Quality of antimalarials in Kinshasa peri-urban areas with regard to local pharmaceutical legislation and regulation

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Background: In the context of old pharmaceutical legislation and regulations not adapted to current realities, the aim of the present study was to evaluate the existing pharmaceutical system in peri-urban areas of Kinshasa.

Methods: A prospective study was carried out during the period 2016–2018. The most used antimalarial medicines were identified through household and pharmaceutical establishment surveys. The samples of the obtained medicines were assayed with generic separation methods using the high-performance liquid chromatography technique coupled to a diode array detector. The registration status was checked for 126 antimalarial brand names. A characterization was carried out in 196 pharmaceutical establishments on the basis of standards set out by the Ministry of Health.

Results: Of the 75 samples assayed, 19% (14/75) were non-compliant. Of the 124 brand names, 46.0% (57/124) were unlicensed and 14.5% (18/124) had an expired licence. Of the 196 pharmaceutical establishments, only 2 (1.0%) had an authorization to practice, none met all the Ministry of Health minimum standards and 24.5% (48/196) met the World Health Organization Guidelines for the Storage of Essential Medicines and Other Health Commodities.

Conclusions: More resources should be mobilized to apply regulator sanctions.

Keywords: Characteristics of pharmacies, Democratic Republic of the Congo, Kinshasa, Peri-urban areas, Testing and Treatment Algorithm, Pharmaceutical legislation and regulation, Quality of antimalarials

Introduction

The alarming proliferation of poor-quality medicines is a real public health concern.[1] The initial difficulty in the fight against this scourge was finding a unanimous definition for the concept of poor-quality medicine. Three definitions have been adopted since May 2017 by the WHO: (i) substandard medical products also called 'out of specification': these are authorized medical products that fail to meet their quality standards, their specifications or both; (ii) unregistered/unlicensed medical products: medical products that have not undergone evaluation and/or approval by the national or regional regulatory authority for the area in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation; (iii) falsified medical products: medical products that deliberately/fraudulently misrepresent their identity, com-

position or source.[2] Falsified medicines may contain no active ingredient, an inappropriate active ingredient or the appropriate active ingredient but at a dosage outside the specification range. They are sometimes contaminated with bacteria and may also contain unknown impurities or toxic chemicals. They promote the development of antimicrobial resistance and medicine-resistant infections.[2,3] Falsification affects all categories of medicines.[3,4] However, antimalarials and antibiotics are most often reported as substandard or falsified medical products.[5,6] This situation is linked to the wide use of these two categories of medicines in both urban and peri-urban areas in sub-Saharan Africa.[1] In many developing countries in Africa, substandard or falsified medicines are estimated to account for >30% of the medicines in circulation.[7] This proportion can be up to 80% in some countries.[1]

In the Democratic Republic of the Congo (DRC), some laws and regulations are no longer appropriate and do not allow an adequate response to the current challenges in the pharmaceutical sector. The informal market and trafficking of falsified medicines involves life-threatening diseases, and these medicines are the most sought after,[8] particularly in the DRC, in order to fight malaria.[9] Malaria has its highest prevalence in peri-urban areas,[10] where the demand for antimalarials is growing exponentially. The issue related to the quality of medicine in Africa's urban and peri-urban areas has been addressed by several authors.[1,8,11] However, aspects directly related to regulation enforcement have not been addressed. Thus the purpose of the present study was to assess the existing pharmaceutical system in peri-urban areas of Kinshasa, mainly with regard to the use of antimalarials and their quality, the proportion of unlicensed antimalarials and the characteristics of pharmaceutical establishments.

Materials and methods

Study setting

The city of Kinshasa is built mainly on two geomorphological sites: the 'lower city' or the 'plain of Kinshasa' and the 'upper city' or the 'hill zone'.[12] The city has expanded much more in the south and southwest than in the east. The expansions to the east have reached the municipality of N'sele. The expansions to the south and southwest include the upper west city, whose most important administrative entity is the municipality of Mont Ngafula.[12,13] The present prospective study was carried out in peri-urban areas of Kinshasa in the four municipalities presented in Figure 1, during the period February 2016–May 2018. The period of the study covers two particular events: the publication in October 2016 of the third edition of the directory of pharmaceutical products registration by the Direction de la Pharmacie et du Médicament (DPM)[14] and implementation of the Kinshasa Health Provincial Division and the Kinshasa Health Provincial Inspectorate.[15]

Sampling and data collection

Study design

Sampling type. Two types of sampling were used: simple random sampling for both surveys of pharmaceutical establishments and the procurement sources for assayed antimalarials, and two-stage cluster sampling for the household survey.

General formula of sampling size. The theoretical sample size (N) was calculated based on the following general formula: $N=p(1-p)z^2/E^2$, where p is the prevalence, z is the confidence interval and E is the margin of error. However, for the household survey, the cluster effect was taken into account, so the theoretical sample size was calculated based on the following formula: $N=[p(1-p)t^2/E^2]DEFF$, where t is the confidence interval for the cluster sampling and $DEFF$ is the cluster effect.

The investigation team. The investigation team consisted of 1 principle investigator, 2 supervisors and 16 investigators. The principle investigator was the contact person with the political, administrative and health authorities of the study site. In addition, the principle investigator had to fully understand the purpose of the study, the languages used for the survey, the survey methods and the data collection tools. Supervisors and investigators had to have a medical background in order to help the respondents understand the questionnaire. Specific additional training related to the main objective of the study was given, particularly on the survey methods and the data collection tools.

Summary of data collection processes and expected results. The three surveys and the outcomes are presented in Figure 2a and b.

Inclusion and non-inclusion criteria. At the household level, the questionnaire was administered to the household head (first target). If the household head was absent, the oldest member (>15 y of age) of the household present at the time of the survey was interviewed.[16] Households that did not satisfy either of these two conditions were not included. At the point of sale, the questionnaire was administered to the seller. Only private pharmacies were included in the study. In 2013, the share of the private sector antimalarial market accounted for 97%.[17] Neighbourhoods with limited geographic access were not included. More details on sampling, sample size, data collection for the household survey, the survey of pharmaceutical establishments and procurement sources for assayed antimalarials are available in the supplementary data.
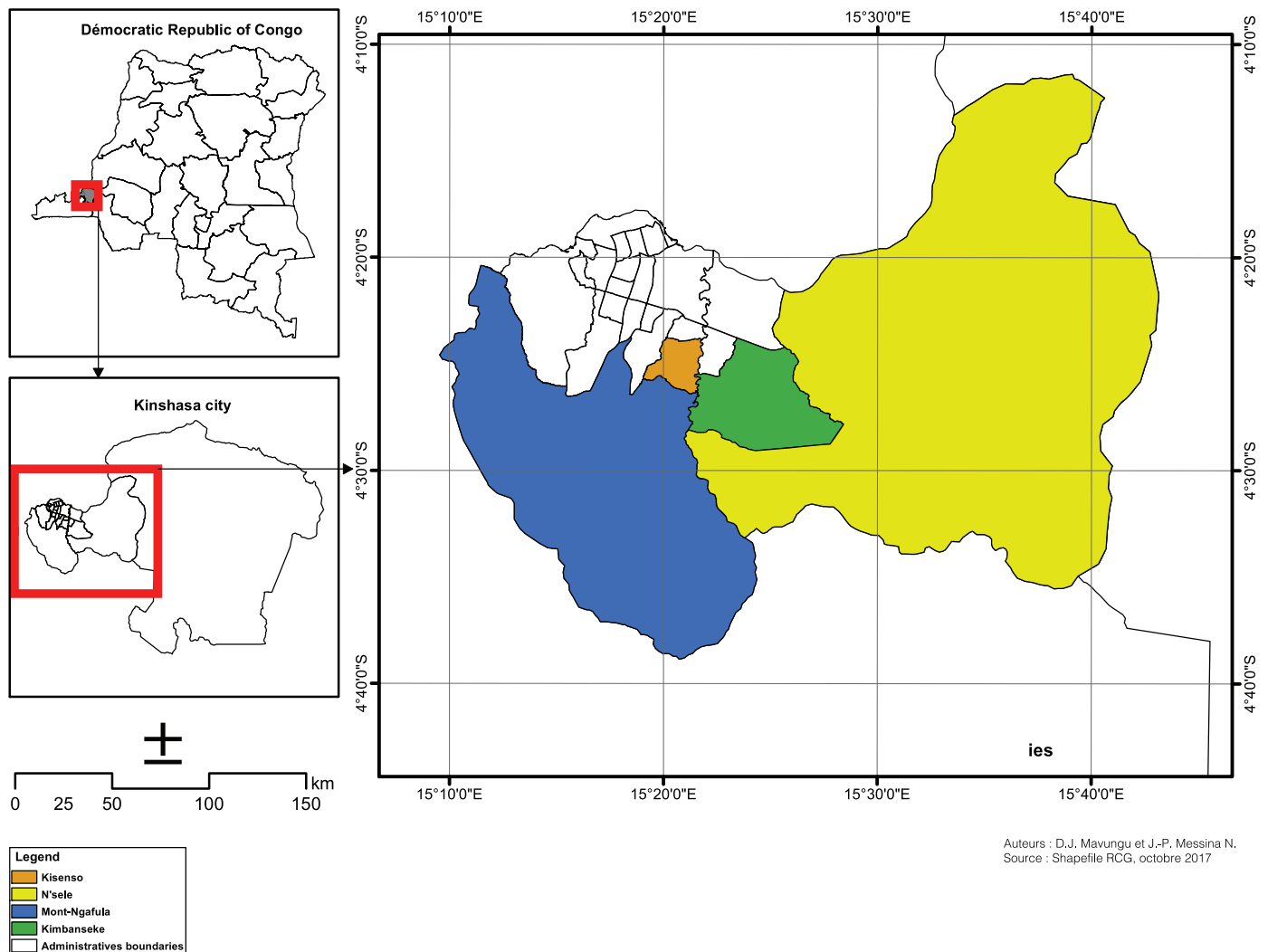
Analyses

Data analyses

Data from the household and the first visit at the pharmaceutical establishments were captured using the Census and Survey Processing System version 6.0.1 (US Census Bureau, Washington, DC, USA). The data were analysed using the Statistical Package for the Social Sciences version 23.0.0 (IBM, Armonk, NY, USA). Data from the second visit to the pharmaceutical establishments were collected through the KoBoCollect application (Harvard Humanitarian Initiative software, Cambridge, MA, USA). The mapping of the study area and the surveyed pharmaceutical establishments was performed using ArcGIS version 10.5 (Environmental Systems Research Institute, Redlands, CA, USA).

Physicochemical analyses

The quality analysis of the collected medicine samples was carried out at the drug testing laboratory at the University of Kinshasa and at the WHO prequalified laboratory (Department of Pharmacy, Liège University) using generic separation methods with the high-performance liquid chromatography technique

Figure 1. Location of the study area in the peri-urban areas of Kinshasa.

coupled to a diode array detector. The physicochemical analyses consisted of identifying the active ingredients, their dosage and in some cases the pH of the solutions and the mass variation.

Ethical considerations

The study protocol was approved by the Congolese National Committee for Health Ethics (authorization no. 016/CNES/BN/PMMF/2016 of 8 January 2016). The ethical principles outlined in the Declaration of Helsinki were observed. In accordance with the Ethical Guidelines for Research Involving Human Subjects in the DRC and based on the nature of the study, the DRC National Ethics Committee for Health authorized verbal informed consent. The investigators explained in detail the purpose of the study before collecting and recording the verbal informed consent of the participants. The participants were not exposed to any experiment, as no biological samples were collected for analysis. They essentially answered a questionnaire and were not

followed up after the interview. The survey questionnaire was anonymous. Thus the study presented no risk or negative effect for the participants; on the contrary, the information provided was beneficial to them.

Results

Interviews and desk reviews

Before investigating, in addition to the desk review of the narrative reports, several interviews were held with the Director of General Inspectorate of Health, the Provincial Medical Inspector and the Chief Medical Officer of the Kinshasa Provincial Division. It was noticed that the quality of medicine in Kinshasa depends very much on the legislation and regulations in force. The entire country is also concerned. A conceptual framework (Figure 3) presents the various aspects resulting from the implementation of legislative and regulatory texts, which ultimately have an influence on the quality of medicines.
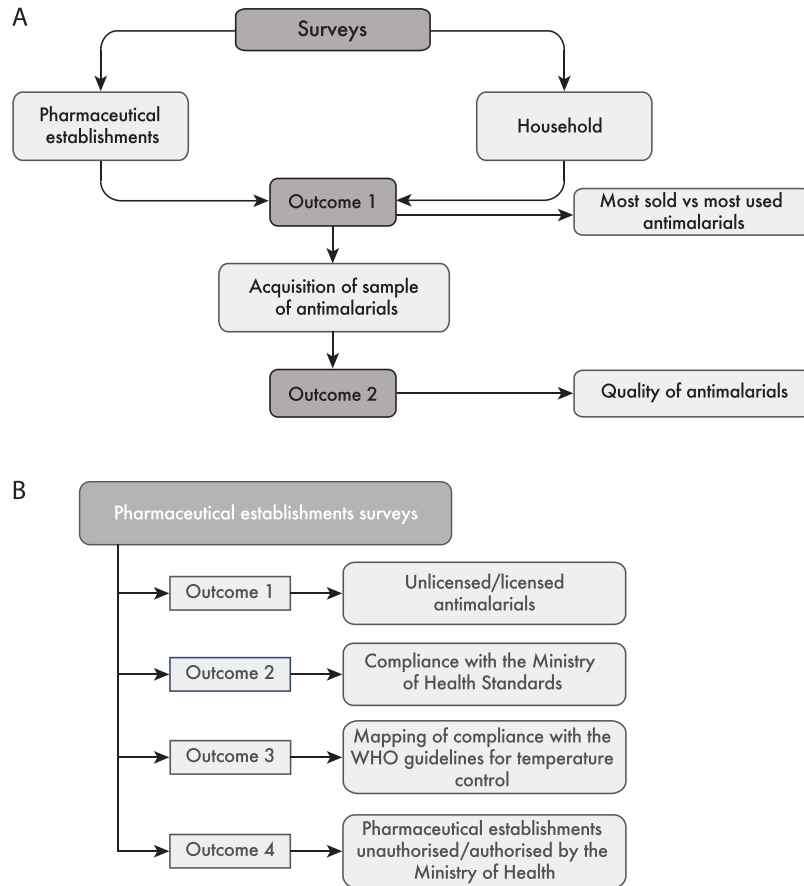
Figure 2. (A) Scheme of two surveys conducted at the level of pharmaceutical establishments and households. (B) Scheme of the third survey conducted at the level of pharmaceutical establishments.
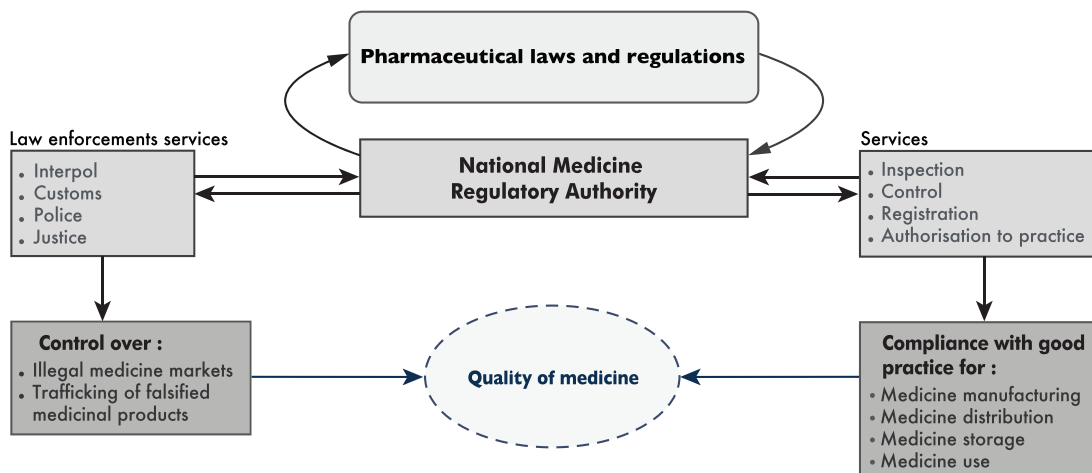

Figure 3. Conceptual framework of factors influencing the quality of medicines. Where laws and regulations are not updated and/or are not properly enforced by the national drug regulatory authority, law enforcement and inspection services become ineffective, resulting in non-compliance with good practices and the circulation of falsified medicines in thriving illicit markets. This has a negative impact on the quality of the medicines consumed.
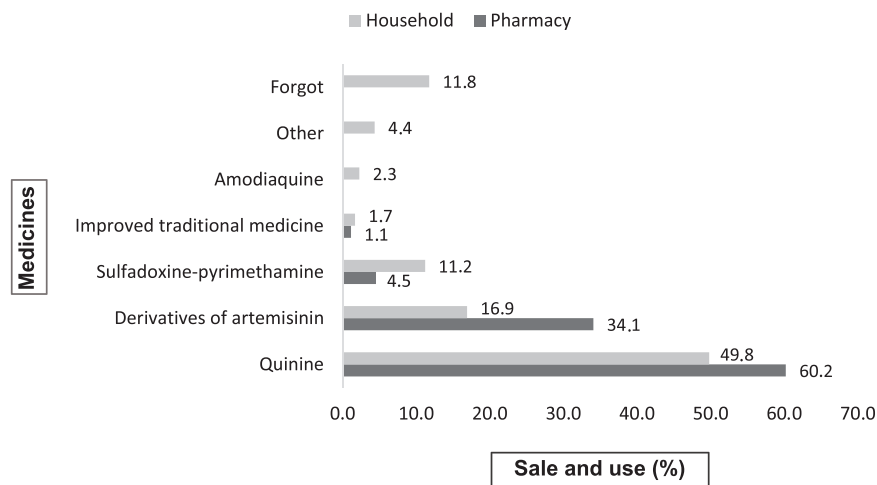
Figure 4. Comparison of the survey results from the pharmaceutical establishments and households in relation to the sale and consumption of antimalarial medicines in peri-urban areas of Kinshasa (pharmacy n=88, household n=526). Of a total of 1150 households surveyed, malaria occurred in 548 households, of which 526 used an antimalarial medicine. Antibiotics, analgesics and vitamins, reported by the respondents, were classified in the 'other' category.
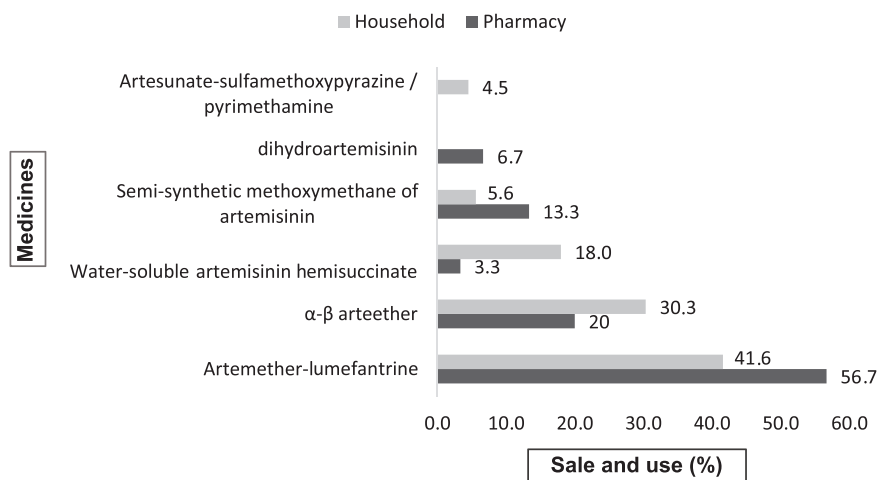

Figure 5. Comparison of the survey results from the pharmaceutical establishments and households in relation to the sale vs consumption of artemisinin derivatives alone or in combination (pharmacy n=30, household n=89).

The most frequently sold and most used antimalarials

Two surveys were conducted concurrently. One included 1150 households and the other included 88 pharmacy sales clerks in order to identify the most used and the most frequently sold antimalarials. In the household, the distribution of the respondents indicated a predominance of women (796/1150) compared with men (354/1150), i.e. a male:female sex ratio of 0.4. The mean age of respondents was 34±13 y (range18–83). In terms of education, 556 of 1150 respondents (49.2%) had completed at least secondary school. A total of 662 of 1150 respondents (57.6%) were married or cohabiting/living together and 630 (55.5%) had a monthly income of >$50 and spent two-thirds of their income on food, with one-third for other expenses (transportation, medical care, etc.). A total of 548 of the 1150 surveyed households (47.7%) reported facing an episode of malaria in the 2 weeks prior to the survey and 526 of the 548 households (96.0%) that faced a malaria episode used an antimalarial medicine. Regarding the surveyed pharmaceutical establishments, the distribution showed a predominance of men (55/88) compared with women (33/88), i.e. a male:female sex ratio of 1.7. The mean age was 35±10 y (range 18–70). In 57 of 88 cases (65%), the seller was not the owner of the pharmaceutical establishment.

Interviews with households (Figure 4) showed that the most used medicine was quinine, followed by artemisinin derivatives and the sulfadoxine–pyrimethamine combination. In the pharmaceutical establishments, these same antimalarials are reported as being the most frequently sold. Also, 11.8% (62/526) of people had forgotten the name of the antimalarial they used. Among the artemisinin derivatives alone or in combination (Figure 5), the artemether–lumefantrine combination was found to be the most frequently sold (17/30) and used (37/89), followed by α-β artemether in terms of sales (6/30) and in terms
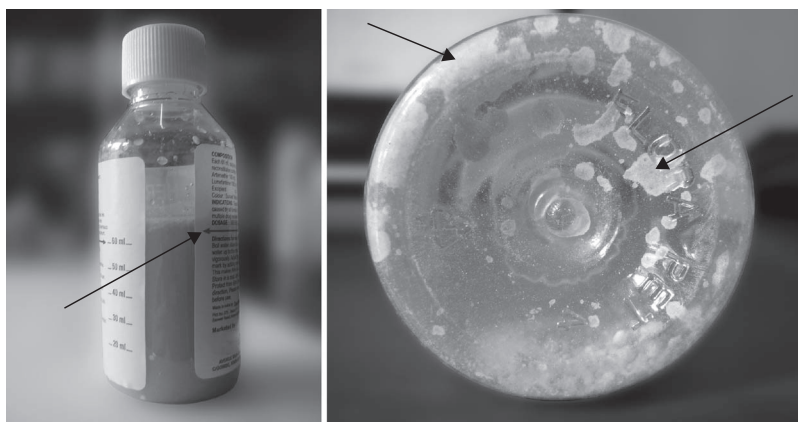
Figure 6. Visual analysis. On the left, improper label positioning. On the right, the presence of moisture traces on the primary packaging.

Table 1. Results of quinine sample assay

Product assayed	Quantity found after assay (%), mean±SD (n=3)*	pH	Uniformity of mass	Decision
Quinine tablet	QD=300 mg 92.7±0.21	–	Compliant	Compliant
Quinine tablet	QD=300 mg 104.1±0.06	–	Compliant	Compliant
Quinine tablet	QD=300 mg 95.2±1.64	–	Compliant	Compliant
Quinine drop 20%	QD=200 mg/ml 104.4±0.50	1.52	NA	Compliant
Quinine drop 20%	QD=200 mg/ml 96.2±1.54	1.52	NA	Compliant
Quinine drop 20%	QD=200 mg/ml 98.3±1.21	1.69	NA	Compliant
Quinine drop 20%	QD=200 mg/ml 98.1±1.05	1.51	NA	Compliant
Quinine drop 20%	QD=200 mg/ml 108.6±1.28	1.59	NA	Compliant
Quinine drop 20%	QD=200 mg/ml 98.6±0.60	1.6	NA	Compliant
Quinine drop 20%	QD=200 mg/ml 95.9±0.51	1.62	NA	Compliant
Quinine injectable	QD=600 mg/2 mL 97.7±0.09	1.83	NA	Compliant
Quinine injectable	QD=500 mg/2 ml 98.9±0.02	2.07	NA	Compliant
Quinine syrup 2%	QD=200 mg/5 mL 108.9±1.05	2.38	NA	Compliant
Quinine syrup 2%	QD=200 mg/5 mL 115.7±0.78	2.86	NA	Non-compliant
Quinine syrup 2%	QD=200 mg/5 ml 128.7±0.85	2.86	NA	Non-compliant

*Range 90.0–110.0%. QD: quantity claimed by the manufacturer.

of use (27/89). In third place, sellers reported semisynthetic methoxymethane of artemisinin (4/30), while other households reported water-soluble artemisinin hemisuccinate (5/89).

Quality of antimalarials and registration status

Visual analysis

The irregularities that were observed mainly concerned the artemether–lumefantrine combination. Twelve of 30 cases (40%) had a labelling issue and 17% (5/30) of the packages showed traces of moisture (Figure 6).

Identification and assay of the antimalarials

Analyses were performed on the two most frequently sold and most used antimalarials, quinine and the artemether–lumefantrine combination. The first decisive step was to confirm the presence of the active ingredients and the content as claimed by the manufacturer. The manufacturer's claims were considered as the reference (100%), with a range of 90.0–110.0%. Molecules whose content was within this range were compliant. Quinine analyses involved 15 samples, comprising 7 oral drops (47%), 3 tablets (20%), 3 syrups (20%) and 2 injectable ampoules (13%) (Table 1). Two syrup samples (13.3%) were found to be non-compliant, with assay results above the specifications. Analyses also included 30 samples containing the artemether–lumefantrine combination in powder for oral suspension (Table 2). Of the 60 analyses, 12 (20%) were non-compliant, among which 7 were due to lumefantrine molecules and 5 were due to artemether molecules with assay results below the specifications.

Registration status

A total of 57 of 124 antimalarials (46.0%) were unlicensed by the DPM (Figure 7).

Characteristics of pharmaceutical establishments

Of 196 outlets, only two had legal authorization from the Ministry of Health. The observations presented in Table 3 indicate that in some cases the front of the pharmaceutical establishment served as a trading venue for products not related to health, such as engine oil (Figure 8). No pharmaceutical establishment met the Ministry of Health minimum standards. The temperature control criteria recommended by the WHO were met by 24.5% (48/196) of the pharmaceutical establishments in the area of study (Figure 9).

Discussion

Interviews and desk reviews

Pharmaceutical legislation and regulations constitute a guarantee for the quality of medicine (Figure 3). Countries with lax pharmaceutical governance and pharmacovigilance are most exposed to substandard and falsified medicines.[21,22] Thus efforts to improve supply chain management, inspection and regulation are essential to control exposure to substandard and falsified medicines.[23]

Table 2. Results of artemether–lumefantrine combination sample assay

Quantity found after assay (%), mean±SD (n=3)*		Decision
Artemether (QD=180 mg)	Lumefantrine (QD=1 080 mg)	
83.6±0.68	90.3±1.59	Non-compliant
99.4±0.60	95.0±1.27	Compliant
85.1±1.84	82.5±2.92	Non-compliant
99.6±0.67	94.1±1.40	Compliant
99.4±0.52	97.1±1.04	Compliant
98.1±1.81	90.7±2.60	Compliant
92.8±1.47	90.6±1.82	Compliant
82.4±0.25	94.1±1.88	Non-compliant
90.8±0.51	78.7±1.54	Non-compliant
94.4±0.78	90.3±1.59	Compliant
95.6±0.41	97.2±1.41	Compliant
108.1±1.01	104.7±1.04	Compliant
91.1±1.31	93.7±1.38	Compliant
90.7±1.49	93.4±0.39	Compliant
95.1±1.42	82.8±0.93	Non-compliant
86.4±0.98	98.3±1.22	Non-compliant
96.6±0.87	87.4±1.01	Non-compliant
90.3±0.98	88.1±2.01	Non-compliant
95.9±1.04	100.4±3.36	Compliant
90.1±0.72	90.2±1.33	Compliant
97.3±0.78	81.5±2.01	Non-compliant
103.7±0.79	96.8±1.78	Compliant
98.4±1.64	99.0±1.81	Compliant
88.1±1.66	88.7±1.01	Non-compliant
105.5±1.12	91.2±0.85	Compliant
98.6±0.98	97.4±1.45	Compliant
99.7±1.78	98.1±1.48	Compliant
96.8±1.66	97.1±2.08	Compliant
99.7±0.78	97.7±1.27	Compliant
97.1±1.78	98.1±1.55	Compliant

The most frequently sold and most used antimalarials

In the case of simple malaria, the National Malaria Control Program recommends artemisinin-based combination therapy (artemether–lumefantrine or artesunate–amodiaquine) as first-line therapy. In case of failure, the Program recommends another artemisinin-based combination therapy or quinine combined with an antibiotic.[22] Note that the care of patients with complicated malaria is undertaken in health facilities, which were not included in our surveys. Pharmacy and household surveys (Figure 4) showed a greater use of quinine compared with the artemisinin derivatives, including the artemisinin-based combinations. In households, the rate of forgetting is quite high, 11.8% (62/526).

In Kinshasa, the Demographic and Health Survey II reported the same trends. The most commonly used antimalarial was quinine (68.2%), followed by artemisinin derivatives (17.7%), includ-

Table 3. Results of the characterization of pharmaceutical establishments

Standard observations	House built of durable materials, electrified with ceiling, comprising at least four rooms
	Building materials: 191 of 196 pharmacies were constructed of brick, except for five that were constructed either of sheet metal or wood.
	Electricity: 185 of 196 pharmacies had an electrical installation, however, only 84 of 185 pharmacies with an electrical installation had electricity at the time of the investigation.
	Generator: Of the 112 pharmacies that either did not have an electrical installation or had the electrical installation without having electricity at the time of the survey, none of them had a generator working at the time of the investigation.
	Rooms: 185 of 196 pharmacies had only one room; four pharmacies had two rooms and one pharmacy had four rooms.
	Ceiling: 73 of 196 pharmacies did not have any ceiling.
Standard observations	The Ministry of Health recommends a building area of about 45 m^2, including 20 m^2 for sales
	Surface: 1 of 196 establishments had an estimated area of 56 m^2, all the others (195/196) had an area $<$45 m^2, with 55 having an area $<$12 m^2.
Standard observations	Suitable air conditioning, a refrigerator, metal or lacquered wood shelves, wall thermometer and hygrometer
	Air conditioning: 191 of 196 pharmacies did not have any air conditioning systems.
	Window: 36 of 196 had no windows. Of the pharmacies with windows, 151 of 160 pharmacies had only one window.
	Fan: 91 of 196 pharmacies had a fan. Of the pharmacies with a fan, only 49 had working fans at the time of the survey.
	Refrigerator: 70 of 196 pharmacies had a refrigerator. However, of the pharmacies with a refrigerator, only 34 had a working refrigerator at the time of the survey.
	Shelves: 194 of 196 pharmacies had wooden shelves and one had metal shelves. The only pharmacy that did not have any shelves had a cabinet and a table.
	Wall thermometer and hygrometer: No pharmaceutical establishment had a wall thermometer or hygrometer.
Other observations	Non-pharmaceutical products were sold in 74 of 196 pharmacies. 46 of 74 activities involved the sale of bottled water, followed by the sale of soft drinks and beer (18/74). The rest of the activities related to foreign exchange trade and the sale of cosmetics, food, jewellery and airtime credits.

ing artemisinin-based combinations (14.6%).[16] This increased use of quinine provides information on non-compliance with good antimalarial use practices, as advocated by the National Malaria Control Program. It should be noted that quinine is more affordable than the artemether–lumefantrine combination and is mostly used for fever.[17,22]

Quality of antimalarials and registration status

For quinine, 2 of 15 samples of an overdosage of syrup were found, which could cause haemolytic anaemia, digestive intolerance, tinnitus, headache and vision problems. This overdosage could be a manufacturing issue. Overall, of a total of 75 molecules assayed, 18.7% (14/75) were non-compliant. This proportion of non-compliant antimalarials is close to that reported by Ozawa et al.'s meta-analysis of 19.1%.[21] The size of the samples analysed was not representative. However, the preliminary survey conducted on households and pharmacies allowed for the selection of the most representative antimalarials used. Quinine, which is the most used medicine, had a lower rate of non-compliance than artemether–lumefantrine.

In the DRC there are 29 production units, only 5 of which apply good manufacturing practices,[15,23] and most of these are based in Kinshasa. The Ministry of Health reports indicate that the main characteristic of the pharmaceutical industry in the DRC is the circulation of poor-quality medicines. Two causes are
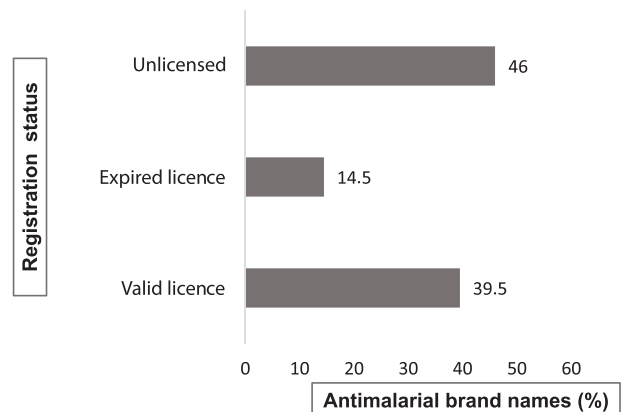

Figure 7. Distribution of antimalarial brand names sold in pharmaceutical establishments in the peri-urban areas of Kinshasa according to the certification status (n=124).

mentioned. The first relates to the dysfunction of the quality assurance system and the second is related to ineffective pharmaceutical inspections. This is caused by a lack of laboratory equipment for quality control.[15,23] Nearly half of the antimalarials in circulation had no marketing authorization (Figure 7). This allowed us to evaluate the size of an illicit market that hinders the efforts of health authorities to improve the health of

Figure 8. A pharmaceutical establishment dealing with the sale of motor oil in a peri-urban area of Kinshasa.
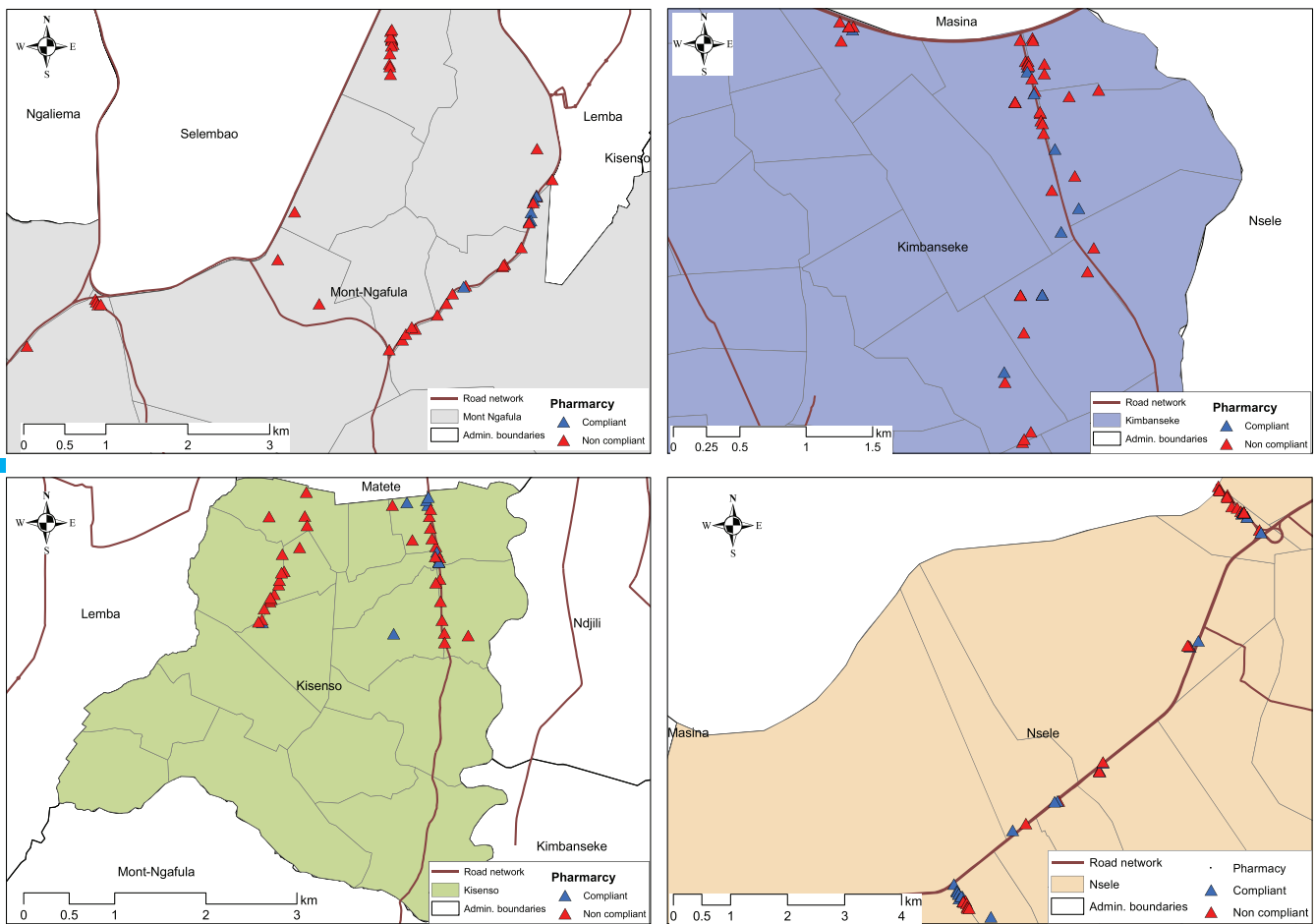

Figure 9. Mapping of pharmaceutical establishments on the basis of the WHO guidelines for temperature control. Four municipalities of the peri-urban areas of Kinshasa are represented: Mont Ngafula (upper left, 59.6%), Kisenso (lower left, 14.0%), Kimbaseke (upper right, 8.0%) and Nsele (lower right, 18.5%).

the population. It is hoped that the General Inspectorate for Health, instituted in 2017, will provided oversight and inspections to improve quality control.[24] Antimalarials authorized on the Congolese market accounted for 56.0% (67/124) of the total,

of which 14.5% (18/124) had an expired licence (Figure 7). A review of the authorized medicines directory reported worrisome information. The review, conducted in December 2017, revealed that half of all authorizations (2322) issued between January

2010 and September 2017 had expired. In addition, 109 marketing authorizations were to expire within 3 months of the review.[25] The worrisome growth of the illicit medicine market is caused by the weakness of the healthcare system. Intersectoral collaboration between the national drug regulatory authority, national law enforcement (customs, police and justice) and international law enforcement services is needed.[15]

Characteristics of pharmaceutical establishments

Only 2 surveyed outlets of 196 were authorized to operate by the Ministry of Health. The DPM recognizes its limits to control this anarchic development of the private market. The total number of pharmaceutical establishments in the DRC remains unknown.[23,26] In the field, the multitude of regulations generates conflicts between different state services within this sector, particularly the Ministries of Health, Environment, Justice, Interior and Economy. To this list of ministries is added the Congolese national police.[23] Almost all (195/196) of the establishments were found not to have any air conditioning systems (Table 3). Nearly three of five outlets (112/196) had no electricity at the time of the survey. Overall, no outlet met all the minimum standards set by the national drug regulatory authority. To control the temperature, the WHO Guidelines for the Storage of Essential Medicines and Other Health Commodities advocates for three conditions: a means of controlling humidity and heat (windows, fan, air conditioner or dehumidifier), the presence of a refrigerator and a power supply.[18] Only 24.5% (48/196) of outlets comply with these WHO guidelines (Figure 9). Therefore, good conservation practices[18,27] are not being followed. In the tropical climate of the DRC, this exposure of medicines to hot, humid weather greatly increases the risk of degradation, making the expiration date meaningless.[1,28]

Good pharmaceutical laws and regulations as well as implementation help safeguard the quality of medicines. The health of the entire Congolese population depends on this quality. The DRC should do more to strengthen the effectiveness of the National Drug Regulatory Authority. They also need legislation and regulations and an effective means of enforcement. It will also be necessary to mobilize more material, financial and human resources to achieve these goals.

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