Chapter 11

Declining Transmission of Malaria in India: Accelerating Towards Elimination

Sunil Dhiman, Vijay Veer and Vas Dev

Additional information is available at the end of the chapter

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Abstract

India is ecologically vast and has close to a billion-population living at risk of malaria. Given the evidence-based present-day intervention tools and large-scale implementation, India has recorded declining trends in disease transmission from 2 million cases in 2001 to close to a million cases in 2017 and embarked upon malaria elimination in keeping with the Global Technical Strategy by 2030. India is malaria endemic, but transmission intensities varied across its landscape with just few States of the east, central and northeast contributing bulk (80%) of total positive cases. *Plasmodium falciparum* and *P. vivax* are the predominant infections of which there has been steady increase in proportions of the former for constituting >60% of total cases what was 50:50 in 2001, a phenomenon attributed to emerging drug resistance. With the rolling out of the available intervention tools, malaria elimination is foreseeable yet there are multiple challenges which must be addressed to overcome the constraints. We strongly advocate continued disease surveillance and monitoring, universal coverage and intensification of core-interventions for prevention and treatment prioritizing high-risk States, strengthening cross-border collaborations for information sharing and coordinated activities, and above all sustained allocation of resources, creating the enabling environment to end malaria transmission.

Keywords: malaria elimination, epidemiology, *Plasmodium falciparum*, drug-resistance, mosquito vectors, insecticide resistance, Southeast Asia

1. Introduction

The advent of new intervention tools including Noble prize-winning discovery of Artemisinin by Tu Youyou for treatment of malaria combined with large-scale implementation of

insecticide-treated netting materials for vector containment has once again renewed the optimism of malaria elimination globally. Malaria map is shrinking with more than 35 countries certified to be malaria free, and another 21 countries that are likely to reach zero indigenous transmission (categorized as E-2020) are set to be declared malaria free by 2020 [1, 2]. Many more countries are moving forward from control to elimination. The Global Technical Strategy for Malaria 2016–2030 envisages: (i) to reduce global malaria mortality rates and case incidence by at least 90% compared to 2015 levels, (ii) to make at least 35 countries malaria free that reported cases in 2015 and (iii) preventing re-establishment in countries with no indigenous transmission [3]. Among member countries of the Southeast Asia Region of WHO (SEAR), Maldives and Sri Lanka have already been certified malaria free in 2015 and 2016, respectively, and Bhutan is targeting elimination in the foreseeable future. In the past decade, India has registered drastic decrease in cases and have formulated National Framework for Malaria Elimination (2016–2030) in close alignment with the Global Technical Strategy for Malaria, Roll Back Malaria Action (RBM), Investment to defeat Malaria (AIM) and the Asia Pacific Leaders Malaria Alliance (APLMA) for shared experiences and coordinated action to eliminate malaria (zero indigenous cases) throughout the country by 2030 [4]. The said task is set to be accomplished in phased manner with the following objectives: (i) eliminate malaria in all 26 low-to-moderate transmission States/Union Territories (UTs) by 2022, (ii) reduce the case incidence to <1 per 1000 population by 2024 in all States/UTs, (iii) interrupt indigenous transmission throughout the country by 2027 and (iv) prevent re-establishment of local transmission and maintain malaria-free status by 2030 and beyond.

India is historically endemic for both *Plasmodium vivax* and *P. falciparum* malaria and has history of successes and resurgences [5, 6]. Malaria was on the verge of elimination post-independence in 1960s with 0.1 million cases and no death, yet it reared its ugly head again in 1970s with record number of six million cases and many deaths attributed to technical and operational constraints. Transmission is largely seasonal corresponding to rainy season with record of focal disease outbreaks characterized by high rise in cases and attributable deaths. In 2017, India reported 0.84 million cases, the highest disease burden in SEAR member countries of WHO [4, 7]. Almost all Indian States and UTs are reporting cases, which can be broadly stratified into three different categories based on Annual Parasite Incidence (API) per 1000 population, that is, Category—I (total of 15 States/UTs including districts with API < 1) that are targeted for elimination phase, Category—II (total of 11 States/UTs with API < 1 with one or more districts reporting > 1 API) marked for pre-elimination phase and Category—III (total of 10 States/UTs with > 1 API) targeted for intensified control operations. With the rolling out of the present day evidence-based intervention tools, disease transmission is on the steady decline presenting window of opportunity to accelerate toward universal coverage for malaria prevention and treatment. India is a huge country (population 1.3 billion) with majority populous (80%) living at risk of malaria. The task is enormous and daunting. Given the political commitment and National Framework developed by the National Vector Borne Disease Control Programme (NVBDCP) of Government of India, malaria elimination is foreseeable, yet there are multiple challenges which must

be addressed to overcome the constraints. In this chapter, we attempt to enumerate some of these issues helping strengthen healthcare services in combating malaria menace enabling elimination by due date.

2. Malaria transmission in India: current distribution and parasite formula

Malaria transmission is heterogenous across Indian landscape for its diverse ecology and multiplicity of disease vectors [8]. Malaria is a serious public health concern and almost all 36 States/UTs are consistently contributing cases, but transmission intensities varied ranging from low-to-moderate (**Table 1**). Among these, north-eastern, eastern and central Indian States consistently contributed 80% of the total disease burden having concentration of cases (API > 10) associated with large forest cover, ethnic tribes, poverty and high rainfall (**Figure 1**). These included States of Odisha (formerly Orissa) and Jharkhand (eastern India), Chhattisgarh and Madhya Pradesh (central India) and Meghalaya and Tripura (northeast India), which together contributed >65% of *P. falciparum* cases. Approximately a billion population of India resides in malaria endemic areas, however, 80% of malaria cases are reported by just 20% of the population living in the forest-fringe, tribal and foothills hard-to-reach areas of the country little aware of disease prevention and access to treatment [9]. These areas are prone to periodic disease outbreaks resulting in flare up of cases and attributable mortality accounting for inter-annual variation in reported morbidity. From the epidemiological data for the past 17 years (2001–2017), disease transmission trends are observed to be declining from two million cases in 2001 to close to a million cases in 2017 (**Figure 2**). However, consequent to the introduction of artemisinin-based combination therapy (ACT) beginning 2010 coupled with insecticide-treated netting materials (ITNs); there has been drastic decrease in cases and deaths. *P. falciparum* and *P. vivax* are the predominant infections of which there has been steady increase in proportions of the former parasite species presently constituting >60% of total cases what was 50:50 in 2001. Every single death was attributed to *P. falciparum*, majority of which were contributed by high-risk States of north-eastern, eastern and central India (**Figure 3**). The distribution of *P. malariae* is patchy, recorded in indigenous tribes of eastern, north-eastern and central India [10–12], but transmission of *P. ovale* except for few sporadic reports could not be clearly ascertained [13–15]. There exists no record of *P. knowlesi* malaria in India making inroads in other Southeast Asian countries [16].

The reported cases and deaths; however, are far from acccurate for disease surveillance that can be best described as fragmented and there is no system in place to capture data from private and public sectors alike, least the asymptomatic cases [17]; WHO estimates are much higher to the tune of >10 million cases and deaths manifold [1]. Nevertheless, the presented data showed disease transmisison trends in relation to existing interventions, and monitoring and evaluation in practice.

No	State/Union Territories	2014			2015			2016			2017		
		Total malaria cases	*Plasmodium falciparum* cases	Deaths	Total malaria cases	*Plasmodium falciparum* cases	Deaths	Total malaria cases	*Plasmodium falciparum* cases	Deaths	Total malaria cases	*Plasmodium falciparum* cases	Deaths
1	Andhra Pradesh	21,077	15,511	0	25,042	18,709	0	23,613	17,443	0	16,913	11,944	0
2	Arunachal Pradesh	6082	2338	9	5088	1714	7	3144	911	2	1538	487	0
3	Assam	14,540	11,210	11	15,557	11,675	4	7826	5686	6	5473	4131	0
4	Bihar	2043	699	0	4006	1286	1	5205	895	0	3175	356	2
5	Chhattisgarh	128,993	108,874	53	144,886	123,839	21	148,220	121,503	61	141,310	115,153	0
6	Goa	824	42	0	651	75	1	742	130	0	653	75	2
7	Gujarat	41,608	6253	16	41,566	7232	7	44,783	6298	6	37,801	3502	2
8	Haryana	4485	45	1	9308	726	3	7866	552	0	6887	904	0
9	Himachal Pradesh	102	1	0	60	1	0	121	19	0	95	9	0
10	Jammu & Kashmir	291	21	0	216	8	0	242	11	0	226	0	0
11	Jharkhand	103,735	46,448	8	104,800	54,993	6	141,414	83,232	15	92,770	42,047	1
12	Karnataka	14,794	1329	2	12,445	1598	0	11,078	1746	0	6529	1118	0
13	Kerala	1751	305	6	1549	400	4	1547	419	2	1194	317	2
14	Madhya Pradesh	96,879	41,638	26	100,597	39,125	24	69,106	22,304	3	46,176	15,554	3
15	Maharashtra	53,385	25,770	68	56,603	31,139	59	23,983	7815	26	18,133	5929	19
16	Manipur	145	72	0	216	119	0	122	58	0	80	22	0
17	Meghalaya	39,168	37,149	73	48,603	43,828	79	35,147	31,867	45	16,433	14,974	11
18	Mizoram	23,145	21,083	31	28,593	24,602	21	7583	5907	9	5710	4978	0

No	State/Union Territories	2014			2015			2016			2017		
		Total malaria cases	*Plasmodium falciparum* cases	Deaths	Total malaria cases	*Plasmodium falciparum* cases	Deaths	Total malaria cases	*Plasmodium falciparum* cases	Deaths	Total malaria cases	*Plasmodium falciparum* cases	Deaths
19	Nagaland	1936	647	2	1527	532	3	828	316	0	394	188	1
20	Orissa	395,035	342,280	89	436,850	369,533	80	449,697	389,332	77	352,140	297,554	25
21	Punjab	1036	14	0	596	13	0	693	8	0	808	12	0
22	Rajasthan	15,118	603	4	11,796	662	3	12,741	1031	5	6837	377	0
23	Sikkim	35	18	0	27	11	0	15	5	0	12	3	0
24	Tamil Nadu	8729	339	0	5587	355	0	4341	242	0	5449	197	0
25	Telangana	5189	4602	0	10,951	10,206	4	3512	2617	1	2688	2170	0
26	Tripura	51,240	49,653	96	32,525	30,074	21	10,546	9545	14	7040	6572	6
27	Uttarakhand	1171	89	0	1466	73	0	961	47	0	532	14	0
28	Uttar Pradesh	41,612	326	0	42,767	371	0	39,238	158	0	32,345	159	0
29	West Bengal	26,484	4981	66	24,208	5775	34	35,236	5928	59	30,008	4632	29
30	A.N. Islands	557	109	0	409	77	0	485	140	0	404	67	0
31	Chandigarh	114	0	0	152	1	1	157	0	0	114	1	0
32	D & N Haveli	669	90	1	418	46	0	375	30	0	297	16	0
33	Daman & Diu	56	4	0	84	18	0	48	7	0	37	4	0
34	Delhi	98	0	0	54	0	0	31	0	0	577	2	0
35	Lakshadweep	0	0	0	4	0	0	2	0	0	1	0	0
36	Puducherry	79	3	0	54	5	1	76	11	0	59	13	0
All India total		1,102,205	722,546	562	1,169,261	778,821	384	1,090,724	716,213	331	840,838	533,481	103

*Source: Ref. [7].

Table 1. Malaria-attributable morbidity and mortality in different States and Union Territories (UTs) of India during 2014–2017*.

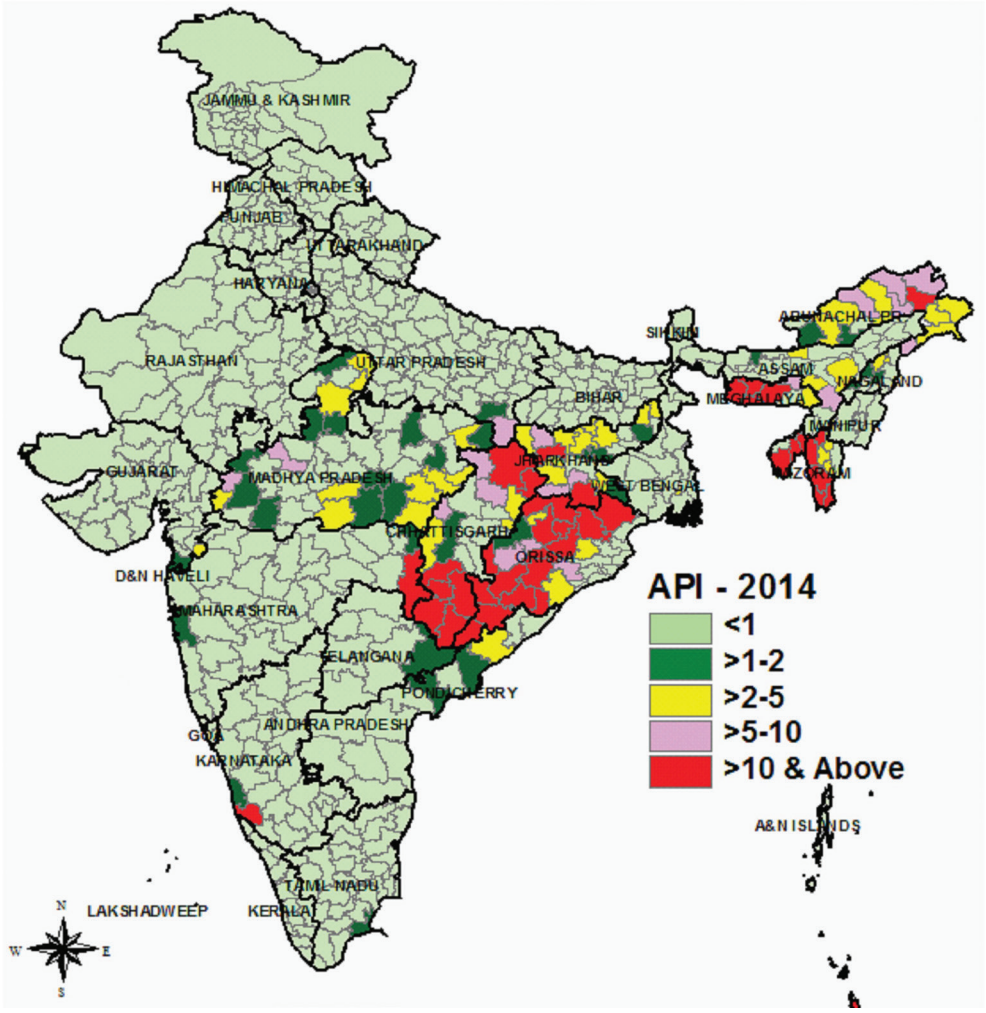

Figure 1. Malaria stratification by Annual Parasite Incidence (API) in Indian States for data based on 2014. API 10 corresponds to 10 confirmed cases per 1000 population. *Source*: Ref. [4].

3. Multiple disease vectors and insecticide resistance

India holds the distinction in malaria epidemiological research for Noble prize-winning discovery that malaria is transmitted by mosquitoes by Sir Ronald Ross on the day of August 20, 1897, and for monumental work on faunistic surveys dating back to 1930s [18]. Of the 58 anopheline species recorded in India [19], six major vector taxa are implicated in malaria transmission, including *Anopheles culicifacies s.l.*, *An. fluviatilis s.l.*, *An. minimus s.l.*, *An. dirus s.l.*, *An. sundaicus s.l.* and *An. stephensi* [20]. All of these, except *An. stephensi*, are species complexes among which members

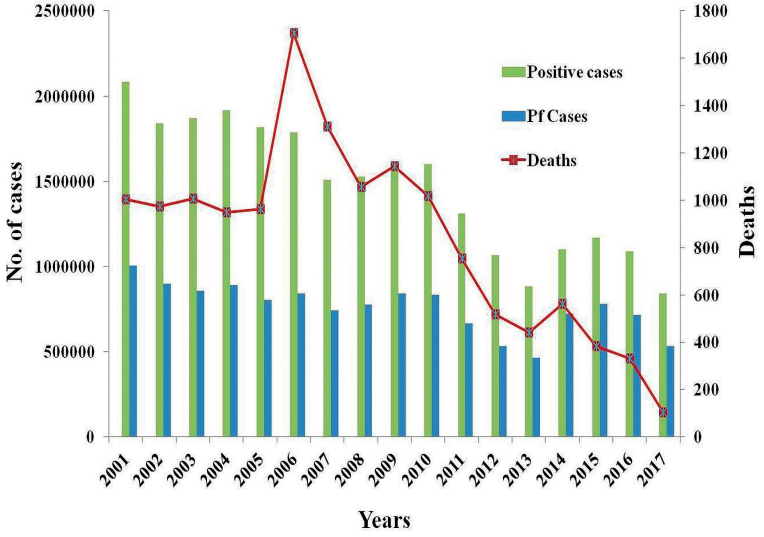

Figure 2. Malaria-attributable morbidity and mortality in India during 2001–2017. Malaria positive cases denote confirmed diagnosis by presence of malarial parasite in finger-prick blood-smears; Pf cases denote positivity for *Plasmodium falciparum;* death cases are attributed to confirmed falciparum malarial infection. *Source*: Ref. [7].

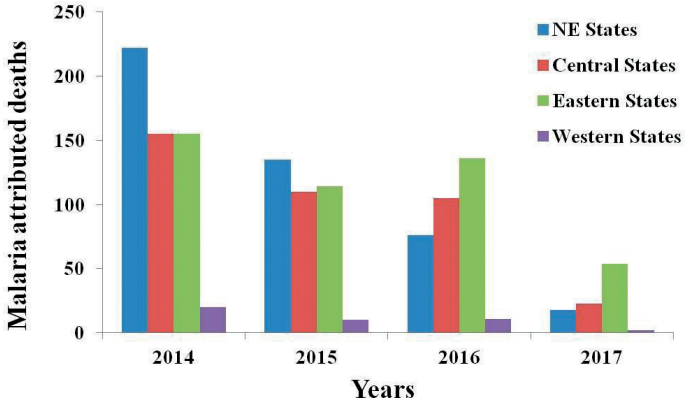

Figure 3. Distribution of malaria-attributed deaths in different geoepidemiological regions of India for data based on 2014–2017. NE refers to group of seven sister States of northeast India including Arunachal Pradesh, Assam, Meghalaya, Manipur, Mizoram, Nagaland and Tripura; Central States include Madhya Pradesh and Chhattisgarh; Eastern States include Bihar, Jharkhand, Odisha (formerly Orissa) and West Bengal; Western States include Maharashtra, Goa, Gujarat and Rajasthan. In the remaining Indian States and Union Territories, death cases were few and far (not shown). *Source*: Ref. [7].

were repeatedly incriminated as vectors evidenced by detection of live sporozoites in salivary glands across range of their distribution [21, 22]. With added tools of molecular taxonomy; however, there have been significant advances in understanding sibling-species composition of these taxa [23–25], distribution and their bionomics helping target species-specific control interventions in place and time (**Table 2**). Among these, *An. culicifacies* is the most widespread and extensively

Anopheles species/ taxa	Sibling species prevalent in India (total identified)	Diagnostic cytotaxonomic/ molecular tools	Breeding habitats	Feeding behavior (peak biting activity)	Resting habitats	Sporozoite infectivity (%)	Insecticide susceptibility status	Distribution range
An. culicifacies s.l.	A,B,C,D and E (5)	Fixed paracentric inversions, PCR based sequencing of 28S-D3 domain; ITS2-PCR-RFLP; rDNA ITS2	Rain water collections, riverine pools, rice fields, seepage water, streams, borrow pits, irrigation channels	Predominantly zoophilic except 'E' (A and B: 22:00–23:00; C and D: 18:00–21:00; no data for E)	Human-dwellings indoors and cattle sheds	Incriminated (0.3–20)	Resistant to DDT, malathion and pyrethroids	Throughout rural India
An. fluviatilis s.l.	S, T, U and Form 'V' (4)	Fixed paracentric inversions; PCR based sequencing of rDNA ITS2; 28S rDNA-D3	Seepage water foothill streams, irrigation channels, river ecology, shallow wells	Sibling species 'S'—highly anthropophilic (20:00–24:00); 'T'—zoophilic	S—human dwellings indoors; T—cattle sheds	Incriminated	Highly susceptible to all residual insecticides	Throughout India except north-eastern States
An. minimus s.l.	*An. minimus s.s.* (3)	rDNA ITS2; 28S rDNA-D3	Perennial foothill seepage water streams	Highly anthropophilic (01:00—04:00)	Human-dwellings indoors	Incriminated (3.0)	Highly susceptible to all residual insecticides	North-eastern of Arunachala Pradesh, Assam, Meghalaya, Manipur, Mizoram, Nagaland, Tripura, and Eastern State of Odisha
An. dirus s.l.	*An. baimaii* (8)	Karyotypic studies, polytene chromosome analysis, gene-enzyme variation, DNA probes, rDNA ITS2; SCAR-PCR	Jungle water pools, Elephant foot-prints	Highly anthropophilic (21:00—24:00)	Exophilic	Incriminated (1.9)	Highly susceptible to all residual insecticides	North-eastern of Arunachala Pradesh, Assam, Meghalaya, Manipur, Mizoram, Nagaland, Tripura
An. sundaicus s.l.	*An. sundaicus* cytotype D (4)	Mitochondrial DNA cytochrome oxidase 1 and cytochrome-b; rDNA ITS2; 28S rDNA-D3	Brackish water including swamps, salt water lagoons, creeks as well as fresh water	Predominantly zoophilic except indoor resting populations (21:00—04:00)	Both indoors and outdoors	Incriminated	Highly susceptible to all residual insecticides	Andaman & Nicobar Islands

Anopheles species/ taxa	Sibling species prevalent in India (total identified)	Diagnostic cytotaxonomic/ molecular tools	Breeding habitats	Feeding behavior (peak biting activity)	Resting habitats	Sporozoite infectivity (%)	Insecticide susceptibility status	Distribution range
An. stephensi	Not applicable		Domestic containers, building construction sites, overhead water storage tanks, underground cement tanks, desert coolers	Predominantly anthropophilic (22:00—24:00)	Endophilic	Incriminated	Resistant to DDT and Malathion	Urban metropolitan cities of India

*Source: Refs. [20, 23–25]; rDNA, ribosomal DNA; SCAR, sequence characterized amplified region; ITS2, internal transcribed spacer 2; PCR, polymerase chain reaction.

Table 2. Bionomics, distribution and sibling-species composition of the dominant mosquito vector taxa of human malaria in India*.

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studied for its sibling species composition (A, B, C, D and E), distribution range, seasonal prevalence, larval ecology, feeding and breeding behavior and disease transmission relationships [26]. Species E is the most efficient malaria vector of all having predilection for human host, while species B is a poor vector for its zoophilic characteristics. The other three species (A, C and D) are responsible for local transmission in areas of their predominance [27]. This taxon is the most abundant rural vector in plains of mainland India generating about 65% of cases annually and held responsible for focal disease outbreaks associated with build-up of vector density. It is regarded as highly adaptive species for its diverse breeding habitats and invading new territories in degraded forests of north-eastern India evidenced by records of rising density and incrimination [28–30]. Its control has become a formidable challenge for having grown multi-resistant virtually to all available insecticides including pyrethroids opening new vistas for research on newer interventions that are sustainable, cost-effective and community-based [31–33].

An. fluviatilis complex is just as widespread and have overlapping distribution with *An. culicifacies* throughout India [20]. Among its sibling species, that is, S, T, U and form 'V'; it is species S which is highly anthropophilic and responsible for maintaining hyperendemic malaria predominantly in foothills of eastern India contributing ~15% of reported cases [34]. It shares similar bionomical characteristics with yet another efficient malaria vector species *An. minimus s.s* for breeding in foothill seepage water streams and resting indoors in human dwellings [35]. Both are highly susceptible to residual insecticides. *An. minimus* instead is the most predominant vector species of north-eastern States of India and has long history of disappearance and re-appearance stymying the control authorities. It is reckoned as the most efficient vector species for its high anthropophily (human blood index > 90%) and fulminating focal disease outbreaks taking heavy toll of human lives [36]. It is a perennial species and widely incriminated practically all months of the year with average sporozoite infection rate of 3% [37]. This species exhibits high behavioral plasticity for avoiding sprayed surfaces for weeks and establishing extra-domiciliary transmission in response to indoor residual spraying (IRS). While this species has staged comeback in eastern State of Odisha after lapse of 45 years [38], the populations of *An. minimus* once again are reported diminishing in erstwhile domains of its distribution in northeast India corroborated by evidence of reducing disease transmission [35]. It presents an unprecedented opportunity to strengthen interventions to keep populations of this species at bay helping achieve malaria elimination specific to the region at sub-national level.

Within the *An. dirus* complex, *An. baimaii* is the only vector occurring in India with a wide prevalence in the north-eastern States and has been recorded in high densities and incriminated in range of its distribution [39]. It is just as efficient vector species with strong predilection for human host but distinct from *An. minimus* for its breeding and resting characteristics [40, 41]. It is a forest dweller affecting forest-fringe human settlements along inter-country and inter-state border areas causing devastating disease outbreaks often in conjunction with *An. minimus*; together they contribute 10% of reported cases in the country [42]. Its control has become difficult for peak biting activity during second quartile (21:00–00:00) of the night as well as exophilic resting behavior avoiding sprayed surfaces. Its populations along with that of *An. minimus* are also depleting owing to deforestation and urbanization [29, 30]. However, niche thus vacated by both these species is accessed by *An. culicifacies s.l.* and has established foothold erstwhile recorded in low-density [26, 28]. Among sibling species of the *An. sundaicus* complex, cytotype species D has been characterized with a regional importance presently confined to Andaman and Nicobar Islands [43]. It is a brackish water species, largely zoophilic and susceptible to residual insecticides.

An. stephensi is the only urban vector species breeding in domestic containers and often associated with tropical aggregation of labor at construction sites in metropolitan cities [44]. The species is resistant to multiple insecticides and its control focused on 'source reduction' to contain urban malaria. Due to continued urbanization and associated labor migration, urban malaria is viewed as a growing menace contributing about 10% of cases in the country [5–7].

Besides these dominant vectors, member species of *An. maculatus s.l.*, *An. annularis s.l.* and *An. subpictus s.l.* are also implicated; however, these species are considered of lesser significance for being predominantly zoophilic [45, 46]. Vector control is an integral part of the malaria control strategy in India and huge investment is made annually to contain build-up of disease vectors averting epidemic malaria. What is tantamount to vector control is the entomological surveillance for developing malaria-risk maps, judicious application of insecticides, monitoring insecticide-resistance and residual efficacy, universal coverage for population at risk and continued research for newer interventions, which are community-based and sustainable. We strongly believe that judicious mix of technologies that are situation-specific and doable would help save operational costs in resource-poor settings. The country is in dire need of skilled entomologist/taxonomists (an expertise that is getting scarce) to meet the human resource requirements for control of malaria, and other vector-borne diseases, as well as vector surveillance post-elimination to prevent re-establishment of local transmission in malaria-free territories.

4. Drug-resistant malaria

Of the two prevalent malaria parasite species, the rising proportions of *P. falciparum* is of grave concern for presently constituting >60% of total reported cases in the country [5, 7]. Rising trends of *P. falciparum* are largely attributed to fast emerging drug-resistance over space and time in parallel with phenomenon happening in countries of the Greater Mekong Subregion (GMS) of Southeast Asia [47]. Historically, chloroquine (CQ) was the most commonly used drug for treatment ever since inception of the control program in 1953 for its efficacy and affordability. It had become obsolete since its first report of treatment failure in Assam (northeast India) way back in 1973 [48]. Subsequently, drug-resistant foci had multiplied for which northeast is considered corridor for spread to rest of peninsular India resulting in steady rise in proportions of *P. falciparum* what was 13% in 1978 to 65% in present day malaria [49]. Northeast India shares wide border with Myanmar contiguous with GMS countries which is porous for cross-border migration, facilitating entry of drug-resistant strains enroute to the rest of India and beyond. Malaria transmission along this border is intense vectored by *An. minimus* and *An. baimaii* (the two most efficient vector species), and healthcare access is inadequate resulting in indiscriminate and sub-optimal doses *inter-alia*, poor vector control, illiteracy and treatment-seeking behavior; all contributing to propagation and spread of drug-resistant malaria strains [50]. Chloroquine therapy was subsequently upgraded to sulfadoxine-pyrimethamine (SP) in 2004 as first-line treatment in selected districts reporting CQ-resistant malaria [51]. The therapeutic efficacy of SP was short lived resulting in substantial rise in cases in the following years [52]. It was in 1990s that the development of artemisinin-derivatives raised new hopes for treatment of drug-resistant malaria for its fast acting schizontocidal properties. Initially, artemisinin was used as monotherapy for treatment of severe and complicated clinical malaria, discontinued in 2009 due to high recrudescence

rate and risk of resistance for being commonly prescribed medicine by private practitioners and public sector alike [53]. In 2010, the program adopted ACT by combining it with SP, that is, artesunate + SP (AS + SP) for treatment of every single case of *P. falciparum* malaria in high-risk districts [54]. Mass scale introduction of this combination did result in appreciable transmission reduction in endemic communities formerly intractable. It continues to be in practice throughout India except in the northeast region where it has been replaced by yet another combination therapy, that is, artemether + lumefantrine (AL) in 2013 due to declining efficacy of AS + SP combination drug [55]. The emergence of artemisinin resistance in Southeast Asia [56]; however, is a matter of grave concern for its movement westwards to India for having it detected in Myanmar close to the Indian border in northeast [57]. Genomic studies have already detected mutations in the '*kelch 13*' propeller region (*Pfk 13*) linked to artemisinin resistance in north-eastern States, but to lesser frequency [58]. It is of utmost importance to periodically monitor the therapeutic efficacy of drug-regimen in force for radical cure and keep vigil on circulation of counterfeit drugs. The cost of spread of artemisinin-resistant malaria would be colossal, threatening the control and elimination efforts.

5. *Plasmodium vivax* malaria: the neglected parasite

The Southeast Asian countries contribute most of the vivax cases (58%) in the World of which India is the largest contributor [1]. Historically, much of the control efforts continue to be focused on control of falciparum malaria due to its associated severity and critical illness; the vivax malaria remained a neglected parasite [59]. Paradoxically, control of falciparum malaria is rather measurable in relation to interventions due to development of gametocytaemia 9–10 days post primary infection; instead the formation of gametocytes in vivax malaria is concurrent within few days of initial infection even before the patient seeks treatment permitting uninterrupted transmission. This biological characteristic of vivax malaria along with intrinsic ability of formation of latent hibernating 'hypnozoites' has made control efforts a difficult proposition. Nevertheless, the control of vivax malaria is gaining eminence in the context of malaria elimination across the continents [60].

The magnitude of vivax malaria is huge but grossly underestimated throughout India and continues to be neglected [61]. The transmission and distribution of vivax malaria varied across Indian States/UTs, but large concentrations of cases are occurring in urban metropolitan cities [7]. Although it remains highly susceptible to CQ therapy [62–66], its elimination is one difficult issue owing to latent stage 'hypnozoites' in the liver causing relapses amounting to extended morbidity over months/years. The only available anti-relapse drug 'primaquine (PQ)' does not guarantee radical cure much due to extended therapy over days coupled with poor compliance resulting in repeated episodes [67–69]. In addition, the administration of PQ is associated with several issues including contraindication in special groups, that is, infants, pregnant or lactating mothers, and inborn glucose-6-phosphate dehydrogenase (G6PD) deficiency syndromes due to associated hemolytic anemia; these population groups are excluded from primaquine therapy. There exists no diagnostics for detection of G6PD at point-of-care in the present surveillance system except few laboratories procedure for which

it is time consuming and impractical in field conditions where the problem exists. Further, given the available technologies, the detection of latent hypnozoites and sub-patent parasitemia is presently not built in the disease surveillance.

The primary attack of vivax malaria is invariably associated with acute paroxysm presenting classical symptoms but treatable and rarely fatal [70–72]; although few sporadic cases of CQ-resistant cases have been reported in India and several other countries [73]. There is acute need of alternative 8-aminoquinolines, which are safe and universally applicable for radical cure across all population groups preventing relapses. As of today, we stand ill equipped to tackle this stubborn parasite calling for renewed attack both on parasite and disease vectors in reducing parasite reservoir which is likely to persist for long.

6. Asymptomatic malaria

India is historically endemic for malaria with record of devastating epidemics in the pre-DDT era and varied population groups have been subject to repeated attacks of malarial bouts, resulting in acquired immunity and consequent build-up of asymptomatic sub-patent parasitemia in the endemic communities, serving as infectious reservoir for continued transmission. In India, the surveillance program is aimed at taking blood-smears from those who are either febrile (active surveillance) or presenting themselves (passive surveillance) for malaria diagnosis or treatment. There is no built-in mechanism to detect asymptomatic cases or even low-density/sub-patent parasitemia in the endemic communities. These infections may go undetected with conventional diagnostic techniques leaving them untreated, except for mass-blood surveys/mass-drug administrations that are conducted only to contain epidemics. Asymptomatic malaria is more abundant than assumed and have been reported in different endemic States of India; however, the extent and distribution vary corresponding to transmission intensities [74–77]. Asymptomatic parasitemia is often associated with gametocyte carriage and may persist infectious throughout the year to mosquito vectors. These gametocytes are unable to cause clinical symptoms of malaria, rather ensure the uninterrupted transmission of malaria in the presence of efficient vectors. Asymptomatic cases remain undetected and not accounted for disease incidence amounting to gross underestimates.

Asymptomatic malaria in India remains entrenched in low-socioeconomic groupings living in forest-fringe communities, particularly along inter-border areas (both inter-province and international borders), which are largely inaccessible (marred with insurgent activities), wherein healthcare infrastructure is meager or even non-existent. Such areas are 'hot-spots' for explosive disease outbreaks due to mixing/importation of drug-resistant strains associated with illegal migration more so in the northeast (the gateway to India) that shares wide international border with Myanmar, a member country of GMS (an epicenter of multi-drug resistant malaria) and other WHO SEAR countries. Asymptomatic malaria has been documented for both *P. falciparum* and *P. vivax*, yet the magnitude was much higher for the former parasite species, more so in the winter months/dry-season, for example, in north-eastern State of Assam, for the high-risk districts surveyed, it varied from 7.1 to 31.1% in *P. falciparum* and 0.6–6.1% in *P. vivax* [78]. But on average, 12.8% of afebrile subjects were positive for malaria

compared to 34.4% of those presenting with fever, and gametocyte carriage varied from 1.31 to 2.16%. Major bottleneck in eliminating asymptomatic malaria parasite is the absence of standard guidelines and diagnostic procedures aimed at targeting asymptomatic carriers. Malaria control program in practice is largely limited to the qualitative detection of parasite mostly in febrile human hosts and subsequently treating with suitable drugs; however, no attention is given on follow up for quantification of malaria parasite till radical cure. Moreover, a universally accepted parasite level for categorizing a patient as asymptomatic is also not available. Quantification and treating asymptomatic malaria has become increasingly important and relevant for disrupting transmission, requisite for achieving malaria elimination.

7. Cross-border malaria

India shares vast international border with Nepal, Bhutan and China to the North, Myanmar to the East, Bangladesh to the South and Pakistan to the West. Among these, borders with Myanmar and Bangladesh are of immediate concern for their high endemicity and common disease vectors and ecology in the adjoining vicinity on either side of the border [79, 80]. These border areas are porous for cross-migration and have high forest cover inhabited by indigenous tribes living in impoverished conditions. These communities have poor access to healthcare services and are at high-risk to disease outbreaks attributed to drug-resistant strains originating from the GMS countries. These populations are largely marginalized and just as reluctant to seek treatment amounting to unattended parasite reservoirs. Border with Myanmar in particular is believed to be the corridor for entry of drug-resistant strains to northeast India for onward spread. The detection of artemisinin-resistant malaria in closer proximity to Indian border is seen as threat for making its way to India and beyond, similar to the path that was followed by CQ-resistant malaria [48, 49]. Cross-border malaria transmission from neighboring endemic countries can be daunting task and has regional implications jeopardizing the elimination efforts [81, 82]. For example, most cases reported in Bhutan (a country that is heading for malaria elimination), are imported from adjoining districts of Assam seeking treatment on other side of the border. Labor migration across borders engaged in developmental projects is unstoppable for want of livelihood and there exists every possibility of re-entry of malaria given the similar vectors and ecology. It is important to characterize the imported malaria strains enabling interventions well in place and time to prevent re-establishment of local transmission in declared malaria-free territories [83]. Inter-country coordinated efforts are deemed essential to maintain vigil and strengthening border-posts (entry/exit doors) with capacity to detect and treat malaria in the migrant/itinerant labor force at the earliest available opportunity. In keeping the same mandate, India has joined hands with the Asia Pacific Malaria Elimination Network (APMEN) countries for shared experiences and coordinated action to achieve malaria elimination by 2030 [84]. Mitigating cross-border malaria should be accorded priority in context of malaria elimination.

8. Strengthening health systems

India has a well-structured vector-borne disease control program in place providing logistics support along with guidance and monitoring/evaluation services to malaria endemic States/

UTs [4, 7]. Utilizing the evidence-based intervention tools and large-scale implementation, India has registered notable decline in cases and malaria-attributable deaths in the preceding few years (**Figures 2** and **3**). Among these, roll-out of ACT for treatment of every single case of *P. falciparum* malaria, rapid diagnostics test (RDT) kits for on-the-spot diagnosis and large-scale provision of long-lasting insecticidal nets (LLINs) for vector control have resulted in rich dividends in reducing disease transmission in areas formerly intractable. Malaria threat is seen receding presenting an unprecedented opportunity for upscaling interventions in achieving universal coverage for populations at any risk making elimination an achievable target. However, the logistics requirement is huge for which increased funding from donors (both national and international agencies) and political commitment for sustained allocation of resources is of paramount importance for strengthening healthcare services reaching the outreach population groups for equitable access. A humble beginning has been made under National Health Mission (NHM), which envisages achievement of universal access to equitable, affordable and quality healthcare services both in urban and rural India [85]. Much needed disease surveillance in the country is further strengthened by Integrated Disease Surveillance Programme (IDSP) to detect early warning signals for impending disease outbreaks instituting interventions to thwart the disease onslaught and spread [86]. Both these establishments have helped the program immensely in strengthening laboratory services averting disease outbreaks, as well as human resource development in providing training to State surveillance officers, rapid response teams and other medical and paramedical staffs. However, continuing education program is need of the hour for upgrading skills to keep pace with the changing technologies as well as to fill the void due to attrition of skilled workforce. The induction of Accredited Social Health Activists (ASHA) have proven boon to the program ensuring door-to-door surveillance raising new levels of confidence in the poverty-stricken communities. Host of Non-Governmental Organizations (NGOs)/media coverage have increased the reach of services in remote/inaccessible areas helping combating illness and saving lives. Collectively, communities today stand better informed and clearly benefitted by increased awareness on disease prevention and control.

9. The way forward

In India, some States (Sikkim and Himachal Pradesh) and UTs (Lakshadweep, Daman & Diu and Puducherry) are already reporting <100 cases, while others recorded substantial decrease (>50%) in cases over past few years, for example, Assam and Karnataka (**Table 1**). Given the reducing transmission levels, malaria elimination at sub-national level is seemingly achievable. However, the emergence of artemisinin-resistant malaria and possible spread, coupled with multiple insecticide resistance in disease vectors (**Table 2**), could reverse the gains for which disease surveillance, monitoring and evaluation should be the corner-stone activity. *P. vivax* and asymptomatic malaria continue to be unattended and should be accorded priority for reducing parasite reservoir in the endemic communities. Priority should be accorded for strengthening healthcare services in high-risk States of eastern, central and north-eastern States helping mitigate disease onslaught and deter entry and spread of drug-resistant strains in India. Inter-sectoral linkages with research establishments and medical colleges for developing innovative newer interventions (possibly vaccines), assessing therapeutic efficacy of

antimalarials and upgradation of drug-treatment policy, human resource development and field-evaluation of newer technologies, including innovative vector control approaches, are vital before these are incorporated in the control program. Disease epidemiology is rapidly changing in the face of fast urbanization, deforestation and anomalous weather conditions opening new vistas, which must be watched for targeting interventions in place and time. Mosquito vectors are invading new territories, and adapting to altered ecology establishing outdoor transmission in response to strengthening insecticide interventions, which are largely based on indoor residual applications. We strongly advocate the judicious mix of technologies used in an integrated manner to overcome the challenges of outdoor transmission and growing insecticide resistance threatening the efficacy of present day intervention tools. There remains of scope of newer interventions in Indian geo-epidemiological conditions, namely, eave tubes, attractive sugar baits, nano-synthesized pesticides loaded with microbial- and plant-borne compounds, for trapping adult mosquito vectors and population reduction presently being put to field evaluation in African countries (Beier, personal communication). It is the high time to strengthen the entomological component at the State/Zonal level for monitoring vector densities and insecticide resistance targeting interventions averting impending disease outbreaks. Above all, educating communities and stakeholders on disease prevention and control should be the guiding principle for increased compliance and harmonious action. Increased allocation of resources (both from State and Central assistance), for ensuring universal coverage of interventions, should be given utmost priority in reducing parasite reservoir much below threshold density disrupting transmission [87]. It is time accelerating towards elimination and let there be no complacency at various echelons of operation for keeping disease at bay. Outside Africa, Southeast Asia is the largest contributor of cases and source of spread of drug-resistant malaria for which it is strongly advocated that larger share of global investments in this part of the World would go a long way in alleviating poverty and malaria. In summary, given the enormity of disease burden and myriad of issues, odds are all against, yet concerted efforts should be made in rendering malaria a thing of the past; together we can beat malaria.

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Acronyms

ACT	artemisinin-based combination therapy
AIM	action and investment to defeat malaria

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AL	artemether lumefantrine
API	annual parasite incidence
APLMA	Asia Pacific Leaders Malaria Alliance
APMEN	Asia-Pacific Malaria Elimination Network
ASHA	Accredited Social Health Activist
AS + SP	artesunate + sulfadoxine-pyrimethamine
CQ	chloroquine
DDT	dichloro-diphenyl-trichloroethane
G6PD	glucose-6-phosphate dehydrogenase
GMS	Greater Mekong Subregion
IDSP	Integrated Disease Surveillance Project
IRS	indoor residual spray
ITN	insecticide treated nets
ITS-2	internal transcribed spacer-2
LLIN	long-lasting insecticidal nets
NGO	Non-Governmental Organization
NHM	National Health Mission
NVBDCP	National Vector Borne Disease Control Programme
PCR	polymerase chain reaction
Pf	*Plasmodium falciparum*
Pfk 13	*Plasmodium falciparum kelch 13*
RBM	roll back malaria
RDT	rapid diagnostic test
r-DNA	ribosomal-DNA
SCAR	Sequence Characterized Amplified Region
SEAR	WHO Southeast Asia Region
SP	sulfadoxine-pyrimethamine
UT	Union Territory
WHO	World Health Organization

Author details

Sunil Dhiman[1]*, Vijay Veer[2] and Vas Dev[3]

*Address all correspondence to: sunildhiman81@gmail.com

1 Defence R&D Establishment (DRDE), Gwalior, Madhya Pradesh, India

2 Defence Research Laboratory, Tezpur, Assam, India

3 Senior Scientist (Retired), formerly with the National Institute of Malaria Research, New Delhi, India

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