Artemisinin drugs in the treatment of *Plasmodium falciparum* malaria in India

The National Anti Malaria Drug Policy envisages treatment of uncomplicated *Plasmodium falciparum* (suspected and laboratory diagnosed) with choloroquine and primaquine and in five provinces by the co-administration of artesunate and sulphoxine pyrimethamine[1]. In this connection, the article on artemisinin-based combination therapy (ACT) by Sushil Kumar and Srivastava[2] is timely. In 2003, the National Vector Borne Disease Control Programme, NVBDCP in short (formerly National Anti Malaria Programme), reported 1.87 million cases of malaria (including 0.86 million *P. falciparum* cases) and 1006 deaths. In 2004, the largest number of malaria cases was reported from Orissa, followed by Gujarat, Chhattisgarh, West Bengal, Jharkhand, Karnataka, Uttar Pradesh and Rajasthan[1]. The epidemic has been occurring with increasing frequency, killing and demoralizing the affected population; and pushing people below the poverty line. For example, in India, 90% *P. falciparum* cases occur in states below the poverty line[3]. Such epidemics prevent national development in all walks of life and retard the gross domestic product (GDP)[4]. Recent examples of malaria epidemics reported by the NVBDCP include *inter alia* Rajasthan, Haryana (1976), Gujarat, Goa, West Bengal (1997), Goa, Maharashtra (1998), Andhra Pradesh, Assam, Bihar, West Bengal (1999), Uttar Pradesh, Madhya Pradesh, Karnataka (2000), and Rajasthan (2003)[5]. Obviously, the disease burden in the country is hugely under-estimated. This is also reflected by the fact that India's chloroquine consumption in 1976 was 61 metric tons (mt) to treat 6.45 million cases; and in 2005 cases have reduced by 70% but antimalarial usage has increased ten fold[6]. Based on environment determinants, the World Health Organization (WHO) estimates 100 million cases in the South East Asia Region (SEARO)[7], 70% of these contributed by India[8]. *P. falciparum*, the killer parasite accounts for 45–50% malaria cases. Control of *P. falciparum* is important but difficult, as was evident from the failure of the Swedish International Development Agency (SIDA) supported Indian *P. falciparum* Containment Programme (1977–88)[9]. *P. falciparum* parasite is present all over the country, but its distribution is highly uneven. It is the major cause of infection in the Northeast, Orissa, tribal settlements across the country and forests. In the plains of India, *Plasmodium vivax* peak is followed by *P. falciparum* and in all other endemic areas *P. falciparum* predominates. *P. falciparum* abounds in communities lacking awareness, resources and suffering from endemic poverty[3,10–12]. With the national antimalaria drug policy of sequential monotherapies and serious compromises in vector control, drug resistance against chloroquine and sulphodoxine pyrimethamine (SP) is on the rise, and more areas are coming under multidrug-resistant malaria[1,12]. Drug pressure is selecting for mutations, for example, Pfcrt K76T mutation, an important determinant of chloroquine resistance is present in 95% of the isolates studied[13]. A direct consequence of drug resistance is the rise in malaria morbidity and mortality, and steep rise in treatment cost by a factor of 40–50 compared to chloroquine[14].

Artemisinin is a compound extracted from the Chinese herb, sweet wormwood *Artemisia annua* plant. It has been used in China in the treatment of fevers for more than 1000 years. Artemisinin has a high therapeutic index in the treatment of malaria[15]. In Vietnam, general use of artemisinins has led to a sustainable drop in the number of infected people dying from malaria. In the case of artemisinin-based drugs as monotherapies, the recrudescence rate is high and there is the possibility of emergence of artemisinin-resistant *P. falciparum* strains[16]. ACT is a scientific approach to tackle this problem. It is a combination of artemisinin derivative drug with one or more long-acting antimalarial drug having different modes of action and different drug targets[17,18]. Artemisinin drugs have a short half-life of 1–4 h or so, but because of their strong anti-plasmodial activity, they reduce biomass of the existing parasites by about 10^{-4} or say by 95% at each dosage of administration, and also kill the sexual stages of the malarial parasite. Residual parasites, if any, and the recrudescences are eliminated by the long-acting antimalarial and the host immunity[16,19]. Unfortunately, fake and sub-standard drugs are prevalent (up to 30% or more) and this may accelerate the development of artemisinin-resistant strains[20]. So far there was no report of resistance against artemisinin derivatives, but a recent article[21] has reported mutations causing resistance to artemisinin in *P. falciparum* from French Guiana and Senegal. The authors conclude this to be due to the uncontrolled use of artemisinin derivatives. A similar situation exists in the Asian countries, with the possibility of hidden foci of artemisinin-resistant *P. falciparum*. Health ministries should therefore take a serious view of this and enforce stringent laws to punish those dealing with fake and sub-standard drugs. In addition, surveillance and quality control of drugs should be reviewed and governments should adopt measures to 'plug the loop-holes', reflecting the 'social will' of those at the risk of malaria.

In April 2001, WHO issued new recommendations for malaria, and this new approach was publicized in 2003. We quote: 'WHO on the advice of international experts, recommends the introduction of combinations of drugs to replace the single drugs in the treatment of *P. falciparum* malaria. WHO recommends in particular the use of drug combinations containing artemisinin compounds, i.e. artemisinin-based combination therapy'[22]. ACT containing SP or amodiaquine, in areas where the parasite is resistant to these drugs, may result in treatment failure. It is therefore important to select a combination of an effective long-acting antimalarial drug with artesunate to treat *P. falciparum*. Roll Back Malaria Partnership has endorsed the recommendation by WHO, that countries in revising malaria treatment policies, should opt for a combination treatment, preferably ACT, and recommended the following four combinations in priority: (i) artemether/lumefantrine; (ii) artesunate + amodiaquine; (iii) artesunate + mefloquine (for low to moderate malaria transmission) and (iv) artesunate + sulphadoxine-pyrimethamind (in areas where SP efficacy remains high). The non-artemisin-based combination of amodiaquine + SP was also an option in areas where efficacy of both drugs remains high[22]. Already there are success stories of the use of ACT in malaria control[17]. In the northwestern border of Thailand, introduction of ACT containing artesunate and melfloquine resulted in 47% reduction in *P. falciparum*

incidence in just one year[23]. In KawZulu Natal, South Africa, introduction of artemether–lumefantrine along with vector control has reduced malaria admissions and deaths by more than 90% over a three-year period[24]. Since 2001, 51 countries, 34 in Africa alone have opted for ACT as the first line of treatment for *P. falciparum* malaria. Demand for ACT has surged from 2 million treatment courses to 30 million in 2003 and 70 million in 2005, with a projected demand[25] of 130 million treatment courses in 2007. There is acute shortage of artemisinin derivatives to fight malaria globally[26]. ACT can be procured by the member countries and institutions at a WHO negotiated price of US $2.40. The drug is supplied through WHO by Novartis on no-profit basis. India should amend the drug policy without loss of time, the poor are badly affected. The new drug policy should opt for fixed dose combination of artemisinin therapy and must take the private sector on-board[27]. While doing so, the importance of effective integrated malaria vector control must be underscored[28]. It may be noted that the switch-over to the new drug policy may require 30–35 million treatment courses of artemisinin-based, fixed-dose combinations a year. Artemisinin production of requisite quantities may take 2–3 years, but work should begin now to meet our own requirement of ACT. This is also an opportunity for the farming community to join 'wake-up-call' by WHO for the production of *A. annua*. This herb grows well in most parts of the country, indigenous high-yielding hybrids are available, extraction of artemisinin technology has been patented and production economics favours the option to grow *A. annua* on large scale[29–31].

Often financial resources are cited as an important constraint in malaria control. We wish to underscore the fact that antimalarial drugs account for 10–15% of the malaria control budget, and bulk of the budget is spent in spraying. Cost enhancement resulting from the introduction of ACT could be adjusted against wasteful spraying in areas with high refusal rates. Emerging new technologies such as rapid diagnostic tests[32,33], drugs[34], herbal preparations[35,36], ACT[37,38], insecticide-treated nets[39], biological control agents[40–42], environmental management methods[43,44], vaccines[45,46] and huge financial commitment by donors, reinforced by the strong will of the nations to fight malaria unitedly, are right signals for a malaria-free life in endemic regions of the world. In the South East Asian Region of WHO, accelerated malaria control in India would open a new window of opportunities and hope of a malaria-free world, and a sure way forward in realizing the targets of Rol Back Malaria[47] and the Millennium Development Goals[48].

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