STRENGTHENING SURVEILLANCE SYSTEMS FOR ANTIMICROBIAL RESISTANCE IN URINARY TRACT INFECTIONS IN KENYA

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ABSTRACT

Background: Urinary Tract Infection (UTI) is one of the most common reasons for outpatient attendance and antibiotic use worldwide. Tackling the problem of antimicrobial resistance (AMR) in Low- and Middle-Income Countries such as Kenya requires laboratory surveillance systems that can correctly identify bacterial pathogens from urine samples and perform antimicrobial susceptibility testing (AST). In Kenya, there are many shortcomings to public-sector microbiology laboratories, including limited professional expertise in clinical interpretation of urine samples.

Methods: This project aimed to deliver training on identification and AST for staff at five hospital laboratories participating in the Kenyan AMR surveillance network. We made local needs assessments, delivered practical training sessions face-to-face and administered written and practical competency assessments for all participants.

Results: Trainings were conducted between November 2021 and January 2022 with a total of 13 laboratory staff trained. Participants had previously received a median of 2.3 months (IQR 1-7 months) of training time in microbiology. There was a substantial improvement in written assessment scores from a median of 46/100 pre-training (IQR 36-64) to a median of 90/100 post-training (IQR 85-92). The largest improvements were seen amongst staff with the lowest prior levels of microbiology training (MLS Diploma), though improvements were also seen for staff with BSc and MSc qualifications. Practical assessment included use of standardized organisms – all participants performed well in this practical assessment.

Conclusion: We found that prior to the training, all staff performed relatively poorly on a standardized assessment regarding knowledge and processing of urine samples. However, all staff substantially improved following this 5-day training delivered by a single trainer. We estimated that the cost of delivering this training for one hospital was approximately KES 500,000. Training microbiology staff in the accurate processing of urine sample will be an important activity for a Kenyan AMR surveillance system. These training materials, if delivered by an experienced trainer, can achieve a clear improvement in knowledge levels and practical competence.

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Chapter 1: INTRODUCTION AND BACKGROUND

1.1 Background and Introduction

Urinary tract infection (UTI) is amongst the most common conditions leading to outpatient visits and is also one of the most common causes of excessive or inappropriate antibiotic usage [1]. Addressing the problem of Antimicrobial Resistance (AMR) requires strengthening of AMR surveillance, particularly in low and middle-income countries (LMIC) like Kenya where UTI is a very common problem [2] [3]. It is responsible for about 70-80% of acute infections. Other gram-negative bacilli causing UTI infection include; *Klebsiella* spp, *proteus* spp, *Enterobacter, pseudomonas aeruginosa and Serratia.* Gram positive cocci causing UTI include *Enterococci, Staph saprophyticus, Staph aureus* and *Staph epidermidis* [4]. Urinary tract infection (UTI) being amongst the most common conditions leading to outpatient visits and is therefore one of the most common causes of excessive or inappropriate antibiotic usage leading to antimicrobial resistance [4] [5]. Antimicrobial resistance is a growing global threat that is increasing animal and human health concerns. Antimicrobial resistance arises when antimicrobial agents fail to effectively kill microorganisms that were previously susceptible to them. The emergence of AMR is attributed to imprudent antimicrobial use arising from inappropriate practices in prescription, misuse, and overuse [5] [6]**.** This leads to exposure of normal flora and pathogens to selection pressure leading to the emergence of antimicrobial resistant strains which can withstand and survive in the presence of antimicrobial agents which would initially kill them. These new strains can be spread from animals to humans and the environment. In low and middle-Income countries (LMICs), antibiotics are used for the treatment and prevention (prophylaxis) of infectious diseases in animals and humans. Most of these antibiotics are accessed from pharmacies and agro-veterinary shops over the counter without prescriptions from clinician's and veterinary professionals and the data on antibiotic use in these countries is scarce [1]. At the same time Health systems have limited capacity for correct laboratory identification of UTI pathogens in resource constrained Sub-Saharan Africa including Kenya [7] [5] [8]. During the current coronavirus disease 2019 (COVID-19) pandemic there are potential threats to delivery of healthcare that could affect antimicrobial stewardship activities and drive antimicrobial resistance [7] [8]. In Kenya most patients with urinary tract infections (UTI) are

treated empirically (meaning without a laboratory-confirmation of diagnosis), as very few facilities have a functional microbiology laboratory [2].

The services provided by public sector microbiology laboratories are limited because of shortages of suitable training, equipment, quality control procedures and professional expertise to make a correct clinical interpretation of urine cultures. These are the most important factors leading to lack of AMR data and therefore poor implementation of prudent AMU in public health. This leads to many microbiology laboratories in Kenya reporting normal flora as pathogens, testing or reporting irrelevant antibiotics, and identifying pseudo-resistance or other false positive results due to lack of suitable quality control measures [1]. At the most fundamental level, there is no cadre of clinical microbiologists in the county levels – these staff are needed to train and empower HCWs on diagnosing and treating specific infective conditions appropriately. Appropriate management of common infections is a critical antibiotic stewardship activity that will help control AMR [9]. Better laboratory diagnosis will inform appropriate management and help deliver AMR surveillance data. There is a huge gap of knowledge on the appropriate laboratory practices and which this project will try to address through delivery of training activities.

Kenya currently has an AMR surveillance system that uses the sentinel site surveillance approach, where a small number of selected institutions contribute data from different regions of the country. This AMR surveillance has been ongoing since 2018 and currently captures data from seven hospital laboratories: Machakos Hospital, Thika Hospital, Malindi Hospital, Kitale Hospital, Nyeri Hospital, Muranga Hospital and Makueni Hospital. There are current plans to add further sites to this surveillance network, potentially including the following hospitals: Nakuru Hospital, Jaramogi Oginga Odinga Teaching & Referral Hospital Kisumu, Bungoma Hospital, Coast General Hospital Mombasa, Kenyatta National Hospital Nairobi and Moi Teaching & Referral Hospital Eldoret. Data from these sentinel sites indicate high rates of resistance for respiratory and enteric infections indicating that many available antimicrobial regimens such as penicillins and cotrimoxazole are unlikely to be effective against common infections [10][11]. The National AMR Surveillance Strategy describes *E. coli*, *S.aureus*, *P.aeruginosa* and Acinetobacter spp. bacteria recovered from urine samples as priority organisms for AMR surveillance [12].

1.1.1 Aim

This project aimed to deliver training on the identification and antibiotic susceptibility testing of bacterial isolates from urine infections at hospitals participating in the Kenyan AMR surveillance network and to measure competency levels in staff participating in the training. More broadly, this work aimed to strengthen capacity of the AMR surveillance system in Kenya.

1.1.2 **Specific objectives**

1. To perform the needs assessment analysis on UTI processing in the selected sites via baseline visits
2. To deliver training to build skills and knowledge of laboratory staff using standardized training materials
3. To perform competency assessments for the laboratory personnel completing the training in objective 2.
4. To summarize data from competency assessments.

Chapter 2: METHODOLOGY

2.1 Sites

In consultation with staff from the AMR Secretariat (Prof. Gunturu Revathi), the following five hospitals were selected for this training project namely: Malindi County Hospital (Coast Region), Jaramogi Oginga Odinga Teaching & Referral hospital (Nyanza Region), Kitale County Referral Hospital (North Rift Region), Nakuru County Referral Hospital (South Rift Region) and Nyeri County Referral Hospital (Central Region). These hospitals are currently either part of the existing AMR surveillance network in Kenya or are planned to join it. There are also AMR surveillance sites that were not included in this training project: Thika County Hospital, Machakos County Hospital and Murang'a County Hospital (Figure 1).

Figure 1: A Map of Kenya showing the AMR Surveillance sites

2.2 Training Materials

Before the initiation of the visits to hospitals, different documents were developed in conjunction with Aga Khan University Hospital which included:

1. Checklist for performing the needs assessment analysis on UTI Surveillance in the selected sites
2. Training materials which were presented in form of PowerPoint slides
3. Question Answer report card used to score the performance of the laboratory staff (Appendix 1)

A pilot session using these materials was done at Aga Khan University Hospital to test the training materials. This was important to identify problems prior to the delivery of the training.

2.3 Delivery of Training Materials

A 5-day in-person training was delivered on urine sample processing at each of the 5 selected hospitals which targeted an average of 2-3 Laboratory staff trained by hospital. The trainings were delivered over a 5-day period at each hospital to allow for identification of suitable staff and incubation time for laboratory isolates. The planned schedule of the training was as follows:

1st day paying a courtesy call, administering a written pre-assessment and media preparation

2nd day intense training to laboratory staff and inoculation of the control organisms

3rd day reading the plates (organism identification, setting antimicrobial susceptibility testing)

4th day interpretation of the antimicrobial susceptibility testing

5th day written post-assessment competency and problem-solving discussions.

2.3.1 Competency Assessments

The competencies of the laboratory staff were assessed by giving them a written pre-assessment and post-assessment. A standardized practical assessment was achieved by use of 5 control organisms sent from National Public Health laboratory to the participating hospitals. These isolates were used for a post-training practical assessment using different organisms including 3 *Escherichia coli* with different AST patterns, 1 *Pseudomonas aeruginosa* and 1 *Proteus mirabilis* to evaluate as they would evaluate isolates from patient samples in the laboratory. The scores were calculated for each individual participant.

2.3.2 Data Management

Statistical analysis was performed using Excel and Stata for this project. Arithmetic means and medians were used to summarize data.

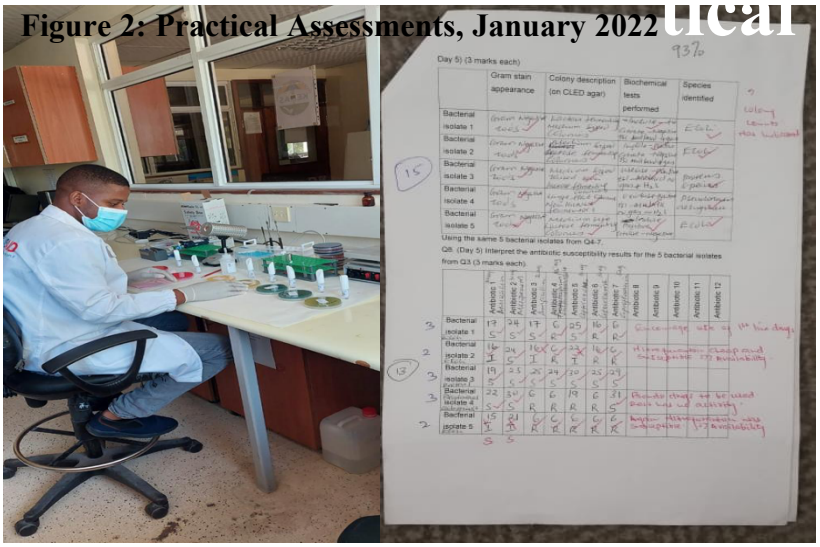


Figure 2: Practical Assessments, January 2022

Chapter 3: RESULTS

3.1 Results

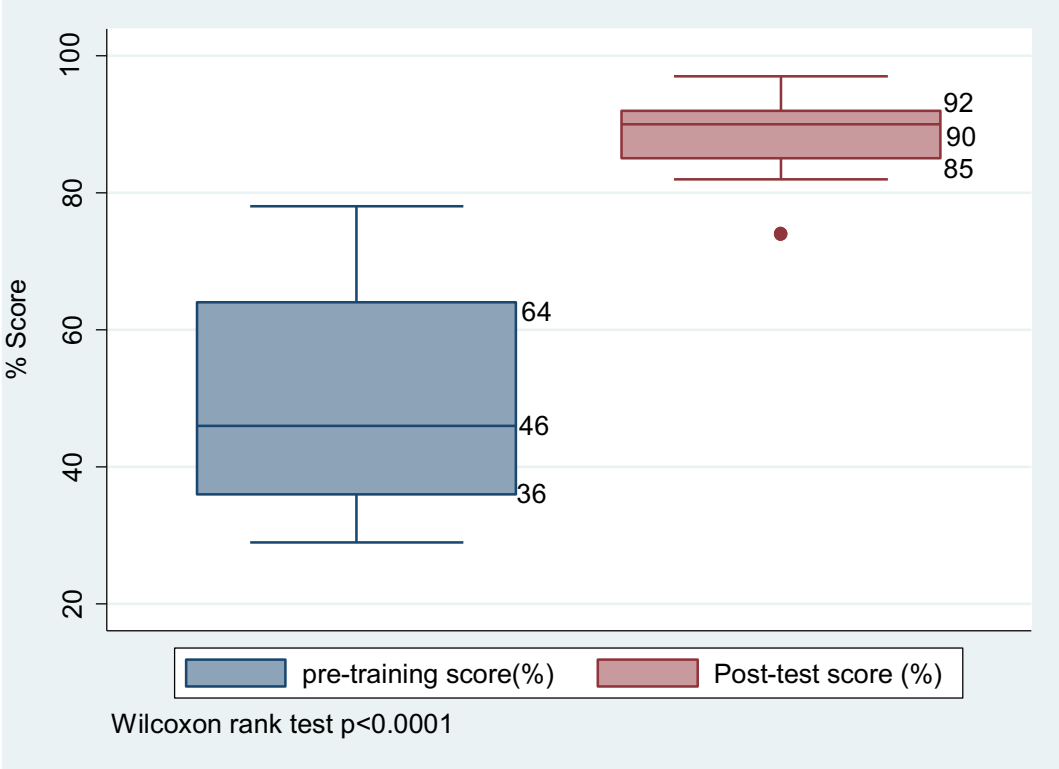
In the 5 selected sites for the training, the 1-day preparatory visit to each of the participating sites was done between October to November, 2021. This was valuable for assessing the capacity of the laboratory in readiness for the training. This was followed by the training which was conducted between November, 2021 and January 2022. The training was conducted by one person (Grace Bartonjo). At each site, either 2 or 3 laboratory staff were trained – these were all staff actively participating in microbiology work on clinical samples across the 5 hospitals. Out of 13 Laboratory staff trained, male were 8 against 5 females, the median number of years since qualification for these staff was 6 years (IQR 2-9 years). The median number of total months of microbiology training time was 2.3 months (IQR 1-7 months). The median pre-training score and post-training score was 46 and 90 percent (Table 1).

Data Variable	P25	P50	P75
Years since Qualification	2	6	9
Months of Microbiology training time	1	2.3	7
Pre-training score	36	46	64
Post-training score	85	90	92

Table 1: Working Experience

Performing non-parametric test Wilcoxon rank test to evaluate whether there was statistical difference between pre-training and post-training. The data showed that there is statistical difference (p-value<0.0001) (Figure)

Figure 3: Pre-training and Post-training



All participants improved from pre-to post- training assessment for 5-day training. The largest improvement in score was amongst from staff with lowest previous level of laboratory training (Table 2).

Qualifications	Pre-training score (%)	Post-training score (%)	Improvement (%)	Post-training practical (%)
Diploma MLS (n=6)	39.8	83.7	43.8	91.7
BSc MLS (n=5)	58.6	90	31.4	93.6
MSc Microbiology (n=2)	55.5	93	37.5	90
All (n=13)				

Table 2: Assessment scores by training

Chapter 4: DISCUSSION

4.1 Discussion

This 5-day training was delivered to staff working on the clinical microbiology service of 5 hospitals participating in the Kenyan AMR surveillance network. We found that prior to the training, all staff performed relatively poorly on a standardized assessment regarding knowledge and processing of urine samples, However, all staff substantially improved following a 5-day training delivered by a single trainer. The largest improvements in training score were seen amongst staff with the lowest previous level of microbiology training (MLS Diploma), though substantial improvements were also seen for staff with BSc and MSc qualifications. In a standardized practical assessment after completion of the training, all staff performed well. Due to positive response from the training, there is need to consider using these training materials in future to scale-up training or to have a step-wise expansion of this training to other AMR sentinel surveillance system to increase the numbers of participating sites. We also propose to have similar trainings repeated after 1 or 2 years depending on availability of resources, which will refresh the staff and build expertise in the processing of urine samples to give a high-quality AMR in relevant pathogenic bacteria.

The delivery of training to AMR surveillance network laboratory staff was possible but expensive, the approximate cost for training materials, travelling, accommodation, subsistence allowances, administration cost, stationary, among others for training 1 site to the 5-day training was approximately KES. 500,000. In future there is need to consider sensitization training to healthcare workers (Doctors, nurses & pharmacists) to acquire knowledge on the necessity of utilizing the microbiology laboratory in diagnosis of UTI and stop treating patients empirically.

Chapter 5: CONCLUSION

5.1 Conclusion and Future Works

Training microbiology staff in the accurate processing of urine sample will be an important activity for a Kenyan AMR surveillance system. These training materials, if delivered by an experienced trainer, can achieve a clear improvement in knowledge levels and practical competence for real-life microbiology identifications.

Future work

1. The findings from the project will be reported to the laboratories to assist in assessing their performance which will help improve or corrective action depending on the results
2. The findings will be disseminated to the policy makers for intervention purposes
3. Need to scale-up the training to other AMR surveillance sites
4. Follow up training to the same AMR surveillance laboratories as a refresher

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- Prof Gunturu Revathi, Department of Pathology, Aga Khan University Hospital, Nairobi
- Dr Alexander Aiken, London School of Hygiene and Tropical Medicine, UK

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Appendix

Appendix 1: Written Assessment

Briefly answer the following questions

Q1. Which bacteria are the most common causes of urinary tract infections?

Give names for the 5 bacteria (10 marks)

1. Escherichia coli

2. *Staphylococcus saprophyticus*

3. *Klebsiella* species

4. *Proteus species*

5. *Enterococcus* species

Q2. Which is the single most common bacterial species causing urine infections? Approximately what proportion of all urine infections are caused by this organism? (2 marks)

1. Escherichia coli

Causing approximately 80% of the total UTI

Q3. Write the meaning of the following medical terms around urine infection: (10 marks)

a) **Cystitis_** Infection of the urinary bladder

b) **Pyuria_**Pyuria is defined as >10 white blood cell (WBC) per high-power field in centrifuged urine.

c) **Pyelonephritis_**Infection of the kidneys

d) **Dysuria_** Painful urination is discomfort or burning with urination, usually felt in the tube that carries urine out of your bladder (urethra) or the area surrounding your genitals (perineum).

e) **Asymptomatic bacteriuria_** The presence of bacteria in the properly collected urine of a patient that has no signs or symptoms of a urinary tract infection. It's caused by bacterial colonization of the urinary tract.

Q4. What happens to a urine sample if it is left for more than 4 hours at room temperature? What methods are possible or how do you prevent these from happening (give 2 approaches)? (4 marks)

Any bacteria or cells present in a urine sample kept at room-temperature for more than one hour will continue to **use glucose (sugar) in the urine**. This may result in a falsely decreased urine glucose measurement

Also, bacteria produce ammonia which makes the urine more alkaline (increases pH).

If the urine sample isn't kept in a fridge, **the bacteria in it can multiply**. This may affect the test results.

Urine normally becomes hazy or cloudy, when let at room temperature. This can be reversed by adding few drops of acid.

If you can't hand your urine sample in within an hour, you should keep it in the fridge at around 4C for no longer than 24 hours.

Borate also **preserves white blood cells in urine** and thereby marginally improved the diagnosis of pyuria. The results confirm that boric acid may with benefit be added to bottles used for transporting specimens of urine to the laboratory.

Q5. Why is CLED agar commonly used for culture of urinary pathogens? (3 marks)

BD CLED Agar (Cystine-Lactose-Electrolyte-Deficient Agar) is a differential culture medium for use in isolating and enumerating bacteria from urine. It **supports the growth of urinary pathogens and contaminants** but prevents undue swarming of Proteus species due to its lack of electrolytes.

Q6. How do you quantify and report the bacterial counts? (2marks)

Count colonies on the plate. Multiply the number counted by 1000 to determine number of CFUs/ml in the original urine sample.

Q7. Describe factors that can affect antibiotic susceptibility testing, leading to inconsistent results (5marks).

1) Thickness of the sensitivity media
2) Number of discs put in one plate
3) Turbidity of the inoculum
4) Incubation time
5) Purity of the culture used