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Neglected *Plasmodium vivax* malaria in northeastern States of India

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Background & objectives: **The northeastern States of India are co-endemic for *Plasmodium falciparum* and *P. vivax* malaria. The transmission intensity is low-to-moderate resulting in intermediate to stable malaria. Malaria control prioritized *P. falciparum* being the predominant and life threatening infection (>70%). *P. vivax* malaria remained somewhat neglected. The present study provides a status report of *P. vivax* malaria in the northeastern States of India.**

Methods: **Data on spatial distribution of *P. vivax* from seven northeastern States (Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland and Tripura) were analysed retrospectively from 2008–2013. In addition, cross-sectional malarial surveys were conducted during 1991-2012 in malaria endemic pockets across the States of Assam, Meghalaya, Mizoram and Tripura to ascertain the prevalence of *P. vivax* in different age groups.**

Results**: Vivax malaria was encountered in all northeastern States but there existed a clear division of two malaria ecotypes supporting ≤30 and >30 per cent of total malaria cases. High proportions of *P. vivax* cases (60–80%) were seen in Arunachal Pradesh and Nagaland in the north with alpine environment, 42-67 per cent in Manipur, whereas in Assam it varied from 23-31 per cent with subtropical and tropical climate. Meghalaya, Tripura and Mizoram had the lowest proportion of *P. vivax* cases. Malaria cases were recorded in all age groups but a higher proportion of *P. vivax* consistently occurred among <5 yr age group compared to *P. falciparum* (*P*<0.05). *P. vivax* cases were recorded throughout the year with peak coinciding with rainy season although transmission intensity and duration varied.**

Interpretation & conclusions**: In northeast India, *P. vivax* is a neglected infection. Estimating the relapsing pattern and transmission dynamics of *P. vivax* in various ecological settings is an important pre-requisite for planning malaria elimination in the northeastern States.**

Key words Malaria burden - malaria control - *Plasmodium vivax* - spatial distribution - transmission dynamics

Northeastern States of India are co-endemic for both *Plasmodium falciparum* and *P. vivax* malaria, and in the past contributed 10 per cent of cases and 20 per cent malaria-attributable deaths in India[1]. Malaria epidemiology is complex due to high aboriginal population, varied terrain, rich forest cover and favourable climatic conditions for transmission. *Anopheles minimus* and *An. baimaii* are the two most efficient malaria vectors with strong predilection for human host[2]. Both vectors were repeatedly incriminated throughout its range of distribution. In addition, *An. nivipes*, *An. maculatus* and *An. culicifacies* are also suspected to contribute some cases[3]. In 2013, the National Vector Borne Disease Control Programme

(NVBDCP) reported 0.88 million malaria cases in the country with nearly equal number of *P. falciparum* and *P. vivax* cases[4]. The proportion of *P. falciparum* and *P. vivax,* however, varied greatly *inter alia* from one ecotype to another due to climate variability and malaria control interventions[5].

During widespread malaria outbreaks in early 1970s epidemiological studies revealed that *P. falciparum* was mainly confined to the northeastern States and its liquidation was considered important to protect rest of the country from *P. falciparum* invasion. With this objective, an additional component of *Plasmodium falciparum* Control Programme (*Pf*CP) was launched in the northeastern region beginning 1976 for intensification of control interventions[6]. Despite this programme in the decade that followed *P. falciparum* spread and invaded States in the mainland affecting >120 million people. Therefore, *Pf*CP was terminated after 11 years of operation. During this period, *P. vivax* remained a neglected parasite. Malaria control relied on indoor residual spraying (IRS), case detection and treatment of *P. vivax* and *P. falciparum*. In addition, all fever cases were given chloroquine presumptive treatment. *P. vivax* responded well to chloroquine therapy and malaria-attributable mortality was solely ascribed to *P. falciparum* infection confirmed by blood-smear examination report[6]. This scenario changed gradually with appearance of reports of resistance in *P. vivax* to chloroquine and cases of severe *P. vivax* malaria from India and many other malaria endemic countries[7-9]. In India, information on *P. vivax* strains and their relapsing pattern remained scanty except one study from Delhi[10]. We undertook this study to provide a status report of vivax malaria in the northeastern States of India.

Material & Methods

Study area: The northeast region of India comprises eight States: Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland and Tripura, and State of Sikkim. All States are malaria endemic except Sikkim, therefore, this study was restricted only to seven States. The forest cover varies from 40 per cent in plain valleys to nearly 80 per cent in hill States of Nagaland and Arunachal Pradesh. Assam is the major constituent State of the northeast with more than 70 per cent population (~32 million) contributing >50 per cent malaria cases[1]. Northeast India shares vast international border with China (South Tibet) in the north, Myanmar in the East, Bangladesh in the southwest and Bhutan to the northwest (Fig. 1). The entire population is largely classified as tribal with at least 220 ethnic groups, rich in cultural heritage, fauna and flora and major river

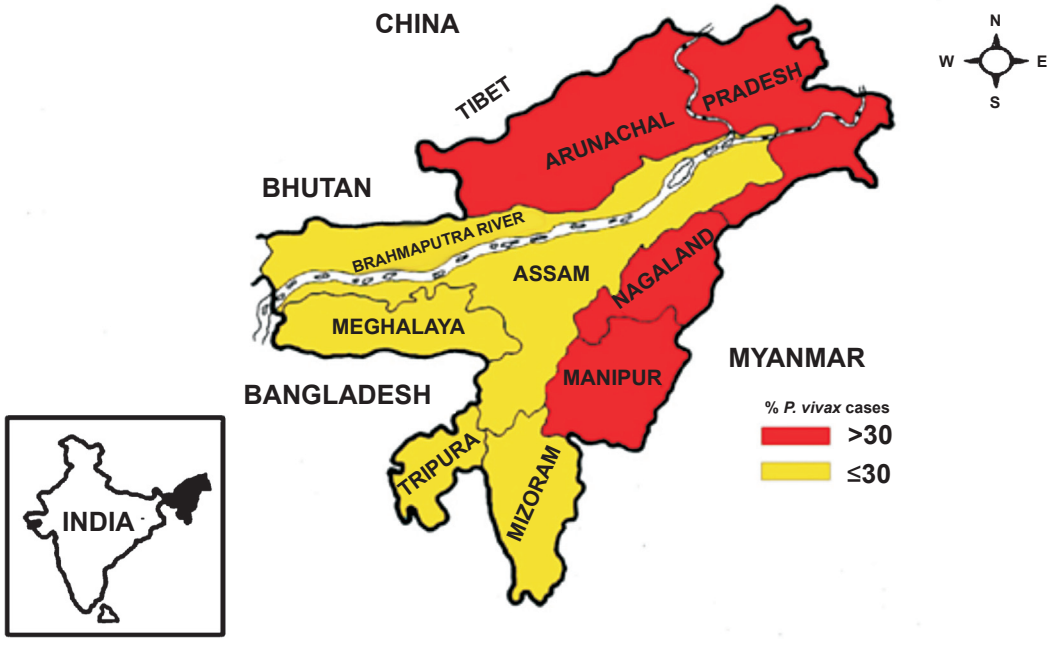

Fig. 1. Distribution of *P. vivax* malaria in northeastern States of India based on pooled data from 2008–2013. International borders are demarcated by bold line and State boundaries are colour coded showing relative abundance of *P. vivax* (% of total malaria reported cases). Inset is the map of India showing geographical location of northeast region (*Source*: Ref. 4).

systems. The population density varies from 13 per sq. kilometer in Arunachal Pradesh to 340 per sq. kilometer in Assam living predominantly in the countryside (84%), and literacy rate is 68.5 per cent[11].

Climate data: Climate in the region varies from temperate to tropical in plains and alpine in the high mountain reaches. In the plain valleys, it is predominantly sub-tropical with hot and humid summers, heavy monsoons, and mild winters. Most parts receive on an average 2-3 m of rainfall during April–September associated with pre-monsoon activity and southwest monsoon.

Malaria control: Transmission is perennial in most parts with seasonal peak during April-September. Malaria is unevenly distributed with varying transmission intensities. Presently malaria control in northeastern States is based on *(i)* DDT indoor residual spraying two rounds at a concentration of 1g/m^2 done on selective basis in areas reporting high incidence of malaria and deaths, and *(ii)* early case detection by microscopic examination of blood smear or the rapid diagnostic test and prompt treatment with chloroquine (CQ) and 14 day primaquine (instead of 5-day PQ therapy in *P. vivax*) as per recommendations of WHO since 2007, and impregnation of community-owned mosquito nets with synthetic pyrethroid and/or supply of long-lasting insecticidal net (LLIN) distributed gratis among high-risk groups[12,13].

Data collection and analyses: This study was a retrospective data analyses of malaria based on State disease surveillance with particular reference to distribution of *P. vivax* in northeastern States of India. Data for respective State for the period from 2008–2013 were accessed online from the Directorate of National Vector Borne Disease Control Programme of Government of India[4]. For district-wise stratification of *P. vivax* malaria, retrospective data for the period from 2000-2013 were analyzed for the State of Assam (State Health Directorate of Assam, personal communication). In addition, cross-sectional malaria prevalence surveys were conducted by the National Institute of Malaria Research, Guwahati (Field Station) during 1991-2012 mostly during high transmission season in ethnic communities in States of Assam, Meghalaya, Mizoram and Tripura to ascertain malaria prevalence by parasite species in different age groups (unpublished data). Furthermore, in 1992 mass and contact surveys were undertaken on the monthly basis in the Sonapur Primary Health Centre (PHC), a typical foothill PHC of Kamrup district of Assam, to ascertain seasonal malaria positivity in febrile and afebrile cases. Malaria data were thus analyzed to study, *(i)* vivax malaria distribution in the northeastern States, *(ii)* seasonal transmission of vivax malaria, *(iii)* results of cross-sectional surveys for distribution of malaria parasite species in three age groups *i.e.* <5, 5-15 and >15 yr, and *(iv)* meteorological data and seasonal prevalence of *P. falciparum* and *P. vivax* malaria in afebrile and febrile cases in Assam State only. All microscopically confirmed malaria positive cases were administered anti-malarial drugs as per prevailing national drug policy[13].

Data on relative prevalence of malaria parasite species in different age groups were analysed by chi-square test using Stata v10 (*http://www.stata.com/*).

Results

Data on malaria cases and per cent contribution of *P. vivax* malaria for the period 2008-2013 in the northeastern States are given in Table I. Vivax malaria is encountered in all States but the number of cases and proportion of parasite species varied from State to State depending on environmental determinants. However, there was a clear division of two malaria ecotypes in the northeast region in respect of *P. vivax* cases, *i.e.* with ≤30 and >30 per cent of total malaria cases (Fig. 1). High proportions of *P. vivax* (60-80%) were seen in Arunachal Pradesh and Nagaland in the

Table I. Number of malaria cases with percentages of *P. vivax* in northeastern States of India

Year	Arunachal Pradesh	Assam	Manipur	Meghalaya	Mizoram	Nagaland	Tripura
2008	29146 (72)	83939 (31)	708 (50)	39616 (8)	7361 (16)	5078 (84)	25894 (9)
2009	22066 (70)	91413 (27)	1069 (42)	76759 (3)	9399 (21)	8489 (66)	24430 (6)
2010	17944 (70)	68353 (29)	947 (49)	41642 (5)	15594 (6)	4959 (62)	23939 (11)
2011	13950 (65)	47397 (27)	714 (56)	25143 (4)	8861 (6)	3363 (72)	14417 (4)
2012	8368 (67)	29999 (31)	255 (67)	20834 (5)	9883 (5)	2891 (72)	11565 (6)
2013	6398 (66)	19542 (23)	120 (65)	24727 (7)	11747 (12)	2285 (77)	7396 (5)

Figures in parenthesis denote per cent *P. vivax* cases of total confirmed malaria positive cases. (*Source*: Ref. 4)

north with alpine environment. In Manipur, *P. vivax* cases varied from 42-67 per cent, whereas in Assam cases varied from 23-31 per cent with subtropical to tropical climate. Meghalaya, Tripura and Mizoram have the lowest population of *P. vivax* cases (Fig. 2). These proportions were rather consistent over several years.

Data on monthly distribution in 2012 of *P. vivax* cases in northeastern States are presented in Fig. 3. *P. vivax* cases were recorded throughout the year with distinct peak coinciding with months of rainfall but transmission intensity and duration varied between States. In Arunachal Pradesh and Nagaland, it was from June-September; in Assam it was from May–September, and in Meghalaya it was form August-November. For all other States, cases were very few with very little variation. Results of cross-sectional malaria prevalence surveys conducted in Assam, Meghalaya, Mizoram and Tripura are presented in Table II. It was observed that *P. vivax* malaria was prevalent in all age groups but cases were significantly higher in children <5 and relatively less in >15 yr age group (P<0.05).

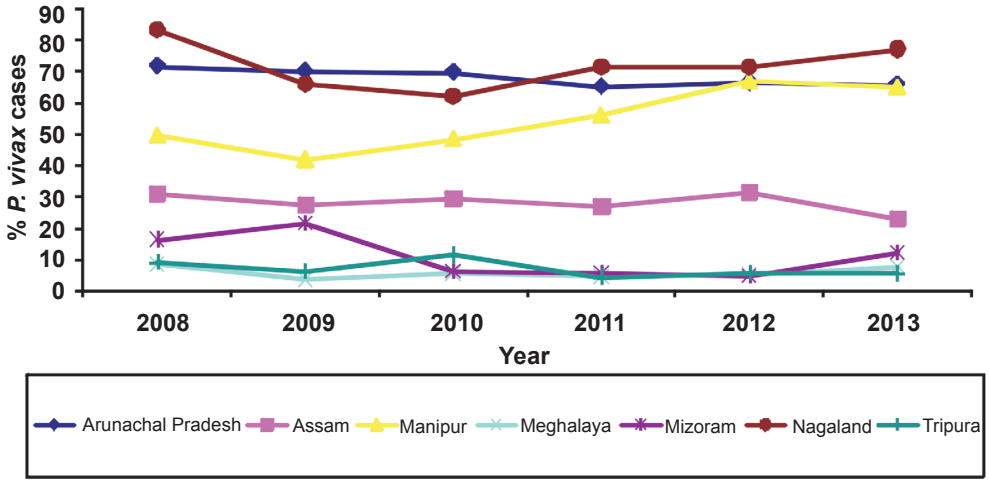

Fig. 2. Relative abundance of *P. vivax* malaria in northeastern States of India during 2008-2013. Arunachal Pradesh and Nagaland showed the highest percentage (60-80%) of vivax malaria, and progressive increase in vivax cases was noted in Manipur beginning 2011 reaching at par with other States. In Assam, this percentage is less than half (≤30%). In Meghalaya and Tripura the percentage of vivax malaria is the lowest (~10%). These percentage figures in these States were almost stable from 2008-2013 except that for Manipur. (*Source*: Ref. 4).

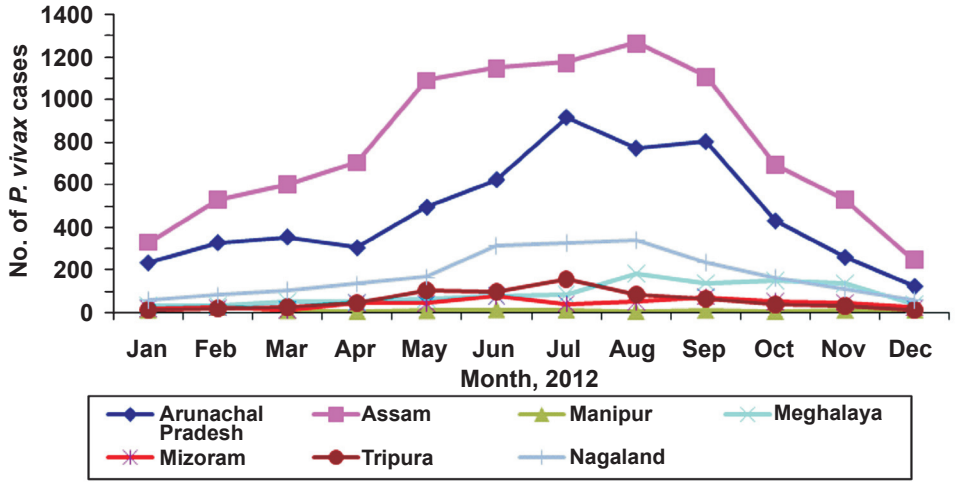

Fig. 3. Monthly distribution of *P. vivax* malaria in northeastern States of India based on 2012 data (*Source*: State Health Directorates of all seven States, personal communication).

Table II. Results of cross-sectional malaria prevalence surveys in ethnic communities of northeast India

Location (District, State)	Study period	Age group, yr								
		<5			5 –15			>15		
		No. of blood-smears examined	No. (%) +ve for		No. of blood-smears examined	No. (%) +ve for		No. of blood-smears examined	No. (%) +ve for	
			P. falciparum	*P. vivax*		*P. falciparum*	*P. vivax*		*P. falciparum*	*P. vivax*
Diphu (Karbi Anglong, Assam)	August, 1991	43	5 (11.6)	2 (4.6)	49	8 (16.3)	0 (0)	87	11 (12.6)	0 (0)
Rangapara (Sonitpur, Assam)	May - June, 1992	409	86 (21)	12 (2.9)	221	72 (32.6)	16 (7.2)	441	139 (31.5)	50 (11.3)
Panerihat (Udalguri, Assam)	August - September, 1992	604	269 (44.5)	56 (9.3)	688	351 (51)	66 (9.6)	1661	798 (48)	117 (7)
Koilamari (Lakhimpur, Assam)	June - July, 1994	230	61 (26.5)	13 (5.7)	411	178 (43.3)	33 (8)	798	340 (42.6)	54 (6.8)
Doomdoma (Tinsukia, Assam)	September, 1994	102	8 (7.8)	2 (1.9)	158	17 (10.8)	10 (6.3)	443	45 (10.2)	11 (2.5)
Umrangsu (N.C. Hills, Assam)	October, 1994	4	1 (25)	0 (0)	4	1 (25)	0 (0)	55	11 (20)	3 (5.4)
Sonapur (Kamrup, Assam)	January - December, 1995	1077	221 (20.5)	130 (12.1)	2337	670 (28.7)	359 (15.4)	6575	1465 (22.3)	860 (13.1)
Goreshwar (Kamrup, Assam)	March, 1995	22	2 (9.1)	1 (4.5)	55	5 (9.1)	0 (0)	89	9 (10.1)	5 (5.6)
Agia (Goalpara, Assam)	April - May, 1995	293	92 (31.4)	61 (20.8)	741	286 (38.6)	115 (15.5)	1263	409 (32.4)	131 (10.4)
Jamaguri (Sonitpur, Assam)	May, 1995	250	58 (23.2)	25 (10)	634	134 (21.1)	74 (11.7)	997	214 (21.5)	124 (12.4)

Contd...

Location (District, State)	Study period	Age group, yr								
		<5			5 –15			>15		
		No. of blood-smears examined	No. (%) +ve for		No. of blood-smears examined	No. (%) +ve for		No. of blood-smears examined	No. (%) +ve for	
			P. falciparum	*P. vivax*		*P. falciparum*	*P. vivax*		*P. falciparum*	*P. vivax*
Mazbat (Darrang, Assam)	July, 1996	259	41 (15.8)	13 (5)	605	114 (18.8)	17 (2.8)	792	130 (16.4)	27 (3.4)
Hamren (Karbi Anglong, Assam)	August, 1996	14	3 (21.4)	1 (7.1)	47	16 (34)	1 (2.1)	125	20 (16)	2 (1.6)
Nellie (Morigaon, Assam)	July - August, 1999	84	26 (30.9)	7 (8.3)	191	81 (42.4)	11 (5.8)	352	141 (40)	8 (2.3)
Boginadi (Lakhimpur, Assam)	April, 2006	204	31 (15.2)	43 (21.1)	469	95 (20.3)	59 (12.6)	793	133 (16.8)	72 (9.1)
Golaghat (Golaghat, Assam)	April, 2006	111	10 (9)	4 (3.6)	444	39 (8.8)	8 (1.8)	537	32 (5.9)	1 (0.2)
Dalu (West Garo Hills, Meghalaya)	May -June, 2007	283	46 (16.3)	12 (4.2)	450	86 (19.1)	18 (4)	403	39 (9.7)	6 (1.5)
Tlabung (Lunglei, Mizoram)	May - August, 2012	228	36 (15.8)	2 (0.9)	278	67 (24.1)	8 (2.9)	447	85 (19)	0 (0)
Silachari (Gomti, Tripura)	July - September, 2012	43	4 (9.3)	1 (2.3)	55	8 (14.5)	0 (0)	124	19 (15.3)	1 (0.8)

Source: Passive surveillance (malaria clinic) conducted by the National Institute of Malaria Research (Field Station), Guwahati, Assam (unpublished data)

Malaria data for each district of Assam for the period from 2000-2013 were analyzed to study distribution of vivax malaria within the State. The State was divisible in two contiguous sections, *i.e*. with ≤30 per cent of vivax malaria in districts located south of Brahmaputra river and >30 per cent in districts located on north bank of total reported cases by the State disease surveillance (Fig. 4).

The relative smear positivity of *P. vivax* and *P. falciparum* in afebrile and febrile malaria cases in four quarters of the year (January-March, April-June, July-September and October-December) was studied in a typical foothill malaria endemic pocket in the Sonapur Primary Health Centre of Kamrup district of Assam (Table III). Data analyses revealed *P. vivax* malaria in both afebrile and febrile subjects but was more pronounced in febrile group in all four quarters. There was, however, comparatively higher abundance of *P. vivax* malaria in afebrile subjects during dry months of October–March (parasite rate 1.99%–3.61%) compared with wet season (April–September) in which parasite rate varied from 0.87–0.97 per cent.

Discussion

The northeast region of India is of strategic importance and categorized high-risk for sharing vast international borders with neighbouring countries. Chloroquine resistance in *P. falciparum* was first detected in 1973 in the Karbi Anglong district, Assam[14]. Studies on drug resistance have revealed that northeast region is an established route for migration and spread of drug-resistant *P. falciparum* malaria to rest of the country[15].

The present analysis revealed that *P. vivax* malaria in northeast India was substantial and likely to perpetuate. With worldwide reported transmission reduction and many countries heading for malaria elimination, control of *P. vivax* malaria is gaining eminence due to its inherent biological characteristics/ parasite resilience[16]. As and when the national control programme embarks upon malaria elimination the presented data on spatial distribution and seasonal abundance of malaria parasite species would be vital in planning malaria control interventions as the strategy for elimination of *P. falciparum* and *P. vivax* would be different. For example, *P. falciparum* elimination would depend heavily on artemisinin based combination therapy (ACT); whereas *P. vivax* elimination would require robust surveillance for case detection and radical treatment to prevent relapses[17].

There are many research gaps which need to be addressed for control of *P. vivax* malaria in continuing efforts for achieving substantial transmission reduction. There are virtually no reports related to relapsing pattern, severe malaria, drug resistance, deaths due to

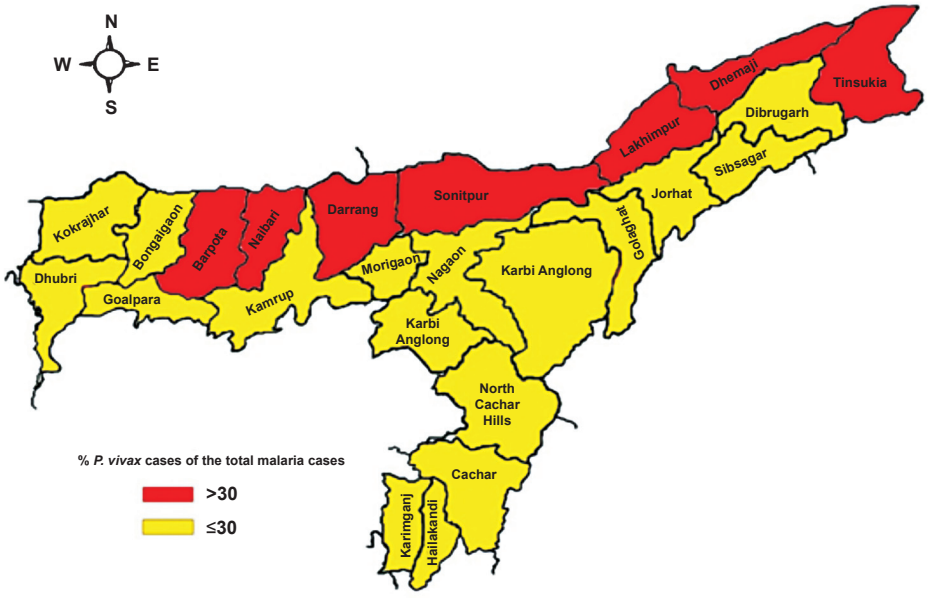

Fig. 4. Distribution of *P. vivax* malaria in Assam for data pooled from 2000–2013. District boundaries are colour coded showing lower proportions of vivax malaria in southern districts and higher in the north (*Source*: State Health Directorate of Assam, personal communication).

Table III. Meteorological data and relative smear positivity of malaria parasite species in afebrile and febrile cases*

Study period, 1992	Meteorological data**			Type of collection	No. of blood smears examined	No. (%) of blood smears positive for parasite	
	Mean temperature (°C) range		Total rainfall (in mm)			*P. falciparum*	*P. vivax*
	Maximum	Minimum					
January - March	22.8 - 29.2	10.7 - 16.7	61.5	Afebrile	1802	136 (7.55)	36 (1.99)
				Febrile	371	69 (18.59)	21 (5.66)
April - June	30.3 - 32.4	20.7 - 24.8	778.6	Afebrile	1148	93 (8.10)	10 (0.87)
				Febrile	392	85 (21.68)	57 (14.54)
July - September	31.2 - 32.5	24.5 - 25.5	926.4	Afebrile	928	188 (20.25)	9 (0.97)
				Febrile	301	106 (35.21)	24 (7.97)
October - December	23.8 - 29.7	10.5 - 21.7	78.8	Afebrile	859	106 (12.33)	31 (3.61)
				Febrile	141	49 (34.75)	17 (12.05)

*Malaria data based on cross-sectional surveys in the Sonapur Primary Health Centre, a typical foothill malaria endemic pocket in Assam, India; **data accessed from Regional Meteorological Centre, Guwahati, Assam, India

P. vivax malaria specific to northeast region[18,19]. Malaria was eliminated from Greece about 60 years ago but in 2011 there was a case of severe vivax malaria[20]. Such a situation can arise in the northeastern States as well. In the background of prevailing vivax malaria situation and the malaria elimination strategy that may be implemented in the years to come, priority areas of field-based research have been identified for the speedy elimination of vivax malaria from the northeastern region[21-23]. These include micro-stratification of vivax malaria[24]; vivax refractory strains for population replacement[25]; *P. vivax* strains and their relapsing pattern[26-28]; clinical trials with 8-aminoquinolines for radical cure of vivax malaria[29]; mixed infections[30]; mass primaquine (PQ) administration to liquidate vivax malaria from the community[31,32]; glucose-6-phosphate dehydrogenase (G6PD) deficiency and prevalence of duffy antigen in various ethnic groups[33]; severe vivax malaria[34]; chloroquine resistance in *P. vivax* malaria[35]; reliable and highly sensitive methodology for detection of *P. vivax* and mixed infections[36]; haemoglobinopathies in various ethnic groups and its relationship with antimalarial drugs[37]; newer treatments for preventing relapses[38]; post-genomic era research and malaria vaccine trials, *etc.*[39-41].

In conclusion, the burden of *P. vivax* malaria is enormous in northeast India. For control of *P. vivax* malaria, it is of utmost importance to strengthen health systems for robust surveillance to ensure case detection and treatment, cross-border initiative for coordinated control interventions along inter-State and international borders, and targeting high-risk foci with enhanced vector control interventions in time and place to interrupt transmission. Given the heterogeneity in transmission intensities of the causative parasites, there is scope for additional research specific to northeast India related to parasite biology, and detection and treatment of hypnozoites to ensure radical cure, system biology approaches facilitating field evaluation of effective vaccine against this relapsing malaria to reduce parasite load that is likely to persist resulting in continued transmission.

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