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Original Article

Over-prescription of Watch antibiotics in primary healthcare settings in Sudan: results from routinely collected prescription data

Enjy Abdou[1], Rayan Hayder[2], Mohamed Salaheldin[3], Elseddig Eltayeb[3]

[1] *World Health Organization, Khartoum, Sudan*
[2] *Federal Ministry of Health, Khartoum, Sudan*
[3] *National Health Insurance Fund, Khartoum, Sudan*

Abstract

Introduction: Antimicrobial resistance represents a significant challenge in Sudan, further exacerbating the burden on healthcare systems already grappling with infectious disease epidemics. This study aims to examine the patterns of antibiotic prescription in primary healthcare settings (PHC) in Sudan and its compliance to the World Health Organization (WHO) Access, Watch and Reserve (AWaRe) antibiotic book.

Methodology: We collected retrospective data on antibiotic prescriptions at 325 PHCs in five states in Sudan for 2022. We collected patient-level data only for prescriptions with at least one antimicrobial prescribed. We used descriptive analysis to identify patterns of antibiotic prescribing according to the WHO AWaRe classification and to calculate the compliance of antibiotic prescriptions against the WHO AWaRe antibiotic book.

Results: A total of 52,274 antimicrobials were prescribed during 41,102 outpatient visits. Antibiotics accounted for 84.1% (n = 43,941) of prescriptions, of which 29.0% (n = 15,160) belonged to the Access antibiotics while 71.0% (n = 37,114) were from the Watch group. None of the prescribed antibiotics were from the Reserve group. Treatment of community-acquired pneumonia showed the highest compliance to the WHO AWaRe antibiotic book (40.1%, n = 447) followed by typhoid (31.5%, n = 53) and urinary tract infection (22.2%, n = 486). Though mostly caused by viral etiology, all patients with bronchitis received antibiotics.

Conclusions: Over-prescribing Watch antibiotics in outpatient settings in Sudan necessitates adopting multifaceted approaches including context-specific antimicrobial stewardship programs and behavioral change interventions targeting patients and prescribers.

Key words: Antibiotic prescription; primary healthcare; antimicrobial resistance; Sudan; AWaRe classification.

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Introduction

The rising threat of antimicrobial resistance (AMR) and drug-resistant infections affects all countries, compromises health outcomes, and increases the costs and complexity of care [1]. The burden of AMR is exacerbated in low- and middle-income countries (LMICs) due to the high burden of infectious diseases, lack or weak enforcement of regulations to prevent over–the–counter sales of antibiotics, and limited awareness among healthcare professionals [2]. Civil unrest and armed conflict can amplify the emergence and spread of AMR due to dysfunctional health systems, interrupted supply chains, poor compliance with infection prevention practices, breakdown of water and sanitation systems, and limited diagnostic capacities [3,4].

Primary healthcare (PHC) is the first contact with the health system. Furthermore, the COVID-19 pandemic has demonstrated the fundamental role of PHC in preventing and responding to epidemics while maintaining continuity of care. There is strong evidence that antibiotics are highly prescribed in PHC settings with a high proportion of inappropriate use, yet most of the interventions implemented to mitigate the burden of AMR target tertiary care and give little attention to PHC [5,6]. A recent systematic review reported that approximately half of the outpatients attending PHCs in LMICs received at least one antibiotic [7]. There is limited data on the extent and pattern of antibiotic use in PHC in fragile, conflict-affected, and vulnerable (FCV) countries.

Sudan is an FCV country that has faced multiple internal conflicts with the recent war that erupted in April 2023, which created a state of deep humanitarian crisis along with the already existing fragile health system [8,9]. The total population of Sudan is estimated to be around 49.4 million where approximately 40% are aged 0-14 years, 56% are aged 15-65 years, and 4% are older than 65 years [10]. Lower respiratory infections, diarrheal diseases, and HIV/AIDS were among the top

10 causes of death in 2019 [11]. There are 538 hospitals and 5,852 PHC in Sudan that are run by both the public and private sectors. The National Health Insurance Fund (NHIF) was established in 1994, and it is the main health insurance provider in Sudan. Membership is mandatory for the formal sector and voluntary in the informal sector. There are disparities in coverage between the formal and informal sectors, urban and rural areas, and between different states. Despite the presence of NHIF in Sudan, the country is still far from achieving universal coverage, and the sustainability of health insurance is questionable, mainly because of low governmental financial resources, especially after the latest war [12].

Antimicrobial resistance in Sudan is alarming with studies reporting the isolation of multidrug-resistant pathogens from hospitals in Khartoum [13-15]. The lack of regulations to control the selling and prescription of antibiotics and the increased demand of patients for antibiotics, even when not necessary, augments the AMR burden [16]. It is estimated that about half of the patients visiting PHCs are prescribed antibiotics, mainly broad-spectrum antibiotics and second-generation cephalosporins, in the absence of culture sensitivity testing, depending mainly on the presenting signs and symptoms for diagnosis [17]. Yet, data on the patterns of antibiotic prescriptions for PHCs are limited and there is no national-level aggregate data on outpatient antibiotic use. This study aimed to explore the pattern of antibiotic prescriptions according to clinical indication, geographical location, age, and prescriber level regardless of whether the antibiotics were dispensed or not. In addition, the study calculated the compliance of the prescribed antibiotic regimen to the treatment guidelines in the WHO AWaRE Antibiotic book that was recently published in 2022 and has a dedicated section for infection management in PHC [18].

Methodology

Study design and settings

This was an observational study. We collected retrospective data on the antimicrobial prescription at 325 PHC affiliated to the NHIF in five states (Red Sea, Sennar, Blue Nile, South Darfur, and North Kordofan) in Sudan. The five states cover an area of 559,877 Km^2 representing the north, south, east, west, and center of Sudan, with approximately 10.491 million residents, representing 25% of the population in Sudan. There are 649 PHCs in the five states (26% of PHCs in Sudan) distributed over rural and urban areas.

We selected 325 study sites based on the availability of a documentation system for patient-level data, where the attending healthcare provider documents the data of each outpatient visit manually on paper form and by the end of each calendar month; all forms are aggregated and archived at the state level NHIF office.

Data collection

We retrospectively collected data on antimicrobial prescriptions for 2022 from paper-form prescriptions at the study sites. We only included prescriptions with at least one prescribed antimicrobial agent. At each of the five states of NHIF, there was a team responsible for extracting data from the eligible paper form prescriptions and entering the data into an Excel database. Afterward, each state database was shared with the study coordinator, who checked for data completeness and inconsistencies and gave feedback to the study teams. In turn, the study teams re-checked the prescription forms and provided adjustments if possible. The study data manager compiled the five databases into one database ready for analysis.

We defined an antimicrobial prescription as any prescription that contains at least one systemic antimicrobial. We collected data on patients' age, sex, location, reasons for antimicrobial prescription, type of requested microbiological and radiological investigations, prescribed antimicrobials, dosage, route of administration, and level of the prescriber (consultant: holds a registered specialist qualification, registrar: has been a doctor for at least 4 years and will generally train for a further 4-6 years until becoming a consultant, house officer: has completed at least one year of postgraduate medical training, medical assistant: non-doctor who performs both administrative and clinical tasks).

Data analysis

We analyzed the data using STATA version 16 [19]. We used descriptive analysis to present the distribution of patients across demographic and clinical variables and to present the reasons for antimicrobial prescription encountered during outpatient visits. We presented the top 10 reasons for antimicrobial prescription, where a single patient could have more than one reason. We categorized the prescribed antimicrobials according to the Anatomical Therapeutic Chemical classification (ATC) for the classification of drugs at the level of the chemical group [20]. Patterns of antibiotic prescribing were categorized according to the WHO Access, Watch, Reserve (AWaRe)

Table 1. Characteristics of patients attending 325 primary care units in 5 states in Sudan, 2022 (n = 41,101).

Patient characteristic	No.	%
Age, median (IQR) (years)	23	(8 – 39)
Age group		
0 - 14	9,843	23.9
15 - 19	1,997	4.8
20 - 65	14,152	34.4
> 65	1,007	2.5
Missing	14,102	34.3
Gender		
Male	15,290	37.2
Female	25,811	62.8
State		
Red Sea	14,411	35.1
North Kordofan	10,059	24.5
Blue Nile	7,571	18.4
South Darfur	6,999	17.0
Sennar	2,061	5.0
Requested investigations		
All types of investigations	640	1.6
X-ray	373	0.9
Blood culture	187	0.5
Ultrasound	67	0.2
Urine cultures	9	0.02
Wound swab	4	0.01

classification, where the Access antibiotics group contains the first and second choice antibiotics for most common infections with maximum therapeutic effect and minimal potential to develop resistance. Watch antibiotic group contains antibiotics with a broader spectrum and a higher potential to develop resistance. Reserve antibiotics are the last resort antibiotics that should be reserved for multidrug resistant infections. Both the Watch and Reserve antibiotic groups should be targets for stewardship programmes.

We calculated the compliance of the antibiotic prescriptions for six clinical indications with the WHO AWaRe antibiotic book. We calculated compliance only for antibiotic prescriptions with ascertained infections (community-acquired pneumonia, enteric fever, urinary tract infection, pharyngitis, gastro-intestinal infection, and bronchitis) and excluded clinical indications with no final diagnosis and non-bacterial infections. We also excluded antibiotic prescriptions with more than one reason for antimicrobial prescription. An antibiotic prescription was considered compliant if the prescribed antibiotics were aligned with either the first or second-choice antibiotics recommended by the WHO AWaRe antibiotic book.

Table 2. Top 10 reasons for antimicrobial prescription in 325 primary care units in 5 states in Sudan, 2022.

Clinical indication	No.	%
Abdominal pain	20,244	49.3
Fever	9,289	22.6
Malaria	3,649	8.9
Bronchitis	2,840	6.9
Urinary tract infection	2,189	5.3
Community acquired pneumonia	1,114	2.7
Gastrointestinal infection	951	2.3
Pharyngitis	704	1.7
Common cold	200	0.5
Typhoid	168	0.4

Results

Patients' characteristics

We collected data on 41,101 outpatient visits to 325 PHCs in five states in Sudan in 2022. The median age of 26,999 patients with available age data was 23 (interquartile range, 8 – 39) years, and 62.8% of the patients (n = 25,811) were females (Table 1). The Red Sea state accounted for 35.1% (n = 14,411) of visits, followed by North Kordofan (24.5%, n = 10,059), Blue Nile (18.4%, n = 7,571), South Darfur (17.0%, n = 6,999), and Sennar (5.0%, n = 2,061). Only 1.6% (n = 640) of the patients were requested either radiological or microbiological investigations, whereas X-ray was the most requested investigation (0.9%, n = 373), while wound swab culture was the least requested (0.01%, n = 4). Table 2 presents the top ten reasons for antimicrobial prescriptions encountered during outpatient visits. Abdominal pain (49.3%, n = 20,244)

Table 3. Types of antimicrobials prescribed in 325 primary care units in 5 states in Sudan in 2022.

Types of antimicrobials (n = 52,274)	No.	%	AWaRe classification
Third generation cephalosporins (J01DD)	10,601	20.28	Watch
Penecillins with extended spectrum (J01CA)	9,535	18.24	Access
Antimalarials (P01B)	8,333	15.94	N/A*
Imidazole (J01XD)	7,381	14.12	Access
Macrolides (J01FA)	4,695	8.98	Watch
Penecillins with beta- lactamase inhibitors (J01CR)	4,399	8.42	Access
Fluoroquinolones (J01MA)	3,141	6.01	Watch
First generation cephalosporin (J01DB)	2,046	3.91	Access
Second generation cephalosporin (J01DC)	1,104	2.11	Watch
Tetracyclines (J01AA)	542	1.04	Access
Carbapenems (J01DH)	237	0.46	Watch
Trimethoprim- sulfamethoxazole (J01EE)	105	0.20	Access
Glycopeptides (J01XA)	69	0.13	Watch
Aminoglycosides (J01GB)	68	0.13	Access
Fourth generation cephalosporin (J01DE)	18	0.03	Watch

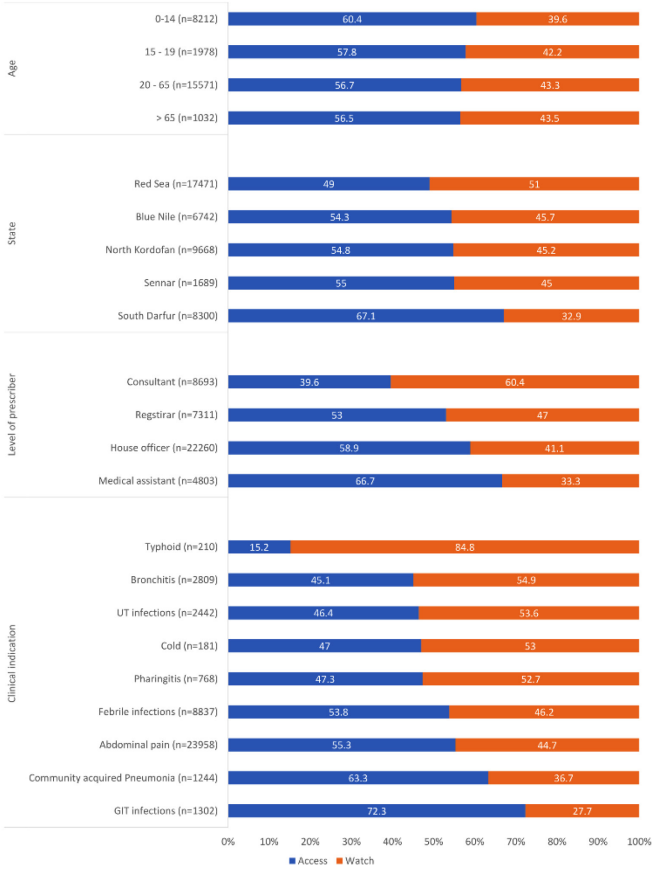
*N/A: not applicable.

was the most prevalent reason for antimicrobial prescription among outpatient visits, followed by fever (22.6%, n = 9,289), and malaria (8.9%, n = 3,649).

Patterns of antibiotic prescribing

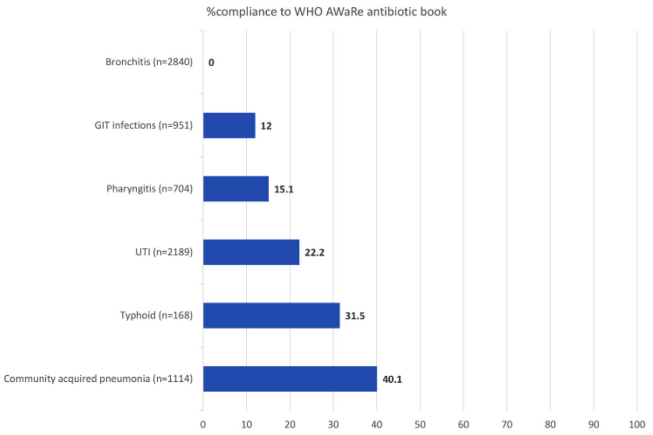
A total of 52,274 antimicrobials were prescribed during the 41,102 visits. Antibiotics accounted for 84.1% (n = 43,941) of total prescriptions, whereas antimalarials accounted for 15.9% (n = 8,333). Table 3 shows the distribution of antimicrobials prescribed during the visits. The top four prescribed antimicrobials were third-generation cephalosporins (20.3%, n = 10,601), penicillin with extended-spectrum (18.2%, n = 9,535), antimalarials (15.9%, n = 8,333), and imidazole (14.1%, n = 7,381). Of the 43,941 antibiotics, 29.0% (n = 15,160) were classified as Access antibiotics according to the WHO AWaRe classification, whereas 71.0% (n = 37,114) were from the Watch group. None of the prescribed antibiotics were from the Reserve group. Figure 1 shows the proportion of the Watch group antibiotics by age group, state, prescriber level, and reasons for antimicrobial prescription. There was

Figure 1. Proportion of Watch antibiotic prescription by reasons for antimicrobial prescription, prescriber level, state and age in 325 primary care units in 5 states in Sudan in 2022.



GIT: gastrointestinal tract; UTI: urinary tract infections.

Figure 2. Proportion of compliance to treatment guidelines in WHO AWaRe antibiotic book by clinical indication.



GIT: gastrointestinal tract; UTI: urinary tract infections.

no significant variation in the proportion of Watch group antibiotics among different age groups, ranging from 39.7% (n = 3,260) in the 0 -14 age group to 44.9% (n = 888) in the 15 – 19 age group. Watch group antibiotics represented more than 45.0% of the antibiotic prescriptions in all states, except for South Darfur (32.9%, n = 2,730). Consultants were the most likely to prescribe Watch group antibiotics, reaching up to 60.4% (n = 2,250). The proportion of Watch group antibiotics was highest for typhoid (84.8%, n = 178) and reached 53.0% (n = 96) and 55.0% (n = 1,545) in common cold and bronchitis, respectively.

Compliance to WHO AWaRe antibiotic book

Figure 2 shows the compliance rate of the treatment of different reasons for antimicrobial prescription with the WHO AWaRe antibiotic book. Bronchitis treatment showed the lowest compliance with the WHO AWaRe book, where all patients with bronchitis received antibiotics. The treatment of community-acquired pneumonia showed the highest compliance with the WHO AWaRe antibiotic book (40.1%, n = 447), followed by typhoid (31.5%, n = 53), and urinary tract infection (22.2%, n = 486).

Discussion

This study aimed to describe antibiotic prescription patterns across 41,101 outpatient visits to 325 PHCs in Sudan. The predominant reasons for antimicrobial prescription were abdominal pain (49.3%, n = 20,244) and fever (22.6%, n = 9,289). Third-generation cephalosporins (20.3%, n = 10,601) emerged as the most frequently prescribed antibiotics, with Watch antibiotics accounting for 71.0% (n = 29,182) of the antibiotic prescriptions, while the absence of Reserve

antibiotics is because it is not included in the Essential Medicine List (EML). Notably, all levels of prescribers tended to prescribe Watch antibiotics, even medical assistants who were legally not allowed to prescribe medications, among whom 33.3% (n = 1,600) of the antibiotic prescriptions fell within the Watch group. Additionally, Watch antibiotics were prescribed for common cold and bronchitis, which are typically of viral origin.

Though Sudan is classified as an FCV country, the prevalence of Watch antibiotics (71.0%) in this study exceeded those reported in other non- FCVs, such as Burkina Faso (58.0%), Ethiopia (56.0%), India (53.7%), Uganda (17.9%), and Vietnam (5.6%) [7,21,22]. The divergence in prescription practices could be attributed to various factors. Research in Sudan has highlighted an escalating patient demand for antibiotics, particularly expensive ones, perceived as more effective. Simultaneously, the NHIF offers 25% patient co-payment for medications, which might incentivize such practices [16,23]. Furthermore, the absence of regulations governing antibiotic purchases has facilitated the prescription and acquisition of Watch antibiotics. In 2021, a qualitative study was conducted in Sudan to explore the factors influencing the behavior of prescribers' antibiotic prescriptions in PHC. Among the findings were the limited knowledge of the antibiotics spectrum, limited communication skills needed to convince the patients, the need to prescribe broad-spectrum antibiotics due to failure to follow up with patients, and because patients have been self-medicated with antibiotics for long periods [23]. This might explain why even the consultants, the most experienced among the prescribers, failed to prescribe more Access antibiotics and preferred prescribing Watch antibiotics, especially third-generation cephalosporins. Such a practice fuels antimicrobial resistance, which is evident in studies in Sudan reporting high rates of Extended spectrum beta-lactamase-producing *Enterobacteriaceae*, up to 45.2% [24]. This dictates the need for a multi-faceted intervention to optimize the prescription of antibiotics in PHC, including policy changes in the NHIF co-payment, establishing stewardship programmes in the PHCs to educate the prescribers on the antibiotics spectrum and improve their communication skills, and the implementation of behavioral change interventions targeting both patients and prescribers.

Similar to other countries in the Eastern Mediterranean Region, the limited availability and utilization of microbiological diagnostics to inform treatment decisions, as evidenced by a mere 0.6% of patients undergoing culture sensitivity testing, contributes to the prevalent over-prescription of antibiotics [25]. Our study revealed that approximately 71.9% (n = 29,552) of the patients lacked a differential diagnosis for their conditions and were all prescribed antibiotic treatment. In low-middle-income countries, fever ranks among the most common reasons for seeking healthcare services, fostering antibiotic overuse, and the under-estimation of fevers caused by viral etiologies [26,27]. Sudan, characterized by endemic/epidemic occurrences of various infections causing acute febrile illnesses, such as malaria, dengue fever, typhoid, chikungunya, and Crimean Congo hemorrhagic fever, is particularly susceptible to this phenomenon [28,29]. Existing studies have underscored the prevalent underutilization of diagnostics in Sudan, leading to suboptimal patient management. For instance, one study reported correct diagnosis rates for malaria patients of only 68.9%, with essential tests conducted for only 11.1%. In another study involving 3961 dengue fever patients, blood cultures were requested for only 1.3% [30,31]. Additionally, deviations from standard recommended tests, such as employing the Widal test for enteric fever diagnosis instead of blood culturing, yielded a high rate of false-positive results (92.5%) and contributed to the overestimation of typhoid [32].

The World Health Organization (WHO) has established targets to combat antimicrobial resistance, recommending that 60% of national antibiotic use should be from Access antibiotics [33]. Moreover, the WHO sets specific guidelines for PHCs, aiming for less than 30% of patients visiting PHCs to receive antibiotics, as per the WHO Rational Drug Use Indicators. In 2022, the WHO introduced the AWaRe Antibiotic Book, offering guidance for optimizing empirical antibiotic prescriptions in both PHCs and hospitals [18]. The WHO AWaRe Antibiotic Book suggests that up to 90% of PHC infections can be effectively treated with oral Access antibiotics, and approximately 50% of minor infections like bronchitis and pharyngitis, can be managed without antibiotics. In our study, we found that compliance with the WHO AWaRe Antibiotic Book guidelines did not exceed 40.1% for any infection in Sudan. This raises questions about the practicality of implementing these guidelines in the country and achieving the WHO targets. However, a study conducted by Ingelbeen *et al.* in African countries with high rates of self-medication, such as Democratic Republic (DR) of Congo and Burkina Faso, revealed promising results. Compliance with the WHO AWaRe Antibiotic Book in these

countries could potentially replace 69% of Watch antibiotics in Burkina Faso and 75% in DR Congo with Access antibiotics or no antibiotics at all [34]. These findings suggest a substantial opportunity for Sudan to benefit from adopting similar practices, where the WHO AWaRe Antibiotic Book can be part of the stewardship programme in PHCs.

To our knowledge, this is the first and largest study to describe antibiotic prescription patterns in PHCs in Sudan using routinely collected data for 41,101 outpatient visits. By utilizing such data, this study effectively mitigated recall and reporting biases. Including five states, our research ensures geographical representation, spanning urban and rural settings in the northern, southern, eastern, western, and central regions of the country. Moreover, this is the first study to use the WHO AWaRe classification to assess the antibiotic prescription patterns stratified by patient demographics, reasons for antimicrobial prescription, and prescriber level, and the first study to measure antibiotic prescriptions compliance with the WHO Antibiotic AWaRe book. Notably, we quantified the proportion of patients who requested investigations, shedding light on the absence of point-of-care diagnostics.

Our study had several limitations. First, the selection of study sites based on the availability of documented antimicrobial prescription data introduces the potential for bias, as sites lacking such documentation may exhibit different prescription patterns. Second, the exclusion of patients who were not prescribed antimicrobials from the study precluded the calculation of the prevalence of antimicrobial prescriptions among all patients. Third, the absence of a final differential diagnosis and documenting only symptoms as indications for some of the prescriptions prevents the differentiation between the children and adult clinical presentation and the calculation of treatment compliance with the WHO AWaRe Antibiotic Book. Fourth, 34.3% of the age-related data were missing, potentially concealing any correlation between antibiotic prescription patterns and age. Fifth, the retrospective nature of the study limited our ability to validate or complete missing data. Lastly, it is important to note that our study was limited to patients covered by the NHIF, and the findings may not be fully representative of the broader population seeking primary healthcare services.

Conclusions

Our study underscores the prevalent use of Watch antibiotics in Sudanese PHCs. As our study was conducted prior to the recent conflict, it is plausible that the situation has been exacerbated since then. Addressing this challenge requires a comprehensive approach, including the formulation of policies to restrict the use of Watch antibiotics at the PHC level, adoption of treatment guidelines aligned with the WHO Antibiotic AWaRe book, ensuring the availability of point-of-care diagnostics, and implementing of targeted behavioral change interventions for both patients and prescribers.

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Corresponding author

Enjy Abdou, MPH, BPS
Technical officer for Antimicrobial Resistance
13 Othman Degna Street, Khartoum, Sudan
Tel: 002 01227310744
Email: hamede@who.int

Conflict of interests

No conflict of interests is declared.

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