Resistance of *Plasmodium falciparum* to Sulfadoxine-Pyrimethamine (*Dhfr* and *Dhps*) and Artemisinin and Its Derivatives (*K13*): A Major Challenge for Malaria Elimination in West Africa

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**Abstract**

The spread of resistance to antimalarials is a major public health problem worldwide and especially in sub-Saharan Africa where the highest morbidity and mortality rates are found with a critical scarcity of data on resistance. The objective of this review is to describe the mutations in the *pfdhfr*, *pfdhps* and *k13* genes associated with resistance to artemisinin and Sulfadoxine-Pyrimethamine reported in West Africa during the decade 2007 to 2017 followed by a meta-analysis of their prevalence. A bibliographic search on the MEDLINE, PubMed, EMBASE and Sciences Direct databases made it possible to find 405 scientific papers relating to resistance to artemisinin and to Sulfadoxine-Pyrimethamine during the period 2007-2017. The analysis has concerned 217 scientific articles after the elimination of duplicates with 57 articles included in this review after the examination of titles and abstracts. The results of the present review show that the *dhfr* and *dhps* mutants are widespread in sub-Saharan Africa. Although, *Kelch* 13 mutants from Southeast Asia associated with artemisinin resistance are still absent in West Africa, studies have reported the presence of synonymous or non-*K13* mutations correlated with a delay in parasite clearance in Burkina Faso (2.26%), Senegal (5.5%) and Togo (1.8%). The increased prevalence of *dhfr* and *dhps* mutants in West Africa could jeopardize its use for intermittent preventive treatment in the near future. Despite the absence of strains...
resistant to artemisinin-based combination therapy in the West African region, increased surveillance is necessary to prevent the rapid occurrence of possible resistance, especially in the context of synonymous or non-K13 mutations correlated with a delay in parasitic clearance.

**Keywords**

Resistance, Mutations, Artemisinin, Sulfadoxine-Pyrimethamine, West Africa

**1. Introduction**

In 2017, WHO estimated that 219 million people experience a malarial illness worldwide with 435,000 deaths, more than 90% of them in tropical Africa and 61% of children under five years of age [1]. About 41.1 million of morbidity and 18,400 deaths were recorded in West Africa [1]. This disease represents a serious threat to health systems in sub-Saharan Africa where morbidity and mortality from malaria are the highest and inadequate surveillance systems to better control its spread [2] [3] [4]. One of the major challenges in malaria elimination is the resistance of *Plasmodium falciparum* to antimalarials today. According to WHO recommendations, artemisinin and Sulfadoxine-pyrimethamine (SP) are currently the most used drugs as the first line of treatment against malaria in Africa [5]. But a decade ago, the first cases of parasites resistant to artemisinin and its derivatives were detected in western Cambodia and then spread to the area of Southeast Asia [6]. In the case of Sub-Saharan Africa, the data in the literature are controversial on the probable relationship between the presence of k13 mutants and resistance to artemisinin [4] [7]. On the other hand, cases of resistance to SP have already been demonstrated by several authors, while SP continues to be offered as an intermittent and preventive treatment against malaria [5] [8] [9] [10] [11]. In the current context of West Africa, the insufficiency of information and the divergence of the conclusions of most of the studies on the *Plasmodium* resistance genes to SP and to artemisinin contribute to disseminate uncertainties on the choice of certain molecules such as SP for intermittent preventive treatment (IPT) and the probable presence of mutations in the k13 gene associated with resistance to artemisinin [12]. To prevent resistance in this area, strict diagnosis of malaria infections prior to treatment and good compliance with antimalarial drugs accompany WHO recommendation of artemisinin-based combinations (ACT) for the management of simple malaria and the administration of 3 doses of SP in IPT in each pregnancy [3] [13] [14]. In the absence of a vaccine with sufficient and lasting efficacy, preserving the efficacy of antimalarials, in particular artemisinin and SP in IPT, therefore constitutes a major challenge for Sub-Saharan Africa and in particular for West African in malaria control.

A synthesis of work on the resistance of *Plasmodium* to these main antimala-
rials is necessary to guide public health policies for the elimination of malaria in endemic areas of sub-Saharan Africa. To take stock of possible resistance to artemisinin and SP, this review will generally describe the situation of the resistance genes *pfdrfr*, *pfdrhs* and *k13* in West Africa during the decade 2007 to 2017. It will then be focused on a meta-analysis of the prevalence of mutations reported by the included studies in order to provide information that can facilitate decision-making on the effectiveness of SP and artemisinin.

### 1.1. Sulfadoxine-Pyrimethamine Mechanism of Action

Sulfadoxine (sulfonamide) is an antibiotic that inhibits the metabolism of folic acid (vitamin B9). Folic acid is essential for Plasmodium development [15]. Plasmodium synthesizes folic acid in 2 enzymatic steps using dihydropteroate synthetase (DHPS) then dihydrofolate reductase (DHFR). Blocking one of these pathways prevents the development of the parasite. Thus, sulfadoxine would inhibit the first synthetic enzyme, dihydropteroate synthetase (DHPS) and pyrimethamine would act on the second enzyme called dihydrofolate reductase (DHFR). SP has an erythrocyte and tissue schizonticidal effect, the action of which is prolonged by sulfadoxine. SP is most often recommended for intermittent and preventive treatment, especially in pregnant women [14] [16] [17].

### 1.2. Resistance to Sulfadoxine-Pyrimethamine

At the genetic level, resistance to SP is caused by mutations in the *dhfr* and *dhps* genes of *Plasmodium falciparum*. Mutations in the *dhfr* gene cause resistance to pyrimethamine; they are amino acid substitutions on codons S108N, N51I, C59R and I164L. For the *dhps* gene, the substitutions responsible for sulfadoxine resistance are located on codons S436A/F, A437G, K540E, A581G and A613T/S [18].

### 1.3. The Mechanism of Action of Artemisinin and Its Derivatives

Artemisinin or qinghaosu is a sesquiterpene lactone extracted from the leaves of a plant called Artemisia annua. Its biosynthesis is not yet fully understood [19]. The semi-synthetic derivatives of artemisinin are dihydroartemisinin (DHA), artemenate, artemether and arteether [20]. Artemisinin and its derivatives are pro-drugs that act on the schizonts of *Plasmodium* in erythrocytes. They cross the membrane of the red blood cells and then that of the parasites and accumulate in the digestive vacuoles of the parasite. Two main mechanisms of action are attributed to them. It would be the blocking of a SERCA (Sarco/Endoplasmic Reticulum Ca$^{2+}$ ATPase) or PfATPase enzyme which would allow the parasite to pump calcium for its development [19] [21]. The other mechanism of action results from the presence in the structure of artemisinin of an endoperoxide bridge playing a major role in the effectiveness of the molecule. The activation of the endoperoxide bridge during the endo-erythrocytic phase generates free radicals which alter the membrane of the parasite thus causing its death by oxidative stress [22] [23].
There are two ways of activating the endo-peroxide bridge. The mitochondria are said to be the seat of the first pathway which is caused by the electron transport chain, the consequence of which is a large production of Reactive Oxygen Species (ROS) [7]. The second way takes place in the digestive vacuoles thanks to the heme (Fe²⁺) resulting from the catabolism of hemoglobin [24]. Artemisinin is toxic to chloroquine resistant strains. It acts mainly on rings and trophozoites in the growth phase. Its toxicity on the early stages of gametocytes gives it effectiveness in inhibiting the transmission of the parasite [19]. Artemisinin is however inactive on merozoites, pre-erythrocytic forms and other forms present in the parasite development cycle at the level of the malaria vector [19]. The World Health Organization issued guidelines in 2015 to recommend Artemisinin and its derivatives as first-line malaria treatment and two artemisinin derivatives can be used together. Children and adults with uncomplicated malaria in endemic area are strongly recommended to be treated with one of the following artemisinin-based combination therapies (ACT): artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydroartemisinin + piperaquine, artesunate + sulfadoxine pyrimethamine (SP).

1.4. Resistance to Artemisinin and Derivatives

Resistance to artemisinin and its derivatives results from certain mutations in the Kelch or k13 gene located on chromosome 13 of Plasmodium falciparum [25] [26] [27]. Any mutation in the Kelch 13 gene does not systematically confer resistance to artemisinin; two main criteria validate the mutations as being associated with artemisinin resistance. Resistance should be correlated with slow parasitic clearance in clinical studies and reduced sensitivity of the drug in vitro [28]. The assessment of drug sensitivity is based on the quantitative microscopic measurement of delayed parasite clearance following the first days of treatment with ACT or artemisinin monotherapy. This results in a longer parasite clearance half-life. The half-life parameter is measurable by the phenotype ring-stage survival assay or RSA which measures the parasite survival rate in the stage of young trophozoites at an exposure of 700 nM of dihydroartemisinin for 6 h [29]. WHO defines eight K13 mutants associated with the resistance of Plasmodium falciparum to artemisinin which are F446I, P553L, N458Y, R561H, M476I, C580Y, Y493H, R539T and I543T. The other mutants with one of the criteria described above are classified as associated candidates [28]. Resistance to an artemisinin derivative or ACT is considered resistance to artemisinin [30].

2. Methodology

2.1. Collection of Data

A bibliographic search on the MEDLINE, PubMed, EMBASE and Sciences Direct databases was carried out using as keywords: “Plasmodium falciparum (+) resistances (+) sulfadoxine-pyrimethamine”, “Plasmodium falciparum (+) resistances (+) Artemisinin”, “Plasmodium falciparum (+) resistances (+) sulfadox-
ine-pyrimethamine (+) Artemisinin AND/OR X (X = countries of West Africa)”. 654 publications were found over the period 1981 to 2018; 405 publications over a 10-year period (2007-2017) were selected. Duplicates have been removed to retain only 217 publications. The articles included in the database were selected on the basis of the title and the abstract. Other articles that escaped our initial research were added based on the reading of the references of the included articles in the review (Figure 1).

2.2. Statistical Analysis

The prevalence of the mutations was calculated with the Epi-info version 6 software and the RevMan 5.3 software was used for the meta-analysis. The Cochran’s Q test was used to calculate the percentage of the total variance (I²) between the studies involved. “I²” reflects the heterogeneity between these studies. It is weak for the values of I² ≤ 25%, moderate for 25% < I² ≤ 50% and strong for I² ≥ 75% [31]. In this comparison, two (2) meta-analyzes concerned the publications

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Figure 1. Method of publications selection in the data bases.
on the DHPS (codon 437) and DHFR mutations (codons 51, 59 and 108) and the DHFR triple mutation (51 + 59 + 108). A first meta-analysis made it possible to target the publications having negatively impacted the variance and a second was made by eliminating these scientific publications.

3. Results

3.1. Dhfr and Dhps Genes in West Africa

In 2010, “DRUG RESISTANCE MAP” had mapped 4 dhfr mutations (51, 58, 108 and 164) and 5 dhps mutations (437, 540, 581 and 613S/T) on the African continent [32]. The data collected over the period 2007-2017 showed that the dhfr and dhps mutants are widespread in sub-Saharan Africa in general and in the countries of West Africa (Ivory Coast, Benin, Burkina Faso, Senegal, Ghana, Mali, Gambia and Nigeria) at quite varied frequencies (Tables 1-3). The highest prevalence of dhfr mutants (codon 51, 59, 108) are found in Benin (Table 1) [33]. The A437G mutation in the dhps gene is the most frequent with high prevalence in Benin and Burkina Faso (Table 2) [34]. The triple dhfr mutation is mainly found in Benin and Senegal (Table 3) [35] [36].

3.2. K13 Mutants in West Africa

In 2016 none of the previously described substitutions had been observed generally in sub-Saharan Africa apart from the P553L mutation which was observed at low frequencies in Kenya (0.53%) and in Malawi (0.59%) [37] [38]. Other studies have however observed the presence of synonymous or non-K13 mutations correlated with a delay in parasite clearance in Burkina Faso (2.26%), Senegal (5.5%) and Togo (1.8%) [8] [39] [40] (Table 4).

3.3. Meta-Analysis of SP Resistance Data in Plasmodium falciparum

A first meta-analysis of the data showed strong heterogeneity ($I^2 > 90\%$) between the studies compared (Tables 1-4). Considering the analysis for each type of mutation and the triple mutation, we observed a decrease in the percentage of variance when the Cochran’s Q test from RevMan 5.3 was repeated without considering the studies which negatively influenced it (Triplet mutation Dhfr + Dhps: heterogeneity chi$^2 = 723.39$; df = 12 ($p < 0.001$; $I^2 = 98\%$. Dhps mutation A437G: heterogeneity chi$^2 = 142.85$; df = 13 ($p < 0.001$; $I^2 = 91\%$. Dhfr mutation N51I: heterogeneity chi$^2 = 410.78$; df = 10 ($p < 0.001$; $I^2 = 98\%$. Dhfr mutation C59R: heterogeneity chi$^2 = 7.979$; df = 10 ($p < 0.001$; $I^2 = 100\%$. Dhfr mutation S108N: heterogeneity chi$^2 = 219.05$; df = 12 ($p < 0.00001$; $I^2 = 95\%$).

4. Discussion

4.1. Dhfr and Dhps Genes in West Africa

The use of SP in West Africa for the intermittent and preventive treatment of malaria has not so far been associated with a loss of birth weight and a drop in
The distribution of mutations at codons 59, 540 and triple/quadruple/quintuple mutations of the \textit{pf}\textit{dhfr} and \textit{pf}\textit{dhps} genes would be highly predictive of treatment failures in SP [42]. Most of these SP resistance markers present at the majority of sites in West Africa could seriously compromise the effectiveness of intermittent preventive treatment for years to come [10] [43]. This situation would call for new approaches and new strategies with regard to the efficient use of SP in West Africa and in general in sub-Saharan Africa.

### 4.2. \textit{K13} Mutants in West Africa

Current data would show that most West African countries have not yet recorded \textit{Kelch} 13 (\textit{K13}) mutations similar to those observed in Southeast Asia and which

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**Table 1.** Prevalence of \textit{dhfr} codons 51, 59, 108 conferring resistance to SP in \textit{Plasmodium falciparum} [5] [10] [34] [35] [43] [45]-[51].

| Authors            | Countries       | Type of study | Sample (N) | N51I (n, % (CI)) | C59R (n, % (CI)) | S108N (n, % (CI)) |
|--------------------|-----------------|---------------|------------|-----------------|-----------------|-------------------|
| Cissé et al., 2017 | Burkina Faso    | Cross-sectional | 101 | 72 | 71.29 (61.30 - 79.64) | 43 | 42.57 (32.91 - 52.80) | 65 | 64.35 (54.14 - 73.46) |
| Somé et al., 2016  | Burkina Faso    | Cross-sectional | 51I (243), 59R (242), 108N (235) | 148 | 148 | 60.90 (54.44 - 67.02) | 130 | 53.72 (47.22 - 60.09) | 150 | 63.83 (57.29 - 69.90) |
| Tahita et al., 2015 | Burkina Faso    | Cross-sectional | 255 | 31 | 12.2 (8.53 - 16.96) | 156 | 61.17 (54.87 - 67.13) | 142 | 55.69 (49.35 - 61.84) |
| Amor et al., 2014  | Africa          | Cross-sectional | 159 | 150 | 94.34 (89.20 - 97.21) | 149 | 93.71 (88.42 - 96.77) | 156 | 98.11 (94.15 - 99.51) |
| Ndiaye., 2013      | Senegal         | Cross-sectional | 416 | 2 | 12.50 (2.19 - 39.59) | 36 | 93.87 (89.50 - 96.56) | 207 | 97.64 (94.28 - 99.13) |
| Fall et al., 2013  | Senegal         | Longitudinal   | 165 | 128 | 77.57 (70.30 - 83.54) | 131 | 79.39 (72.26 - 85.13) | 135 | 81.81 (74.90 - 87.21) |
| Ougouyemi-Hounto et al., 2013 | Benin | Cross-sectional | 212 | 204 | 96.23 (92.43 - 98.23) | 199 | 93.87 (89.50 - 96.56) | 207 | 97.64 (94.28 - 99.13) |
| Doumbo et al., 2013 | Mali            | Cross-sectional | 16 | 2 | 12.50 (2.19 - 39.59) | 12 | 74.17 (66.86 - 80.33) | 143 | 82.18 (75.51 - 87.40) |
| Wurtz et al., 2012 | Senegal         | Longitudinal   | 174 | 145 | 83.33 (76.77 - 88.38) | 129 | 74.71 (66.86 - 80.83) | 143 | 82.18 (75.51 - 87.40) |
| Duah et al., 2012  | Ghana           | Cross-sectional | 945 | 522 | 55.24 (52 - 58.43) | 623 | 65.92 (62.79 - 68.92) | 647 | 68.46 (65.38 - 71.40) |
| Fabrice et al., 2011 | Burkina Faso   | random sample  | 51I/108N (260), 59R (261) | 151 | 50.08 (51.81 - 64.10) | 143 | 54.79 (48.53 - 60.90) | 143 | 55 (48.73 - 61.12) |
| Faye et al., 2011  | Senegal         | Cross-sectional | 480 | 179 | 37.29 (32.98 - 41.80) | 177 | 36.87 (32.58 - 41.38) | 241 | 50.21 (45.65 - 54.76) |
| Alam et al., 2011  | Ghana           | Cross-sectional | 2 | 1 | 1 (2.66 - 97.33) | 1 | 50 (2.66 - 97.33) |
| Nahum et al., 2009 | Benin           | Cross-sectional | 25 | 17 | 68 (46.45 - 84.27) | 46 | 38.98 (30.26 - 48.42) |
Table 2. Prevalence of dhps codon 431, 436, 437, 540, 581 and 613 conferring resistance to SP in *Plasmodium falciparum* [5] [9] [10] [33] [34] [36] [41] [43] [45] [47]-[51].

| Authors          | Countries     | Type of study | Sample (N) | 431V n | 431V % (CI) | S436A/F n | S436A/F % (CI) | A437G n | A437G % (CI) | K540E n | K540E % (CI) | A581G n | A581G % (CI) | A613T/S n | A613T/S % (CI) |
|------------------|---------------|---------------|------------|--------|-------------|------------|----------------|--------|-------------|--------|--------------|--------|--------------|--------|---------------|
| Cissé et al., 2017 | Burkina Faso | Cross-sectional | 101        | 80.20  | (70.84 - 87.21) | 81         | (70.84 - 87.21) |        |             |        |              |        |              |        |               |
| Somé et al., 2016 | Burkina Faso | Cross-sectional | 236        | 64     | (57.46 - 70.03) | 64         | (57.46 - 70.03) |        |             |        |              |        |              |        |               |
| Oguike et al., 2016 | Nigeria    | Retrospective | 589        | 37.86  | (33.95 - 41.93) | 53.99      | (49.87 - 58.06) | 98.13  | (96.58 - 99.01) | 75.04  | (71.30 - 78.45) | 70.11  | (66.21 - 73.75) |        |               |
| Tahita et al., 2015 | Burkina Faso | Cross-sectional | 231        |        |             |            |               | 34.19  | (28.18 - 40.75) |        |              |        |              |        |               |
| Amor et al., 2014 | Africa       | Cross-sectional | 159        | 8      | (5.08 - 14.61) | 74         | (66.57 - 80.67) | 23.90  | (17.66 - 31.43) | 7      | (1.94 - 9.21) |        |              |        |               |
| Fall et al., 2013 | Senegal      | Longitudinal  | 165        | 38.79  | (31.40 - 46.70) | 54.54      | (46.63 - 62.24) | 0.6    | (0.031 - 3.841) | 2      | (0.21 - 4.76) |        |              |        |               |
| Ogouye-mi-Hounto et al., 2013 | Benin | Cross-sectional | 210        |        |             |            |               | 71.43  | (64.73 - 77.33) |        |              |        |              |        |               |
| Moussiliou et al., 2013 | Benin    | Prospective  | 212        |        |             |            |               | 81.60  | (75.58 - 86.45) |        |              |        |              |        |               |
| Doumbo et al., 2013 | Mali        | Cross-sectional | 200        |        |             |            |               | 25     | (19.28 - 31.70) |        |              |        |              |        |               |
| Wurtz et al., 2012 | Senegal      | Longitudinal  | 174        | 35.06  | (28.09 - 42.69) | 40.23      | (32.96 - 47.94) | 70     | (32.96 - 47.94) | 3      | (0.45 - 5.36) |        |              |        |               |
| Duah et al., 2012 | Ghana        | Cross-sectional | 945        |        |             |            |               | 72.91  | (69.93 - 75.70) | 0.32  | (0.08 - 1.00) |        |              |        |               |
| Fabrice et al., 2011 | Burkina Faso | random sample | 259        | 35.52  | (29.76 - 41.71) | 56.76      | (50.47 - 62.83) |        |              |        |              |        |              |        |               |
| Faye et al., 2011 | Senegal      | Cross-sectional | 480        |        |             |            |               | 47.50  | (42.97 - 52.07) |        |              |        |              |        |               |
| Alam et al., 2011 | Ghana        | Cross-sectional | 436S (21); 437G (63) | 14.28  | (3.76 - 37.35) | 36.51      | (25.02 - 49.65) |        |              |        |              |        |              |        |               |
| Nahum et al., 2009 | Benin        | Cross-sectional | 437G (30); K540 (3) | 83.33  | (64.55 - 93.69) | 33.33      | (1.76 - 87.46) |        |              |        |              |        |              |        |               |
| Djaman et al., 2007 | Côte d'Ivoire | Cross-sectional | 118        | 65.25  | (55.87 - 73.63) | 51.70      | (42.35 - 60.92) |        |              |        |              |        |              |        | MEASUREMENT SYNONYM 1 |
Table 3. Prevalence of dhfr triple mutation (51 + 59 + 108) conferring resistance to SP in *Plasmodium falciparum* [5] [9] [10] [33] [34] [36] [41] [43] [45] [47]-[51].

| Authors            | Countries    | Type of study         | Sample (N) | Triple mutation dhfr (N51I + C59R + S108N) |
|--------------------|--------------|-----------------------|------------|-------------------------------------------|
| Ruizendaal et al., 2017 | Burkina Faso | Longitudinal and cross-sectional | 921        | 625.00 (64.72 - 70.85)                     |
| Cissé et al., 2017   | Burkina Faso | Cross-sectional       | 101        | 26 (17.79 - 35.57)                        |
| Somé et al., 2016    | Burkina Faso | Cross-sectional       | 90         | 50 (55.55 (44.73 - 65.90)                  |
| Tahita et al, 2015   | Burkina Faso | Cross-sectional       | 255        | 2900 (11.4 (7.90 - 16.08)                  |
| Amor et al., 2014    | Africa       | Cross-sectional       | 159        | 140 (88.05 (81.73 - 92.47)                |
|Ndjaye et al., 2013   | Senegal      | Cross-sectional       | 416        | 358,00 (86.06 (82.27 - 89.16)             |
|Fall et al., 2013     | Senegal      | Longitudinal          | 165        | 121 (73.33 (65.80 - 79.77)                |
|Ogouyemi-Hounto et al., 2013 | Benin     | Cross-sectional       | 212        | 194 (91.51 (86.70 - 94.75)                |
|Moussouliou et al., 2013 | Benin     | Prospective           | 212        | 187 (88.20 (82.90 - 92.08)                |
|Wurtz et al., 2012    | Senegal      | Longitudinal          | 174        | 131 (75.29 (68.07 - 81.36)                |
|Duah et al, 2012      | Ghana        | Cross-sectional       | 945        | 379 (40.10 (36.97 - 43.31)                |
|Faye et al., 2011     | Senegal      | Cross-sectional       | 480        | 109 (22.70 (19.09 - 26.77)                |
|Alam et al, 2011      | Ghana        | Cross-sectional       | 98         | 57 (58.16 (47.76 - 67.91)                 |

Table 4. Prevalence of Kelch 13 (K13) mutations conferring resistance to artemisinin in *Plasmodium falciparum* [5] [10] [35] [36] [43] [45] [47] [49] [50] [52].

| Authors            | Countries    | Type of study         | Sample (N) | K13 mutations |
|--------------------|--------------|-----------------------|------------|---------------|
| Somé et al., 2016  | Burkina Faso | clinical study        | 244        | C469C (2), Y493Y (1), G496G (1), V589V (1) |
| Ogouyemi-Hounto et al., 2016 | Benin     | Cross-sectional       | 108        | No detectable polymorphisms |
| Dieye et al., 2016  | West Africa  | Cross-sectional       | 463        | No mutations for Kelch 13 (K13) |
| Dorkenoo et al., 2016| Togo       | Cross-sectional       | 523        | K13 propeller domain, only 9 (1.8%) mutations were reported. |
| Boussarque et al., 2015 | Senegal  | Cross-sectional       | 103        | N554H, Q613H, and V637I in K13 region (5.5%) |
| Taylor et al., 2015 | Subsaharian Africa | Longitudinal | 1100       | P553L for Kenya (0.53) and Malawi (0.59); 15 coding mutations and 12 novel mutations |
| Torrentino-Madamet et al., 2014 | Senegal | Cross-sectional       | 138        | T149S (6.3%) and K189T (42.2%), (N) or two (NN) asparagine insertion at the codon 142 (4.7% and 6.3%, respectively) |
| Issaka et al., 2013  | Niger        | Experimental          | 89         | Parasites remained highly susceptible to new (dihydroartemisinin, lumefantrine, pyronaridine, and piperaquine) |
| Ibrahim et al., 2009 | Niger        | Cross-sectional       | 92         | The pfATPase6S769N, candidate mutation of resistance to artemisinin was not found. However the pfATPaseA623E mutation was found in 4 % of samples |
| Kaddouri et al., 2008 | Mali         | Cross-sectional       | 96         | No decreased susceptibility to dihydroartemisinin or lumefantrine was detected |

are associated with resistance to artemisinin [37]. Taking as reference the list of validated mutations (F446I, N458Y, M476I, Y493H, R539T, I543T, P553L,
R561H, C580Y) and candidates (P441I, G449A, C469F, A481V, P527H, N537I, G538V, V5 F673I, A675V) which may be associated with resistance to artemisinin [28], we found that the P553L mutant was present in Kenya (0.53%) and Malawi (5.5%) at fairly low frequencies. Most of the mutations reported in the reviewed publications relate to delayed parasite clearance but are not confirmed to be resistant to artemisinin. Artemisinin, its derivatives and artemisinin-based combinations (ACT) still remain effective as the first line of treatment for malaria in West Africa [28] [38].

4.3. Meta-Analysis of SP Resistance Data in *Plasmodium falciparum*

The first meta-analysis revealed a large disparity ($I^2 > 90\%$) between the studies compared, which would not make the result obtained credible. A second comparison in the absence of certain studies made it possible to obtain better results with low or moderate heterogeneity. Analysis of the bias between the studies considered shows that there is a likely influence of the type of study and prevalence. This bias was minimized during the second comparison. The prevalence of each *Dhps* (A437G) or *Dhfr* mutant (N51I, C59R, S108N) is relatively high, unlike that of the triple *Dhfr* mutation. These data would suggest that SP could still be recommended with caution in the intermittent preventive treatment against malaria in the West African Region. However, the residual risk of increasing malaria could be high in the coming years with the emergence of double, triple, quadruple and quintuple mutations [44].

5. Conclusion

Despite the increasing prevalence of *dhfr* and *dhps* mutants in the West African region, SP is still recommended for prevention against malaria in this area. In addition, the emergence of triple, quadruple or quintuple *Dhfr/Dhps* mutation could in the near future dangerously jeopardize the use of SP for intermittent preventive treatment in West Africa. However, artemisinin, its derivatives and artemisinin-based combinations (ACT) are said to be still effective in West Africa at this time. The challenge of protecting the effectiveness of ACT for this region, is to maintain a high wakefulness level in the monitoring to prevent the rapid onset of possible resistance to artemisinin.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] World Health Organization (2018) World Malaria Report.
[2] Organisation mondiale de la Santé (2014) Statistiques Sanitaires mondiales.
[3] WHO (2017) World Malaria Report 2017.
Organisation mondiale de la Santé (2017) Résistance aux médicaments antipaludiques.

Amor, A., Toro, C., Fernandez-Martinez, A., Baquero, M., Benito, A. and Berzosa, P. (2012) Molecular Markers in *Plasmodium falciparum* Linked to Resistance to Anti-Malarial Drugs in Samples Imported from Africa over an Eight-Year Period (2002-2010): Impact of the Introduction of Artemisinin Combination Therapy. *Malaria Journal, 11*, 100. https://doi.org/10.1186/1475-2875-11-100

Ménard, D., Khim, N., Beghain, J., Adegnika, A.A., Shafiul-Alam, M., Amoudou, O., *et al.* (2016) A Worldwide Map of *Plasmadium falciparum* K13-Propeller Polymorphisms. *New England Journal of Medicine, 374*, 2453-2464. https://doi.org/10.1056/NEJMoa1513137

Kamau, E., Campino, S., Amenga-Etego, L., Drury, E., Ishengoma, D., Johnson, K., *et al.* (2014) K13-Propeller Polymorphisms in *Plasmodium falciparum* Parasites from Sub-Saharan Africa. *Journal of Infectious Diseases, 211*, 1352-1355. https://doi.org/10.1093/infdis/jiu608

Somé, A.F., Sorgho, H., Zongo, I., Bazie, T., Nikiéma, F., Sawadogo, A., *et al.* (2016) Polymorphisms in *K13, pfcrt, pfmdr1, pfdhfr, and pfdhps in Parasites Isolated from Symptomatic Malaria Patients in Burkina Faso*. *Parasite (Paris, France), 23*, 60. https://doi.org/10.1051/parasite/2016069

Ougnigue, M.C., Falade, C.O., Shu, E., Enato, I.G., Watíla, I., Baba, E.S., *et al.* (2016) Molecular Determinants of Sulfadoxine-Pyrimethamine Resistance in *Plasmodium falciparum* in Nigeria and the Regional Emergence of dhps 431V. *International Journal for Parasitology: Drugs and Drug Resistance, 6*, 220-229. https://doi.org/10.1016/j.ijpddr.2016.08.004

Cisse, M., Awandare, G.A., Soulama, A., Tinto, H., Hayette, M.-P. and Guiguemdé, R.T. (2017) Recent Uptake of Intermittent Preventive Treatment during Pregnancy with Sulfadoxine-Pyrimethamine Is Associated with Increased Prevalence of Pf dhfr Mutations in Bobo-Dioulasso, Burkina Faso. *Malaria Journal, 16*, 38. https://doi.org/10.1186/s12936-017-1695-1

Basco, L.K., Tahar, R., Ako, A.B., Djaman, J.A., Roman, J., Ngane, V.F., *et al.* (2017) Molecular Epidemiology of Malaria in Cameroon and Côte d’Ivoire. XXXI. Kelch 13 Propeller Sequences in *Plasmodium falciparum* Isolates before and after Implementation of Artemisinin-Based Combination Therapy. *The American Journal of Tropical Medicine and Hygiene, 97*, 222-224. https://doi.org/10.4269/ajtmh.16-0889

Basco, L.K. and Ringwald, P. (2000) Molecular Epidemiology of Malaria in Yaoundé, Cameroon. VI. Sequence Variations in the *Plasmodium falciparum* Dihydrofolate Reductase-Thymidylate Synthase Gene and *in Vitro* Resistance to Pyrimethamine and Cycloguanil. *American Journal of Tropical Medicine and Hygiene, 62*, 271-276. https://doi.org/10.4269/ajtmh.2000.62.271

World Health Organization (2012) World Malaria Report.

Douamba, Z., Bisseye, C., Djigma, F.W., Compaor, T.R., Bazie, T., Pietra, V., *et al.* (2012) Asymptomatic Malaria Correlates with Anaemia in Pregnant Women at Ouagadougou, Burkina Faso. *Journal of Biomedicine and Biotechnology, 2012*, Article ID: 198317. https://doi.org/10.1155/2012/198317

Yameogo, N., Valérie, B., Jean, E., Bazie, T., Ouattara, A.K., Yameogo, P., *et al.* (2017) Major Polymorphisms of Genes Involved in Homocysteine Metabolism in Malaria Patients in Ouagadougou, Burkina Faso. *Malaria Research and Treatment, 2017*, Article ID: 3468276. https://doi.org/10.1155/2017/3468276

Pierre Aubry, B.-A.G. (2017) Paludisme [Internet]. Medecine Tropicale. 1-27. http://www.medecinetropicale.com%0A1
[17] Douamba, Z., Ginette, N., Dao, L., Zohoncon, T.M., Bisseye, C., Compaoré, T.R., et al. (2014) Research Article Mother-to-Children Plasmodium falciparum Asymptomatic Malaria Transmission at Saint Camille Medical Centre in Ouagadougou, Burkina Faso. *Malaria Research and Treatment*, 2014, Article ID: 390513. 
https://doi.org/10.1155/2014/390513

[18] World Health Organization (2010) Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000-2010.

[19] Bruneton, J. (2009) Pharmacognosie Phytochimie Plantes médicinales. 4th Editions.

[20] Chekem, L. and Wierucki, S. (2007) Extraction de l’artémisinine et synthèse de ses dérivés: Artésunate et artéméther. *Phytothérapie*, 5, 90-95. 
https://doi.org/10.1007/s10298-007-0218-6

[21] Artémisinine [Internet]. Wikipédia, l'encyclopédie libre, 2018.
https://fr.wikipedia.org/wiki/Art%C3%A9misinine#m
https://fr.wikipedia.org/wiki/Artémisinine
http://fr.wikipedia.org/w/index.php?title=Art%C3%A9misinine&action=history

[22] Cooper, R.A., Conrad, M.D., Watson, Q.D., Huezo, S.J., Ninsiima, H., Tumwebaze, P., et al. (2015) Lack of Artemisinin Resistance in Plasmodium falciparum in Uganda Based on Parasitological and Molecular Assays. *Antimicrobial Agents and Chemotherapy*, 59, 5061-5064. https://doi.org/10.1128/AAC.00921-15

[23] Isozumi, R., Uemura, H., Kimata, I., Ichinose, Y., Logedi, J., Omar, A.H., et al. (2015) Novel Mutations in K13 Propeller Gene of Artemisinin-Resistant Plasmodium falciparum. *Emerging Infectious Diseases*, 21, 490-492. 
https://doi.org/10.3201/eid2103.140898

[24] Ouattara, A., Kone, A., Adams, M., Fofana, B., Maiga, A.W., Hampton, S., et al. (2015) Polymorphisms in the K13-Propeller Gene in Artemisinin-Susceptible Plasmodium falciparum Parasites from Bougoula-Hameau and Bandiagara, Mali. *The American Journal of Tropical Medicine and Hygiene*, 92, 1202-1206. 
https://doi.org/10.4269/ajtmh.14-0605

[25] Straimer, J., Gnädig, N.F., Witkowski, B., Amaratunga, C., Duru, V., Ramadani, A.P., et al. (2015) K13-Propeller Mutations Confer Artemisinin Resistance in Plasmodium falciparum Clinical Isolates. *Science*, 347, 428-431. 
https://doi.org/10.1126/science.1260867

[26] Ariey, F., Witkowski, B., Amaratunga, C., Beghain, J., Langlois, A.-C., Khim, N., et al. (2014) A Molecular Marker of Artemisinin-Resistant Plasmodium falciparum Malaria. *Nature*, 505, 50-55. https://doi.org/10.1038/nature12876

[27] Phompradit, P., Chaijaroenkul, W. and Na-Bangchang, K. (2017) Cellular Mechanisms of Action and Resistance of Plasmodium falciparum to Artemisinin. *Parasitology Research*, 116, 3331-3339. https://doi.org/10.1007/s00436-017-5647-z

[28] World Health Organization (2018) Artemisinin Resistance and Artemisinin-Based Combination Therapy Efficacy.

[29] Das, D., Price, R.N., Bethell, D., Guerin, P.J. and Stepniewska, K. (2013) Early Parasitological Response Following Artemisinin-Containing Regimens: A Critical Review of the Literature. *Malaria Journal*, 12, 125. 
https://doi.org/10.1186/1475-2875-12-125

[30] Sugawara, E. and Nikaido, H. (2014) Status Report on Artemisinin and ACT Resistance. *Antimicrobial Agents and Chemotherapy*, 58, 7250-7257. 
https://doi.org/10.1128/AAC.03728-14

[31] Higgins, J.P.T. and Green, S. (2005) Cochrane Handbook for Systematic Reviews of Interventions 4.2.5. The Cochrane Library.
[32] London School of Hygiene and Tropical Medicine (2010) Drugs Resistance Maps (Mapping the Distribution of Resistance Genes of Malaria in Africa) [Internet]. Drug Resistance Maps. http://www.drugresistancemaps.org/maps/haplootype/dhfr

[33] Ogouyemi-Hounto, A., Ndam, N.T., Kinde Gazard, D., d’Almeida, S., Koussihoude, L., Ollo, E., et al. (2013) Prevalence of the Molecular Marker of Plasmodium falciparum Resistance to Chloroquine and Sulphadoxine/Pyrimethamine in Benin Seven Years after the Change of Malaria Treatment Policy. Malaria Journal, 12, 147. https://doi.org/10.1186/1475-2875-12-147

[34] Nahum, A., Erhart, A., Ahounou, D., Bonou, D., Van Overmeir, C., Menten, J., et al. (2009) Extended High Efficacy of the Combination Sulphadoxine-Pyrimethamine with Artesunate in Children with Uncomplicated Falciparum Malaria on the Benin Coast, West Africa. Malaria Journal, 8, 37. https://doi.org/10.1186/1475-2875-8-37

[35] Ndiaye, D., Dieye, B., Ndiaye, Y.D., Tyne, D., Daniels, R., Bei, A.K., et al. (2013) Polymorphism in dhfr/dhps Genes, Parasite Density and ex Vivo Response to Pyrimethamine in Plasmodium falciparum Malaria Parasites in Thies, Senegal. International Journal for Parasitology: Drugs and Drug Resistance, 3, 135-142. https://doi.org/10.1016/j.ijpddr.2013.07.001

[36] Moussiliou, A., De Tove, Y.S.-S., Doritchamou, J., Luty, A.J.F., Massougbodji, A., Alifrangis, M., et al. (2013) High Rates of Parasite Recrudescence Following Intermittent Preventive Treatment with Sulphadoxine-Pyrimethamine during Pregnancy in Benin. Malaria Journal, 12, 195. https://doi.org/10.1186/1475-2875-12-195

[37] Taylor, S.M., Parobek, C.M., DeConti, D.K., Kayentao, K., Coulibaly, S.O., Greenwood, B.M., et al. (2015) Absence of Putative Artemisinin Resistance Mutations among Plasmodium falciparum in Sub-Saharan Africa: A Molecular Epidemiologic Study. The Journal of Infectious Diseases, 211, 680-688. https://doi.org/10.1093/infdis/jiu467

[38] Dieye, B., Affara, M., Sangare, L., Joof, F., Ndiaye, Y.D., Gomis, J.F., et al. (2016) Therapeutic Efficacy Trial of Artemisinin-Based Combination Therapy for the Treatment of Uncomplicated Malaria and Investigation of Mutations in k13 Propeller Domain in Togo, 2012-2013. Malaria Journal, 15, 331. https://doi.org/10.1186/s12936-016-1381-8

[39] Boussarroque, A., Fall, B., Madamet, M., Camara, C., Benoit, N., Fall, M., et al. (2016) Emergence of Mutations in the K13 Propeller Gene of Plasmodium falciparum Isolates from Dakar, Senegal, in 2013-2014. Antimicrobial Agents and Chemotherapy, 60, 624-627. https://doi.org/10.1128/AAC.01346-15

[40] Dorkenoo, A.M., Yehadjii, D., Agbo, Y.M., Layibo, Y., Agbeko, F., Adjeloh, P., et al. (2016) Therapeutic Efficacy Trial of Artemisinin-Based Combination Therapy for the Treatment of Uncomplicated Malaria and Investigation of Mutations in k13 Propeller Domain in Fana, Mali. Bulletin de la Societe de pathologie exotique (1990), 106, 188-192. https://doi.org/10.1007/s13149-013-0301-1

[41] Duah, N.O., Quashie, N.B., Abuaku, B.K., Sebeny, P.J., Kronmann, K.C. and Ko-
ram, K.A. (2012) Surveillance of Molecular Markers of Plasmodium falciparum Resistance to Sulphadoxine-Pyrimethamine 5 Years after the Change of Malaria Treatment Policy in Ghana. The American Journal of Tropical Medicine and Hygiene, 87, 996-1003. https://doi.org/10.4269/ajtmh.2012.12-0202

[44] Méndez, F., Muñoz, A., Carrasquilla, G., Jurado, D., Arévalo-Herrera, M. and Cortese, J.F. (2002) Determinants of Treatment Response to Sulfadoxine-Pyrimethamine and Subsequent Transmission Potential in Falciparum Malaria. American Journal Epidemiology, 156, 230-238. https://doi.org/10.1093/aje/kwf030

[45] Tahita, M.C., Tinto, H., Erhart, A., Kazzienga, A., Fitzhenry, R., VanOvermeir, C., et al. (2015) Prevalence of the dhfr and dhps Mutations among Pregnant Women in Rural Burkina Faso Five Years after the Introduction of Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine. PLoS ONE, 10, e0137440. https://doi.org/10.1371/journal.pone.0137440

[46] Ogouyémi-Hounto, A., Ndam, N.T., Fadégnon, G., Azagnandji, C., Bello, M., Moussiliou, A., et al. (2013) Low Prevalence of the Molecular Markers of Plasmodium falciparum Resistance to Chloroquine and Sulphadoxine/Pyrimethamine in Asymptomatic Children in Northern Benin. Malaria Journal, 12, 413. https://doi.org/10.1186/1475-2875-12-413

[47] Wurtz, N., Fall, B., Pascual, A., Diawara, S., Sow, K., Baret, E., et al. (2012) Prevalence of Molecular Markers of Plasmodium falciparum Drug Resistance in Dakar, Senegal. Malaria Journal, 11, 197. https://doi.org/10.1186/1475-2875-11-197

[48] Fabrice, S.A., Zongo, I., Rouamba, N., Compaaore, Y.D., Dokomajilar, C., Rosenthal, P.J., et al. (2011) Plasmodium falciparum Drug Resistance Molecular Markers under Intermittent Preventive Therapy with Dihydroartemisinin-Piperaquine (DP) vs. Amodiaquine-Sulfadoxine/Pyrimethamine (AQ-SP) in Burkina Faso. American Journal of Tropical Medicine and Hygiene, 85, 361.

[49] Faye, B., Ndiaye, M., Ndiaye, J.L., Annie, A., Tine, R.C., Lo, A.C., et al. (2011) Prevalence of Molecular Markers of Plasmodium falciparum Resistance to Sulfadoxine-Pyrimethamine during the Intermittent Preventive Treatment in Infants Coupled with the Expanded Program Immunization in Senegal. Parasitology Research, 109, 133-138. https://doi.org/10.1007/s00436-011-2236-9

[50] Alam, M.T., de Souza, D.K., Vinayak, S., Griffing, S.M., Poe, A.C., Duah, N.O., et al. (2011) Selective Sweeps and Genetic Lineages of Plasmodium falciparum Drug-Resistant Alleles in Ghana. The Journal of Infectious Diseases, 203, 220-227. https://doi.org/10.1093/infdis/ijq038

[51] Djaman, J.A., Mazabraud, A. and Basco, L. (2007) Sulfadoxine-Pyrimethamine Susceptibilities and Analysis of the Dihydrofolate Reductase and Dihydropteroate Synthase of Plasmodium falciparum Isolates from Cote d’Ivoire. Annals of Tropical Medicine and Parasitology, 101, 103-112. http://doi.org/10.1179/136485907X154584

[52] Ruizendaal, E., Tahita, M.C., Geskus, R.B., Versteeg, I., Scott, S., d'Alessandro, U., et al. (2017) Increase in the Prevalence of Mutations Associated with Sulfadoxine-Pyrimethamine Resistance in Plasmodium falciparum Isolates Collected from Early to Late Pregnancy in Nanoro, Burkina Faso. Malaria Journal, 16, 179. https://doi.org/10.1186/s12936-017-1831-y