Baseline Study for Improving Diagnostic Stewardship at Secondary Health Care Facilities in Nigeria

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Abstract

Background

Blood culture diagnostics are a critical tool for sepsis management and antimicrobial resistance (AMR) surveillance. A baseline study was conducted to assess existing sepsis case finding, blood culture diagnostics and antimicrobial susceptibility testing (AST) at secondary health care facilities to inform the development of diagnostic stewardship improvement strategies in Nigeria.

Methods

A cross-sectional online survey was conducted among 25 public secondary health care facilities in Abuja, FCT and Lagos State in Nigeria to evaluate the capacity for pathogen identification and AST. Following this, data were prospectively extracted on all patients with suspected sepsis from electronic medical records at two facilities in Abuja from October 2020 to May 2021 to further assess practices concerning sepsis case-finding, clinical examination findings, samples requested, and laboratory test results. Data were descriptively analysed, and a multivariate logistic regression analysis was conducted to determine factors associated with blood culture requests among suspected sepsis patients.

Results

In the online survey, 32% (8/25) of facilities reported performing routine blood cultures. Only one had access to a clinical microbiologist, and 28% (7/25) and 4% (1/25) used standard bacterial organisms for quality control of media and quality control strains for AST, respectively. At the two facilities where data abstraction was performed, 7.1% (2924/41066) of patients were found to have suspected sepsis. A majority of the suspected sepsis patients came from the paediatrics department and were outpatients, and the median age was two years. Most did not have vital signs and major foci of infection documented. Blood cultures were only requested for 2.7% (80/2924) of patients, of which twelve were positive for bacteria, mainly *Staphylococcus aureus*. No clinical breakpoints were used for AST. Inpatients (adjusted odds ratio [aOR]: 7.5, 95% CI: 4.6 – 12.3) and patients from the urban health care facility (aOR: 16.9, 95% CI: 8.1 – 41.4) were significantly more likely to have a blood culture requested.

Conclusion

Low blood culture utilisation remains a key challenge in Nigeria. This has implications for patient care, AMR surveillance and antibiotics use. Diagnostic stewardship strategies should focus on improving access to clinical microbiology expertise, practical guidance on sepsis case finding and improving blood culture utilisation and diagnostics.

Background

In 2017, the Nigeria antimicrobial resistance (AMR) surveillance technical working group identified limited utilisation of diagnostics and inadequate laboratory quality assurance as major factors affecting
effective pathogen identification and antimicrobial susceptibility testing (AST) at health care facilities in Nigeria (1). This contributes to the spread of AMR and undermines the ability to make effective patient management decisions. It also hinders the development of a functional AMR surveillance system (2).

Blood culture diagnostic is a critical tool for guiding clinical therapy decisions among patients with suspected bloodstream infections and sepsis. Sepsis is defined as a “life-threatening organ dysfunction caused by a dysregulated host response to infection” (3). Sepsis is often caused by bacteria such as Staphylococcus aureus, Streptococcus pyogenes, Klebsiella spp., Escherichia coli, and Pseudomonas aeruginosa (3, 4). It is estimated that sepsis affects over 30 million people worldwide annually with six million deaths attributed to sepsis (5). Africa bears a disproportionately high burden of sepsis-related deaths with approximately two million cases (a figure that is suspected to be grossly underestimated) of sepsis-related deaths occurring in Africa each year (6). Blood culture diagnostics in suspected sepsis are often underutilised in low-resource settings such as Nigeria due to lack of financing for consumables (e.g., patients are often unable to cover the costs of such diagnostics), limited microbiological capacity, and inadequate reporting of results for use. This is especially true at secondary level facilities where shortages of human resources, laboratory infrastructure, logistics and financial resources are more acute (7).

According to the World Health Organization, diagnostic stewardship can be defined as the “coordinated guidance and interventions to improve appropriate use of microbiological diagnostics to guide therapeutic decisions. It should promote appropriate, timely diagnostic testing, including specimen collection, and pathogen identification and accurate, timely reporting of results to guide patient treatment” (8). The design and implementation of effective diagnostic stewardship strategies should be guided by a good understanding of the existing diagnostic capacities and practice.

We conducted a baseline study to assess existing sepsis case finding and the use of blood culture diagnostics, antimicrobial susceptibility testing (AST), and antimicrobial therapy at secondary health care facilities to inform the development of diagnostic stewardship improvement strategies in Nigeria.

Methods

The baseline study was conducted in the context of an ongoing collaboration between the Nigeria Centre for Disease Control (NCDC) and the Robert Koch Institute (Berlin, Germany), aimed at improving diagnostic stewardship and expanding antimicrobial resistance (AMR) surveillance capacity, particularly at secondary healthcare facilities in Nigeria.

This study consisted of two stages. In the first stage, a cross-sectional online survey was conducted in 2019 to evaluate the capacity for pathogen identification and AST at public secondary health care facilities in Abuja, Federal Capital Territory (FCT) and Lagos State in Nigeria. Abuja, the capital city of Nigeria located in the centre of the country, has three public tertiary and 21 public secondary health care facilities (9), as well as a range of community pharmacies and patent medicine vendors (i.e. informal drug sellers with minimal or no training) where patients can directly buy antimicrobials (10, 11). Lagos
has two public tertiary and 44 public secondary health care facilities (9). (12). The national AMR surveillance assessment checklist was sent to the head of the microbiology laboratory and Medical Directors, at 65 public secondary health care facilities in Lagos and FCT via email and WhatsApp. Of this, 25 hospitals completed the survey. The respondents were the heads of the laboratories in the selected health care facilities.

In the second stage, four health care facilities were selected (two in each state) because of their capacity to conduct blood culture diagnostics and antimicrobial susceptibility testing. In addition, taking into consideration urban/rural distribution of the hospitals, one health care facility was situated in an urban area and another in the rural setting. The on-site assessment of these facilities was conducted by a team of experts: two microbiologists, a medical doctor and an epidemiologist. A semi-structured assessment tool was adapted to focus on the availability of the following: staffing capacity in the laboratory, existing infrastructure including laboratory equipment, culture media production, IT facilities, and the quality management system.

From the two healthcare facilities in Abuja, existing practices related to sepsis case finding, pre-analytics, laboratory testing and post-analytics data were prospectively abstracted from the electronic medical record (EMR) systems, from October 2020 to May 2021. The selected secondary health care facilities in Abuja regularly use EMR systems, although some forms and archiving remained paper-based. EMR systems is a computerised system used in hospitals to accurately capture clinical operations and enable storage and tracking of patient clinical records such as patients demographics, medical history, medications, test results, costs of services provided as well as access patients state instantly (13).

Data from the electronic medical records (EMR) were extracted using a pretested tool adapted and developed using the Open Data Kit (ODK) v1.30.1 software (14). The tool was adapted from the WHO Proof-of-Principle (PoP) AMR Routine Diagnostics Surveillance Project Protocol and pretested before use (2). Extracted variables included sociodemographic, clinical examination findings, antibiotic use, samples requested, laboratory test results and therapy changes (i.e., pre-analytic, analytic, and post-analytic phases of the diagnostic pathway). Data abstracted included records of all patients with suspected bloodstream infection or sepsis in the following departments: Emergency, Paediatrics, Neonatal, Obstetrics and Gynaecology, General Outpatient and Medical wards. The terms used to search the electronics database included: “sepsis”, “septicaemia”, “septic shock”, “septic arthritis”, “neonatal sepsis”, “bacteraemia” and, patients without these diagnoses listed but got a blood culture request or test done.

Data was extracted 8:00am the following day after patient consultation, 72 hours after sample collection (for preliminary microscopy, culture and sensitivity results) and 10 days after sample collection (for final laboratory results) respectively. For patients whose results were not posted on the EMR, data were sourced from the laboratory registers. Daily data quality checks were conducted to assess and correct for missing and/or erroneous data. Six research assistants and two epidemiologist supervisors were trained on data collection methods/processes and extracted the data accordingly.
Data were cleaned using MS Excel 2019 and analysed using IBM SPSS Statistics 25 (15) and R-4.1.0 statistics (16). Using descriptive analysis, categorical variables were summarized using frequencies and proportions and numeric variables as medians and interquartile ranges (IQR). For proper analysis of the variables in the regression table, variables were recoded; antibiotics use pre-consult, was coded; thus, “No” and “Unknown” together as “No”; Department, was coded thus “Emergency” and “OPD” as “Others”. Antibiotic use was reported according to AWaRe classification of antibiotics: Access (i.e. first- or second-line treatments for common infections), Watch (i.e. applied only to a limited group of well-defined syndromes), Reserve (i.e. applied as a last resort to treat multi- or extensively-drug resistant bacteria) (17). Univariate and multivariate logistic regression analyses were conducted to assess factors associated with blood culture requests, such as patient age, gender, admission department, health insurance status, patient type, antibiotic use, and health care facility. Significant variables were added into the multivariate logistic regression model and adjusted odds ratio (aOR) with their corresponding 95% confidence intervals (CI) were reported, using a 5% significance for all statistical tests.

Results

Twenty-five secondary health care facilities participated in the online survey during the first stage of the baseline study (Table 1). Among these, only four laboratories (16%) reported the use of an electronic database for laboratory data management. While all facilities reported having at least one laboratory scientist and a technician, only one had a pathologist or clinical microbiologist. Four (16%) laboratories reported at least one staff having had a form of training on any of pathogen identification, AST and/or AMR data analysis in the preceding year. Although most [20, (80%)] laboratories reported having standard operating procedures (SOPs) for quality management, only 28% (7/25) reported use of standard bacterial organisms for quality control of media and only 4% (1/25) reported reference quality control strains for AST (Table 1). Eight (32%) of the laboratories reported performing routine blood culture diagnostics with a median of ten blood samples processed per month and six laboratories regularly performed AST. However, only one laboratory used any form of guideline to interpret the result of the AST test.
Table 1
Reported capacities and practices at participating secondary healthcare facilities in Abuja and Lagos, Nigeria, 2019

| Capacities and practices                                                                 | n (%) |
|----------------------------------------------------------------------------------------|-------|
| **N = 25**                                                                             |       |
| **A) Laboratory infrastructure**                                                       |       |
| i. Perform routine blood cultures                                                      | 8 (32)|
| ii. Perform routine cultures of urine, wound, stool and/or cerebrospinal fluid         | 24 (96)|
| iii. Perform routine AST                                                               | 22 (88)|
| iv. Regular supply of electricity including local back-up                              | 11 (44)|
| v. Has a database and information system for laboratory data management                 | 4 (16)|
| **B) Staff and training**                                                              |       |
| i. Has at least one pathologist                                                        | 1 (4)|
| ii. Has at least one laboratory scientist and technician                                | 25 (100)|
| iii. Has at least a data clerk                                                        | 8 (32)|
| iv. Trained laboratory staff in pathogen identification and AST in the preceding year   | 4 (16)|
| **C) Quality management**                                                              |       |
| i. Has SOP for sample collection and processing                                         | 21 (84)|
| ii. Has SOPS/workflows for the preparation and quality control of media                 | 20 (80)|
| iii. Use standard bacterial organisms for quality control of media                      | 7 (28)|
| iv. Has SOPs/workflows for the identification of bacterial isolates                    | 18 (72)|
| v. Use reference quality control strains for quality assurance of AST                    | 4 (16)|
| vi. Performs regular external quality assurance                                         | 1 (4)|

* SOP: Standard Operating Procedures, AST: Antimicrobial Susceptibility Testing

In the second stage of the baseline study, 7.1% (2924/41066) of all patients were found to have suspected sepsis at the two participating secondary health care facilities in Abuja, Nigeria from October 12, 2020, to May 15, 2021. This included 7.4% (1777/24129) with suspected sepsis at the rural health care facility and 6.8% (1147/16937) at the urban health care facility (Table 2). Most of these cases came from the paediatrics department 64.2% (1876/2924) and were outpatients 82.2% (2404/2924). More than half 52.1% (1523/2924) were males and the overall median age was two years (IQR: 6.2). (Table 2).
Only 13.2% (387/2924) of suspected sepsis patients had documented fever (>38°C) and a majority did not have documented heart rate 84.6% (2473/2924), respiratory rate 91.4% (2673/2924), or blood pressure 92.4% (2701/2924) measurements, respectively. Among 28.3% (827/2924) patients with a documented major focus of infection, gastrointestinal tract 14.8% (432/2924) and respiratory tract 7.1% (207/2924) were the most commonly recorded. A total of 54.4% (1591/2924) patients had a documented full blood count (FBC) including 3.3% (97/2924) with a leukocyte count of < 4000 mcL and 12.2% (357/2924) with a count of > 12000 mcL; 24.1% (705/2924) were reported as positive for malaria parasite. (Table 2).
### Table 2
Characteristics of suspected-sepsis patients in two secondary healthcare facilities, Abuja, October 2020 to May 2021

| Characteristics                          | n (%)  |
|-----------------------------------------|--------|
|                                         | N = 2924 |
| Hospital                                |        |
| Rural                                   | 1777(60.8) |
| Urban                                   | 1147(39.2) |
| Age                                     |        |
| ≤ 5 years                               | 2105 (72.0) |
| 6–14 years                              | 430 (14.7) |
| 15–34 years                             | 197 (6.7) |
| 35–54                                   | 130 (4.4) |
| ≥55 years                               | 62 (2.1) |
| Sex                                     |        |
| Male                                    | 1523 (52.1) |
| Female                                  | 1401 (47.9) |
| Place of residence (LGA)                |        |
| Bwari                                   | 1858 (63.6) |
| Abuja Municipal Area Council (AMAC)     | 928 (31.7) |
| *Other                                   | 138 (4.7) |
| Patient type                            |        |
| Outpatient                              | 2404 (82.2) |
| Inpatient                               | 418 (14.3) |
| Emergency                               | 102 (3.5) |
| Department                              |        |
| Paediatric                              | 1876 (64.2) |
| General outpatient                      | 477 (16.3) |

*Other includes Abaji, Gwagwalada, Kuje, Kwali, Outside Abuja and Unknown

**Other includes ear, throat, eye, left leg, neck, muscles, pelvis
| Characteristics                          | n (%)     |
|-----------------------------------------|-----------|
|                                        | N = 2924  |
| Emergency                               | 491 (16.8)|
| Neonatal                                | 41 (1.4)  |
| Female/male medical ward                | 23 (0.8)  |
| Obstetrics and Gynaecology              | 16 (0.5)  |
| Temperature (°C)                        |           |
| <36                                     | 28 (1.0)  |
| 36–38                                   | 1141 (39.0)|
| >38                                     | 387 (13.2)|
| Unknown                                 | 1368 (46.8)|
| Heart rate (beats/min)                  |           |
| ≤90                                     | 312 (10.7)|
| >90                                     | 139 (4.8) |
| Unknown                                 | 2473 (84.6)|
| Respiratory rate (breaths/min)          |           |
| ≤20                                     | 53 (1.8)  |
| >20                                     | 198 (6.8) |
| Unknown                                 | 2673 (91.4)|
| Systolic blood pressure (mmHg)          |           |
| <100                                    | 24 (1.0)  |
| 100–130                                 | 116 (4)   |
| >130                                    | 83 (2.8)  |
| Unknown                                 | 2701 (92.4)|
| Neurologic characteristics              |           |
| Altered mental state                    | 22 (1)    |
| Conscious and alert                     | 901 (30.8)|

*Other includes Abaji, Gwagwalada, Kuje, Kwali, Outside Abuja and Unknown

** Other includes ear, throat, eye, left leg, neck, muscles, pelvis
| Characteristics                        | n (%)     |
|---------------------------------------|-----------|
| **N = 2924**                          |           |
| Not specified                         | 1996 (68.3)|
| Suspected focus of infection          |           |
| Gastrointestinal                      | 432 (14.8)|
| Respiratory tract infection           | 207 (7.1) |
| Skin or soft tissue                   | 46 (1.6)  |
| Bone or joint                         | 25 (0.9)  |
| Urinary tract                         | 24 (0.8)  |
| Wound or burn                         | 24 (0.8)  |
| Central nervous system                | 21 (0.7)  |
| Genital                               | 10 (0.3)  |
| Cardiac                               | 7 (0.2)   |
| Other*                                | 31 (1.1)  |
| Not stated                            | 2097 (71.7)|
| Leukocyte count (mcL)                 |           |
| < 4000                                | 97 (3.3)  |
| 4000–12000                            | 1135 (38.8)|
| >12000                                | 357 (12.2)|
| Unknown                               | 1335 (45.7)|
| Neutrophils (mcL)                     |           |
| <1500                                 | 25 (0.9)  |
| 1500–8000                             | 4 (0.1)   |
| >8000                                 | 1560 (53.3)|
| Unknown                               | 1335 (45.7)|
| Malaria parasite test                 |           |
| Positive                              | 705 (24.1)|

*Other includes Abaji, Gwagwalada, Kuje, Kwali, Outside Abuja and Unknown

** Other includes ear, throat, eye, left leg, neck, muscles, pelvis
Out of 2,924 patients with suspected sepsis, blood culture was requested for 80 (2.7%) patients, and among these, 57 (71.3%) had a blood sample drawn for blood culture diagnostics. Twelve (21.0%) of these samples were positive for bacteria, a majority *Staphylococcus aureus* (Fig. 1). No clinical breakpoints were used for AST and resistance was reported only by visual inspection. Half of the *S. aureus* isolates were reported resistant to erythromycin although inconsistencies in antibiotic discs tested were found and no susceptibility or resistance to oxacillin was tested.

Among patients with suspected sepsis, the proportion on antibiotics increased from 15% (440/2924) pre-consultation to 67% (1958/2924) after consult following contact with the doctor. After consultation, more antibiotics in the Watch category (66.8%, 1628/2436 antibiotic prescriptions) for suspected sepsis patients were prescribed compared to the Access category antibiotics (33.2%, 808/2436; Table 3). The proportion of Access antibiotics used pre-consult was 47.5%, which reduced to 33.2% after consultation. The commonest antibiotics used in the Access category were Amoxicillin combination, Gentamycin and Metronidazole, while Cefuroxime, Ceftriaxone Cefpodoxime constituted the commonest antibiotics in the Watch category (Table 3).
### Table 3
AWaRe classification of antibiotics pre and post hospital consultation in two secondary healthcare facilities Abuja

| Antibiotics used          | Reported prior to consult | %     | Prescribed after consult | %     |
|---------------------------|---------------------------|-------|--------------------------|-------|
| **ACCESS group**          | N = 251                   |       | N = 808                  |       |
| Amoxicillin combination   | 197                       | 78.5  | 419                      | 51.8  |
| Gentamycin                | 23                        | 9.2   | 268                      | 33.2  |
| Metronidazole             | 23                        | 9.2   | 101                      | 12.5  |
| Other                     | 8                         | 3.2   | 20                       | 2.5   |
| **TOTAL (ACCESS)**        |                           | 33.2  |                          | 47.5  |
| **WATCH group**           | N = 277                   |       | N = 1628                 |       |
| Cefuroxime                | 114                       | 41.2  | 667                      | 41.1  |
| Ceftriaxone               | 34                        | 12.3  | 323                      | 19.8  |
| Cefpodoxime               | 50                        | 18.1  | 236                      | 14.5  |
| Cefixime                  | 48                        | 17.3  | 210                      | 12.8  |
| Ciprofloxacin             | 18                        | 6.5   | 100                      | 6.2   |
| Other                     | 13                        | 4.7   | 92                       | 5.6   |
| **TOTAL (WATCH)**         |                           | 66.8  |                          | 52.5  |

Suspected sepsis patients at the urban healthcare facility were significantly more likely to have a blood culture requested than those at the rural healthcare facility (adjusted odds ratio [aOR]: 16.9, 95% CI: 8.1–41.4). Furthermore, inpatients were significantly more likely to have a blood culture requested than emergency and outpatients (adjusted odds ratio [aOR]: 7.5, 95% CI: 4.6–12.3) (Table 4). Factors such as health insurance status and age did not appear to play a significant role in affecting blood culture request. The model significance was < 0.001 and our model explains 25% of the variations in the outcome (blood culture request).
| Variable | Blood culture request | Bivariate | Multivariate |
|----------|-----------------------|-----------|--------------|
|          | Yes (%) | No (%) | OR(95% CI) | aOR(95% CI) |
| Hospital |          |         |           |            |
| Urban    | 73 (6.4) | 1074 (93.6) | 17.2 (7.9–37.5) | **16.9 (8.1–41.4)** |
| Rural    | 7 (0.4) | 1770 (99.6) | Reference | Reference |
| Age (Years) |          |         |           |            |
| <=5      | 54 | 2051 | 0.3 (0.1–0.8) | 0.7 (0.2–2.1) |
| 6–14     | 8 | 422 | 0.2 (0.07–0.7) | 0.7 (0.2–2.8) |
| 15–34    | 7 | 190 | 0.4 (0.1–1.4) | 0.5 (0.1–1.8) |
| 35–54    | 6 | 124 | 0.6 (0.2–1.9) | 0.6 (0.2–2.5) |
| ≥ 55     | 5 | 57 | Reference | Reference |
| Gender  |          |         |           |            |
| Female   | 41 (2.9) | 1360 (97.1) | 1.1 (0.7–1.8) | - |
| Male     | 39 (2.6) | 1484 (97.4) | Reference | - |
| Health insurance status |          |         |           |            |
| Not enrolled | 64 (2.9) | 2131 (97.1) | 1.3 (0.8–2.3) | - |
| Enrolled | 16 (2.2) | 713 (97.8) | Reference | - |
| Patient type |          |         |           |            |
| Inpatients | 42 (10.0) | 376 (90.0) | 7.6 (4.7–12.0) | **7.5 (4.6–12.3)** |
| Emergency | 3 (2.9) | 99 (97.1) | 2.1 (0.6–6.8) | 1.1 (0.2–3.7) |
| Outpatients | 35 (1.5) | 2369 (98.5) | Reference | Reference |
| Patients on antibiotics before consultation |          |         |           |            |
| Yes      | 4 (0.9) | 436 (99.1) | 0.3 (0.1–0.8) | 0.8 (0.2–2.0) |
| No       | 76 (3.1) | 2408 (96.9) | Reference | Reference |
| Patients on antibiotics after consultation |          |         |           |            |
| Yes      | 49 (2.5) | 1909 (97.5) | 0.8 (0.5–1.2) | - |

*Significant values are in bold*
### Discussion

In Nigeria, three components of the health care sub-system are the primary, secondary and tertiary levels, governed by the Local government area, State and Federal levels respectively. The secondary health care facility exists to “provide specialised services to patients referred from the primary health care level through out-patient and in-patient services at hospital centers for general, medical, surgical and paediatric patients” (18). Users of secondary health care facilities often live within the same administrative area, which is different from tertiary hospitals where at least half of the clientele reside out of State, seeking highly specialised services and care at such facilities.

Desire to have access to quality health services, competent staff especially being seen by a doctor and access to equipment required for clinical investigation, thereby avoiding subjective diagnosis, are key reasons for seeking higher levels of care in Nigeria (19, 20). However, an assessment of the 25 hospitals in Lagos and Abuja (former and present capital cities of Nigeria) showed that laboratory infrastructure remains weak at secondary health care facilities as only a few of the laboratory staff had received training on pathogen identification, used SOPs or had access to information technology tools, and amplifies the dearth of pathologists and microbiologist. Laboratory diagnostics such as antimicrobial susceptibility testing should guide the management of health conditions caused by bacteria such as sepsis. But, limited access to such services impedes accurate diagnosis and results in poorer health outcomes among patients. It also hinders availability of quality microbiologic data to inform empiric treatment guidelines, thus highlighting of strengthening AMR surveillance in Sub-Saharan Africa with evidence-based interventions that use participatory approaches (21, 22).

At the two health facilities where data were abstracted over seven months, less than one in ten of patients in the department studied were found to have suspected sepsis, largely among children 1–5 years from the paediatric outpatient department. The preponderance of sepsis among paediatric patients is similar to other local studies in Nigeria and low-resource settings (23–25). This is likely the result of poor access to vaccines and other prevention and control measures for common preventable infections among children. However, the finding may also be influenced by sepsis case-finding practices at the facilities. Most patients with suspected sepsis did not have their vital signs documented. This may be due to the lack of patient notes and quality data capture, but it is also related to the choice of clinical criteria which doctors and nurses measure, record and use during clinical examinations. Evaluation of vital signs (i.e., body temperature, heart rate, respiratory rate, and blood pressure) is an important triage examination of both children and adults for early recognition, diagnosis, and management of sepsis (26), particularly for

| Variable | Blood culture request | Bivariate | Multivariate |
|----------|-----------------------|-----------|-------------|
|          | Yes (%) | No (%) | OR(95% CI) | aOR(95% CI) |
| No       | 31 (3.2) | 935 (96.8) | Reference | - |

*Significant values are in bold
patients admitted in the emergency setting (mainly in overloaded and most resource-limited ones). In low-resources settings, the systemic inflammatory response syndrome (SIRS) criteria (i.e., fever or hypothermia, tachycardia, tachypnea, leukocytosis, or leukopenia) and, more recently, the quick Sequential Organ Failure Assessment (qSOFA) criteria (i.e. increased respiratory rate, altered mentation, decreased systolic blood pressure) have often been cited as screening tools to identify patients with suspected sepsis. However, their usefulness in routine practice has been questioned given that the SIRS criteria have demonstrated high sensitivity but low specificity and the qSOFA was validated on patients that already had suspected infection (7). In a review on the best practices of blood cultures in low- and middle-income countries, Ombelet et al suggest a revised set of clinical indications for sampling blood cultures that could be more feasible in such settings including fever or hypothermia and one sign of severity (e.g., hypotension, confusion, increased respiratory rate, suspicion of severe localised infection, or suspicion of other severe infection) (7).

Identification of the focus of infection is also important in sepsis management and optimisation of treatment, especially for cases where a site of infection can be removed or drained, as seen in abdominal infections and soft-tissue abscesses. Although this study found the gastrointestinal and respiratory tracts to be common foci of infection among the suspected sepsis patients as seen in other Nigerian studies, most patients did not have foci of infection recorded, highlighting again potential areas for improvement during clinical examination and data recording (23, 24). In our study, 1 out of 5 suspected sepsis patients tested positive for malaria parasite. Malaria is a common cause of fever with significant morbidity and mortality in Nigeria (29–31) and fever is also a common symptom of sepsis. While people who contract malaria are at risk of developing sepsis and could potentially benefit from antibiotics, especially in malaria-endemic regions and low resource settings like Nigeria (32), the evidence is conflicting. Guidance on diagnostic stewardship and sepsis case finding should also consider malaria diagnostic using the rapid diagnostic test and early treatment while awaiting blood culture result.

Blood culture is considered crucial to isolate microorganisms, guide appropriate antimicrobial therapy, and improve sepsis management. Only 2.7% of all suspected sepsis patients in this study were sent for blood culture, and only 1.9% had an actual blood sample drawn. This is lower than the findings from a previous study in Nigeria where about 12.5% of the patients who met sepsis diagnostic criteria had a blood culture to guide therapy (27). It differs even more significantly from findings in high-resource settings such as in the study by Otto et al. where more than 80% of patients were reported to have had blood sampling done for cultures (33). The low rate of blood culture requests may be attributed to the fact that patients are expected to pay for blood culture diagnostics out-of-pocket which is often a financial burden that cannot be met and may be wariness of clinicians in making this request due to the long turnaround time for blood cultures. According to this study's multivariate analysis, inpatients and those from the urban health care facility were significantly more likely to have a blood culture requested despite the fact that there were more suspected sepsis patients in outpatients compared to in-patients whereas health insurance status was not associated such requests, suggesting that access remains an overall issue for all patients. The fact that there were more suspected sepsis patients in outpatients compared to in-patients, yet inpatients were more likely to have a blood culture request may be attributed
to severity of disease. However, such poor utilisation of blood culture diagnostics has been shown to contribute to delayed patient recovery, missed diagnosis of sepsis resulting in delay in the institution of targeted antibiotics and long hospitalization (34). Diagnostic stewardship improvement strategies should consider advocacy approaches towards health care facilities, particularly secondary level health care facilities; and provision of essential commodities such as blood culture bottles, in order to improve access and availability of quality diagnostics.

Among the limited number of isolates, the most common causative agents of sepsis found in this baseline study were *Staphylococcus aureus*, *Coagulase-negative Staphylococci*, *Klebsiella spp.* and *Escherichia coli*, a similar distribution to other studies in Nigeria (32, 33). Overall, only one-fifth of blood culture samples in this study yielded growth. Low positive yield may be due to high contamination rates and quality issues along the pre-analytic and analytic pathway, e.g., inadequate asepsis during sample collection, sub-optimal transport and handling of samples, as has been seen in large hospital studies (37). These high rates of contamination along with long result turnaround time or lack of reporting causes mistrust in the diagnostic pathway and results. Accordingly, diagnostic stewardship strategies should include not only laboratory quality improvement efforts but also improved communication mechanisms to build trust between clinicians and laboratory scientists.

Low positive culture yields are also influenced by the use of antibiotics by patients before presenting to facilities (37). In our baseline study, 3 out of 20 suspected sepsis patients reporting to the healthcare facilities were already on antibiotics pre-consult. This could indicate the antibiotic misuse i.e. procuring such prescription-only medicines over-the-counter antibiotics (38). After consultation, the proportion of patients on antibiotics increased to 14 out of 20 patients. In addition, two-thirds of the antibiotics used in our study were in the Watch category. This is in contrast with the target set by the World Health Organization for measuring appropriate, which is that Access antibiotics should constitute 60% of antibiotic consumption by 2023(39, 40). Increased use of Watch antibiotics and broad-spectrum or high-priority agents such as cephalosporins have been reported in Nigeria and other low-resource settings (41–44), although the overuse of Access antibiotics, often first and second choice therapy for common infections, has also been described in such settings (45, 46). Such findings have important local implications for antimicrobial stewardship programs and prioritisation of guidance.

This baseline study is a large-scale study and arguably the first of its kind in Nigeria. The use of standard tools for data collection makes it reliable. However, there are limitations that should be considered. In the first stage, the online survey was completed by the heads of laboratories at 25 out of 65 public secondary health care facilities, so results may have been influenced by non-response bias. In the second stage, although the selected facilities reported regularly using EMR systems, the extraction of data on certain variables such as patients’ clinical characteristics was often incomplete. This was likely due to both lack of measurement during clinical examinations and poor data recording. Laboratory data were extracted from the EMR and manual laboratory registers, but this does not exclude the possibility of missing data and misclassification bias.
Conclusion

The study provides important baseline information on the diagnostic process and antibiotic use among patients with suspected sepsis in secondary health care facilities in Nigeria, which will be used to inform diagnostic stewardship improvement strategies. Low blood culture utilisation remains a key challenge in these settings. Key study findings highlighted the need for improved access to clinical microbiology expertise particularly at the secondary health care facility level, renewed practical guidance on sepsis case finding, and antibiotic use.

List Of Abbreviations

AMR Antimicrobial Resistance
AST Antimicrobial Susceptibility Testing
BC Blood culture
BSI Bloodstream Infections
EMR Electronic Medical Records
FBC Full blood count
FCT Federal Capital Territory
GLASS Global Antimicrobial Resistance Surveillance System
ICU Intensive Care Unit
LMIC Low- and Middle-Income Countries
NCDC Nigeria Centre for Disease Control
RKI Robert Koch's Institute, Germany
SOP Standard Operating Procedure
WHO World Health Organization

Declarations

Ethics declarations and consent for publication

Ethical approval of the study was obtained from the Federal Capital Territory (FCT) Health and Human Services Secretariat Ethical Review Committee with approval number: FHREC/2020/01/35/04-05-20.
Permission was gotten from the respective health care facilities’ management board and heads of the selected departments.

**Availability of data and materials**

The data that support the findings of this study are available from the Nigeria Centre for Disease Control, Abuja, Nigeria but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the Nigeria Centre for Disease Control.

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**Authors’ contributions**

ARE: Conceptualization, designing, validation, formal analysis, investigation, resources, data curation, supervision, writing—original draft. AE & STA: Conceptualization, designing, validation, formal analysis, writing—review and editing, supervision, project administration, and fund acquisition. AVL & OA: Conceptualization, designing, validation, formal analysis, writing—review and editing, supervision, project administration. OO: Conceptualization, designing, data collection, project administration. SI & RY: Conceptualization, designing. TO, CO, HDA, IOA, AO, TE& CI: Conceptualization, writing-review, fund acquisition. The authors read and approved of this manuscript.

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**Competing interests**

The authors declare that they have no conflict of interest.

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**Figures**

**Figure 1**

Blood-culture uptake by suspected-sepsis patients at two healthcare facilities, Abuja, October 2020 to May 2021