ANTIMICROBIAL DRUG MISUSE IN THE EASTERN DEMOCRATIC REPUBLIC OF THE CONGO A CROSS-SECTIONAL STUDY: FACTORS INFLUENCING THE EMERGENCE OF ANTIMICROBIAL RESISTANCE

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Abstract
Background
Antimicrobial resistance is a major global public health challenge. In sub-Saharan Africa, Plasmodium resistance to new molecules on the market continues unabated. This increase in resistance is mostly due to unhealthy community practices, and also to microbial control methods that are ineffective because of our health policies. This study aimed to analyze factors involved in the emergence of antimicrobial resistance in ancient Kivu, in the eastern part of the Democratic Republic of Congo (DRC).

Materials and methods
A cross-sectional study was carried out from November 2023 to February 2024 in two cities east of the Democratic Republic of the Congo, surveying pharmacies using a standardized questionnaire. We focused on four elements within the pharmacies: the nature of the provider, the way medicines are sold (consumption), the location of the pharmacies, and the nature of drugs.

Results
Our study included 98 (56.9%) pharmacies, 66.3% (65/98) of which were located in peripheral areas with most of the untrained providers (91.7%; 11/12; p = 0.006) and in all pharmacies, 81% (47/58; p < 0.001) of their sales were based on patients' wishes. Nursing sales are 76.9% (20/26; PR: 1.9; 95% CI: 0.5-7.4; p = 0.009) undocumented among qualified staff involved in pharmacy sales.

Conclusions
The risk factors for developing antimicrobial resistance in these two cities in eastern DRC are related to undocumented drug sales and qualified providers in pharmacies. This requires a high level of awareness among those involved in the sale of medicines and those who receive them.

Recommendation
Our proposal is for strict protection of antimicrobial resources through regulation of their sale in the region.

Introduction
Given the growing threat of antimicrobial resistance, the World Health Organization (WHO) recommends, as part of its health promotion activities, rigorous monitoring of antimicrobial consumption to ensure rational and proportionate use and to prepare an effective response to resistance (1,2).

In recent years, antimicrobial resistance (AMR) has increased worldwide, particularly in sub-Saharan Africa, with Plasmodium becoming increasingly resistant to the new drugs on the market, including artemisinin, one of

the best products available, either alone or in combination. Despite this, we are seeing an increasing number of malaria-related deaths in the affected regions, due not only to the severity of the disease but also to the increasing resistance of Plasmodium to the product, characterized by an increase in parasite clearance time (3,4).

This resistance has been observed in most of the neighboring countries of the Democratic Republic of the Congo (DRC), particularly in the east, especially in Uganda and Rwanda. It is thought to be the cause of some of the treatment failures observed in clinics, making it difficult to control and eradicate the endemic disease (2,3). In ancient Kivu, in the eastern part of the country, few studies have been carried out in this area. This is despite the vulnerability of the population.

Observing the practices behind the emergence of antimicrobial resistance implies that the concerned actors have a fairly rigorous system for monitoring the factors that can trigger or maintain the rise of resistance to various pathogens, including Plasmodium, in the region. This study aimed to analyze the factors involved in the emergence of antimicrobial resistance (AMR) in general and of antimalarials in particular.

Material and method
Study design
This was a cross-sectional descriptive and analytical study.

Setting Study
The study took place in two cities in the region, Bukavu and Kindu, the two capital cities of three provinces in the ancient Kivu, in the eastern part of the DRC. Data was collected over approximately 4 months, starting on the 1st day of November 2023 and ending on the 29th day of February 2024.

Participant
The study population consisted entirely of pharmacies. In the two cities, we surveyed different pharmacies according to where they were located: those located in the city center and those located on the outskirts.

Selection criteria
The study included pharmacies that were recognized and authorized to operate by the provincial health department. It also included pharmacies where there was an adult provider with an acceptable level of education (from the fourth year of secondary school, the former primary and secondary education system in the DRC) and where the provider was willing to participate freely. On the other hand, pharmacies without a name, with minor providers, or with a low level of education were excluded from the study.

Data sources/ measurement
A standardized questionnaire was used to collect data from providers in different pharmacies through a semi-structured interview.

Bias
To reduce bias within the study, a mechanism was introduced to prevent the investigator from affecting participants' responses or behavior. We used semi-structured interviews to ensure that the questions were simple and clear, and we interviewed service providers who had a good level of education.

Study size
Sample size took into account the number of pharmacies reported by the provincial health departments to ensure that the results that could be estimated and reported with confidence were statistically significant, as variability within the study population could affect the results.

Study target and definition
The study focused on four elements within pharmacies: The nature of the provider, the way drugs are sold (consumed), the location of the pharmacies, and the drugs.

We had two types of providers: qualified (trained) providers, consisting of nurses, doctors, and pharmacists. And unqualified (untrained) providers, consisting of anyone without medical training.

In terms of sales methods, we had two concepts that were scored on a scale of 0 to 10: documented sales (relatively high presence of medical prescriptions; score 6-10) and undocumented sales (those who did not have a regular frequency of medical prescriptions; score 0-5).

The partial sales were defined as incomplete consumption of antimicrobials, either with or without a doctor's prescription. A quantity of products used for less than three days, depending on the type of product, was considered a partial sale, whereas a complete sale was defined based on a quantity of products estimated to last for three days or more.

The different medicines were grouped into families, including antibiotics, antimalarial, antipyretics, and other medicines (antihistamines, corticoids, etc.).

Statistical collection and analysis
They were entered and recorded in Excel 2013 and analyzed using Jamovi 2.3.26 software, where the different qualitative variables were expressed as numbers and percentages. Comparisons between groups were made using the Chi-2 test. Univariate and multivariate analyses were performed on factors associated with the sale of antimicrobials, looking for the concepts of documented sale of antimicrobials, quality of providers within pharmacies, and their locations, with a p-value < 0.05 for a statistical significance threshold using epi info software version: 7.2.5.0.

Ethical considerations
The study was approved by the academic institution and the provincial health authorities. We respected the rights of the participants and the principle of confidentiality after obtaining their informed consent.

Results

Figure 1: Pharmacy distribution flow chart
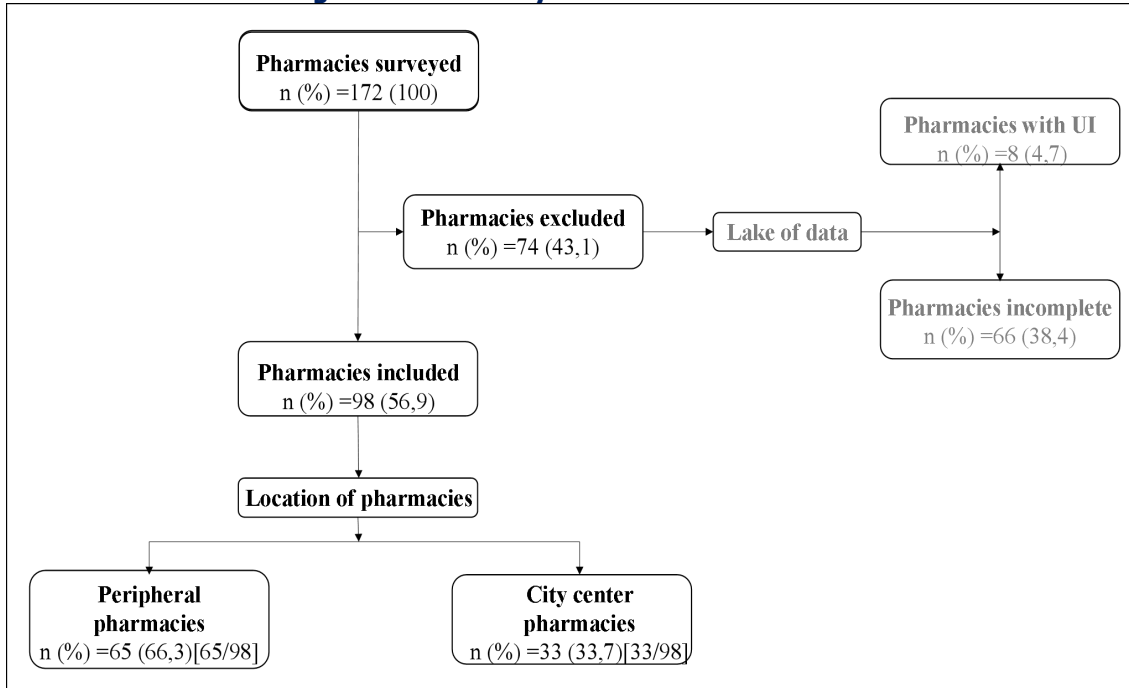
Note: n: number, %: percentage, UI: unclear information

A total of 172 pharmacies were surveyed in the two cities, of which 98 (56.9%) were included in the study and 74 (43.1%) were excluded for lack of data. To highlight the factors involved in the emergence of antimicrobial resistance in general and antimalarial resistance in particular, the analyses of the different variables were designed as follows.

The location of pharmacies, the nature of the providers, and the basis for selling medicinal products

During our study, we found that pharmacies in peripheral areas were the most present in the study, with 66.3% (65/98), significantly different from pharmacies in the city center (Table 1); they also had a majority of untrained providers (staff), 11/12 (91.7%; p = 0.006), and 81% (47/58; p < 0.001) of their sales were based on patient (beneficiary) wishes. Antibiotics were sold by nurses in 27% of cases (95% CI: 16.6-39.9; p < 0.001), while antimalarials were sold by pharmacists in the same proportion as antibiotics, i.e. 20% (95% CI: 5.7-43.7; p = 0.012) in Table 1. Sales of antimalarials represent 20% (95% CI: 4.3-48.1; p = 0.035) and antibiotics represent 33.3% (11.8-61.6) of sales in pharmacies that receive prescriptions fairly frequently, but 16% (95% CI: 4.5-36.1; p < 0.001) of pharmacies sell based on their suggestions and 13.8% (95% CI: 6.1-25.4; p < 0.001) based on patients' (beneficiaries') wishes (Table 1)

Table 1: The location of pharmacies, nature of the providers, and the basis for selling medicinal products

Variables	Location of pharmacies		P	Total	Antibiotics		P	Antimalarial		P	Antipyretics		P	Other		p
	CC f (%)	Pe f (%)			f	% (CI 95%)		f	% (CI 95%)		f	% (CI 95%)		f	% (CI 95%)	
Nature of the providers																
Nurse	25 (41,7)	35 (58,3)	0,245	60	17	27 (16,6-39,7)	< 0,001	9	15 (7,1-26,6)	< 0,001	24	40 (27,6-53,5)	0,15	10	16,7 (8,2-28,5)	< 0,001
Doctor	1 (16,7)	5 (83,3)	0,219	6	1	16,7 (0,4-64)	0,219	1	16,7 (0,4-64)	0,219	4	66,7 (22,2-95,7)	0,68	0		
Pharmacist	6 (30)	14 (70)	0,11	20	4	20 (5,7-43,7)	0,012	4	20 (5,7-43,7)	0,012	9	45 (23,1-68,5)	0,824	3	15 (3,2-37,9)	0,003
US (UP)	1 (8,3)	11 (91,7)	0,006	12	5	41,7 (15,2-72,3)	0,77	1	8,3 (0,21-38,5)	0,006	6	50 (21,1-78,9)	1	0		
Basis of sale																
MP	10 (66,7)	5 (33,3)	0,302	15	5	33,3 (11,8-61,6)	0,302	3	20 (4,3-48,1)	0,035	5	33,3 (11,8-61,6)	0,302	2	13,3 (1,6-40,5)	0,007
PP	12 (48)	13 (52)	1	25	7	28 (12,1-49,4)	0,043	4	16 (4,5-36,1)	< 0,001	9	36 (18-57,5)	0,23	5	20 (6,8-40,7)	0,004
PW	11 (19)	47 (81)	< 0,001	58	15	25,9 (15,3-39)	< 0,001	8	13,8 (6,1-25,4)	< 0,001	29	50 (36,6-63,4)	1	6	10,3 (3,8-21,2)	< 0,001

Note: MP: medical prescription; PP: providers' proposal; PW: patients' wishes; US (UP): untrained staff (untrained providers); other: antihistamine (2), anti-inflammatory (6), corticosteroids (2), antacid and proton pump inhibitor (1); CC: city center; Pe: periphery; f: number; CI: confidence interval; p: significance threshold; p-value significant at 0.05.

Provider profiles and risk factors associated with developing AMR

In Table 2, we see that nurses are the profile of providers making 76.9% (20/26; PR: 1.9; 95% CI: 0.5-7.4; p = 0.009) of undocumented sales of antimicrobials in a statistically significant way, and selling antimicrobials is associated with 60% (PR: 1.6) of undocumented sales, but without a substantial difference.

The proportion of partial undocumented sales of antimicrobial agents (without a medical prescription) by nurses working in pharmacies was 13/14 (92.9%; p = 0.002), with a significant difference. Undocumented partial sales of antimicrobials by different pharmacy providers were 80% more frequent than documented partial sales (RP: 1.8; 95% CI: 0.13-58; p=0.6).

However, 50% of dispensed antimalarials were associated with medical documentation (PR: 1.5; p = 0.57), twice as much with qualified providers (PR: 2.1; p = 0.6), and city center location (PR: 2.6; p = 0.07), but this was not statistically significant. Our observations are an indication that there is no evidence of partial sales of antimalarial drugs in pharmacies.

Table 2: Provider profiles and risk factors associated with developing AMR

Variables	Types of service providers f (%)				Drugs f (%)	PR	CI 95%	p
	Nurse	Doctor	Pharmacist	US	Antimicrobials			
Documented sales								
Yes (n= 15)	6 (23,1)	0	2 (25)	0	8 (53,3)	1,6	0,5-5,2	0,35
No (n= 84)	20 (76,9)	2	6 (75)	6	34 (40,4)			
P	0,009		0,289					
Documented partial sale								
Yes (n= 3)	1 (7,1)	0	1	0	2 (66,6)	1,8	0,13-58	0,6
No (n= 45)	13 (92,9)	5	0	5	23 (51,1)			
P	0,002							
					Antimalarial			
Documented sales								
Yes (n= 15)	2 (22,2)	0	1 (25)	0	3 (20)	1,5	0,3-6,1	0,57
No (n= 84)	7 (77,8)	1	3 (75)	1	12 (14,2)			
P	0,18		0,625					
Documented partial sale								
Yes (n= 0)	0	0	0	0	0			
No (n= 45)	5	0	2	0	7			
P								
Qualification of the service provider								
Yes (n= 86)	9	1	4	0	14 (16,2)	2,1	0,25-17,9	0,6
No (n= 12)	0	0	0	1	1 (8,3)			
P								
Pharmacy location								
City-center (n= 33)	5 (55,6)	1	2 (50)	0	8 (24,2)	2,6	0,74-9,5	0,07
Periphery (n= 65)	4 (44,4)	0	2 (50)	1	7 (10,7)			
P	1		1					

Note: PR: Prevalence Ratio; CI: Confidence Interval; p: Significance Level, p-value significant at 0.05; US: Untrained Staff, f: Number of personnel.

Discussion

Pathogen resistance to antimicrobial agents is on the rise and taking its toll on healthcare systems around the world. It is now considered a major health scourge, and despite progress in control measures, concerns remain. Sub-Saharan Africa in general, and the Democratic Republic of Congo in particular, are making considerable efforts to curb this rapidly growing problem.

Observations show that it is in the peripheral areas of our cities that there are the most pharmacies and, curiously, a high proportion of unqualified providers who sell antimicrobials at the request of patients (beneficiaries).

However, qualified personnel are also negatively involved in the undocumented sale of antimicrobials, which is thought to be an important element in the emergence of antimicrobial resistance in infectious agents in the region.

Regarding the sale of antimalarials, despite the different methods used, we did not find any evidence of partial sales in any of the providers' pharmacies; it's the opposite for other antimicrobials.

As for antibiotics, for which partial sales are common, various studies show that the worrying figures continue to rise, such as the results for pathogen resistance to third-generation cephalosporins, which reached 97.63% and 100% for *Klebsiella pneumonia and Salmonella spp.* (5).

This inappropriate use of medicines and the limited resources of the health system, on the one hand, and divergent practices, on the other, is due either to ignorance or to the destruction of the country's socio-economic base, which is at the root of the population's poverty. This context makes access to quality care difficult and the population turns to less recommended methods, including the use of all kinds of medicines without biological proof.

The use of antimicrobial agents is problematic in situations where there is a lack of diagnostic resources (equipment); treatment is based on different clinical approaches like algorithms and/or probabilistic treatment guidelines. In almost all countries where bacterial infections and malaria are known to be the main causes of death, patients are very often treated indiscriminately with antimicrobials on admission. Data from one study shows that in sub-Saharan Africa, between 83% and 100% of children admitted to our health facilities are treated with antibiotics on admission (6).

Alongside known healthcare facilities and pharmacies where antibiotic use is well controlled, there is a parallel, uncontrolled system (the black market) offering a range of non-compliant and counterfeit medicines. There is also inappropriate use of antibiotics in humans and animals, all of which would be facilitated by the free movement of drugs (7–9). This availability of antimicrobials outside formal channels leads to high consumption and compromises not only rational antimicrobial regulation but also the means to combat AMR (2,5).

This suicidal attitude should be eradicated by raising awareness among the population and service providers, as the WHO in the DRC insists, by making health workers and laboratory technicians aware of the importance of carrying out antibiotic susceptibility testing before prescribing, and also by making patients aware of the importance of following doctors' instructions (5).

In addition to the liberalization of the sale of antimicrobials in general, a new practice is currently taking place in the region: the policy of free distribution of antimalarial drugs, with or without biological proof, as part of the eradication of malaria, a practice that is not in line with WHO recommendations (10,11). This unilateral eradication approach, which ignores the role of the environment on both the vector and the host, is inappropriate and would be a major factor influencing the emergence of AMR, either through inappropriate treatment or increased drug pressure. The antimalarial drugs used would be at the root of both the emergence of resistant strains and mutations in Plasmodium genes leading to resistance to the molecules concerned, as well as the development and spread of Plasmodium resistance to antimalarial drugs. Studies have shown high levels of parasite resistance in the Mekong Basin and in several East African countries, including Uganda, Rwanda, and Eritrea, DRC's eastern neighbor, where these attitudes may be related (2,3,12).

In the case of malaria, however, partial consumption of antimalarials has not been detected for several reasons. The widespread availability of easy-to-use rapid diagnostic tests (RDTs) would explain the absence of documented partial sales of antimalarials in pharmacies. Another hypothesis is that the packaging of the best-selling oral antimalarials (artemisinin-based combination therapies: ACTs), which are blister-packed co-formulated tablets corresponding to weight classes for complete individual treatment, makes partial sales more difficult. However, it should be noted that most pharmacists are qualified and also try to reduce the impact of inadequate treatment that contributes to developing resistance (5,13).

Conclusion

Antimicrobial resistance policy still faces many challenges in the DRC, so it is important to monitor the various emerging factors involved in antimicrobial resistance in general and antimalarials in particular, to implement control strategies.

Most pharmacies are located in peripheral areas and providers are selling antimicrobials at the request of patients (beneficiaries).

The undocumented sale of antimicrobials involves qualified personnel.

There is no evidence of the partial sale of antimalarial drugs in the pharmacies.

Generalizability

Several parameters were taken into account to ensure the generalizability of the study. The size of the sample, despite the case of exclusion, is still fairly representative, based on pharmacies with the approval of the provincial health departments.

The method used to select the sample allowed the pharmacies included to benefit from a random selection

that took into account the two study sites: the city center and the peripheral areas of the two cities. The study was representative of all providers, qualified and unqualified, working in pharmacies and covered more than one quarter and was completed over two years.

Limitations
However, the study was limited to a few pharmacies in the two urban centers of two provinces in the region. This is not enough, as it would have been better to also have an idea of antimicrobial sales in rural and semi-urban areas.

Recommendation
To protect antimicrobial resources, these results could help the health authority to properly regulate the sale of antimicrobial drugs in the region.
But also to promote the rational use of antimicrobials among the general public, and especially among healthcare professionals involved in prescribing and selling.

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List of abbreviations
Democratic Republic of Congo (DRC), World Health Organization (WHO), Antimicrobial Resistance (AMR), Rapid Diagnostic Tests (RDTs), Artemisinin-based Combination Therapies (ACTs).

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Not

Conflict of interest
We have no conflicts of interest related to this study.

Authors' contributions
MML, BAC, and KMB designed and supervised the study.
MML, BAM, and WBF received agreements from pharmacies to participate in the study, collected information for the questionnaires, and coded the data.
MML carried out the analysis and interpretation of the data as well as being primarily responsible for drafting the manuscript.
GMS, BNN, IMF, CMS, MMG, KMB, and WBF revised manuscript.
All authors have read and approved the final manuscript.

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