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Review Article

A Systematic Review of Antibiotic Use in Humans in Nigeria and its Potential Contribution to Rising Antimicrobial Resistance

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Introduction: The value of medicines is lost when these resources are not used rationally. Out of 12 developing countries, Nigeria has the third highest percentage of antibiotic prescriptions, at 48%. Antibiotic misuse results in limited efficacy, which can lead to the emergence of antimicrobial resistance. We conducted a systematic review to synthesise the evidence on antibiotic use in humans in Nigeria.

Methods: We conducted a systematic review of medicine use behaviour by patients and prescription behaviour by health workers, which were searched for in articles published in English from 2000 to 2017. Data was entered into purpose-built templates. Key quantitative indicators were extracted and summarised as frequencies and proportions, while free-text responses were synthesised.

Results: The systematic review determined that the median prevalence of persons using antibiotics without prescription is 46.7%. The drivers of irrational antibiotic use included poor regulation of medicines and premises, a chaotic medicine distribution system, limited licensed medicine prescribers, over-the-counter (OTC) sales of antibiotics, patients' demand for antibiotics, and access to health insurance.

Discussion: Irrational antibiotic use is widespread in humans and animals. We recommend that the government enforce regulations on antibiotic sales to humans and animals and increase awareness of irrational antibiotic use and AMR in Nigerian communities through a whole-of-society approach. The collated information was used to develop a National Action Plan on AMR in 2017.

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Introduction

Since the advent of the first antibiotic (penicillin), 20 new classes of antibiotics have been introduced or approved for use between 1935 and 2012 (Figure 1) [1]. Concomitantly, there has been an increase in antibiotic use by animal and human populations. Global antibiotic consumption grew by over 30% in 71 countries between 2000 and 2010, with substantial increases recorded for low- and middle-income countries (LMICs) [2]. Notably, Nigeria contributes 60% of the health products consumed in the Economic Community of West African States (ECOWAS) sub-region, which has a population of 600 million [3].

Rational use of medicines (antibiotics), an important component of good clinical practice, requires that "patients receive medicines (antibiotics) appropriate to their clinical needs and at the lowest cost" [4][5]. In many countries, 80% of antibiotics used occur outside healthcare facility settings; more than half are unnecessary and inappropriate [6]. Out of 12 developing countries, Nigeria had the highest average number of medicines prescribed to patients per encounter (3.8 medicines/encounter) and the third highest percentage of antibiotic prescriptions (48%) during a field test [7].

While some patients are prescribed unnecessary courses of antibiotics, access remains an issue for others. In LMICs, 40% of antibiotics prescribed are insufficient doses, and half of those on therapy adhere to their regimens. Barriers to antibiotic access may be due to limited access to healthcare facilities, the unavailability of antibiotics in local markets, the cost of medicines, often in the face of high out-of-pocket spending, or ineffective medicine supply chain systems [8][9][10]. Patients may also be consuming counterfeit antimicrobials, which often contain suboptimal doses of the agent [11][12].

In May 2015, the 68th World Health Assembly (WHA) recognised AMR as a threat to global health and requested that member States participate in an integrated global programme for surveillance of AMR and adopt the global action plan. Nigeria committed to establishing a national AMR surveillance system in 2016, in conformity with the global action plan on AMR.

To provide baseline information to guide the proper implementation of the national AMR response, we conducted a systematic review to synthesise the evidence on antibiotic use in humans in Nigeria.

Methods

The protocol for the systematic review was developed by an AMR Working Group set up by the Nigeria Center for Disease Control (NCDC). We searched for articles published in English between January 2000 and January 2017 using Medline via PubMed and African Journals Online (AJOL) databases. The following search terms were used: “rational use”, “antibiotic consumption”, “antimicrobials”, “antibiotic”, “Nigeria”, “purchase of antibiotics” and “over the counter”.

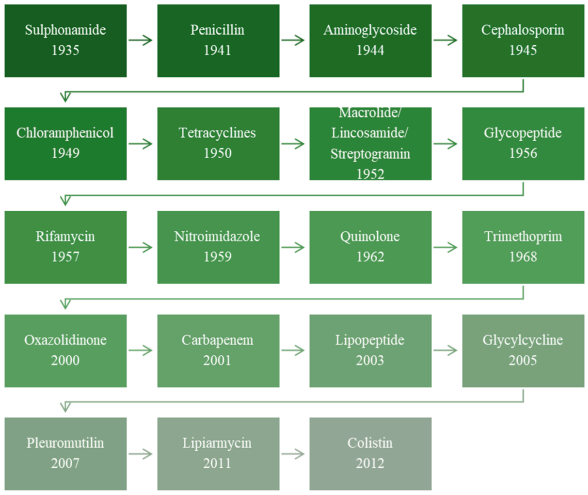

Figure 1. *Classes of antibiotics introduced or approved from 1935 to 2012*

The titles and abstracts of all potential papers were assessed independently by three of the authors (A.E., Y.E., O.A.), and the lists were compared to ensure that all studies had been identified and duplicates removed. Titles and abstracts of compiled studies were thereafter screened and followed by a full-text review. Articles that were not published in Nigeria were excluded ab initio. We extracted the relevant data using a database that listed the variables: author, year of study, location of study, study design, study setting and demographics, sample size and sampling method, exclusion criteria, commonest antibiotic used/prescribed, quantitative indicators and possible drivers of irrational antibiotic use. We extracted data and reported it as outlined by the reviewers without any alteration using the PRISMA statement, the preferred reporting system for systematic review and meta-analysis [13]. Any inconsistencies were discussed and finalised by the team members. Following our search, 849 articles were identified (Figure 2). Duplicates were removed, and 770

records were excluded based on incompatible titles and abstracts. Other articles were excluded because the article's outcome was not relevant to our objectives (3), only abstract data was available (11), three were reports (no primary data), and one was a field test. From the systematic reviews, drivers of irrational medicine were also compiled.

Data management

Two dimensions of irrational antibiotic use were searched: prescription behaviour by prescribers (supply) and medicine use behaviour by patients (demand). The possible drivers of irrational antibiotic use were summarised. Data was entered into purpose-built Word and Excel templates. The data was analysed as frequencies and proportions, while free-text responses were synthesised.

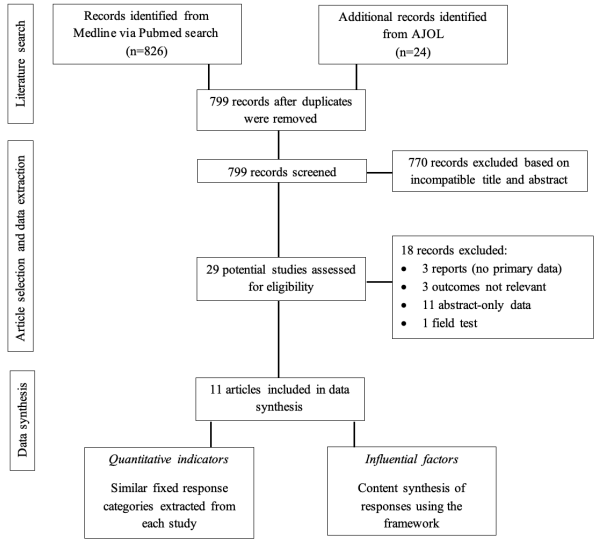

Figure 2. *Summary of the systematic review process*

Results

In total, 11 articles were included in the final data synthesis (Figure 2). All articles included used a cross-sectional design, and the majority (90%) were conducted in clinical settings. Three (27%) of the studies were from the southeast zone, four (36%) from the southwest, and two (18%) each were from south-south and north-central parts of Nigeria. No compatible articles were identified from the north-west or north-eastern zones. The study population in two (18%) of the identified studies comprised entirely of medical doctors.

Regarding antibiotic prescription, four articles (36%) reported the percentage of antibiotics prescribed per patient encounter. Among these articles, the percentage of antibiotics prescribed per encounter ranges from 26.8% among persons ≥15 years to 71.1% in children <5 years with a median of 44.7% [14][15][16]. One study (9%) found that 49.4% of patients attending NHIS clinics were prescribed antibiotics compared with 33.6% attending general outpatient (non-NHIS) clinics [17]. From three studies (27%), the percentage of antibiotics of all prescribed medicines among children under five years ranged from 13.0% to 53.7% [14][16][18]. Unnecessary prescription of antibiotics by medical doctors was also reported, with 56.4% of prescribers providing antibiotics empirically to children less than five years old visiting four clinics in one study [19]. Concerning the underuse of antibiotics, 25.5% of house officers were not confident in prescribing antibiotics to patients.

Concerning antibiotic use, three studies (27%) reported using antibiotics without a prescription. The proportion of persons using antibiotics without prescription ranged from 31.7% to 71.7%, with a median of 46.7% and the highest proportion reported among children <5 years [20][21][22]. One study (9%) found that only 42% of adults completed the recommended antibiotic course [22]. Eight (73%) articles, as outlined in Figure 3, reported the commonest antibiotic used or prescribed, which were Metronidazole for diarrhoeal diseases (71.4%), Penicillins (71.2%), Amoxiclav (70.9%), and Cotrimoxazole for sore throat (53.1%) [14][15][16][18][19][20][21][22].

From these studies, poor regulation of medicines, premises and practitioners, the volume of counterfeit medicines, the chaotic drug distribution system and over-reliance on imported medicines were some health system factors that may contribute to irrational antibiotic and medicine use in humans and animals [23][24]. Non-client-friendly opening hours by licensed prescribers/health facilities and geographical accessibility to OTC premises were also contributory [25]. Prescribers with longer years of practice who were non-specialised and older were more likely to give antibiotics empirically to children. In comparison, doctors with shorter years of practice were not confident in prescribing antibiotics to patients without supervision [19][26]. Patients on the National Health Insurance Scheme and demand for antibiotics by patients or their caregivers were also highlighted as some patient-related factors predisposing Nigerian

communities to higher antibiotic prescriptions [17][27]. Furthermore, having a caregiver with a lower education level, older age of caregivers and being a child contributed to higher chances of antibiotic use or prescription [20][21][27].

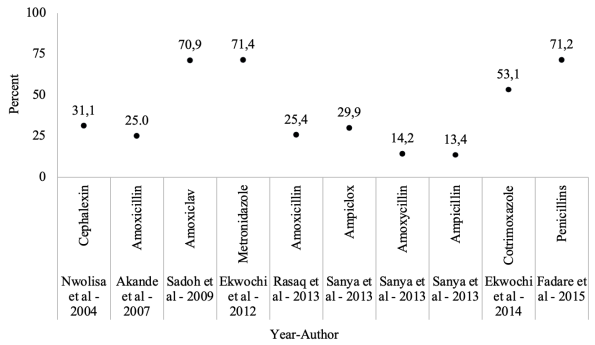

Figure 3. *Antibiotics used by or prescribed to humans in Nigeria, 2000-2017 (n=11)*

Discussion

Overall, one in two persons took unprescribed antibiotics or left the health facility with an antibiotic prescription, with higher proportions reported among children. At the health facility, irrational antibiotic prescriptions may be attributable to clinicians' lack of diagnostic support and tools and the prohibitive cost of healthcare to the majority of the population, worsened by limited health insurance coverage [28][29]. The national standard treatment guidelines (STG) aid empiric medicine prescriptions in Nigeria. However, the guidelines are not widely accessible, and AMR surveillance data do not guide the antibiotic recommendations [30][31]. Increasing access to diagnostic assays and tools for the healthcare provider and the patient (including financial access) are important interventions that would enhance appropriate antibiotic use and improve AMR detection in LMICs such as Nigeria, especially for children who appear to be more at risk [29].

The most common antibiotic used or prescribed was the penicillin group. According to a study on global antibiotic consumption, the most consumed antibiotics were cephalosporins and broad-spectrum penicillins, at 55% of the total standard units, with both medicines accounting for the largest absolute increases in consumption between 2000 and 2010 worldwide [2]. The implication is that the selective pressure on this class of antibiotics remains high and may account for the reduction in the therapeutic effect of these antibiotics, which may worsen if no action is taken. AMR in humans results from selection pressure on human microbiota following constant exposure to antibiotic residues or acquisition of resistant microbial genes from animals and/or the environment [29]. As such, a One Health approach to AMR surveillance is necessary to break the chain of transmission in the tripartite sectors, and quantifying the antibiotics sold for use in animals is a critical step in defining a strategy for AMR prevention in humans and animals.

Concerning drivers of irrational antibiotic use in this review, enrollment in the National Health Insurance Scheme (NHIS) clinic resulted in higher chances of being prescribed antibiotics [17]. The NHIS is a social security mechanism aimed at improving access to health services, encouraging the use of generic medicines, including antibiotics, and patients' contributions to co-payments are sometimes as low as 10% of total costs [28][32][33]. However, delays in reimbursing premiums to the healthcare facilities, combined with shortfalls in the amounts disbursed, as the government-set prices for health services are lower than the real costs, result in healthcare providers prescribing antibiotics empirically to minimise financial loss [34][35].

Another driver was patients' demand for antibiotics, which may be real or perceived by the healthcare provider [36][37]. Patients' beliefs that antibiotics are medications that can cure or prevent any illness often increase their expectations of antibiotic therapy [38]. At other times, healthcare providers may feel that patients would prefer an antibiotic prescription; the patient takes the medication because they feel the health provider is more knowledgeable [38][39]. These perceptions form the basis for a vicious cycle of demand and supply for unnecessary antibiotics during patient-health provider interactions. This highlights the need for patient and health provider education as a key factor in reducing antibiotic misuse in Nigerian communities and health facilities.

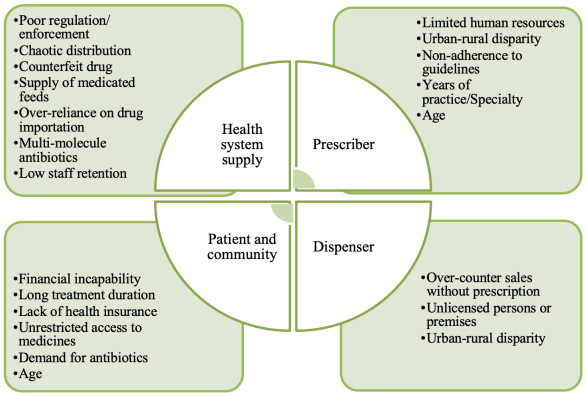

Figure 4. *Factors contributing to irrational antibiotic prescription and or use*

We also found that over-the-counter antibiotic access was a driver for irrational antibiotic use. The sale of antibiotics without prescription is widespread and poorly controlled [40][41][42]. By law, medical doctors in tertiary, secondary and private hospitals are authorised to prescribe medicines, including antibiotics and pharmacists are licensed to dispense antibiotics [43]. However, a high patient-to-doctor ratio has been reported in Nigeria, far below the 100 per 100,000 population recommended by the WHO, and these data is likely to be an underestimate given that the numbers reported do not account for deaths for doctors that are no longer practising or those practising outside the country [31]. The patient-to-pharmacist ratio is even higher. The paucity of licensed healthcare workers contributes significantly to increased work pressure and longer waiting hours in the clinic, thus limiting healthcare worker-patient interaction. In combination with other factors such as medicine stockouts at healthcare facilities, sparseness of licensed retail pharmacies and geographical accessibility of OTC premises, clients are "pushed" to seek care outside the healthcare facility [44][45]. These OTC premises often stock counterfeit medicines and are closer to poorer, hard-to-reach communities where regulatory oversight by the Food and Drug Administration agencies is limited. The National Drug Policy, Essential Medicines List and the National Drug Distribution Guidelines are some documents developed as part of the country's efforts to streamline medicine distribution [46][47][48].

We acknowledge that the data search ended in 2017 when the situation analysis was conducted in Nigeria. For the systematic review, we only searched PubMed and AJOL for literature; some journals are not indexed on these databases. We did not explore possible grey literature by contacting known experts for potential articles that are yet to be published. However, the evidence provided by this review represents a baseline assessment of the situation on antimicrobial use, which provides a comparator for future assessments. Understanding the situation in Nigeria is an excellent case study of the challenges low-income countries face in detecting and preventing AMR.

In conclusion, Nigeria has many legislations, albeit outdated, the workforce for health remains low and irrational antibiotic use is widespread in humans and animals, driven by uncontrolled access to antibiotics. Therefore, educating the public on irrational antibiotic use and AMR is crucial, and antibiotic prescription and sales regulations must be enforced. Universal health coverage and surveillance of resistant microorganisms should be prioritised in Nigeria. This will entail advocacy and training of the stakeholders and a whole-of-society approach. The gaps identified from these reviews formed part of the formative data to develop the first National Action Plan for AMR in 2017.

Statements and Declaration

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and its additional files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors reviewed, analysed and interpreted information related to antibiotic use and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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Declarations

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