

Letter to Editor

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Active case detection using bi−valent malaria rapid diagnostic test in non−transmission season impacts upcoming malaria transmission

Hari Shankar[1], Syed Shah Areeb Hussain[2], Mrigendra Pal Singh[2], Sobhan Phookan[3], Kuldeep Singh[3], Neelima Mishra[2]✉

[1]*Indian Council of Medical Research, Ansari Nagar, New Delhi−110029, India*

[2]*ICMR−National Institute of Malaria Research, Dwarka, New Delhi, India*

[3]*ICMR−National Institute of Malaria Research, Field Station Guwahati, Assam, India*

Despite a considerable global effort to eradicate malaria in the last few years, the disease burden in 2020 was 241 million, with 627 000 deaths. India accounted for 83% of cases reported in the World Health Organization (WHO) South-East Asia Region (WHO malaria report 2021). Nevertheless, India has shown its commitment to eliminating malaria from the country by framing the National Strategic Plan (NSP), according to which the districts have been stratified into four categories based on the malaria transmission intensity and the indicator used for categorization of the districts was annual parasite incidence (API). In North-East India, many highly endemic districts (API>2) are in the "Intensified Control Phase" and fall under category ⅢⅠ[1]. A few pockets in such districts have disproportionate (API>10) due to forest and tribal dominance in those regions. The previous reports demonstrated a high malaria burden (API>10) in the district East Garo Hills[2]; however, a few pockets of the district Udalguri are malaria hotspots with the API>5[3].

Evidence suggests that malaria-endemic areas harbor mainly subclinical infections in the dry season due to the presence of low-density asymptomatic *Plasmodium* infections[4], and the infectious reservoir peaks between the end of the dry season and the start of the wet season[5]. Such low-density asymptomatic infections sustain malaria transmission throughout the dry season[6], requiring treatment to alleviate clinical malaria episodes' risk[7]. In the present study, we have highlighted the importance of bi-valent *Plasmodium falciparum*/*Plasmodium vivax* (Pf/Pv) rapid diagnostic test (RDT) during mass blood surveys in the dry season that helped reduce malaria case incidence in high API districts.

A mass blood survey was conducted as an intervention during February-April 2017, considered a dry malaria season in the district East Garo Hills (high API district) of Meghalaya state and the district Udalguri (low API district) of Assam district. We used bi-valent Pf/Pv RDT kit to screen for malaria. Malaria-positive cases were given treatment according to the National Antimalarial Drug Policy of India[8]. In parallel, finger-pricked blood was used to prepare thin and thick smears on glass slides for performing light microscopy and applied on Whatman filter paper for *Plasmodium* species-specific polymerase chain reaction (PCR). A total of 9 118 participants were screened for malaria, 3 165 from high and 5 953 from low API districts. The villages for malaria screening were selected using the probability proportional to size sampling (PPS) method. Briefly, two Primary Health Centres (PHCs) from each district were selected at random (one from a high malaria-endemic PHC and one from a low-endemic PHC). Further, 10 villages from each PHC were selected using PPS sampling technique. In a situation where the required sample from the selected village was not available, the shortfall was covered from adjacent villages. The detailed methodology of the sampling technique and methods performed during the mass survey are described previously[4].

The epidemiological data (2010-2019) related to malaria cases, slide positivity rate (SPR), and API of the districts under intervention were obtained from the respective district units of the National Center for Vector Borne Diseases Control (NCVBDC), erstwhile

✉To whom correspondence may be addressed. E-mail: neelima1.nimr@gmail.com

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known as the National Vector Borne Disease Control Programme (NVBDCP). In addition, malaria epidemiological data of adjoining districts as a control (non-intervention district) was also obtained from the NVBDCP to quantify the impact of mass blood surveys in reducing malaria burden in the districts under intervention (Supplementary Tables 1-4).

We estimated the significance of the differences observed in each year (by taking the year of intervention as a reference year, *i.e.*, 2017) to determine the importance of the change. The same exercise was performed for the adjoining districts (district South Garo Hills adjoining with a high API district and district Darrang with a low API district), where no such intervention was carried out. It was done to compare the change in the malaria burden between the non-intervention and intervention districts.

The median age of participants was 12 years (IQR 7 to 28), 56.8% (5 197/9 118) were females, and 6.1% (554/9 118) had a history of fever. Overall malaria prevalence during the mass survey by RDT was 6.5% (596/9 118), out of which 84.4% (503/596) were asymptomatic *Plasmodium* infections with a higher prevalence in young children than in adults (Table 1).

Malaria prevalence during the mass blood survey in 2017 was 16.6% (524/3 165) and 1.2% (72/5 953) using RDT in high and low API districts, whereas PCR reported 14.7% (284/1 936) and 6.6% (100/1 521) *Plasmodium* infections in the respective districts. It reflects that RDT in high API districts could detect *Plasmodium* infections near the diagnostic ability of PCR but lost nearly 6-fold cases in low API districts. The reason for the lower detection ability of RDT in the low API district was the high persistence of low-density infections in this district[4,9].

The reported SPR by the district health department in 2017 was 3.7% (3 090/82 739) in high and 1.3% (1 129/85 062) in low API districts. In the intervention year, the high API district reported a nearly 5-fold reduction in SPR (3.7%) compared to RDT prevalence (16.6%) observed during the mass survey. This reduction in SPR was observed due to the active malaria case detection in the dry season using RDT, thereby abridging malaria transmission for the upcoming rainy season. Contrary to that, the low API district did not show any impact of the mass survey due to the low diagnostic accuracy of RDT[10] in this region, which is why the district reported SPR (1.2%) and the prevalence reported in the mass survey (1.3%) found similar in 2017.

Malaria data of preceding and following years from the year of intervention *i.e.* 2017 show that overall mean percent change in malaria cases (-27.4, 95% *CI* -132.9 to 78.1) and API (-104.1, 95% *CI* -341.3 to 133.1) was declined but SPR (14.2, 95% *CI* -54.9 to 83.3) increased over the period in high API intervention district. In 2018, there was a sudden drop in malaria cases (3.1 fold; -343.3% *vs.* -111.4%), SPR (4.5 fold; -261.4% *vs.* -57.6%), and API (3.0 fold; -330.0% *vs.* -111.4%) in high API district compared to the control district. This decline showed a reversed trend in the subsequent year, 2019 with a fold change decline remained 0.6 fold (-385.1% *vs.* -642.2%) in malaria cases, 0.2 fold (-130.5% *vs.* -612.6%) in SPR, and 1.8 fold (-1 195.3% *vs.* -671.3%) in API of high API district (Supplementary Figure 1).

On the other hand, low API intervention district showed an overall increase in the mean percent change in malaria cases (46.0, 95% *CI* 2.0 to 89.9), API (46.0, 95% *CI* 1.7 to 90.1) and SPR (35.4, 95% *CI* -16.4 to 87.2). There was no impact of mass survey observed in 2018 on malaria cases (0.97 fold; 52.5% *vs.* 54.2%), SPR (0.96 fold; 61.3% *vs.* 63.6%), and API (0.97 fold; 52.5% *vs.* 54.2%) in low

Table 1. Malaria prevalence during mass blood survey, 2017 conducted in the districts East Garo Hills (high API district) and Udalguri (low API district).

Variables	RDT			Microscopy			PCR		
	Participants	Detected case	Prevalence, % (95% *CI*)	Participants	Detected case	Prevalence, % (95% *CI*)	Participants	Detected case	Prevalence, % (95% *CI*)
Overall	9 118	596	6.5 (6.0-7.1)	8 585	187	2.2 (1.9-2.5)	3 457	384	11.1 (10.1-12.2)
District									
East Garo Hills (high API)	3 165	524	16.6 (15.3-17.9)	2 651	149	5.6 (4.8-6.6)	1 936	284	14.7 (13.2-16.3)
Udalguri (low API)	5 953	72	1.2 (1.0-1.5)	5 944	38	0.6 (0.5-0.9)	1 521	100	6.6 (5.4-7.9)
Type									
Symptomatic	707	93	13.1 (10.8-15.9)	625	33	5.3 (3.8-7.3)	468	56	12.0 (9.3-15.2)
Asymptomatic	8 409	503	6.0 (5.5-6.5)	7 970	154	1.9 (1.6-2.2)	2 989	328	11.0 (9.9-12.1)
Sex									
Female	5 196	324	6.2 (5.6-6.9)	4 912	99	2.0 (1.7-2.4)	1 991	228	11.4 (10.1-12.9)
Male	3 883	271	7.0 (6.2-7.8)	3 680	88	2.4 (1.9-2.9)	1 464	156	10.7 (9.2-12.3)
Age categories according to malaria susceptibility									
≤1 years	192	10	5.2 (2.8-9.5)	165	5	3.0 (1.2-7.1)	87	6	6.9 (3.1-14.7)
>1-≤4 years	853	100	11.7 (9.7-14.1)	790	42	5.3 (3.9-7.1)	419	58	13.8 (10.8-17.5)
>4-≤8 years	1 988	184	9.3 (8.1-10.6)	1 832	67	3.7 (2.9-4.6)	845	120	14.2 (12.0-16.7)
>8-≤14 years	2 481	158	6.4 (5.5-7.4)	2 393	40	1.7 (1.2-2.3)	849	86	10.1 (8.3-12.3)
>14 years	3 602	144	4.0 (3.4-4.7)	3 415	33	1.0 (0.7-1.4)	1 257	114	9.1 (7.6-10.8)

PCR: polymerase chain reaction; RDT: rapid diagnostic test kit.

API district compared to the control district. The reason is that there was an outbreak in 2018 at a sub-center situated in the intervention district, which contributed to a sudden increase in the number of malaria cases and resulted in the dilution of our interpretations of the low API district[11]. Nevertheless, a sharp decline in malaria cases (17.2 fold; -172.0% *vs*. -10.0%), SPR (1.6 fold; -229.7% *vs*. -147.0%), and API (62.6 fold; -173.8% *vs*. -2.8%) was observed in 2019 (Supplementary Figure 2) which was attributed to the extra efforts laid-down by the district health department for the management and control of an outbreak.

To conclude, a mass blood survey using RDT in the dry season detected a significant proportion of *Plasmodium* infections that persisted in asymptomatic individuals during the dry season. Such infections, *i.e*., gametocytes, can potentially transmit in the upcoming favourable monsoon season in high API areas. Mass surveys in the dry season resulted in the contraction of the malaria reservoir, which is responsible for the transmission in the next transmission season[12]. That is why the year of the mass survey and the following year had a significant reduction in malaria, which was not observed over the preceding years. However, this reduction started losing the trend in the succeeding year, *i.e.*, 2019, which further supports the observations that a single mass survey could only derail the transmission in the intervention year or maximally by the following year but cannot have prolonged effects further.

We advocate the strategic use of bi-valent RDTs by stratifying the districts based on API and conducting mass screening for malaria during the non-transmission season in high API districts. In contrast, low API districts should deploy advanced molecular tools to deal with low-density infections.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics approval

The study was approved by the Institutional Ethics Committee of the National Institute of Malaria Research (ECR/NIMR/EC/2015/490). All subjects or their representatives gave written informed consent prior to enrollment.

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Authors' contributions

SP was the principal investigator of the study. SP and NM conceived the idea and designed the study. HS contributed to the data collection, analysis and interpretation. HS, SP, KS and MPS executed the field operations. HS, SSAH and MPS performed the analytic calculations and performed the numerical simulations. HS performed laboratory experiments under the supervision of NM. SP, KS and NM coordinated the field operations and logistics arrangements. MPS and NM critically reviewed the manuscript for important intellectual content. HS drafted the first version of the manuscript. All authors provided intellectual inputs and reviewed and approved the final version.

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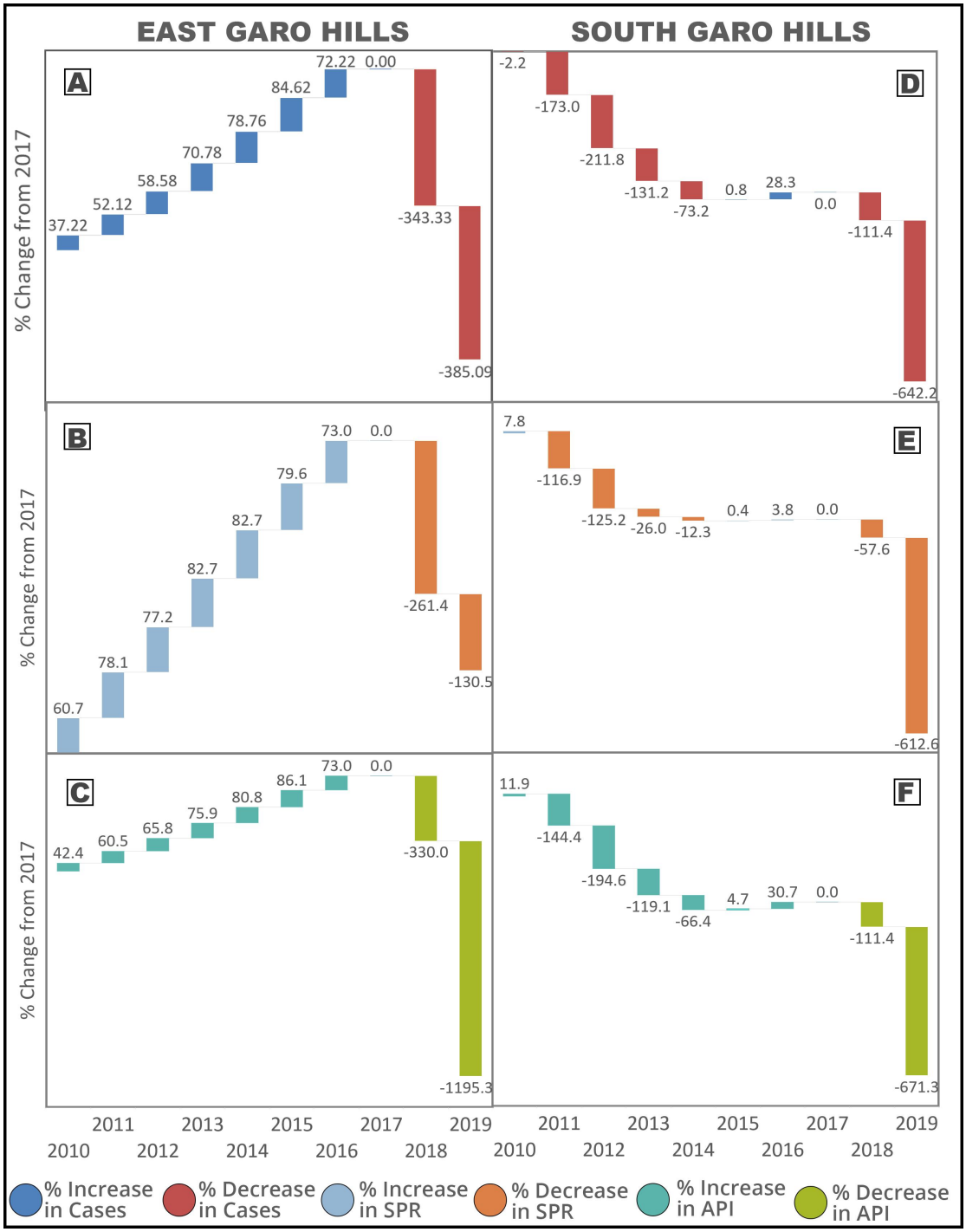

Figure 1. Impact of intervention (mass blood survey 2017) on malaria burden in East Garo Hills (high API district) and South Garo Hills (adjoining control district). Cases: malaria cases; SPR: slide positivity rate; API: annual parasite incidence.

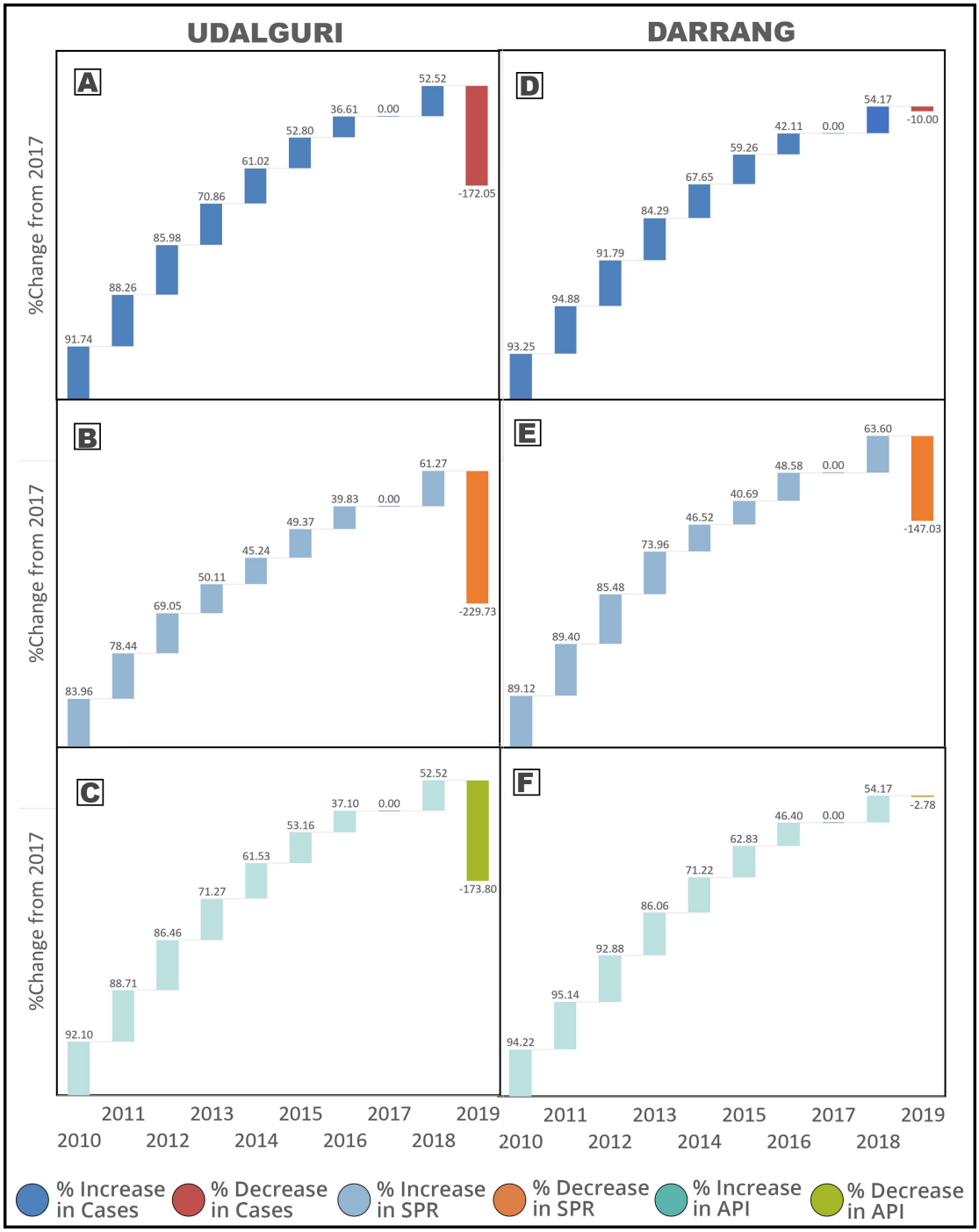

Figure 2. Impact of intervention (mass blood survey 2017) on malaria burden in Udalguri (low API district) and Darrang (adjoining control district). Cases: malaria cases; SPR: slide positivity rate; API: annual parasite incidence.

Supplementary tables

Active case detection using bi-valent malaria rapid diagnostic test in non-transmission season impacts upcoming malaria transmission.

Table 1. Malaria epidemiology in the district East Garo Hills (high API intervention district).

Year	Population (in 1000)	BSC	BSE	Pv	Pf	Pv+Pf	Total	SPR	API	Deaths
2010	337	51859	51859	5	4917	0	4922	9.5	14.6	16
2011	303	37849	37849	217	6237	0	6454	17.1	21.3	6
2012	303	45568	45568	252	7209	0	7461	16.4	24.6	19
2013	303	48898	48898	910	9665	0	10575	21.6	34.9	21
2014	332	67262	67262	324	14221	0	14545	21.6	43.8	28
2015	332	109783	109783	1079	18050	961	20090	18.3	60.5	25
2016	356	80482	80482	871	8095	2156	11122	13.8	31.2	8
2017	367	82739	82739	338	2752	0	3090	3.7	8.4	1
2018	356	67457	67457	34	663	0	697	1.0	2.0	1
2019	393	97280	97280	17	620	0	637	1.6	0.7	1

BSC: blood slide collected; BSE: blood slide examined; Pv: *Plasmodium vivax*; Pf: *Plasmodium falciparum*; Pv+Pf: mixed infection; SPR: slide positivity rate; API: annual parasite incidence.

Table 2. Malaria epidemiology in the district South Garo Hills (control for high API district).

Year	Population (in 1000)	BSC	BSE	Pv	Pf	Pv+Pf	Total	SPR	API	Deaths
2010	132	38969	38969	628	8556	0	9184	23.6	69.6	11
2011	137	34301	34301	6	3431	0	3437	10.0	25.1	8
2012	144.58	31173	31173	13	2996	0	3009	9.7	20.8	7
2013	145	23524	23524	10	4045	3	4058	17.3	28.0	9
2014	147	27983	27983	33	5384	0	5417	19.4	36.9	8
2015	147	43352	43352	122	9305	32	9459	21.8	64.3	17
2016	148	57935	57935	447	12646	0	13093	22.6	88.5	11
2017	153	43166	43166	652	8730	0	9382	21.7	61.3	6
2018	153	32167	32167	119	4318	0	4437	13.8	29.0	2
2019	159	41446	41446	28	1236	0	1264	3.1	8.0	2

BSC: blood slide collected; BSE: blood slide examined; Pv: *Plasmodium vivax*; Pf: *Plasmodium falciparum*; Pv+Pf: mixed infection; SPR: slide positivity rate; API: annual parasite incidence.

Table 3. Malaria epidemiology in the district Udalguri (low API intervention district).

Year	Population (in 1000)	BSC	BSE	Pv	Pf	Pv+Pf	Total	SPR	API	Deaths
2010	868	165154	165154	10431	3236	0	13667	8.3	15.7	2
2011	873	156168	156168	6425	3189	0	9614	6.2	11.0	1
2012	877	187688	187688	5887	2163	0	8050	4.3	9.2	0
2013	895	145632	145632	2643	1231	0	3874	2.7	4.3	0
2014	896	119491	119491	1219	1677	0	2896	2.4	3.2	1
2015	901	91246	91246	1222	1170	0	2392	2.6	2.7	0
2016	901	80743	80743	741	1040	0	1781	2.2	2.0	0
2017	908	85062	85062	851	278	0	1129	1.3	1.2	0
2018	908	69389	69389	534	1844	0	2378	3.4	2.6	0
2019	914	103096	103096	130	285	0	415	0.4	0.5	0

BSC: blood slide collected; BSE: blood slide examined; Pv: *Plasmodium vivax*; Pf: *Plasmodium falciparum*; Pv+Pf: mixed infection; SPR: slide positivity rate; API: annual parasite incidence.

Table 4. Malaria epidemiology in the district Darrang (control for low API district).

Year	Population (in 1000)	BSC	BSE	Pv	Pf	Pv+Pf	Total	SPR	API	Deaths
2010	948	95871	95871	96	67	0	163	0.2	0.2	0
2011	950	127340	127340	161	41	0	202	0.2	0.2	0
2012	959	109377	109377	111	26	0	137	0.1	0.1	0
2013	981	102681	102681	47	24	0	71	0.1	0.1	0
2014	984	102433	102433	17	17	0	34	0.0	0.0	0
2015	1009	90219	90219	19	8	0	27	0.0	0.0	0
2016	1024	68237	68237	20	5	0	25	0.0	0.0	0
2017	1026	61610	61610	11	1	0	12	0.0	0.0	0
2018	1027	49848	49848	15	7	0	22	0.0	0.0	0
2019	1033	139166	139166	7	3	0	10	0.0	0.0	0

BSC: blood slide collected; BSE: blood slide examined; Pv: *Plasmodium vivax*; Pf: *Plasmodium falciparum*; Pv+Pf: mixed infection; SPR: slide positivity rate; API: annual parasite incidence.