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7 **QUALITY OF ANTIMALARIALS IN KINSHASA PERI-URBAN AREAS WITH**  
8 **REGARDS TO THE LOCAL PHARMACEUTICAL LEGISLATION AND**  
9 **REGULATION**

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## 32 **Abstract**

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

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

43 **Results:** Of the 75 samples assayed, 19% (14/75) were non-compliant. Of the 124 brand-  
44 names, 46.0% (57/124) were unlicensed and 14.5% (18/124) had an expired license. Of the 196  
45 pharmaceutical establishments, only two 1.0% (2/196) had an authorization to practice, none of  
46 them met all the ministry of health minimum standards, 24.5% (48/196) met the World Health  
47 Organisation Guidelines for the Storage of Essential Medicines and Other Health Commodities.

48 **Conclusion:** More resources should be mobilized to apply regulator sanctions.

49 **Keywords** CHARACTERISTICS OF PHARMACIES, DEMOCRATIC REPUBLIC OF  
50 CONGO, KINSHASA, PERI-URBAN AREAS, PHARMACEUTICAL LEGISLATION AND  
51 REGULATION, QUALITY OF ANTIMALARIALS

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## 54 **Introduction**

55 The alarming proliferation of poor-quality medicines is a real public health concern.<sup>1</sup> The fight  
56 against this scourge was initially faced with the difficulty of finding a unanimous definition for  
57 the concept of poor-quality medicine. Three definitions have been adopted since May 2017 by  
58 the World Health Organization (WHO): (i) Substandard medical products also called “out of  
59 specification”: these are authorized medical products that fail to either meet their quality  
60 standards or their specifications, or both; (ii) Unregistered/unlicensed medical products:  
61 Medical products that have not undergone evaluation and/or approval by the national or  
62 regional regulatory authority for the market in which they are marketed/distributed or used,  
63 subject to permitted conditions under national or regional regulation and legislation; (iii)  
64 Falsified medical products: Medical products that deliberately/fraudulently misrepresent their  
65 identity, composition or source.<sup>2</sup> The falsified medicines may either contain no active  
66 ingredient, or an inappropriate active ingredient, or at least the appropriate active ingredient but  
67 at a dosage outside the specification range. They are sometimes contaminated with bacteria and  
68 may also contain unknown impurities or toxic chemicals. They promote the development of  
69 antimicrobial resistance and medicine-resistant infections.<sup>2,3</sup> Falsification affects all categories  
70 of medicines.<sup>3,4</sup> However, antimalarials and antibiotics are the most often reported as  
71 substandard or falsified medical products.<sup>5,6</sup> This situation is linked to a wide use of these two  
72 categories of medicines in both urban and peri-urban areas in sub-Saharan Africa.<sup>1</sup> In many  
73 developing countries in Africa, substandard or falsified medicines are estimated to account for  
74 more than 30% of medicines in circulation.<sup>7</sup> This proportion can be up to 80% in some  
75 countries.<sup>1</sup> In the Democratic Republic of Congo (DRC), some laws and regulations are no  
76 longer appropriate and do not allow an adequate response to the current challenges in the  
77 pharmaceutical sector. The informal market and the trafficking of falsified medicines concern  
78 life-threatening diseases whose medicines are the most sought-after<sup>8</sup> particularly in the DRC,

79 in order to fight malaria.<sup>9</sup> Malaria has its highest prevalence in peri-urban areas<sup>10</sup> where the  
80 demand for antimalarials is growing exponentially . The issue related to the quality of medicine  
81 in Africa's urban and peri-urban areas has been addressed by several authors.<sup>1,8,11</sup> However,  
82 aspects directly related to the regulation enforcement have not been addressed. Thus, the  
83 purpose of the present study was to assess the existing pharmaceutical system in peri-urban  
84 areas of Kinshasa, mainly in regard with the use of antimalarials and their quality, the  
85 proportion of unlicensed antimalarials and the characteristics of pharmaceutical establishments.

## 86 **2. Materials and methods**

### 87 **2.1 Study setting**

88 The city of Kinshasa is built mainly on two geo-morphological sites : "the lower city" or "the  
89 plain of Kinshasa" and "the upper city" or "the hill zone".<sup>12</sup> The city has extended much more  
90 in the south and southwest than in the east. The extensions of the eastern buildings have  
91 reached the municipality of N'sele. The extensions of the south and south-west buildings have  
92 been concerned with the upper west city whose most important administrative entity is the  
93 municipality of Mont Ngafula.<sup>12,13</sup> The present prospective study, was carried out in peri-urban  
94 areas of Kinshasa, in the four municipalities as presented in figure 1, during the period of  
95 February 2016 to May 2018. The period of the study covers two particular events: Firstly, the  
96 publication in October 2016 of the 3rd edition of the Directory of the pharmaceutical products  
97 registration by the Direction de la Pharmacie et du Médicament (DPM),<sup>14</sup> secondly, the health  
98 sector reform was at the phase of implementation of the Kinshasa Health Provincial Division  
99 and the Kinshasa Health Provincial Inspectorate.<sup>15</sup>

### 100 **2.2 Sampling and data collection**

#### 101 **2.2.1 Study design**

##### 102 **Sampling type**

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

### 106 **General formula of sampling size**

107 The theoretical sample size ( $N$ ) was calculated based on the following general formula:  $N = p$   
108  $(1-p) z^2 / E^2$  with  $p$  the prevalence,  $z$  the confidence interval and  $E$  the margin error. However,  
109 for the household survey, the cluster effect was taken into account, so the theoretical sample  
110 size ( $N$ ) was calculated based on the following formula:  $N = [p (1-p) t^2 / E^2] DEFF$  with  $t$  the  
111 confidence interval for the cluster sampling and  $DEFF$  the cluster effect.

### 112 **The investigation team**

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

### 121 **Summary of data collection processes and expected results**

122 The three surveys and the outcomes are presented in Figures 2a and 2b.

### 123 **Inclusion and non-inclusion criteria**

124 At the household level, the questionnaire was administered to the household head (first target).  
125 In case of absence of the household head, the oldest member (aged 15+) of the household

126 present at the time of the survey was interviewed.<sup>16</sup> Households which did not satisfy to these  
127 two conditions were not included. At the point of sale, the questionnaire was administered to  
128 the seller. Only private pharmacies were included in the study. In 2013, the share of the private  
129 sector antimalarial market accounted for 97%.<sup>17</sup> Neighbourhoods with limited geographic  
130 access including erosion were not included.

## 131 **2.2.2 Household survey**

### 132 **2.2.2.1 Sampling**

133 The most used antimalarials were identified in Mont-Ngafula, using a two-stage cluster  
134 household survey. In case the survey area was too extensive and the population of households  
135 dispersed, this kind of survey was preferred in the countries of the South.<sup>16</sup>

### 136 **2.2.2.2 Sample size**

137 With the prevalence of antimalarials use estimated at 38.1% ( $p = 0.38$ ),<sup>16</sup> the significance  
138 threshold was set at 5% for cluster sampling with the margin of error ( $E$ ) of 4% ( $t = 2.045$ ). The  
139 cluster effect ( $DEEF$ ) set at 1.7. The calculated sample size was 1048 households. In order to  
140 compensate for non-responders, the initial sample size was increased by 10% (1153  
141 households).<sup>18</sup> However, during the investigation, three households refused to be interviewed  
142 with a condition that the investigators provide them with mosquito nets or antimalarials. Then,  
143 the sample size reduces to 1150 households.

### 144 **2.2.2.3 Data collection**

145 The questionnaire in French was translated into Lingala (the language spoken in the area of  
146 study) and were pre-tested in small areas similar to the principal area of study. Apart from  
147 socio-demographical characteristics collected in the households, questions were related to the  
148 antimalarial used at the last episode of malaria.

## 149 **2.2.3. Survey of pharmaceutical establishments**

### 150 **2.2.3.1 Sampling**

151 Pharmacies were visited twice. For each field visit, pharmacies were counted, and random  
152 sampling applied. The first field visit was done in the municipality of Mont Ngafula (in the  
153 health area Mont Ngafula I) and was aimed at determining the most frequently sold and widely  
154 used antimalarials. The second field visit was conducted in four health areas within the  
155 municipalities (Mont Ngafula I, Kisenso, Kikimi, N'sele) and aimed at collecting information  
156 about the characteristics of both, pharmacies and antimalarials.

### 157 **2.2.3.2 Sample size**

#### 158 **- Sample size at the first field visit (Sale of antimalarials)**

159 With the percentage of households resorting to pharmacies estimated at 29.3 % ( $p = 0.293$ ),<sup>16</sup> the  
160 significance threshold was set at 5% with the margin of error ( $E$ ) of 10 % ( $z = 1.96$ ), i.e. 80  
161 pharmacies. In order to compensate for non-responders, the sample size was increased to 88.

#### 162 **- Size at the second visit (Characterization of pharmacies)**

163 With the percentage of pharmacies complying with the minimal standards – enacted by the  
164 national drug regulatory authority – estimated at 50% ( $p = 0.5$ ). The value of 50% was generally  
165 assumed in case of unknown phenomenon. The significance threshold was fixed at 5% with the  
166 margin of error ( $E$ ) of 7% ( $z = 1.96$ ), i.e. 196 pharmacies. Since the mystery shopper survey was  
167 applied, the risk of non-response was not taken into account.

### 168 **2.2.3.3 Data collection**

#### 169 **- First visit to the pharmacies (Sale of antimalarials)**

170 The sociodemographic characteristics and information related to the most frequently sold  
171 antimalarials were collected.

#### 172 **- The second visit to pharmacies (characterization)**

173 Data collection was conducted thanks to the KoBo Collect application

174 (<https://kf.kobotoolbox.org>). This allowed the collection of geographic coordinates. The data

175 collected were related to the characteristics of pharmacies, particularly the compliance with the

176 DRC Health Ministry standards<sup>19</sup> and the WHO Guidelines for the Storage of Essential  
177 Medicines and Other Health Commodities,<sup>20</sup> the pharmaceutical establishments authorized to  
178 operate. The marketing authorization for antimalarials has been checked with DPM<sup>14</sup> and with  
179 the National Health Inspectorate.

## 180 **2.2.4 Procurement sources for assayed antimalarials**

### 181 **2.2.4.1 Sampling**

182 The samples were obtained using the mystery shopper approach to avoid bias in randomly  
183 selected outlets in a pre-built sample frame. It should be noted that the selection of  
184 antimalarials to be purchased (quinine or artemether-lumefantrine combination) was based on  
185 the directory of pharmaceutical products registered and licensed by the DPM in the DRC. So,  
186 whenever the mystery shopper went to a pharmacy, he would ask for different antimalarials  
187 available in that pharmacy.

### 188 **2.2.4.2 Sample size**

189 With the percentage of substandard / falsified medicines estimated at 30% ( $p = 0.3$ ),<sup>7</sup> the  
190 significance threshold was set at 5% with the margin of error ( $E$ ) of 10% ( $z = 1.96$ ), i.e. 81  
191 samples. However, in view of the constraints, especially the available funds, Only 75 samples  
192 were collected.

## 193 **2.3 Analyses**

### 194 **2.3.1 Data analyses**

195 Data from the household and the first visit at the pharmacies were captured using the Census  
196 and Survey Processing System version 6.0.1 (US Census Bureau, Washington DC, USA). The  
197 data were analysed using Statistical Package for the Social Sciences version 23.0.0 (IMB, New  
198 York, USA). Data from the second visit to the pharmaceutical establishments were collected  
199 through KoBo Collect Application (A Harvard Humanitarian Initiative software based in  
200 Cambridge, Massachusetts, USA).

201 The mapping of the study area and the surveyed pharmaceutical establishments was performed  
202 using the software ArcGIS version 10,5 (Environmental Systems Research Institute, Redlands,  
203 California, USA).

### 204 **2.3.2 Physicochemical analyses**

205 The quality analysis of the collected medicine samples was carried out at the Drug-testing  
206 laboratory (University of Kinshasa) and at the WHO-prequalified laboratory (Department of  
207 Pharmacy, Liege University), using generic separation methods with the high-performance  
208 liquid chromatography (HPLC) technique coupled to a diode-array detector. The  
209 physicochemical analyses consisted to identify the active ingredients, their dosage, and in some  
210 cases the pH assay of the solutions and the mass variation.

### 211 **2.4 Ethical considerations**

212 The study protocol was approved by the Congolese National Committee for Health Ethics  
213 (Authorization No. 016/CNES/BN/PMMF/2016 of 08/01/2016). The ethical principles outlined  
214 in the Declaration of Helsinki have been observed. In accordance with the Ethical Guidelines  
215 for Research Involving Human Subjects in DRC and based on the nature of the study, the DRC  
216 National Ethics Committee for Health has authorized verbal informed consent. The  
217 investigators explained in detail the purpose of the study before collecting and recording the  
218 verbal informed consent of the participants. The participants were not exposed to any  
219 experiment since no biological samples were collected for analysis. They essentially answered  
220 a questionnaire and were not followed up after the interview. The survey questionnaire was  
221 anonymous. Thus, the study presented no risk or negative effect for the participants, on the  
222 contrary, the information provided was beneficial to them.

## 223 **3. Results**

### 224 **3.1 Interviews and desk reviews**

225 Before investigating, in addition to the desk review of the narrative reports several interviews  
226 were held with the Director of General Inspectorate of Health, the Provincial Medical Inspector  
227 and the Chief Medical Officer of Kinshasa Provincial Division. It was noticed that the quality  
228 of the medicine in Kinshasa depends very much on the legislation and regulations in force. The  
229 entire country is also concerned. A conceptual framework (Fig. 3) presents the various aspects  
230 resulting from implementation of legislative and regulatory texts and that ultimately have an  
231 influence on the quality of medicines.

### 232 **3.2 The most frequently sold and most used antimalarials**

233 Two surveys were conducted concurrently. One conducted on 1150 households and the other  
234 on 88 pharmacy sales clerks, in order to identify the most used and the most frequently sold  
235 antimalarials.. In the household, the distribution of the respondents indicated a predominance of  
236 women (796/1150) compared to men (354/1150), i.e. a male / female sex ratio of 0.4. Mean age  
237 of respondents was  $34 \pm 13$  years with ages between 18 and 83 years. In terms of education,  
238 556 of 1150 respondents (49.2%) had completed at least secondary school. Six hundred and  
239 sixty-two of 1150 respondents (57.6%) were married or cohabiting/living together. Six hundred  
240 and thirty of them (55.5%) had a monthly income of more than \$50 and spent two-thirds of  
241 their income on food and one-third for other expenses (Transportation, Medical Care, etc.).  
242 Five hundred and fortyeight of 1150 surveyed households (47.7%) reported facing an episode  
243 of malaria in the two weeks prior to the survey. Five hundred and twenty-six of 548 households  
244 (96.0%) that faced a malaria episode used an antimalarial medicine. Regarding the surveyed  
245 pharmacy sellers, the distribution showed a predominance of men (55/88) compared to women  
246 (33/88), i.e. a male / female sex ratio of 1.7. The age ranged from 18 to 70 with mean age of  $35$   
247  $\pm 10$  years. In 57 cases out of 88 (65%), the seller was not the owner of the pharmacy.  
248 Interviews with households (Fig. 4) showed that the most used molecule was quinine, followed  
249 by artemisinin derivatives and the sulfadoxine-pyrimethamine combination. In the

250 pharmaceutical establishments, these same antimalarials are reported in the same figure of sales  
251 as being the most frequently sold. Also 11.8% (62/526) of people had forgotten the name of the  
252 antimalarial used. Among the artemisinin derivatives alone or in combination (Fig. 5), the  
253 artemether-lumefantrine combination was found to be the most frequently sold (17/30) and  
254 used (37/89), followed by  $\alpha$ - $\beta$  artemether in terms of sales (6/30) and in terms of use (27/89). In  
255 third place, sellers reported semi-synthetic methoxymethane of artemisinin (4/30) while other  
256 households reported water-soluble artemisinin hemisuccinate (5/89).

### 257 **3.3 Quality of antimalarials and registration status**

#### 258 **3.3.1 Visual analysis**

259 The irregularities that were observed mainly concerned the artemether-lumefantrine  
260 combination. Twelve out of 30 cases (40%) have labelling issue and 17% (5/30) of the  
261 packages showed traces of moisture (Fig. 6).

#### 262 **3.3.2 Identification and assay of the antimalarials**

263 Analyses were performed on the two most frequently sold and most used antimalarials, quinine  
264 and the artemether-lumefantrine combination. The first decisive step was to confirm the  
265 presence of the active ingredients and the content as claimed by the manufacturer. The  
266 manufacturer's claims were considered as 100% references with the specifications of 90.0% -  
267 110.0%. Molecules whose content were between those ranges were compliant. Quinine  
268 analyses involved 15 samples, including seven oral drops (47%), three tablets (20%), three  
269 syrups (20%) and two injectable ampoules (13%) (Table 1). Two syrup (13.3%) samples were  
270 found non-compliant, assay results being above the specifications. Analyses also included 30  
271 samples containing the two molecules artemether-lumefantrine combination in powder for oral  
272 suspension (Table 2). Out of the total of 60 analyses, 12 (20%) were non-compliant among  
273 which seven due to lumefantrine molecules and five due to artemether molecules with assay  
274 results below the specifications.

275 **3.3.3 Registration status**

276 Fifty seven of 124 antimalarials (46.0%) were unlicensed by the DPM (Fig.7).

277 **3.4 Characteristics of pharmaceutical establishments**

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

284 **4. Discussion**

285 **4.1 Interviews and desk reviews**

286 Pharmaceutical legislation and regulations constitute the guarantee for the quality of medicine  
287 (Fig.3). Countries with fragile pharmaceutical governance and pharmacovigilance are most  
288 exposed to substandard and falsified medicines<sup>21,22</sup>. Thus, efforts to improve supply chain  
289 management, inspection and regulation are essential to control exposure to substandard and  
290 falsified medicines<sup>23</sup>.

291 **4.2 The most frequently sold and most used antimalarials**

292 In the case of simple malaria, the National Malaria Control Program recommends the  
293 artemisinin-based combination therapy (artemether-lumefantrine or artesunate-amodiaquine) as  
294 first-line therapy. In case of failure, the program recommends another artemisinin-based  
295 combination therapy or quinine combined with an antibiotic.<sup>24</sup> Note that care of patients with  
296 complicated malaria is undertaken in health facilities that were not included in our surveys.  
297 Pharmacies and households' surveys (Fig. 4) showed a greater use of quinine compared to the  
298 artemisinin derivatives including the artemisinin-based combinations. In households, the rate of  
299 forgetting is quite high 11.8% (62/526). Comparison between data from pharmacies and

300 households has minimized the importance of this loss of information. In Kinshasa, the  
301 Demographic and Health Survey II reported the same trends. The most commonly used  
302 antimalarial was quinine (68.2%), followed by artemisinin derivatives (17.7%), of which  
303 artemisinin-based combinations (14.6%).<sup>16</sup> This increased use of quinine by the population  
304 provides information on non-compliance with good antimalarial use practices, as advocated by  
305 the NMCP. It should be noted that quinine is more affordable than artemether-lumefantrine  
306 combination. It is therefore mostly used for fever.<sup>17,24</sup>

### 307 **4.3 Quality of antimalarials and registration status**

308 For quinine, 2/15 samples of over dosage of syrup were found. This could be a manufacturing  
309 issue as well as for the artemether-lumefantrine combination with a low dosage. Overall, out of  
310 a total of 75 molecules assayed, 18.7% (14/75) were non-compliant. This proportion of non-  
311 compliant antimalarials is close to the one reported by the Sachiko Ozawa team's meta-analysis  
312 of 19.1%.<sup>23</sup> The size of the samples analysed was not representative. However, the preliminary  
313 survey conducted on households and pharmacies allowed for the selection of the most  
314 representative antimalarials used. The quinine, which is the most used molecule, presented less  
315 non-compliance traits than artemether-lumefantrine. In DRC there are 29 production units of  
316 which only five apply, in an acceptable manner, good manufacturing practices,<sup>15,25</sup> and most of  
317 them are based in Kinshasa. The Ministry of Health reports indicate that the main characteristic  
318 of the pharmaceutical industry in the DRC is the circulation of poor-quality medicines. Two  
319 causes are essentially mentioned. The first relates to the dysfunction of the quality assurance  
320 system, and the second is related to the inefficacy of pharmaceutical inspection. This is caused  
321 by the lack of laboratory equipment for the quality control.<sup>15,25</sup> The operationalization of the  
322 General Inspectorate for Health since 2017 raises hope for the implementation of the control of  
323 regulatory acts.<sup>26</sup> Nearly half of the antimalarials in circulation had no marketing authorization  
324 (Fig. 7). This figure allowed us to evaluate the size of an illicit market that hinders efforts of

325 health authorities to improve the health of the population. Antimalarials authorized on the  
326 Congolese market accounted for 56.0% (67/124) of the total, of which 14.5% (18/124) had an  
327 expired license (Fig. 7). The review of the authorized medicines directory reported more  
328 worrying proportions. This review conducted in December 2017, revealed that half of all  
329 authorizations (2 322) issued between January 2010 and September 2017 had expired. In  
330 addition, 109 marketing authorizations were to expire within three months of the review.<sup>27</sup> The  
331 worrying growth of the illicit medicine market is caused by the weakness of the health system.  
332 Intersectoral collaboration between the National drug regulatory authority, the national  
333 (Customs, Police and Justice) and the international law enforcement services are all in fault.<sup>15</sup>

#### 334 **4.4 Characteristics of pharmaceutical establishments**

335 Only two surveyed outlets out of 196 were authorized to operate by the Ministry of Health. The  
336 DPM recognizes its limits to control this anarchic development of the private market. The total  
337 number of drugstore retailers in the DRC remains unknown.<sup>25,28</sup> In the field, the multitude of  
338 regulatory texts generates conflicts of competence between different state services within this  
339 sector, particularly the Ministries of Health, Environment, Justice, Interior and Economy. To  
340 this list of Ministries is added the Congolese national police.<sup>25</sup> Almost all (195/196) of the  
341 establishments were found not to have any air conditioning systems (Tab. 3). Nearly three out  
342 of five outlets (112/196) had no electricity at the time of the survey. Overall, no outlet met all  
343 the minimum standards set by the National drug regulatory authority. To control the  
344 temperature, the WHO Guidelines for the Storage of Essential Medicines and Other Health  
345 Commodities advocates for three conditions: the means of controlling humidity and heat  
346 (windows, fan, air conditioner or dehumidifier), the presence of a refrigerator and a power  
347 supply.<sup>20</sup> Only 24.5% (48/196) of outlets comply with these WHO Guidelines (Fig. 9). Under  
348 these conditions, good conservation practices<sup>20,29</sup> are not respected. In a tropical climate, this

349 exposure of medicines to hot weather greatly increases the risk for medicine degradation even  
350 before the expiration date.<sup>1,30</sup>

351 Good pharmaceutical laws and regulations along with implementing measures constitute  
352 safeguard for the quality of medicines. The health of the entire Congolese population depends  
353 on this quality. The DRC should do more to strengthen the effectiveness of the National Drug  
354 Regulatory Authority. It expects to have legislation and regulations that are better adapted to  
355 the international context and endowed with regulator sanctions. It would also be necessary to  
356 mobilize more material, financial and human resources to achieve repressive actions  
357 proportional to the extent of this scourge of public health.

358

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454 **Figure legends**

455 **Figure 1: Location of the study area in the peri-urban areas of Kinshasa**

456 **Figure 2.a: Scheme of two surveys conducted at the level of pharmaceutical establishments and**  
457 **households**

458 **Figure 2.b: Scheme of the third survey conducted at the level of pharmaceutical establishments.**

459 **Figure 3: Conceptual framework of factors influencing the quality of medicines**

460 Where laws and regulations are not updated and / or are not properly enforced by the national drug  
461 regulatory authority, law enforcement and inspection services become ineffective resulting in non-  
462 compliance with good practices and the circulation of falsified medicines in thriving illicit markets. This  
463 has a negative impact on the quality of the medicines consumed.

464 **Figure 4: Comparison of the survey results from the medicine outlets and the households in**  
465 **relation to the sale and consumption of antimalarial medicines in peri-urban areas of Kinshasa**  
466 **(Pharmacy n = 88 and Household n = 526).** Out of a total of 1150 households surveyed, malaria  
467 occurred in 548 households of which 526 resorted to an antimalarial medicine. Antibiotics, analgesics,  
468 and vitamins, reported by the respondents, were classified in the "other" category.

469 **Figure 5: Comparison of the survey results from the medicine outlets and the households in**  
470 **relation to the sale versus consumption of artemisinin derivatives alone or in combination.**  
471 (Pharmacy n = 30 and Household n = 89)

472 **Figure 6: Visual analysis**

473 On the left, improper label positioning. On the right the presence of moisture traces on the primary  
474 packaging.

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

477 **Figure 8: A pharmaceutical establishment dealing with the sale of motor oil in peri-urban areas of**  
478 **Kinshasa.**

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

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484 **Author's statements**

485 ***Authors' contributions***

486 D.J.M., M.F., J.M.K., P.H., R.D.M. contributed to the study conception and design.

487 RDM coordinated the study, from conception to validation of the final manuscript.

488 MF, PH, and RDM supervised the collection of medicine samples and their quality control and  
489 validated the results and their interpretation.

490 JMK supervised the household and pharmacy surveys and validated the results and their  
491 interpretation.

492 DJM was the principal investigator of the study. He worked with the different teams in the  
493 design, data and samples collection, quality control and their interpretation.

494 DJM and CBN conducted household and pharmacy surveys, they designed the figures and  
495 tables;

496 DJM, JKM, and SL carried out the collection of AL samples and carried out their quality  
497 control in the laboratory.

498 DJM, NKT, and PCH collected the quinine samples and performed their quality control in the  
499 laboratory.

500 MKM translated questionnaires of household and pharmacy surveys from French to Lingala  
501 (the language spoken in the study sites), conducted the pre-test of the field questionnaire and  
502 translated the manuscript, tables, and figures into English as well.

503 All authors contributed to the writing of the manuscript and critically revised the manuscript for  
504 important intellectual content.

505 All authors read and approved the final manuscript.

506 RMD and DJM are the guarantors of paper.

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510 ***Ethical approval:*** The study protocol was approved by the Congolese National Committee for  
511 Health Ethics. Authorization number 016/CNES/BN/PMMF/2016 of 08/01/2016. The ethical  
512 principles outlined in the Declaration of Helsinki have been observed. In accordance with the  
513 Ethical Guidelines for Research Involving Human Subjects in DRC and based on the nature of  
514 the study, the DRC National Ethics Committee for Health has authorized verbal informed

515 consent. The investigators explained in detail the purpose of the study before collecting and  
516 recording the verbal informed consent of the participants. The latter were not exposed to any  
517 experiment since no biological samples were collected for analysis. They essentially answered  
518 a questionnaire and were not followed up after the interview. The survey questionnaire was  
519 anonymous. Thus, the study presented no risk or negative effect for the participants, on the  
520 contrary, the information provided was beneficial to them.

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