

## Knowledge, Attitudes, and Practices Regarding Antimicrobial Resistance among Healthcare Professionals (HCPs) in Anambra State, Nigeria

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### Abstract

**Background:** Antimicrobial resistance (AMR) is a major global health threat. In Anambra State, underfunding, poor infrastructure, and underutilization of public healthcare facilities contribute to suboptimal antimicrobial use, increasing the risk of healthcare-associated infections and resistant organisms. As the behavioral and systemic drivers of prescribing remain understudied in resource-limited settings, assessing healthcare providers' knowledge, attitudes, and practices (KAP) is essential.

**Purpose:** The survey was carried out to assess HCPs' knowledge, attitudes, and practices regarding antimicrobial resistance, stewardship principles, and antibiotic policy awareness.

**Method:** The study employed a descriptive cross-sectional design using physical and online questionnaires to survey 150 healthcare professionals, including physicians, pharmacists, and nurses, practising in Awka metropolis, Anambra State. The study assessed awareness and knowledge of AMR, stewardship principles, antibiotic policy familiarity, attitudes, confidence, and antimicrobial practices.

**Results:** Overall awareness of antimicrobial resistance (AMR) was high, with 83.3% recognizing AMR as a problem in Anambra State and 90% rejecting antibiotic sharing. Physicians and pharmacists demonstrated significantly better knowledge of AMR causes and WHO AWaRe antibiotic classifications than nurses ( $p < 0.001$ ). Only 22.1% were aware of institutional or national antibiotic guidelines. Lower scores were observed for narrow-spectrum antibiotic use, avoidance of unnecessary prophylaxis, and limiting treatment duration. Active prescribers demonstrated higher stewardship practice scores than non-prescribers. Respondents reported positive attitudes toward AMR prevention and strong patient counselling practices, particularly pharmacists. Educational campaigns, stewardship guidelines, infection control, and antimicrobial sales regulation were the most commonly identified AMR control strategies.

**Conclusion:** Low awareness of antimicrobial policies highlights a major challenge to stewardship implementation.

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*The findings suggest the need for multidisciplinary stewardship education, better guideline dissemination, stronger institutional stewardship programs, and greater integration of pharmacists and nurses into stewardship initiatives.*

**Keywords:** Antibiotic Misuse and Overuse, Antimicrobial Stewardship Programs (ASPs), Infection Control, Prescribing Practices, Antibiotic Policy and Guidelines, One Health Approach

## 1. Introduction

Antimicrobial resistance (AMR) is a critical global health challenge, defined as the ability of microorganisms to withstand the effects of antimicrobial agents that were previously effective against them [1]. This phenomenon poses a serious threat to public health, contributing to increased morbidity, mortality, prolonged hospital stays, and escalating healthcare costs worldwide [2]. Current estimates attribute approximately 700,000 deaths annually to AMR, with projections suggesting that this figure could exceed cancer-related mortality by 2050 if urgent interventions are not implemented [3]. The emergence and rapid spread of AMR have been largely driven by the indiscriminate and inappropriate use of antibiotics in both human and animal health sectors [2]. Consequently, addressing AMR requires a coordinated One Health approach, integrating human, animal, and environmental health systems [4].

In Anambra State, the healthcare system is challenged by inadequate funding, limited infrastructure, and underutilization of public health facilities, which collectively hinder effective healthcare delivery and infection control practices [5,6]. These systemic weaknesses contribute to suboptimal antimicrobial use and increase the risk of healthcare-associated infections (HAIs) and the proliferation of resistant organisms [7]. Evidence from local and regional studies indicates that inappropriate antibiotic use, often driven by gaps in knowledge, attitudes, and prescribing practices remains a major contributor to AMR [8].

Despite the recognized importance of antimicrobial stewardship programs (ASPs), their effectiveness is constrained by persistent challenges, including overtreatment, inadequate professional training, limited diagnostic support, and poor adherence to treatment guidelines among healthcare providers [9]. Furthermore, behavioural and systemic factors influencing prescribing decisions are often underexplored, particularly in resource-limited settings.

Given these complexities, there is a pressing need for a comprehensive assessment of healthcare providers' knowledge, attitudes, and practices (KAP) regarding antimicrobial use. Such an evaluation will help identify critical gaps and contextual barriers, thereby informing targeted interventions to strengthen antimicrobial stewardship efforts and mitigate the growing burden of AMR.

## 2. Methodology

### 2.1. Study Design, Area, and Population

This survey was a descriptive cross-sectional study conducted between February and April 2024 among healthcare professionals, including physicians, pharmacists, and nurses practising in Awka metropolis.

### 2.2. Inclusion and Exclusion Criteria

Healthcare professionals involved in patient care and antimicrobial-related activities in selected facilities in Anambra State, with at least six months of work experience and who consented to participate, were included. Healthcare professionals with less than six months of work experience, those on leave during the study period, interns, students, non-clinical staff, and individuals who declined participation were excluded.

### 2.3. Ethics Considerations

Ethical approval for the survey was obtained from the Ethics committee of the Chukwuemeka Odumegwu Ojukwu University Teaching Hospital (COOUTH), Awka, with reference number 'COOUTH/HREC/ETH.C/VOL.1/FN:04/316'. All respondents gave oral or written informed consent to participate in the study. Information obtained during the study was handled confidentially and used solely for research purposes.

### 2.4. Data Collection Instrument and Quality Assurance

Data were collected using structured questionnaires developed by the research team from existing literature [10]. The instrument covered respondents' demographics; knowledge, attitudes, and perceptions; current practices; and barriers to adopting AMR policy guidelines, and included open-ended questions for additional insights. After review by two subject experts, a pilot study was conducted, and revisions were made based on feedback from participating HCPs. Completed questionnaires were checked for errors and completeness, and only those with adequate data were included in the statistical analysis.

### 2.5. Data Management and Analysis

Data were cleaned, standardized, and analyzed using Python (pandas/NumPy), with outputs generated via openpyxl, python-docx, and Pillow. Multi-select responses were converted to binary variables, and missing data were handled via available-case analysis. Categorical data were summarized using frequencies (%); continuous/ordinal variables used means (SD) or medians (IQR). Group comparisons used chi-square, Fisher's exact, and Kruskal-Wallis tests. Relationships and outcomes were assessed via logistic regression, Spearman correlation, and Cronbach's alpha. Statistical significance was set at  $p < 0.05$ . A sensitivity analysis compared prescribing outcomes between all respondents and active prescribers.

## 3. Results

### 3.1. Socio-Demographic Characteristics

Table 1 outlines the socio-demographic characteristics and baseline professional profiles of the surveyed healthcare workers, stratified by their specific clinical occupations.

Variable	Overall (N=150)	Physicians (n=31)	Pharmacists (n=65)	Nurses (n=54)
<b>Sex, n (%)</b>				
Female	97 (64.7%)	14 (45.2%)	33 (50.8%)	50 (92.6%)
Male	53 (35.3%)	17 (54.8%)	32 (49.2%)	4 (7.4%)
<b>Years of Experience, n (%)</b>				
<5 years	58 (38.7%)	15 (48.4%)	34 (52.3%)	9 (16.7%)
5–15 years	63 (42.0%)	14 (45.2%)	22 (33.8%)	27 (50.0%)
>15 years	29 (19.3%)	2 (6.5%)	9 (13.8%)	18 (33.3%)
<b>Healthcare Facility Type, n (%)</b>				
Public Tertiary Hospital	118 (78.7%)	23 (74.2%)	47 (72.3%)	48 (88.9%)
Non-Tertiary / Other Facilities*	32 (21.3%)	8 (25.8%)	18 (27.7%)	6 (11.1%)
<b>Facility Location, n (%)</b>				
Urban	98 (65.3%)	18 (58.1%)	41 (63.1%)	39 (72.2%)
Sub-urban	42 (28.0%)	13 (41.9%)	17 (26.2%)	12 (22.2%)
Rural	10 (6.7%)	0 (0.0%)	7 (10.8%)	3 (5.6%)
<b>Professional Qualification, n (%)</b>				
Medical Degree (MBCbB)	29 (19.3%)	29 (93.5%)	0 (0.0%)	0 (0.0%)
Postgraduate Medical Fellowship/MD	2 (1.3%)	2 (6.5%)	0 (0.0%)	0 (0.0%)
Bachelor of Pharmacy (B.Pharm)	59 (39.3%)	0 (0.0%)	59 (90.8%)	0 (0.0%)
Postgraduate Pharmacy (PharmD/MPharm/PhD)	6 (4.0%)	0 (0.0%)	6 (9.2%)	0 (0.0%)
Diploma in Nursing	17 (11.3%)	0 (0.0%)	0 (0.0%)	17 (31.5%)
Bachelor in Nursing (BNSc)	34 (22.7%)	0 (0.0%)	0 (0.0%)	34 (63.0%)
Postgraduate Nursing (MSc/PhD)	3 (2.0%)	0 (0.0%)	0 (0.0%)	3 (5.6%)

**Table 1: Demographic Characteristics of Participants**

### 3.2. Knowledge and Awareness of AMR

Table 2 presents the participants' general awareness of antimicrobial resistance (AMR), their understanding of its primary

drivers, and their knowledge regarding the WHO AWaRe antibiotic classifications

Knowledge/Awareness Item	Overall % (n/N)	Physician %	Pharmacist %	Nurse %	p-value
Considers AMR a major problem in Anambra	83.3% (125/150)	77.4%	92.3%	75.9%	0.081
Aware of national/facility antibiotic policies	22.1% (33/149)	20.0%	23.1%	22.2%	0.507
<b>Identified AMR Causes (Selected)</b>					
- Treating viral infections with antibiotics	58.7% (88/150)	74.2%	76.9%	27.8%	<0.001*
-AMR cause: given when not needed	80.7%	93.5%	92.3%	59.3%	<0.001*
-Prolonged unnecessary use	61.3% (92/150)	74.2%	69.2%	44.4%	0.006*
-AMR cause: wrong dose	69.3%	90.3%	80.0%	44.4%	<0.001*
- Broad-spectrum antibiotic overuse	70.7% (106/150)	83.9%	81.5%	50.0%	<0.001*
- Use before culture/sensitivity results	66.0% (99/150)	48.4%	73.8%	66.7%	0.048
<b>AWaRe Classification (Correct Selection)</b>					
- Watch: Carbapenems	21.8% (31/142)	25.8%	30.2%	8.3%	0.019*
- Reserve: Tigecycline	21.8% (31/142)	32.3%	26.2%	10.0%	0.034*
- Reserve: 5th Gen Cephalosporins	54.9% (78/142)	61.3%	63.9%	40.0%	0.080

Note: statistical significance =  $p < 0.05^*$

**Table 2: AMR Awareness, Knowledge, and Policy Familiarity**

### 3.3. Attitude and Confidence

Table 3 summarizes confidence and attitude measures. Significant

differences were observed for confidence in AMR knowledge, whereas most other confidence domains did not differ significantly.

Practice Item (1 = Never, 5 = Always)	Overall Mean (SD)	Physician	Pharmacist	Nurse	p-value
<b>Stewardship Practices</b>					
- Uses narrowest antimicrobial spectrum	2.95 (1.39)	3.35	3.14	2.48	0.006*
- Evidence-based antimicrobial use	3.72 (1.43)	3.74	3.82	3.59	0.874
- Avoids antibiotic prophylaxis	3.19 (1.39)	3.10	3.23	3.20	0.867
<b>Patient Counseling</b>					
- Counsel: Complete course even if better	4.23 (1.19)	4.42	4.43	3.87	-
- Counsel: Do not share antimicrobials	4.19 (1.19)	4.32	4.42	3.83	-
- Counselling: proper disposal	3.77 (1.38)	3.35	3.80	3.98	-
<b>Behaviour Change</b>					
- Changed prescribing in past 5 years (%)	43.3%	45.2%	41.5%	44.4%	0.926

Note: NS = not significant; SD = standard deviation; statistical significance =  $p < 0.05^*$

**Table 3: Reported Antimicrobial Stewardship and Patient Counselling Practices**

### 3.4. Strategies for Combating AMR

Table 5 synthesizes the multi-sectoral strategies preferred by the respondents to combat AMR alongside the multivariable logistic

regression analysis identifying the independent predictors of high stewardship compliance.

Strategy/Predictor	Finding
<b>Top Strategies to Combat AMR (% Selected)</b>	
1. Educational campaigns	83.2%
2. Development of therapeutic guidelines	63.8%
3. Control of antimicrobial sales	55.7%
4. Antibiotic Stewardship Programs	53.5%

**Table 4: Preferred Strategies for Combating AMR**

Outcome	Overall Mean ± SD	Physician	Pharmacist	Nurse	p-value
<b>Knowledge score</b>	55.2 ± 19.1	74.5 ± 12.3	56.4 ± 14.1	38.2 ± 16.5	<0.001*
<b>Confidence score</b>	3.72 ± 1.04	3.59 ± 1.25	3.91 ± 0.95	3.58 ± 0.98	0.261
<b>Attitude score</b>	3.80 ± 0.53	3.75 ± 0.45	3.86 ± 0.52	3.75 ± 0.58	0.448
<b>Practice score</b>	3.44 ± 1.12	3.56 ± 1.15	3.65 ± 1.22	3.09 ± 0.92	0.052
<b>High practice n (%)</b>	60 (40.0%)	14 (45.2%)	32 (49.2%)	14 (25.9%)	0.021*

Note: Knowledge scores were transformed to a 0–100 scale; confidence, attitude, and practice scores used a 5-point Likert scale, with higher scores indicating stronger performance.

**Table 5: Summary KAP and Stewardship Scores by Profession**

Group	N	Mean ± SD	Median [IQR]	High practice n (%)
<b>Full sample</b>	150	3.44 ± 1.12	3.69 (2.91–4.25)	60 (40.0%)
<b>Prescribers</b>	75	3.70 ± 0.96	3.88 (3.19–4.31)	35 (46.7%)
<b>Non-prescribers</b>	75	3.18 ± 1.22	3.62 (2.12–4.00)	25 (33.3%)

**Table 6: Sensitivity Analysis of Stewardship Practice Scores**

Predictor	Adjusted OR (95% CI)	p-value
<b>Higher professional confidence</b>	1.74 (1.16–2.61)	0.007*
<b>Less experience (&lt;5 years)</b>	0.45 (0.21–1.00)	0.050
<b>Physician vs nurse</b>	2.03 (0.75–5.52)	0.166
<b>Policy awareness</b>	1.20 (0.84–1.72)	0.315

Note: OR = odds ratio; CI = confidence interval. Models were exploratory and used ridge stabilization because some survey categories were sparse

**Table 7: Multivariable Predictors of High Stewardship Practice**

#### 4. Discussion

Most respondents (83.3%) considered AMR a problem in Anambra State, indicating strong overall awareness. Pharmacists showed the highest recognition (92.3%), while physicians and nurses reported lower proportions. Although these occupational differences were not statistically significant, the trend suggests pharmacists may have greater exposure to antimicrobial stewardship and medication

management. However, awareness alone does not necessarily translate into optimal prescribing behavior, as shown in both this study and previous literature [11]. The study also found encouraging awareness regarding antibiotic sharing, with 90% of respondents rejecting the use of another person's antibiotics. This suggests strong understanding of appropriate antibiotic use. However, significant occupational differences were observed in knowledge

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of AMR causes. Physicians and pharmacists showed greater recognition than nurses of inappropriate practices contributing to AMR, including unnecessary antibiotic use, wrong dosing, prolonged use, broad-spectrum antibiotic overuse, and treatment of viral infections with antibiotics. These differences likely reflect greater training in pharmacology, microbiology, and stewardship among physicians and pharmacists. Lower recognition among nurses, particularly regarding viral infections and broad-spectrum antibiotic misuse, is concerning given their role in medication administration, patient counselling, and infection prevention. Differences in provisional knowledge scores further reinforce profession-specific knowledge gaps. These findings support the need for role-specific AMR education. Physicians may require advanced stewardship training, while nurses may benefit from focused education on antibiotic indications, infection prevention, and recognition of antimicrobial misuse.

Knowledge of reserve and watch antibiotics was limited across all professional groups. Although some respondents correctly identified reserve antibiotics such as polymyxins, daptomycin, tigecycline, aztreonam, and fifth-generation cephalosporins, recognition remained generally low. Pharmacists and physicians performed better than nurses, with several occupational differences reaching statistical significance. These findings are concerning because the WHO AWaRe classification is central to antimicrobial stewardship. Poor recognition of reserve antibiotics may contribute to inappropriate prescribing and increased resistance pressure. Similar studies in Africa and Asia have also reported limited familiarity with the AWaRe framework among healthcare workers [12,9]. Pharmacists' relatively better performance may reflect their training in pharmacology and formulary management. However, the low identification rates across all professions suggest broader educational gaps.

Respondents generally reported moderate-to-high confidence in antimicrobial stewardship, with median scores of 4 out of 5 across most domains. Pharmacists reported the highest confidence, particularly in AMR knowledge, antimicrobial selection, dosage selection, therapy duration, combination therapy, and de-escalation. Physicians, despite lower confidence in general AMR knowledge, showed relatively strong confidence in interpreting microbiology results. The significant difference in confidence regarding AMR knowledge ( $p = 0.008$ ) suggests that professional roles may influence self-perceived competence, possibly reflecting pharmacists' medication-focused training. However, the absence of significant differences in overall confidence scores indicates that healthcare workers across professions generally perceive themselves as competent in antimicrobial-related activities. These findings should be interpreted cautiously, as self-reported confidence (3.72) does not always reflect actual prescribing competence (3.44). The gap between moderate confidence and limited AWaRe knowledge supports previous research highlighting the risk of overconfidence in antimicrobial stewardship [13].

Participants demonstrated positive attitudes toward AMR prevention and stewardship, strongly agreeing that AMR is a major problem, antibiotics are frequently misused, missed

doses contribute to resistance, and antimicrobial regulations are inadequate. Significant occupational differences were observed regarding perceptions of inadequate antimicrobial regulations ( $p = 0.040$ ), with physicians and pharmacists expressing stronger agreement than nurses. This aligns with reports from Nigeria and other LMICs describing weak regulation, over-the-counter antibiotic access, poor enforcement of prescription laws, and inconsistent stewardship implementation. Although respondents recognized AMR as a serious problem, they showed only moderate agreement that they might personally contribute to resistance. This may reflect a tendency among healthcare workers to attribute AMR mainly to other professionals, patients, or systemic failures. These findings highlight the need for interventions that encourage personal accountability and reflective stewardship practices [14].

Educational campaigns were the most commonly identified AMR control strategy (83.2%), followed by therapeutic guidelines, improved infection control, and regulation of antimicrobial sales. This aligns with global literature emphasizing education and stewardship guidelines as key interventions against AMR [14]. Physicians and pharmacists more frequently identified therapeutic guidelines and infection-control measures than nurses, likely reflecting differences in professional training and stewardship exposure. Fewer respondents recognized vaccination campaigns and reduced antimicrobial use in agriculture as important strategies, suggesting limited awareness of the broader One Health dimensions of AMR. Awareness of alternative approaches such as phage therapy and probiotics was also low, indicating limited familiarity with emerging therapeutic alternatives.

One of the most important findings was the very low awareness of national or facility antibiotic policies and guidelines, reported by only 22.1% of respondents. Exploratory regression analysis did not identify occupation or years of experience as significant independent predictors of policy awareness, suggesting that limited familiarity with antibiotic guidelines may represent a system-wide issue rather than a problem confined to specific professional groups. This suggests major implementation gaps within healthcare institutions and may reflect inadequate dissemination of stewardship policies, limited institutional support, and poor integration of stewardship activities into routine clinical practice. Respondents demonstrated moderate prescribing-practice scores overall, performing better in correct dose and route selection, evidence-based prescribing, and microbiology-guided therapy. However, weaker performance was observed in narrow-spectrum antibiotic use, avoidance of unnecessary prophylaxis, and limiting treatment duration. A significant occupational difference was found for narrow-spectrum antibiotic use ( $p = 0.006$ ). Sensitivity analysis showed that active prescribers demonstrated higher practice scores than non-prescribers ( $3.70 \pm 0.96$  versus  $3.18 \pm 1.22$ ), with a greater proportion achieving high practice scores (46.7% versus 33.3%), although inclusion of non-prescribers remained useful for understanding overall institutional stewardship culture. The observed practice gaps are consistent with previous evidence showing that broad-spectrum antibiotic overuse remains a major stewardship challenge in LMICs, often

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driven by diagnostic uncertainty, limited microbiology services, fear of treatment failure, high infectious disease burden, and weak stewardship oversight [14].

Respondents reported strong patient counselling practices, particularly on completing antibiotic courses, correct dosing intervals, avoiding antibiotic sharing, and proper antimicrobial disposal. These findings are encouraging, as patient counselling is an important stewardship strategy for improving adherence and reducing misuse. Pharmacists demonstrated the highest counselling scores, consistent with their role in medication education and antimicrobial stewardship. However, counselling on proper antimicrobial disposal received comparatively lower scores, indicating a need for targeted educational intervention.

The findings have important implications for antimicrobial stewardship policy and practice in Nigeria. First, despite high AMR awareness, important gaps remain in stewardship principles, AWaRe classification, and appropriate prescribing practices. Educational interventions should therefore focus on competency-based stewardship training rather than general awareness alone. Second, nurses demonstrated lower stewardship-related knowledge in several domains, highlighting the need for more inclusive multidisciplinary training. Stewardship programs in many LMICs remain physician-centered despite nurses' important role in patient care. Third, low awareness of institutional and national antibiotic guidelines suggests weak stewardship implementation within healthcare facilities. Policymakers and hospital administrators should prioritize dissemination of stewardship guidelines, establishment of stewardship committees, continuing professional education, audit and feedback systems, and improved microbiology support services. Fourth, the findings reinforce the importance of pharmacists in stewardship programs. Pharmacists demonstrated relatively strong AMR knowledge, confidence, and counselling practices, supporting their integration into multidisciplinary stewardship teams. Finally, persistent inappropriate prescribing practices, particularly broad-spectrum antibiotic overuse, indicate that awareness alone is insufficient to change practice. Stewardship interventions should therefore combine education with institutional regulation, surveillance, and behavioral change strategies. Multivariable analysis further showed that higher professional confidence was independently associated with stronger stewardship practice scores. This suggests that confidence in antimicrobial decision-making may positively influence stewardship behaviors. However, confidence should be interpreted cautiously because self-perceived competence does not always correspond with objective knowledge. Respondents with fewer than five years of experience also demonstrated lower odds of high practice scores, suggesting that practical clinical exposure may contribute to improved stewardship behaviors.

This study has several limitations. The cross-sectional design limits causal inference, and the use of self-reported responses may introduce recall and social desirability bias. The predominance of respondents from tertiary healthcare facilities may limit generalizability to primary and rural healthcare settings. However,

the findings regarding policy awareness may be optimistic, as tertiary facilities typically have better resources than the rural/primary settings mentioned in the Introduction. Additionally, because practice measures were self-reported rather than directly observed, reported behaviors may not fully reflect actual clinical practice.

## 5. Conclusion

This study showed that healthcare professionals in Anambra State have substantial awareness of antimicrobial resistance and generally positive attitudes toward stewardship. However, important gaps remain in stewardship knowledge, policy awareness, and optimal prescribing practices. Professional differences were evident, with pharmacists and physicians generally demonstrating stronger stewardship-related knowledge than nurses. Respondents actively involved in antimicrobial prescribing also demonstrated stronger stewardship practice scores than non-prescribers, although fewer than half met the threshold for high practice. Despite moderate-to-high self-reported confidence, knowledge gaps persisted, particularly regarding WHO AWaRe classifications and stewardship principles. Low awareness of antimicrobial policies and guidelines highlights a major systems-level challenge that may weaken stewardship implementation. Overall, the findings are consistent with studies from Nigeria and other LMICs showing that although AMR awareness is improving, effective stewardship remains limited by educational, institutional, and regulatory barriers. Future interventions should prioritize multidisciplinary stewardship education, guideline dissemination, stronger institutional stewardship programs, and greater integration of pharmacists and nurses into stewardship initiatives.

## Declarations

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### Conflict of Interest

The authors declare no conflict of interest.

### Ethical Approval

Ethical approval for the survey was obtained from the Ethics committee of the Chukwuemeka Odumegwu Ojukwu University Teaching Hospital (COOUTH), Awka, with reference number 'COOUTH/HREC/ETH.C/VOL.1/FN:04/316'.

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### Author Contributions

1. Chinelo Kene Ezejiegu: Research article concept, analysis
2. Benjamin O. Anyigor: Research design, data collection, write-up
3. Ezeinne C. Aniето: Data collection, write-up

4. Chidalu B. Ikeotuonye: Data collection, Literature review
5. Ijeoma Ebenebe: Research design, analysis, literature review

### Data Availability Statement

data available upon reasonable request.

### AI Usage Statement

Generative AI tools were used to support language editing and improve manuscript clarity. All interpretations, analyses, and final manuscript decisions were reviewed and approved by the authors.

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