

Burden of Malaria in three Endemic Districts of Bhutan: Road to Malaria Elimination

Vishal Chhetri^{*1}, Tobgyel Dukpa², Rinzin Namgay², Kesang Wangchuk², Hari Prasad Pokhrel³

¹Gelephu Central Regional Referral Hospital, Ministry of Health, Bhutan

²Vector Borne Disease Control Programme, Ministry of Health, Bhutan

³Gidakom Hospital, Ministry of Health, Bhutan



*Corresponding author: vishal_srmc@yahoo.com

Abstract

Introduction: Bhutan is considered as a low endemic country for malaria. In the last decade, Bhutan has successfully reduced the number of malaria cases with the support from Global Fund and WHO. Sarpang, Samtse and Samdrup Jongkhar districts located in the Southern foothills of Bhutan records the most cases. **Method:** This retrospective study was undertaken with the available census record maintained in health centers of the three endemic districts and VDCP. **Results:** There were 892 confirmed malaria cases in 2009 and 41 cases in 2017 in three endemic districts. The slide positivity rate (SPR) declined from 2.2% in 2009 to 0.1% in 2017. The distribution of disease was significantly higher ($p < 0.05$) amongst the male population with the increasing trend of *Plasmodium vivax* infection. The study found predominance of *P. vivax* in Samtse (93%), and Sarpang (62%) and *Plasmodium falciparum* in Samdrup Jongkhar (61%). The last four years (2014-2017) data showed that maximum cases detected were imported, followed by indigenous and introduced malaria; with 50%, 44% and 6%, respectively. The mortality and morbidity due to malaria has magnificently declined in the last decade. **Conclusion:** The large-scale implementation of vector control interventions, such as insecticide-treated bed nets, indoor residual spraying, free health care service and active vector surveillance has achieved a marked reduction in malaria incidence. Cross border malaria is still a huge challenge for elimination of malaria in Bhutan. Thus, imported malaria is an increasing problem due to high receptivity, and vulnerability.

Keywords: Bhutan, Elimination, Malaria, *Plasmodium falciparum*, *Plasmodium vivax*

Introduction

Malaria is a parasitic infection caused by five different *Plasmodium* species in human, which is transmitted via blood meal of infected female *Anopheles* mosquitoes. Globally there are at least 300-500 million clinical cases of malaria reported annually^[1] and climate change is yet another factor contributing to the malaria menace.^[2,3] In the South Asian region, *Plasmodium vivax* and *Plasmodium falciparum* are the predominant species causing human malaria and the situation remains the same in Bhutan.^[4] In Asia, 19 countries are considered malaria endemic and 62% of the total population in those countries are at the risk of malaria infection. Yet, remarkably Sri Lanka was declared malaria-free on 5 September, 2016 by the World Health Organization (WHO).^[5]

Bhutan started to fight against malaria with the support from global fund for AIDS, Tuberculosis and Malaria (GFATM) and WHO. Initially, the program was launched in 1964 as National Malaria Eradication Programme.^[6] The vector surveillance system was in its embryonic stage with few health center reporting cases. Later, vector control intervention started with indoor residual spray (IRS) with Dichloro-diphenyl-trichloro-ethane (DDT). The impact of IRS was rapidly apparent, reducing the annual parasite index (API) from 5.1 per 1000 population in 1965 to 2.6 in 1967.^[6] Beginning 1971 malaria cases rapidly escalated due to increase in surveillance

system and access to passive case detection as population became more aware and accessible to health care facility. The program was renamed to National Malaria Control Programme (NMCP) in 1971. Approximately, 8000 cases were reported each year from 1975 onwards with highest number reported in 1994 (39,852).^[6] During this period, DDT resistance and drug resistance of *P. falciparum* strains to chloroquine and sulfadoxine-pyrimethamine were also noted.^[7] Interestingly, a recent study by Wangchuk, Drukpa^[8] stated there is no evidence of chloroquine-resistant *P. vivax* in Bhutan. The IRS vector control is done with synthetic pyrethroid, such as deltamethrin and cyfluthrin.^[9] The population living in malaria risk area were advised to use insecticide treated bed nets (ITBN).^[3] In 2003, the NMCP was renamed to Vector-borne Disease Control Programme (VDCP) extending its activity over other vector diseases and by then Bhutan stepped into Malaria elimination phase.

The vectors suspected for malaria transmission in Bhutan are *Anopheles pseudowillmori*, *An. culicifacies*, *An. minimus*, and *An. fluviatilis* and these species are relatively abundant during the peak transmission season.^[1,2,10] Bhutan has been a low endemic country for malaria and most of the cases are recorded in the Southern districts. Since 1990s, Bhutan has made major progress towards malaria control resulting in pre-elimination and now in the elimination phase, through integrated vector control activities and

active vector surveillance.^[2] Elimination is defined by the WHO as interruption of local transmission to zero indigenous cases of malaria parasite species in a defined geographic area.^[11] Despite the reduction of malaria cases in Bhutan, population living along the southern belt are at higher risk of being infected with malaria parasite due to high receptivity and vulnerability. Therefore, the objective of this paper is to present the overview of the malaria situation in the three malaria endemic districts of Bhutan, highlight the progress made by VDCP in controlling and eliminating malaria to achieve National goal 'Bhutan free of indigenous Malaria'.

Material and Methods

This study was a routine to research retrospective survey. The survey used the data of health centers under Samtse, Sarpang and Samdrup Jongkhar districts from January 2009 to December 2017. All the patients visiting malaria unit with fever were screened for malaria parasites. Patients' personal information recorded in laboratory register were anonymized for the study. Fingertip or venous blood sample were collected and both the thick, and thin blood film were prepared on clean glass slide according to the standard operating procedure (SOP). Fresh Giemsa stain solution was prepared and stained following SOP. Examination of Giemsa-stained blood films was performed by experienced microscopist, with at least 200 microscopic fields for thin blood films, and at least 200 leukocytes for thick blood films.^[9]

The entire malaria positive diagnosed either by Microscopy and/or rapid diagnostic test (RDT) were included for the study. The cases were segregated either as N1, N2/N3^[9] based on their Nationality (N1: Bhutanese, N2&N3: Non Bhutanese residing in Bhutan & Non Bhutanese not residing in Bhutan). Furthermore, case classification was done based on foci investigation, and other epidemiological and entomological findings classified as either indigenous, imported, introduced or re-introduced malaria. The data were collected from the VDCP information unit (Epi-info, CDC, USA 2006 database) and validated with the District Malaria supervisor (DMS) and health center based malaria record sheet. Data entry was done using Microsoft excel and analyzed using SPSS. Descriptive information are presented as frequencies, means and percentages. T, and Z test were used to assess the statistical association considering a p-value of <0.05 as statistically significant.

Results and Discussion

The present retrospective study was undertaken to better understand malaria disease burden in the three endemic districts of Bhutan. In last decade, Bhutan has successfully reduced the malaria cases from 39,852 cases in 1994 to just 62 cases in 2017^[9] moving towards the national goal of malaria elimination in the country in-line with the regional goal of 'Malaria-Free South-East Asia Region by 2030'.^[7]

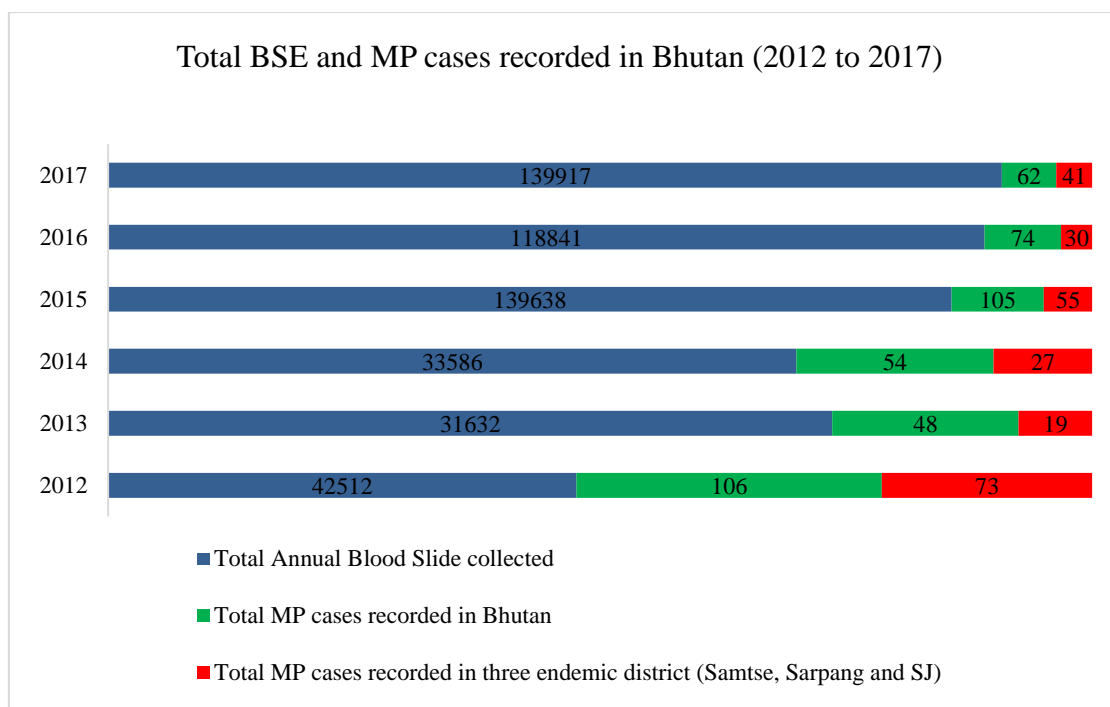


Figure 1: Total Blood slide examined, malaria parasite detected in Bhutan, and in the three endemic districts from 2012-17

A total of 18 death cases due to malaria were recorded from 2007 to 2012, and one case in 2017, of which 58% (n=11 cases) death cases were recorded from Sarpang district. The mortality due to malaria cases has declined to negligible in 2016 from 2.3% per 100,000 in 2000 (<http://www.health.gov.bt>). Samtse, Sarpang and Samdrup Jongkhar districts, reported maximum number of malaria

cases, significantly higher at $p < 0.05$. In 2009, the average slide positivity rate (SPR) in these three endemic districts was 2.2% and this continuously declined to 0.9%, 0.7%, 0.2% and <0.2% in 2010, 2011, 2012, 2013, respectively and currently (2017) stands at 0.1%.

Table 1: Nine years (2009-2017) Malaria case record in the three endemic districts (Sarpang, Samtse and Samdrup Jongkhar)

Year	Total BSE	Malaria Positivity																	SPR %				
		Total MP slide	Nationality						Sex						Malaria Spp.					Case classification*			
			N1		N2+N3		Male		Female		Pf+Mix		Pv		Indigenous	Imported	Introduced						
			n	%	n	%	n	%	N	%	n	%	N	%									
2009	41042	892	718	80%	174	20%	542	61%	350	39%	556	62%	336	38%								2.2%	
2010	38083	348	316	70%	32	30%	222	64%	126	36%	147	42%	201	58%								0.9%	
2011	25758	177	124	70%	53	30%	123	69%	54	31%	111	63%	66	37%								0.7%	
2012	29561	73	56	73%	17	23%	43	59%	24	33%	37	51%	30	41%								0.2%	
2013	19067	19	13	68%	6	32%	15	79%	4	21%	10	53%	9	47%								0.1%	
2014	30253	27	21	78%	6	22%	19	70%	8	30%	13	48%	14	52%	17 (63%)	9 (33%)	1					0.1%	
2015	32599	60	49	82%	11	18%	48	80%	12	20%	27	45%	33	55%	31 (52%)	27 (45%)	2					0.2%	
2016	29331	30	20	67%	10	33%	29	97%	1	3%	8	27%	22	73%	15 (50%)	15 (50%)	0					0.1%	
2017	42575	41	32	78%	9	22%	22	54%	19	46%	5	12%	36	88%	11 (27%)	18 (44%)	12					0.1%	

BSE (Blood Slide Examined), N1 (Bhutanese), N2&N3 (Non Bhutanese residing in Bhutan & Non Bhutanese not residing in Bhutan),

MP (Malaria positive), Pf (*Plasmodium falciparum*), Pv (*Plasmodium vivax*), Mix (Pv+Pf), SPR (Slide Positivity Rate)

*Case classification: Indigenous case: any case contracted locally (i.e. within national boundaries), without strong evidence of a direct link to an imported case. Imported case: a case whose origin can be traced to a known malarious area outside the country in which it was diagnosed. Introduced case: a case acquired locally with strong epidemiological evidence linking it directly to a known imported case.

The gender distribution of disease was found significantly higher ($p < 0.05$) in male population than in female and the infected population were mostly farmers.^[12] This could be probably because the paddy fields and irrigation channels located in the wetland are optimal breeding habitats for all vectors.^[12] Though *P. falciparum* was major parasite species until 2013, *P. vivax* has emerged as dominating species after 2014. This incidence shows the true burden of *P. vivax* malaria infections^[13] and this increasing trend of *P. vivax* is similar to other South Asian country.^[14] Importantly,

P. vivax exhibits dormant liver stages, which is the main characteristic for emergence of gametocytes before the onset of clinical symptoms and highly prone to resurgence and development of drug resistance.^[2,15] Fortunately, the recent study by Wangchuk, Drukpa^[8] reported that the *P. vivax* found in Bhutan can still be treated with chloroquine and primaquine. Moreover, there was no notable difference between the *P. vivax* found in Bhutanese or non-Bhutanese isolates in the neighbor-joining tree.

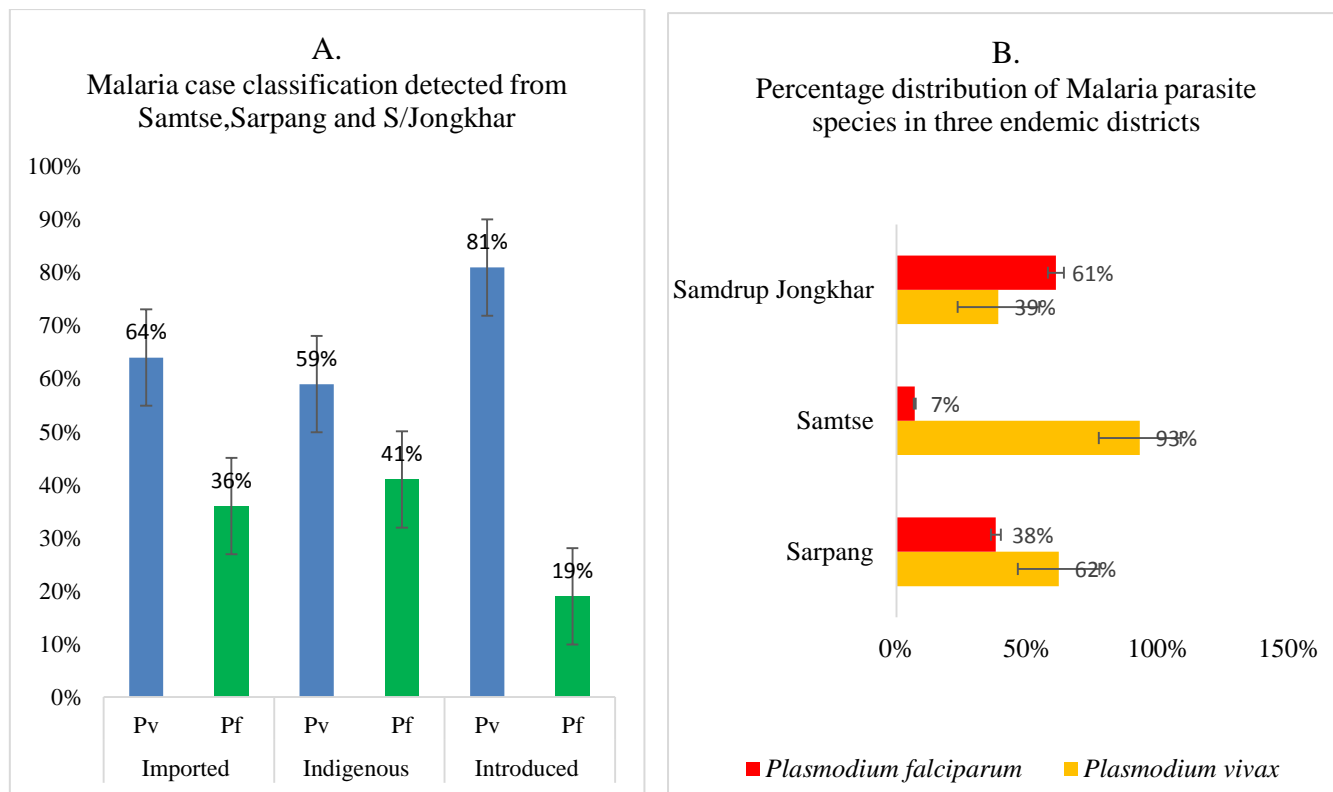


Figure 2: Four consecutive year (2014 to 2017) malaria case detected in the three endemic districts of Bhutan. Fig. A) Percent of Malaria case classification Fig. B) Percent of different malaria species distribution.

The total number of malaria cases detected in Bhutan also includes the foreigners who have entered Bhutan either for a short duration (N2) or stayed for longer (N3), and further based on patient source of infection, epidemiological linkage and travel history, it is classified either as indigenous, imported, induced, introduced or relapse case.^[16] In the past four years (2014-2017), the maximum case detected were imported cases, followed by indigenous and introduced malaria with 50%, 44% and 6%, respectively in the three endemic districts. In contrast to the previous study by Yangzom et al., (2012) which reported the dominance of imported *P. falciparum* in Bhutan, the current study shows *P. vivax* (64%) as the predominant imported species. The number of imported malaria positive includes active case detection at the mega-project sites. All malaria cases are treated with the anti-malarial drug therapy, as per the National Guidelines for management of malaria in Bhutan, 2014.^[2,4] The imported cases might transmit parasite to community if the vectors are present thus, imported malaria is an increasing problem in many countries^[17] and a threat to malaria

elimination. In Bhutan there is no evidence of malaria case transmitted either by blood transfusion or congenital.^[18,19]

The past four years (2014-2017) data showed the diversity of parasite species in the three endemic districts. Samtse and Sarpang detected the predominance of *P. vivax* with 93% and 62%, whereas, Samdrup Jongkhar has seen predominance of *P. falciparum* (61%). This could be due to the cross border transmission, as *P. falciparum* is the predominant parasite species in Assam that share border to Samdrup Jongkhar and Sarpang.^[4] Moreover, every year Sarpang district recorded the majority of indigenous cases which is in congruent with the earlier finding by Yangzom et al., (2012). Sarpang shares its border with the Indian state of Assam where malaria is endemic and contributes to more than 5% of the total cases recorded in India. In addition, malaria transmission is perennial with both winter vector (*An. fluviatilis*) and the monsoon species (*An. dirus*)^[4] and is therefore, considered high risk malaria transmission. Nevertheless India is also moving towards malaria elimination by 2027.^[11]

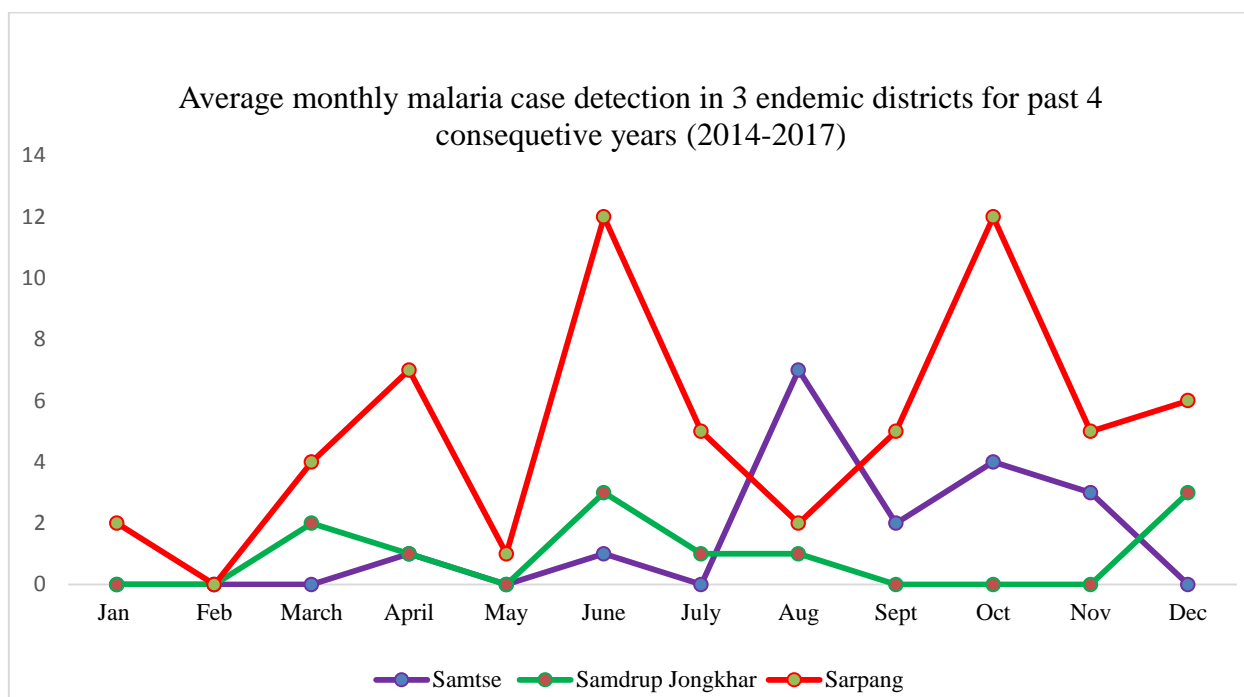


Figure 3: Seasonal distribution of malaria in the three endemic districts of Bhutan. Although the malaria cases were detected throughout the year, the highest number of cases are detected during monsoon season.

The study of seasonal distribution of malaria parasite showed that malaria is detected almost throughout the year but increased during the monsoon, with no notable difference between the two common malaria parasite species. Wangdi et al., (2010) reported that temperature and rainfall were the two predictors to forecast malaria infection, true to which the three endemic district shows increased malaria cases during monsoon. Moreover, the prevalence of malaria vectors in all three endemic districts possess the risk of transmission throughout the year.^[1,4] Though the vector control interventions is done with IRS in March and August targeting the early and post monsoon months, as malaria transmission is accelerated during rainy season^[15] but the effect is short-lived.^[2]

Malaria transmission in Bhutan occurs as sporadic epidemic along the Southern districts. The evidence-based strategies implemented by the VDCP with early diagnosis and treatment are prospective root of Bhutan's malaria success.^[2] The large-scale implementation of control interventions, such as insecticide-treated bed nets, indoor residual spraying, better information and free health care, free-of-charge diagnosis and treatment has achieved a marked reduction in malaria incidence. The universal coverage of indoor residual spray (IRS) and usage of long lasting insecticide bed nets (LLIN) for vector control is found effective. A total of 62,538 LLIN was distributed in 2017 covering to almost 89,176 population residing under Sarpang, Samtse and Samdrup Jongkhar (Source: VDCP data, 2018). Both the LLIN and IRS use same group of pyrethroid compound as a blanket cover-up and the coverage of IRS is almost 99% and the usage of LLIN is >95%.^[2] Finally the success of IEC (inform, educate and communicate), and advocacy along with the formation of active community action group (CAG) and the healthy and happy Bhutanese population.^[4] with improved hygiene and sanitation hereby is a factor, reducing the risk of disease and malaria like fever.

Furthermore, all case investigations were integrated with vector surveillance with focused intervention in the targeted foci, thereby

interrupting local transmission of malaria. Active vector surveillance in foci area and active case detection was initiate during elimination phase. Of recent, malaria surveillance system has been integrated with health information and management system (HIMS) and developed customized, and effective surveillance module (District Health Information System-DHIS2), Malaria Tracing System with two tools of malaria case diagnosis, treatment, outcome and case investigation and another to track foci identification being introduced. The bio-assay test on both LLIN and IRS chemical is conducted to study the efficacy of insecticide used. Overall, all of these strategies are stepping stones towards reducing the burden of malaria, and then eliminate malaria. Non-availability of blood sample for genetic analysis and absence of comprehensive fever records were important limitations in this study.

Challenges

Though Bhutan has successfully reduced the malaria cases, we are still at risk of malaria infection due to high vulnerability and receptivity. The re-emergence of malaria in previously cleared foci and loss of immunity in the population adds risk to both morbidity and mortality. Moreover, sporadic occurrence of cases in 'hard-to-reach' villages makes it difficult to implement vector control measures on time. Most importantly the cross border malaria; due to the dependent on migrant laborer for socio-economic development and the porous border is of high concern. The high malaria transmission across the border has direct impact on the malaria situation in Bhutan as India contributes to almost 61 per cent of malaria cases and 41 per cent of malaria deaths in SEAR countries.^[6] The presence of various malaria parasites and vector species, climatic and susceptible human population facilitates malaria transmission in tribal areas of the Eastern and North-Eastern Indian states.^[10] that share international border with Bhutan. So there is a greater risk of focal outbreaks due to lack of coordinated vector control operations.^[4] Commitment and financial

support from the government and strategies to control cross border malaria needs to be strengthened to achieve malaria elimination in the region.^[20] Limited human resources, false history from the malaria infected patients, increasing *P. vivax* infection and development of drug resistance and, *P. vivax* highly prone to resurgence especially when control efforts cannot be sustained makes it difficult to contain malaria elimination.^[13] Though Bhutan ambitiously targeted 'zero indigenous malaria in 2018' but there were still reported cases of indigenous malaria. Nevertheless, Bhutan still strives to eliminate malaria by 2020 and achieve national goal in line with regional aim Malaria free SEAR 2030.

Conclusion

Sarpang, Samtse and Samdrup Jongkhar districts despite being located along the porous border of India (Assam, Arunachal Pradesh and West Bengal), where the malaria control activity across the border (tribal area) is minimum, the number of malaria cases had been reduced over the last one decade, from 892 in 2009 to just 41 cases in 2017. Most of the malaria cases are imported, followed by indigenous and introduced cases, 50%, 44% and 6%, respectively, with the predominance of *P. vivax* (64%) mainly among the male population. The cross border malaria still remains a challenge to be resolved. The evidence-based strategies implemented by the VDCP with early diagnosis and treatment are prospective root of Bhutan's malaria success. Though there are population at risk to malaria due to high receptivity and vulnerability, the VDCP ambitiously targets to eliminate malaria; zero indigenous malaria by 2020' and contribute towards malaria free South East Asia 2030.

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Conflict Of Interest

Authors declare no conflict of interest.

Ethical Clearance

Ethical clearance for this study was granted by Research Ethics Board of Health (REBH), Ministry of Health, Royal Government of Bhutan via letter no: REBH/Approval/2018/066.

Authors Contribution

CV Conceived and designed the study. PH assisted in data analysis and interpretation. TD, RN and KW participated and helped in data collection and verification. All authors read and agreed for the submission of this manuscript.

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