Commentary

Battling the malaria iceberg with chloroquine in India
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Abstract

The National Vector Borne Disease Control Programme (NVBDCP) of the Ministry of Health, Government of India is reporting about 2 million parasite positive cases each year, although case incidence is 30-fold or more under-estimated. Forty five to fifty percent of Plasmodium infections are caused by Plasmodium falciparum, the killer parasite. Anti-malaria drug policy (2007) of the NVBDCP recommends chloroquine (CQ) as the first line of drug for the treatment of all malarias. In a Primary Health Centre (PHC) reporting 10% or more cases of CQ resistance in P. falciparum, ACT blister pack is recommended and, so far, the policy has been adopted in 261 PHCs of 71 districts. The NVBDCP still depends on CQ to combat malaria and, as a result, P. falciparum has taken deep roots in malaria-endemic regions, causing unacceptable levels of morbidity and mortality. This policy was a subject of criticism in recent Nature and Lancet articles questioning the World Bank's decision to supply CQ to the NVBDCP. Continuation of an outdated drug in the treatment of P. falciparum is counterproductive in fighting drug resistant malaria and in the containment of P. falciparum. Switchover to Artemisinin-based Combination Therapy (ACT) in the treatment of all P. falciparum cases, ban on artemisinin monotherapy and effective vector control (treated nets/efficient insecticide spraying) would be a rational approach to malaria control in India.

Background

The National Vector Borne Disease Control Programme (NVBDCP) is reporting about 2 million parasite positive cases a year, 50% of these Plasmodium falciparum. The WHO estimates 100 million cases in the South East Asian Region, 70% of these occur in India [1,2]. Independent studies by the Indian Council of Medical Research have unequivocally established that malaria incidence is hugely under-estimated [3-6]. Health is the state's responsibility, therefore, malaria control is carried out by the states, under the overall guidance of the NVBDCP. To monitor the impact of interventions surveillance is organized to detect malaria cases by examining fever cases in the entire country. In rural areas, blood smears are collected at fortnightly intervals by multi-purpose workers i.e. Active Case Detection (ACD) and also collected at the Primary Health Centres (PHCs) i.e. Passive Case Detection (PCD). In urban areas, PCD is carried out at the malaria clinics. The blood smears are examined in the laboratory for parasite identification and results are used for follow-up action. Cases found positive are given radical treatment, as per the policy of the NVBDCP. This data is used in calculating epidemiological indices at the various levels of health services. PHCs reporting cases of drug failure are referred to the drug monitoring teams for further investigation on drug sensitivity in P. falciparum. If 25% (now reduced to 10%) of the cases tested show resistance to CQ, the drug policy is changed for the second line of drug. Thirteen NVBDCP teams routinely monitor P. falciparum drug sensitivity in the country. These teams are located in various regions so as to cover the entire country. P. falciparum monitoring for drug sensitivity is done using
the World Health Organization (WHO) methodology of in vivo (28-day) test procedure for determining the status of resistance to CQ and other antimalarial drugs in P. falciparum. Malaria Drug Policy (2007) of the NVBDCP provides inter alia the following treatment guidelines countrywide [7].

1. All fever cases should preferably be investigated for malaria by microscopy or Rapid Detection Test (RDT).

2. The first line of treatment is chloroquine and the second line is ACT (artesunate-sulphadoxine/pyrimethamine) combination in case resistant to these formulations and to treat severe and complicated malaria, quinine will be the drug of choice.

3. Microscopically positive P. falciparum cases should be treated with chloroquine in therapeutic dose of 25 mg/kg body weight over three days and a single dose of primaquine 0.75 mg/kg body weight on the first day. The practice is to be followed at all levels including Voluntary Health Workers (VHWs) like Drug Distribution Centres (DDCs)/Fever Treatment Depots (FTDs)/Accredited Social Health Activist (ASHA) as well.

The antimalarial drug policy states that all Plasmodium vivax cases, undiagnosed fever cases, and clinical malaria cases should be treated with chloroquine in full therapeutic doses. ACT (artesunate-sulphadoxine/pyrimethamine) is the first line of antimalarial drug for treatment of P. falciparum in chloroquine resistant areas. Chloroquine, therefore, remains the main drug for the treatment of all malarias in India except in PHCs with 10% or more cases found resistant to it. The objective of this paper is to highlight the realistic and evidence-based malaria situation in the country, and how the changes in drug policy and efficient vector control can wipe out malaria, thus bringing out the importance of the WHO recommendation of a switch over to artemisinin-based fixed-dose combination therapy (ACT) to treat all P. falciparum cases (sensitive or resistant to CQ/SP).

Discussion

Studies on re-emergence of malaria revealed countrywide presence and spread of P. falciparum e.g. P. falciparum is found in all states and union territories except Lakshadweep Island (Malaria situation 2002–2006, NVBDCP). It may be noted that P. falciparum occurrence is highly uneven in time and space [8,9]. Furthermore, the NVBDCP is reporting malaria epidemics in five or six states each year, and frequent focal outbreaks [10]. In some parts of the country, malaria epidemics cover two or more districts, dominated by P. falciparum [11-14]. Currently an epidemi of malaria is raging in Assam, a region more frequently visited by annual exacerbations [15,16]. The country-wide presence of P. falciparum is facilitated by inter- and intra-state population movement, particularly for civil works, agriculture, rail road construction, rural urban migration; thus providing opportunities for the mutant strains to disseminate across district and state boundaries [17-19].

It is important to highlight the resilience of P. falciparum in India. During the early years of malaria resurgence [20], a focus of P. falciparum and detection of CQ resistant foci in Karbi-Anglong district in Assam [21] in the north-eastern states required steps for its containment and prevention of its spread to the mainland. Therefore, a special drive was launched under the P. falciparum Containment Programme (PfCP), financed by the Swedish International Development Agency (SIDA). PfCP was first launched in 1978 in 18 high P. falciparum districts in the north-eastern states, gradually extended to 55 districts (311 PHCs in 14 states) and in 1982 to 110 districts (1410 PHCs in 18 states). Despite of PfCP operations that heavily depended on Dichloro-Diphenyl-Trichloroethane (DDT) and Chloroquine (CQ), P. falciparum occupied larger territories and covered the entire county's transmission belts and remained firm. The purpose and the strategy of PfCP was defeated and PfCP was terminated in 1988 [22]. Epidemiological investigations revealed that P. falciparum was replacing P. vivax in central India [23]. It is noteworthy to mention that decadal P. falciparum rise has been substantial, an increase of 120% since the first resurgence decade (1971–80). P. falciparum is rising slowly but steadily [24] over these decades as shown in Figure 1.

Malaria epidemiology and its control are complicated by poverty as it is a dominant disease in poverty stricken societies. For example, Indian states with population exceeding the national average of 26.1% population below poverty line (BPL) contributed 88% P. falciparum in 2000 [25]. Addressing the plenary session of United Nations Conference on Human Environment at Stockholm, 14 June 1972, the former Prime Minister of India Smt. Indira Gandhi said "Are not poverty and need the greatest polluters? [26] Poverty alleviation is on the national and United Nations agenda. How to fight poverty which is at the roots of all ills? Certainly malaria control is an important tool to alleviate human suffering caused by poverty and ill health. Therefore, priorities in malaria control should remain high, national and international bodies should work in tandem to eradicate this age old "King of all Diseases".

Plasmodium falciparum monitoring for drug sensitivity is conducted by thirteen NVBDCP teams. Monitoring is done on the line of WHO methodology of in vivo (28-day) standard techniques for determination of resistance in P falciparum to CQ and other antimalarials. India is a vast
country, so it is difficult to generalize. However, between 1978 and June 2001, a total of 15,069 *P. falciparum* cases in 178 districts of 28 states and union territories have been completed. Of these 3,965 (26.3%) were sensitive to CQ; 7,661 (50.8%) were S/RI; 752 RII resistant (5%) and 549 (3.6%) RIII resistant to CQ [27].

In 2004, the *P. falciparum* monitoring teams collected 45,966 blood smears, of which 4,756 were positive for malaria and 3,850 for *P. falciparum* (80.95%). Results based on CQ sensitivity of 209 samples, showed Adequate Clinical and Parasitological Response (ACPR) 98 (47.9%), Early Treatment Failure (ETF) 27 (12.9%) and Late Treatment Failure (LTF) 84 (40.2%). Drug resistance to CQ is presenting countrywide, although proportion of resistant strains varies greatly [28-33]. Already the *Pfcrt* K76T mutation, an important determinant of CQ resistance, is present in >95% of *P. falciparum* isolates [34].

In addition to these clear indicators of resistance in the parasite populations, there are important changes in disease outcomes. For example, in patients with *P. falciparum* infections, acute renal and multi-organ failures have almost doubled in the last 5–7 years. Although it is not possible to attribute this directly to the decreasing efficacy of CQ, but it may be an important factor, as it has been in malaria-related deaths in African children [35]. The deteriorating trends in *P. falciparum* demands urgent radical changes in antimalarial drug policy. ACT is currently used in 261 PHCs (71 districts) as against approximately 14,000 malaria endemic PHCs. The process of adoption to ACT is painfully slow and may take a long time, until then CQ remains the first line drug in India. In 2006 a series of articles in The Lancet [36-38] and Nature [39] concerned funding of antimalaria drugs by the World Bank. The Lancet paper criticized the World Bank for funding the purchase of CQ by the Indian government. There is substantial evidence that CQ is no longer effective against *P. falciparum* in many areas of India, and under those circumstances the purchase of CQ supports a dangerous public health practice. One response to the criticism was that CQ is used in India only to combat *P. vivax*, a species against which it is mostly still effective. This statement contradicts the drug policy of the NVBDCP which recommends the use of CQ to treat all malaria cases, including *P. falciparum*, the more lethal pathogen.

It may be underscored that malaria situation in India is worsening due to ineffective vector control largely the result of DDT spraying [40] and the poor choice of antimalarials, for example India’s CQ consumption in 1976 was 61 metric tons (mt) to treat 6.45 million cases (the highest since resurgence) and, in 2005, cases have been reduced by 70%, but CQ consumption has increased ten times [41]. Table 1 illustrates one example among many, of the impact of inefficient spraying and increasing dependence on CQ. In Betul district, Madhya Pradesh, a malaria epidemic was building-up due to inefficient and inadequate DDT spraying and the decreasing effectiveness of CQ. Thus, the CQ use increased enormously with no signs of epidemic abatement. Several measures were required to finally control the epidemic: a switch from DDT to synthetic pyrethroid (SP) indoor residual spraying, introduction of larvivorous Gambusia (*Gambusia affinis*) and Guppy (*Poecilia reticulata*) fishes, and on-spot diagnosis to cover all households was initiated. Then with correct diagnosis, only *P. vivax* was treated with CQ; *P. falciparum* was treated with sulfadoxine-pyrimethamine (*P. falciparum* was susceptible to it). With these changes, the district was nearly malaria free by 2005 [42].

The WHO recommends fixed dose artemisinin combination therapy for *P. falciparum* [43]. In light of the clear evidence for CQ-resistance in *P. falciparum*, and the
recommendation for using CQ as the treatment for all malaria, not just *P. vivax*, the NVBDCP should respond to the recommendation of the Lancet Viewpoint and abandon CQ, in favour of ACT. Indian states with high prevalence of *P. falciparum* have the problem of CQ resistance, although the proportion remains undetermined. CQ and sulphadoxine/pyrimethamine (SP) resistance is more pronounced in the north-eastern states and Orissa. Multidrug-resistant strains abound on the international borders with the Indian NE states [44-46]. Artesunate with SP combination (blister pack) is now recommended in drug resistant areas. In seven states in the northeastern region of the country, ACT is being introduced in one district in each state in the pilot phase. Further expansion would depend on the experience gained in the districts in north-eastern region. This switch over to ACT would take place in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to depend on the experience gained in the districts in north-eastern region. This switch over to ACT would take place in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to in 71 districts in the country (261 PHCs, but there are approximately 14,000 high risk PHCs requiring ACT) to

**Table 1: Malaria in Betul District, Madhya Pradesh, India**

| Year | DDT (50% WP) sprayed in mt against 200 mt required | Synthetic Pyrethroid sprayed in Kg | CQ Tablets (150 mg base) | Fansidar Tablets | Total malaria cases | P. falciparum cases |
|------|---------------------------------|----------------------------------|--------------------------|-----------------|--------------------|-------------------|
| 1990 | Nil                             | Nil                              | Nil                      | Nil              | 496                | 91                |
| 1991 | Nil                             | Nil                              | Nil                      | Nil              | 949                | 281               |
| 1992 | 4.00                            | Nil                              | 5.00,000                 | Nil              | 805                | 196               |
| 1993 | 1.60                            | Nil                              | 5.00,000                 | Nil              | 626                | 213               |
| 1994 | 9.40                            | Nil                              | 5.00,000                 | Nil              | 1,503              | 602               |
| 1995 | 3.00                            | Nil                              | 6.00,000                 | Nil              | 1,280              | 739               |
| 1996 | 7.40                            | Nil                              | 7.70,000                 | Nil              | 2,290              | 662               |
| 1997 | 5.90                            | Nil                              | 9.80,000                 | Nil              | 5,279              | 1,764             |
| 1998 | 14.90                           | Nil                              | 9.60,000                 | Nil              | 8,872              | 3,340             |
| 1999 | 10.20                           | Nil                              | 13.88,000                | Nil              | 14,133             | 3,919             |
| 2000 | 18.0                            | Nil                              | 20.30,000                | Nil              | 16,764             | 7,126             |
| 2001 | Nil                             | 4698.4                           | 36.83,000                | 49,520           | 18,440             | 7,398             |
| 2002 | Nil                             | 3512.9                           | 25.33,000                | 59,094           | 4,911              | 992               |
| 2003 | Nil                             | 6429.8                           | 29.82,000                | 45,400           | 1,080              | 168               |
| 2004 | Nil                             | 2528.8                           | 16.28,000                | 4,600            | 1,063              | 855               |
| 2005 | Nil                             | 1352.0                           | 12.22,000                | 2,740            | 373                | 193               |

Source: District Malaria Officer, Betul district M.P.

holding correct malaria treatment for unfounded reasons, lacking sound scientific basis and wise clinical judgment, is both unethical and discriminatory. Malaria is predominantly the disease of the poor lacking health equity. This inequity should be leveled by following correct drugs and drug schedule to the needy and unprotected for a relentless war against malaria. Setting the house in order is a formidable challenge. Therefore, *inter alia* policy issues must be addressed by the NVBDCP first and the foremost.

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**References**

1. WHO: First meeting of the Regional Technical Advisory Group on Malaria, Manesar, Haryana, India 15–17 December 2004 World Health Organization, Regional Office for South-East Asia, New Delhi SEA-MAL- 239:1-38.
2. WHO: Strategic Plan to Roll Back Malaria in the South-East Asia Region World Health Organization, Regional Office for South-East Asia, New Delhi SEA-MAL- 237:1-25.
3. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI: The global distribution of clinical episodes of *Plasmodium falciparum* malaria. Nature 2005, 434:214-217.
4. Choudhury DS, Malhotra MS, Shukla RP, Ghosh SK, Sharma VP: Resurgence of malaria in Gadarpur PHC district Nainital, Uttar Pradesh. Indian J Malariol 2003, 49:49-58.
5. Yadav RS, Bhart RM, Kohli VK, Sharma VP: The burden of malaria in Ahmedabad city, India – a retrospective analysis of reported cases and deaths. Ann Trop Med Parasit 2003, 97:793-802.
6. Sharma VP, Choudhury DS, Ansari MA, Malhotra MS, Menon PKB, Razdan RK, Bhat CP: Studies on the true incidence of malaria in Kharkhoda (Distt. Sonepat, Haryana) and Kichha (distt. Nainital, U.P.) Primary Health Centers. Indian J Malaria 1983, 20:21-34.
7. NVBDCP: Malaria Drug Policy 2007 [http://www.nvbdcp.gov.in/Doc/Revised%20drug%20policy.pdf].
