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The Importance of Diagnostics in the Treatment of Urinary Tract Infections in the United Kingdom

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Abstract: Current diagnosis of urinary tract infections (UTIs) in the UK initially relies on self-reported patient symptoms with no point-of-care test robust enough to accurately identify the causative pathogen and inform on antibiotic susceptibility. In serious UTI cases, standard urine culture is regarded as the gold standard for diagnosis and involves direct isolation, culture and antibiotic susceptibility testing of pathogens. These methods are not suitable in initial UTI diagnosis and treatment because of the time taken to conduct these analyses (≥3 days). Inaccurate and slow diagnostics can lead to unnecessary or incorrect antibiotic prescribing, which can lead to increased antimicrobial resistance and poorer patient outcomes. Novel point-of-care testing devices are urgently needed to improve the diagnostics of UTIs. In this article, we highlight novel point-of-care tests which are in development that can detect UTI-causing pathogens rapidly and accurately. These devices require additional studies to prove their clinical utilities. Adoption of these technologies can empower general practitioners (GPs) and pharmacists in prescribing decisions and improve antimicrobial stewardship.

Keywords: urinary tract infections, diagnostics, antibiotics, antimicrobial resistance, point-of-care test, vivalytic test

Introduction

Urinary tract infections (UTIs) include any infections associated with the bladder (cystitis), urethra (urethritis), ureter (ureteritis) or the kidneys (pyelonephritis) and are some of the most common infections in community and hospital settings.[1] The most common causative pathogens of UTIs are bacteria including *Escherichia coli, Proteus mirabilis, Enterococcus faecalis* and *Klebsiella pneumoniae*.[2–4] Less commonly, UTIs can be caused by fungi including *Candida albicans* or by viruses.[5] UTIs can be defined as uncomplicated or complicated depending on the severity of symptoms and patient presentation. Uncomplicated UTIs are where the infection is caused by common pathogens and there are no comorbidities or abnormalities of the urinary tract. Conversely, complicated UTIs can occur in patients with compromised urinary tracts and as a result these infections have an increased likelihood of difficulties.[6] UTIs and genital tract infections can be commonly misdiagnosed or underdiagnosed due to similar clinical symptoms and a lack of suitable diagnostics.[7]

UTIs disproportionally impact children, women and elderly individuals. In general, females are more at risk of UTIs because of anatomical differences including a shorter urethra than in males, which can allow easier pathogen colonization of the bladder.[8] In children, developmental and urinary problems including vesicoureteral reflux and bladder and bowel dysfunction can increase the risk of UTIs.[9] In elderly individuals, various factors including incontinence, catheterization and increased postvoid residual urine volume can increase the risk of UTIs.[10]

Worldwide prevalence of UTIs was estimated in 2019 at >404 million cases, which resulted in a loss of 520,200 disability adjusted life years and 236,790 deaths.[11] These estimates represented a substantial increase (>60%) in UTI infections worldwide compared to 1990 estimates. While the majority of UTI cases are resolved without the need for hospital admission, UTIs considerably impact secondary care. In England, over a 5-year period (2018–2023) there were 800,000 hospital admissions due to a primary diagnosis of a UTI and when a UTI was included as a secondary diagnosis an additional 160,000 patients were admitted to hospital.[12] It was estimated that the total cost to the National Health

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Service (NHS) in England between 2017 and 2018 for non-elective hospital admissions for kidney infections or UTIs was £386.1 million.[13] In the USA, in 2011, >400,000 (18.4 per 10,000 people) patients were admitted to hospital with a UTI at an estimated cost of >$2.8 billion associated with these admissions. Alarmingly, this study showed that UTI-related hospital admissions had increased by 52% between 1998 and 2011.[14]

Current UTI Diagnosis in the UK is Limited

Standard urine culture (SUC) is regarded as the gold standard approach to UTI diagnosis. SUC allows direct isolation of UTI-causing microbes and subsequent antibiotic susceptibility testing (AST). SUC is typically reserved for diagnosis of specific pathogens in patients with chronic or recurrent UTIs because of the time taken to isolate pathogens. Indeed, SUC usually cannot inform initial treatment options because culture times and subsequent susceptibility testing can exceed 72 hours.[15] SUC is also limited in diagnosing polymicrobial infections because it can favour growth of easy to culture aerobic microbes and may miss other disease-causing microbes including anaerobic microbes.[16] Additionally, SUC requires follow-up methods such as matrix-assisted laser desorption ionisation time of flight mass spectrometry (MALDI-TOF) to accurately give a species identification.[17] Diagnosis of infection through SUC usually relies on bacterial counts exceeding specific colony forming unit (CFU) cut-offs. These cut-offs, however, can range considerably with different laboratories adhering to different cut-off ranges. In governmental guidelines, CFU cut-offs vary according to pathogen identity, patient symptoms and sex. For example, in Public Health England guidelines (GW-1263), bacterial growth of 10^4–10^5 cfu/mL is usually indicative of a UTI. However, in symptomatic patients, culture growth of $>10^3$ cfu/mL is sufficient for *E. coli* and *Staphylococcus saprophyticus* diagnosis. There can be lower cut-offs ($>10^2$ cfu/mL, GW-1263) if urine has not been sterilely collected (voided) and even urine collection devices designed to improve sterility do not reduce the risk of urine contamination.[18] Additionally, the urine collection method, preservation and storage can majorly impact the results of urine culture.[19] While efforts have been made to standardize SUC[20] the time taken to obtain results limits its utility in informing initial treatment of UTIs.

The inability to conduct urine culture for all patients with a suspected UTI means that UTIs are primarily diagnosed in UK primary care through self-reported patient symptoms. Under current guidelines from the National Institute for Health and Care Excellence (NICE), UTIs are diagnosed primarily via the presence of key urinary symptoms. To diagnose UTIs in patients <16 years old, a urine dipstick test is conducted when patients present with UTI-like symptoms eg frequency, cloudy/ darker urine, and dysuria.[21] In men, a UTI diagnosis is confirmed based on urine culture only, and in women <65 years, guidance has recently changed, where a UTI diagnosis is now made based on the presence of two or more urinary symptoms ie dysuria, new nocturia, or cloudy urine.[22] To standardize general practitioner (GP) diagnosis, Public Health England and NHS Scotland have generated reference tools (based on NICE guidelines) for UTI diagnosis (GW-1263 and SIGN160, respectively). However, a recent study[23] demonstrated that both the GW-1263 and SIGN160 guidelines were insufficient for negative uncomplicated UTI diagnosis based on patient-reported symptoms and dipstick results.

To-date, the only rapid diagnostics test recommended to aid diagnosis of some patients with suspected UTIs are urine dipsticks. These are cheap tests which can be used to detect urine levels of nitrites, leukocyte esterase (LE) and red blood cells (RBC) within minutes. However, contradictory advice exists on the utility of urine dipsticks when diagnosing UTIs. Using Public Health England guidance (GW-1263), if a dipstick is negative for nitrite, LE and RBCs, a UTI is deemed less likely and other diagnoses may be considered. Various studies have indicated that urine dipsticks lack the sensitivity and specificity to accurately diagnose UTIs.[24–27] For example, Gurung et al[28] determined that urine dipstick screening for UTIs resulted in high false positive rates and a sensitivity of 43.75% and a positive predictive value of 35.59%. Another study demonstrated an area under the curve of 0.583 for a positive nitrite and LE result and when comparing dipstick diagnosis with SUC found insufficient agreement between both approaches with a Cohen's kappa value of <0.6.[29] Urine dipsticks are now not recommended for use in the diagnosis of UTIs in patients with catheters, in women aged ≥65 years or in men. Additionally, urine dipsticks are limited in that they cannot indicate the type of microbe causing infection and give no indication of antibiotic susceptibility. The lack of accurate and rapid diagnostic testing and the reliance on self-reported patient symptoms rather than empirical testing make accurate initial treatment (before culture results are obtained) of UTIs impossible at present.

Good Antibiotic Stewardship Relies on Accurate and Rapid Diagnostics

Inappropriate usage of antibiotics threatens the current and future control of pathogenic bacteria through the development of antimicrobial resistance (AMR). For example, the COVID-19 pandemic led to increased antibiotic misuse which resulted in increased antimicrobial resistance.[30,31] Many UTI-causing pathogens rapidly evolve antimicrobial resistance through various mechanisms including enzymatic inactivation of antibiotics, alteration of antibiotic target proteins and removal of antibiotics from pathogen cells via efflux.[32–34] Worldwide, a recent study estimated that in 2019, 4.95 million deaths were associated with bacterial AMR with 1.27 million of these deaths directly attributable to bacterial AMR.[35] Without sustained interventions, these numbers are likely to increase with a report predicting that worldwide, 10 million deaths per year will be attributable to AMR by 2050 with a cumulative cost to the worldwide economy of $100 trillion.[36] In England in 2022, overall antibiotic usage increased for the first time since 2014 with antibiotic consumption increasing across all healthcare settings.[37] In the UK in 2022, 58,224 infections were estimated to be caused by severe antibiotic-resistant microbes with 2202 estimated deaths associated with these infections.[37] While there is a clear need to develop new antibiotics to combat AMR,[38–40] a policy of antimicrobial stewardship is essential to slow the development of antibiotic resistance and is a key pillar in the UKs AMR action plan.[41] For good antimicrobial stewardship it is essential to select an appropriate drug and optimize its dose for the treatment of a specific infection. The problems associated with UTI diagnosis in the UK (discussed above) mean that good antimicrobial stewardship when treating UTIs is currently not achievable without accurate and rapid diagnostics.

While many UTIs self-resolve, primary treatment involves the use of antibiotics. In the UK, the primary antibiotics recommended for treatment of lower UTIs[42] and recurrent UTIs[43] are trimethoprim and nitrofurantoin. This advice differs in the European Union, where according to the European Association of Urology guidelines, trimethoprim is only regarded as an alternative antibiotic to be used to treat uncomplicated cystitis when local resistance for *E. coli* is low.[44] To determine UK-wide trends in UTI-related drug prescriptions we profiled available GP prescribing data for the last five years. From 2019–2023 the number of UTI-associated drug prescriptions per capita remained relatively stable across the four devolved nations of the UK (Figure 1). There were notable differences in the overall prescribing of UTI-associated antibacterials across the different nations. Scotland and Northern Ireland prescribe more trimethoprim compared to England and Wales, although trimethoprim usage has been declining in most nations. It is notable that in all nations of the UK, the prescription of methenamine hippurate has been increasing (Figure 1). Methenamine hippurate is an antiseptic which can be used as an alternative treatment to chronic or recurrent lower UTIs instead of antibiotics. NICE guidelines currently do not recommend its usage due to lower efficacy than antibiotic prophylaxis.[43] A recent study has, however, indicated that methenamine hippurate is not inferior to antibiotics in preventing recurrent UTIs and supported its use as a first-line treatment for recurrent UTIs.[45]

UK guidelines currently recommend three-day courses of trimethoprim and nitrofurantoin for uncomplicated lower UTIs in children and non-pregnant women.[42] A recent review into the use of nitrofurantoin demonstrated that this advice differs from most other international guidelines that instead recommend longer courses of nitrofurantoin.[52] Alarmingly, this review also highlighted that there is limited evidence supporting the clinical effectiveness of three-day courses of nitrofurantoin with NICE guidelines supported by the evidence of three-day course effectiveness for quinolones rather than nitrofurantoin. Indeed, some studies have indicated that three-day courses of trimethoprim and nitrofurantoin can lead to higher treatment failure rates when compared to five- or seven- day courses.[53] While shorter courses of antibiotics can reduce antibiotic usage and improve antibiotic stewardship, if antibiotic prescriptions are ineffective at clearing infection, this will inevitably cause increased antibiotic resistance.

There have been multiple reports of resistance to commonly used antibiotics for UTI treatment. A global report estimating deaths associated with bacterial antimicrobial resistance found that UTIs were the fourth highest cause of death, after respiratory tract infections, blood stream infections, and intra-abdominal infections.[35] A study in Northern Ireland reported a prevalence of trimethoprim resistance in 34.1% and 21.2% of *E. coli* and *Klebsiella* spp., respectively, with nitrofurantoin resistance reported in 8.8% and 30.3% of *E. coli* and *Klebsiella* spp., respectively.[54] Another study in Scotland reported trimethoprim resistance in 41.05% of *E. coli* isolates.[55] Increasing resistance to trimethoprim and nitrofurantoin threaten their continued usage. Despite these reports of high trimethoprim resistance, trimethoprim is still primarily prescribed in Scotland and Northern Ireland (Figure 1).

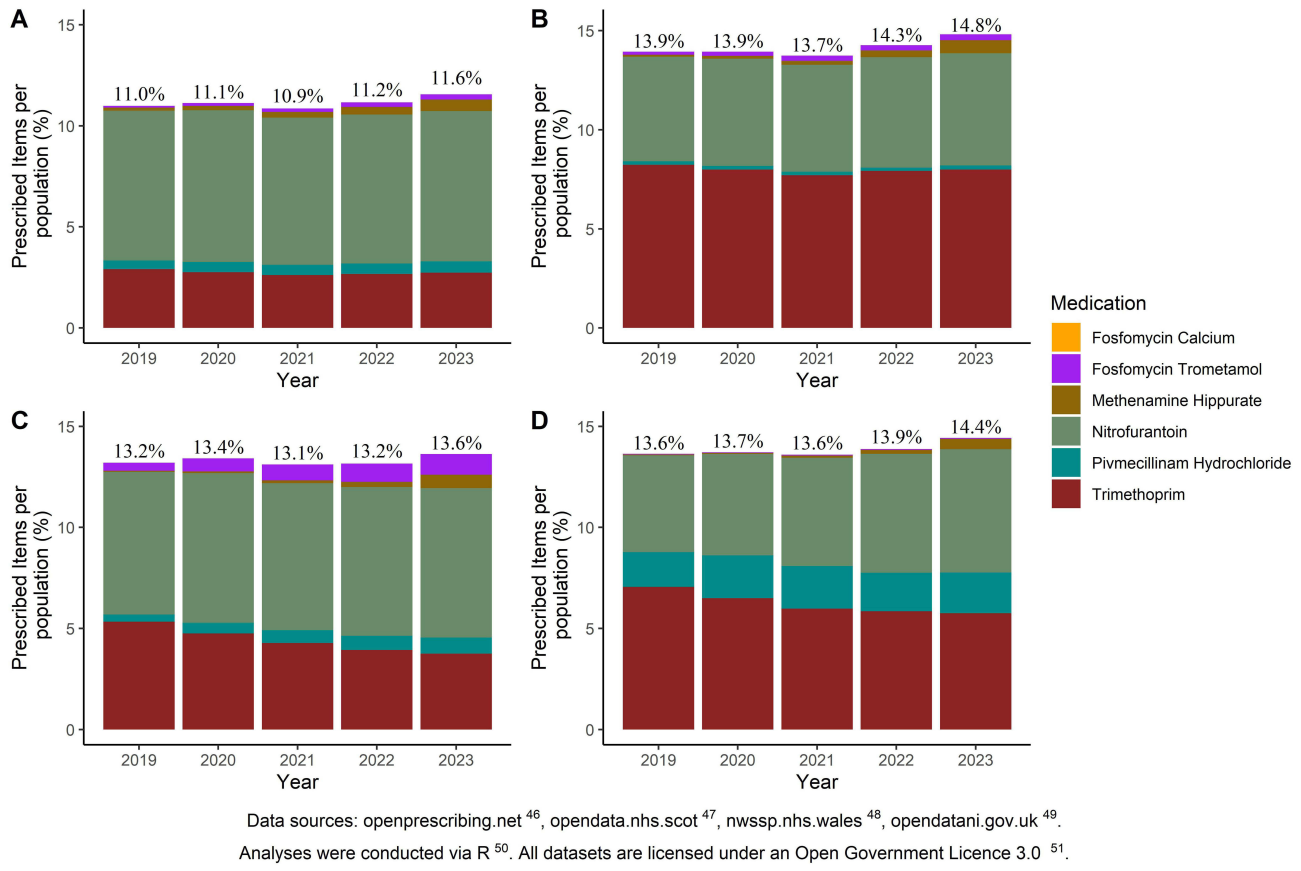

Figure 1 The number of general practice prescribed items per capita used to treat urinary tract infections (UTIs) in (**A**) England, (**B**) Scotland, (**C**) Wales and (**D**) Northern Ireland. Prescribing data for fosfomycin calcium (British National Formulary, BNF code 0501130S0), fosfomycin trometamol (BNF code 0501130D0 or 0501070AE), methenamine hippurate (BNF code 0501130H0), nitrofurantoin (BNF code 0501130R0), trimethoprim (BNF code 0501080W0) and pivmecillinam hydrochloride (BNF code 0501015P0) were obtained for England (openprescribing.net/),[46] Scotland (opendata.nhs.Scot),[47] Wales (nwssp.nhs.wales)[48] and Northern Ireland (opendatani.gov.uk),[49] and were normalized by the latest census population estimate for each nation. All analyses were conducted via R.[50] All datasets are licensed under an Open Government Licence 3.0.[51] Note that these data do not include all potential antibiotics that may be prescribed for UTI infections and not all of the antibacterials included may be exclusively used to treat UTIs.

Currently, in most of the UK, community pharmacies can issue antibiotics for uncomplicated UTIs in women aged 16–64 through the Pharmacy First systems based on local guidelines. UTI pharmacy prescriptions have been available in Scotland since 2020, Northern Ireland since 2022, and England since January 2024, with a limited number of pharmacies offering the service in Wales. Although improved access to treatment will undoubtably reduce pressures on primary care, there may be problems associated with treatment of UTIs via community pharmacies. In the UK, there are currently inconsistencies in the diagnosis of UTIs in community pharmacies. For example, in England, in the recently introduced Pharmacy First system, there will be no diagnostic tests (urine dipsticks) used.[56] Conversely, patients in Scotland with two key urinary symptoms must also have a positive nitrite dipstick result (NHS Scotland Patient group direction: PCA(P)(2022)26) and in Northern Ireland a dipstick test is required if patients only have one of three key diagnostic symptoms.[57] These inconsistencies in diagnosis criteria may lead to increased unnecessary antibiotic prescribing. Additionally, increased access to antibiotics with insufficient diagnostics in community pharmacies may exacerbate antibiotic resistance. Recently, in an open letter to the UK prime minister, a group of academics warned that access to antibiotics via community pharmacies could escalate antimicrobial resistance.[58] Instead, the authors suggested that the development of rapid and accurate diagnostics should be prioritized and would support pharmacies in the prescription of antibiotics.

Are We Approaching a New Age of UTI Diagnostics?

There are a number of new UTI diagnostic tools currently in development that will enable better diagnosis of UTIs and allow for more targeted treatment. NICE recently evaluated 12 point-of-care devices to improve antimicrobial prescribing

for UTIs.[59] These included five rapid (results in less than 40 minutes) and seven culture-based tests which are summarized in Table 1. All seven culture-based tests were not recommended in primary or community care settings because they were not expected to improve antimicrobial prescribing due to the time taken to obtain results. NICE determined that two tests (Sysmex Astrego PA-100 system with PA AST panel U-0501 and Savyon Diagnostics Uriscreen™) showed promise in directing antimicrobial prescribing but could not be currently recommended for use and required additional information on their accuracy and impact on antimicrobial prescribing in practice.[59] The Sysmex Astrego PA-100 system[60] uses nanofluidics and phase contrast microscopy to detect bacterial infection within 15 minutes and conduct AST within 30–45 minutes. However, this system is unable to perform bacterial species identification. The Uriscreen™ test[61] detects bacteriuria within two minutes by detecting urine catalase levels. However, it is not able to detect catalase-negative organisms (*Streptococcus* and *Enterococcus* spp. etc.) and a positive result still requires urine culture and AST testing to determine species identification and susceptibility to antibiotics.

Next generation sequencing (NGS) technologies have also been highlighted as an upcoming diagnostic tool for UTIs.[15] The detection of a urinary microbiota in healthy patients has refuted the idea that urine is sterile[67] and urinary microbiome sequencing can detect infection without the need for urine culture. Various studies have shown NGS approaches to UTI diagnosis have high sensitivity and specificity.[68–71] Additionally, NGS can detect bacterial resistance genes and can therefore inform on potential antibiotic susceptibility to sequenced isolates. However, NGS can take multiple days to get a result and requires expensive machinery and analysis pipelines, which prevent its use in point-of-care settings.

Polymerase chain reaction (PCR) methods can also be applied to diagnose UTIs. These methods work through amplification and detection of pathogen-specific DNA and can also include detection of antibiotic resistance genes. PCR allows for pathogen identification much faster than traditional SUC, with results possible within a few hours. A recent systematic review found that both multiplex PCR and reverse transcription PCR were comparable to SUC in

Table 1 Summary of NICE Evaluated Point-of-Care Devices for the Diagnosis of Urinary Tract Infections[53]

Diagnostic Device	Description	Species ID	AST	Additional Limitations
Rapid Tests (<40 minutes)				
PA-100 AST System (Sysmex Astrego)[60]	Initial detection of bacteriuria in 10–15 minutes. Assesses antibiotic sensitivity to five antibiotics within 45 minutes.	No	Yes	
Lodestar DX (Llusern Scientific)[62]	Detects six common UTI-causing pathogens within 40 minutes.	Yes	No	Limited to detection of six pathogens
TriVerity (Inflammatix)[63]	Can determine whether a blood-borne infection is bacterial or viral, along with severity of the infection.	No	No	Requires a blood sample
UTRiPLEX (Global Access Diagnostics)[59]	Detects urinary inflammatory biomarkers in six minutes	No	No	
Uriscreen (Savyon Diagnostics)[61]	Detects bacterial catalase in two minutes	No	No	Cannot detect catalase-negative pathogens
Culture-based tests (18–24 hours)				
Flexicult Human (SSI Diagnostica)[64]	Quantifies bacteria and assesses antibiotic susceptibility to five antibiotics	Yes	Yes	Requires overnight incubation at 35°C and manual colony counting
Uricult, Uricult trio, Uricult plus (Aidian)[65]	Detects bacteriuria in 16–24 hours.	Yes	No	Requires overnight incubation at 36°C and manual colony counting
Diaslide, DipStreak, ChromoStreak (Novamed)[66]	Detects bacteriuria in 16–24 hours.	Yes	No	Requires overnight incubation at 35–37°C and manual colony counting

Abbreviations: AST, antibiotic susceptibility testing; ID, Identification; UTI urinary tract infection.

terms of sensitivity and specificity.[72] A caveat of traditional PCR testing is that it is associated with higher costs and requires a molecular laboratory setup and a high level of technical expertise.[15] However, new innovations in developing automated PCR machines can circumvent these limitations. For example, the Bosch Vivalytic[73] developed with Randox Laboratories Ltd., is a fully automated point-of-care PCR platform which removes the need for laboratory equipment or highly trained staff to operate. Currently, the Vivalytic can be used in point-of-care settings to detect viruses including SARS-CoV-2 and Influenza A and B. Multiple studies have shown the high sensitivity and specificity of the Vivalytic for detection of SARS-CoV-2. In a study with 75 lower respiratory tract samples, the Vivalytic SARS-CoV-2 test had a sensitivity of 96% and a specificity of 100%.[74] Another study profiling 120 hospitalized patients demonstrated a sensitivity of 88% and a specificity of 96% when compared to an external molecular diagnostics laboratory.[75] Notably, a Vivalytic UTI test is currently being developed which can detect 16 pathogens and seven resistance genes (Supplementary Table 1) which can inform pathogen antibiotic susceptibility. In a preliminary evaluation of the Vivalytic UTI test in hospital patients, accuracies >90% were reported for the five most common UTI-causing pathogens in the study.[76] The Vivalytic could be deployed in any point-of-care setting including GP offices, care homes, sexual health clinics and diabetic clinics in order to provide rapid diagnosis in patients with suspected UTI diagnoses.

A recent analysis determined that current evidence to support the clinical effectiveness of point-of-care testing in UTI diagnosis is insufficient and requires further study.[77] Further investigations into the application of these potential diagnostic tools could be transformative to the treatment of UTIs across the UK. By accurately diagnosing the causative agents of UTIs early, appropriate treatments determined based on species identification and antibiotic susceptibility could allow for tailored usage of narrow spectrum antibiotics or modified antibiotic course durations which would improve antibiotic stewardship and limit antibiotic resistance. In addition, early diagnosis and more accurate treatment could reduce the number of UTI associated hospitalizations and associated costs.

Conclusions

The diagnosis of UTIs is a complex issue owing to the diverse causes and pathologies associated with the infections and the high potential for misdiagnosis. Current UTI diagnostic methods used in primary and secondary care have barely changed in decades and it is clear that the current approach to diagnosis of UTIs in the UK is insufficient. The current situation means that accurate diagnosis of the causative agents of the infections only come after treatment with antibiotics has already started. This leads to unnecessary usage of antibiotics that may not improve patient outcomes and that will lead to elevated antibiotic resistance. We have highlighted upcoming UTI diagnostic innovations that could transform the treatment and surveillance of urinary infections across the UK and worldwide. Further study and application of these new technologies into primary and secondary care could empower healthcare providers to make better decisions in UTI treatment and would help to fix an unsustainable system where treatment comes before accurate diagnosis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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