

Potential factors responsible for the development of *Plasmodium falciparum* and *Plasmodium vivax* resistance to anti-malarial drugs in some parts of India

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Author's contribution

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Short communication/Commentary

ABSTRACT

In India chloroquine resistance in *Plasmodium falciparum* is fast spreading in all regions of India and the proportion of *P. falciparum* has increased to more than 50 percent in last three decades. Chloroquine resistance to *Plasmodium vivax* is also emerging in some parts of India. Poor drug quality of antimalarials and under dose treatment are potential factors of drug resistance to malaria parasites. A caution is required for quality control of antimalarial drugs and under dose treatment. There is a need to strengthen national drug control policy by Central Drugs Standard Control Organization to enforce antimalarial legislations and to improve quality control of antimalarials in emerging pharmaceutical market.

Key words: drug resistance, antimalarials, malaria, *Plasmodium falciparum*, *Plasmodium vivax*, India.

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1. INTRODUCTION

Malaria continues to be a major public health problem. Globally 3.3 million people are at risk of malaria and the disease kills 0.66 to 1.2 million people every year with 90% of death occurring in sub-Saharan Africa [1, 2]. In India 95% population are residing in malaria endemic areas and 80.5% are in malaria risk areas. In India malaria nearly eradicated in the early 1960s as a major public health problem even in areas which were at one time free from this disease. In 1976 malaria resurged with a peak at 6.47 million cases [3]. After implementation of new strategy in 1977, malaria cases declined to 1.49 million by year 1995 but the decline in *P. falciparum* and *P. vivax* cases was not proportionate. The proportion of Pf cases has increased from 13% in 1978 to 38.84% in 1995 and 52.12 % in 2010. A total of 253 primary health centres of 46 districts showed failure to chloroquine [4]. The disease has remained uncontrolled as the parasite rapidly develops resistance to existing antimalarial drugs [5]. In India Chloroquine (CQ) resistance in *P. falciparum* was first reported in 1973 from Assam [6] and since then it is spreading to other regions of the country and now detected in at least 21 states or union territories [7]. Studies on efficacy of antimalarial drugs carried out in India since 1978 show that resistance of *P. falciparum* to CQ has increased over time and is now present across all region of the country [8]. Drug resistance occurs mainly in *P. falciparum* but few reports of CQ-resistance in *P. vivax* from different geographical regions of India have also been reported [9]. CQ resistance in this parasite may have serious repercussion since second line drug sulfa-pyrimethamine (SP) is not very effective [10]. Poor drug quality of antimalarials derivatives and ACTs has been documented in many African malaria endemic countries. Recently Gaurvika *et al.* [11] reviewed poor quality of antimalarials drugs in South Asia and sub-sharan Africa. Out of 1437 samples of drugs from seven countries in south East Asia, 497 (35%) failed chemical analysis. Bate *et al.* [12], reported failure of 7 percent samples of drugs CQ in India during 2008-2009. Earlier the World Health Organization (WHO) reported that Indian pharmaceuticals manufacturer estimates 20 % of drugs in major Indian city markets were sub standard [13]. In another pilot study of essential drug quality in two major cities in India indicated 9 % of CQ samples failed in quality control in Delhi and 5 % in Chennai city [14]. Poor quality antimalarials are known to develop drug resistance and may be the important factor responsible and other possible factor for development of resistance to antimalarials of *P. falciparum* and emerging resistance to *P. vivax* is under dose treatment in India, which needs further proper and thorough evaluation. Batra *et al.* [15] while investigating the malaria in district Jodhpur, Rajasthan observed that the most important factor which explained the persistence of malaria was the inadequate treatment.

2. DISCUSSION

Chloroquine is the drug of choice for the treatment of all falciparum and vivax cases in India but after the development of CQ resistance, mainly to *P. falciparum*, the National drug policy on malaria which was formulated in 1982 has been revised and guideline in 2010 prepared by National Institute of Malaria Research and National Institute of Vector Borne Disease Control Programme and implemented for diagnosis and treatment of Malaria in India by Government of India [16]. All the fever cases diagnosed as malaria by RDT or microscopy as vivax malaria should be treated with CQ with full therapeutic dose of 25 mg/kg divided over 3 days and for relapse cases primaquine should be given at a dose of 0.25 mg/kg body weight for 14 days under supervision. For the treatment of confirmed *P. falciparum* malaria cases, artemisinin combination therapy (ACT) is recommended. ACT consists of an artemisinin derivative combined with a long acting antimalarial.

In India there are about 5000 Primary Health Centres and more than 24000 Primary Sub Centres with large number of man power including 840 Accredited Social Health Activist (ASHAs) to take care of malaria cases under national malaria control programme. Government is making significant efforts in combating malaria by adopting ACTS which is helping to check morbidity and mortality. In spite of all the efforts, however, malaria continues to be a major health problem with around 2 million malaria cases per year and drug resistance cases are increasing year by year and spreading to more regions of the country. Potential two factors responsible for the development of *P. falciparum* and *P. vivax* resistance to anti malarial drugs are poor quality of antimalarial drugs and under dose treatment of patients.

Domestic pharmaceutical industry is projected to grow by 16 % annually due to rising income, health insurance coverage, government efforts, lifestyle changes and ageing population. It is estimated that there are about 0.6 million chemist and business of industry is 90,000 crores of which 40 % is exporting. In India antimalarial drugs is given through public health programme, by private practitioners and private hospitals. Large number of persons purchases the drugs directly from chemists without physician's prescription which is a strong culture of self medication in the country. Local markets often have poor quality of antimalarials drugs. [17]

The Central Drugs Standard Control Organization checks the quality of drugs in India, but has inadequate staff like drugs inspectors, inadequate sampling, limited chemical laboratories and antimalarial drug analysis is at minimum level. Since poor quality of drugs is factor responsible for emerging drug resistance, it is urgent need to improve sampling for antimalarial quality control, establishment of analytical laboratories at district and state level, and strict regulatory enforcement is required. It is estimated that central drug control organization need 3200 Drug Inspectors (DIS) for its 0.6 million chemists and only 1000 DIS are available. Due to weak drug control infrastructure, inadequate testing facilities, shortage of Inspectors, non availability of information about antimalarials, outdated legislations, and complicated legal proceedings which are time consuming needs improvement, so that in emerging pharmaceuticals market basic quality control standards are followed.

In district Jodhpur (Rajasthan) malaria patients were given suppressive treatment with intramuscular injection of chloroquine (40-80 mg base) by private practitioners, which was inadequate for complete cure and leads to CQ resistance [15]. Recently Batra (personnel communication) also observed similar trend in other states like Chhattisgarh, Uttarakhand and Uttar Pradesh, where patients more rely on intramuscular injections by private practitioners and are refractory to take tablets given by government programme. It needs further evaluation and needs urgent education to public about treatment.

3. CONCLUSION

Two leading factors are responsible for the development of *P. falciparum* and *P. vivax* resistance to antimalarials drugs which are poor quality of antimalarials and under dose treatment to malaria patients. These factors need urgent action so that poor quality of manufacturing antimalarials and under-dose treatment may be discontinued at this stage to avoid serious problems in future.

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COMPETING INTERESTS

The author declares that I have no competing interests.

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