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Antibiotic Overconsumption in Pregnant Women With Urinary Tract Symptoms in Uganda

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Background. Urinary tract infections (UTIs) are one of the most common bacterial infections in women. During pregnancy physiological changes, like frequency, mimic UTI symptoms, and therefore bacteriological cultures are needed to confirm the diagnosis. However, in developing countries antibiotic therapy is commonly initiated without culture confirmation.

Methods. We investigated the prevalence of bacteriuria among pregnant women with and without UTI symptoms in Uganda. In total 2 562 urine samples were evaluated with nitrite and leukocyte esterase tests, using urine culture and/or dipslide with species identification as reference.

Results. The prevalence of culture-proven UTI among pregnant women with UTI symptoms was 4%. Since treatment is initiated based only on the presence of symptoms, 96% were erroneously given antibiotics. Further, there is a high prevalence of resistance to commonly used antibiotics, with 18 % ESBL and 36 % multidrug resistant *Escherichia coli* strains. Nitrite, leukocyte esterase tests, and urine microscopy alone were of poor diagnostic value. Using dipslide, gynecologists and nurses, not trained in microbiology, were mostly able to identify *E. coli* and negative cultures. Mixed Gram-negative flora, suggesting fecal contamination was, however, in the majority of cases interpreted as a single pathogenic bacterium and would have resulted in antibiotic treatment.

Conclusions. To prevent excessive use of antibiotics, dipslide possibly supported by a combination of nitrite and leukocyte esterase tests can be used. Trained frontline health care professionals correctly diagnosed *E. coli* UTI and negative urine cultures, which would help preventing antibiotic misuse. In addition, regular screening for antibiotic resistance would improve correct treatment.

Keywords. urinary tract infections; *E. coli*; antibiotics; pregnant women; Uganda.

Urinary tract infections (UTIs) belong to the most common bacterial infections worldwide, primarily affecting women and are a frequent indication for antibiotic therapy [1]. In contrast, asymptomatic bacteriuria (ABU), is often benign and does not require antibiotic therapy in nonpregnant and otherwise healthy women [2]. However, during pregnancy, 25–30% of pregnant women with ABU are at risk of developing acute pyelonephritis [3], associated with complications such as preterm birth [4]. Although screening for and antibiotic treatment of ABU in pregnant women to reduce the risk of acute pyelonephritis is common in developed countries [5], the beneficial effects of such an intervention have recently been questioned [6].

In nonpregnant women, management of uncomplicated UTI relies on clinical diagnosis and empiric antibiotic therapy [7]. During pregnancy, physiological changes, such as micturation frequency, and during the later part of the pregnancy, also nocturia and suprapubic pain [8], may mimic UTI. Therefore, bacteriological diagnosis is particularly important during pregnancy, especially because antibiotic exposure in utero may have deleterious effects on the fetus [9]. However, in countries like Uganda, with limited diagnostic resources, diagnosis of UTI is based on clinical symptoms. Moreover, midwives hand out antibiotics free of charge to pregnant women with suspect UTI. The extensive and widespread use of antibiotics, dispensed without prescription, is a leading cause of resistance among pathogenic bacteria, thus complicating management of infections in the long run [10]. *Escherichia coli* and other Enterobacteriaceae account for the majority of UTI [1]. We recently reported high antibiotic resistance among *E. coli* isolates from Uganda compared to those from Sweden [11], further demonstrating this relation. The increasing antibiotic resistance calls for deliberate actions to change the current treatment policy. We speculate that a high proportion of pregnant women with lower UTI symptoms receive antibiotics without having an infection. The limited diagnostic services available in Uganda and other low-income countries, leading to overconsumption of antibiotics, is likely an important reason promoting the high prevalence of antibiotic resistance.

We here investigate the prevalence of bacteriuria in pregnant women with and without symptoms consistent with lower UTI

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and the antibiotic susceptibility of *E. coli* isolates in relation to the empirically prescribed antibiotics in Uganda. Further, the reliability of nitrate and leukocyte esterase tests, as well as microscopy for identification of bacteriuria in pregnant women, and lastly, the possibility to use point of care dipslide for urine culture in areas without clinical laboratories were investigated.

METHODS

Study Design and Patients

The current study was carried out in 4 steps with a total of 2562 patients out of which 1621 were pregnant women (Figure 1). In Uganda, 20 patients were randomly recruited on a daily basis. We first established the prevalence of bacteriuria using traditional urine culture in 578 women presenting with symptoms consistent with cystitis and in 595 asymptomatic pregnant women in Mulago hospital, Kampala, Uganda. Next we evaluated dipslide, as well as the nitrite and leukocyte esterase tests, in outpatients with symptoms consistent with cystitis. These are methods with potential for use in outpatient clinics without access to microbiological laboratory. The results were evaluated by a clinical microbiologist in parallel with a gynecologist, who was introduced to the method during 1 week with daily feedback on the results and interpretation. This part of the study was done at the Karolinska University Hospital, Stockholm, Sweden, and traditional urine culture was used as a reference (n = 469). Thereafter we investigated if these methods were possible to transfer to an antenatal clinic in Uganda. This part was performed by another gynecologist with only 3 hours introduction on how to culture urine samples and how to evaluate already precultured dipslides. The gynecologist was given immediate feedback on the interpretation of results. This part had primarily the aim to evaluate if it was possible for a gynecologist not trained in microbiology to distinguish *E. coli* from other bacterial growth and correctly evaluate no bacterial growth (n = 448). The different ways of introducing the gynecologists was based on the assumption that the situation will differ depending on where and how the dipslide will be used. Finally, we evaluated the same methods in Uganda, performed and evaluated by nurses alone in order to investigate if the tests could be used in clinical settings where no medical doctors are available. The 2 nurses were trained by the gynecologist, who himself had 1 week of prior training. They were first introduced to the method and how to culture urine samples. The following day, the gynecologist evaluated the samples together with them and gave them support during 1 week. The nurses analyzed the dipslide, nitrite, and leukocyte esterase tests independently of each other in outpatients with UTI symptoms (n = 472). Based on the diagnostic results, the nurses decided if the patient would get antibiotics. Traditional urine culture was used as reference method.

Urine Analyses

Nitrite and Leukocyte Esterase Tests

All urine samples were analyzed for nitrite and leukocyte esterase using Multistix 10 SG reagent strip (Siemens, Munich, Germany) following the manufacturer's instructions. Results were manually read and recorded by laboratory technicians in

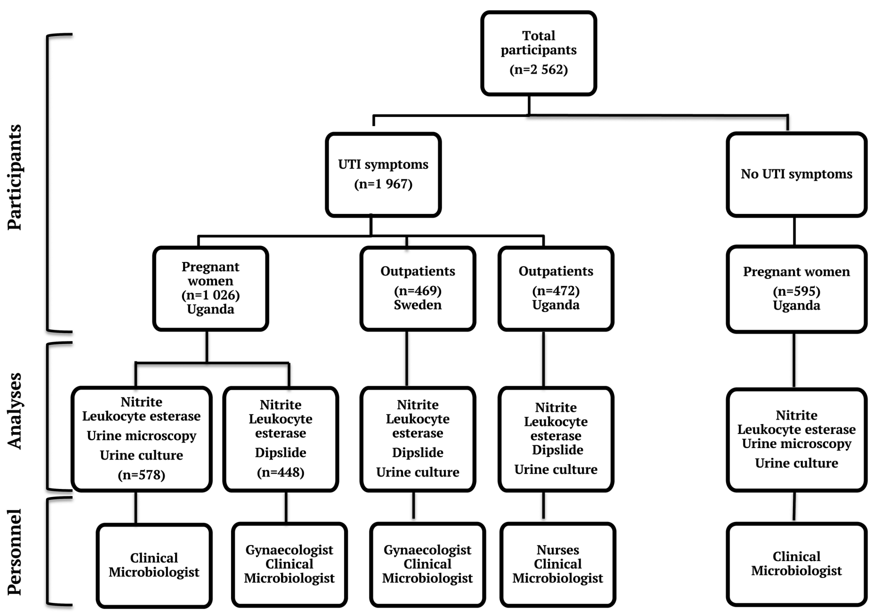

Figure 1. Study design. Urinary tract infection and asymptomatic bacteriuria were determined in a total of 2562 urine samples using nitrite and leukocyte esterase tests together with microscopy, dipslide and/or urine culture. Clinical microbiologists, gynecologists, and/or nurses did the evaluation as indicated. Abbreviation: UTI, Urinary Tract Infection.

Sweden and by laboratory technicians and nurses in Uganda. Nitrite and leukocyte esterase tests were evaluated together *vs* bacterial growth for calculation of sensitivity and specificity. Single growth of Enterobacteriaceae was regarded as significant, whereas growth of Gram-positive bacteria, mixed bacteria, and no growth were regarded as negative.

Microscopy Examination

In Uganda, urine samples were examined for the presence of leukocytes by light microscopy. An aliquot of approximately 3–5 mL well-mixed urine was centrifuged at 450× *g* for 5 minutes, the supernatant was decanted, and the pellet was suspended in approximately 1 mL urine. Fifteen microliters were transferred to glass slides and covered with coverslips. A qualified laboratory technician examined 10 fields at a 40× magnification using Olympus CX21 (New York Microscope Company Inc, US) light microscope; an average of >10 leukocytes per high power field was considered significant leucocyturia.

Bacteriological Culture and Dipslide

Samples from clean catch midstream urine were cultured according to standard procedures on blood and CLED (cystein lactose electrolyte deficient) agar (Bio-Rad, Budapest, Hungary) in Kampala, Uganda, whereas blood and chrome agar (Oxoid) were used in Stockholm, Sweden. UTI was defined by a bacterial concentration of $\geq 10^3$ CFU/mL of *E. coli,* other Enterobacteriaceae $\geq 10^4$ and $\geq 10^5$ for Gram-positive uropathogens [12]. In patients with ABU, significant bacteriuria was defined as $\geq 10^5$ CFU/mL [2]. All urine cultures were evaluated by clinical microbiologists.

In addition to traditional urine culture, dipslide culture, Uricult Trio (Orion Diagnostica, Espoo, Finland) was done on midstream urine. The dipslide has 3 culture media; CLED, MacConkey, and an *E. coli* specific agar based on β-glucuronidase activity [13] and monitored by brown-gray-black color change. Bacteria considered significant in bacterial culture were later species identified as described below.

Species Confirmation and Antibiotic Susceptibility Testing

In Uganda, species identification was confirmed by their biochemical profile. For Gram-negative bacteria indole, methyl red, Voges Proskauer, citrate, lactose, sucrose, glucose, urea, oxidase, and motility were used. For Gram-positive bacteria catalase, coagulase and novobiocin were used. Bacterial isolates were stored in deep agar tubes at +4°C before shipment to Sweden. To ensure diagnostic uniformity between Uganda and Sweden, all isolates, were species identified and antibiotic susceptibility testing performed also in Sweden. Species were confirmed biochemically using the VITEK 2 automated microbiology system for Gram-negative bacteria (GN card; bioMérieux, Marcy l'Etoile, France); or by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonik GmbH, Bremen, Germany) following the manufacturers' recommendations. Bacterial susceptibility testing was performed using the VITEK 2 system (AST-N217 card) for ampicillin, amoxicillin-clavulanic acid, ciprofloxacin, cephalexin, mecillinam, nitrofurantoin, and trimethoprim. Testing enabled identification of extended spectrum beta lactamase (ESBL)-producing isolates [14]. Isolates resistant to 3 or more antibiotic classes were classified as multidrug-resistant (MDR) [15].

Statistical Analysis

All statistical analyses were performed using GraphPad Prism, version 6 (San Diego, CA, USA). Differences between patient groups were analyzed using Mann-Whitney test, and prevalence data were compared by Fisher exact test. Differences with *P*-values <.05 were considered statistically significant.

RESULTS

Low Prevalence of Culture Verified Urinary Tract Infection Among Empirically Treated Pregnant Women

During pregnancy the symptoms used in the definition of UTI are common but unspecific complaints. We therefore sought to establish the prevalence of culture verified significant bacteriuria among pregnant women with UTI symptoms and the prevalence of culture verified ABU in the same group. Although there was no difference in age and parity between the 2 groups, the gestational age of women complaining of symptoms was slightly but significantly higher ($P < .05$), in line with the assumption that progression of pregnancy induces UTI-like symptoms (Table 1).

All pregnant women with UTI symptoms were given antibiotics, free of charge, in the antenatal clinic. However, only 4% (23/578) had significant bacterial growth, 17 of these (74%) due to Enterobacteriaceae, out of which 12 (52%) were caused by *E. coli.* ABU was observed in 2% (14/595) of the pregnant

Table 1. Characteristics of Study Participants. Urine Samples Were Collected From 1621 Pregnant Women With and Without Symptoms of Urinary Tract Infection

	Pregnant women UTI symptoms (n=1 026)		Asymptomatic (n=595)	
Characteristic	Median (Range)	n (%)	Median (Range)	n (%)
Age (years)	24 (16–42)		24 (16–42)	
16–20		206 (20)		144 (24)
21–30		698 (68)		398 (67)
31–42		120 (12)		53 (9)
Parity	1 (0–9)		1 (0–8)	
Nulliparous		370 (36)		219 (37)
1–4		604 (59)		359 (60)
≥ 5		52 (5)		17 (3)
Gestational age (weeks)	28 (4–41)		24 (6–40)	(p<0.05)
4–12		84 (8)		61 (10)
13–24		387 (38)		250 (42)
25–41		555 (54)		284 (48)

Abbreviation: UTI, Urinary Tract Infection.

women. Similarly, *E. coli* (n = 9, 66%) was the most common microorganism.

Commonly Used Antibiotics are Not Effective in Treatment of Urinary Tract Infection

We then evaluated the susceptibility pattern of *E. coli* to antibiotics used for pregnant women with UTI in Uganda. We found that 66% of *E. coli* were resistant to ampicillin here reported in place of amoxicillin because of its equivalence in spectrum of antimicrobial activity [16], 38% to amoxicillin-clavulanic acid, and 18% to cephalexin. Interestingly, only 8% were resistant to nitrofurantoin and 13% to mecillinam. Moreover, 18% of the *E. coli* strains were ESBL-producing and 36% were multidrug resistant (Figure 2).

Nitrite and Leukocyte Testing is Not Sufficient to Detect Urinary Tract Infection

To improve the diagnostic accuracy of UTI, we evaluated nitrite and leukocyte esterase tests, commonly available and largely affordable. To evaluate only one of these parameters was not effective in the diagnosis of UTI. In many countries the combination of nitrite and leukocyte esterase tests is performed to ensure true cystitis. The sensitivity, based on positive nitrite and leukocyte esterase tests was low, in samples from pregnant women with either cystitis or ABU. The specificity, on the other hand, was higher in both of these patient groups (Table 2).

No Correlation Between Microscopy and Leukocyte Esterase

In addition to the leukocyte esterase test, urine samples were microscopically analyzed for leucocyturia in pregnant women with (n = 578) and without (n = 595) UTI symptoms. Microscopy is in many countries still regarded as the golden standard for evaluating leucocyturia. However, the agreement between microscopy and leukocyte esterase test was only 18/47 (38%). Moreover, there was wide variation in the number of leukocytes reported per high power field, further underscoring the diagnostic challenges of microscopy in UTI.

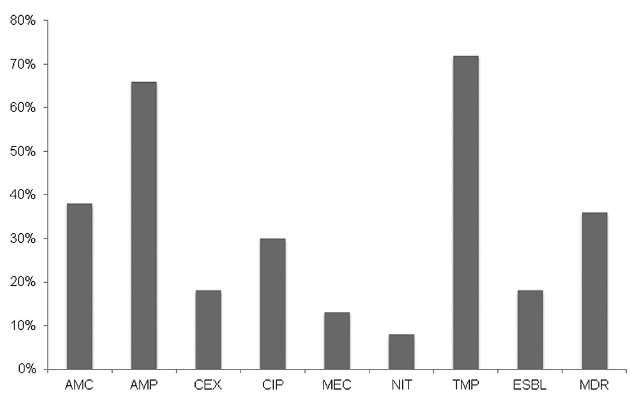

Figure 2. Antimicrobial resistance of *Escherichia coli* from pregnant women in Uganda to commonly used antimicrobial agents (n = 39). Abbreviations: AMC, amoxicillin-clavulanic acid; AMP, ampicillin; CEX, cephalexin; CIP, ciprofloxacin; ESBL, extended-spectrum beta-lactamases; MDR, multi-drug resistant isolates; MEC, mecillinam; NIT, nitrofurantoin; TMP, trimethoprim.

Table 2. Bacterial Growth in Urine Culture vs Nitrite and Leukocyte Esterase Tests

Country and Category of Participants	Nitrite Positive n (%)	Leukocyte Esterase Positive n (%)	Combined Nitrite and Leukocyte Esterase Positive	
			Sensitivity	Specificity
Sweden outpatients				
UTI symptoms (n = 469)	…	…	16%	73%
Culture results				
Enterobacteriaceae (n = 148)	76 (52)	55 (37)	…	…
Gram-positive bacteria (n = 39)	3 (8)	9 (23)	…	…
No significant bacterial growth (n = 282)	5 (2)	68 (24)	…	…
Uganda pregnant women				
UTI symptoms (n = 1026)	…	…	15%	66%
Culture results				
Enterobacteriaceae (n = 57)	16 (28)	37 (65)	…	…
Gram-positive bacteria (n = 18)	3 (17)	6(33)	…	…
No significant bacterial growth (n = 951)	97 (10)	298 (31)	…	…
Uganda pregnant women				
Asymptomatic (n = 595)	…	…	8%	91%
Culture results				
Enterobacteriaceae (n = 13)	2 (16)	4 (30)	…	…
Gram-positive bacteria (n = 1)	0 (0)	1(100)	…	…
No significant bacterial growth (n = 581)	1 (0.1)	67 (11)	…	…
Uganda outpatients			Nurse 1	
UTI symptoms (n = 472)	…	…	10%	80%
Culture results			Nurse 2	
Enterobacteriaceae (n = 61)	15 (24)	18 (30)	5%	79%
Gram-positive bacteria (n = 8)	1 (13)	0 (0)	…	…
No significant bacterial growth (n = 403)	17 (4)	76 (18)	…	…

The sensitivity and specificity was calculated based on the combination of these 2 tests vs bacterial growth. Single growth of Enterobacteriaceae was regarded as significant, whereas Gram-positive bacteria, mixed bacteria, and no growth were regarded as negative.

Abbreviation: UTI, urinary tract infection.

Dipslide Correlates Well With Urine Culture With Respect to *Escherichia coli*

The very low prevalence of culture-proven UTI among pregnant women in combination with poor help by leukocyte esterase and nitrite tests, low access to clinical laboratories, generous antibiotic use, and high antibiotic resistance observed in Uganda, prompted us to investigate the dipslide test, a culture test possible to use among outpatients.

The dipslide test was first evaluated in Sweden by a trained clinical microbiologist in parallel with, but independently of, a gynecologist who had 1 week training to evaluate dipslide. *Escherichia coli* was correctly identified in 98% and 87% of cases ($P < .01$ respectively), indicating its high reliability even for moderately trained persons. Apart from *E. coli*, other Gram-negative bacteria were correctly identified at a relatively high degree, with corresponding agreement between the clinical microbiologist and gynecologist (Figure 3).

Gynecologist Evaluating Dipslide Test in an Antenatal Clinic in Uganda

The encouraging results from dipslide performed also by a gynecologist inexperienced in clinical microbiology encouraged us to evaluate dipslide among pregnant women with UTI symptoms in an antenatal clinic in Kampala, Uganda. A gynecologist who had 3 hours introduction to the dipslide performed and evaluated the results. A clinical microbiologist validated the results.

The gynecologist correctly identified only 8 of 30 (27%) *E. coli* isolates, diagnosed all 40 samples with other Gram-negative bacterial growth but was not able to distinguish the mixed Gram-negative bacterial growth from single bacterial growth. Samples with no bacterial growth were correctly identified.

Nurses Mostly Made Correct Conclusions When Evaluating Dipslide

In Uganda most antenatal clinics are located in rural areas and run by nurses or nurse assistants with no or only occasional consultation by medical doctors. To decrease antibiotic consumption, the nurses have to be able to evaluate the diagnostic tests by themselves. Two nurses, with 1 day of introduction to the dipslide test and 1 further week of support, performed and evaluated the bacterial growth independently of each other. The nurses were also asked to evaluate the nitrite and leukocyte esterase tests and to conclude if they would have prescribed antibiotics. Of 472 urine samples, 69 were culture positive, and 22 revealed mixed Gram-negative bacterial flora suggesting contamination from the fecal flora. Nurses correctly identified 41/52 (79%) of *E. coli* and negative urine samples, with no bacterial growth. However, 20/22 (91%) of patients with mixed Gram-negative flora indicating fecal contamination would have erroneously received antibiotics (Figure 4). Moreover, the low sensitivity of the nitrite and leukocyte esterase dipstick resulted in limited diagnostic help.

DISCUSSION

Clinical diagnosis and empiric antibiotic therapy of UTI among pregnant women lead to massive antibiotic misuse, inadvertently rendering the first line of drugs ineffective. Diagnostic tests, easy to carry out and evaluate also by inexperienced staff, are therefore necessary.

In this study, we investigated a total of 2 562 patients for bacteriuria. Of these 1 621 were urine samples from pregnant women in Uganda with and without UTI symptoms, in order to verify the prevalence of cystitis and ABU. Because physiological changes during pregnancy might cause symptoms similar to cystitis, a low frequency of bacteriologically confirmed UTI among patients with symptoms was anticipated. Although the prevalence of UTI among pregnant women in our study is close to those reported regionally [17, 18], it is particularly alarming that our observations show that as many as 96% of patients are routinely treated with antibiotic therapy that they do not require. The positive correlation between antibiotic misuse and development of drug resistance [19] may in part explain the high antibiotic resistance seen in developing countries as we and others have demonstrated [11, 20].

To improve the diagnosis, we evaluated nitrite and leukocyte esterase tests and a simplified culture method, dipslide. In line with previous reports, nitrite and leukocyte esterase tests alone demonstrated insufficient diagnostic value in this study.

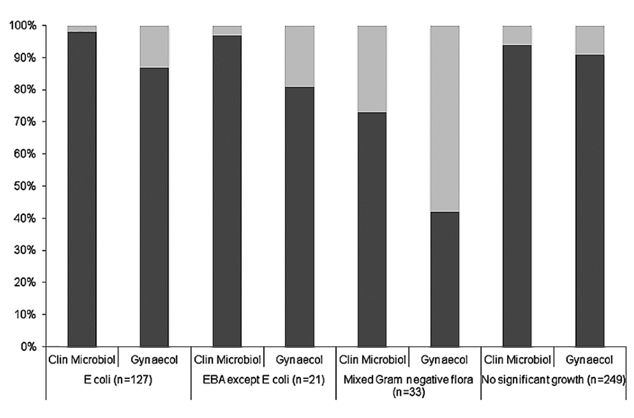

Figure 3. Dipslide testing performed in Sweden, comparison between clinical microbiologist and moderately trained gynecologist. Dark bars: results consistent with urine culture. Light bars: results different from urine cultures performed in the laboratory. Abbreviation: EBA, Enterobacteriaceae.

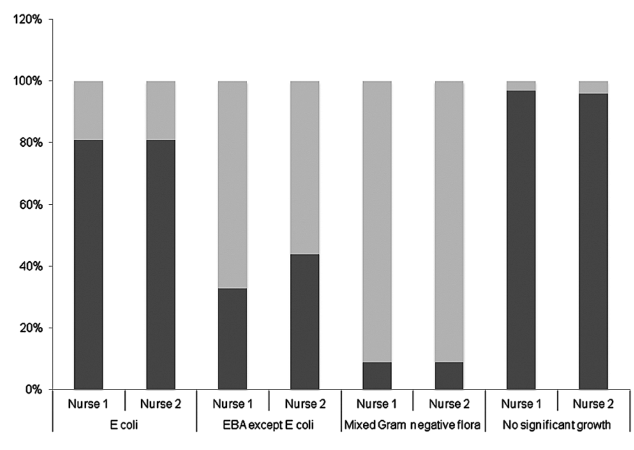

Figure 4. Dipslide testing evaluated independently by 2 nurses in Uganda; results were compared with urine culture and species identification. Dark bars: Results consistent with the laboratory. Light bars: Results different from urine cultures performed in the laboratory. Abbreviation: EBA, Enterobacteriaceae.

The combined results of these 2 tests demonstrated acceptable specificity and low sensitivity but were still of limited value. Although the nitrite test had high specificity, the sensitivity was low, especially among pregnant women, which is line with other studies [21] and may relate to frequent urination leading to reduced bacterial concentration. Further, presence of vitamin C in urine is another confounding factor [22], which cannot be ruled out among our patients.

During pregnancy, the specificity of urinary leukocytes as an indicator for bacteriuria per se might be questionable because of elevated urine specific gravity that may give false negative results [22]. Similarly, low sensitivity was obtained in urine samples collected from nonpregnant women. Moreover, false negative results have been reported with common antibiotics like cephalosporins [23]. Also, the poor correlation between enzymatic activity and microscopic detection of leukocytes in urine is a major concern. Even though microscopy is regarded as the golden standard for this analysis, high variability between replicate leukocyte counts suggest that the analysis suffers substantial draw backs, when performed in the clinical setting. Moreover, false negative results might be due to cell lyses if analysis is delayed. In addition, microscopic analyses of leukocyturia are time consuming if carried out with care. Taken together, detection of leukocytes especially using microscopy but also leukocyte esterase test are poor markers for the detection of UTI particularly among pregnant women and is in line with previous studies [24, 25].

The use of dipslide culture was, on the other hand, particularly rewarding in urine samples with no bacterial growth. These samples constitute the majority and were correctly diagnosed. Therefore, even in the hands of inexperienced healthcare providers this would substantially decrease the antibiotic use.

The identification of *E. coli* and other Enterobacteriaceae was also satisfactorily evaluated with the dipslide test even with inexperienced medical doctors and nurses. This can in part be attributed to the *E. coli*–specific agar containing β glucuronidase, resulting in a color change. However, false negative results can occur in rare cases if the strain lacks the enzyme [13]. Also, false positive results may occur among *Citrobacter* spp. [26]. Interestingly, we demonstrated that nurses with very limited training, and with no access to a professional microbiological laboratory or expert personnel, correctly diagnosed *E. coli* UTI in almost 80% of cases. To accurately define mixed fecal flora using dipslide [27] was problematic, and the nurses prescribed antibiotics in 91% of such cases. In the current study, contamination was observed in 5%, whereas others have demonstrated up to 10% [28], which would implicate risk of overinterpretation. Another drawback for dipslide culture especially among pregnant women is the failure to detect GBS, which is in line with observations made employing 2-medium dipslides [29].

Treatment recommendations differ between countries. In Uganda, pregnant women with UTI receive amoxicillin, amoxicillin/clavulanic acid, or cephalexin without laboratory verification and susceptibility testing, whereas nitrofurantoin or amoxicillin are recommended in Kenya, Tanzania, and Rwanda [30–32]. The use of nitrofurantoin and pivmecillinam are also recommended by international guidelines [33]. In our study, *E. coli* was highly resistant to many of the drugs used for treatment of pregnant women like 66% resistant to ampicillin (amoxacillin), 38% to amoxicillin/clavulanic acid, and 18% to cephalexin, which decreases the treatment options. In addition, we report a high ESBL prevalence (18%), even higher than the general ESBL prevalence in Africa [34]. As a consequence, almost all pregnant women presenting with UTI symptoms will receive antibiotics either not indicated at all or with high risk of being ineffective. International and East African regional guidelines recommend nitrofurantoin and during the last 2 trimesters also pivmecillinam. An appropriate alternative would therefore be nitrofurantoin or pivmecillinam, where low resistance is observed [30, 32, 33].

The high antibiotic consumption proves the importance of continuously reviewing the susceptibility pattern of uropathogens. It also calls for diagnostic methods possible to use in clinics with no access to laboratory service. To the best of our knowledge, this is the first study investigating the practicability of the dipslide culture test under clinically relevant conditions in a low-resource country. To introduce dipslide in clinical routine, possibly supported with nitrite and leukocyte esterase tests would substantially reduce the misuse of antibiotics. Healthcare professionals can learn to correctly evaluate samples with no bacterial growth. Compared to clinical diagnosis alone, the use of dipslide would imply substantially decreased antibiotic consumption and as a consequence decreased risk for development of resistance among bacterial pathogens. The massive amount of saved antibiotics might furthermore outweigh, at least in part, the costs associated with the increased diagnostic efforts.

Notes

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Potential conflict of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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