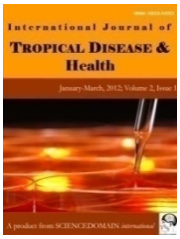

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Potential Factors Responsible for the Development of *Plasmodium falciparum* and *Plasmodium vivax* Resistance to Anti-malarial Drugs in Some Parts of India

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Author's contribution

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Commentary

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ABSTRACT

Indiscriminate use of chloroquine (CQ) has resulted in chloroquine resistance in *Plasmodium falciparum* (Pf) in almost all regions of India. Due to the emergence of resistance to CQ in India, the current recommended first line of treatment for Pf has been the combination of artesunate with sulfadoxine-pyrimethamine (SP). Recently, chloroquine resistance to *Plasmodium vivax* (Pv) has also emerged in some parts of India. Poor drug quality and under dosing of antimalarial treatment are potential factors of drug resistance to malaria parasite. A caution is thus required for quality control of antimalarial drugs now in use and also inadequate treatment. There is an urgent need to strengthen National Drug Control Policy to empower Central Drugs Standard Control Organization to enforce definitive antimalarial drug legislations. Improvement in quality control in production and distribution of antimalarial drugs in India, combined with informed and enforced national guidance on the treatment of malaria, will help to combat the emergence of resistance to antimalarial drugs.

Keywords: Chloroquine resistance; spurious antimalarials; malaria; Plasmodium falciparum; Plasmodium vivax; India.

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Malaria continues to be a major public health problem in India. Nearly 85% of populations living in malaria zones. The causative agents responsible for malaria in humans in India are mainly *P. falciparum and P. vivax*. 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 [1]. The deadliest form of malaria is caused by *P.falciparum* and reports show that the number of deaths of malaria patients has increased because of development of drug resistance of *P. falciparum* [2]. Malaria has remained uncontrolled as the parasite *P. falciparum* rapidly develops resistance to existing use of antimalarial drugs namely chloroquine [3]. Recently, chloroquine resistance to *Plasmodium vivax* has also emerged in some parts of India and *P. vivax* severity has increased. Dua et al. [4] reported, from Mathura (Uttar Pradesh, India) that *P. vivax* cases did not responded to chloroquine standard doses. Resistance was also reported in a study on 75 patients from Bihar [5]. Valecha et al. in 2006 emphasized, need to be vigilant on P. vivax resistance to CQ [6]. The rising severity of the *P. falciparum and P. vivax* malaria disease and emerging resistance of the parasite has emphasized the need for the search of potential factors to provide treatment strategy and update national malaria control policy.

Choloroquine 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 was implemented for diagnosis and treatment of Malaria in India by Government of India [7]. Drug effectiveness monitoring by the national programme is necessary because second line of treatment drug sulfa-pyrimethamine (SP) are also not very effective [8]. Therefore, we have to be cautious and aware and elucidate possible indices which may lead to development of resistance to new drugs namely artesunate plus sulfadoxine-pyrethamine which is now first line of treatment throughout India since 2010.

Nicholas J White et al. in 2009 emphasized a resistance selection opportunity in patients with low dosing and high parasite burdens [9]. Much of the *P. falciparum* morbidity and mortality could be avoided with the use of high quality, efficacious and correct use of antimalarial drugs. In India, antimalarial drugs are freely available in endemic regions. We do not have an effective drug monitoring system for checking the quality control and knowledge of the useable drugs. Awareness to poor drug quality of antimalarial drugs and derivatives has increased because of growing concern and reporting of resistance. Malaria is endemic in India and India is a growing world pharmaceutical market with numerous mushrooming of local manufacturers. This has led to deliberate counterfeiting, substandard production and inappropriate storages of antimalarials, resulting in degradation and subsequently a reduction of therapeutic efficacy. Recently Gaurvika et al. [10] reviewed poor quality of antimalarials drugs in South East Asia and sub-Saharan Africa. Out of 1437 samples of drugs from seven countries in south East Asia, 497(35%) failed chemical analysis. Bate et al. [11], 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 [12]. In a yet 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 [13].

Poor quality antimalarials have low concentration of active pharmaceutical ingredient and thus have sub therapeutic levels of drug *in vivo* and therefore may lead to develop drug resistance. The definition of poor quality drugs fall into two categories namely drugs failing chemical assay (fraudulently manufactured) and drugs with spurious packaging (inadequate

active ingredient and degraded due to inappropriate storage) by pharmacopeia standards. Poor quality antimalarials are difficult to identify because no definitive research is available. In India no regulatory system is available primarily because of weak drug control infrastructure at state and central levels. Inadequate testing facilities, shortages of drug inspectors and lack of trained staff at Primary Health Centre's for antimalarial drug analysis, it's samplings, poor enforcement and outdated legislations which leads to manufacturing of spurious drugs.

Domestic pharmaceutical industry is projected to grow due to rising income, increased health insurance coverage, government efforts to improve public health, and growing ageing population. 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 antimalarial drugs. [14] Since poor quality of drugs is a 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. 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 02/08/2012) 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 [15].

The Indian Govt should harmonize regulatory requirements across states as recommended by WHO. It should increase penalties for those involved in sale of substandard drugs. There is an urgent need to educate private practitioners and public about the treatments and strategies to monitor drugs intake needs proactive role and support.

2. CONCLUSIONS

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 dosing of antimalarial treatment to malaria patients. Continuous intervention, elimination of spurious production and distribution and empowering medicine regulatory authorities needs further proper and thorough evaluation to avoid serious resistance problems in future.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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