Chapter

New Ways to Tackle Malaria

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Abstract

Malaria is one of the oldest tropical diseases and still remains a focus of attention. Sub-Saharan African countries contribute 90% of the total malaria cases in the world. The World Health Organization (WHO) has advocated eliminating this disease by 2030 with the existing strategies and tools. Many initiatives are underway by several organizations, and 38 countries have achieved the elimination goal. The main backbone of the elimination process is smart surveillance followed by prompt public health responses. The control of the disease mainly relies on treatment of malaria positive cases with anti-malarials namely artemisinin-based combination therapy (ACT) for *Plasmodium falciparum*. In India, chloroquine is still effective against *P. vivax*. Use of 8-aminoquinolines primaquine and more recently tefenoquine warrants testing of G6PD deficiency status to avoid unnecessary hemolysis. Vector control operations mainly depend on the use of long-lasting insecticidal nets (LLINs) and indoor residual spray (IRS) with insecticides. The threat of resistance draws an open challenge in both treatment and vector management. New initiatives on surveillance, treatment, chemoprevention, and vector control using modern techniques of artificial intelligence, machine learning, genetic engineering, and digital approach of community engagement have great potential to accelerate the malaria elimination process.

Keywords: malaria, elimination, smart surveillance, treatment, vector management, community engagement

1. Introduction

Malaria is one of the oldest parasitic tropical diseases, and it takes a huge toll on human lives. It also causes great economic loss. Almost half of the population in the world is under the threat of malaria mostly in the tropical and sub-tropical countries. About 90% of the total malaria burden occurs in sub-Saharan African countries. Efforts to eradicate/or eliminate malaria began after the discovery of the role of mosquitoes in malaria transmission by Ronald Ross in 1897. In the beginning of the 20th century, most of the mosquito control operations were aimed at larval control using larvicidal oil, larvivorous fish and environmental management. These efforts made significant impacts on malaria control. Everything changed with the introduction of dichloro diphenyl trichloroethane (DDT) in the mid-1940s. Many European countries and the USA successfully eradicated malaria with the application of DDT and vector sanitation strategies, and improving general living standard [1].

Malaria eradication program in India haves had mixed success. After successful results from pilot studies on DDT, the National Malaria Eradication Program (NMEP) was launched in 1958 from the National Malaria Control Program (NMCP) in 1953. There was a huge success that resulted in almost complete malaria eradication in

the mid-1960s with 0.1 million cases and no deaths. A kind of complacency led to a slow rise in malaria cases, and a total of 6.4 million cases were reported in 1976. This was due to the development of resistance to DDT by vector species, especially by *Anopheles culicifacies* s.l. and chloroquine resistance by *P. falciparum* malaria [2].

A Modified Plan of Operation (MPO) was launched aiming to treat each fever case suspected to be malarial infection with a presumptive dose of anti-malarial drug especially chloroquine. This provided some respite but the malaria cases remained at a static level with occasional regional outbreaks. In 1995, a revised guideline named Modified Action Plan (MAP) gave some lead which renamed as National Malaria Eradication Program (NMEP) in 1999. Subsequently this program was more disease centric and named as National Vector Borne Disease Control Program (NVBDCP) in 2002 [3].

In 2017, 0.84 million malaria cases with 174 related deaths were reported from India, while WHO estimated 9.6 million cases with 16,723 malaria-related deaths. This may be due to different methods of case estimation. From this state of current situation in India, malaria elimination has been envisaged with an aim to achieve it by 2030 [1, 4].

2. Malaria elimination initiatives

The global malaria elimination framework was launched in 2007, and a detailed Global Technical Strategy (GTS) was released in May 2015 aiming to eliminate malaria by 2030. The three recommendations to achieve this goal strongly emphasize strengthening of smart surveillance; prompt diagnosis and treatment; and enhance elimination process. The GTS thus focuses on 35 countries in which to eliminate malaria by 2030, and India is one of them [4].

India is one of the countries that have signed the National Framework for Malaria Elimination (NFME). The WHO estimated 219 million malaria cases with 435,000 related deaths in the world in 2017. This was higher than the previous years. The WHO Director-General has called an aggressive new approach `High Burden to High Impact' [1]. Of the 11 high malaria burden countries 10 are from Africa, but India is also under this category. Nearly half of the global malaria occurred in Nigeria (25%), the Democratic Republic of the Congo (11%), Mozambique (5%) and 4% each by India and Uganda. This means India needs a special attention. The NFME has been designed to ease the burden in most high burden Indian states especially Odisha, Madhya Pradesh, Chhattisgarh and Jharkhand. The major attention should be on strengthening the surveillance which is still poor in many states [1, 3].

3. Strengthening of ongoing surveillance

Surveillance is the main pillar in the malaria elimination process. In most situations, ongoing surveillance is not consistent with the national guidelines resulting in poor estimates of malaria burden. This needs to be converted into smart surveillance. In the digital era, all surveillance systems should follow the concept of the 'test–treat–track' strategy [5]. Android-based mobile apps can be applied for quick dispensation of surveillance data from the field to the local administrator for immediate action. This system at district-level management is implemented in many African countries. In this way, the time lag between diagnosis and treatment can be minimized [6]. Tracking the patient for completion and follow-up of the treatment has wider effects on the local cycle of malaria [1]. WHO has developed surveillance and data analysis dashboards

using district health information software 2 (DHIS 2) [4]. Such digital-based data systems will make the surveillance system smart and efficient.

Strategy to change in surveillance is also an important step to accelerate the malaria elimination process. China adopted the '1-3-7' strategy that promoted the elimination process with zero indigenous malaria cases in 2017. This strategy envisions the strategic action from diagnosis to treatment within 3 days and public health responses to vector management within day 7 of the case detection. This also makes an easy platform for establishment of personal communication in the community [7]. Indonesia also adopted the '1-2-5' strategy for surveillance and response protocol in malaria elimination; on day 1 case management and notification; on day 2 case classification and foci investigation; and by day 5 foci response and elimination [8].

In southwestern coastal Mangaluru city, Karnataka state, India, malaria has been endemic over two decades. The local authority has implemented indigenously developed digital handheld tablets (TABs) for smart surveillance. These TABs have been allotted to each health worker after proper training. Now no manual data collection is used in the city. The link of the software was also provided to the local hospitals and diagnostic labs. The data can be accessed to the local administrators for taking action on the feedback received. Here the '1-3-7-14' strategy has been adopted where positive case is registered with start of treatment on day 1; completion of treatment by day 3; on day 7 vector control activities with follow-up smear check, and on day 14 follow-up smear check and completion of radical treatment for *P. vivax* cases with primaquine. In this way, the initial response of the antimalarial drugs can be assessed. The best part of this system is that all the data can be retrieved, and the program can be monitored at all levels, assessing the opening and closing of each case. This system creates a great scope of community awareness through person-to-person communication [9]. In the dashboard of this system, algorithms of specific data can be incorporated for possible prediction of malaria outbreaks. Thus, the concept of 'predict–perform–protect' can be established using artificial intelligence (AI) and machine learning.

A recent study in Bangladesh has found that the movement of people can be tracked from the mobile phone network which can help prediction of outbreaks of diseases such as malaria. This enables the health authorities to take preventive measures in time [10].

4. Quick, efficient and point-of-care diagnosis

Malaria microscopy is still the best method and gold standard for malaria diagnosis. A microscopist normally examines 60 blood smears per day. This includes staining and data maintaining. Now expert microscopist can detect 20 to 50 parasites/μl blood that means a 0.001 to 0.005% level of parasitemia. This is not the cases with regular microscopists where the sensitivity is low. Routine in-house training on the line of continued medical education program can improve the efficiency of the microscopists [11].

Recent deployment of Rapid Detection Tests (RDTs) have changed the malaria diagnosis at large, but it has failed to detect when the level is <100 parasites/μl blood. This has become a nagging problem in detecting very low numbers of infected red blood cells and sub-microscopic parasites especially gametocytes in *P. falciparum* cases. This necessitated an alternate system of diagnosis. An indigenously developed handheld real-time micro-PCR based PDA (personal digital assistant) device that can detect parasites as low as 1.3/μl blood has been used successfully. This is a point-of-care device that performs tests onsite within 40 minutes. About 80 cases can be performed per day. The result of the cases can be shared

through an internet system. Thus, case management becomes more efficient and effective [12]. Recently, a genome mining based identical multi-repeat sequences (IMRS) qPCR assay has been developed for diagnosis of malaria infection. This diagnostic method can detect very low level of parasitemia that cannot be detected by the routine 18S rRNA-based diagnostic system [13].

5. Tackling sub-microscopic and asymptomatic cases

In recent years, asymptomatic and sub-microscopic cases are reported from many endemic countries. In fact, these two aspects are non-synonymous. Sub-microscopic malaria cases present very low levels of parasitemia which generally missed in the routine microscopic examinations. Such cases may be symptomatic, and in most situations, these are asymptomatic cases. It has also been observed that in most high endemic areas asymptomatic cases with detectable levels of parasites do not show symptoms. This is because of a high immune status of the individual patients. It is suggested that such cases may be monitored under hospital supervision and clinical algorithms can be drawn to know more specific symptoms. Possibly such patients may show some kind of symptoms and may be on alternate days which are indicative of chronic malaria cases. Differential diagnosis of such cases becomes very difficult since they normally do not show any routine symptoms. However, experience clinicians can diagnose and successfully treat them with scheduled anti-malarials.

On the other hand, asymptomatic cases do not show presentable routine symptoms. Once proper diagnosis is confirmed treatment becomes very easy. In our experience, patients having malaria-like symptoms who could not be diagnosed with routine tests even with RDTs, had been treated for other diseases, mostly with antibiotics, but also with anti-tubercular therapy (ATT) for a long time even months. It has been observed that most antibiotics with quinoline molecules and ATT with rifampicin have anti-malarial properties. But these therapies cannot completely eliminate malarial parasites rather reduces the cure rate [14]. Such cases show sub-microscopic level of parasites. Normally these parasites do not show normal morphological features under microscopy. Only expert microscopists can identify such drug-affected parasites. In such cases, it may deem necessary first to stop all medicines and wait for the fever or fever-like symptoms to appear, then treat them with effective anti-malarials after expert microscopy. All these exercises should be done under medical supervision. The post response and relief from agony of such patients are remarkable.

Generally an important question is raised by most public health experts whether asymptomatic cases may cause potential risk of source of malaria transmission in endemic areas. In most endemic areas with high *P. falciparum* cases, residual load of gametocytes remain active in the blood circulation for a considerable period even after successful treatment, either with artemisinin-based combination therapy (ACT) or radical treatment with primaquine [1]. This can be solved with a simple *ex vivo* tests for detecting the presence of exflagellation. If this happens, it will indicate the potency of the gametocytes. This can be further extended to artificial membrane or direct feeding on patients (after obtaining human ethical approval) to *Anopheles stephensi* which will be kept at temperature of 28°C and 70–75% relative humidity (RH) in a controlled chamber for 7–8 days. Gut dissection on day 7 post-feeding will confirm the presence of oocysts. The presence of oocysts will indicate the potential threat of such gametocytes and their role in active transmission. It would be better to know the male and female gametocyte ratio before the experiment is performed. Generally 1 male to 3–5 female gametocytes sex ratio is found

in *P. falciparum* [15]. Post-treatment gametocytemia is commonly detected by a quantitative nucleic acid sequence-based amplification (QT-NASBA) method [16]. It is better to kill all the fed mosquitoes on day 8 post-feeding so that there will be no threat of accidental release of infected mosquitoes for possible malaria infections.

6. Treatment of malaria cases

Chloroquine the cheapest anti-malarial drug is no longer prescribed for the treatment of *P. falciparum* malaria cases. Even monotherapy with artemisinin is also not recommended. Currently different ACTs are prescribed for treatment of *P. falciparum* malaria including some *P. vivax* cases. The partner drugs are sulfadoxine-pyrimethamine, piperaquine, lumefantrine, pyrrolidine, etc. In India, chloroquine is still efficacious against *P. vivax* even in the presence of *Pvcrt-0* and *Pvmdr-1* mutations [17]. On the other hand, the presence of *kelch 13* (*k13*) mutations in *P. falciparum* is linked to artemisinin resistance. Recent report from eastern India indicated the presence of two mutations G625R and R539T in 5/72 *P. falciparum* cases treated with artemisinin that linked to its presence of resistance [18]. In Africa, where *P. falciparum* is predominant there is no sign of artemisinin resistance even with more than 200 non-synonymous *k13* mutations recorded. A recent report suggested that artemisinin resistance in a patient can be addressed by changing the partner drugs which is responding to the local parasites [19]. Such combination should be selected for *P. falciparum* treatment. Several studies indicated the absence of S769 N mutation in *Pf*ATPase6 gene responsible for artemisinin resistance [20]. Possibly this marker would be the better one for monitoring of artemisinin resistance in most malaria-endemic settings.

6.1 Primaquine and tefenoquine for radical treatment

Primaquine – an 8-aminoquinoline is used for radical cure. In case of *P. vivax* 15 mg per day for 14 days and for *P. falciparum* a single dose of 45 mg is administered for eliminating hypnozoites for the former and gametocytes for the later, respectively. Recently tefenoquine, another 8-aminoquioline, has been recommended. But both of these drugs may cause possible hemolysis in G6PD-deficient patients [21]. Attempts are being made to find newer molecules to address this issue. In this regard, Medicines for Malaria Venture (MMV) is playing a primary role [22].

7. Change in vector control strategy

There are 465 *Anopheles* mosquitoes in the world, of which many members have sibling species complexes. Approximately 70 of them are capable for human malaria transmission [23]. Application of public health insecticides is the main strategy for vector control. DDT is the main insecticide and is partially responsible for most malaria elimination in Europe and Americas along with general improvement of living standards, and an effective detection and treatment program. Other countries missed out this opportunity to achieve this feat. Prolongation of its use lead to the development of resistance in the mid-1970s and also recorded the highest number of malaria cases. Other insecticides namely malathion (organophosphorous) and subsequently synthetic pyrethroids (deltamethrin, alphacypermethrin, lambdacyhalothrin, cyfluthrin, etc.) are used in the program. In some endemic areas, triple resistance has been recorded against the main rural vector *An. culicifacies*. Currently long lasting insecticidal nets (LLINs) impregnated with synthetic

pyrethroids are widely used in the program. In general, behavioral changes of vector mosquitoes are a common phenomenon due to continuous use of IRS insecticides. This leads to outdoor resting and feeding behavior which are responsible for outdoor transmission. Some species change their biting time also, and thus becomes difficult in managing vector control operations [24].

7.1 Outdoor and residual transmission

Generally outdoor and residual transmissions are considered as the same phenomenon. But these are separate issues and would be dealt separately. Outdoor transmission occurs when local community engages on outdoor duties due to professional compulsion. This is most prevalent in forest fringe areas. For example, *An. dirus s.l*. is the most dominant species in Southeast Asia region. Here LLINs have very limited role. Many methods have been suggested, but none have been used for any practical purposes. Several traps have been developed in recent years; some are light-based, some CO_2- based, some octanol, commercial attractants based, and some with combination of all. Many experts recommend covering the whole body with proper clothing especially for security personnel, use of mosquito repellents and chemoprevention [1]. Recently Center for Disease control and Prevention (CDC) has approved the lemon eucalyptus oil for general use as mosquito repellent [25].

The most disturbing fact is that in most village settings human and cattle have mixed dwellings. This encourages the zoophagic mosquitoes to move from the bovine host to the humans. Here, a community-level action is needed. Experts recommend that all cattle dwellings should be located on the periphery of the village so there would be a spatial barrier between the foraging mosquitoes and humans. In this way, a strong zooprophylaxis would be established and direct human biting can be avoided [26].

7.2 Removing shrubs around houses

Outdoor transmission can be effectively contained when flowering shrubs around houses are removed. A study in Mali supports such concepts. The selected villages where flowering branches of invasive shrub *Prosopis juliflora* were removed experienced a 69.4% drop in *Anopheles* population density and a shifting of species composition [27].

7.3 Attractive toxic sugar bait (ATSB)

Like removing shrubs, ATSB is an alternate strategy to eliminate mosquitoes. Sugar bait of 10% sucrose mixed with 0.01% ivermectin soaked in sponge bait knocked down over 95% of *An. arabiensis* population [28]. But it requires community engagement for proper implementation [29].

Studies should be carried out to define the bionomics of local vectors. This will provide valuable information for planning proper vector control strategies. This should be an ongoing program. In the malaria elimination program, routine monitoring of vectors will allow appropriate decisions for effective control. Residual transmission is a resultant of presence of sub-microscopic level of malarial parasites in the community. This happens when intensive control measures overlook the residual presence of parasites. Such a situation happens when a type of complacency prevails and the surveillance system becomes fatigued. Many local-level focal outbreaks happen, and the public health response activities for vector control fail to decimate such foci [30]. It is, thus important to have a strict surveillance system in place to avoid such residual transmission and outbreaks.

7.4 Gene editing

The recent advances in genetic engineering technology of CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/Cas9), a system targets specific stretches of DNA and edit genomes at specific locations. This tool of gene editing/drive technology can revolutionize malaria elimination efforts by identifying and targeting the local vectors. The aim should be to create transgenic mosquitoes that will not be able to carry the malaria parasites. Some success to create transgenic species of the main malaria vector of African countries, *An. Gambiae,* has been achieved [31]. Gene-driven mosquitoes do not follow the Mendelian law of inheritance. This technology can be effectively applied to eliminate the invasive and endemic species to maintain the conservation of biodiversity [1].

7.5 Fungal application for vector control

Entomopathogenic transgenic fungus *Metarhizium pingshaense* expressing the spider neurotoxin hybrid (met-hybrid) killed 99% of the mosquito population in a controlled trial in Burkina Faso. The study was conducted in a trial village of 600 square meters area or `mosquito sphere'. The test mosquitoes were killed within 45 days. The researchers hope to find out a new tool to eliminate malaria when insecticide resistance is a major problem [32]. Before this field trial, extensive laboratory experiments were carried out on the two important malaria species *An. coluzzii* and *An. gambiae s.l* [33].

7.6 Bioenvironmental control of disease vectors

This is a holistic approach of vector control practiced in the beginning of the 20th century. The main aim of this approach is source reduction of larval breeding habitats. In other words, larval source management is the key strategy that mitigates challenges of larval control. Minor engineering, filling up of pools and puddles near human habitats, and biological control are some methods of this strategy. Since the mid-1980s the ICMR- National Institute of Malaria Research, New Delhi, India has made pioneering work on this front with great successes. In this strategy, health education and community engagement is an integral part [34].

7.7 Paratransgenesis

Paratransgenesis is a process by which the genetically modified symbionts from a target insect express molecules within the vector that show refraction to pathogens they transmit. This is a novel approach, now used for the control of malaria, trypanosomiasis and dengue. Recently, for the first time, we found *Veillonella* sp. in the gut of *An. stephensi* which may play an important role in paratransgenesis. A diverse microbial community was recorded in the salivary glands in *An. culicifacies*—the main malaria vector in rural India [35]. However, this strategy has to go a long way for the involvement of gene modification technology [36].

7.8 Jhum cultivation

Jhum or jhoom cultivation or slash and burn cultivation is a common practice of cultivation among tribal populations of northeast India and also in some hilly districts of Bangladesh. This practice of cultivation is linked with malaria transmission [37]. Besides using LLINs, it is important to find the main breeding habitats of vector species mainly *An. dirus* s.l. during the dry season. Control of such vector

species can be obtained with the application of larvivorous fish mainly in wells which act as the ecological niche [1]. Further research may find a new way of intervention strategies.

7.9 Intervention with endectocide

Use of endectocide namely ivermectin in mass drug administration program is a potential intervention strategy to reduce residual transmission of malaria. This drug is used in elimination of human lymphatic filariasis and onchocerciasis programs. This old drug was developed from a natural substance by Satoshi Omura from Kitasato Institute, Japan and was further developed by William Campbell from Merck Lab originally for use in veterinary health program. But its use in onchocerciasis program was recognized for Nobel Prize for Physiology or Medicine in 2015. This is used as a potential tool in vector control program when anti-mosquito activities were recognized. Twenty-three projects under Malaria Elimination Science Alliance (MESA) are underway and their results will be available by 2020 that will be able to take a decision on the future use of endectocides in malaria control operations [38]. Besides the mentioned diseases, recent publication has given an overview on the use of ivermectin for various neglected tropical diseases (NTDs) that include ascariasis, trichuriasis, strongyloidiasis, loiasis (human *Loa loa*) and mansonelliasis [39]. However, adverse effects of ivermectin on local environment have been reported. Certain effects on dung beetles *Caccobius jessoensis, Copris ochus* and *Co. acutidens* have been reported in Japan [40].

7.10 Improved method of mosquito culture

It is important to grow fit and healthy mosquitoes under laboratory conditions for anyone working on them. Various methods of culturing of several species of mosquitoes are available. Most of malaria research is linked with several species *Anopheles* mosquitoes. Of them *An. stephensi* is widely used for its easy adaptation under laboratory conditions. Routine procedures were followed to colonize this species [41–43]. But some modifications in the routine methods gave a significant result in mass rearing of *An. stephensi* [44]:

i. Larval and adult rooms were maintained separately.

ii. For larval room RH was maintained at 45–50%, while temperature at 28°C.

iii. The adult room was maintained 12 hour dark and light periods; temperature at 28°C, and RH at 70–75%. Strict monitoring of temperature and humidity was maintained.

iv. The eggs laid by adult females in containers were bleached with freshly prepared 1% sodium hypochlorite solution for 1 minute under controlled pressure in a vacuum pump. For all purposes reverse osmosis (RO) water was used in the laboratory and pH of the water maintained around 7.00. About 250 bleached eggs were placed in especially designed white polypropylene trays (Polylab®, India, 375 × 300 × 75 mm^3) within a triangle made from disposable small straight straw pipes.

v. First instar larvae were emerged within 24 hours after bleaching. No food was given in the next 24 hours of hatching. Brewer's yeast powder dissolved in RO water was added in the tray water (300 ml) for the next 2 days.

vi. Subsequently a special larval food (Brewer's yeast and dog food at 70:30 ratio) were given daily for a specific amount depending on the stage of the larvae. Special scoop measuring 5–10 gm larval food in each tray depending on the larval age was provided. Pedigree brand dog food (chicken and vegetable mixed) were powered in a small grinder and mixed with Brewer's yeast. This formulation was different from earlier report. Pupae were visible from day 8 onwards.

vii. All pupae were harvested that developed up to day 12, and rest larvae were discarded following proper procedure. The pupae were bleached with freshly prepared 1% sodium hypochlorite solution for 1 minute, and placed in mosquito cages for emergence in to adults.

viii. The adult mosquitoes were provided with a mixture of 8% sucrose, 2% glucose mixed with 3% multivitamin kid syrup (Polybion® L, Merck Limited, India).

ix. Strict operational procedures were followed for maintaining sterile conditions for all steps.

x. This modified protocol would be very useful for mosquito research.

8. Discussion

The very decision to go for malaria elimination with the existing tools and intervention strategies was very challenging. Many initiatives have been undertaken. The President's Malaria Initiative (PMI) in 2005 to Malaria Elimination Research Alliance—India (MERA—India) in 2019 are all to accelerate the process of malaria elimination in all the high burden areas especially in Africa, Mekong Delta region and India, respectively [1]. A special initiative by the WHO in 2016, 21 endemic countries was identified for malaria elimination by 2020 i.e. E-2020 initiative [1]. In this direction zero malaria cases were reported from China and El Salvador in 2017. In 2018, Paraguay was certified as malaria free by the WHO. In 2019, Algeria achieved this goal. Three countries—the Islamic Republic of Iran, Malaysia and Timor-Leste—achieved zero malaria cases in 2018. In 2016, Sri Lanka achieved zero malaria certification, but in 2018 local transmission was reported from a case imported from India. But the local authorities immediately took action. Such quick public health response is required to maintain no transmission threat [45].

Vector control operations mainly rely on insecticide sprays. In most situations the spray operations are carried out by the local contract workers not properly trained; the spray equipments also not maintained properly; pressure not maintained while spraying; patchy and low coverage spraying; late supply of materials that force to defer the spray schedule; lack of supervision, low quality materials, improper storing warehouse, etc. All these confounding factors are responsible for continuation of transmission. Vector behavior also changes for prolonged insecticidal mode of operations [24].

Assessment of two important parameters—human blood index (HBI) and entomological inoculation rate (EIR) of important local vectors enable workers to develop an effective vector management. The global map of HBI of important malaria vectors revealed the highest index exists in African countries [26]. This indicates low ratio between human and animal populations forcing the vector mosquitoes feeding on human host. Emphasis on encouraging the local community to

grow animals should be given priority which will change the transmission potential if the local vectors are primarily zoophagic [1].

Bioenvironmental control of vector populations is a part of the integrated vector management (IVM) concept. In this process control of other vectors of related diseases can also be achieved. *Swachh Bharat Abhiyan/Mission* (Clean India Movement) can be linked in such activity to gain better results. Larval Source Management using larvivorous fish is one of the intervention tools under IVM. This strategy is very effective when implemented at grass root levels with proper supervision and monitoring. Little or no serious emphasis has been given to this strategy. In many situations, it is overlooked and demeaned compared to other methods, mostly insecticides are available in hand. In fact, it works as a `social vaccine'. Globally, around 300 fish species have been identified as larvivorous nature. Two Poeciliid fish *Poecilia reticulata* and *Gambusia affinis* are widely used. The former is best for wells and other confined water bodies, while the later one is best for ponds and lakes [1]. There are many reports on adverse effects of the non-native fish on the local fish, but recent meta-analysis does not support this theory [46].

A new anti-larval product Aquatain AMF™ is available for anti-larval operation. It is a silicon-bases liquid (polydimethylsilicone—PDMS) formulation that forms a very thin film on standing water surface causing physical cover over its entire extension. The mosquito larvae are killed due to physical and mechanical action. There does not seem to develop insect resistance to this technique [47].

Community engagement through health education and empowering local policymakers help in taking appropriate decisions in vector control. Engaging some local school children as volunteers will laterally support such program [48]. In India, every year June is observed as anti-malaria month. Several activities highlighting the program on malaria are displayed. Local administration also actively takes part and makes some decisive actions.

Two vaccine candidates RTS, S/AS01 (TRADE NAME Mosquirix) and PfSPZ are under trial even though their protection level is moderately low. The former is undergoing phase 3 trial in children in three African countries. Possibly this will help reducing child mortality which is a major concern in most of African countries [1].

India contributes most of *P. vivax* malaria cases outside the high burden districts where *P. falciparum* is most dominant. Recent studies also indicate the presence of *P. ovale curtisi* and *P. ovale wallikeri*. *P. malariae* is also co-existent in the high burden tribal districts. All these are possible due to application of molecular diagnostic techniques [49]. Expert recommended genome mining studies which will unravel some underlying issues of malaria epidemiology [13]. Moreover, molecular DNA bar coding of parasites will also help in identifying their actual geographic origin [50]. This will surely assist in managing the drug resistance problem.

The recent identification of *P. knowlesi* as a human malaria with a zoonotic source prevalent in Malaysia and Southeast Asian countries may be very important [51]. Another disturbing factor is recent discovery of *P. falciparum* infection in two common Indian non-human primates *Macaca mulatta* and *M. radiata* [52]. This matter should be taken seriously when malaria elimination is underway. A distinct barrier between human and animal is essential to the ongoing elimination efforts.

9. Conclusion

There is a great movement and opportunity for malaria elimination globally. Many countries have already achieved this goal. The most success part of this movement is reporting zero malaria cases in China in 2017 and 2018, and preparing for malaria elimination certification in 2020. China made elaborate arrangements

with full financial, administrative and operational commitment. This indicates that malaria elimination is possible with the existing tools and strategies. In the present situation dependence of insecticide should be minimized and promote other alternate strategies to avert the issue of insecticide resistance. India is making all efforts for a successful mission. Reduction of malaria cases and related deaths in 2017 is an indication. This was mainly the efforts made in eight most high burden districts in Odisha with the implementation of a program called *Durgama Anchalare Malaria Nirakaran* (DAMaN malaria elimination in inaccessible areas). Such initiatives should be implemented in other areas also [1].

In the elimination phase, there is a need to strengthen the existing public health system. The local health system should be quick and responsive to any malaria-related fevers. Routine in-house training, workshops should be conducted to maintain the malaria elimination momentum. A recent 5 days WHO workshop for South-East Asia Region (SEAR) recommended the global vector control response (GVCR). Entomologists from 11 countries participated in this workshop. Detailed reviews were exercised to find out the ongoing program implementation in each country. Such state-level workshops would help in malaria elimination and also other vector borne diseases [53].

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Conflict of interest

The authors declare no conflict of interest.

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