Status of antimicrobial stewardship programs in Nigerian tertiary healthcare facilities; findings and implications

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ABSTRACT
Objectives: The problem of antimicrobial resistance (AMR) is increasing worldwide with health-related and economic consequences. This is a concern in Africa, including Nigeria the most populous country in Africa, with its high rates of infectious diseases. Approaches to reducing AMR include instigating antimicrobial stewardship programs (ASPs) in hospitals. Currently, no information is available regarding the extent of ASPs in Nigerian hospitals. Consequently, the objective was to address this starting in tertiary hospitals. METHODS: Cross-sectional, questionnaire-based study among tertiary healthcare facilities. Tertiary hospitals were chosen initially since if there are concerns in these training hospitals, such concerns will likely to be exacerbated in others. RESULTS: Completed questionnaires were received from 17 out of 25 tertiary healthcare facilities across five of the six geo-political regions of Nigeria. 10 (58.8%), four (23.6%), two (11.8%) and one (5.8%) respondents were in internal medicine, infectious diseases, medical microbiology and clinical pharmacology respectively. Only six (35.3%) healthcare facilities had a formal organizational structure and a team responsible for ASP. Facility-specific treatment recommendations, based on local AMR patterns, were available in only four (23.5%) facilities. Policies on approval for prescribing specified antimicrobial agents and formal procedures for reviewing their appropriateness after 48 hours was present in only 2 (11.8%) facilities. The cumulative antimicrobial susceptibility report for the previous year was available in only three (17.6%) facilities and only one facility routinely monitored antimicrobial use. CONCLUSION: Significant inadequacies in the availability of ASPs programmes were seen. This needs to be urgently addressed to reduce AMR rates in Nigeria.

1. INTRODUCTION

Antimicrobial resistance (AMR) is a growing public health problem with consequences including therapeutic failure, increasing morbidity and mortality and higher healthcare costs [1-3]. The inappropriate use of antimicrobials, especially in hospitals, has been shown to be responsible for the development of resistance to different classes of antimicrobials, especially those used for the treatment of nosocomial infections [4], with a pan-European study identifying a direct link between the quantity of consumed antibiotics and AMR [5]. The situation regarding rising AMR rates is compounded by the slow development of novel antimicrobial agents during the past two decades [3]. The establishment of antimicrobial stewardship programs (ASPs) in healthcare institutions, as well as regulation of access to and prescribing of antimicrobials, are some of the approaches employed towards reducing AMR [6-9]. The principal function of ASPs is the promotion of the rational use of antimicrobials in the hospital setting through formulary restrictions and pre-authorization [6, 9,10]. Additional strategies are prospective audits and feedback to prescribers as well as guideline development and dissemination [10-12]. Many developed countries have well-entrenched ASPs that have resulted in better patient outcomes and reduction in healthcare costs [13]. A meta-analysis of studies evaluating the effect of ASPs in inpatient setting in the United States showed that there was decreased antimicrobial use and improvement in antimicrobial resistance patterns following the instigation of ASPs [14]. A significant reduction in healthcare costs, especially relating to the direct cost of antimicrobials and indirect costs (reduction in hospital stay, and improved therapeutic outcomes), was recorded with ASPs in studies conducted in Saudi Arabia, Sweden and China [15-17]. Similarly, the impact of a functional ASP has been demonstrated in South Africa with a reduction in the quantity of antimicrobial use and costs in the hospital without negatively affecting patients' outcomes [18]. However, the optimal strategies for ASPs including membership and activities has yet to be fully defined [9].

The inappropriate use of antimicrobials is well documented in many studies conducted across Nigeria [19,20]. This is worrisome not only because of associated potential adverse effects and drug-drug interactions, but also the financial impact as only a small proportion of the population in Nigeria currently enjoys the coverage of health insurance schemes [21]. In view of this, the presence of any program promoting improved use of antimicrobials by physicians in healthcare facilities should be encouraged, although concerns exist about the most appropriate method [9,22]. Currently, there is little information regarding the availability and functionality of ASPs among Nigerian hospitals. This lack of information needs to be urgently addressed given the size of the population in Nigeria versus other African countries, and growing AMR rates in Nigeria [23-25].

The principal objective of the study was to investigate the availability and mode of operation of ASPs among selected tertiary healthcare facilities across different regions of Nigeria as a basis for providing future direction.

2. METHODS

2.1 Study setting

This study was conducted among public sector tertiary healthcare facilities located in different regions of Nigeria. Nigeria is the most populous country in Africa with an estimated population of over 170 million. The country, which is divided into six geo-political zones, also operates a federal system comprising 36 states and one Federal Capital Territory. Tertiary healthcare facilities comprise mainly Federal Medical Centres and University Teaching Hospitals, and they are the best-equipped in terms of personnel and equipment. Consequently, if there are issues regarding the nature and extent of ASPs among tertiary hospitals, these issues and concerns are likely to be magnified in secondary hospitals. There is some benefit for healthcare professionals to be part of hospital ASP programmes, either financial or as part of career development, although this may not be universal.

The healthcare needs of the Nigerian population are catered for by both private and public healthcare facilities. The public healthcare system of the country currently comprises three levels of care: primary, secondary and tertiary. The primary level of care incorporates health centres, while the secondary level comprises general hospitals. As mentioned, tertiary healthcare comprises mainly Federal Medical Centres

and University Teaching Hospitals. Presently there are 50 university teaching hospitals owned by the federal or state governments in Nigeria.

2.2 Study design
A descriptive cross-sectional survey was conducted, using a self-administered mailed questionnaire, to ascertain the extent and nature of ongoing ASPs among tertiary hospitals.

2.3 Sampling
Purposive sampling was undertaken, using hospitals with reliable personal contacts. Five tertiary healthcare facilities in each of the five out of the six geo-political regions of the country were selected for this initial study since personnel with the highest levels of qualifications and expertise are mostly found in such centres. The North-eastern zone was excluded because of ongoing militant insurgency in the region during the study period.

2.4 Data collection instrument
The study instrument was an adaptation of the instrument developed by the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) Expert Panel on Stewardship Structure and Process Indicators [26]. The 17-item instrument consists of core indicators categorized into infrastructure, policy and practice and monitoring and feedback (Appendix A).

2.5 Data collection process
The questionnaires were sent via email to the focal persons of the selected institutions after initial contact by telephone. The focal person for each selected tertiary hospital was either a consultant medical microbiologist, clinical pharmacologist or a consultant physician. A time frame of two weeks was allowed for the return of the completed questionnaires as well as via email. Return of the completed questionnaire by respondents was taken as consent to participate in the study.

2.6 Data analysis
Data from the questionnaires were coded and entered into an MS Excel spreadsheet, cleaned, and imported into SPSS version 19 (IBM Corporation, Armonk, NY, USA) for analysis. Results were expressed as means, frequencies and percentages. For the non-quantitative data, content analysis using themes was used to summarize the responses.

2.7 Ethical considerations
The study was exempted from ethical approval according to the National Code of Health Research Ethics of Nigeria because it dealt with information of existing programs and services with the primary aim of improving the future outcome of patients with infection among hospitals in Nigeria.

3. RESULTS

Completed questionnaires were received from 17 out of 25 tertiary healthcare facilities across five out of the six geo-political regions of the country.

According to the area of specialization, 10 (58.8%), four (23.6%), two (11.8%) and one (5.8%) respondents were specialists in internal medicine, infectious diseases, medical microbiology and clinical pharmacology respectively. Only four (23.5%) healthcare facilities had formal ASPs while another two had other committees responsible for monitoring antimicrobial use in their facilities. None of the surveyed healthcare facilities gave financial compensation for the time dedicated to AMS activities. In the area of policy and practice, four (23.5%) hospitals had treatment guidelines that were based on local antimicrobial susceptibility patterns while preauthorization for certain antibiotics was currently being practiced in only two hospitals. A review of prescribed antimicrobial agents after 48 hours was carried out in only three (17.6%) of the tertiary healthcare facilities.

With regards to monitoring and feedback, only two centres had produced a cumulative antimicrobial susceptibility report in the preceding year. Similarly, regular audit of surgical antimicrobial prophylaxis was being undertaken in only four tertiary healthcare facilities. Monitoring of antimicrobial consumption using

either the Defined Daily Dose (DDD) or Days of Therapy (DOT) was currently being undertaken in only one healthcare facility. Full details about the availability and functionality of other components of the AMS programs are shown in Table 1.

Table 1: Showing collated responses from completed questionnaires

Infrastructure

Statement	Yes	No
Does your facility have a formal antimicrobial stewardship program accountable for ensuring appropriate antimicrobial use	4(23.5)	13(76.5)
Does your facility have a formal organizational structure responsible for antimicrobial stewardship (e.g. a multidisciplinary committee focused on appropriate antimicrobial use, pharmacy committee, patient safety committee, or other relevant structure)?	6(35.3)	11(64.7)
Is an antimicrobial stewardship team available at your facility (e.g. greater than one staff member supporting clinical decisions to ensure appropriate antimicrobial use)?	6(35.3)	11(64.7)
Is there a physician identified as a leader for antimicrobial stewardship activities at your facility?	5(29.4)	12(70.6)
Is there a pharmacist responsible for ensuring appropriate antimicrobial use at your facility?	3(17.6)	14(82.4)
Does your facility provide any salary support for dedicated time for antimicrobial stewardship activities (e.g. percentage of full-time equivalent [FTE] staff for ensuring appropriate antimicrobial use)?	0(0)	17(100)
Does your facility have the information technology (IT) capability to support the needs of the antimicrobial stewardship activities?	4(23.5)	13(76.5)

Policy and Practice

Statement	Yes	No
Does your facility have facility-specific treatment recommendations based on local antimicrobial susceptibility to assist with antimicrobial selection for common clinical conditions?	4(23.5)	13(76.5)
Does your facility have a written policy that requires prescribers to document an indication in the medical record or during order entry for all antimicrobial prescriptions?	7(41.2)	10(58.8)
Is it routine practice for specified antimicrobial agents to be approved by a physician or pharmacist in your facility (e.g. preauthorization)?	2(11.8)	15(88.2)
Is there a formal procedure for a physician, pharmacist, or other staff member to review the appropriateness of an antimicrobial at or after 48 hours from the initial order (post-prescription review)?	3(17.6)	14(82.4)

Monitoring and Feedback

Statements	Yes	No
Has your facility produced a cumulative antimicrobial susceptibility report in the past year?	2(11.8)	15(88.2)
Does your facility monitor if the indication is captured in the medical record for all antimicrobial prescriptions?	4(23.5)	13(76.5)
Does your facility audit or review surgical antimicrobial prophylaxis choice and duration?	4(23.5)	13(76.5)
Are results of antimicrobial audits or reviews communicated directly with prescribers?	2(11.8)	15(88.2)

Does your facility monitor antimicrobial use by grams (Defined Daily Dose [DDD]) or counts (Days of Therapy [DOT]) of antimicrobial(s) by patients per days?	1(5.9)	16(94.1)
Has an annual report focused on antimicrobial stewardship (summary antimicrobial use and/or practices improvement initiatives) been produced for your facility in the past year?	1(5.9)	16(94.1)

4. DISCUSSION

4.1 General

Instigation of ASPs is one of the major interventions against AMR worldwide. However in our study, only four (23.5%) of the surveyed tertiary facilities in Nigeria had ASPs in existence. This will have a significant impact on the rational use of antimicrobials and attendant patient outcomes in Nigeria unless addressed, especially if our findings are replicated or even worse in secondary care facilities that currently lack the infrastructure of tertiary facilities. Having said this, these concerns are also seen in more developed countries where there are also variable levels of ASPs [9, 16,27,28]. A study conducted in 2013 among 38 children hospitals in the USA, concluded that only 16 of them had existing ASPs, while 15 were in the process of establishing them [28]. Another study characterizing the structure and functioning of ASPs in Veterans healthcare facilities across the USA in 2012 also found ASP teams present in only 38% of the surveyed hospitals [29]. The relatively low number of healthcare facilities having functional ASPs was also highlighted in a 2014 study conducted in Queensland, Australia, with only 19% of facilities having ASPs [30]. In contrast, 92.6% of hospitals surveyed in a Korean study had functional ASPs [27].

Research has shown the positive impact of having infectious diseases physician, clinical microbiologist, clinical pharmacologists and clinical pharmacists trained in infectious diseases in addition to management staff as members of the ASP team [6]. In this study, a physician was identified as the team leader of the ASPs in five (83.3%) of the healthcare facilities where ASPs had been instigated while three tertiary facilities (50%) had a pharmacist responsible for appropriate antimicrobial use. Due to manpower constraints, especially in clinical sub-specialties such as infectious diseases, clinical microbiology and clinical pharmacology in Nigeria, it is impossible currently to meet these membership criteria in existing ASPs. However, physicians from other sub-specialties, nurses and other healthcare professionals such as pharmacists can be incorporated after pre-requisite training to facilitate the functioning of ASPs in their facilities. This is already happening in other countries [8], and has already led to the development of guidelines and positioning statements among pharmacists and other professionals in South Africa [10,31].

None of the centres that participated in this study had any special salary or funding support for the members of their ASP teams. This is not peculiar to Nigeria as lack of adequate funding for ASP teams has been identified in studies conducted in different parts of the world [30].

4.2 Policy and Practice

At the level of policy and practice, only four (23.5%) tertiary hospitals had facility-specific treatment recommendations based on local antimicrobial susceptibility. This suggests that treatment with antimicrobials in the majority of these hospitals was being undertaken empirically with potential consequences such as therapeutic failure, higher costs of healthcare, and increasing levels of AMR.

Pre-authorization is typically the most common form of intervention used in ASPs; however, only 8% of tertiary hospitals in this study had pre-authorization programmes in place. In practice, this means that all cadres of physicians (from interns to consultants) can prescribe any type of antimicrobial even the so-called “reserved” antimicrobials. This is in contrast to 92.6% and 88% of hospitals in South Korea and Australia respectively having pre-authorization as a core interventional strategy [27,30]. The pre-authorization of ciprofloxacin prescriptions, in a study conducted in the USA, was associated with a positive effect on the susceptibility of *E. coli* isolates to ciprofloxacin [32]. The importance of pre-authorization in reducing the use of broad-spectrum antibiotics, and its associated higher healthcare costs, have also been reported in other studies [33,34]. Another way of limiting the inappropriate use of antimicrobials in the hospital setting is post-prescription reviews after 48 hours when the results of the microbial culture and sensitivity would have been reported. In this study, only three (17.6%) hospitals had post-prescription reviews in place. While this may indicate a lack of consideration towards bacterial

culture and sensitivity in some cases, most physicians would typically review the prescribed antimicrobials based on culture and sensitivity results without a formal post-prescription review. The clinical advantages of a post-prescription review, which has been shown in several studies, include a reduction in patients' exposure to antibiotics, shortening the duration of hospital stay, and a reduction in the rate of relapse of infections [35].

4.3 Monitoring and Feedback

Local knowledge of antimicrobial susceptibility is essential especially when choosing antibiotics for the empiric treatment of infections. Only two (11.8%) hospitals in this study had produced a cumulative antimicrobial susceptibility report in the preceding year. Although there are several small and isolated cross-sectional antimicrobial susceptibility, and/or resistance studies, conducted in Nigerian hospitals [36,37], a need exists for more comprehensive annual facility sponsored studies to be conducted using either the Clinical Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [38]. This should be a priority for the future building on examples in other African countries [39], with ongoing plans also in place among a number of African countries as part of National Antimicrobial Plans to improve sensitivity testing and their use, with the findings guiding future empiric use [39].

The documentation of the indication for antibiotic use is also important as part of ASPs to improve the quality of prescribing. The indications for antimicrobial use were captured in patients' case notes in only four (23.5%) of the participating hospitals. The use of surgical antimicrobial prophylaxis was also only monitored in four participating hospitals in this study. This practice was typically suboptimal, which is a concern as non-compliance with guidelines regarding the use of antimicrobial surgical prophylaxis would likely contribute to the development of AMR. We also see concerns with the use of surgical antimicrobial prophylaxis in other African countries [40,41]. Finally, only one hospital monitored antimicrobial use in its facility using either of the standard indices and tools for quantification of drug use, namely Defined Daily Dose (DDD) or Days of Therapy (DOT). This however might be a consequence of inadequate knowledge of drug utilization research methodology in Nigeria, which is starting to be addressed with the formation of Pan-African groups such as the MURIA group (Medicines Utilisation Research in Africa) with the help of the World Health Organisation and others [42,43]. The lack of usage of standard tools and methodologies limits the ability of physicians and other healthcare providers to monitor the quantity and quality of antibiotic use over time in their facilities. It also does not allow for the correlation of antibiotic consumption and resistance patterns within their facilities to improve future antibiotic prescribing.

LIMITATIONS

The study was conducted only in public tertiary level healthcare facilities across several regions of the country and as such our findings may not reflect the reality in among private and faith-based healthcare facilities in Nigeria However, there was a good geographical spread. In addition, if concerns regarding ASPs were found in public tertiary hospitals in Nigeria, these are likely to be magnified in secondary care hospitals with their lack of trained specialists and other structures. The purposive nature of the sampling approach used may also be associated with an element of bias. We also explored descriptively the availability and structure of ASPs but did not investigate in depth how ASPs function in practice. This will be followed up through mixed-method research in the future. The impact of the ASP services on antimicrobial utilization and resistance was also not explored, and this will be another area for future research. However, we believe our findings are robust necessitating an urgent need for the Nigerian Government to instigate ASPs staring in tertiary hospitals and progressing wider to reduce current AMR rates.

5. CONCLUSIONS

ASPs are lacking in a substantive proportion of tertiary Nigerian hospitals, and they furthermore function sub-optimally where available. Given the highlighted problems of inappropriate antimicrobial use in Nigeria and its associated consequences, there is an urgent need for concerted efforts to make ASPs functional in Nigeria, starting initially with the tertiary healthcare facilities. This could begin with educational programs in healthcare facilities organized by the Ministry of Health highlighting the importance of appropriate antibiotic use, and followed up with structures to monitor the establishment of

ASPs and their influence on future antibiotic use. The program could thereafter be cascaded to secondary and primary care levels for optimal results across the country.

Highlights

- AMR is a growing concern especially in sub-Sahara Africa with its high rate of infectious diseases.
- Reducing AMR rates can be aided through initiatives such as antimicrobial stewardship programmes (ASPs). However, little is currently known about ASPs among leading hospitals (tertiary hospitals) in Nigeria
- The qualitative research showed limited implementation of ASPs among tertiary hospitals in Nigeria, with only just over one third of tertiary hospitals having a formalized structure and team responsible for ASPs
- Under a quarter of tertiary hospitals have specific treatment recommendations in place based on local antimicrobial resistance patterns, and only 12% of tertiary hospitals had a formal procedure in place for reviewing the appropriateness of antibiotic prescribing after 48 hours
- Susceptibility reports of antimicrobial resistance patterns the previous year were only available in 18% of facilities and only one out of 25 surveyed hospitals currently routinely monitor antimicrobial utilization
- The Ministry of Health and other key stakeholders need to get together to urgently address the lack of ASPs and other initiatives in hospitals to improve antimicrobial use in Nigeria else AMR rates will continue to grow

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APPENDIX A

ANTIBIOTIC STEWARDSHIP PROGRAM SURVEY QUESTIONNAIRE

Kindly complete this questionnaire by typing YES/NO in front of each question. The aim of this study is to assess antibiotic stewardship program in selected Nigerian healthcare facilities. We will appreciate your timely completion and return of the questionnaire.

The completed questionnaire can be sent to: jofadare@gmail.com

Thank you.

Name of Respondent (Optional**)**:

Work Title (Consultant Physician, Consultant Medical Microbiologist, Other):

If other, please state:

Name of Healthcare Facility/Organization:

Location (City):

Category of Healthcare Facility (Secondary/Tertiary):

Infrastructure

1. Does your facility have a formal antimicrobial stewardship program accountable for ensuring appropriate antimicrobial use? Yes/ No
2. Does your facility have a formal organizational structure responsible for antimicrobial stewardship (e.g., a multidisciplinary committee focused on appropriate antimicrobial use, pharmacy committee, patient safety committee, or other relevant structure)? Yes/ No
3. Is an antimicrobial stewardship team available at your facility (e.g., greater than one staff member supporting clinical decisions to ensure appropriate antimicrobial use)? Yes/ No
4. Is there a physician identified as a leader for antimicrobial stewardship activities at your facility? Yes/ No

5. Is there a pharmacist responsible for ensuring appropriate antimicrobial use at your facility? Yes/ No

6. Does your facility provide any salary support for dedicated time for antimicrobial stewardship activities (e.g., percentage of full-time equivalent [FTE] staff for ensuring appropriate antimicrobial use)? Yes/ No

7. Does your facility have the information technology (IT) capability to support the needs of the antimicrobial stewardship activities? Yes/ No

Policy and practice

8. Does your facility have facility-specific treatment recommendations based on local antimicrobial susceptibility to assist with antimicrobial selection for common clinical conditions? Yes/ No

9. Does your facility have a written policy that requires prescribers to document an indication in the medical record or during order entry for all antimicrobial prescriptions? Yes/ No

10. Is it routine practice for specified antimicrobial agents to be approved by a physician or pharmacist in your facility (eg, preauthorization)? Yes/ No

11. Is there a formal procedure for a physician, pharmacist, or other staff member to review the appropriateness of an antimicrobial at or after 48 hours from the initial order (post-prescription review)? Yes/ No

Monitoring and feedback

12. Has your facility produced a cumulative antimicrobial susceptibility report in the past year? Yes/ No

13. Does your facility monitor if the indication is captured in the medical record for all antimicrobial prescriptions? Yes/ No

14. Does your facility audit or review surgical antimicrobial prophylaxis choice and duration? Yes/ No

15. Are results of antimicrobial audits or reviews communicated directly with prescribers? Yes/ No

16. Does your facility monitor antimicrobial use by grams (Defined Daily Dose [DDD]) or counts (Days of Therapy [DOT]) of antimicrobial(s) by patients per days? Yes/ No

17. Has an annual report focused on antimicrobial stewardship (summary antimicrobial use and/or practices improvement initiatives) been produced for your facility in the past year? Yes/ No