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Defeating malaria in the North-East region: the forerunner for malaria elimination in India

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Running title: Defeating Malaria in North-East India

Abstract

India is a malaria endemic country which is targeting malaria elimination by 2027. Transmission intensities are low-to-moderate depending on the region supported by multiple disease vectors. Among these, comparatively North-East India contributes to high proportions of malaria cases annually, the majority of which are due to *Plasmodium falciparum* (90%). *Anopheles minimus* and *An. baimaii* (sibling species in the *An. dirus* complex) are widely

prevalent and incriminated as vectors of malaria. Number of intervention tools were field-evaluated beginning 1988 to date against disease vectors and causative parasites to contain the spread of malaria. These included (i) insecticide-treated netting materials (ITNs) for vector control, (ii) rapid diagnostic tests (RDTs) for *in situ* diagnosis, and (iii) therapeutic efficacy of artemisinin-based combination therapies (ACTs) for improved drug-policy; all of which were incorporated in healthcare services resulting in substantial disease transmission reduction. Populations of both *An. minimus* and *An. baimaii* were observed depleting, instead *An. culicifacies s.l.* recorded to be fast invading degraded forests and assessed to be resistant to multiple insecticides. Of the two prevalent *Plasmodium* species, while *P. vivax* continued to be susceptible to chloroquine therapy, *P. falciparum* had emerged resistant to most available antimalarial drugs except ACTs over space and time and spreading to peninsular India threatening elimination efforts. Disease transmission trends were observed to be declining for which the state of Assam has made huge strides reporting steady fall in cases each passing year vis-à-vis Meghalaya, Mizoram and Tripura (all sharing international border with Bangladesh), in which malaria transmission remained uninterrupted. Consequently, control of malaria in the North-East region of India is of immediate importance and needs prioritization for intensified disease surveillance and control interventions coupled with improved access to healthcare services mitigating risk of disease outbreaks and spread of drug-resistant malaria helping realize the goal of malaria elimination in the country.

Keywords: Malaria transmission, Vector control, Drug-resistance, Malaria elimination, Cross-border malaria, North-East India.

1. Introduction

The North-East region of India is of strategic significance for sharing vast international borders with other South-East Asian countries of Bhutan, Myanmar and Bangladesh. All these neighbouring countries are historically endemic for drug-resistant malaria for which North-East (NE) is believed to be corridor for spread to peninsular India and further westwards (Sharma, 2012b). Malaria transmission is perennial and persistent in most parts of the NE region (22⁰N – 29⁰5'N latitude and 88⁰ E - 97⁰30'E longitude) contributing >10% of recorded *Plasmodium falciparum* cases in the country (Dev et al., 2003a). Among its seven sister states including Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, and Tripura (Fig. 1), Assam is the major state constituting 66% of the total population of the NE region and gateway for economic activities having major industries, educational institutions, and state of the art healthcare facilities. Malaria has been a major debacle in British India (before 1947, pre-DDT era) with 75 million cases and 0.8 million deaths, of which 10% of cases and 20% of deaths are estimated to have occurred in the NE region alone, known for having history of devastating disease outbreaks (Sharma, 1998). DDT proved to be panacea containing malaria in large tracts of land across India, but transmission continued in some foci due to poor accessibility to prophylaxis and treatment, as well as inadequate interventions perpetuating development of hidden sea of drug-resistant malaria. Host of challenges, including drug-resistant parasite, insecticide-resistant vector populations, poor logistics, and complacency post-1960s, contributed to resurgence of malaria in the 1970s characterized by recurring disease outbreaks and high rise in cases and deaths solely attributed to *P. falciparum* (Sharma, 1996, 2012a). In 1976, as many as 6.45 million cases were recorded to have occurred in the country, 90% of which were *P. vivax* cases, the remaining 10% were due to *P. falciparum*, proportions of the latter were seen rising each

passing year. To arrest the development and spread of drug-resistant malaria, *P. falciparum* Containment Programme (*PfCP*) during the 1978-1988 period helped mitigate the disease onslaught to some extent but malaria transmission continued unabated (Ray, 1979; Ray et al., 1988). Disease outbreaks were returning amidst public outcry affecting industrial growth and socio-economic development of the region. It was amply clear that control interventions against both disease vector and parasite were inapt calling for renewed strategies that are community-based, self-sustainable and cost-savvy.

Taking stock of the situation, the 'Integrated Disease Vector Control (IDVC)' project was conceived to address the multiple challenges to contain upsurge of cases in different epidemiological transmission settings across the country (Sharma, 1987; Sharma et al., 1986). The strategy included understanding the disease epidemiology afresh including: (i) vector bionomics and disease transmission relationships in a given ecological context, (ii) field-testing alternate interventions that are eco-friendly for vector control, (iii) monitoring therapeutic efficacy of antimalarials for improved drug-policy in place and time for radical cure, and (iv) health education and awareness campaigns for eliciting participation of endemic communities. Included in this communication are the salient observations of aforementioned research activities and outcome that helped rolling back malaria in high-risk areas of the NE region once considered intractable.

2. Malaria transmission and changing dynamics

Historically, the NE region consistently contributed significant number of malaria cases in relation to population share of the country (Dev et al., 2003a). In 2019, NE representing 4% of the national population generated 14.6% of *P. falciparum* and 22.1% of reported death cases (Table 1). Drug-resistant malaria (chloroquine resistance) was first recorded in the region in 1973 for which NE is considered nidus for proliferation and spread (Sehgal et al., 1973). Both *P. falciparum* and *P. vivax* are prevalent, but the former is by far the dominant

parasite (90%). Disease transmission trends are seen steadily declining commencing 2006, however, *P. falciparum* continues to be the predominant infection (Fig. 2). All malaria-attributable deaths were invariably attributed to confirmed diagnosis of *P. falciparum* (Dev et al., 2001b).

In most parts of NE, transmission of both plasmodial species is perennial with distinct seasonal peak corresponding to months of rainfall (April-September); for remainder of the year, cases were recorded but much less in number (Fig. 3). Amongst NE states, up until turn of the millennium, Assam invariably contributed nearly to 50% of the reported cases marked by sporadic focal disease outbreaks (Dev et al., 2006), post which states of Meghalaya, Tripura and Mizoram (the bordering states to Bangladesh) consistently constituted bulk of malarial morbidity mostly due to *P. falciparum* (>90%) (Table 2). Conversely, *P. vivax* was the most predominant infection in sub-tropical climate zones of up northern states of Arunachal Pradesh and Nagaland, except Manipur in which both parasite species occurred nearly in equal proportions, while in Assam *P. vivax* proportions remained $\leq 30\%$ (Sharma et al., 2015) (Fig. 1).

Table 1 Relative contribution of malaria cases and attributable mortality from North-Eastern states of India for data based on 2019*

No. of cases	India (pop. ~1.37 billion)	North-Eastern states (pop. ~52 million)	% share contribution of cases from North-Eastern states (pop. ~4 %)
No. of malaria cases	338,494	25,229	7.45
No. of <i>P. falciparum</i> cases	156,940	22,918	14.60
No. of deaths	77	17	22.07

*Source: National Vector Borne Disease Control Programme, India. Data of 2020 is yet provisional, thus not included.

Table 2 Comparative epidemiological data of malaria transmission in North-Eastern states of India during (2016-2019)*

State	Year	Pop. (millions)	No. of blood-smears examined for malaria parasite	No. of malaria positive		Annual blood-smear examination rate (%)**	Annual parasite incidence***	No. of malaria-attributable deaths
				<i>P. falciparum</i>	<i>P. vivax</i>			
Arunachal Pradesh	2016	1.57	151,590	895	2,233	9.65	1.99	2
	2017	1.60	153,620	488	1,058	9.60	0.97	0
	2018	1.63	145,353	154	471	8.91	0.38	0
	2019	1.67	139,689	27	112	8.36	0.08	0
Assam	2016	33.90	3,032,997	5,686	2,140	8.94	0.23	6
	2017	34.49	2,669,423	3,494	1,787	7.74	0.15	0
	2018	35.01	2,364,621	2,859	957	6.75	0.11	2
	2019	35.60	4,352,477	872	587	12.22	0.04	4
Manipur	2016	2.97	94,115	58	64	3.17	0.04	0
	2017	3.21	115,733	22	58	3.60	0.02	0
	2018	3.27	98,375	3	9	3.01	0.004	0
	2019	3.37	231,833	5	11	6.88	0.004	0
Meghalaya	2016	3.21	468,254	31,867	3,280	14.58	10.95	45
	2017	3.47	421,145	14,418	2,036	12.14	4.74	12
	2018	3.53	326,051	6,065	329	9.23	1.81	6
	2019	3.68	422,237	2,364	251	11.47	0.71	4
Mizoram	2016	1.20	267,747	5,907	1,676	22.31	6.32	9
	2017	1.23	213,601	4,974	741	17.37	4.65	4
	2018	1.26	218,178	3,937	359	17.31	3.41	3
	2019	1.28	232,916	8,010	533	18.19	6.67	8
Nagaland	2016	2.98	252,232	316	512	8.46	0.28	0
	2017	3.12	254,038	188	206	8.14	0.13	1
	2018	3.20	255,888	24	89	7.99	0.03	0
	2019	3.27	225,519	4	16	6.89	0.006	0
Tripura	2016	3.94	351,392	9,545	1,001	8.91	2.68	14
	2017	4.42	392,452	6,571	480	8.87	1.59	6
	2018	4.54	483,982	12,600	479	10.66	2.88	13
	2019	4.68	619,912	11,636	801	13.24	2.66	1

*Source: National Vector Borne Disease Control Programme, India, **% of population screened for malaria parasite,

***number of malaria cases per thousand population. Data of 2020 is yet provisional, thus not included.

In Assam, even though *P. falciparum* continued to be predominant (~70%), case incidence declined substantially commencing 2006 (Fig. 4). In 2019, the number of cases declined by >80% compared to 2016 (NVBDCP, 2020). Malaria map in the state of Assam is clearly shrinking. In 2017, most districts of Assam (except those dominated by indigenous tribes including Karbi-Anglong, Kokrajhar and Udalguri) reported <1 case incidence per 1,000 population (Fig. 5). Transmission was observed to be deaccelerating with steady decline in case incidences each passing year with all districts reporting <1 annual parasite incidence (API) in 2019. Distribution of *P. vivax* cases, however, varied among districts. Districts of upper Assam including Tinsukia, Dibrugarh and Dhemaji had preponderance of *P. vivax* cases (>60%) opposed to south Assam in which *P. falciparum* predominated (>70%) (Source: Vector Borne Disease Control Programme of Assam). In the remaining districts of central and lower Assam, *P. vivax* proportions varied anywhere between 31%-60%. These data are of significance for formulating species-specific control interventions and allocating resources for logistics and preparedness to combat the disease illness. Nevertheless, the state of Assam has made laudable progress in achieving substantial disease transmission reduction over the past decade (Dev, 2009b), which was accomplished based on research data and implementation of technologies as detailed below.

3. Malaria vectors, bionomics and evolution of control interventions

North-East India receives heavy rainfall (1.5-2 meters/year) and climatic determinants including relative humidity (70-80%) and mean temperatures (20-30⁰C) are conducive for mosquito proliferation during most parts of the year. NE region is one of the richest tropical bio-sphere having large evergreen forest cover supporting diverse fauna and flora. Mosquito fauna is rich and breeding sources are innumerable encompassing wide range of ecological habitats, viz., rice-agroecosystem, foothill seepage-water streams, jungle water pools, riverine ecology, etc. Malaria transmission is supported by multiple vector species that are proven

efficient *Plasmodium* vectors for their strong predilection for human host (Dev and Sharma, 2013). Among these, *Anopheles minimus* was incriminated across NE states and held responsible for fulminating disease outbreaks in the pre-DDT era (Viswanathan et al., 1941). With the advent of DDT and large-scale application of residual spraying in 1960s, *An. minimus* was believed to have disappeared and other mosquito species, viz., *An. philippinensis*, were implicated in disease agents transmission (Rajagopal, 1976). There was substantial transmission reduction under vertical execution of control programme, except few residual foci rendered inaccessible due to incessant rains and poor communication means. For variety of logistic and operational constraints during 1970s, malaria resurged with ‘vengeance’ and active disease transmission resumed in large tracts of hills and valleys (Sharma, 1996). Focal outbreaks were returning with insurmountable morbidity and mortality amidst public chaos and penury of living in poverty. Communities had turned hostile for not permitting indoor residual spraying (IRS) resulting in inadequate coverage of risk-populations years together and build-up of vector density well beyond threshold. Under modified plan of operation beginning 1977 (horizontal execution), operational costs were seen rising but not resulting in transmission reduction proportional to inputs. Instead, transmission continued uninterrupted prompting new vistas for operational research inventing newer interventions that are community-based, feasible and cost-savvy.

At the very outset, it was considered essential first to ascertain the prevalence of disease vectors and their bionomical characteristics *de novo* in the given ecological context enabling targeting species-specific interventions (Table 3). Amidst speculations, entomological surveillance revealed that the main vector species, *An. minimus*, had staged comeback with bionomical characteristics intact and was abundant, recorded resting indoors human dwellings and incriminated by detection of live/motile sporozoites in salivary glands (Dev, 1996a; Dev and Manguin, 2016). Given the vector control interventions in force, sporozoite

infections were recorded in all seasons of the year with peak vector density and transmission intensities corresponding to the wet season (April–September). Foothill villages located nearer (<1 km) to perennial seepage streams (breeding habitats of *An. minimus*) and those away from the nearest healthcare facility (>5 kms) were assessed to be at high-risk requiring prioritization for interventions both against vector and parasite (Dev et al., 2004). Invariably, active disease transmission was supplemented by *An. baimaii* (sibling-species within the *An. dirus* complex and major malaria vector in Asia) in the forest-fringe villages during summer and *An. fluviatilis*, later identified as hyper-melanic form of *An. minimus*, in winter season (November–March/April) (Dev and Sharma, 1995; Singh et al., 2010). Nevertheless, *An. baimaii* (jungle/forest breeder) was reckoned equally efficient vector in forested villages in upper Assam districts bordering Myanmar and implicated in transmission and spread of drug-resistant malaria across borders (Dutta et al., 1989; Prakash et al., 2001).

Despite the fact that both species, *An. minimus* and *An. baimaii*, remained sensitive to DDT for decades of IRS operations, control of these mosquito populations was in vain for variety of reasons, viz., (i) spray coverage of target population remained off target (<50%) for lack of community acceptance, (ii) poor quality control and lack of intermediate supervision, (iii) delayed spraying operations (often not coinciding to peak transmission season), and missing rounds (restricted to one of scheduled two rounds of DDT) for logistic reasons, (iv) outdoor resting characteristics of *An. baimaii* (Prasad, 2009); all that compounded to operational failure. To overcome these constraints, the advent of insecticide-treated netting materials (ITNs) in 1990s ushered a new era for vector control using pyrethroids (Jana-Kara et al., 1995). Field-evaluation of pyrethroid-impregnated mosquito nets, first attempted in Assam beginning 1988 against *An. minimus* as malaria vector, proved to be an effective intervention tool preventing infective mosquito bites. The strategy involved judicious use of insecticide and was widely accepted by communities at risk averting malarial attacks. This

technology was instant success and put to field-test for feasibility studies in different epidemiological settings across endemic states (Dev and Dash, 2008). However, it required re-impregnation of community-owned nets every six-monthly interval for which coverage remained <5% of the target risk population in a given year during 2009-2011 (Source: Vector Borne Disease Control Programme of Assam).

Table 3 Molecular taxonomy and bionomical characteristics of the mosquito vector species prevalent in North-East India (Manguin et al., 2008)

<i>Anopheles</i> species/taxa	Diagnostic tools*	Breeding habitats	Feeding behaviour (peak biting activity)	Seasonal abundance (resting habitats)	Incrimination status (average sporozoite infectivity rate)	Insecticide susceptibility status	Remarks
<i>An. minimus</i> s.s..	PCR based sequencing of rDNA ITS2; 28S rDNA-D3 AS-PCR, RFLP-PCR, SSCP-PCR	Perennial foothill seepage water streams, irrigation channels	Highly anthropophilic (01:00 – 04:00)	Perennial species (human-dwellings indoors)	Incriminated (3%)	Highly susceptible to DDT, Malathion & Pyrethroids (deltamethrin)	Populations are reportedly depleting. The only species present in India among three within the Minimus complex
<i>An. baimaii</i>	Polytene chromosome karyotype, cross-fertility data, PCR based sequencing rDNA ITS2; SCAR based PCR, AS-PCR, RFLP	Jungle and forest water pools, elephant foot-prints	Highly anthropophilic (23:00 – 03:00)	Monsoon species/wet season (outdoor biting, essentially exophagic and outdoor resting exophilic species)	Incriminated (3%)	Highly susceptible to DDT, Malathion & Pyrethroids (deltamethrin)	Populations are reportedly depleting. One out of two species present in India among the eight species within the Dirus complex
<i>An. fluviatilis</i> s.l. = hyper-melanic <i>An. minimus</i>	Polytene chromosome karyotype/fixe	Seepage water foothill streams, irrigation	Highly anthropophilic (20:00-24:00)	Winter species, human dwellings	incriminated (3%)	Highly susceptible to DDT,	Populations of what formerly identified as <i>An.</i>

	paracentric inversions, PCR based sequencing of rDNA ITS2; 28S rDNA-D3	channels, riverine ecology, terraced rice-fields, shallow wells		indoors, foothill ecotype		Malathion & Pyrethroids (deltamethrin)	<i>fluviatilis</i> have now been characterized to be hyper-melanic variant of <i>An. minimus s.s.</i>
<i>An. culicifacies s.l.</i>	Polytene chromosome karyotype/fixed paracentric inversions, PCR based sequencing of rDNA 28S-D3, ITS2, 28S-D2 domain; RFLP-PCR; AS-PCR; RFLP-PCR; mt-DNA COII	Rainwater collections, riverine pools, rice fields, seepage water, streams, borrow pits, irrigation channels	Predominantly zoophilic	Monsoon species/wet season (human-dwellings indoor and cattle sheds)	Incriminated, sporozoite infection rate of (<1%)	Resistant to DDT, Malathion & Pyrethroids (deltamethrin) (Unpublished data)	Among its 5 sibling-species within the Culicifacies complex, species B, which is non-vector, has been characterized as prevalent in NE region

*rDNA: ribosomal DNA; AS-PCR: Allele-specific polymerase chain reaction; SCAR: Sequence characterized amplified region; ITS2: Internal transcribed spacer 2; RFLP: Restriction fragment length polymorphism; mtDNA COII: mitochondrial DNA Cytochrome oxidase II; SSCP: Single-strand conformation polymorphism.

Subsequently, ITN technology was further upgraded to factory manufactured long-lasting insecticidal nets (LLINs) made of either polyester (pyrethroid coated) or polyethylene fibre (pyrethroid incorporated) adequate for retaining residual bio-efficacy 3-4 years (net serviceable life) of continuous use without any need for re-impregnation (Dev, 2009c). The advent of LLINs have galvanized vector control, which were evaluated to be sustainable intervention in India and elsewhere mandating mass-scale distribution. This technology is presently being continuously upgraded with newer class or combination of insecticides and subject to field-evaluation to contain resistant vector populations (Gunasekaran et al., 2020; Sahu et al., 2019). LLINs are widely accepted and increasingly in demand for blanket coverage globally. The Indian national control programme has endorsed the implementation

of this intervention targeting increased coverage of risk populations so much so that as many 49.5 million nets have been distributed in high-risk districts/states during 2016-2018 (Source: National Vector Borne Disease Control Programme). In NE region, the state of Assam (besides supplies from the National Control Programme) has taken the lead for large scale procurement from its own resources and supplied gratis resulting in appreciable transmission reduction in pockets once considered intractable (Fig. 4). Mosquito populations of both *An. minimus* and *An. baimaii* are reportedly depleting, instead *An. culicifacies* s.l. is fast invading degraded forests of Assam and its populations have been recorded as multi-insecticide resistant rendering less amenable to control (Akhtar et al., 2016; Raghavendra et al., 2017; Sharma and Dev, 2015). However, among the five sibling-species of the Culicifacies complex, it is species B, a non-malaria vector, which has been characterized to be prevalent in NE region; yet there are reports of invasion of other sibling-species as well with records of malaria transmission incrimination (Nutan Nanda, personal communication). NE region is largely rural barring few town areas for which blanket coverage of populations at any risk holds the key in keeping vector populations at bay disrupting transmission to conquer malaria. Logistic requirement, however, is huge for which greater allocation of resources is required at this time.

4. Monitoring therapeutic efficacy of antimalarials and drug-policy

Although NE is endemic for both *P. falciparum* and *P. vivax* malaria, distribution and proportion of parasite species varied across states (Fig. 1). Active disease surveillance and treatment had been the key-elements ever since inception of the National Malaria Elimination Programme (NMEP) in 1958. Chloroquine had been the choice drug for treatment of blood schizont stage infections of both parasite species (Sharma, 2007). While *P. vivax* is still susceptible to standard chloroquine therapy (Valecha et al., 2006), drug-resistance in *P. falciparum* had surfaced in NE (Karbi-Anglong district of Assam) as early as 1973 (Sehgal et

al., 1973), but in practice chloroquine therapy remained in vogue up until turn of the century. The drug-resistant foci soon became widespread throughout the NE region and certain high-risk districts of other endemic states resulted in steady increase of *P. falciparum* cases across the country (Sharma, 2012a; Valecha et al., 2009a). In addition, the rise in proportions of *P. falciparum* cases was unstoppable due to multitude of factors including fragmented disease surveillance, lack of entomological data and inadequate vector control interventions, and above all poor access to treatment resulting in sea of asymptomatic reservoir and continued transmission (Fig. 6) (Dev, 2019b).

Focal disease outbreaks were recurring and invariably held solely due to high rise in *P. falciparum* cases (Dev, 1996b; Dev et al., 2001a; Prakash et al., 2000). The drug-policy first came into being in 1982 focused on evidence-based data for radical cure of *P. falciparum* cases and has evolved significantly over time and space (Anvikar et al., 2014; Shah et al., 2011) (Fig. 7). Systematic *in-vivo* follow up investigations revealed that chloroquine-resistant malaria was widely prevalent in alarming proportions than assumed, more so along Indo-Myanmar and Bangladesh border districts (Dev et al., 2003b; Mohapatra et al., 2003). The alternate therapy for treatment of chloroquine-resistant malaria by sulfadoxine-pyrimethamine (SP) beginning 2004 also did not help for long and resistance to this combination surfaced rather fast leaving quinine the only viable option for radical cure (Fig. 7) (Dua et al., 2003). It was at fag end of the 20st century that induction of artemisinin (the “wonder drug”) brought sea change in treatment choices for its fast action and being easier to administer reaching out in remote high-risk pockets (Dev et al., 1998). As a matter of policy, artemisinin derivatives (arteether/artemether/artesunate), initially intended to be used selectively for complicated cases, were widely used in private practice (Mishra et al., 2011), and later monotherapy was banned at turn of the millennium in 2009 ushering in artemisinin-

based combination therapies (ACTs) using variety of long-acting partner drugs to clear the resistant parasite populations (Fig. 7) (Dev, 2009a).

Among available options globally, artesunate+ sulfadoxine-pyrimethamine (ASP) was used in the programme for treatment of resistant malaria firstly in selected districts and later rolled out for all endemic districts across the country for every single case of *P. falciparum* (Dev et al., 2009; Mishra et al., 2012). And to no surprise, resistance to this combination surfaced within few years in border districts of NE resulting in replacement with artemether+lumefantrine (AL) specific to this region, which is currently used in the programme since 2013 (Mishra et al., 2014; Valecha et al., 2009b). There are already signs of emerging artemisinin resistance evidenced by molecular markers along international borders for delayed parasite clearance, including *Kelch 13* protein mutations (Das et al., 2018; Mishra et al., 2015). Number of newer ACTs are in pipeline for therapeutic efficacy, but it would be long before these regimens become available (Tse et al., 2019). The advent of rapid diagnostic test kits (RDT) and rollout of ACTs have helped achieve appreciable transmission reduction by early diagnosis and radical cure to large extent (Fig. 2); challenge now is to reach out the marginalized population groups ensuring access to prompt diagnosis and treatment. The declining malaria transmission trends in NE might as well be attributed to strengthening healthcare services in rural areas by door-to-door surveillance by accredited social health activist (ASHA) female workers; an initiative under National Health Mission (NHM) of the Government of India that helped ensure on-the-spot diagnosis and treatment.

NE is considered gateway of drug-resistant malaria for sharing vast border with Myanmar emanating from Greater Mekong Subregion (GMS) on way to peninsular India and westwards (Sarma et al., 2019). The international borders are porous and cross-migration is unstoppable, permitting mixing of parasite strains and resulting in disease outbreaks in non-immune population groups particularly deployed at military border outposts. To prevent entry

and spread of multi-resistant strains across borders, there is an imperative need to strengthen cross-border initiative for sharing data on disease surveillance and monitoring therapeutic efficacy of drug-regimen in force periodically before it is too late. The NE region is heavily fortified with defence personnel hailing from different states of India and have been diagnosed to be suffering from malaria in high frequencies often presenting severe clinical picture due to varied immune-status (Dhiman et al., 2010; Pardal et al., 2009; Patra and Dev, 2004). These service personnel are invariably on the move within and outside NE states resulting in spread of drug-resistant parasite strains to the rest of India. The relentless march of *P. falciparum* malaria is of grave concern for rising proportions making malaria elimination a herculean task (Dev, 2019b). The ecological accession and spread of multi-insecticide resistant populations of *An. culicifacies* s.l. in NE region is further exacerbating the situation amounting to inadequate interventions perpetuating transmission of multi-resistant malaria (Raghavendra et al., 2017).

While *P. falciparum* malaria remains amenable to control interventions due to late appearance of gametocytaemia; *P. vivax* malaria is stubborn parasite for its continuing transmission and relapsing characteristics resulting in extended morbidity (no mortality recorded in India). Even though proportions of this parasite constituted miniscule of total cases (~10%) for data based on 2019 specific to NE region (Fig. 2), transmission of this parasite is likely to persist due to latent hypnozoites, one that to look out for post-elimination calling for concerted action against all parasite species to end malaria (Lover et al., 2018).

5. Perspectives

With many countries certified to be malaria-free, the world is already aspiring malaria eradication (Dev and Manguin, 2020; Feachem et al., 2019). India is aiming towards malaria elimination by 2027 (Narain and Nath, 2018), seemingly an achievable target given the

steady decline in cases with less than a half a million cases in 2019 and deaths fewer than 100 maintaining trends downwards. However, reported cases represent only trends for many cases not captured in the present surveillance system. Disease surveillance itself is far from complete and can be best described as fragmentary. Besides, cases treated by the private and public sector alike are not included in the annual tally. WHO estimates 5.5 million cases compared to the 338,500 reported, and mortality to be 100-fold higher at 7,700 (WHO, 2020c). Nevertheless, India has made impressive gains in achieving 83.34% reduction in malaria morbidity and 92% in malaria mortality between 2000 (2,031,790 cases, 932 deaths) to 2019 (338,494 cases, 77 deaths) (WHO, 2020c). India holds the capacity to defeat malaria with the vast human resource and accumulated knowledge on disease vectors and transmission dynamics (Dev, 2020). At this juncture, given the declining transmission trends (Dhiman et al., 2018), complacency at any level of operation and diversion of resources would prove to be catastrophic reversing the gains in battle against malaria. Still there are many slips to recount a few: (i) huge asymptomatic parasite reservoir still untapped, (ii) emergence and spread of insecticide-resistant mosquito vector populations, (iii) an emerging paradigm of outdoor transmission establishing extra-domiciliary transmission hard to control, (iv) multi-drug resistant malaria and rising proportions of *P. falciparum* (the killer parasite), (v) hard to control vivax malaria due to latent hypnozoites responsible for relapse phases, (vi) and above all, huge funding gap for universal coverage of interventions of populations at risk (Dev, 2019a; Ghosh and Rahi, 2019). However, hope is there with an ample scope of newer innovative technologies to contain an emerging paradigm of outdoor transmission, for instance by according protection in forest dwellers/forest-fringe settlements (Beier et al., 2018; Carnevale and Manguin, 2021; Durnez and Coosemans, 2013). It is an opportune time for increased allocation of resources prioritizing NE region spearheading high-risk states of Tripura, Mizoram and Meghalaya ensuring blanket coverage with improved access to

prevention and treatment (Khetrapal Singh and Travis, 2019; Lahariya, 2019). There is every likelihood that vectors of lesser significance, viz., *An. philippinensis/nivipes*, *An. annularis s.l.*, *An. subpictus s.l.*, *An. maculatus s.l.* may assume greater role in transmission post-elimination in absence of major vector species of *An. minimus* and *An. baimaii* populations of which are depleting (Dev, 2020; Prakash et al., 2004). Thus, entomological surveillance, monitoring and evaluation of the control programme are tantamount to malaria elimination and should be the continuing activity post-elimination to maintain malaria-free status.

6. Conclusions

Conquering malaria in NE region is of paramount importance for two main reasons: (i) for consistently contributing bulk of reported *P. falciparum* cases (>10%) and malaria-attributable deaths (20%) in the country annually and (ii) for being an epicentre for multiplication and spread of drug-resistant malaria. Even though, NE states are reporting reducing transmission trends each passing year, yet disease burden is enormous and deserves priority for larger share of allocation of resources. However, among seven sister states, Assam, formerly contributing most cases (>50% of total reported cases from NE region) up until earlier part of the 21st century, has made huge strides in reducing transmission over the past decade presently contributing <6% of total cases for data based on 2019 despite its largest share of population (66% of total NE region). Transmission trends are clearly decelerating in the state of Assam commencing 2006 with substantial disease transmission reduction each passing year. In contrast, states of Meghalaya, Mizoram and Tripura; the trio (17% of population share) contributed nearly 90% of disease burden mostly *P. falciparum* cases. All these three states have a lot more in common for sharing vast international border with Bangladesh and having large concentration of indigenous tribal populations living in the forest-fringe/inter-border villages. Transmission intensities in these states/bordering districts are intense and are prone to disease outbreaks evidenced by high rise in cases and attributable

deaths (Dev et al., 2015; Dev et al., 2010b; Zomuanpuii et al., 2020). Periodic monitoring of therapeutic efficacy of anti-malarial drug-regimens revealed fast dissipating radical cure mandating continuous follow up investigations in states/districts sharing international border not only with Bangladesh in the south and but also Myanmar in the east ensuring informed drug-policy in time and place (Mishra et al., 2014; Mishra et al., 2015; Mishra et al., 2012; Valecha et al., 2009b). India is signatory to Asia Pacific Malaria Elimination Network (APMEN) and Asia Pacific Leaders Malaria Alliance (APLMA) for coordinated action towards common goal of 'freedom from malaria' based on shared data and experiences (Dev, 2020). There is ample body of evidence that radical cure by rollout of ACTs has helped transmission reduction to greater extent and should be enforced for compliance inclusive of public and private sector alike. There is an imperative need to maintain vigil forbidding circulation of counterfeit antimalarials and prioritizing strengthening healthcare services in the marginalized population groups living under impoverished conditions averting impending disease outbreaks and spread of drug-resistant malaria. With demonstrated success of LLINs in preventing infective mosquito bites and reducing mosquito vector density (Dev et al., 2010a; Prakash et al., 2009), it is the opportune time aiming universal coverage of population at any risk of malaria helping achieve target of malaria elimination by 2027. What even more important (that has been clearly overlooked) is to make extra-provision for net replacement every three years of worn-out LLINs in beneficiary population groups to provide uninterrupted protection (Dev et al., 2016). In addition, a greater involvement to control outdoor malaria transmission should be implemented for achieving the goal of malaria elimination (Durnez and Coosemans, 2013; Killeen, 2014). Let the pandemic due to COVID-19 not disrupt the supply chain of logistics to end malaria in the region rather avail the opportunity in strengthening health systems to address infectious diseases (Nema et al., 2021; WHO, 2020a, b). Defeating malaria in NE would ensure success in both achieving cherished

goal of malaria elimination in India and helping prevent re-establishment of transmission in malaria-free territories. Besides, the experience gained in India would also benefit neighbouring countries of Bhutan and Nepal fast accelerating towards elimination, as well as Bangladesh and Myanmar with strategies that could be implemented to reduce the burden of malaria and move faster towards malaria elimination (Wangdi et al., 2016).

Author contributions

VD: Conceptualization, data analyses, writing initial draft. SM: Data analyses, writing, review and editing. Both authors analysed the literature data.

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Legend of figures

Fig. 1. Localization of the 7 states in North-East India with the prevalence of *Plasmodium vivax* and *P. falciparum* cases in each state from data based on 2016-2019. International borders are demarcated by bold line and state boundaries are color-coded showing relative abundance of malaria parasite species. Inset is the map of India showing geographical location of North-East region. Source: National Vector Borne Disease Control Programme, India.

Fig. 2 Reducing trends of malaria transmission in North-Eastern states based on cumulative data of the seven sister states, including Arunachal Pradesh, Assam, Meghalaya, Mizoram, Nagaland, Manipur and Tripura (2014-2019). SFR (smear falciparum rate) and SVR (smear vivax rate) denote % blood-smears positive for malaria parasite. Pf = *Plasmodium falciparum*, Pv = *Plasmodium vivax*. Data source: National Vector Borne Disease Control Programme, India.

Fig. 3 Transmission of *Plasmodium falciparum* (Pf) and *Plasmodium vivax* (Pv) malaria for data based in Assam, North-East India. During 2006 *Plasmodium falciparum* cases were treated with sulfadoxine-pyrimethamine (SP), and *Plasmodium vivax* with chloroquine + primaquine for 5 days schedule @ 0.25mg/kg/day. Beginning 2007, SP was replaced with artesunate + SP (ASP) for *P. falciparum* cases, and for *Plasmodium vivax*, 5-day course of primaquine was replaced with 14-day treatment @ 0.25 mg/kg/day for radical cure. Beginning 2013, drug-policy was upgraded replacing ASP with AL (artemether + lumefantrine) for treatment of *P. falciparum* specific to North-East India. Data source: Vector Borne Disease Control Programme of Assam. Given the proven efficacy of AL, transmission trends are clearly deaccelerating.

Fig. 4 Malaria transmission in Assam (1991-2019). SPR denotes smear positivity rate of blood-smears examined for malaria parasite. Pf = *Plasmodium falciparum*. %Pf relates to per cent of *P. falciparum* cases of total positive cases for any malaria parasite. API represent number of malaria positive cases per 1,000 population/year. Data source: Vector Borne Disease Control Programme of Assam.

Fig. 5 District map of the Assam state stratified by annual parasite incidence (API) for data based on 2017. High-risk districts reporting >1 case per 1,000 population are colour coded with red. However, in 2018, all high-risk districts except Udalguri reported API <1; but in

2019 all districts reported API <1. API denotes the number of cases per 1,000 population/year. Data source, Vector Borne Disease Control Programme of Assam. Inset is the map of India, showing the geographical location of Assam in the North-East region of India.

Fig. 6 Rising proportions of *Plasmodium falciparum* cases in India. Data source: National Vector Borne Disease Control Programme. While malaria cases have consistently declined from 1996 onwards, *P. falciparum* prevalence have steadily increased from 29% in 1985 to 65% in 2016 (Dev, 2019b).

Fig. 7 Malaria cases and evolution of antimalarial drug policy in India (1961-2019). Acronyms NMCP, NMEP, CQ, ACT (AS+SP), AL and NER denote National Malaria Control Programme, National Malaria Eradication Programme, chloroquine, artemisinin-based combination therapy (artesunate + sulfadoxine-pyrimethamine), (artemether + lumefantrine), and North-East Region respectively (Courtesy: Anup Anvikar, National Institute of Malaria Research, New Delhi).

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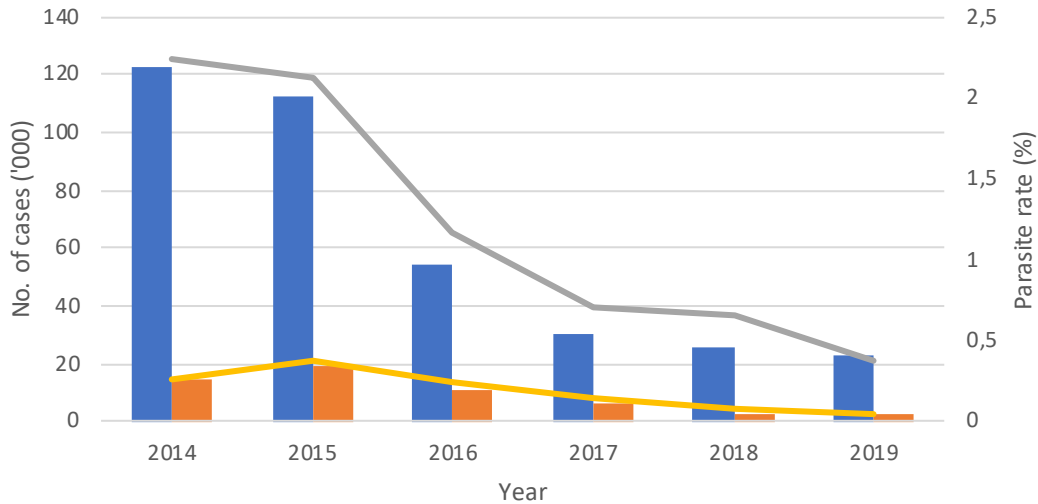
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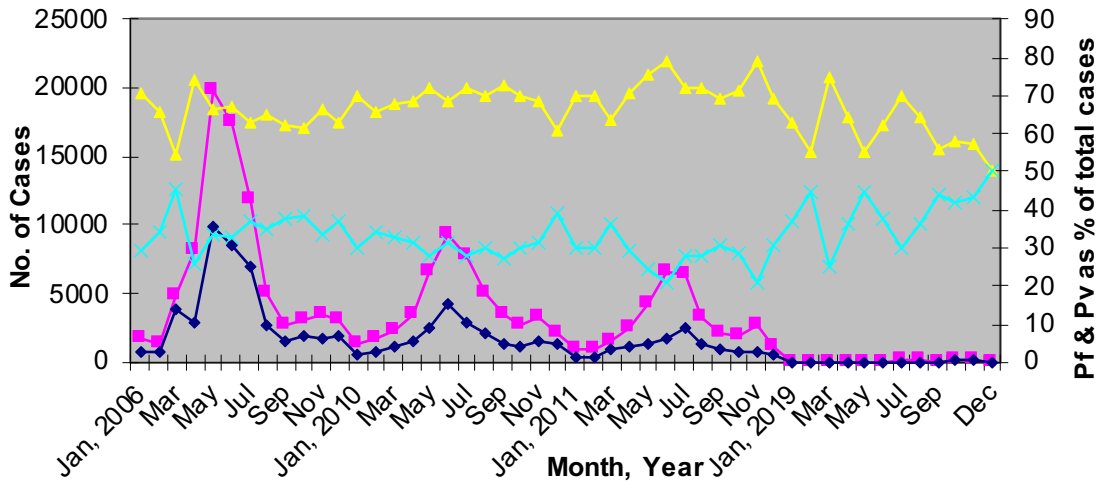
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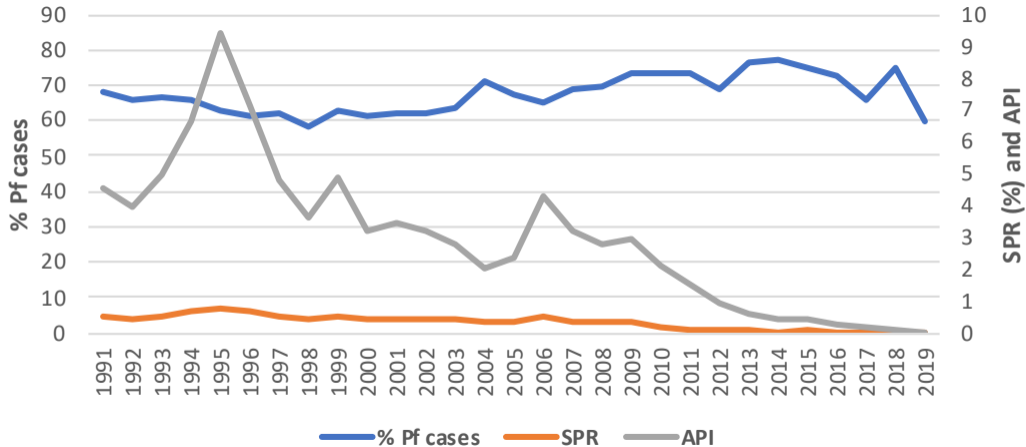
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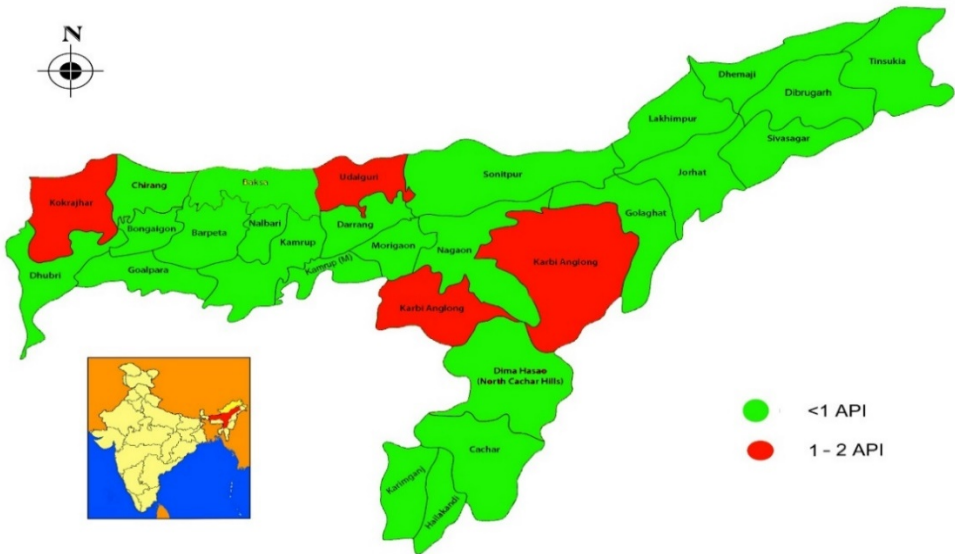


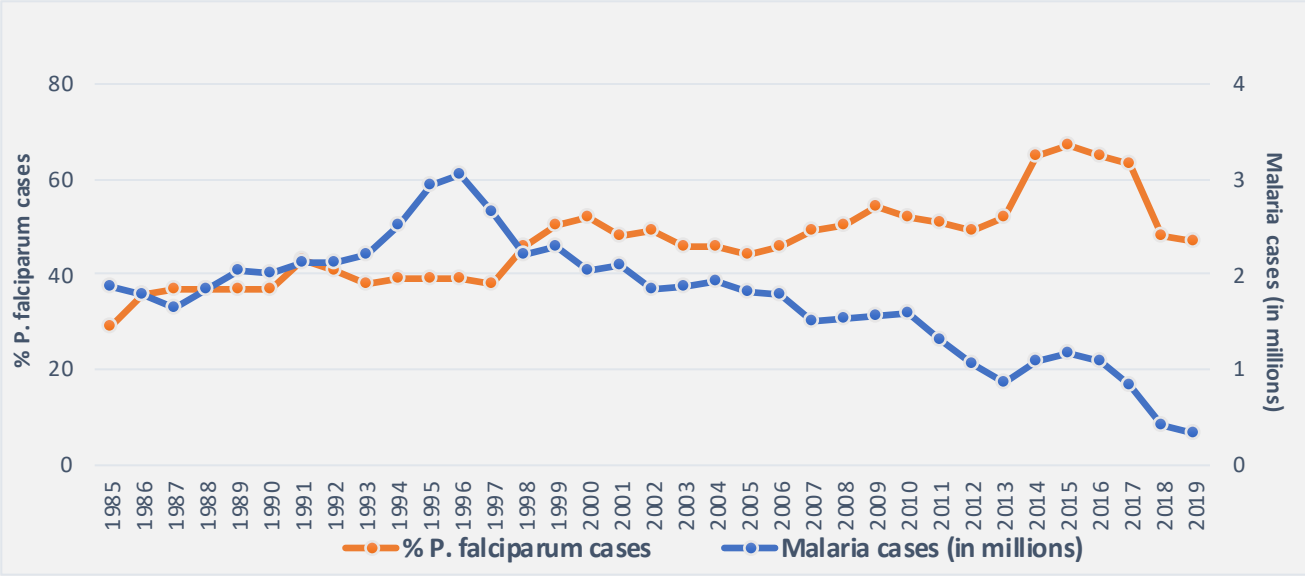
■ Pfcases ■ Pvcases — SFR — SVR

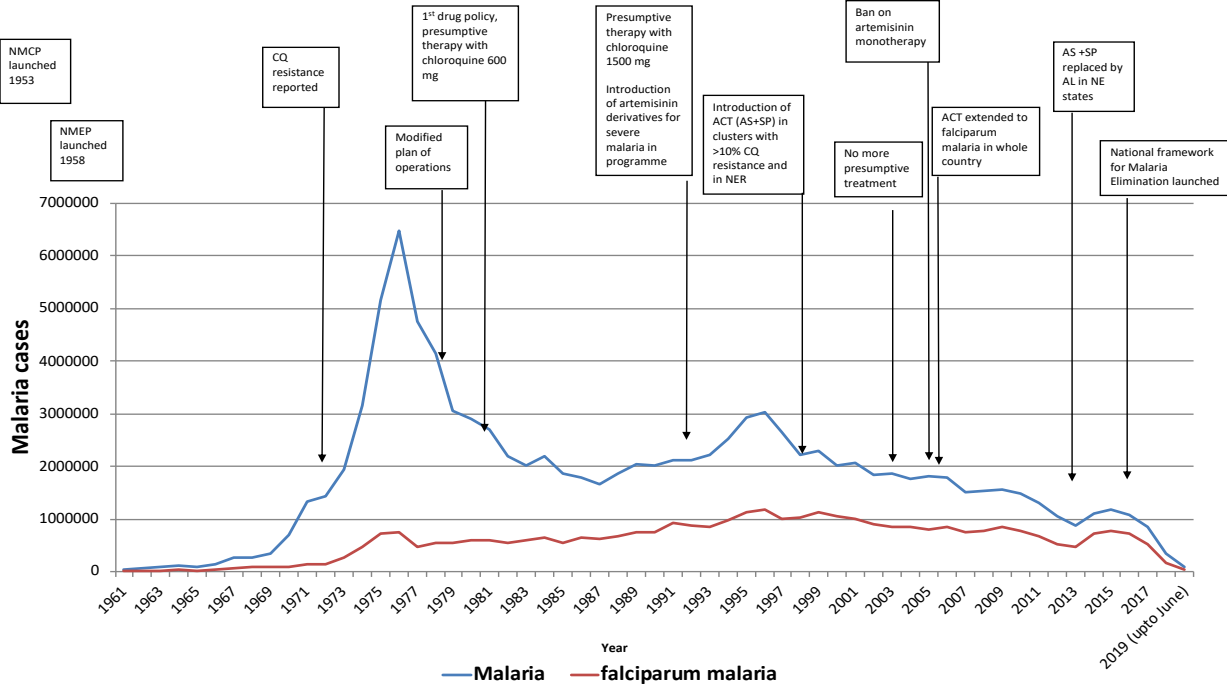


■ Pf cases
 ◆ Pv cases
 ▲ %Pf
 × %Pv









Defeating malaria in the North-East region: the forerunner for malaria elimination in India

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Abstract

Prioritizing interventions for control of malaria in the North-East region of India is of immediate importance as India is targeting malaria elimination by 2027.

