Malaria control initiatives that have the potential to be gamechangers in India's quest for malaria elimination

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The Lancet Regional Health - Southeast Asia 2022;2: 100009
https://doi.org/10.1016/j.lansea.2022.04.005

Summary

Malaria continues to have devastating effect on people's lives especially in developing countries. India is slated for malaria elimination by 2030. Though India has sustained a decline in malaria burden at the national level the epidemiological picture remains heterogenous. India's road to malaria elimination plan is riddled with many roadblocks. Major challenges include insufficient surveillance, slow and aggregated data reporting especially in exigent situations like cross-border areas and vulnerable high-risk groups. More than half of total malaria cases were due to *Plasmodium vivax* (*P. vivax*) in India as reported by national malaria control programme in 2019. This translates into substantial burden of *P. vivax* malaria in absolute numbers. *P. vivax* malaria, which is difficult to resolve as compared to other species, poses a threat to India's elimination plans by virtue of its tendency to develop hypnozoites, due to poor compliance to primaquine (PQ), due to host factors like G 6 PD deficiency and other genes that affect PQ metabolism. Also, India's malaria endemic areas largely coincide geographically with tribal regions which are poor in healthcare infrastructure. The tribal population disproportionately bears a huge burden of malaria. They also harbour more G6PD deficient individuals than non-tribal regions. Therefore, in addition to inadequate diagnostic facilities (for both malaria and G6PD testing) these remote rural and tribal communities suffer from lack of timely treatment, incomplete radical treatment due to poor compliance and thus repeated episodes of *P. vivax* due to relapses and/or reinfections. Another challenge is that the the current diagnostic tools in the national programme in India and other countries are mostly available only via the programme and are able to detect patent infections on the whole. These therefore miss low-density infections which are another major limitation for their use in malaria endemic countries. Drug and insecticide resistance need to be constantly monitored as they have direct impact on the efficacy of the current tools. Need for better vector control products for the diverse entomological requirements is also felt. India is the second most populous country in the world with majority of its population at risk of malaria. Despite many agencies (government and non-government) working in the field of malaria, there needs to be more synergy at the local or central level for malaria control. Here, we have proposed solutions for specific facets of the malaria programme. Surveillance, data visualization and analysis can all be supported through over the counter availability of rapid diagnostics, adoption of molecular tools like PCR (requiring additional infrastructure and expertise), mobile applications for data capture and use of malaria data dashboard. Management could be augmented by inclusion of tafenoquine for treatment of *P. vivax* malaria with a companion point-of care diagnostic which has been developed to assess G6PD enzyme activity. A switchover to artemether-lumefantrine for the entire country can also be considered. Vector control can be strengthened by commercial availability of insecticidal bednets and exploration of novel vector control tools like ivermectin. Lastly, enhancing synergy amongst various stakeholders would also catalyze the malaria elimination plans.

Funding The authors have received no funding for this paper.

Keywords: Malaria; Elimination; Gamechanger; India; Interventions

Introduction

Malaria is a vector borne infection of public health significance which led to ~241 million malaria cases and ~627000 fatalities globally in 2020 as per World Malaria Report (WMR) 2021.[1] The burden is predominantly borne by African countries (95%) and brunt of mortality is caused by *Plasmodium falciparum* in

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children younger than five years (~ 77%) - majorly in Africa (~ 96%). *Plasmodium vivax* contributed 4.5 million cases (2%) to total malaria cases mostly from Asia. Year 2020 witnessed a rise in malaria case incidence and deaths owing to the disruptions in services due to Covid-19 pandemic.[1] Out of the global malaria caseload, ~ 2% is borne by South East Asian countries. India contributed 83% of estimated malaria cases and 82% of malaria deaths in SEAR in 2020 according to WMR 2021. The World Health Organization on 6 October, 2021 recommended RTS, AS/01 vaccine against *P. falciparum* malaria in young children for moderate to high transmission settings, and this aims at curtailing hospitalizations due to severe malaria.[1] However, India may not be a suitable candidate for the roll-out of RTS, AS/01. For its consideration, the following factors are important: India as per national data is a very low transmission setting with an overall API of less than 1 since 2012 (API < 100 or 0%–1% prevalence of *P. falciparum* malaria in 2–10 year old children) with few deaths i.e., 77 deaths in 2019. For vaccine deployment, significant public health impact and cost-effectiveness is projected for moderate to high transmission areas, which again India is not. In addition, *P. falciparum* vaccine will not be able to reduce *P. vivax* malaria burden.[2]

The World Health Organization (WHO) launched Global Technical Strategy for Malaria 2016–2030 with the vision to accelerate malaria elimination efforts and assist countries, including India, in achieving malaria elimination by 2030. As malaria control efforts were underway, it was realised that it was important to consolidate the gains made in malaria control so far. The currently available tools such as antimalarials and vector control products/strategies could become ineffective at some point of time. Threat of drug resistance, especially Artemisinin combination therapy (ACT) resistance, prompted the WHO and global malaria expert community to shift gears from malaria control to elimination. Aligning with the WHO goal, and endorsing the Region's Malaria Elimination Roadmap by Asia Pacific Leaders Malaria Alliance, India too strategized its national control programme towards elimination and launched National Framework of Malaria Elimination 2016–2030 (NFME). Thus, India is slated for malaria elimination by 2030. India has sustained an annual incidence of less than 1 per 1000 population under surveillance from 2012 onwards.[3] In 2020 national malaria programme reported ~ 0.18 million cases and 93 deaths.[4] The strategies and activities under elimination have borne fruit. According to the World Malaria Report (WMR) 2020, India reported a decline in 2019 of ~ 17.6% as compared to 2018.[5] As per national malaria control programme too a decline in malaria cases and deaths has been observed. With the launch of NFME in 2016, the Government of India strategized its malaria control efforts to elimination activities and made special efforts in the provision of microscopes, rapid diagnostics and long lasting insecticidal nets. This led to a decline of 27.7% in cases (844,558 in 2017) and 49.5% in deaths (194 in 2017) from 2015 to 2017.[3] The burden has further declined to 338,494 cases and 77 deaths in 2019 and to 158,326 cases and 80 deaths in 2021 despite disruptions by Covid-19 (as per NVBDCP)[4] While India has managed to sustain the decline in the overall burden (as per WHO estimates and country's own reported numbers), the occurrence of malaria is heterogeneous and its elimination plans are fraught with many challenges.

India's malaria elimination challenges and possible gamechanger solutions

Despite decline in numbers, it is recognized that there are several challenges to India's malaria elimination plans, as also experienced in the past.[6–8] Malaria, known as 'king of diseases' caused enormous morbidity (75 million cases) and mortality (0.8 million deaths) in India in the 1950s. The devastating effects of malaria on India impacted the economic growth of the country as well. With the successful trials of DDT, National Malaria Control Programme was launched in 1953 (keeping urban malaria out of its ambit) and converted to National Malaria Eradication Programme in 1958. The switch to eradication was aimed at achieving the extermination of malaria before development of wide scale insecticide resistance to DDT. This was indeed a huge success, with 49,151 recorded cases in 1961, the lowest thus far. A decade of successful malaria control paved the way for economic growth and the country witnessed green revolution, industrialization and all round development. However, this success was short-lived as it led to complacency, diversion of resources, and diminished expertise in malaria control. Coupled with resistance to DDT and chloroquine, these factors contributed to full-fledged resurgence of malaria in 1976, with cases shooting to 6.45 million. In 1977, the government reverted to control strategy. Targeted programme to contain *P. falciparum* malaria was launched but later abandoned as new areas continued to be infested by drug resistant *P. falciparum* malaria. The pattern of *P. vivax* and *P. falciparum* varied with time and seasons. *P. vivax* accounted for 80–85% cases in 1970s and was reduced to 50% by 2010, the other 50% was contributed by *P. falciparum* which was largely resistant to chloroquine.[9] Chloroquine resistant *P. falciparum* malaria was reported for the first time in 1973 from Assam, and it was monitored closely by creating regional monitoring teams to conduct therapeutic efficacy studies from 1978 onwards. The first drug policy was formulated in 1982. Areas were stratified according to the susceptibility/resistance status and proportion of *P. falciparum* cases. Policy changes in the diagnosis/management and drug combinations to be used were brought in at different time points in alignment with

WHO recommendations and local epidemiological evidence.[10]

There is a possibility that similar challenges as above can reappear and mar the success of the national programme. The initial success of the national control programme, which heavily relied on DDT spraying, led to de-prioritization by programme managers, implementers, field workers and community. This became detrimental to the malaria elimination programme and the country was forced to revert to control mode again. The declining expertise also dealt a blow to the elimination programme. Despite evidence on emerging drug resistance in the 1970s and 1980s, the changes in drug policy did not keep pace with the therapeutic responses and evolving epidemiological situation.[10]

The national programme may once again face the same challenges. When malaria cases and deaths plummet, other diseases and health conditions may take priority. Currently used ACT therapies are effective but it is important not to be complacent and to maintain high vigil on the efficacy trends of the different ACTs used in the country. The declining expertise in health personnel, lack of trained microscopists and entomologists, dilution of verticality of the national programme, other responsibilities of grassroot workers and health care staff can seriously impede the path to success. Support from international and national donor organizations may dry up once we achieve elimination. Drug resistant and vector resistance are looming threats on the malaria control efforts. Achieving malaria elimination is a race against time and it is important that we stay on the delineated timelines of malaria elimination roadmap and achieve elimination as planned. Achievement and sustenance of malaria elimination will require continuous political will, funds and commitment from all quarters.

Past experiences point out the significance of taking cognizance of these challenges and addressing them most prudently lest we fail in our efforts and miss the goal of 2030. Some of the important impediments are briefly described below. To circumvent some of these challenges, we propose a list (not exhaustive) of solutions/tools/strategies which have the potential to act as gamechangers to support or enhance the chances of achieving malaria elimination well on time. The proposed solutions in this article have been developed, deliberated and technically assessed by Indian Council of Medical Research's National Institute of Malaria Research. The challenges are many and we have attempted to address some of them. These proposed initiatives are opportunities to augment our capacities to detect, report, act, prevent and respond more effectively to malaria:

Challenge 1: surveillance

Inadequate, incomplete, paper-based aggregated surveillance, especially in vulnerable groups: India's surveillance system of active and passive case detection is understood to be weak with the ability to capture ~8% of the actual burden (WMR 2018).[11] This is due to non-inclusion of private sector, of government sector other than public health programme, of semi-government sector, of missionary hospitals etc in the reporting system despite malaria being made notifiable in 31 states of India.[12] Role of private sector in healthcare is of paramount importance. As per National Health Accounts (2017–18), expenditure on health in India is met majorly by the communities themselves via out-of-pocket expenses which accumulates to ~1.6% of GDP. Government expenditure share was ~40.8% as compared to ~48.8% by the communities themselves.[13] National sample survey (NSS) estimated (2014–15) that ~75% of the out-patient care and ~62% of in-patient care was rendered by private healthcare providers.[14] A study in the malarious area of Mizoram revealed that over 60% respondents sought healthcare for febrile illnesses in non-government facilities/providers.[15] Singh et al 2017 reported similar trends in preference of communities to seek malaria healthcare from private sector (65%) as compared to government health providers (35%).[16]

India is the second most populous country in the world and is heterogenous socio-culturally, demographically, economically and in ethnicities. This diversity presents as a special challenge to the healthcare systems of the country. The healthcare needs of the people are addressed by public facilities (paid by government) and by the private sector (paid by individuals or insurance companies). The multiple healthcare partners that address burden of malaria add complexity to the control and elimination efforts. Besides the public health facilities at different levels in the form of district hospitals (tertiary), community health centres (secondary) and primary health centres (primary), there are other government bodies which diagnose and manage malaria such as medical colleges, industries, railways, army, tea plantations, mines etc. In private health care sector there are several actors such as large corporate hospitals, private hospitals, nursing homes and clinics, health facilities by NGOs and missionaries, pharmacies and chemists, doctors practising at home, traditional/faith healers, informal volunteers, untrained providers and gypsies. This large variety of healthcare providers cater to malaria affected communities but the cases are not always reported to the national malaria control programme thus undermining the existing surveillance system. There is also no cross-communication between the different partners and stakeholders and this poses a challenge to the malaria elimination plans of India. Multiplicity of partners, working in silos and in absence of one digital single platform makes efficient data reporting and data utilization nearly impossible.[12]

The current surveillance system continues to be aggregated, paper-based and restricted to a limited number of public healthcare facilities. The need of the

hour is to modernize the existing sluggish surveillance and data reporting systems into a near-time digital data collection (for eg. mobile applications) with platforms like dashboards where data could be uploaded. Provision of such digital systems will also encourage and facilitate the private sector health care providers to share malaria case numbers with the government. A similar web enabled patient management system of Ministry of Health and Family Welfare for tuberculosis (targeted for elimination by 2025), called Nikshay, is already functional across India. The portal is being used to report, register, manage and monitor tuberculosis patients by public and private sector in India. The portal facilitates in pooling various datasets into the National TB Surveillance System.[17]

The surveillance system in India is an underperforming system leading to delays in detection of outbreaks and hotspots, delays in data visualization, and thus delayed analysis and decision making. The data aggregation also results in loss of granularity below district level. This leads to a failure or long delays in detection of hotspots and hence a poor response towards mitigation of outbreaks situation. Alert epidemiological systems that can be more real-time and granular are missing in India at present.[18] Under the current surveillance system, either active or passive, symptomatic febrile cases are tested by rapid diagnostics or microscopy. However, there is a substantial burden of malaria cases who do not have overt symptoms of malaria and thus they escape detection and hence treatment. Submicroscopic infections are typically those which are below the threshold levels of detection by routine malaria diagnostics. Studies have suggested that the malarious regions in India have as high as 70–80% of asymptomatic infections and 30–45% are sub-patent infections.[19] These are known to contribute to malaria transmission.[20] As the routine diagnostics are not effective tools, use of more sensitive molecular tools is needed in the national programme at least at the district level (tertiary care level). Due to infrequent use of sensitive molecular tools since it is not in national policy, asymptomatic and sub-patent malaria infections are left undetected and hence contribute to unabated malaria transmission.

Vulnerable and high risk groups: Among the vulnerable groups, the forest dwellers, antenatal women, indigenous/urban slum populations, migrants and mobile populations are insufficiently captured in the surveillance system This is a crucial missing link in the current surveillance systems. This is evident by the fact that ~6.6% of population living in forested areas disproportionately contributes to ~ 21% of cases and ~ 53% of deaths due to malaria.[19] According to an analysis done by our group, the malaria incidence in the forested areas was four fold higher as compared to non-forested areas in 2000 and three times in 2019.[19] The more malignant species of *Plasmodium falciparum* is the predominant one in forest regions and drug/insecticide resistance are major threats. These forest groups are not completely included in routine surveillance. The forest dwellers and indigenous communities live mostly in inaccessible, hard to reach, under-served, remote and rural interiors which are often impenetrable by the routine healthcare system especially during malaria transmission periods. The urban marginalized and migratory population are also typically out of the ambit of local community database and hence are not beneficiaries of healthcare services. Thus, these vulnerable groups remain invisible to the healthcare system. Surveillance mechanisms need to target at-risk populations ("hot pops") like the migrant and mobile populations, and regions ("hot spots") with persistent malaria which despite deployment of effective tools continue to maintain malaria endemicity and fail to decimate malaria foci.[21] Similarly, pregnancy poses as an additional risk to the women living in endemic areas in a developing country like India. A review carried out on the caseload of malaria in pregnancy has revealed malaria in the range of 10-30%. Altered immune status, susceptibility to severe *P. falciparum* malaria, placental malaria, first pregnancy, belonging to poor socio-economic strata with limited access to quality healthcare etc all these expose the pregnant women to increased chances of complications. Strengthening surveillance by integrating intermittent screening and treatment with the routine antenatal care has already been proposed by authors.[22] Following mothers post-delivery for administering of radical cure for *P. vivax* malaria is also important but largely neglected under the national programme.[22] These population groups and endemic areas need robust and agile surveillance systems which can detect and manage malaria cases proactively.

Cross-border malaria tracking: Among the WHO regions, SEAR is the only region which is on track in its progress towards malaria elimination. In 2020, nine South East Asian countries were malaria endemic. *P. falciparum* was the predominant species and *P. vivax* was responsible for one-third of cases. Sri Lanka is malaria free since 2016, Bhutan and Nepal, Timor-Leste have not experienced any mortality since past few years.[1] Cross-border malaria is of critical importance in checking any enhanced threat to and from any neighbouring country. Monitoring of international borders to prevent exchange of parasites (via movement of people) and vectors is essential to curtail transmission of malaria especially for the countries which are nearing malaria elimination. In an attempt to study Indo-Bhutan malaria scenario, key foci areas (Udalguri, Kokrajhar, Chirang and West Kameng) were delineated and factors like epidemiological data, levels of surveillance, climatic conditions, movement of people were analysed. Joint epidemiological and entomological surveillance needs were once again highlighted. Transparent and near real time data sharing across the countries is of paramount

importance to address the complex issue of cross border malaria.[23] However, this is not being actively pursued currently at the India's international border areas. Some efforts were made in the past by WHO to ramp up monitoring at Indo-Bhutan border but concrete steps could not be taken as yet.

Possible solutions to challenge 1: surveillance

1. *FeverTracker App*: As the malaria incidence plummets in India, it is time that India transitions from conventionally collected and aggregated data to digital, near real-time data collection and collation. One such tool is 'FeverTracker', a mobile application which has been highlighted by National Institute of Malaria Research in collaboration with North Eastern Space Application Centre, Meghalaya, and ICMR-Regional Medical Research Centre, Dibrugarh, India. This tool is envisaged to replace the paper based surveillance with digital surveillance reporting with near real time functions at district/block level. Utilizing Geographical Information System (GIS) and web application messages and further instructions can be issued to district and state level authorities in real time. The app is user friendly and can be used at the level of grassroot workers for malaria surveillance as well as by the community itself thus supplementing each other.[24] The FeverTracker app is being used by the Government of Tripura in the northeast of India.

Malaria DashBoard: We have taken a step ahead in modernization of our surveillance systems to empower the national programme with a digital dashboard for integrated data collation, visualization and analysis.[25] The National Institute of Malaria Research has developed **M**alaria **D**ash**b**oard (MDB) by utilizing district level data shared by national malaria programme from 2000–2019. It is an application that works in both modes of online and offline. The input data source is via MS Excel file and MDB yields an agile and interactive epidemiological analysis of malaria data. MDB can prove to be a very useful digital tool for decoding the malaria epidemiological situation and tailoring our strategies accordingly. Huge data generated by the national programme at national, state and district level on numerous parameters of malaria viz number of slides/RDT examined, confirmed cases, species, fatalities has been converted to an interactive, user friendly, integrated, intuitive and flexible digital platform that facilitates easy data visualization and analysis.[26] This digital platform can also be easily transformed to incorporate data from other healthcare providers also it can expand to include data on vector prevalence, drug and insecticide resistance and other parameters. The shift from paper based aggregated data to digital platforms will revolutionize the way are data visualised, interpreted and used for decision making.

2. *Malaria card:* Understanding the vast differences in socio-economic status, education, accessibility, ethnic diversity and several other socio-ecological indicators among Indian masses, uniform adoption of digital tools may be difficult. Hence, to complement it we also proposed a simple paper 'malaria card' for health and epidemiological record keeping of episodes of malaria, species and co-morbidities, G6PD deficiency status and treatments given. The malaria card is envisaged to be used by community health workers like Accredited Social Health Activist (ASHA) and Auxillary Nurse Midwife (ANM) during their routine surveillance (passive or active). Once filled, the cards would be given to the community to use just like immunization cards for their children. We do not anticipate that entering/maintaining the record of malaria cases in form of 'malaria card' will increase the burden of the grassroot workers like ASHA. The information to be filled in the malaria card, though pertinent, is simplistic and minimal. She already fills these details in her register, it will not be time/effort consuming for her to enter the details of malaria detection and treatment on the card. Moreover, certain entries are pictorial and hence can be promptly filled. The malaria card would go a long way in empowering the malaria endemic population to maintain a record of the episodes they suffer and also in assisting healthcare workers in tracking these patients.[27]

3. *Integration of three eliminable diseases:* India is looking forward to elimination of other two parasitic vector borne infections i.e., lymphatic filariasis and visceral leishmaniasis. There are co-endemic areas where the two/three diseases overlap since the ecological and sociological vulnerabilities remain the same. In 197 districts of India any of the two diseases and in 25 districts all three diseases co-exist. Currently, the National Centre of Vector Borne Diseases is responsible for the control programme of six vector borne diseases, malaria, lymphatic filariasis, visceral leishmaniasis, dengue, chikungunya and Japanese Encephalitis in a vertical and independent fashion. There is no cross talk among the control programmes of these individual diseases. As the three parasitic diseases are in elimination phase, the burden of the three diseases has plummeted in the past decade. It would be more cost effective and resource efficient if the control programmes are unified as one single programme. Though the current policy still views them as separate programmes horizontalization of the programmes with the general health services is the future call for these diseases. It will be pragmatic to have a joint surveillance programme for the three diseases as they share most of the health workforce at all levels and have similar mechanisms of active and passive case detection, reporting and data collation. Integration of the three control programmes has been proposed by the authors[28]

Challenge 2: *P. vivax* malaria

Incomplete resolution of P. vivax: India reported ~ 68 K cases of *P. vivax* malaria (36% of total malaria) in

2020.[4] Besides the blood stage infection, *P. vivax* has the peculiar feature of latent hypnozoites which get activated to initiate a fresh onslaught of red blood cell infection. The recommended radical treatment of *P. vivax* malaria to clear hypnozoites is a 14-day regime of primaquine (PQ). However, there is poor compliance by the communities and there is no mechanism of ensuring PQ compliance in the form of directly observed treatment. The prevalence of G6PD deficiency disorder has been reported from 0.8% to 6.3% with a prevalence of 1.9% at the national level.[29] PQ is contraindicated in pregnant and lactating women and thus puts them at risk of relapses. In addition to inadequate G6PD testing facilities, the burden of asymptomatic *P. vivax* and its relapses, the inadequately mapped prevalence of CYP2D6*10 allele, SNPs in cytochrome P450 NADPH: oxidoreductase (CPR) and monoamine oxidase (MAO) in Indian populations all together complicate PQ efficacy. These are thus are some significant challenges to satisfactory redressal of *P. vivax* malaria in India.[30]

Possible solutions to challenge 2: *P. vivax* malaria

Deployment of tafenoquine after due consideration: India shoulders substantial *P. vivax* malaria burden globally. It is acknowledged that *Plasmodium vivax* will be more difficult to eliminate than *Plasmodium falciparum*. To circumvent the limitations of poor PQ compliance to regime of 14 days, we propose deployment of tafenoquine with the companion G6PD point of care diagnostic after due regulatory approvals in India. Tafenoquine is a robust alternative to PQ as a hypnozoiticidal drug and India must consider it in due course of time[31] though there are certain limitations to the use of the drug.

Challenge 3: diagnostics

Limited access to diagnostics and lack of sensitive methods: Malaria diagnosis predominantly is facility based and/or is dependent on healthcare worker majorly via rapid diagnostic kits and microscopy. Private practitioners (trained and untrained) may be able to purchase the rapid diagnostic tests but these are not available for the communities to purchase and use as commonly as blood sugar testing devices, urine pregnancy kits, pulse oximeters etc. The limited access to malaria diagnostics to communities thus leads to delays in case identification and treatment - indirectly leading to Backspace continued malaria transmission.

The recommended diagnostic methods of rapid diagnostic tests and light microscopy are based on the premise of detecting patent infections. However, these diagnostic methods miss and sometimes misdiagnose sub-microscopic and mixed parasite infections. Malarious regions in India have reported 70–80% of asymptomatic infections and 30–45% sub-patent infections which thus go undetected by the use of currently used diagnostics.[32] An additional challenge is the inability of HRP2 based RDTs to detect *P. falciparum* with HRP2 and HRP3 deletions. According to a study conducted in 16 sites among eight malaria endemic states i.e., Chhattisgarh, Gujarat, Jharkhand, Maharashtra, Madhya Pradesh, Rajasthan, Odisha and Tripura the prevalence of *P. falciparum* with HRP2 and HRP3 genes deletions ranged from 0–8%.[33]

Unknown burden of neglected species owing to lack of right diagnostic tools: Species other than *P. falciparum* and *P. vivax* such as *P. malariae* (Pm) and *P. ovale* (Po) also exert significant burden in India but are missed, understudied and go unaccounted for. States like Tripura have reported mixed infections of Pm and Pf and other areas of NER (North East Region) like Assam and Arunachal Pradesh have also reported mono infections of Pm and Po. These can act as a deterrent to malaria elimination plans of India.[34]

Possible solutions challenge 3: diagnostics

(a) *Market availability of RDTs will enhance access:* At this juncture of malaria elimination, India should explore new channels of provision of quality assured RDTs other than via the national malaria programme. This will ensure timely confirmatory diagnosis even in peripheral settings. Authors have proposed availability of RDTs to private practitioners, drug stores and pharmacies after certain training in dispensing the tests and reporting the positive cases to the health authorities as has been done in other South Asian countries. It is important that government recognizes the presence and contribution of private sector in healthcare of population and includes them in the national programme.[35]

(b) *Adoption of molecular tools in routine diagnosis:* Both RDTs and microscopy suffer from widely known limitations and hence a case for adoption of molecular tools such as PCR and others in routine malaria diagnosis for confirmation at district level was made recently. Molecular tools are sensitive in detecting sub-patent infections, non-Pf/Pv species, mixed infections, detection of peripheral parasitemia placental malaria and gametocytes. Molecular tools like Polymerase Chain Reaction (PCR), Loop-mediated isothermal amplification (LAMP) and other platforms can be brought into the folds of mainstream programme and diagnosis of the neglected species can be made a routine procedure.[32] Inclusion of PCR-based diagnostic tools in the ambit of national malaria control programme would be challenging in terms of resources, manpower, expertise and infrastructure. However, countries like India with heterogenous malaria burden need new approaches to comb through communities for parasite load. Several regions in India persistently report high malaria despite deployment of effective

interventions. One of the reasons could be the presence of asymptomatic and sub-microscopic infections.[32] We propose that molecular tools be incorporated in the national programme in certain scenarios and in selected pockets of high and persistent malaria. These modern tools may also be employed in foci at the risk of outbreaks.

Challenge 4: Drug resistance

Threat of drug resistance:

Artemisinin-based antimalarials are the backbone of effective drug therapy. However, threat of losing their efficacy is making malaria elimination a race against time. In Greater Mekong Sub Region (Cambodia, Laos, Myanmar, Thailand, and Vietnam), out of six ACTs, more than 2 ACTs have failed in 4 countries.[36] In India, highly resistant parasite isolates against Sulfadoxine-Pyrimethamine (SP) were reported from the NER which brought in the change from Artesunate-Sulfadoxine Pyrimethamine (ASSP) to artemether lumefantrine (AL) in 2013.[37] In recent times, studies have suggested that resistance is emerging towards SP, the partner drug in ACT AS-SP which is the dominant ACT used in the country except in northeastern (NER) states of India. The longevity of the ACT AS-SP in India is doubtful due to resistance mutation acccumulation.[38] Periodic monitoring of clinical efficacy via therapeutic efficacy studies and molecular epidemiology are needed to keep a vigil for detection resistance. Prompt changes to an effective ACT combination may be needed in coming time. Also, there is a need to generate data on the Pf-K13 mutations (among the fifty in South Asia) for artemisinin resistance. Nine have been validated but ~30 mutations though reported from South Asia require corresponding clinical data on treatment failure. Work is also needed on the fourteen K13 mutations found in India that include four mutations (S549Y, G625R, N657H, D702N) not reported earlier.[39-41]

Possible solutions to challenge 4: drug resistance

Consider a switchover to artemether-lumefantrine for P. falciparum malaria: The emergence of resistance to ACT AS-SP in the northeastern states motivated the government to shift to AL in 2013. The presence of SP resistance markers in a number of studies indicates the need to prepare for a policy change from AS-SP to AL proactively before the clinical failures become evident.[38] Also, new ways to safeguard the efficacy of artemisinin based combination therapies are being devised. One strategy is to add another partner drug to the existing combination of artemisinin and partner drug called as Triple ACT (TACT). For example, mefloquine is added to the ACT dihydroartemisinin–piperaquine (DHA–PPQ) and amodiaquine is added to artemether–lumefantrine (AL). Both these combinations have been found, safe, tolerable and very efficacious in Asian countries Thailand, Cambodia and Vietnam.[42]

Challenge 5: vector bionomics and control

Insecticide treated nets and indoor residual spray (IRS) are the mainstay of vector control strategies against malaria in India as in other countries. DDT, malathion and synthetic pyrethroids are predominantly used for control of adult mosquitoes via IRS; deltamethrin and alpha-cypermethrin are used for impregnated bednets. Though very much needed the data on insecticide resistance, frequency, intensity and mechanism of resistance is not routinely generated by the national programme. Also, there is a lack of data on intensity assays which as per WHO's recommendation should be taken into account for decision making on when to switch over to other effective insecticides. In a bid to phase out DDT, synthetic pyrethroids are being used in IRS and LLINs. Cross-resistance within the same class of insecticides is a common occurrence. Therefore, where deltamethrin resistance has occurred, resistance to other synthetic pyrethroids is not far. Use of insecticides of the same class and same mode of action in LLIN and IRS at the same time and place (which is being done in some malaria endemic areas in India) can accelerate development of insecticide resistance due to selection pressure. Though insecticide resistance management strategies like rotation, mosaic, mixtures and combinations are recommended but these are not actively pursued or planned in India despite evidence of emergence of insecticide resistance.[43] Another possible challenge is the limitation of the two predominant vector control tools of IRS and LLIN. IRS targets indoor resting (endophilic) mosquitoes and LLINs protects against mosquitoe bites only when one sleeps underneath the net i.e., at night. Both the vector control tools impact anthropophilic, endophagic mosquito leaving a caveat for more zoophilic, exophagic and exophilic vectors. These mosquitoes can circumvent the contact with insecticide treated bednets and wall surfaces and thus contribute to continued transmission. Outdoor biting in early evening hours when the people are devoid of protection of bednet and residual spray can promote residual/persistent malaria in India.[44] Also, with years of use of these tools, there is a shift in mosquito behaviour via evolutionary mechanisms such as behavioural plasticity, protective behaviour and behaviouristic resistance.[45,46] Studies have revealed changes in vector behavior from indoor resting to outdoor resting in cattle sheds. Similarly, early biting in order to circumvent contact with IRS and blood meal feeding before people sleep under LLINs has been observed.[47] It is important to acknowledge the challenge of incursion of malaria vectors to newer areas. *An. culicifacies* has expanded its presence to North-eastern states of India and is now established

as a vector of malaria there.[48] Such incursion to newer areas presents a new challenge to the malaria elimination plans. These developments need continued monitoring in the form of regular bionomics studies. Government's national malaria control program is the only channel for communities to have access to insecticide treated nets. This limitation also creates a coverage deficit for households with more members, visitors, inaccessible populations, during emergencies such as floods and creates a time gap in replacements.

Possible solutions challenge 5: vector bionomics and control

(1) *Over the counter availability of insecticide treated bednets:* It is important that India explores alternative channels for making LLINs available at a subsidized cost to the public. Provision of LLINs in private space offers several benefits like enhancing the ownership by community thus effectively covering the vulnerable i.e., pregnant women and children, freeing up government resources for more needy ones, covering up deficits in government supply, and catering to families who can use additional nets for visitors or for gifting. There would be challenges to the adoption of the above and dialogue with industry, government, communities is thus of utmost importance to resolve these issues.[49]

(2) *Ivermectin as an endectocide:* ivermectin, a potent insecticide and anthelmintic drug, is under trial as endectocide in cattle and humans. Feeding on blood of treated cattle/human reduces the survival of mosquitoes irrespective of biting pattern or host preferences. India should consider testing and evaluation of ivermectin in cattle as an endectocide in the first instance as the major primary malaria vector *An. culcifacies* that is responsible for ~70% of malaria transmission is zoophilic. We have delineated the steps for its evaluation in Indian settings beginning from assessing the susceptibility of Indian vectors to ivermectin, followed by finding the lethal dose, preclinical studies and finally cattle and human trials recently. India is already administering ivermectin as part of mass drug administration for preventive chemotherapy of lymphatic filariasis. Therefore, expansion of indications for use of ivermectin should be feasible.[50]

(3) *Toxic Sugar Baits:* Traps with and without attractant (Toxic Sugar Bait/Attractive Toxic Sugar Bait) are being tested in Africa, Israel and USA. These can be useful as an outdoor vector control tool against malaria and dengue vectors. Recently, efficacy of TSB (without attractant) against malaria vectors *Anopheles culicifacies, An. stephensi* and *Aedes aegypti* has been evaluated. Results are quite promising in the laboratories and warrant further field trials[51] We anticipate that TSB could be a useful vector control tool for outdoor transmission of malaria. However, a standard methodology for testing TSB/ ATSB in the laboratory and in the field needs further attention and development.

Challenge 6: multi-stake holder partnerships

Lack of synergy: For public health programmes such has malaria elimination, besides national programe, there are several other agencies like research organizations, non-government bodies, philanthropic organizations, universities/colleges which work in some domain of malaria control and elimination. However, there is little cross-talk among these bodies and they continue to work in silos. There are several instances wherein these organizations generate evidence which is of value to the national programme but either is not recognized or there is delayed translation of evidence into policy owing to the absence of partnership and synergy among the different players.

Possible solution to challenge 6: multi-stake holder partnerships

ICMR is the research body of Ministry of Health and Family Welfare and has a country-wide footprint via its institutes and their field stations in malaria endemic areas. In Table 1, we enumerate examples wherein research outputs by ICMR have provided evidence for policy change for different facets of malaria elimination (clinical research, diagnostics and surveillance, vector control and models of elimination). Additionally, ICMR functions as a strong support to the national programme in training, monitoring and evaluation not only for malaria but for all vector borne infections. Similarly, other national and international, government and non-government organizations through their expertise and strengths have the potential to constructively contribute to the success of the national malaria programme. A closer collaboration in terms of exchange of data, field experiences and interactions is needed with all stakeholders and partners in this space in a complimentary way. We have proposed convergence and coalescence of evidence generated and expertise of these organizations, which are currently fragmented and working in silos.[25]

Conclusions

In summary, India, despite its sustained decline in malaria burden, faces several challenges and roadblocks in its journey towards malaria elimination by 2030. The challenges are incomplete paper based aggregated surveillance, missing private sector involvement, lack of a platform for digital integration of data and the need for more sensitive diagnostic tools. Poor compliance to primaquine and presence

a) Clinical research and policies

Research output	Year of study	Policy change
Drug resistance to SP monotherapy shown by teams of national programme, research institutes[52]	2004	Artesunate (AS) + Sulfadoxine-Pyrimethamine (SP) replaced SP monotherapy for management of *P. falciparum* malaria in chloroquine (CQ) resistant areas in 2005.
Widespread use of artemisinin monotherapy despite recommendation of artemisinin combination therapy (ACT) in *P. falciparum* areas was reported[53]	2008	Ban on sale of oral artemisinin monotherapy since 2009
Therapeutic efficacy studies reported (CQ) resistance in *P. falciparum*[54]	2003-2006	AS + SP made as the first line treatment in high risk districts and in CQ resistant areas in 2007. Same later throughout the country in 2010.
AS + SP treatment failure exceeded the threshold in North-East India prompting change in drug policy[55]	2012	Artemether plus lumefantrine replaced AS+ SP as the new first-line treatment in the northeast in 2013.
Phase III clinical trials of alpha- beta arteether, bulaquine, arterolane piperaquine artesunate amodiaquine, artesunate mefloquine, dihydro-artemisinin, piperaquine[8]	2011−2014	Central Drugs Standard Control Organization (CDSCO) approved these drugs and they can be included into the National Drug Policy for severe malaria.
Single dose radical cure for *P. vivax* malaria via Tefanoquine − India participated in multi-country dose selection phase 2 b trial[56]	2011-2013	In view of its potential to control *P. vivax* relapse, the drug is under consideration for regulatory approval in India.

b) Diagnostics and surveillance strategies in India

Research output	Year	Policy change
Evaluation of malaria rapid diagnostic tests for use in the programme at NIMR[57-59]	1997 onwards	The data generated for over 20 rapid diagnostic tests (RDTs) helped their introduction and registration in the national programme. Monitoring assures the supply of quality RDTs in the public health system.
Studies on *P. falciparum* histidine rich protein2/3 (hrp2/3) gene deletions as *P. falciparum* encoded (HRP2) based malaria RDTs are used[33,60-62]	Constantly monitored	National programme apprised of findings and alerted.
Use of dried blood spots (DBS) collected under National family Health Survey-5 (NFHS-5) to assess the presence of molecular markers of drug resistance in *P. falciparum* and *P. vivax* - monitor presence of hrp2/hrp3 gene deletions in *P. falciparum*	2020 (ongoing at NIMR)	The results would alert the national control programme of emerging drug resistance and may point at need for change in hrp2 based RDTs.
Development and deployment of mobile FeverApp as a smart surveillance tool [24]	2020 (Ongoing at NIMR)	FeverApp has the potential to transform aggregate paper based data collection to near real time surveillance prompting quick mitigation actions.
Development and use of Digital Dashboard for collating malaria data from all sources including public, private and non-government agencies [26]	2022 (Ongoing at NIMR)	Epidemiological, entomological and commodity surveillance data transmitted in near real time will allow evidence backed policies.

c) Vector control research and policies in India

Research Output	Year	Policy change
Monitoring of vector susceptibility to the insecticides by ICMR and NVBDCP [43,63]	Constantly monitored	Change from dichloro-diphenyl-trichloroethane (DDT) to synthetic pyrethroid in IRS over a variable period of time.
Evaluation of public health pesticides and introduction in the national programme[64-70]	Ongoing activity	• Biolarvicides such as *Bacillus thuringiensis israelensis* (Bti), *Bacillus sphaericus* (BS) and *Bti Aqueous* introduced in the national programme. • Deltamethrin (wettable powder formulation) was introduced in the programme. • Insect Growth regulators (IGRs) like Diflubenzuron and pyriproxiphen were introduced in national programme. • Different brands of LLINs are registered in India and can be introduced in national programme.

Table 1 *(Continued)*

a) Clinical research and policies Research output	Year of study	Policy change
Comparison of effectiveness of IRS using DDT WDP 75% to DDT WDP 50% [71]	2016	• Residual efficacy of DDT WDP 75% better than DDT WDP 50% after two rounds of spraying. • National Programme can consider switching over to DDT 75%.
Examined the behavioural change in malaria vectors in three sites with long use of LLINs [47]	2012	• Both LLIN and IRS target malaria vectors resting and biting indoors. • The information generated would be useful to the programme for assessing their existing vector control strategies and to expand vector control for outdoor transmission.
Bionomics of malaria vectors [43,72,73,74] (periodic multi-centre studies)	Constantly monitored	• Regularly shared with national programme
d) Models of malaria control/elimination in India		
Research Output	Year	Policy change
Comprehensive Case Management Programme (CCMP) by joint efforts of State VBDCP (Odisha), NIMR and supported by Medicines for Malaria Venture (MMV) /WHO[75]	2013	Adopted by State Government as DAMaN Project in 2017 in high malarious areas in 23 districts.
DAMaN Assessment and its effectiveness[76]	Ongoing 2019	Comprehensive assessment of the DAMaN project and possible replication in other parts of the country.
Malaria Elimination Demonstration Project (MEDP) in Madhya Pradesh, Central India[77]	Ongoing 2017-22	Successful results that could be replicated by other states
ICMR's Malaria Elimination Research Alliance-India[78,79] platform for operational research studies with direct programmatic implications	Ongoing 2020-2025	Studies on low density infections, vector bionomics and community behaviour expected to influence programme policy for malaria control and management.

***Table 1*: Some important examples of evidence generated through research that has influenced programme policies in India.**

of G 6 PD deficiency further adds layers of complexity to elimination of *P. vivax* malaria. Threats of drug and insecticide resistance in malaria continue to loom large for the world. In addition, outdoor transmission of malaria and behavioural change of vectors make current vector control tools less effective. Lack of collaboration and synergy between national malaria programme and other players in the field also poses a barrier to successful adoption of lessons learnt and evidence generated by other agencies working in this space. We have proposed several solutions and suggestions which can be prove to be gamechangers in India's battle against malaria and can catapult India towards elimination of malaria.

Contributors

MR and AS contributed equally to the paper.

Ethics committee approval

Not Applicable.

Declaration of interests

Nothing to declare.

Role of funding source

The authors have received no funding for this paper.

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