinary tract infections (UTIs) are a common reason for presentation to primary care with 10% of adult women experiencing at least one episode per year. Dysuria, which is one of the most common symptoms suggestive of a UTI, is reported in 2%–5% of presentations in general practice. While dysuria and other urinary symptoms such as frequency and urgency may be attributed to acute bacterial cystitis, they are by no means specific. Symptoms can be due to a wide range of infectious agents as well as to other non-infectious causes (table 1). In high-income settings, acute bacterial cystitis is the most common cause of UTI symptoms in women presenting to primary care. Thus, the symptom complex is treated empirically with antibiotics, and diagnostic tests are not deemed routinely necessary. Patients whose symptoms do not respond to first-line antibiotics are reassessed.
for other diagnoses or infections with organisms resistant to first-line antibiotics.4

The prevalence of positive urine cultures in patients presenting with presumed UTIs varies widely across different settings. This is particularly true when comparing studies from high-income and low-income settings.2 5 Possible explanations include (1) differences in prevalence of other conditions causing similar symptoms, (2) unregulated access to antibiotics leading to partially treated infections or (3) differences in laboratory techniques affecting the limit of detection.

This study aimed to evaluate possible causes of negative urine cultures in patients presenting with symptoms of UTI to primary health clinics in Harare.

**METHODS**

Adults (aged 18 years and above) presenting with symptoms of UTIs to nine primary health clinics in Harare were enrolled into the Antimicrobial Resistance in Gram-negative Bacteria from Urinary Specimens (ARGUS) study. In Zimbabwe, primary health clinics are nurse-led and serve the population living in their catchment area. Patients accessing the acute medical services have to pay a user fee. Access to diagnostic tests is limited beyond HIV, tuberculosis and malaria. The eligibility criteria and enrolment procedures for the ARGUS study were previously described.6 Patients were included in the study if they presented with at least two symptoms suggestive of UTI (dysuria, urgency, frequency, suprapubic pain and/or flank pain).

This is a cross-sectional study reporting on a subset of participants from the ARGUS study who were consecutively enrolled between March and July 2020. Mid-stream urine samples were collected from study participants and underwent dipstick testing, microscopy and culture using conventional microbiology methods.6 Leucocyturia was considered to be present if the sample had ≥106 white blood cells/L on microscopy or a positive dipstick for leucocytes. Antibacterial activity of urine indicating possible prior antibiotic exposure was ascertained using a urine bioassay. Briefly, 20 µL urine was inoculated on a 6 mm filter paper disc that was incubated on Mueller-Hinton agar and using *Escherichia coli* (ATCC25922) as an indicator organism.7 Antibacterial activity was considered to be present in the sample if a growth inhibition zone of any size around the disc was observed following incubation for 24 hours at 37°C.

Urine samples were tested for sexually transmitted infections (STIs), specifically *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. For women only, urine samples were also tested for *Trichomonas vaginalis*. STI testing was done using the GeneXpert platform (Cepheid, Sunnyvale, California, USA) according to the manufacturer’s instructions. Treatment for STIs was prescribed during the initial
visit by the clinic nurse according to routine practice following the Zimbabwean national guidelines and independent of study procedures. Participants with positive tests were notified of their result and offered treatment for themselves and their partners if they were not treated on their initial appointment. To ascertain if symptoms had resolved, a follow-up phone call was conducted 28 days postenrolment.

**Statistical analysis**

Data were analysed using Stata V.15. Categorical data were described using counts and percentages, and continuous data were described using medians and IQRs. Differences between categorical and continuous variables were evaluated using the $\chi^2$ and Mann-Whitney U tests, respectively. The level of significance was set at a $p$ value of $\leq0.05$.

**Patient and public involvement**

There was no patient and public involvement in the study design. Results from this study were disseminated to nurses working in the polyclinics from where the study participants were recruited in order to improve patient care.

**RESULTS**

The study included 425 participants with a median age of 37.3 years (IQR 26.8–48.0), of whom 275 (64.7%) were women and 172 (40.5%) were HIV-positive. All samples were tested for the presence of leucocytes, underwent conventional urine culture and were tested for *C. trachomatis* and *N. gonorrhoeae*. Samples from 175 women were tested for *T. vaginalis*. Of 425 urine samples collected, 420 were stored for the antibiotic bioassay; volume was insufficient for storage for the remaining 5 samples. In 255 (60.0%) of the participants, at least one of the tests was positive, while in 170 (40.0%) participants, all of the tests were negative. In 170 (40.0%) of the participants, the cause of their symptoms could not be determined or suspected. Figure 1 shows the distribution of positive test results (STI positive, while in 170 (40.0%) participants, all of the tests were negative, and the cause of their symptoms could not be determined or suspected. Figure 1 shows the distribution of positive test results (STI positive

![Figure 1](https://example.com/figure1.png)

**Figure 1** Distribution of positive tests among study participants (170/425 samples; 40% were negative for all tests). STI, sexually transmitted infection.
who reported having taken their prescribed treatment and in 9/20 (45%) of those who had not.

**DISCUSSION**

This study found that only one in five people presenting to primary care in Harare with UTI symptoms had a positive urine culture with a uropathogen explaining their presenting symptoms. There was a high prevalence of STIs and evidence of prior antimicrobial use among study participants as possible explanations for the low proportion of positive urine cultures. However, in 40% of patients, symptoms remained unexplained.

-only 20% of study participants had a positive urine culture, which is similar to findings from studies conducted among women with cystitis in high-income countries, mostly from Europe and the Americas, where 75%–80% of urine cultures reveal significant growth of uropathogens. This may be explained by differences in access to healthcare, regulated antimicrobial use and prevalence of other conditions. In contrast, studies conducted in low-income countries where infection rates are much higher, particularly in patients with leucocyturia, where symptoms may be explained by residual inflammation. Dysuria and leucocyturia may be due to other causes such as urogenital tuberculosis, schistosomiasis and other inflammatory conditions. However, other infections are unlikely to be the cause of symptoms in patients with positive urine cultures in this study because of the delay in accessing healthcare or self-treatment in less than 1%

**Table 2** Characteristics of the study participants according to the test result

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N=425 (%)</th>
<th>STI positive n=83 (%)</th>
<th>Urine culture positive n=96 (%)</th>
<th>Leucocyturia n=130 (%)</th>
<th>Prior antibiotics n=89 (%)</th>
<th>All tests negative n=170 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) median (IQR)</td>
<td>37.3 (26.8–48.0)</td>
<td>28.4 (23.5–39.2)</td>
<td>39.8 (26.0–50.0)</td>
<td>34.2 (24.8–47.0)</td>
<td>37.6 (27.6–49.4)</td>
<td>39.4 (29.6–49.6)</td>
</tr>
<tr>
<td>Female sex</td>
<td>275 (64.7)</td>
<td>51 (61.5)</td>
<td>73 (76.0)</td>
<td>88 (67.7)</td>
<td>51 (57.3)</td>
<td>107 (62.9)</td>
</tr>
<tr>
<td>Completed at least secondary education</td>
<td>359 (84.5)</td>
<td>71 (85.5)</td>
<td>75 (78.1)</td>
<td>108 (83.1)</td>
<td>77 (86.5)</td>
<td>141 (82.9)</td>
</tr>
<tr>
<td>HIV-positive*</td>
<td>172 (42.4)</td>
<td>20 (25.6)</td>
<td>42 (47.2)</td>
<td>53 (43.4)</td>
<td>38 (44.2)</td>
<td>76 (46.1)</td>
</tr>
<tr>
<td>Pregnancy*</td>
<td>35 (13.0)</td>
<td>4 (7.8)</td>
<td>7 (9.7)</td>
<td>15 (17.2)</td>
<td>5 (9.8)</td>
<td>16 (15.5)</td>
</tr>
<tr>
<td>Married/have a partner</td>
<td>325 (76.5)</td>
<td>66 (79.5)</td>
<td>74 (77.1)</td>
<td>91 (70.0)</td>
<td>67 (75.3)</td>
<td>132 (77.7)</td>
</tr>
<tr>
<td>Duration of symptoms prior to presentation</td>
<td>7 (5–12)</td>
<td>7 (4–12)</td>
<td>7 (4–11)</td>
<td>7 (5–10)</td>
<td>7 (5–12)</td>
<td>9 (6–12)</td>
</tr>
<tr>
<td>Symptoms resolved on follow-up*</td>
<td>334 (80.0)</td>
<td>70 (92.1)</td>
<td>74 (83.2)</td>
<td>105 (89.0)</td>
<td>73 (89.0)</td>
<td>127 (79.9)</td>
</tr>
</tbody>
</table>

*19 participants did not know their HIV status; 5 women did not know if they were pregnant; follow-up information available for 393 participants.

STI, sexually transmitted infection.

**Figure 2** Presenting symptoms in study participants according to urine culture and STI test result. Severe symptoms were defined as positive urine culture and STI test result. Severe symptoms were defined as positive urine culture and STI test result.
antibiotics prior to presentation to primary care. While only 7% of the study participants reported antimicrobial use in the previous 2 weeks, 17% had evidence of antimicrobial activity in their urine. Although antibiotic access from pharmacies is highly regulated in Zimbabwe, antibiotics can be acquired from the informal market. Patients may not report on self-treatment at clinic presentation due to social desirability bias. Prior antimicrobial use was similar to that reported by patients from Senegal, which had a culture positivity of 27% but lower than that in studies from the USA. This suggests that asking patients about antimicrobials may not be sufficient in determining prior exposure as shown in findings from Ghana. On the other hand, the antibiotic bioassay may overestimate antimicrobial use for treatment of infections by also detecting antimicrobials consumed unintentionally in food and water. Alternative explanations for symptoms suggestive of UTIs such as dysuria include irritant hygienic products, spermicides and certain foods.

STIs are highly prevalent in some sub-Saharan African settings, and there is some symptom overlap between STIs and UTIs. A meta-analysis of studies from sub-Saharan Africa reported a pooled prevalence for *C. trachomatis* of 7.8% in women of reproductive age, while a study from Zimbabwe testing mainly asymptomatic adolescents and young people found a prevalence of 17% of *C. trachomatis* and/or *N. gonorrhoeae*. While STIs may be asymptomatic particularly in women, patients with symptoms due to STIs frequently experience diagnostic and treatment delays leading to prolonged symptoms prior to presentation. One of the study eligibility criteria included recent symptom onset (within 2 weeks). This was aimed at increasing the likelihood of UTIs compared with STIs. Despite this, STI prevalence in our study was almost 20%. Importantly, 1 in 15 women and 1 in 8 men tested positive for *N. gonorrhoeae*. The high prevalence of STIs may also explain the large proportion of men enrolled into the study who are generally more likely to experience symptoms from STIs which are similar to symptoms of UTIs. The study may have missed other STIs because testing was limited to three major pathogens but did not include other organisms that may cause urethritis and urinary tract symptoms such as *Mycoplasma genitalium*, leading to an underestimation of STI prevalence. Furthermore, STIs may have been missed because the study used mid-stream urine samples, while first-catch samples are recommended for the diagnosis of STIs for optimal yield on urine samples. Genital ulcers caused by herpes simplex and vaginitis due to *Candida spp.* may explain symptoms in some patients. Also, men were not tested for *T. vaginalis* as this is less frequent in men. Potential participants who did not seek care because of not being able to afford the clinic fees would have been missed.

Only a quarter of participants who tested positive for an STI underwent STI treatment on the initial clinic presentation because the attending nurse did not suspect an STI. This highlights the difficulties in differentiating the two conditions on clinical grounds. Access to diagnostic testing at primary care level is thus urgently needed. The prevalence of STIs is not generalisable to all primary healthcare attendees, as the participants were selected on the basis of STI/UTI symptoms.

**CONCLUSIONS**

This is the first study exploring the causes for negative urine cultures among adults presenting with UTI symptoms to primary care in a low-income setting. The findings of this study highlight the high STI burden in this patient population. The overlap in symptoms in patients diagnosed with UTIs and STIs, respectively, results in underdiagnosis and undertreatment of STIs. Diagnostic testing is paramount to ensure appropriate treatment. Very few participants who had an STI received appropriate treatment on clinic presentation because STIs were not suspected, emphasising the missed opportunities for diagnosis and treatment. The high prevalence of prior antibiotic exposure in patients presenting to primary care should prompt an improvement of regulations around antibiotic access to prevent development of antimicrobial resistance.

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**Competing interests** None declared.

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**Data availability statement** Data are available upon reasonable request. All data relevant to the study are included in the article. Data availability statement: the data

underlying this study can be obtained upon request by emailing the corresponding author.

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