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# Drug resistance keeps malaria threat alive in India

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**Drug resistance keeps malaria threat alive in India**

The current anti-malarial market in India is approximately $80 million (Rs 450 crore) with an annual growth rate of 17 percent, says a report by ORG IMS in Nov 2011. According to statistics available with the directorate of National Vector Borne Disease Control Programme (NVBDCP), close to 12 lakh cases of malaria have been reported in India till December 2011. Out of them, 436 have been cases of deaths.

Around 50 percent (6.4 lakh cases) were caused by the single-celled parasite *Plasmodium falciparum*. Increasing drug resistance is a possible cause for the continued rise in cases of *P. falciparum* caused malaria in recent years, gradually increasing from 39 percent in 1995 to above 50 percent in 2008.

With *P. falciparum*, which causes the most dangerous forms of the disease, becoming resistant to the drug chloroquine, Artemisinin-based treatments have become popular. Globally, the number of courses of Artemisinin-based therapies (ACT) procured by the public sector jumped nearly seven-fold between 2005 and 2006, and then more than doubled, reaching 181 million, in 2010, according to the World Malaria Report 2011. The demand for these drugs was around 287 million treatments in 2011 and is expected to touch 295 million courses in 2012.

**Resistance causes worry**

The malarial burden has increased both globally and in India due to the resistance developed to anti-malarial medicine used so far. For instance, child mortality in Africa increased as *P. falciparum* strains that were resistant to chloroquine spread in the continent in the 1970s and the 1980s. Raising an important issue of possible artemisinin resistance, Dr Virander S Chauhan, director, International Centre for Genetic Engineering & Biotechnology (ICGEB), says, "There have been reports of resistance in Cambodia, Thailand and, if it reaches Burma and the Northeastern part of India, then things can get very messy."

"A looming threat to malaria control is the emergence of parasites that are resistant to anti-malarial medicines," stated World Health Organisation (WHO) in its 'Global Plan for Artemisinin Resistance Containment' published in 2011. The strains that are resistant to even artemisinin have emerged in parts of South East Asia and could potentially spread, as has happened

with previous anti-malarial drugs.

Delivering Artemisinin and its derivatives as monotherapies, instead of as a cocktail with another drug, create opportunities for resistant forms of the parasite to arise and spread. Although oral Artemisinin-based monotherapies are effective when taken as the full seven-day course, patients often stop taking them after a few days when symptoms subside. Parasites that are sensitive to the drug get eliminated, allowing drug-resistant strains to proliferate and get transmitted to other people. WHO, in 2006, called for a halt on using oral Artemisinin monotherapies for treating uncomplicated malaria. A year later, a resolution was adopted by the World Health Assembly, WHO's apex decision-making body, that urged its member states to "cease progressively" the provision, in both public and private sectors, of such monotherapies and promote the use of ACTs.

However, according to the latest World Malaria Report 2011, 25 countries are still allowing the marketing of these products and 28 pharmaceutical companies, as against 39 a year ago, are making these drugs. The report has also warned that there are Indian pharmaceutical companies among those manufacturing and marketing drugs that are likely to foster resistance to artemisinin in the malaria parasite. Ten of the 28 manufacturers of monotherapies are reportedly based in India.
The Drug Controller General of India (DCGI) initiated action earlier this year to stop the production and export of these drugs. It wrote to all state drugs controllers requesting them to cancel licenses for manufacturing oral Artemisinin-based monotherapies with immediate effect.

**Addressing the menace**

According to WHO, India is of greatest concern as there is widespread DDT-resistance and patches of resistance to pyrethroid and organophosphate (malathion). WHO has recommended that an Artemisinin-based combination therapy (ACT) should be the first-line treatment for uncomplicated malaria caused by *P. falciparum*. The two-drug combination reduces the chances of the parasite developing resistance. Moreover, a three-day course of a recommended ACT generally clears the parasites from the body.

Guidelines of National Institute of Malarial Research (NIMR) too recommends combination therapy for *P. falciparum*. Arterolane maleate, a rapidly acting drug in combination with long-acting piperaquine phosphate, is an anti-malarial product in line with WHO-recommended combination therapy for the treatment of uncomplicated *P. falciparum* malaria. Though insecticide and spraying materials and insecticide-treated nets are other possible solutions to control malaria, but they have not been very successful in India so far.

Dr P L Joshi, faculty, National Institute for Health and Family Welfare (NIHFW), New Delhi, points out that apart from having the support of external agencies, developing nations must have their own redressal mechanism in place. Appreciating the fundings from World Bank and technical guidance from WHO, he says unless a proper preventive mechanism is enforced, it will be difficult to tackle the menace. "The government of India has stepped up its efforts. This is clearly visible from the change in the drug policy. There are various programs educating people about the preventive measures. In place of small projects a decade ago, there are currently projects worth $89 million (Rs 500 crore) focusing on malarial research," he adds.

Many awareness programs are being run by the government through media and various NGOs. Ranbaxy has launched an action malaria campaign that includes patient awareness and education, and assistance to physicians in diagnosis and treatment of malaria.

**Fresh hopes**

The unavailability of options has created need for new anti-malarial drugs that can tackle these challenges. The success of phase III trials of a GSK vaccine, which the company has been developing along with PATH Malaria Vaccine Initiative, has raised the hopes of an anti-malarial vaccine. GSK has already invested $300 milion in the project and will invest further $50 million to $100 million in it.

In India, Ranbaxy has developed Arterolane maleate, a rapidly acting drug in combination with long-acting piperaquine phosphate. It has also developed a New Chemical Entity, Arterolane, in combination with Piperaquine, which is expected to have superior benefits over the currently available anti-malarial therapies. According to sources in Ranbaxy, the drug has received approval from the Indian Health authorities and the product is in line with WHO recommendations.Research done by Dr Virander Chauhan and Dr Chetan Chitnis at the International Centre for Genetic Engineering & Biotechnology (ICGEB) has led to the developement of a first generation vaccine, MJAIVAC1, which is based on combination of two merozoite antigens (MSP-119 and EBA-175). The vaccine is presently being tested for safety and immunogenicity in a phase I clinical trial, the first for a malaria vaccine developed in India. The ICGEB has also developed a portfolio of novel antigens that is currently at different stages of pre-clinical development. Also, the center has developed a vaccine, PvDBPII, for Plasmodium vivax and it is being produced by a biotechnology company for phase I trial.

Under a government-funded project, Mumbai-based IPCA Labs, along with Jamia Hamdard University, New Delhi, has developed a genetically modified variety of Artemisinin Annua that can generate high yield of Artemisinin. Once approved, the variety will be put to confined-field trials for evaluation and then patented and commercialized for cultivation by farmers. The group expects that this variety will fetch more than one percent Artemisinin in field trials.