Journal of Biosciences and Medicines, 2020, 8, 82-95
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Resistance of *Plasmodium falciparum* to Sulfadoxine-Pyrimethamine (*Dhfr* and *Dhps*) and Artemisinin and Its Derivatives (*K*13): A Major Challenge for Malaria Elimination in West Africa

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How to cite this paper: Bazie, V.B., Ouattara, A.K., Sagna, T., Compaore, T.R., Soubeiga, S.T., Sorgho, P.A., Yonli, A.T. and Simpore, J. (2020) Resistance of *Plasmodium falciparum* to Sulfadoxine-Pyrimethamine (*Dhfr* and *Dhps*) and Artemisinin and Its Derivatives (*K*13): A Major Challenge for Malaria Elimination in West Africa. *Journal of Biosciences and Medicines*, **8**, 82-95.
https://doi.org/10.4236/jbm.2020.82007

Received: December 24, 2019
Accepted: February 11, 2020
Published: February 14, 2020

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 *k*13 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-*K*13 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-*K*13 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 *k*13 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 *k*13 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 *pfdhfr*, *pfdhps* and *k*13 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), artesunate, 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 (Fe^{2+}) 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 *k*13 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 *K*13 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% < I^2 ≤ 50% and strong for I^2 ≥ 75% [31]. In this comparison, two (2) meta-analyzes concerned the publications

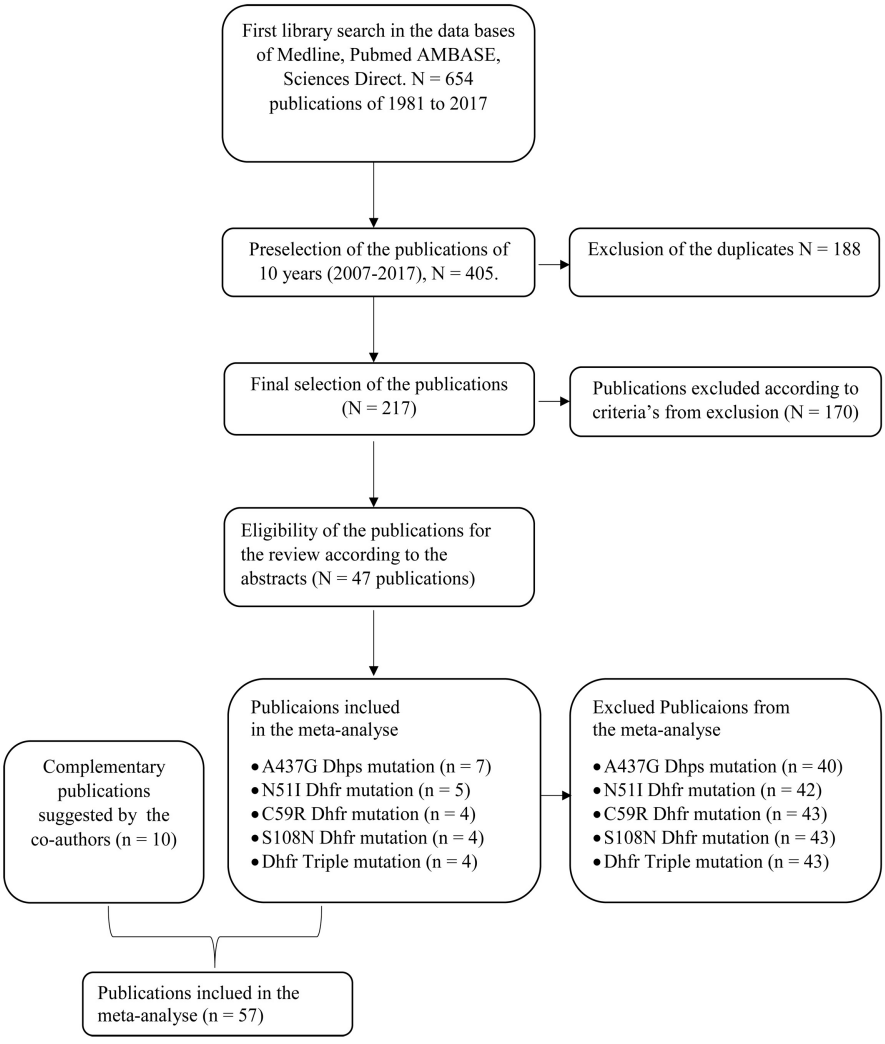

Figure 1. Method of publications selection in the data bases.

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. *K*13 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-*K*13 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 (Triple 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

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

Authors	Countries	Type of study	Sample (N)	N51I		C59R		S108N	
				n	% (CI)	n	% (CI)	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	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					368	88.46 (84.90 - 91.29)
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)
Ogouyemi-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)				
Wurtz *et al*., 2012	Senegal	Longitudinal	174	145	83.33 (76.77 - 88.38)	129	74.17 (66.86 - 80.33)	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	50 (2.66 - 97.33)
Nahum *et al*., 2009	Benin	Cross-sectional	25			17	68 (46.45 - 84.27)		
Djaman *et al*., 2007	Côte d'Ivoire	Cross-sectional	118					46	38.98 (30.26 - 48.42)

the level of maternal hemoglobin [41]. The distribution of mutations at codons 59, 540 and triple/quadruple/quintuple mutations of the *pfdhfr* and *pfdhps* 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. *K*13 Mutants in West Africa

Current data would show that most West African countries have not yet recorded *Kelch* 13 (*K*13) mutations similar to those observed in Southeast Asia and which

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		S436A/F		A437G		K540E		A581G		A613T/S	
				n	% (CI)	n	% (CI)	n	% (CI)	n	% (CI)	n	% (CI)	n	% (CI)
Cissé *et al.*, 2017	Burkina Faso	Cross-sectional	101					81	80.20 (70.84 - 87.21)						
Somé *et al.*, 2016	Burkina Faso	Cross-sectional	236					151	64 (57.46 - 70.03)						
Oguike *et al.*, 2016	Nigeria	Retrospective	589	223	37.86 (33.95 - 41.93)	318	53.99 (49.87 - 58.06)			578	98.13 (96.58 - 99.01)	442	75.04 (71.30 - 78.45)	413	70.11 (66.21 - 73.75)
Tahita *et al*, 2015	Burkina Faso	Cross-sectional	231					79	34.19 (28.18 - 40.75)						
Amor *et al.*, 2014	Africa	Cross-sectional	159			14	8 (5.08 - 14.61)	118	74 (66.57 - 80.67	38	23.90 (17.66 - 31.43)	7	4.4 (1.94 - 9.21)		
Fall *et al.*, 2013	Senegal	Longitudinal	165			64	38.79 (31.40 - 46.70)	90	54.54 (46.63 - 62.24)	1	0.6 (0.031 - 3.841)			2	1.21 (0.21 - 4.76)
Ogouye-mi-Hounto *et al.*, 2013	Benin	Cross-sectional	210					150	71.43 (64.73 - 77.33)						
Moussiliou *et al.*, 2013	Benin	Prospective	212					173	81.60 (75.58 - 86.45)						
Doumbo *et al.*, 2013	Mali	Cross-sectional	200					50	25 (19.28 - 31.70)						
Wurtz *et al.*, 2012	Senegal	Longitudinal	174			61	35.06 (28.09 - 42.69)	70	40.23 (32.96 - 47.94)	70	40.23 (32.96 - 47.94)			3	1.72 (0.45 - 5.36)
Duah *et al.*, 2012	Ghana	Cross-sectional	945					689	72.91 (69.93 - 75.70)	3	0.32 (0.08 - 1.00)				
Fabrice *et al.*, 2011	Burkina Faso	random sample	259			92	35.52 (29.76 - 41.71)	147	56.76 (50.47 - 62.83)						
Faye *et al.*, 2011	Senegal	Cross-sectional	480					228	47.50 (42.97 - 52.07)						
Alam *et al.*, 2011	Ghana	Cross-sectional	436S (21); 437G (63)			3	14.28 (3.76 - 37.35)	23	36.51 (25.02 - 49.65)						
Nahum *et al.*, 2009	Benin	Cross-sectional	437G (30); K540 (3)					25	83.33 (64.55 - 93.69)	1	33.33 (1.76 - 87.46)				
Djaman *et al.*, 2007	Côte d'Ivoire	Cross-sectional	118			77	65.25 (55.87 - 73.63)	61	51.70 (42.35 - 60.92)					32	27.11 (19.54 - 36.21)

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)	
				n	% (CI)
Ruizendaal *et al*., 2017	Burkina Faso	Longitudinal and cross-sectional	921	625.00	67.86 (64.72 - 70.85)
Cissé *et al*., 2017	Burkina Faso	Cross-sectional	101	26	25.74 (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)
Ndiaye *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)
Moussiliou *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 (*K*13) 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)	*K*13 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 (*K*13)
Dorkenoo *et al*., 2016	Togo	Cross-sectional	523	*K*13 propeller domain, only 9 (1.8%) mutations were reported.
Boussaroque *et al*., 2015	Senegal	Cross-sectional	103	N554H, Q613H, and V637I in *K*13 region (5.5%)
Taylor *et al*., 2015	Subsaharian Africa		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 pfATPsaeA623E 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 (P441l, 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.

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