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EPIDEMIOLGY OF DRUG RESISTANT FALCIPARUM MALARIA WITH SPECIAL REFERENCE TO ORISSA

Malaria imposes great socio-economic burden in about 100 countries/territories. Of the four species of human malaria parasites, P. falciparum is most lethal and responsible for most of the deaths. Every year about 1.1-2.7 million people die of malaria all over the world and more than 75% of them are from Africa, south of Sahara[1]. In India, malaria is mostly contributed the most by the state of Orissa. Although Orissa has a population of 36.5 million (3.5%), it contributes 25% of a total of 1.5-2 million reported annual malaria cases, 39.5% of P. falciparum malaria and 30% of deaths caused by malaria in India[2]. However, independent studies by the Indian Council of Medical Research have unequivocally established that the reports on the incidence of malaria and deaths due to it are highly under-estimated[3]. Amid such a disease burden and absence of a suitable vaccine, the development of resistance to the available drugs has a significant influence on the control of malaria in the affected areas.

At present mainly three categories of drugs are being used for the treatment of malaria. They are (i) 4-amino-quinolines and amino alcohols, which act on haemoglobin degradation and parasite food vacuole (e.g. chloroquine and quinine); (ii) antifolates, which are dihydrofolate reductase (DHFR) (e.g. pyremethamine, cycloguanil and chlorcycloguanil) and dihydropteroate synthase (DHPS) (e.g. sulphonamides and sulphones) inhibitors; and (iii) sesquiterpenes (artemisinin and its derivatives)[4]. Among all these antimalarials chloroquine is most widely used because of its efficacy, safety and cost effectiveness. Resistance of P. falciparum to chloroquine (CQ) was first observed in 1960-61 in Colombia of South America and Thailand-Cambodia border area of Southeast Asia. The two foci were evidently quite separate and probably represented a unique event. Accordingly the foci are designated as South American and South-East Asian[5]. In India the CQ resistance in P. falciparum was first detected from Diphu, Karbi Anglong district, Assam in 1973[6]. In Orissa it was detected in 1977 in Bolangir, Koraput and Sambalpur districts[7].Today chloroquine resistance occurs all over the globe, wherever P. falciparum occurs. Strains of falciparum parasites have also developed resistance to sulphadoxine-pyremethamine (Fansider) and mefloquine in many parts of the world. The development of resistance to sulphadoxine-pyremethamine is particularly serious; because this combination is the only alternative to 4-aminoquinolines[8]. Based on available literatures it has been observed that the parasites usually develop resistance to an antimalarial within 10-15 years of its uninterrupted use (Table I).

Table I. Dates of introduction and first report of antimalarial drug resistance.

Antimalarial drug	Introduced	First reported resistance	Difference (Years)
Quinine	1632	1910	278
Chloroquine	1945	1957	12
Proguanil	1948	1949	1
Sulphadoxine-Pyremethamine	1967	1967	0
Mefloquine	1977	1981	5
Atovaquone	1996	1996	0

The antimalarial drug resistance pattern in each geographical region provides useful treatment guidance, because there are no bedside methods of assessment for drug susceptibility. Although drug resistance occurs in both P. falciparum and P. vivax, only the former has been discussed in this article because more than 85% of malaria cases in Orissa are due to P falciparum and no resistance has been documented for P. malariae and P. ovale.

Historical Perspectives

Quinine is the oldest antimalarial known so far. But its use has never been as widespread as that of more contemporary drugs. It occurs naturally in the bark of Cinchona trees growing in Peru and other parts of South America. Cinchona bark was introduced into Europe in the early 17th century as a cure for fevers. In 1820, alkaloid quinine was isolated from Cinchona bark which replaced the crude preparation and continued to be the major antimalarial drug till 1942[9]. The world's supply of Cinchona bark for producing quinine was met by Java and neighbouring countries. This was cut off from the Germans during World War I and from Allies during World War II. Due to enormous military importance of malaria and its treatment intense activity was aroused for the development of antimalarial drugs.

During early part of the 20th century, a series of organic compounds (beginning with methylene blue) were evaluated, which led to the discovery of pamaquine and quinacrine and ultimately chloroquine, a 4-aminoquinoline. Chloroquine was first synthesized in Germany in 1934 but was not recognized as a potent antimalarial until the 1940s. By 1946, it was found to be far superior to other contemporary synthetic antimalarials. It became the cornerstone of antimalarial chemotherapy for the next 40 years. However, the advent of chloroquine resistance led to the development of other drugs such as mefloquine, sulphadoxine-pyremethamine, artemisinin derivatives and atovaquone - proguanil (Malarone)[10].

In China, infusions prepared from wormwood (Artemisia annua) were used in traditional medicine as Quinghaosu for the treatment of malarial fever for the last thousand years. The efficacy of the infusions has been ascribed to be the sesquiterpene lactone, artemisinin. Artemisinin is poorly soluble in water as well as oil. Several derivatives of this have been produced of which two have been recently marketed in India: Artemether which is soluble in oil and Artesunate (Sod) which is water soluble. Another compound Arteether is also being developed in India. As a result of increasing drug-resistant malaria, artemisinin from wormwood and semisynthetic derivatives of this substance have become a very important antimalarial drug group.

Assessment of Drug Efficacy

The WHO has outlined three ways of measuring the drug efficacy: (i) the clinical responses of patients (in vivo) to drug treatment; (ii) the in vitro sensitivity of parasites to drugs, or (iii) the accepted molecular markers as complementary tools. The in vivo response to drugs was originally defined by WHO in terms of parasite clearance (sensitive [S] and three degrees of resistance [RI, RII, RIII]). This classification remains valid for areas with low or no malaria transmission, but is difficult to apply to areas with intense transmission, where new infections may be mistaken for recrudescence. Therefore WHO introduced in 1996 a modified protocol based on clinical outcome (adequate clinical response, early treatment failure, and late treatment failure) targeted at a practical assessment of therapeutic responses. The protocol has also been adapted for use in areas of low to moderate endemicity, taking into consideration that the objectives of malaria treatment are both parasite clearance and disappearance of symptoms[11]. A summary of the original and modified protocols is shown in Table II.

The in vitro assays measure the inhibition of growth or schizont maturation to assess the intrinsic sensitivity of P. falciparum to the drug[12]. Recently the use of molecular markers has been proposed as an additional tool for the early detection of drug resistance in malaria[4]. Each assessment method has its advantages and disadvantages, and the results may not be directly comparable with each other. in vitro test results, in particular, do not necessarily

Table II. Classification of in-vivo antimalarial-drug sensitivity test outcomes according to the original WHO protocol and modification (1996) for areas with substantial malaria transmission.

Classification	Definition
Original Classification	
S (sensitive)	Clearance of asexual parasitaemia within 7days of the initial treatment without subsequent recrudescence.
RI response	Asexual parasites disappear by day 7 of the treatment but return within 28 days. However, reinfention is to be excluded.
RII response	Asexual parasitaemia does not clear but is reduced to 25% or less of the original pre-test level during the first 48 hours of treatment.
RIII response	Asexual parasitaemia is reduced by <75% during the first 48 hours or if it continues to rise following treatment.
Modified Classification (1996)	
Early treatment failure (ETF)	Aggravation or persistence of clinical symptoms in the presence of parasitaemia during the first 3 days of follow-up.
Late treatment failure (LTF)	Reappearance of symptoms in the presence of parasitaemia during days 4-14 of follow up.
Adequate clinical and parasitological response (ACPR)	Absence of parasitaemia on day 14 irrespective of fever, or absence of clinical symptoms irrespective of parasitaemia in patients not meeting ETF or LTF criteria.

correspond to in vivo outcomes, largely owing to the role of host immunity in the latter. In addition, pharmacokinetic information may be required for differentiation between true resistance and failure to achieve adequate drug concentration profile.

Determinants of Resistance

Development and spread of antimalarial drug resistance is determined by many factors. Gene mutations conferring resistance to antimalarial drugs do occur in natural parasite populations, independently of drug effect (the commonly used antimalarial drugs are not mutagenic). Although the proportion of such mutants in the parasite population is low, and malaria isolates from populations and individuals show heterogeneity, selection of the most fit parasites occurs under drug pressure. Single or multiple point mutations in the Plasmodium genome may confer resistance in the face of chemotherapy. The factors that determines the frequency of development and spread of drug resistance has been depicted in Table III[13].

Table III. Determinant of antimalarial drug resistance

Factors and Characteristics	Example
Drug	
Half-life	Resistance to chlorproguanil plus dapsone (short half-life) develops more slowly than that of sulphadoxine-pyremethamine (long half-life)
Dosing	Use of subtherapeutic doses in self treatment such as with antifolate drugs, poor drug compliance, mass drug administration with sub therapeutic doses, use of chloroquinised salt
Non-target drug pressure	Presumptive use of antimalarial drugs without laboratory diagnosis or for indications other than malaria
Pharmaco-kinetics	Use of drug formulations with reduced bioactivity
Cross-resistance	Sulphadoxine-pyremethamine and sulphamethoxazole-trimethoprim
Human	
Host immunity	Non immune migrant workers/gem miners, etc.
Maintenance of resistant parasite reservoir	Non-detection of drug failure
Parasite	
Genetic mutations	Pfcrt K76T for chloroquine, DHFR-DHPS point mutations for S-P drugs, Pfmdr1 for mefloquine
Transmission level	Whether low or high transmission has more influence on drug resistance is debatable, prevalence of drug resistance is higher in regions of low transmission, whereas model suggests the benefits of transmission control in delaying resistance development
Vector and environment	
Vector affinity of parasites	Increased infectivity and productivity of chloroquine resistant parasites in An. dirus and the propagation of chloroquine resistance in South-east Asia and Western Oceania

Characteristics of the drug are important determinants of resistance. First, drugs with a long elimination half-life such as mefloquine may exert substantial residual selection on new infections contracted after the treatment of the primary infection when the drug persists at subtherapeutic concentrations in the plasma especially in areas with intense malaria transmission. Second, the maintenance of adequate drug concentrations over a long enough time is important for clearing the entire population of parasites within a given individual. Subtherapeutic drug concentrations eliminate the most susceptible parasites and leave those that may be more fit to recover and reproduce. As a result, the necessary therapeutic dose may increase beyond the maximum tolerated, and manifested drug resistance will emerge. Third, widespread use of drugs at high intensity serves to increase drug pressure and is a determinant for selection of resistant parasite populations[14].

More potent immune responses increase the efficacy of chemotherapy. A semi-immune patient might be cured by a drug despite the fact that these parasites are partially drug resistant. Individuals who are naïve to malaria generate a non-specific immune response that is not as effective as the specific immunity elicitated by repeated infections. Thus the introduction of resistant malaria into non-immune populations such as refugees or migrants increases the opportunity for manifestation and spread of resistance, because parasites with low or moderate resistance would be cleared in semi-immune populations[8].

Level of transmission influences the rate of development and spread of drug resistance but its exact role is complex and is most probably multifactorial. Increased risk of drug resistance development has been postulated to occur in areas of both low and high transmission. The general observations that resistance developed earlier in areas of low transmission (such as Thailand and Brazil) and is still more prevalent in such areas than in those with higher transmission tend to support the low transmission hypothesis. As an example of the high transmission hypothesis, full chloroquine resistance in children occurred and spread within 2-5 years in an area of high transmission in east Africa that had been under massive chloroquine pressure[15].

Finally vector and environmental factors may influence the proliferation of resistant parasites. For example, chloroquine-resistant parasites may be more fit for reproduction in certain anopheline mosquitoes than non-resistant strains[14].

Distribution of Drug Resistance

Chloroquine

Resistance in P. falciparum to chloroquine has been documented in most of the countries where there is transmission, except Central America and Caribbean. In early 1960s, resistance to chloroquine was noted on the Thai-Cambodian border and in Colombia. All endemic areas in South America were affected by 1980 and almost all in Asia and Oceania by 1989. In Africa chloroquine resistance was first documented in the east in 1978. Resistance spread to the central and southern parts of the continent before arriving in west Africa in 1983. By 1989, chloroquine resistance was widespread in sub-saharan Africa[8]. In Orissa, CQ resistance in P. falciparum was first suspected during a study in June in 1977 in Koraput (samples collected from Umarkote, Boipariguda, Narainpatna and Bisamcuttack PHC) and Sambalpur (Deoghar and Belpahar PHC) districts. In the study 3.8% of P. falciparum cases in Koraput district and 12% in Sambalpur district were found to be parasite positive on 7th day of presumptive treatment with an adult dose of 600mg of Chloroquine[7]. This report led to a number of independent surveys in different geographical areas besides continuous in vivo monitoring of CQ resistance by the drug monitoring unit located at Regional Office for Health and Family Welfare, Government of India, Bhubaneswar. In 1978, indigenous cases of RII resistance were detected in Gumagarh PHC of Phulbani and Keonjhar town of Keonjhar district[16]. Subsequently in 1989 Mohapatra and others[17] showed 10.1% CQ resistance (7.9% RI, 1.4% RII and 0.7% RIII) in Malkangiri PHC of Koraput and in 1992 Ghosh etal[18] reported 31.2% resistance (15.6 %RI, 9.4%RII and 6.2% RIII) in Sundergarh district. The analysis of resistance data reported by the drug monitoring unit indicates an interesting trend of CQ resistance in P. falciparum in Orissa (National Vector-borne Disease Control Programme: Unpublished data). During the period between 1978 to 2002 about 79 sample surveys were conducted for standard in vivo parasite clearance test in more than 60 PHCs belonging to 24 districts (out of total 30 districts in the state) and from 2003 onwards about 23 sample surveys were conducted in 15 districts for clinical outcome test. The over all test results from 1978 to 2007 reveal that the frequency of resistance ranges from 0% to as high as 95% in different places. From the analysis it is evident that the RII/RIII level resistance has shown 1.8 fold increase during 1991-2002 compared to 1978-1990 (Fig 1). But interestingly the clinical response tests conducted during

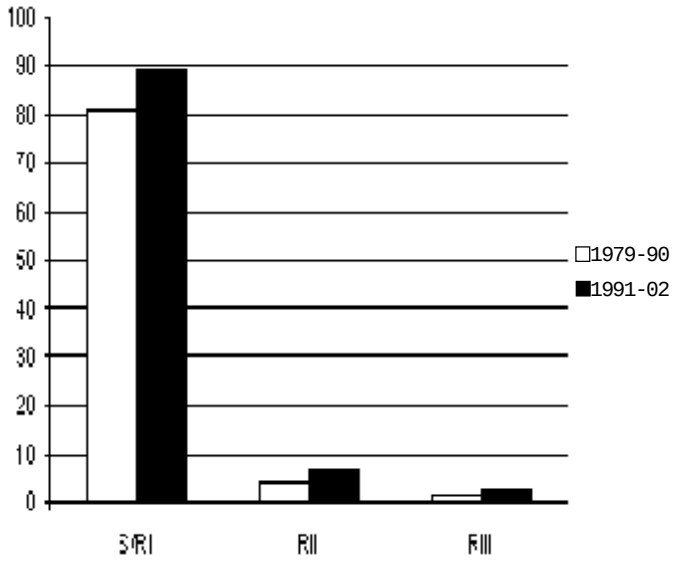

Fig.1. Level of drug resistance in two different period of time in Orissa

2003 to 2007 have shown a sudden rise of resistance (ETF+LTF) to 45% ie. about 4.7 fold rise compared to the period from 1991 to 2002. This rapid rise of drug resistance might be due to the population movement because a lot of developmental work has been initiated during this period in the state.

The district wise distribution of drug resistance level conducted during 1978-2002 in 24 districts revealed that 13 districts already had developed RIII level of resistance, 5 had RII level of resistance and 6 RI level of resistance (Fig2). Thereafter the therapeutic efficacy tests conducted in 14 of these districts during 2003 to 2007 showed high percentages (10 to 95%) of ETF+LTF indicating an alarming situation in the state. Therefore the drug policy needs an urgent evaluation for entire state.

Polymorphisms in two genes of the P. falciparum genome are focus of the studies on the molecular basis of chloroquine resistance. The Pfcrt gene is located on

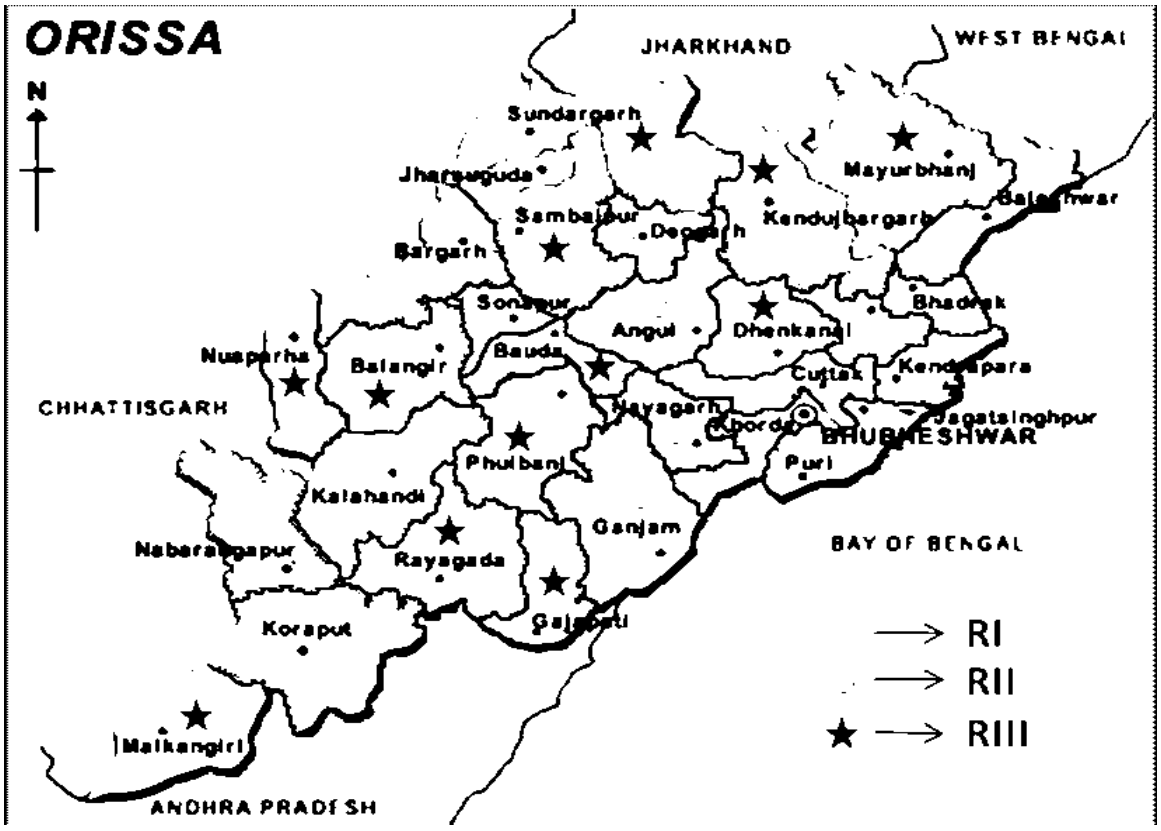

Fig.2. Distribution of drug resistance level in different districts of Orissa (Surveyed during 1978-2002)

chromosome 7 and codes for Pfcrt, a vacuolar membrane transporter protein. Many polymorphisms that are associated with chloroquine resistance have been identified but the substitution of threonine for lysine in codon 76 was recently shown in vitro to associate absolutely with resistance in isolates from Africa, South America, Asia and Papua New Guinea. Findings from an in vitro study of isolates from various origins and several clinical studies in diverse geographical areas support the association between the Thr 76 mutation and chloroquine resistance in Africa (Mali[19], Cameroon[20], Sudan[21], Mozambique[22]), Asia (Laos[23], Thailand[24], India including Orissa[25]) and South America (Brazil)[26].

Another gene, Pfmdr1 which is located on chromosome 5 and codes for P-glycoprotein homologoue1 (Pgh1) has generated interest in resistance to chloroquine and other antimalarials. The aspartic acid to tyrosine point mutation in codon 86 has been associated with chloroquine resistance in some clinical and in vitro studies (Mali[19], The Gambia[27], Sudan[21], Uganda[28], Thailand[29], Brazil[30]) but not in others (Uganda[31], Laos[23], Thailand[32] and Brazil[33]). Several other Pfmdr1 polymorphisms notably Phe 184, Cys 1034, Asp 1042 and Tyr 1246 have been implicated to varying degrees in chloroquine resistance. Although evidence for the association of Pfmdr1 with chloroquine resistance has not been as convincing as for Pfcrt, a recent parasite transfection experiment showed that polymorphisms in the Pfmdr1 gene modulate susceptibility to chloroquine (as well as to mefloquine and the structurally related compounds quinine and halofantrine)[22].

In a study conducted by the Regional Medical Research Centre (RMRC), Bhubaneswar in 7 districts (Cuttack, Anugul, Jajpur, Keonjhar, Sundergarh, Phulbani and Malkangiri) of Orissa with 269 samples, 68.7% Pfcrt 76T mutation and 54% Pfmdr1 86Y mutation (Fig.3) were observed (RMRC : Unpublished data). In a similar study conducted in Sundergarh district it has been found that the Pfcrt 76T mutation is 87.9 %. The molecular analysis performed in both the study have shown that the parasite isolates found in Orissa are related to isolates found in Southeast Asia as well as South America[34,35]. This is an unique situation and indicates that this is a separate foci for origin of the resistance. This needs an in depth study.

When the occurrence of Pfcrt and Pfmdr1 point mutations were combined, total 9 genotypes were found to be circulating among the parasite population of Orissa. Amongst them Pfcrt 76T + Pfmdr1 86Y (mutant plus mutant) genotypes are more prevalent (41.26%) than other

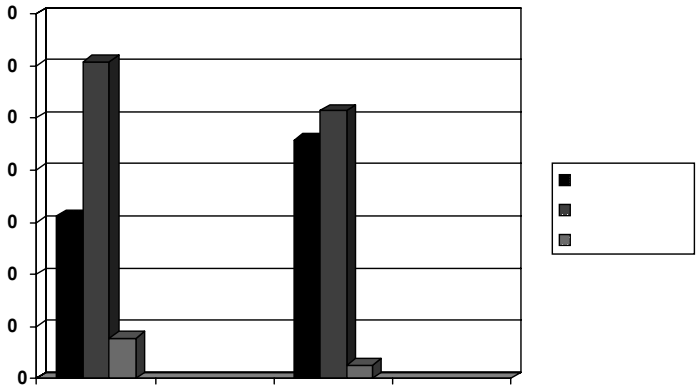

Fig 3: Prevalence of Pfcrt and Pfmdr1 genotypes among clinical isolates of P. falciparum in Orissa.

genotypes. This indicates that the CQ resistant P. falciparum isolates are more frequent than wild types in Orissa and corroborates the in vivo test records of NVBDCP.

Sulphadoxine - pyremethamine

Resistance to sulphadoxine-pyremethamine (SP) was first noted in the Thai-Cambodian border during mid 1960s[36] and currently, high level resistance (up to 90%) is found in a large part of Southeast Asia, southern China and in Amazon basin. Lower degrees and frequencies of resistance are observed on the pacific coast of South America, southern Asia, east of Iran and western Oceania[12]. In Africa, sulphadoxine-pyremethamine sensitivity started declining in the late 1980s. Resistance is rapidly gaining ground in this continent more so in the east than in the west. In east Africa the degree of resistance is variable. High percentages of RII/RIII responses were documented in children in an endemic area of Tanzania as early as 1994[37]. This finding was thought to be attributable to previous drug pressure due to the use of pyremethamine-dapsone prophylaxis. The 1999-2000 data from the east African Network for monitoring antimalarial treatment indicated that the proportion of clinical failures (combined late and early treatment failures) at some sentinel sites in Kenya was already more than 25% and the proportion of parasitological failures at day 7 in children has reached 45% at one site in Tanzania. Focal areas of low to moderate sulphadoxine-pyremethamine resistance exist throughout Africa[38-41]. Resistance is likely to progress geographically and in its intensity at an alarming rate if nothing is done to interrupt its course. Although the available data on SP resistance is limited in India, it seems that efficacy for this drug is within acceptable limit except in limited areas as the Indo-

Myanmar border in Arunachal Pradesh and some parts of Assam and West Bengal[42,43]. In Orissa one isolated report is showing that out of 8 isolates tested invitro in Sundergarh district 5 are resistant to SP drug combination[18].

The molecular basis of resistance to SP is best characterized of all antimalarial resistance. Specific mutations in P. falciparum that lead to resistance to both sulphadoxine and pyremethamine have been identified. Sulphadoxine and pyremethamine act synergistically. The former inhibits dihydropteroate synthase (DHPS) and latter inhibits dihydrofolate reductase (DHFR). These two enzymes are involved in folate synthesis.

Point mutations in the following five codons of the DHPS gene are known to confer resistance to Sulphadoxine by decreasing the binding affinity of the enzyme: serine to alanine or phenylalanine at codon 436; alanine to glycine at 437; lysine to glutamic acid at 540; alanine to glycine at 581; alanine to serine or threonine at 613. Glycine 437 and Glu 540 have been reported to occur together or singly in various parts of the world (Indonesia, Vietnam, Malawi, Kenya, Bolivia and Gabon)[44-47]. Gly 581 has been observed in South America alone or with Gly 437[48,49].

Similarly specific point mutations in the DHFR gene are also known to be associated with pyremethamine resistance: alanine to valine at 16, asparagine to isoleucine at 51, cysteine to asparagine at 59, serine to asparagine or threonine at 108 and isoleucine to leucine at 164. This combination of mutations has been observed in Thailand, where high level SP resistance has been reported. The triple mutation of Ile 51, Arg 59 and Asn 108 has been observed in Vietnam and East Africa (Kenya and Malawi)[48]. Asn 108 and Arg 59 have been observed in combination in Indonesia. Asn 108, Ile 51, Leu 164 accompanied by mutation of cysteine to arginine at 50 and a repeat between codons 30 and 31 were also noted in Bolivia and Brazil[50]– areas where SP resistance is prominent in South America. Arg 50 in addition to Asn108 and Ile 51 was also associated with sulphadoxine-pyremethamine resistance in Venezuelan isolates[49]. Leu 164 has so far been reported only from areas with high level of SP resistance (Southeast Asia[46], Bolivia[48] and Brazil[50]). The Ala16, Thr 108 genotype is known to be specific for cycloguanil resistance and does not confer resistance to pyremethamine[51].

The change from serine to asparagine at codon 108 is known to be the key mutation for pyremethamine resistance while additional mutations in three other codons, Ile 51, Arg 59, and Leu 164 progressively increases the level of resistance. Thus quadruple mutants (those with the Leu 164 mutation) confer the most severe resistance, more severe than those triple mutants (those with Ile 51 and Arg 59). Although the precise relation between mutations in the DHFR and DHPS genes in clinical sulphadoxine-pyremethamine resistance is unclear, current data show that the presence of a sensitive DHFR allele is highly predictive of sulphadoxine-pyremethamine treatment success irrespective of the DHPS allele[51]. The DHFR and DHPS point mutations have been investigated in 7 districts (Cuttack, Anugul, Jajpur,Keonjhar, Sundergarh, Phulbani and Malkangiri) with 269 samples (RMRC, Bhubaneswar : unpublished data), where 40.6% of the samples with DHFR 108 point mutation, 9.7% of the sample with DHPS 540 point mutation and only 1.05 % of the parasite populations with both the mutation have been observed (Table IV). While analyzing the different combinations of point mutations in DHFR and DHPS genes it is observed that quadruple mutation combination is nil. Only double mutation combination has been observed in 4.4 % of the parasite population. This indicates that the parasite population of Orissa has not developed resistance to S-P drug combination and the drug can be introduced safely (Fig 4).

Table IV. Frequency distribution of DHFR and DHPS alleles in P. falciparum isolates of Orissa.

	DHFR				DHPS			
	51	59	108	164	436	437	540	581
	No(%)	No(%)	No(%)	No(%)	No(%)	No(%)	No(%)	No(%)
Wild	197 (73.2)	129 (47.9)	160 (59.9)	253 (94.1)	251 (93.3)	238 (88.5)	240 (89.2)	222 (82.5)
Mutant	62 (23.1)	135 (50.2)	109 (40.5)	16 (5.9)	18 (6.6)	26 (9.7)	26 (9.7)	26 (9.7)
Mixed	10 (3.7)	5 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.9)	3 (1.1)	21 (7.8)

Quinine

Nearly 100 years ago quinine resistance was noted in Brazil but successive observations of clinical resistance to quinine began to accumulate only during the mid 1960s especially in the Thai-Cambodian border[52]. Currently clinical resistance to quinine immunotherapy occurs sporadically in Southeast Asia and western Oceania. Data from invitro assays indicate that resistance is less frequent in South

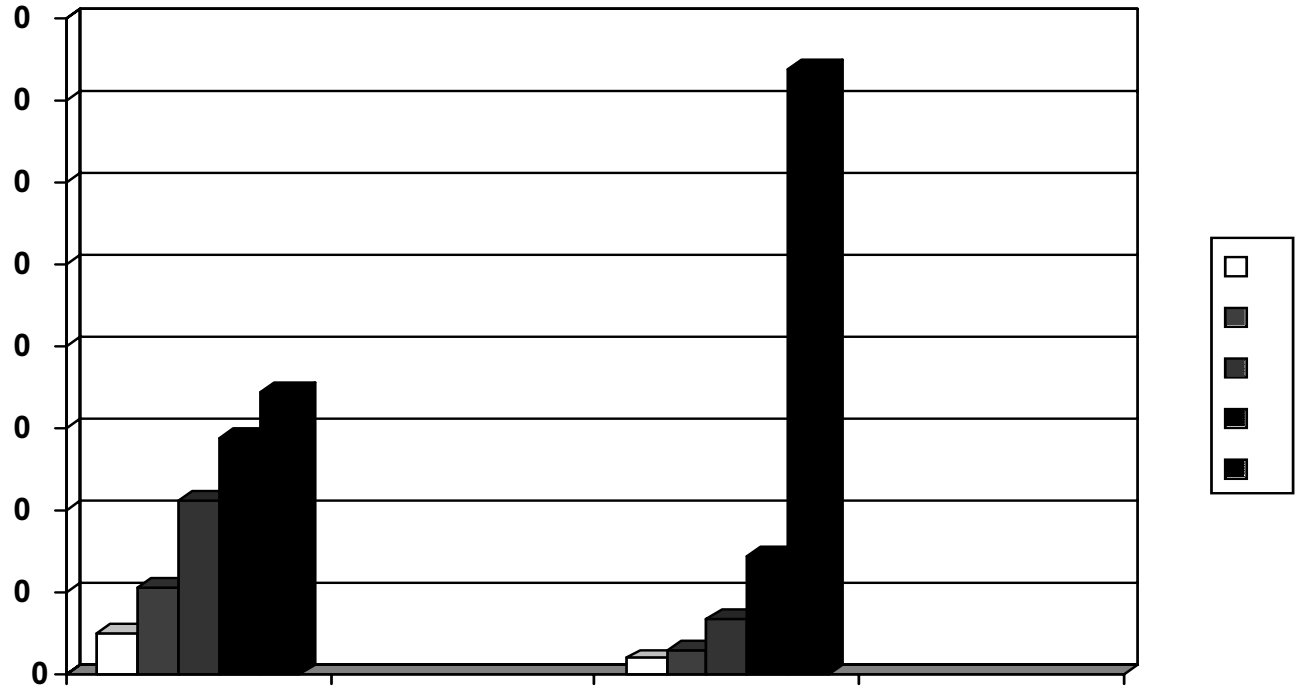

Fig 4. Frequency of DHFR and DHPS genotypes based on presence of number of point mutations.

Q : quadruple mutations, T: triple mutations, D: double mutations, S: single mutation, N : No mutation

America[30] and Africa[53]. Wide spread use of quinine in Thailand in the early 1980s as an interim therapy in the face of declining SP efficacy resulted in significant reduction of its sensitivity[14]. Therefore for the past two decades quinine has been consistently used in combination with the partner antibiotics such as tetracycline or doxycycline to increase the effectiveness of treatment. Quinine is presently reserved as a second-line or third-line drug and is used in cases of severe malaria. In India the in vivo tests conducted in North Eastern states, West Bengal, Karnataka ,Madhya Pradesh and Tripura have shown low level of resistance (RI: 7.6% and RII:1.2%)[54].However, till now no cases of resistance to quinine has been reported from Orissa.

Some studies have shown the association of the Pfmdr1 86Y point mutation in P. falciparum with reduced susceptibility to quinine. In a Brazilian study of Pfmdr1 mutations (Asn 184, Cys 1034, Asp 1042, Tyr 1246), chloroquine resistant strains were found to have low susceptibility to quinine. In the Gambia Pfmdr1 Tyr 86 was weakly associated with decreased sensitivity[55].

Mefloquine

Mefloquine resistance was first observed near the Thai-Cambodian border in late 1980s[56]. Mefloquine alone is no longer effective on the Thai-Myanmar and Thai-Cambodian borders although it is still operationally useful in most other endemic areas in and around Thailand with field efficacy of more than 75%. There are also case reports of mefloquine resistance from the Amazon Basin. Though in vitro sensitivity has been found to be low in Africa, yet clinical mefloquine resistance is rare in Africa[53,57]. Till now no report on resistance to mefloquine has been found from Orissa.

The copy number and polymorphisms of the Pfmdr1 gene have been investigated as molecular markers of mefloquine resistance. The evidence on increased Pfmdr1 copy number as a molecular marker for mefloquine resistance remains conflicting. Two studies in Thailand suggested that a higher copy number confers mefloquine resistance but other studies did not confirm that finding

(Thailand, Brazil, Africa). Some studies have shown increased sensitivity to mefloquine with the Pfmdr1 Tyr 86 mutation suggesting a possible inverse relation between sensitivity to mefloquine and to chloroquine[55].

Artemisinin

Artemisinin and its derivatives (eg. artemether, artesunate, and dihydroartemisinin) are associated with a high rate of recrudescences after monotherapy, probably because of the pharmacodynamic properties of these agents[58]. Therefore artemisinins are not used alone for clinical treatment; they are usually combined with longer acting antimalarials such as mefloquine or lumefantrine. On the whole both in vivo and in vitro sensitivity testing of P. falciparum in the multidrug resistance area of the Thai-Myanmar border, where combination of artesunate and mefloquine has been the first-line regimen for the past 7 years, remains satisfactory.Till now no report on resistance to artemisinin has been documented from Orissa.

The development of artemisinin resistance may be delayed by the characteristics of this drug like short elimination half-life and ability to reduce gametocyte-carriage rate[58]. In mice artemisinin resistance has been associated with diminished drug uptake and the over expression of a potential target protein, the translationally controlled tumour protein[59]. A molecular study has suggested that the Pfmdr1 Tyr 86 variant may also be associated with increased sensitivity to artemisinin[55]. The transfection study also has shown that Ser 1034, Asn 1042 and Asp 1246 mutations additionally alter the sensitivity of P. falciparum to artemisinin[60].

Multidrug Resistance

Multidrug resistance of P. falciparum is defined as resistance to more than two operational antimalarial compounds of different chemical classes[14]. Established multidrug resistance occurs mainly along the border regions of Thailand and emerging multi drug resistance seems to be limited to the areas of East Africa (such as Tanzania and Kenya) and the Amazon basin .The available data do not indicate any evidence of the presence of multi drug resistance P. falciparum strains in Orissa.

Conclusions

Drug resistance is probably the greatest challenge that most malaria control programmes are facing. The problem of drug resistance malaria is world-wide. Development of high level of resistance to the chloroquine in P. falciparum has forced to introduce ACT (artesunate plus sulphadoxine/pyremethamine) in about 17 PHCs of Orissa. But given the limited resources for other malaria control measures rational drug use is critical although this is known to be hampered by economic constraints and scarcity of drug choice. Since the prevalence of drug resistance is >25% in about 32 surveyed PHCs and between 11-25% in about 8 surveyed PHCs spread over19 districts, the change of drug policy is to be considered for the entire state. Further, there is also suggestive evidence from China[61], Malawi[62], Vietnam and Thailand[5] that a long term decline in the use of chloroquine for prophylaxis and treatment of P. falciparum malaria, largely brought about by problems of CQ resistance , can lead to resurgence of the drug-sensitive population of P. falciparum. This raises the possibility that, in time, the CQ could be reintroduced. Therefore complete withdrawal of CQ from the entire state with continuous monitoring by using molecular based tools will help to analyze the effect of today's drug choice on future drug policy. Most importantly, since there is no evidence of multi drug resistance in the state; constant surveillance is needed for the early detection of development of multi drug resistance.

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This write-up has been contributed by Dr. M.R. Ranjit, Scientist D, Regional Medical Research Centre, Bhubaneswar.

ICMR NEWS

The following meetings of various Technical Groups/ Committees of the Council were held:

Meetings of Expert Groups (EGs)/Task Forces (TFs) held at New Delhi

EG on National Acute Coronary Events Registry	June 12, 2008
EG on School-based Interventions for Cardiovascular Risk Factors	June 12, 2008
TF on Urban Mental Health Problems and Their Services Needs	June 20, 26 & July 20, 2008
TF on Mental Health Services Needs and Service Delivery Models in Disaster Affected Population in Gujarat	July 27, 2008
TF on Relation of Candidate Gene Variant Regulating Triglyceride Metabolism in Serial Changes in Childhood Body Mass Index and Coronary Artery Risk Factors in Young Adulthood	August 8, 2008
TF on Development of Functional Status of the Older Indians	August 19, 2008
TF on Development of a Model for Strengthening of Existing Health System to Address Non-Communicable Diseases In India	August 20, 2008

Meetings of Project Review Committees (PRCs) held at New Delhi

PRC on Oncology	June 5-6, 2008
PRC on Mental Health	June 10, 2008
PRC on Cardiovascular Diseases	June 13, 2008
PRC on Ophthalmology	June 23, 2008
PRC on Neurology	July 15, 2008
Special PRC on North-East Projects	August 12, 2008

Participation of ICMR Scientists in Scientific Events

Dr. K. Ghosh, Director, National Institute of Immuno-haematology (NIIH), Mumbai, participated in the XXVIII International Congress of the World Federation of Haemophilia at Istanbul (June 1-5, 2008).

Dr. S. Cherian, Scientist D, National Institute of Virology (NIV), Pune, participated in the II International Conference on Vaccine Technology at Algarve (June 1-6, 2008).

Dr. Smita D. Mahale, Scientist E, National Institute for Research in Reproductive Health (NIRRH), Mumbai, visited

the Laboratory of Dr. James A. Dias, David Axelord Institute for Public Health, New York (June 1-14, 2008). She also participated in the Royan International Twin Congress at Teheran (August 27-29, 2008).

Dr. Triveni Krishnan, Scientist D, National Institute of Cholera and Enteric Diseases (NICED), Kolkata, participated in the VIII International Rotavirus Symposium at Istanbul (June 3-4, 2008).

Dr. Rajeshwari Ramachandran, Scientist F, Tuberculosis Research Centre (TRC), Chennai, participated in the Workshop on Clinical Trials for Drug Resistant Tuberculosis at Cambridge, Massachusetts (June 10-12, 2008).

Dr. Sunita Saxena, Director, Institute of Pathology (IOP), New Delhi participated in the World Cancer Congress 2008 at Shanghai (June 12-17, 2008).

Dr. P.K. Nag, Scientist F and Officer-in-Charge, National Institute of Occupational Health (NIOH), Ahmedabad, participated in the VII International Congress of Ergonomics and Usability, Design Interfaces and Human Computer Interaction at Sao Luis, Maranhao (June 19-20, 2008).

Dr. Neena Valecha, Scientist F, National institute of Malaria Research (NIMR), Delhi; and Dr. V.G. Rao, Scientist E, and Dr. Jyoti T. Bhat, Scientist B, Regional Medical Research Centre (RMRC) for Tribals, Jabalpur, participated in the XIII International Congress of Infectious Diseases at Kuala Lumpur (June 19-22, 2008).

Dr. K.V.R. Reddy, Scientist E, NIRRH, Mumbai, participated in the V International Conference on Innate Immunity at Chanio, Crete, Greece (June 21-26, 2008).

Dr. S.P. Tripathy, Scientist F, National AIDS Research Institute (NARI), Pune, participated in the Adult AIDS Clinical Trials Group Meeting at Washington, D.C. (June 21-26, 2008).

Dr. P.R. Narayanan, Director, TRC, Chennai, participated in the Meeting of the Strategic and Technical Advisory Group on Tuberculosis at Geneva (June 23-25, 2008).

Dr. Sanjay Basak, Scientist B, National Institute of Nutrition (NIN), Hyderabad, participated in the I Global Conference on GMO Analysis at Como, Italy (June 24-27, 2008).

Dr. P.K. Sinha, Scientist E, Rajendra memorial Research Institute of Medical Sciences (RMRIMS), Patna, participated in the DNDi Stakeholders Meeting at New York (June 25-29, 2008). He also participated in the Ethics Committee Survey Training at Bangkok (July 20-23, 2008).

Dr. B. Ravichandran, Scientist B, Regional Occupational Health Centre, Bangalore, participated in the XVIII World Congress on Safety and Health at Work at Seoul (June 29 -July 2, 2008).

Dr. Aruna Singh, Scientist F, IOP, New Delhi, participated in the VI Meeting of the European Society for Chlamydia Research at Aarhus (July 1-4, 2008).

Dr. T. Ramamurthy, Scientist E, NICED, Kolkata, participated in the 2008 Annual Scientific Meeting of the Australian Society of Microbiology at Melbourne (July 6-10, 2008).

Dr. B.K. Tyagi, Scientist F and Officer-in-Charge, Centre for Research in Medical Entomology (CRME), Madurai, participated in the II Intensive Workshop on Wild Type and Genetically Sterile Aedes Mosquitoes at Kuala Lumpur (July 7-8, 2008).

Dr. V. Kumaraswamy, Scientist F, TRC, Chennai, participated in the V Meeting of Regional Programme Group for Elimination of Lymphatic Filariasis at Kathmandu (July 10-11, 1008).

Dr. K.K. Mohanty, Scientist D, National JALMA Institute for Leprosy and Other Mycobacterial Diseases (NJIL&OMD), Agra, participated in the XX International Congress of Genetics at Berlin (July 12-17, 2008).

Dr. Anup Anvikar, Scientist D, NIMR, Delhi, participated in the Training on Invitro Sensitivity of P. falciparum isolates at Bundarban (July 13-19, 2008).

Dr. R.S. Paranjape, Director, NARI, Pune, participated in the Meeting of Bill and Melinda Gates Foundation's Evaluation Advisory Group at London (July 17-18, 2008).

Dr. Taruna Madan, Scientist D, NIRRH, Mumbai, participated in the Meeting on Immunochemistry 1967-2008 at Oxford (July 18-21, 2008).

Dr. N. S. Wairagkar, Scientist E, and Mr. P.N. Yergolkar, Scientist D, NIV, Pune, participated in the Regional Meeting of Virologist and Technicians at Bangkok (July 21, 2008).

Dr. Neeru Singh, Director, Regional Medical Research Centre (RMRC) for Tribals, Jabalpur, participated in the Technical Working Group Meeting on Iron and Malaria Interactions and Interventions: Where are we now and Where do we go from here? at Rockville, Maryland (July 28-29, 2008).

Prof. Arvind Pandey, Director, National Institute of Medical Statistics; Dr. J. Mahanta, Director, RMRC,

Dibrugarh; Dr. S.P. Tripathy, Scientist F, and Dr. Sheela Godbole, Scientist D, NARI, Pune; and Dr. Beena E. Thomas, Scientist B, TRC, Chennai, participated in the XVII International AIDS Conference at Mexico City (August 3-8, 2008).

Dr. S. Subramanian, Scientist D, Vector Control Research Centre (VCRC), Pondicherry, participated in the Workshop on Programmes to Eliminate Lymphatic Filariasis at Geneva (August 7-8, 2008).

Dr. A.P. Dash, Director, NIMR, Delhi, participated in the I AHXO International Malaria Symposium at Accra New Town, Ghana (August 12-13, 2008).

Dr. A.C. Mishra, Director, and Dr. M.S. Chadha, Scientist E, NIV, Pune, participated in the CDC Cooperative Agreement Meeting at Cairo (August 13-15, 2008).

Dr. R.S. Paranjape, Director, NARI, Pune, participated in the RPC Mid-term Review held in UK (August 18-19, 2008).

Dr. N. Balkrishna, Scientist C, NIN, Hyderabad, participated in the Conference on Responsive Feeding at Montreal (August 25-28, 2008).

Dr. J.M. Deshpande, Director, Entrovirus Research Centre, and Sh. P.N. Yergolkar, Scientist D, NIV, Pune, participated in the WHO Meeting of Virologists, from Polio Laboratory Network in South East Asia at Jakarta (August 28-29, 2008).

Appointments

Dr. P.K. Nag took over as Director of Council's National Institute of Occupational Health, Ahmedabad w.e.f. August 1, 2008.

Trainings/Fellowships

Dr. Rekha Devi, Scientist C, RMRC, Dibrugarh, availed JSPS RONPOKU Fellowship (June 1 - August 31, 2008).

Dr. C. Padmapriyadarsini, Scientist C, TRC, Chennai proceeded to avail Brown University/Tufts University Fogarty International AIDS Training and Research Programme for 2 years at Boston (w.e.f. July 2008).

Dr. Avninder Pal Singh, Scientist B, IOP, New Delhi, proceeded to avail Indo-US Research Fellowship 2008 at the National Cancer Institute, Bethesda for 3 months (w.e.f. August 1, 2008).

Dr. Soumya Swaminathan, Scientist F, TRC, Chennai, proceeded to avail Advanced Training in HIV/AIDS Clinical Trials at Miriam Hospital/Brown University, USA for 6 months (w.e.f. June 15, 2008).

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