

Continuing challenge of malaria in India

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Historical account

Malaria is an ancient disease in India. Known as the 'king of diseases', malaria was estimated to cause 75 million cases and 0.8 million deaths annually. In epidemic years, morbidity and mortality used to increase 2–3 times. Ravages of malaria were so rampant and devastating, that the economic growth of the country remained paralysed. Economic loss to the nation due to malaria was estimated at Rs 75,000 million annually, at 1940 rupee value¹. Malaria was the single biggest disease with which Indians had to suffer perennially. Etiology of malaria remained obscure, and so was its scientific treatment. Briefly, the major discoveries that led to the scientific approach to malaria control started with the discovery of its causative agent in 1880 by Charles Louis Alphonse Laveran. While working in a military hospital in Constantine, Laveran discovered that the cause of malaria is a protozoan parasite and for the discovery he received the Nobel Prize in 1907. In 1897, Ronald Ross demonstrated malaria transmission by mosquitoes in Hyderabad and a year later, in 1898, in Calcutta (now Kolkata). He received the Nobel Prize in 1902. The Indian Society for Parasitology celebrated 100 years of this epoch-making discovery on 20 August 1987 in Hyderabad, and paid homage to this great genius of his times. Following this discovery, malaria control was attempted by Ross in Mian Mar town (now in Pakistan), but the results were disappointing. The discovery of residual insecticidal action of DDT by Paul Muller for the control of vectors of malaria and yellow fever raised hopes of malaria control worldwide. For this discovery Muller received the Nobel Prize in 1939. Initial impact of DDT spraying produced spectacular results by killing malaria-carrying mosquitoes for several months. Thus rural malaria control had become a reality².

From control to eradication

Initial trials with DDT in malaria control received worldwide appreciation. Father of the Nation, Mahatma Gandhi, approved

the malaria control initiative. Success in field trials in malaria control with DDT led to the launching of the National Malaria Control Programme (NMCP) in 1953. Urban malaria was a minuscule problem and its control was outside the NMCP, to be managed by the local governments. Within a few years of DDT indoor residual spraying (IRS), reports of mosquitoes developing DDT resistance started surfacing. To counter the DDT resistance problem, in 1958 the Government of India converted NMCP to the National Malaria Eradication Programme (NMEP). This decision was taken to achieve malaria eradication before the large-scale onset of insecticide resistance. By the early 1960s, DDT spraying eliminated malaria from two-thirds of the country and the NMEP was heading towards its final goal of malaria eradication. Disappearing malaria led to diversion of resources to more demanding economic developments, and NMEP was put on the back burner. By 1961, malaria cases were the lowest recorded, 49,151 (*Plasmodium falciparum* (Pf) 17,141) cases (estimated 100,000) all over the country¹. Thus the existing health infrastructure was considered good enough to eliminate the residual malaria foci. Consequently malaria expertise diminished and resources dissipated. A decade of successful malaria control allowed economic growth of the country that included the green revolution, industrialization and released enormous human resource for all-round development of the country.

Malaria resurgence

Malaria cases were then seen in towns that were free from malaria. The disease was seen diffusing to rural areas. The disease situation rapidly deteriorated as a result of the insurmountable administrative, financial and technical problems. At that time, the preparedness of NMEP in tackling outbreaks that followed in the 1970s was at its lowest ebb. By this time DDT IRS successful campaigns had also eliminated malaria control expertise at all levels. DDT shortages further aggravated the situation and malaria re-emer-

ged countrywide. In the following decades of the 1980s, malaria epidemics had become commonplace and deaths due to malaria that had been zeroed returned. DDT and chloroquine, gradually lost their killing power due to resistance in vectors and the parasite. Furthermore, spraying operations started failing due to refusals, environmental concerns, and poor impact on vectors and transmission. The malaria situation continued to deteriorate and peaked in 1976, touching 6.45 million parasite-positive cases and 59 deaths, the highest since the resurgence³. In 1977, the Government of India scrapped the eradication strategy and reverted to malaria control under the Modified Plan of Operations (MPO)⁴. In the same year, the Swedish International Development Agency (SIDA)-financed *P. falciparum* containment programme (PfCP) was launched to contain *P. falciparum* and drug-resistant malaria confined principally to the northeastern states. Unfortunately, *P. falciparum* continued to occupy new territories in the mainland and established the seasonal cycles of *vivax* followed by *falciparum* malaria. This march of *P. falciparum* along with drug-resistant strains was unstoppable. PfCP was terminated after 11 years of intensified efforts^{5,6}. MPO followed the eradication strategy, but more targeted and investing in research⁴. Of the two malaria parasites, viz. *P. vivax* and *P. falciparum* prevalent in India, the former accounted for 80–85% and the latter 10–15% in the early 1970s, although this proportion varied seasonally and geographically (Figure 1). Though malaria relented under MPO, the proportion of *P. falciparum*, the killer parasite, was rising and touched 50% by 2010. Excessive dependence on chloroquine was inimical to *P. vivax* parasites, but induced resistance in *P. falciparum*. Malaria continued to occupy centre stage in public health despite heavy investments by the Government of India and State Health Departments, and foreign assistance from SIDA, World Bank, GFATM, etc.

Situation analysis

Malaria is endemic in 106 countries, and in 2009, there were 225 million malaria

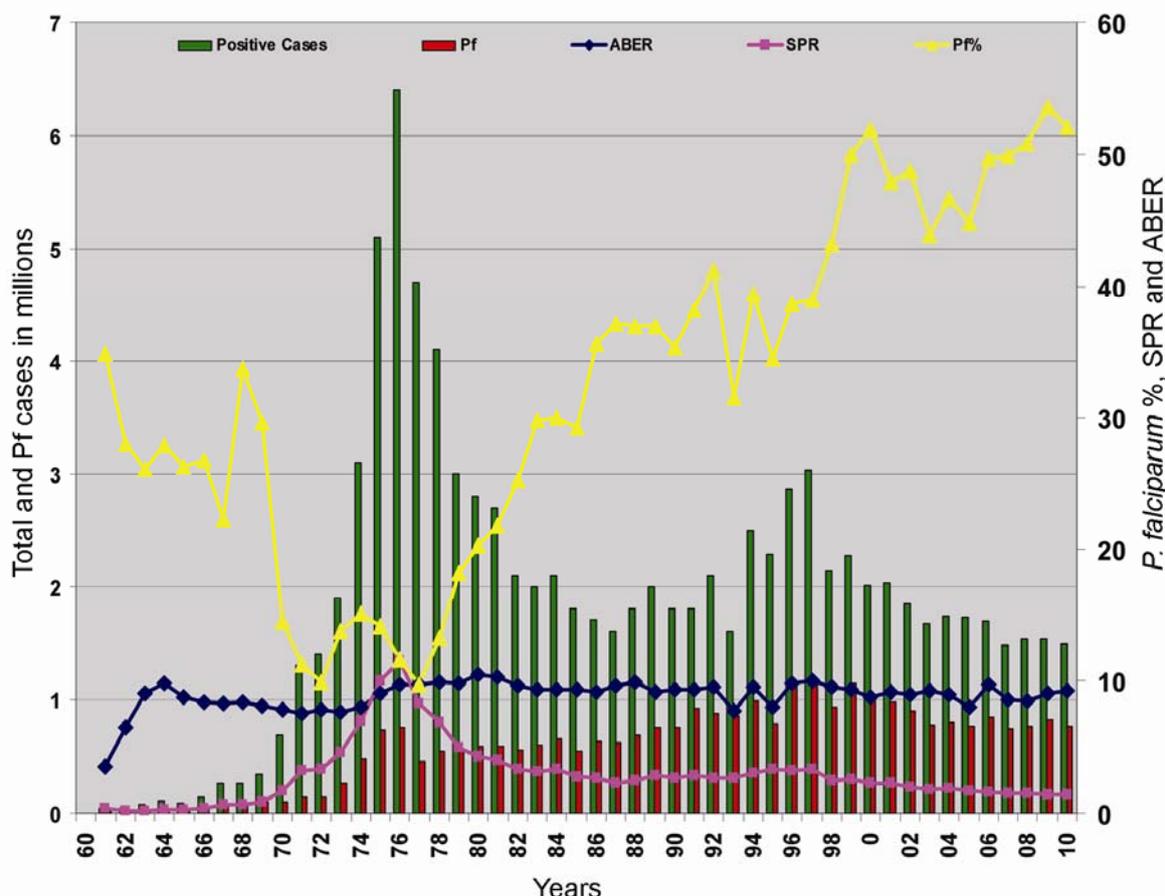


Figure 1. Malaria cases in India (1960–2010) as recorded by the NVBDCP. Cases started rising in 1970, peaking in 1976 to 6.45 million, and after the implementation of the Modified Plan of Operations in 1977, malaria cases declined, but mainly *Plasmodium vivax* malaria due to its sensitivity to chloroquine. *P. falciparum* was about 10% in 1977, but due to fall in *vivax* malaria, this has risen to about 50% and the parasite has become mono to multi-drug resistant (data source: NVBDCP). SPR, Slide Positivity Rate; ABER, Annual Blood Examination Rate.

cases and 781,000 malaria deaths⁷. Of the six WHO regions, ten malaria-endemic countries in the South East Asian (SEA) region contributed 15% malaria cases and 6% malaria deaths in 2009. India, Bangladesh, Indonesia and Myanmar make up 97% of all malaria cases in the SEA region⁷. In India, an estimated 95% population lives in areas where malaria transmission has been reported or climatic conditions favour transmission. Eighty per cent malaria in India is confined to 20% population, mainly aboriginal population living in hilly, difficult and inaccessible terrain. An epidemiological study revealed that malaria is highly unevenly distributed at the macro and micro levels. For example, 8% tribal population in India contributed 30% malaria cases, 60% *P. falciparum* cases and 50% deaths due to the disease⁸. The malaria situation in the tribal settlements has remained static even after

five decades of malaria control (V. P. Sharma, unpublished). Rural malaria accounts for 65–70% cases. Rural malaria is unstable and uneven peaking at an interval of 5–10 years or more^{9–11}. In 2010, National Vector Borne Disease Control Programme (NVBDCP) reported 1.5 million parasite-positive cases, 52% *P. falciparum* and 1023 deaths. The proportion of asymptomatic carriers has remained undocumented and is an important source of parasite dissemination, particularly migrant labour from and to endemic areas. In-depth reviews of NVBDCP and several independent studies have reported that incidence of malaria in the country is grossly underestimated^{12–14}. This is basically due to lack of proper surveillance. The high malaria burden states in the country are Chhattisgarh, Jharkhand, Madhya Pradesh, Orissa, West Bengal and the northeastern states. In 2010 these states together

contributed 72% malaria cases, 90% *P. falciparum*, and 67% deaths. Malaria incidence and mortality figures have been questioned in various fora. WHO¹⁵ estimated 30 million cases and 15,000 deaths (5000 children and 10,000 adults) due to malaria. WHO Hqs. estimated 100 million cases in the SEA region, of which 70% occurred in India. A recent study by Dhingra *et al.*¹⁶ reported 200,000 (range 125,000–277,000) deaths annually due to malaria in India. A team comprising national and international scientists reported that in Madhya Pradesh alone, malaria in pregnancy (MiP) is responsible for 220,000 cases annually, with 76,000 abortions, 19,800 stillbirths and 1000 maternal deaths¹⁷. Anti-malarial drug consumption also suggests high malaria morbidity and mortality, e.g. chloroquine consumption in 1976 was 61 metric tonnes for treatment of 6.45 million cases; and in 2005

cases were reduced by 70%, but chloroquine consumption increased tenfold in addition to other antimalarials drugs¹⁸.

Resistance to chloroquine in *P. falciparum* was first detected in the Karbi Anglong District, Assam in 1973. In about a decade, *P. falciparum* spread from its initial focus in the northeastern states to the entire country¹⁹. Replacement of chloroquine with amodiaquine and later with sulphadoxine pyrimethamine (SP) led to multiple drug resistance, and use of new drugs like mefloquine by the private sector further worsened the situation of drug resistance in areas of its use. The return of malaria was now armed with the formidable enemy of mono and multi-drug resistance and vector resistance. Despite the widespread resistance to chloroquine, NVBDCP continued to use it in the treatment of *P. falciparum*²⁰. Excessive use of chloroquine has resulted in several reports of chloroquine resistance in *P. vivax*, which was hitherto fully sensitive to the drug²¹. Chloroquine resistance has become a serious obstacle in the treatment of *P. falciparum*. The problem is further compounded with the substandard and fake drugs frequently encountered in the market^{22–24}. Pharmaco-vigilance must be strengthened to control fake/substandard drug menace in the SEA region. Drug resistance in malaria parasites is a serious problem in the treatment and control of the disease²⁵. Chloroquine resistance in *P. falciparum* was reported from 20 states (285 PHCs) as monitored by the drug-resistant monitoring teams. Based on this information and the global malaria control strategy of using artemisinin-based combination therapy (ACT), NVBDCP introduced SP artesunate combination therapy (ACT) in 2004 in chloroquine-resistant areas²⁶. Continuous monitoring of ACT resistance is in place jointly by NIMR/NVBDCP. ACT combined with long-lasting insecticide-treated nets (LLINs) is effective in the control of malaria transmission, e.g. in Assam the changed policy of malaria control has drastically reduced malaria cases in areas of its implementation²⁷.

Furthermore, malaria transmission was accelerated by widespread and sustained vector breeding in habitats created by the economic development of the country under the Five-Year Plans. In the beginning, emerging malaria foci were small, but gradually these led to country-wide malaria outbreaks under favourable

climatic conditions. India's malaria is largely a rainfall phenomenon. *Anopheles culicifacies*, the vector of rural malaria responsible for about 65% of new malaria cases annually, invaded new territories in the plains, particularly irrigation tracts²⁸. Control of *An. culicifacies* is the most formidable challenge, as its control takes away nearly 75% of the NVBDCP budget. In the 1980s and 1990s malaria epidemics occupied larger territories covering the entire ecotypes in several states involving millions of people^{29,30}. Malaria vectors invaded new habitats in the upcoming townships, urban agglomerations, industrial belt, and agriculture fields, and proliferated uninterruptedly. The ecological changes in the new environment encouraged vector breeding, causing malaria upsurge. Malaria control tools had blunted and no new technology was available to suppress the rising trend of malaria. A similar trend was witnessed in towns. *An. fluviatilis* generates 15% malaria and 30% *P. falciparum* cases, and *An. minimus* contributes 5–7% cases, and both vectors breed in slow-flowing streams. *An. fluviatilis* control has become a major challenge due to vector breeding in forested terrains with poor accessibility, e.g. in Odisha. *An. minimus* populations were decimated in the 1960s under pressure of DDT, but returned mainly in the northeastern states after widespread resurgence. There are reports of ecological succession by this mosquito vector species in Assam for occupying ecological niches erstwhile dominated by *An. minimus* (Vas Dev, pers. commun.). *An. sundaicus*, a brackishwater breeder retracted from the mainland has remained the main vector in the Andaman and Nicobar Islands, contributing a few thousand cases annually. *An. dirus*, the vector in deep jungles contributed 5–7% malaria cases²⁸, but malaria control in *An. dirus* areas has remained extremely difficult.

Urban malaria

The problem of *An. stephensi*-transmitted malaria in India was initially confined to the port cities. For example, malaria in Mumbai was a serious problem in the early part of the 20th century. Covell³¹ successfully demonstrated malaria control in Bombay (now Mumbai), and malaria transmission was maintained at a low ebb till the system collapsed in the

1990s. *An. stephensi* is an invasive species and prefers urban environment with clean water to support mosquito breeding. From its initial focus in port cities, *An. stephensi* first invaded riparian towns and then towns with excessive wells, e.g. Delhi, Lucknow, Hyderabad, etc. In the early 1960s when malaria incidence in rural India was lowest, cases were multiplying in towns creating panic. Taking note of the deteriorating malaria situation in the towns, the Government of India implemented the Madhok Committee recommendations to control malaria in the urban areas³². Consequently, the Urban Malaria Scheme (UMS) was launched in the country in 1971–72. Initially 131 towns with a population of >40,000 (revised to >50,000) and reporting >2API were included in the UMS. *An. stephensi* continued to expand its territories and entered new towns. The invasion was further facilitated by piped water supply. The opening of hinterlands by a network of roads, electrification and rural water supply, tropical aggregation of labour, migration of population, and lands under industrial development provided additional vector-breeding opportunities and disease transmission. Malaria in peri-urban and industrial townships is transmitted by *An. stephensi* and *An. culicifacies*. While *An. stephensi* was implicated in malaria transmission, its distribution was not delimited in the country. Climatic conditions, and water-storage practices and erratic water supply suggest that almost all towns in the plains will have some population of *An. stephensi* and possibility of malaria transmission. UMS was launched in phases starting from 23 towns and it took nearly three decades to cover 131 towns. This is an area of neglect requiring immediate attention. Malaria cases in 131 towns is showing an upward trend each year, i.e. 2007, 102,829 cases; 2008, 113,810 cases; 2009, 166,065 cases and 2010, 207,094 cases. Urban malaria contributed 10–12% cases in the country. In Tamil Nadu, urban malaria is most prominent; Chennai reported 9789 or 64.1% cases. Mumbai reported³³ 76,755 or 55.41% malaria cases, 13,363 or 41.26% *P. falciparum* cases and 145 or 76.31% malaria deaths in 2010. The problem of urban malaria should be seen in the background of Census 2011. India has 7935 towns with more than 377 million people (31.16%). Class I UA (urban agglomerations)/towns with a population

of at least 100,000 are 468 (264.9 million persons constituting 70% urban population). Million plus UA/city population was 160.7 million persons (or 42.6% of the urban population). Among these, three mega cities with more than 10 million people are Greater Mumbai UA (18.4 million), Delhi UA (16.3 million) and Kolkata UA (14.1 million)³⁴.

Urban malaria control is based on source reduction, larviciding with abate or fenthion, and application of *Bacillus thuringiensis* or *B. sphaericus*; fishes (Guppy/Gambusia), minor engineering interventions, legislative measures, building bye laws and limited spraying in peri-urban and jhuggies, but the implementation is weak and often wanting. Urban malaria problem is the 'tip of the malaria iceberg'. It is getting more complex with heavy breeding of *Aedes aegypti* in many urban situations. *A. aegypti* is the vector of dengue and dengue hemorrhagic fever and Chikungunya fever. Most breeding habitats of *An. stephensi* and *A. aegypti* overlap. The onset of rainy season gives rise to enormous vector breeding and other water-borne diseases making correct diagnosis and treatment difficult, thus endangering life.

Prevailing formidable challenges

The epidemiology of malaria revolves around the vectors. Of the six malaria vectors, the problem of vector control is complex in *An. culicifacies*, *An. stephensi* and *An. dirus*. Control of *An. culicifacies* has always been a formidable challenge. India's 70–80% malaria control budget is spent in the control of *An. culicifacies*; yet its control is always transient requiring annual spraying programme. *An. culicifacies* has become multiple insecticides-resistant, so that *An. culicifacies*-transmitted malaria control requires the use of new insecticides which are more expensive and toxic. The new insecticides also have a short window of effectiveness due to resistance. NVBDCP has about five decades of field experience in the control of malaria in some of these areas. A rational approach to *An. culicifacies* should rely on ecological methods by taking advantage of the health impact assessment, bio-environmental methods, and limiting the use of insecticides strictly for emergencies and epidemic control. *An. stephensi* is invading urban and industrial areas

throughout the country. Expansion of *An. stephensi* populations is linked to the economic development of the country. Health impact assessment and integration of remedial measures from the very beginning are essential pre-requisites. Malaria control methods developed by Covell³¹ should be followed for rational approach to urban and industrial malaria control. *An. dirus* is the most difficult mosquito to control. *An. dirus* populations pulsate from the mother foci to spread to neighbouring areas during favourable wet season and retract during dry season, spilling new parasite strains. *An. dirus* (= *baimaii*) is an efficient malaria vector and confined to the closed forest in India, Bangladesh, Myanmar and Thailand. In 2005, 70 million people in South East Asia were at risk of malaria under the influence of *An. dirus*³⁵. Almost the entire population is aboriginal, the environment is congenial for vector proliferation, and difficult and inaccessible terrain and wildlife make entry into the forests life-threatening. Resistant *P. falciparum* that originates from Thai-Cambodia border passes through *An. dirus* areas, and circulates in the protected reserve forests³⁶. Drug-resistant parasites eventually enter India via the northeastern states and get mingled in hard-core malaria endemic areas³⁷. Malaria control in *An. dirus* areas in the closed forests is a formidable challenge. Addressing this would require innovative technologies coupled with improved access and communication to facilitate the delivery of health services to these areas. Other areas of concern where malaria control has been tardy is cross-border malaria at the international borders, i.e. India–Bangladesh, India–Bhutan, India–Nepal and India–Myanmar.

Malaria elimination strategy

Malaria elimination strategy is based on the elimination of malaria parasites and not the vectors, although vector control is an integral part of the elimination strategy. At the turn of century, old tools used in malaria eradication are being supplemented by new technologies in malaria prevention, diagnosis and treatment. These technologies are: malaria prevention by IRS with an effective insecticide³⁸ and insecticide-treated mosquito nets replaced by LLINs³⁹. For early diagnosis, laboratory services were

strengthened and supplemented by Rapid Diagnostic Test (RDT)⁴⁰ where microscopy was not available or during emergencies. Treatment for malaria cases was given within 24 h of the onset of fever or the reporting of the case to the nearest health facility. *P. vivax* cases were given 1500 mg chloroquine adult dose in 3 days and 14-day course of primaquine. *P. falciparum* cases were treated with ACT⁴¹. This drug policy provided radical cure of *P. vivax* and *P. falciparum* malaria. Major global resources converged to establish a Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM)⁴². GFATM provided funds globally to projects that followed WHO guidelines. Partnership with stakeholders provided additional resources. This strategy when applied in malaria-endemic countries with at least 80% coverage produced dramatic impact on malaria transmission, even in countries south of the Sahara, where malaria control was not considered feasible. Endemic countries are continuously making efforts to upscale various interventions so as to meet universal coverage as recommended by WHO. The steps involved in malaria elimination are to demarcate the region or the country targeted for elimination. Intensify malaria control so that malaria cases in the unstable areas decline to <5 SPR in fever cases, or in stable malaria areas move to the consolidation phase. When malaria is reduced to these levels, the region (target population) moves to the pre-elimination phase. This is the beginning of the first programme orientation. Interventions continue to further reduce malaria incidence to <1/1000 case in populations at risk. At that level of success, the target population moves from the pre-elimination to the elimination phase. In the elimination phase, indigenous transmission of malaria must completely stop at zero level. As and when this happens, the area moves to the second programme orientation for malaria elimination. This phase lasts for a minimum of three years. In the elimination phase, prevention of re-introduction of malaria must be ensured throughout this period. The population then becomes eligible for WHO certification of malaria elimination. The challenge for India is to proceed with malaria elimination in areas with maximum feasibility and continue to bring more regions under <5 SPR for unstable areas and consolidation phase in stable

areas. So far the entire country is in the malaria control phase and has not moved to the pre-elimination or the first orientation phase⁴³. Already 39 countries in the world are in the advanced stage of malaria elimination and more countries are likely to join them. In the Asian countries, Bhutan, Nepal and Sri Lanka are heading towards malaria elimination (SEARO, WHO, unpublished).

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