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Evaluation of Anti-malarial Drugs Use in Gbadolite Health Area in Democratic Republic of the Congo: A Cross-Sectional Study

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Abstract

Gbadolite health area is located in the Ubangi eco-region where Malaria is hyper-endemic stable with a perennial transmission. The aim of this study was to evaluate the anti-malarial drugs use in this health area in Nord Ubangi Province, Democratic Republic of Congo. A retrospective cross-sectional study design was conducted using selected patient cards from January 2016 to December 2017. 400 patient records have been randomly selected and analyzed. Obtained results indicate that 69% of patients are between 6 and 71 years old, and 31% of cases are children under 5 years. 56% of patients are male compared to 44% of female. 63% of patients are literate while 37% are illiterate. The majority of anti-malarial drugs prescribers are physicians (54%) followed by nurses (46%). 54% of cases concern simple malaria, 37% of cases, severe malaria and 9% of cases concern other pathologies. However, the rapid diagnostic test for confirmation indicates that 46% of those surveyed have simple malaria, 37% have severe malaria, and 17% have other diseases (diabetes, ulcer, dermatitis and cardiovascular disease). Seven types of anti-malarials drugs (alone or combined: Cether-L®, Artemether, Artesun®, ACT, Quinine, Co-artem® and ARH-L forte®) are used in Gbadolite city. The tablet is the most commonly used pharmaceutical form (51%) followed by the injectable form (47%) and syrup (2%). These AMD are associated with antibiotics (35% of cases), vitamins (20%), anti-helminthics (19%) and anti-cough (4%). In 94% of cases, the dose of anti-malarials administered to patients is consistent. However, in 4% of cases, there is overdose while the sub-dose is estimated at 2% of cases. Based on current knowledge, this is a first report concerning cross-sectional study on the use of antimalarial-based drugs in Gbadolite health area and revealed that the use of anti-malarial drugs is not fully in agreement with the guideline despite good practice.

Keywords

Malaria, Artemisinin-Based Combination Therapy, Survey, Pharmaco-Vigilance, Gbadolite

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1. Introduction

Malaria is a parasitic disease endemic to tropical regions, and it is a major challenge of public health in Democratic Republic of the Congo [1-5]. At Gbadolite city in the province of Nord Ubangi, official statistics annually show some of the thousands of cases [6], and it is due to the where environmental ecology of this place which is favorable to the maintenance and proliferation of the vector. It is a transition zone (ecotone) between the Sahel and the large equatorial rainforest with tropical climate of type AW_2 according to Koppen classification and part of the Ubangi freshwater eco-region [7, 8]. More than 50 years ago, quinoline-based anti-malarial drugs (Quinine, Amodiaquine, Chroroquine, etc.) were considered as the drug of choice for malaria treatment in Africa because of their cost-effectiveness. In addition, Chloroquine, a 4-aminoquinoline, was long used in the malaria prevention and treatment, as it was cheap and widely available, before the most dangerous malarial parasite *Plasmodium falciparum* started to develop resistance to it [2, 9, 10].

However, the increasing resistance of some strains of *Plasmodium* to chloroquine has led to a renewed interest in combination therapeutic based on Artemisinin and its derivatives [6].

The misuse of anti-malarial drugs due to the non-compliance with the use of health authority treatment regimen (guidelines of the national malaria control program ie the prescription of CTA after biological confirmation) by the health care staff at the provincial level led us to conduct this study to identify the molecules and dosage forms used for anti-malarial chemotherapy in Gbadolite city to confirm or refute their compliance. The interest of this study is obvious, because, in case of validation of our hypothesis, it would make it possible to determine the weak points of the prescription of anti-malarial drugs in the Nord Ubangi province, to correct errors by proposing short and long term sustainable solutions.

2. Materials and Methods

A retrospective cross-sectional study on the prescription of anti-malarial drugs (AMD) from January 2016 to December 2017 was carried out in four health facilities in the urban-rural health area of Gbadolite: Gbadolite General Referral Hospital, Gbadolite Health Center, KRATOS Health Center and Saint Joseph Health Center. The Gbadolite health zone is located in the province of Nord Ubangi, North-Western of DRC and consists of 13 health areas with 13 functional health Centers and one referral General Hospital, all supported by World Fund and offering freely the treatment of malaria to patients [6].

In each health Centre, patient records containing the prescription of AMD were randomly selected according to the WHO recommendation for drug use investigations in health centers (n = 100x4) [11].

The data were collected through survey questionnaire containing socio-demographic variables (sex, age, educational level and occupation), clinical variables (reasons for consultation, nature of malaria, rapid diagnosis test realization) and pharmacological variables (name of products, dosage form, dosage and duration of treatment) and analyzed by using Microcal Origin 7.5 software.

3. Results and Discussion

Figure 1 shows that 69% of patients are between 6 and 71 years old have developed anti-malarial immunity (6-71 years) against 31% of children under 5 years, and therefore vulnerable. These results show that despite the anti-malarial immunity of the premunition type (caused by repeated anopheles infections), all subjects have the same chance of developing malaria disease in this hyper-endemic outbreak. If not, the majority of patients should be in the age group of less than eight years. It is noted here that the majority of patients are persons who should be asymptomatic carriers of malaria parasites (infection malaria) [12]. This contradiction can be justified by the use of mosquito nets which cause the collapse of the population's anti-malarial immunity inhibiting contact with the vector.

The evaluation of the use of antimalarial drugs in endemic regions is one of the most important tools in standardizing their use in order to overcome the wide spread malaria parasites resistance development. It is known that malaria parasite may become resistant to drugs by various strategies like enzyme elaboration, target modification, drugs decreased influx, drugs increased efflux, and change in parasite cellular structure [13]. Patterns of antimalarial drug use were reported to be one of keys factors of pharmaco-resistance [14]. In the present study, socio-demographic characteristics revealed that males were more susceptible to *Plasmodium* infection than a female. These results are comparable to study done elsewhere [15]. According to age distribution, the present study revealed also that all age groups were affected indicating thus the negative impact of malaria disease on both education and economy of Nord Ubangi province which affects productivity of young generation, causes absenteeism of state employees at work or of students at school. This situation is also alarming in many households of Gbadolite city for which patients are Non-Timber Forest Products (NTFPs) traders or farmers.

Indeed, NTFPs are a principal source of income for households and these forest products contribute in livelihood security in Gbadolite city and surroundings, thus aggravating poverty [16-19]. The climate of the study site could be one factor for the prevalence and persistence of malaria parasite and disease in studied health area. Indeed, Gbadolite city is located in the Ubangi eco-region, a subgroup of Northeastern Congolese lowland forests where Malaria is highly hyper-endemic stable with a perennial transmission. This eco-region is one of the 200 globally priority terrestrial eco-regions (hotspots of biodiversity) known as the "G200" [7, 8].

It was observed in this study that less educated people are found in hospitals for malaria test and receive proper treatment. Many rely on self-medication against malaria due to the fact they recognize malaria symptoms and start the treatment without any prior check up in the hospital.

Parasitological diagnosis of malaria, using microscopy or alternatively rapid diagnostic test is recommended by the WHO guidelines for malaria control prior initiation of treatment [20, 21]. According to such guidelines, the laboratory test-directed prescribing practice is useful in preventing the development of chemo-resistant malaria parasite strains to the therapy. In Africa, antimalarial self-medication is a wide practice among people with post-secondary school level [22, 23]. The reasons for non-compliance with the recommended guideline can be explained by the fact that such category of people presume to well know malaria symptoms and epidemiology and generally does not consult healthcare workers or attend health facilities prior offering anti-malarial self-medication. Long distance from the center, overcrowding at the facilities were also cited as additional factors influencing self-treatment [23]. Despite the fact that such practice should not be encouraged, it is important to highlight that some research works advocate presumptive treatment of malaria in endemic region without prior parasitological confirmation when diagnostic tests are not readily available in order to advert the possibility of mortality in high stable transmission zones. Unfortunately, malaria symptoms may be confused with other life threatening conditions like enteric fever, gastroenteritis, urinary tract infections, etc. [24].

In this study, 56% of patients are male and 44% are female (See Figure 2) indicating that males were more susceptible to *Plasmodium* infection than females. These finding are in agreement with [13]. 63% of patients are literate and 37% are illiterate (See Figure 3), and education level shows that among the literate patients, 43% have a primary education level, 40% secondary education level education and 17% higher level of education (See Figure 4). This study also investigate the professional of the patients (Figure 5) shows that 26% of patients are students, 22% are state employees, 14% are housewives, and 8% are farmers, 1% is constitutes by Businessmen while 29% do not have specific activities. Figure 6 shows that the majority of prescribers are physicians. However, the nurse plays an important role in the prescription of anti-malarial drugs.

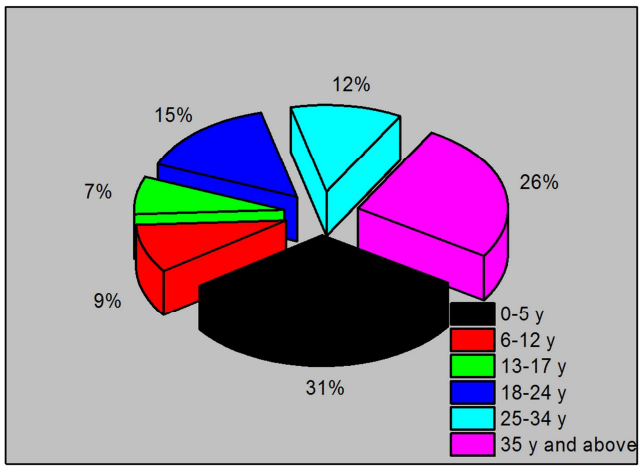


Figure 1. Presentation of age of the respondents.

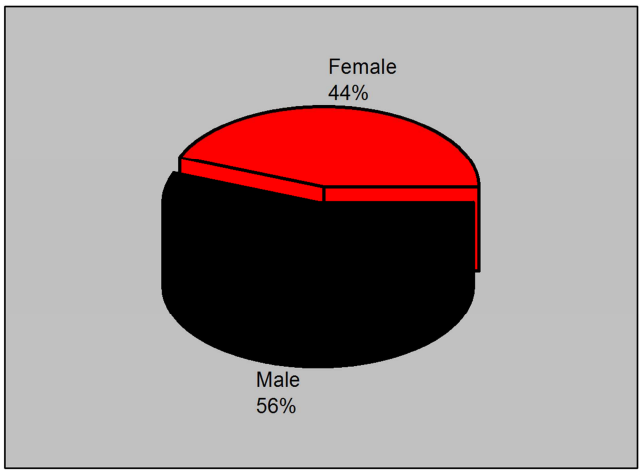


Figure 2. Patient Gender (sex).

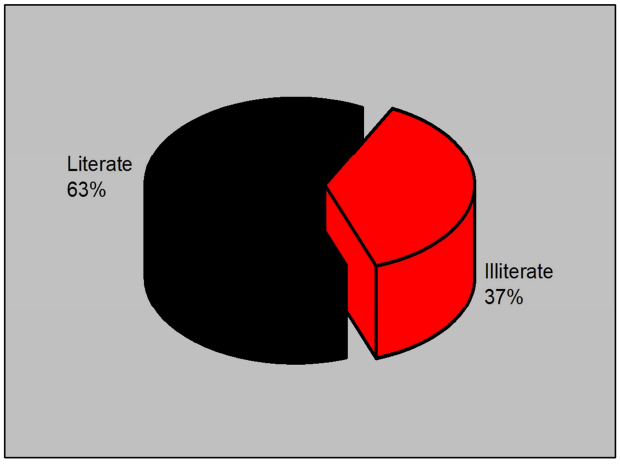


Figure 3. Number of literate patients and illiterate.

Figure 7 gives the result of the presumptive diagnosis retained by the anti-malarial drug prescriber in the inspected Health Zone

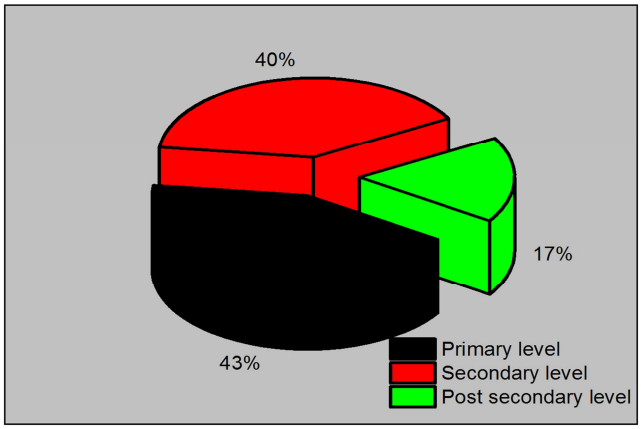


Figure 4. Education level of literate patients.

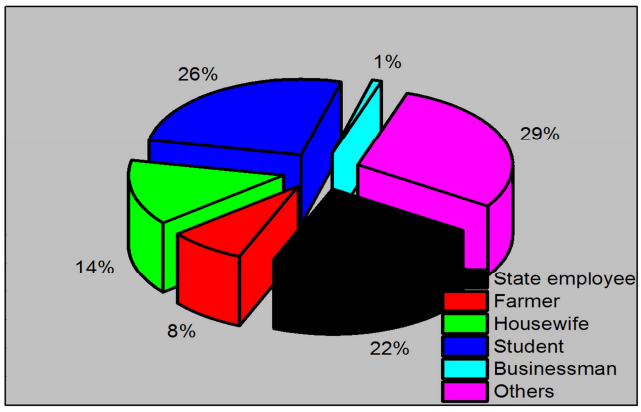


Figure 5. Professional activities (occupation) of different patients.

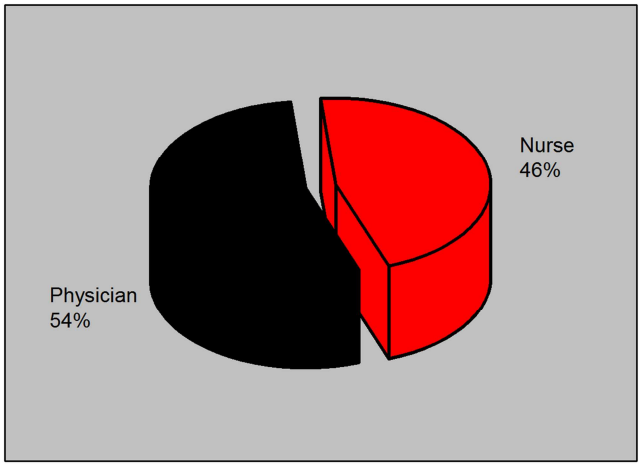


Figure 6. Quality of the anti-malarials prescriber.

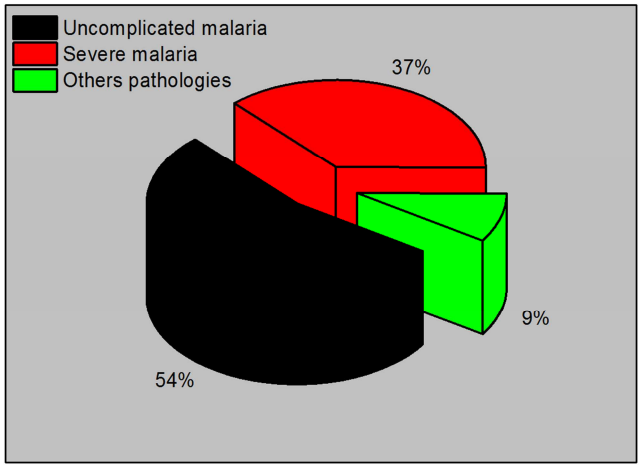


Figure 7. Presumptive diagnosis retained by the prescriber.

This figure shows that 54% of cases concern simple malaria, 37% of cases, severe malaria and 9% of cases concern other pathologies. However, the rapid diagnostic test (RDT) for confirmation indicates that 46% of those surveyed have simple malaria, 37% suffer from severe malaria and 17% of cases have revealed other diseases (diabetes, ulcer, dermatitis and cardiovascular diseases). The diagnosis of malaria, using the rapid test (RDT), reveals 91% of cases of parasitic infections caused by plasmodium falciparum. It should be noted that the prescription of anti-malarial drugs without prior parasitological analysis of the blood could contribute to the inefficiency and the resistance development. Indeed, drug-use pattern of anti-malarial has been associated with development of resistant strain and therapeutic failure. This descriptive cross-sectional study was carried out to evaluate the use of anti-malarial drugs in Gbadolite health area. If drug-use pattern of anti-malarials is not monitored, there is possibility of early emergence of resistance to the highly effective anti-malarial drugs presently in use [**25**]. To meet the goal of universal access to right interventions for all populations at risk of malaria, it is required that the proper clinical investigation is conducted prior to treatment with effective antimalarial drugs. Appropriate treatment of malaria and the correct use of anti-malarial drugs are thus needed in order to reduce malaria related death in endemic regions like Gbadolite city.

Figure 8 shows the different antimalarial drugs prescribed in the Gbadolite Health Zone.

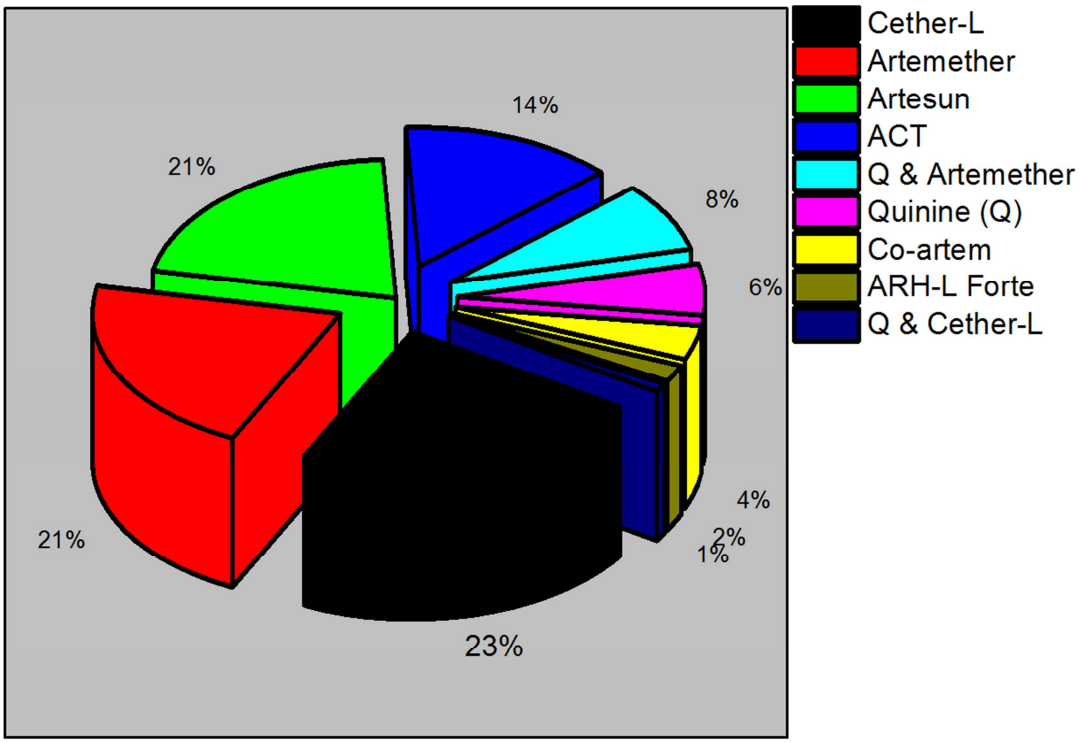


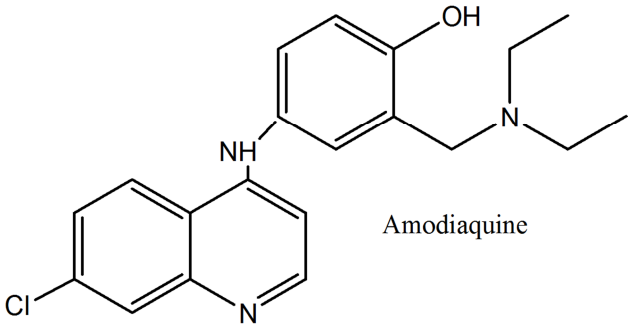
Figure 8. Types of Anti-malarial Drugs prescribed in the Gbadolite Health Zone.

It can be seen from Figure 8 that seven types of antimalarial drugs (alone or combined: Cether-L®, Artemether, Artesun®, ACT (artesunate-amodiaquine combination), Quinine, Co-artem® and ARH-L forte®) are used in Gbadolite for the management of simple or pernicious malaria attacks. At the molecular level, these antimalarials belong to two classes: quinoline-based antimalarial drugs (Quinine, Amodiaquine and Lumefantrine) and sesquiterpenic lactones with an endoperoxide bridge (Artesunate, Artemether) (see Figure 9).

The endoperoxide bridge of semi-synthetic derivatives of Artemisinin reacts with the iron atom released during the degradation of hemoglobin (hemin) by the parasite to form free radicals. The formation of free radicals causes macromolecular damage and death of the parasite cell [26].

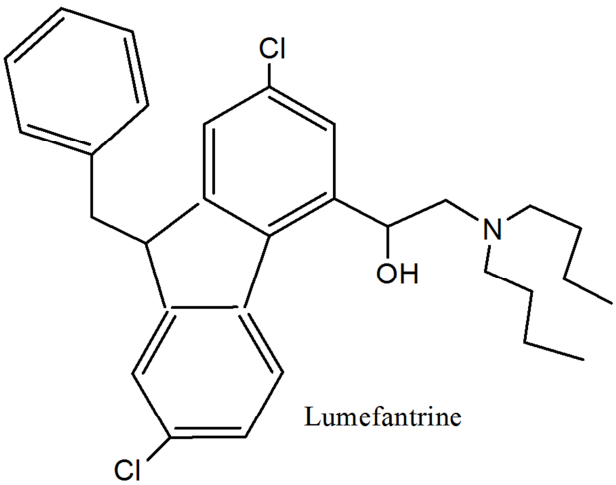
The antiplasmodial activity of quinoline-based antimalarials drug is attributed to the cytotoxic complexes they form with hemin in the parasite's digestive vacuole by inhibiting the formation of hemozoin or malarial pigment [2, 9, 10]. All these antimalarial drugs are erythrocytic schizonticides.

The high prescribing rate of Cether-L could be explained by its fairly pronounced pharmaco-therapeutic properties and compliance with one of the recommendations of the national malaria control program, namely the prescription of artemisinin-based combination therapies (ACT) in the treatment of simple malaria [6].



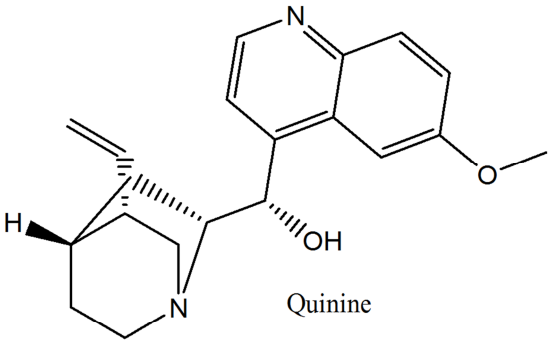
Amodiaquine

4(7-chloroquinolin-4-yl) amino-2- (diéthylamino) méthyl phenol

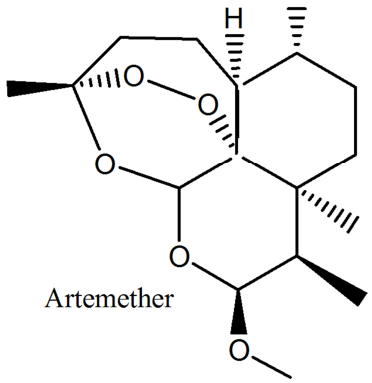


Lumefantrine

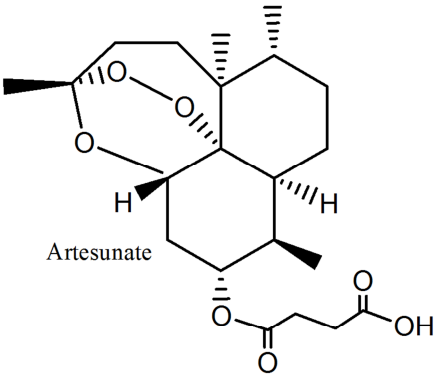
2- (dibutylamino)-1-(9 Z)-2,7-dichloro
-9-(4chlorobenzylidene)-9H fluorén-4-yl éthanol



(R) ((6-méthoxyquinolin 4-yl)(2S,4S,8R)-8-vinylquinuclidin-2-yl) méthanol (R)-(5-éthényl-1-azabicyclo 2.2.2 oct-2-yl)-(6-méthoxyquinolin-4yl) -méthanol.



(3R, 5aS, 6R, 8aS, 9R,12aR)-décahydro-10 methoxy-3,6,9 triméthoxy-3,6,9 triméthyl-3,12-époxy- 12-époxy -12H-pyrano (4,3-j)-1,2-benzodioxepine.



acide 4-oxo-4-(3R,5a,6R,8aS, 9R, 10S,12R,-3,6,9-Triméthyldécahydro-3,1 époxypyrano 4,3-j 1,2 benzodioxépin-10-yl oxy butanoique

Figure 9. Antimalarial drugs (molecules) used in Gbadolite.

Figure 10 shows the different pharmaceutical forms administered to patients in the Gbadolite Health Zone.

It appears from this figure that tablet is the most commonly used pharmaceutical form (51%) followed by the injectable form (47%) and syrup (2%). The preponderance of compressed forms is due to the problem of drug preservation. The research work of Getachew et *al*. on the evaluation of anti-malarial drugs' use in Fitche Hospital in Ethiopia revealed also that the most common dosage was tablet (61.6%) followed by injection (30.4%). As for this work, syrup was the less prescribed dosage form (8%) [**13**]. It is important to highlight that, if used inappropriately; injections are toxic, dangerous and life-threatening. This situation necessitates a special program for training of health staff and public education [13].

Table 1. Pharmaceutical form, dosage, posology and treatment duration of antimalarial-based drugs used in Gbadolite Health Area (Democratic Republic of the Congo).

Anti-malarial drug	*Formulation*	*Dosage & Mode of administration*	*Duration*	*Observation*	*Side effects*
ACT	Tablet	25/67.5 mg (1 tablet day1 & 2 tablets/day)	3 days	Consistent	Yes (*)
ARH Forte®	Liquid injection	225 mg (1 phial/day)	3 days	Consistent	No
Artesun®	Liquid injection	60 mg (2.4 mg/day)	3 days	Non Consistent	No
Artemether	Liquid injection	80 mg (1 phial/day)	3 days	Consistent	No
Artemether	Liquid injection	80 mg (1/2 phial/day)	3 days	Consistent	No
Artemether	Liquid injection	80 mg (2 phial day1 & 1 phial/day)	3 days	Consistent	No
Cether-L®	Liquid injection	22 mg (1 phial/day)	3 days	Consistent	No
Cether-L®	Syrup	According to body weight (1.4 mL/Kg/day)	7 days	Non Consistent	No
Cether-L®	Liquid injection	75 mg (1 phial/day)	3 days	Consistent	No
Cether-L® (infant)	Liquid injection	180/1080 mg (1 phial/day)	3 days	Consistent	No
Coartem®	Tablet	20/120 mg (2x4 tablets/day)	3 days	Consistent	No
Quinine	Liquid injection	500 mg (20 mg/Kg & 10 mg/Kg)	7 days	Non Consistent (ǂ)	No
Quinine	Liq. Inj. & tablet	500 mg (20 mg/day: IM) & 500 mg (10 mg/Kg: p.o.)	14 days	Non Consistent	Yes (**)
Quinine & Arthemether	Liquid injection	500 mg (10 mg/day) & 75 mg (1 phial/day)	5 days	Non Consistent	Yes (**)
Quinine & Cether-L® (infant)	Liquid injection	500 mg (20 mg/Kg) & 80 mg (160 mg/Kg)	7 days	Consistent	No

Legend: (ǂ) The WHO recommendation for quinine is 20 mg/Kg first time and 10 mg/Kg every 8 hours for 5 days (*) Asthenia; (**) Ears buzzing.

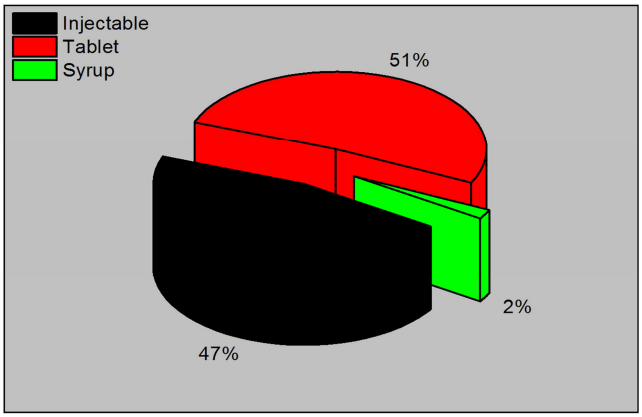


Figure 10. Different pharmaceutical forms given (administered) to patients.

Figure 11 provides information on the doses of antimalarial drugs administered to patients in the Gbadolite Health Zone.

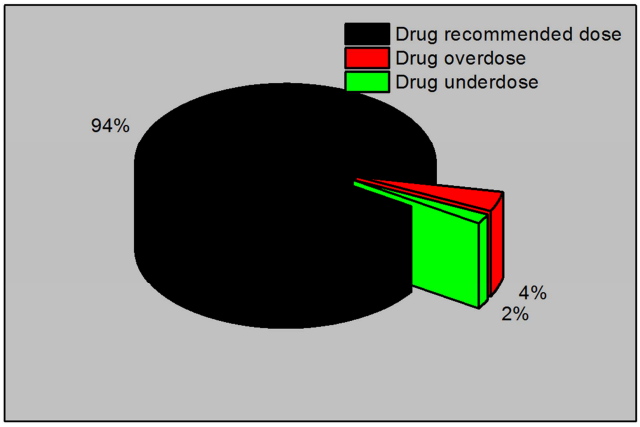


Figure 11. Antimalarial drug doses administered to patients.

Figure 11 shows that in 94% of cases, the antimalarial drug dose administered to patients is consistent. However, in 4% of cases, there is overdose while the sub-dose is estimated at 2% of cases. These results show the need for the creation of a pharmacovigilance unit in this health zone, because the overdose can be the basis of side effects or can result in renal failure and death through depression of the respiratory system. Indeed, it should be noted that Amodiaquine or 7-chloro-diethylaminomethyl-3'-hydroxy-4'-anilino-4-quinoline has recently been reported as highly cytotoxic because its biotransformation by polymorphonuclear leucocytes would lead to the formation of toxic iminoquinonic derivatives [27-29].

Figure 12 shows the different drugs associated with antimalarial drugs for the treatment of malaria in the Gbadolite Health Zone.

It appears from Figure 12 that antibiotics are drugs associated with anti-malarial drugs in the treatment of malaria (35% of cases) followed respectively by vitamins (20%), deworming (19%) and antitussive (4%). Other drugs account for 22% of registered cases. The association of anti-malarial drugs with other drugs like antibiotics in the management of malaria in endemic region was also reported elsewhere to shorten the duration of therapy and minimize toxicity [13]. However, it should be noted that the combination of ACTs with antioxidants (vitamins C and E) may interfere with the antiparasitic activity of these artemisinine derivatives because of the anti-radical property of antioxidants. Some Congolese prescribers assume inexplicably that better management of malaria requires addition of antibiotics, anti-cough and anti-helminthic to antimalarial drugs. Neither the WHO guidelines nor the Congolese guidelines recommend co-prescribing of such drugs in the management of malaria. This situation was also reported previously elsewhere [30].

Figure 13 shows the duration of malaria treatment in the Gbadolite Health Zone.

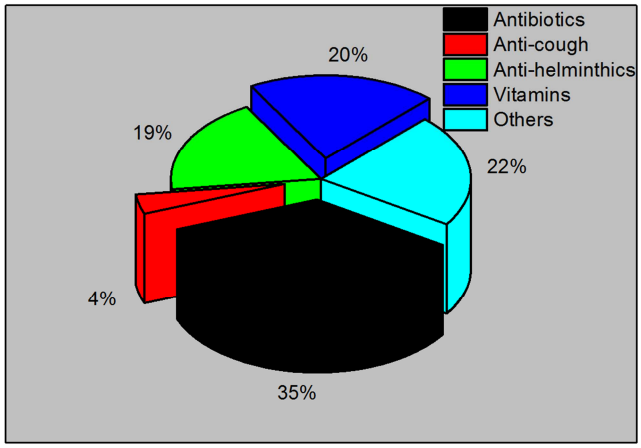


Figure 12. Different drugs associated with antimal-arial drugs in the treatment of malaria.

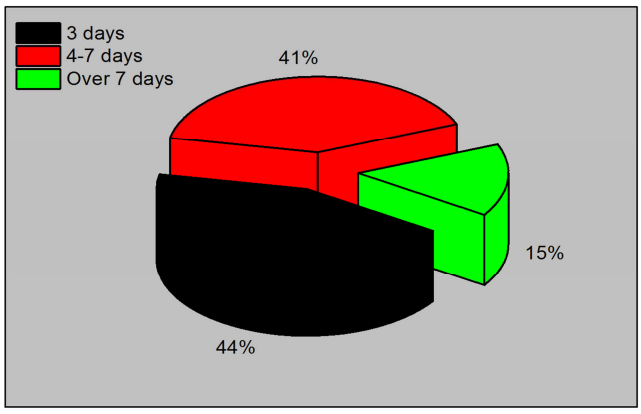


Figure 13. Duration of malaria treatment in the Gbadolite Health Zone.

This figure shows that the duration of malaria treatment is variable: three days (44% of cases), four to seven days (41% of cases) and more than seven days (15% of cases).

Figure 14 shows the result of malaria treatment in the Gbadolite Health Zone.

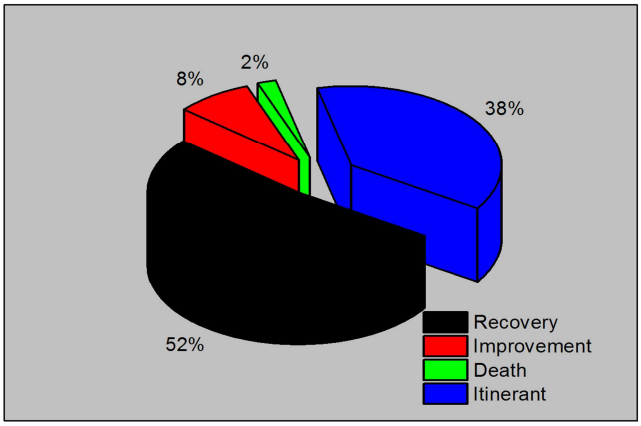


Figure 14. Result of malaria treatment in the Gbadolite Health Zone.

This figure revealed that 52% of people have been healed after treatment, 38% followed an ambulatory treatment. 8% of the patients saw their state of health improved while 2% of people died.

Despite the access of anti-malarial dugs, DRC is still highly affected by malaria and concentrates 10% of all deaths related to malaria worldwide, most of whom are children under the age of 5 years.

Inappropriate use of drugs in the management of malaria was reported to play a significant role in this counter performance. Indeed the World Health Organization (WHO) and the Congolese National program for malaria control have recommended biological confirmation of malaria by either Rapid Detection Test or microscopy before initiation of treatment. However, the performance of diagnostic tests prior to treatment is not a guarantee of optimal use of anti-malarial drugs. Indeed, an antimalarial drug like amodiaquine was reported to be very toxic because it could be bio-transformed via hepatic metabolism into immino-quinonic derivative which could explain the death rate observed in this study [27-29]. According to the present study carried out in four facilities in Gbadolite Health area, anti-malarial drugs were not used in complete agreement with the official guideline even though the practice is judged as good (high prescription of ACT). Indeed, nowadays the WHO recommends the use of artemisinin-based combination therapy (ACT) because of their efficacy and safeties have been scientifically validated [6]. However, minor error in prescribing and adherence to drugs was observed in Gbadolite city (Table 1) and can cause parasite pharmaco-resistance if medical staff is not regularly trained.

4. Conclusions

The aim of the present study was to identify the molecules and pharmaceutical forms used for the treatment malaria in Gbadolite health zone. Results indicate that the majority of patients are over 5 years old and male and literate. Medications are prescribed by doctors and nurses. Seven types of antimalarials are used. These include: Cether-L®, Artemether, Artesun®, ACT (artesunate-amodiaquine combination), Quinine, Co-artem® and ARH-L forte®. Tablet is the most commonly used pharmaceutical form followed respectively by the injectable form and the syrup. They are associated with antibiotics, vitamins, anti-helminthics and anti-cough. Although the dose of antimalarials drugs administered to patients is in accordance with national guidelines, cases of overdose and underdose have been reported in this health zone. The use of Amodiaquine and/or overdose may justify the few recorded deaths.

5. Recommendations

These results show the need for the creation of a pharmacovigilance unit in this health zone. Based on current knowledge this is a first report concerning cross-sectional study on the prescription of antimalarial-based drugs in Gbadolite health area.

Therefore, rational use of anti-malarial drugs should be promoted by the governing body particularly during prescribing and dispensing of drugs through a continuous in service training, journal club, seminar, and workshop.

There should also be future research direction on the rational use of anti-malarial-based drugs to identify the root cause of irrational anti-malarial drugs use reported in this study.

Conflicts of Interest

The authors declare that they have no competing interests

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