Effectiveness of Joint 3+1 Malaria Strategy Along China-Myanmar Cross Border Areas

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Abstract

Background: Cross-border malaria in Laiza City of Myanmar seriously affected Yingjiang County of China and compromised the national malaria elimination goal. A pilot project on 3+1 strategy of joint cross-border malaria prevention and control was carried out in building border malaria buffer area in the both sides since 2017; Here, 3 was the three preventive lines in Yingjiang County to strengthen targeted measures of elimination malaria in China and +1 was a defined border area in Laiza City to adopt the integrated measures of malaria control in Myanmar.

Methods: A retrospective analysis from 2015 to 2019 was conducted that included case detection, parasite prevalence and vector surveillance. Descriptive statistics was used and the incidence or rates were compared. The annual parasite incidence in +1 area of Myanmar, the annual importation rate in Yingjiang County of China and the density of *An.Minimus* were statistically significant indictors to assess the effect of the joint interventions.

Results: In +1 area of Myanmar from 2015 to 2019, the average of annual parasite incidence was (59.11±40.73) / 1000 and *plasmodium vivax* accounted for 96.27 % of total confirmed cases. After the pilot project, the annual parasite incidence, microscopic parasite prevalence rate and density of *An. Minimus* reduced by 89%,100% and 93.93% respectively, but the submicroscopic parasite prevalence rate was no significant difference between the two surveys (p =0.084). In Yingjiang County of China, neither indigenous nor introduced case was reported and 100% cases were imported from Myanmar since 2017. The average of annual importation rate from 2015 to 2019 was (0.47±0.15)/1000. After the pilot project, it reduced by 53% of whole county, 67% of the first preventive line, 52% of the second preventive line and 36% of the third preventive line respectively. The density of *An. Minimus* in the first preventive line reduced by 94.51% and did not have significant difference between that of+1 area of Myanmar (Z value=-1.18 p value=0.24).

Conclusion: The pilot project on 3+1 strategy has made remarkable effectiveness and a buffer area of border malaria was successfully established between Laiza City of Myanmar and Yingjiang County of China. The combined use and expanded coverage of indoor residual spraying and long-lasting insecticidal nets (LLINs) was more effective than only use of LLINs in reducing the transmission of *plasmodium vivax* caused by *An. Minimus*. It is necessary to adopt submicroscopic infection interventions to eliminate potential sources of infection in Laiza City of Myanmar.

Background

Although, significant progress has been documented in the National Malaria Elimination Programme, cross-border/imported malaria remains a major challenge in malaria elimination in China. China 1-3-7 malaria strategy which refers case reporting within one day, case confirmation and investigation within three days, and focus response within seven days has led to significant achievements and milestones in malaria control to elimination [1–3]. Its performance and key technical specification had remarkable impact in shrinking the national map of indigenous malaria from 762 counties to 2 counties and with 4262 cases to 3 cases from 2010 to 2016 respectively [4, 5] .Yet in 2016, the World Health Organization(WHO)identified 21 countries, including China, those are on track to reach the goal of malaria elimination by 2020[6].

Yunnan Province of China (YNC) shares a land border of 4060 km with Myanmar, Lao PDR and Vietnam in the Greater Mekong Sub-region. Among them, 18 counties in the West of YNC are adjacent to 5 special regions in the North of Myanmar with a land border of 1997 Km. Myanmar is still one of the highest malaria burden country in the world [6], especially in the 5 special northern regions due to the limited health resources [7, 8]. In 18 counties of YNC, most malaria cases are imported from neighbor owing to intensive and regular daily cross-border activities. Consequently, curbing and controlling China-Myanmar cross-border malaria has become a major challenge to malaria elimination in YNC [9.10, 11].

WHO defines border malaria as malaria transmission or potential transmission that takes place across or along boundaries between countries sharing a land border, it includes movement of infected people crosses boundaries, and/or mosquito transmission crosses or occurs along boundaries [12]. In order to reduce the malaria burden in China-Myanmar border area, an effective joint cross-border malaria prevention and control mechanism was setup between YNC and Myanmar supported by the sixth and tenth round of China malarial project in the Global Fund to Fight AIDS, Tuberculosis and Malaria (refer to as “GF malaria program”) since 2007 [13–20]. It was comprised of bilateral malaria programs and capacity transfer, as well as exchange of epidemic information[13, 15, 17], YNC’s provision of malaria capacity transfer and training, and establishment of 66 malaria consultation posts in the 18 border counties to detect and treat malaria for entry people, and to deliver a malaria protective pack for exit people [19, 20]. Myanmar’s establishment of 80 malaria medical stations in the 5 special regions to carry out malaria case detection and management, providing distribution of long-lasting insecticidal nets (LLINs) or insecticide treated nets (ITNs) and promoting health education [14, 16]. These integrated approaches led to significant achievements including the annual parasite incidence (API) reduction in Myanmar side from 41.7/1000 in 2008 to 7.1/1000 in 2013; whereas YNC API reduced from 1.9/1000 in 2006 to 0.09/1000 in 2013, both malaria burden dropped by 89% and 95% in Myanmar and China respectively [20]. These milestones and achievements were not sustained due to the GF Malaria Program interruption for China in January 2014, and interesting a high level health official’s bilateral memorandum of understanding was signed in Tengchong City of YNC in 2016.

Laiza City (LZC) of Myanmar is the political center of Kachin Special Region II (KSR II) and shares a land border of 20.5 km with Nabang Township of Yingjiang County (YJC) of YNC. After the regional conflict in KSR II in 2012, more than 30,000 internally displaced persons(IDP)migrated to LZC and resettled along the boundary. These greatly aggravated the malaria burden in both sides, resulting in the malaria incidence of KSR II rebounded from 2.1% in 2012 to 5.1% in 2016 [18], whereas the number of reported cases in YJC sharply raised from 58 (23 indigenous cases) in 2012 [15] to 186 (1 indigenous case) in 2016, which accounting for 59.23% of the total cases in YNC in 2016. This was what happened only in YJC since the National Malaria Elimination Programme launched in YNC in 2010, when the number of reported cases raised rather than fallen and local transmission continued to 2016[5].

Whether or not China can meet the goal of malaria elimination as scheduled by 2020 depends on efforts devoted in reaching zero indigenous case by 2017 and maintaining no case for 3 consecutive years in YJC. The pilot new joint cross-border malaria prevention and control project termed 3 + 1 strategy was initiated for establishing a buffer area of border area in both sides since 2017, i.e. +1 was as a catchment area in LZC of Myanmar (refer to as “+1 area”), a defined region with a length of 20.5 Km and a width of 2.5 Km along the boundary. Here, the implementation of joint working group and adoption of integrated malaria control and elimination measures aimed at reinforcing the existed local GF malaria programs. These included funding and technical assistance, capacity transfer and training early case detection and management, focus response, vector surveillance and control, health education, and radical treatment. 3 mean to establish three preventive lines (TPLs) in YJC of China and took the targeted measures for each line under performing the national 1-3-7 strategy. The first preventive line (1st PL) was the same defined region in the border areas of YJC corresponding to + 1 area of Myanmar, where the core interventions were vector surveillance and control, entry-exit person management, reactive and proactive case detection aiming at reducing the risk of case importation and local transmission interruption. The second preventive line (2nd PL) included others border areas in YJC besides 1st PL with core interventions including proactive malaria case detection and mobile population management in transmission re-establishment prevention. The third preventive line (3rd PL) covered the non-border areas including downtown of YJC where the core interventions were passive case detection for early detection and prompt treatment to maintain zero indigenous case in China.

The study assesses the impact of joint 3 + 1 strategy implementation in China-Myanmar cross-border malaria and summarizes joint experiences and lessons in accelerating malaria elimination agenda.

Methods

Study areas and population

The study areas were the catchment areas of pilot project based on 3+1strategy. +1 area of Myanmar covered the urban of LZC, 4 natural villages, a high school and 2 camps of IDP, and the population was about 20,000. The 1stPL of YJC covered 10 natural villages in 2 border townships with population of about 2,000. The 2ndPL covered 51 administrative villages in 8 border townships of YJC with population about 147,000. The 3rdPL covered 27 administrative villages in 6 non-border townships and downtown of YJC with population about 160,000. Figure 1 shows a map of the study area with the location of the pilot project.

Data resources and collection

Case detection: In LZC of Myanmar, the data of routine malaria and population size from January 2015 to December 2019 were collected from the office of GF malaria program in KSR II that monthly collected at the facility level via the health information system which established and maintained by GF malaria program since 2007 [20]. Data of confirmed cases and blood examination in +1 area were extracted from the monthly data reporting of Laiza central hospital (that including the data of LZC hospital), the camp clinic of Je Yang Hka and the camp clinic of Hpum Lum Yang. In YJC of China, Data of registered malaria cases from January 1, 2016 to December 31, 2019 were collected from the information management system specific to malaria elimination [1] and nationwide notifiable infectious diseases reporting information system [21]. The data of blood examination were extracted from the monthly report of each sentinel hospital that collected by County Center for Disease Control and Prevention (CDC) as part of GF malaria program management since 2003. Data of population size were extracted from the statistical yearbook of YJC.

Parasite prevalence: The data of +1 area of Myanmar were collected from the joint working group set up laboratory records in Nabang Township hospital, and conducted the survey of prevalence in the 2 IDP camps by using a novel technique termed capture and ligation probe-PCR (CLIP-PCR)[22,23] in April 2017 and December 2019. Each participant body temperature was measured and 2 dried blood spots were collected, immediately with rapid diagnosis tests (RDTs) done if the body temperature was higher than 37.5^{oC} or had a fever within one week. One of 2 dried spotted bloods was tested by using CLIP-PCR in the next day, then the participants whose PCR positive were followed up.

Vector surveillance: The data of +1 area of Myanmar were collected from the monitoring records of the joint working group whom conducted periodic vector surveillance from 2018 to 2019. Monitoring was conducted in Ja Htu Kawng Village and 2 IDP camps as capture sites, and then a house or a shelter was fixed as a capture point in the East, West, North, South and Middle of each site. Briefly, CDC light trap was hanged in indoor of each point; a 3-overnight capture was conducted in every 15 days from June to September. The data of 1st PL of YJC were collected from county CDC, which carried out the national malaria vector surveillance project in Nangbang Township since 2015 same as +1area of Myanmar. The data of *Anopheles minimus* (*An. minimus)* females were extracted.

Statistical analysis

The databases were generated with Microsoft Excel 2010 and analyzed with Statistical Product and Service Solutions (SPSS) software version 20. Descriptive statistics was used and the statistically significant differences (SSD) of incidence or rate were compared with chi-square test and odds ratio (OR) with 95% confidence interval (CI). The level of significance was set at *p* value ≤0.05 and (1-OR) multiply 100 was used to indicate the degree of reduction or increment. To assess the case detection, API (number of new parasitological confirmed malaria case per 1000 population per year [24]) with 95% CI was computed as a key indicator in +1 area of Myanmar, whereas annual importation rate (AIR, number of registered to imported case per 1000 population per year) with 95% IC was computed after getting rid of indigenous cases in YJC of China and TPLs. Both SSD were analyzed by comparing with last year and between 2019 and 2016, respectively. Annual blood examination rate (ABER), malaria test positivity rate (MTPR) and proportion of *Plasmodium vivax* (*P. vivax*) were also evaluated. The parasite prevalence rate (PPR, number of positive cases per 100 investigated participants), with 95% IC was calculated by using PCR, microscopic and submicroscopic, and SSD results were compared between the submicroscopic PPR of the two surveys. The monthly density (number of females per trap per night per month) of *An. minimus* was calculated and its reduction rate was calculated by using average density in June and September between 2018 and 2019. The correlation between monthly density and number of malaria cases was measured with bivariate Pearson correlation, and SSD of the density between +1 area of Myanmar and 1stPL of YJC was compared with rank sum test of nonparametric tests.

Results

Evaluation of malaria case detection and confirmation in various suited sites

In + 1 area of Myanmar, a total of 5847 cases were confirmed during 2015 to 2019, in which *P. vivax* accounted for 96.27% (5629/5847) and *P. falciparum* was 3.73% (218/5847). The average of API was (59.11 ± 40.73)/ 1000, all of API had SSD compared with last year and the API in 2019 reduced by 89% (95%CI 95: 88%-91%) than 2016 (Table 1). In YJC of China, a total of 737 cases were registered from 2015 to 2019, in which 98.37% (725/737) was *P.vivax* and 1.63% (12/737) was *P. falciparum*; 0.95% (7/737) was indigenous cases and 99.05% (730/737) was imported cases. We found that six of seven indigenous cases occurred in 2015 (five in 1st PL and one in 2nd PL) and one of seven in 2nd PL in 2016. There were no any new indigenous cases and introduced cases since 2017. Among the 730 imported cases, only one case in 3rd PL came from Thailand in 2015, the rests were influx from Myanmar. The proportion of reported cases by TPLs in the total cases of YJC was 56.99% of 1st PL, 14.52% of 2nd PL and 28.49% of 3rd PL. The average of AIR was (0.47 ± 0.15)/1000, all had SSD compared between AIR in 2019 and 2016.The AIR reduced by 53% (95%CI: 39%-63%), 67% (95%CI: 52%-77%), 52% (95%CI: 10%-75%) and 36% (95%CI: 3%-57%) in YJC and TPLs in 2019 than 2016 respectively (Table 1). The trend of API in + 1 area of Myanmar, and the trend of AIR and cases composition in YJC and TPLs from 2015 to 2019 were depicted in Fig. 2.

Table 1
The results of case detection in each catchment area of the pilot project

Area	Year	Population	No. of malaria tests	No. of confirmed or registered cases	Proportion of *Pv* (%, No.)	ABER(%)	MTPR(%)	API or AIR (‰, 95% CI)	Compared with last year		Com and
									X^2 (P Value)	OR (95%CI)	X^2 (P Valu
+1	2015	19470	5361	940	99.36(934)	27.53	17.53	48.28(45.27–51.29)	-	-	1462 0.00
	2016	19583	9275	2080	97.69(2032)	47.36	22.43	104.77(100.51-109.03)	442.43(< 0.001)	2.31(2.13–2.5)	
	2017	19754	8754	1936	98.19(1901)	44.32	22.12	98.01(93.86-102.15)	4.97(0.026)	0.93(0.87–0.99)	
	2018	20560	8095	664	95.63(535)	39.37	8.20	32.3(29.88–34.71)	720.97(< 0.001)	0.31(0.28–0.34)	
	2019	18640	7644	227	100(227)	41.01	2.97	12.18(10.6-13.75)	178.13(< 0.001)	0.37(0.32–0.43)	
The first preventive line	2015	1822	1163	110	100(110)	63.83	9.46	60.37(49.43–71.32)	-	-	36.84 0.00
	2016	1897	1293	100	100(100)	68.16	7.73	57.63(46.92–68.34)	0.43(0.512)	0.91(0.69–1.21)	
	2017	2067	1369	119	96.64(115)	66.23	8.69	57.57(47.52–67.62)	0.45(0.504)	1.1(0.84–1.44)	
	2018	2097	1424	52	98.08(51)	67.91	3.65	24.8(18.14–31.46)	**28.39(< 0.001)**	**0.42(0.3–0.58)**	
	2019	2165	1415	39	100(39)	65.36	2.76	18.01(12.41–23.62)	2.35(0.126)	0.72(0.47–1.1)	
The second preventive line	2015	141107	4989	23	100(23)	3.54	0.46	0.16(0.09–0.22)	-	-	5.38(
	2016	144339	5532	30	96.67(29)	3.83	0.54	0.20(0.13–0.27)	0.81(0.368)	1.29(0.74–2.24)	
	2017	147084	5001	22	95.46(21)	3.40	0.44	0.15(0.09–0.21)	1.39(0.239)	0.72(0.42–1.25)	
	2018	148477	5353	18	94.44(17)	3.61	0.34	0.12(0.07–0.18)	0.44(0.508)	0.81(0.43–1.51)	
	2019	145741	4772	14	100(14)	3.27	0.29	0.1(0.05–0.15)	0.43(0.513)	0.79(0.39–1.59)	
The third preventive line	2015	158872	12553	42	97.62(41)	7.90	0.33	0.26(0.18–0.34)	-	-	4.52(
	2016	165853	13785	56	96.43(54)	8.31	0.41	0.34(0.25–0.43)	1.44(0.229)	1.28(0.86–1.91)	
	2017	160314	12395	38	97.37(37)	7.73	0.31	0.24(0.16–0.31)	2.86(0.091)	0.7(0.46–1.06)	
	2018	161782	10005	35	100(35)	6.18	0.35	0.22(0.14–0.29)	0.15(0.696)	0.91(0.58–1.44)	
	2019	179325	6553	39	100(39)	3.65	0.60	0.22(0.15–0.29)	0.001(0.982)	1.01(0.64–1.59)	
Yingjiang County	2015	301801	18705	175	99.43(174)	6.20	0.94	0.56(0.48–0.64)	-	-	35.82 0.00
	2016	312089	20610	186	98.39(183)	6.60	0.90	0.59(0.51–0.68)	0.29(0.592)	1.06(0.86–1.30)	
	2017	309465	18765	179	96.65(173)	6.06	0.95	0.58(0.49–0.66)	0.06(0.815)	0.98(0.79–1.2)	
	2018	312356	16782	105	98.1(103)	5.37	0.63	0.34(0.27–0.4)	**19.99(< 0.001)**	**0.58(0.46–0.74)**	
	2019	327231	12740	92	100(92)	3.89	0.72	0.28(0.22–0.34)	1.57(0.210)	0.84(0.63–1.11)	

Notes: 1) Pv = Plasmodium vivax; 2) ABER = annual blood examination rate; 3) MTPR = malaria test positivity rate; 4) API = annual parasite incidence; 5) AIR = rate which was calculated after getting rid of the indigenous cases; CI = Confidence interval; 6) X2 = chi-square test; 7) OR = odds ratio.

Determination of malaria parasite prevalence in survey settings in Myanmar

The average PCR PPR was 1.58% in + 1 area. In the first survey, 83 PCR positives were screened from 5570 participants (Table 2), in which 3 were RDTs positive tested in the field among 37 who had fever at present or within a week and they were confirmed as *P. vivax* by both PCR and microscopy, 16 were confirmed as *P. vivax* by microscopy in the later follow-up of PCR positives, and the rests (64) were negative by microscopy. There was no SSD between the submicroscopic PPR of the two surveys, and the microscopic PPR reduced from 0.34(0.19–0.49) % in 2017 to zero in 2019, the rate of reduction was 100%.

Table 2
The results of parasite prevalence survey in + 1 area of Myanmar

Date	No.of test	Positive of PCR		Microscopic positive		submicroscopic		submicroscopic PPR compared	
		No. of cases	PPR(%,95%C)	No. of cases	PPR(%,95%C)	No. of cases	PPR(%,95%C)	X^2 (*P* Value)	OR (95%CI)
Apr.2017	5570	83	1.49(1.17–1.81)	19	0.34(0.19–0.49)	64	1.15(0.87–1.43)	2.99(0.084)	1.45(0.95–2.21)
Dec.2019	1992	33	1.66(1.1–2.22)	0	-	33	1.66(1.1–2.22)		

Notes: 1) PPR = parasite prevalence rate; 2) PCR assay was using Capture and Ligation Probe-PCR; 3) CI = confidence interval; 4) OR = odds ratio.

Examining the effects of vector surveillance activities in these settings

Our findings showed *An. minimus* in female anopheles proportion of 63.7% (186/292) in + 1 area of Myanmar and 70.95% (105/148) in 1st PL of YJC. After pilot project, the average monthly density reduced by 93.93% and 94.51% in September than June in both sides, respectively. The monthly density of *An. minimus* in + 1 area of Myanmar had a significant positive correlation with monthly number of malaria case (r = 0.74,p = 0.04), but no correlation in 1st PL of YJC (r = 0.45，p = 0.25).There was no SSD between the densities of both sides. The trend of average monthly density of *An. minimus* and monthly number of malaria cases was summarized in Fig. 3.

Discussion

It is important to note that the National Malaria Control Programme in Myanmar was launched in 2016 and its goal is to eliminate malaria by 2030 [25, 26]. However, National Malaria Elimination Programme in China was initiated in 2010 and its final goal is by 2020 [1–3]. It is a 10-year difference and distinct stage in achieving the goal of elimination malaria between China and Myanmar. Despite national programme has included KSR II, but the support from national programme barely covered KSR II in Myanmar due to conflict with central government since 2012 [27]. This situation resulted in an imbalance on border malaria control capacities between China and Myanmar, malaria including KSR II threatens the border areas of YNC.

In order to reduce malaria transmission and enhance the control capacities in KSR II, the pilot project on 3 + 1 strategy of joint cross-border malaria prevention and control was initiated in both sides and supported by both local funds. Due funding limitation and human recourses, + 1 area of Myanmar and 1st PL of YJC was set in a defined region, the width was limited to 2.5 Km from boundary that was based on the fact that *An. Minimus* is dominant malaria vector in this area [28–30], its maximum flight distance is 2.32 Km [31, 32], which purpose was to prevent mosquito transmission cross or along boundary by reducing vectorial capacity and building a flight buffer.

There was an outbreak in + 1 area of Myanmar in 2016 which API unusually increased 2.31 times higher than 2015 (OR 95%CI: 2.13–2.50, *p* value < 0.001) that matched the WHO description on malaria outbreak (Fig. 2 and Table 1) [33].Usually, malaria outbreaks in the Greater Mekong Sub-region are mostly ascribed to population movement and rarely to climatic factors [25]. In spite of the difference of population between 2015 and 2016 was little (Table 1), the rate of bednet ownership and proportion (97.3% in 2013) of sleeping under bednet was high [27, 34], especially sleeping under LLINs/ITNs (76.1% in 2013) [27], malaria outbreak unexpectedly occurred during the implementation of local GF malaria program in 2016. Several reasons could explain included that most of male adult conscribed into the ethnic army and stationed in the forest where malaria high-transmission [25], they often returned home and carried malaria back communities or Usage of LLINs had expired [27]. Why scaling up the proportion of LLINs distribution, coverage and use in the catchment areas of Myanmar during the tenth round China GF malaria program from 2011 to 2013, and those LLINs expired by 2015 [27]. Also IDPs moving into local GF malaria program did not have enough LLINs to cover them again and rarely implemented indoor residual spraying (IRS) and treated bednets due to funding gaps to potential rebound of malaria transmission to pre-existing level [23].

Our findings showed that 96.27% of confirmed cases was *P. vivax* in the studied area, as WHO mentioned[35] that it is more difficult to control or eliminate than *P. falciparum* due to its several distinct biological characteristics such as gametocytes in peripheral blood is matured to transmit to merozoites before symptoms appear; As malaria parasite density is often low to miss detection with microscopy or RDTs, hypnozoites in liver cell cause multiple relapse and need a 14-day course treatment of primaquine which patients may not fully adhere. Implemented pilot project had remarkable results in controlling malaria outbreak in + 1 area of Myanmar, effects of core WHO recommended malaria interventions and classical Chinese measures such as radical treatment at the resting stage [24, 35] (see Table 1).

In the first year (2017) of the pilot project, vector control in + 1 area of Myanmar was one net per bed to distribute new LLINs provided by Health Poverty Action (HPA) of nongovernmental organization. IRS and vector surveillance were not carried out due to preparation of materials and documents, other interventions were performed since April 2017. Our findings showed the API in + 1 area of Myanmar in 2017 had SSD than 2016 (*p* value = 0.026). This meant the results of malaria control in + 1 area of Myanmar in the first year was effective, but the API only reduced by 7% (95% CI: 1%-13%), malaria transmission was still high. In the middle of June in the second (2018) and third (2019) years, all houses in + 1area of Myanmar and 1st PL of YJC were simultaneously IRS used high-efficiency cypermethrin with WHO recommended dosage [36], and malaria vector was periodically monitored from the early of June to end of September, the other interventions were continue same as 2017. The results of malaria control in + 1 area of Myanmar had notably achievements in the past two years and both years' API was sharply reduced by over 60% due the combinative effectiveness of IRS and LLINs. This is also trues as the proportion of *An. minimus* in the female anopheles was 63.7% high and had a positive correlation with number of malaria case ($r = 0.74, p = 0.04$), which unequivocally confirmed again it was predominant malaria vector in this area. Dong XS's study had proven this mosquito rests indoor, prefers human blood and the biting peaks are in the sunset and midnight [37]

Consequently, IRS protects residents against this mosquito biting before they go to bed by killing mosquito that rest indoor, whereas LLINs protect residents after they go to bed by killing mosquito that rest on bednets, meanwhile, both interventions were high coverage and use in + 1 area of Myanmar. The combined effectiveness of both was maximally to reduce the human biting rate and vector survival, which significantly reduce vectorial capacity and transmission. Figure 3 showed the average monthly density of *An. minimus* sharply reduced in July after actualized IRS, the number of malaria case correspondingly sharply reduced in August. IRS and LLINs/ITNs are core interventions of vector malaria control recommended by WHO [24], both may be less effective in reducing *P. vivax* transmission. Conversely, our finding revealed that combined use of interventions in both settings have a significant positive effects and effectiveness in reducing *An. Minimus* vectorial capacity and competency.

Our findings revealed the average PCR PPR was1.58% in + 1 area of Myanmar, both result of the two surveys were low, but it was reliable and fitting the actual epidemic. This was because 3 RDTs positives were positive again detected with PCR and microscopy, if the 3 positives were as gold standards, the sensitivity and specificity of assay was both 100%, this result was same to findings by Zhou *et al* [23]. CLIP-PCR is a high-throughput and highly sensitive PCR assay for detection *Plasmodium spp.* with a limits of detection of 0.01 parasites/μ l, which used dried blood spot and 96-well plate to directly detect parasite without purification of nucleic acid and tested at least 36 samples per well by pooling strategy [22, 23]. Additionally, 64 of 83 PCR positives were the submicroscopic infection, it accounted for 77% of all PCR positives, this result was similar to 67% of findings that overview of submicroscopic *P. vivax* infections by Moreira *et al*. [38] and Cheng *et al*. [39].Furthermore, Our finding indicated the average API in + 1 area of Myanmar was (59.11 ± 40.73) /1000 and ratio of *P. falciparum*/*P. vivax* was 0.04, consequently its transmission intensity was belonging to very low transmission according to the WHO category [24], especially, and the two surveys were conducted at the pre-epidemic and post-epidemic respectively. Due to limited sensitivity of microscopy and RDTs, measuring the accurate parasite prevalence in the low or very low transmission area are challenging [24]. Findings showed the PPR of microscopy reduced by 100%, which proved the core interventions of case detection were very effective, local GF malaria program worked in a high ABER (Table 1).In spite of the submicroscopic PPR of the later survey was little higher than the previous, but there was no SSD between the two surveys, that related to low transmission and recently transmission reduction [40], this indirectly proved the effectiveness of the pilot project due to submicroscopic infection regarding as infectious parasite reservoir [41]. These findings prompted contextual adoption of targeted interventions to control or eliminate this infection reservoir, such as to track the person who had same trip as case administer a same treatment, to administer a dose of chemprophylactics for case neighbors and families or to take radical treatment for *P.vivax* case at the resting stage. This finding also hinted that the source of infection still existed in + 1 area of Myanmar, once the vector control was weakened, malaria transmission would rebound again.

Interestingly, our findings showed that the number of cases reported by 1st PL accounted for 57% of the total cases in YJC and its AIR determined the trend of AIR in YJC. Meanwhile, Fig. 2 and Table 1 showed except that in 2018, the AIR in 1st PL reduced significantly with the decrease of API in + 1 area of Myanmar (p value < 0.001), the others were little difference and did not change with API in + 1area of Myanmar. This finding revealed that most of the imported cases in 1st PL of YJC were from + 1 area of Myanmar, whereas 2nd PL and 3rd PL imported from Myanmar outside + 1 area. Because the explanation could be the annual cross-border population of YJC was relatively stable in recent years, and only small groups were population at risk (PAR) who stayed overnight or lived abroad. Usually, PAR were the certain residents of 1st PL and 2nd PL who long rent land of KSR II close to the border for cash crop cultivation, and a few of non-local and 3rd PL went to the interior of KSR II for planting and mining. However, among the border of 214.6 Km between YJC and KSR II, only LZC was the most serious malaria epidemic area and transmission was perennial with seasonal peak due to low altitude and dense population, the others were low epidemic areas and transmission was interrupted in the cold season due to high altitude. In particular, most of PAR in 1st PL lived in foothill and lowland plantations within + 1 area of Myanmar had high malaria transmission, which were relatively isolated and far away from Burmese villages [27].

Also the malaria consultation post in 1st PL of YJC which established by GF malaria program since 2007 was still working normally, most of PAR would take a dose of chemprophylactics before leaving the country and the new LLINs were freely available. That was why the AIR in 1st PL from 2015 to 2017 showed little difference and did not change with API of + 1area of Myanmar, but it sharply reduced in API after implementing all house IRS in 2018, then stable in 2019 due to a part of PAR lived outside + 1 area of Myanmar where no IRS. The research also found that all had SSD compared AIR in YJC and TPLs between 2019 and 2016 and proved the strategy of TPLs and its targeted local communities measures for each preventive line were effective.

Our study limitations include the average ABER was 40% of + 1 area and 66% of 1st PL, they were much higher than 2nd PL and 3rd PL due to the number of malaria tested in + 1 area including the number of tested in passive case detection and active case detection combined in report monthly. However, that number in TPLs was only passive case detection, not included active case detect. So, there was no comparability between + 1 area of Myanmar and TPLs of YJC. Furthermore, passive case detection in 1st PL detected all febrile patients, but 2nd PL and 3rd PL detected only 3 types of fever such as malaria fever, suspected malaria fever and fever of unknown cause. Bias due to the number of cases reported by 3rd PL was more than 2nd PL, this was because the rich people and non-local mobile population prefers to go to county-level hospitals where they could get better medical resources, as part of cases were transferred from 1st PL and 2nd PL to the county hospital for treatment.

Conclusion

The joint cross-border pilot project of 3 + 1 strategy on malaria control and elimination has made remarkable achievements as a border malaria buffer area of was successfully established between YJC of China and LZC of Myanmar. In + 1 area of Myanmar, the integrated malaria preventive and control measures got great results: the API and microscopic PPR were reduced by 89% and 100% respectively. Findings were the combined use and high coverage of IRS and LLINs showed more effective than only use of LLINs in reducing the transmission of *P. vivax* caused by *An. Minimus*, and the targeted interventions should be adopted to control or eliminate the infection reservoir of submicroscopic infections. In YJC of China, the targeted malaria measures for each preventive line showed significant milestones in local transmission interruption since 2017 and AIR reduction by 53% in county-wide.

Abbreviations

ABER- Annual Blood Examination Rate

AIR- Annual Importation Rate

API- Annual Parasite Incidence

CDC- Center for Disease Control and Prevention

CI- Confidence Interval

CLIP- Capture and Ligation Probe

GF- Global Fund to Fight AIDS, Tuberculosis and Malaria

IDP- Internally Displaced Persons

ITNs- Insecticide Treated Nets

KSR II - Kachin Special Region II

LLINs- Long-Lasting Insecticidal Nets

LZC- Laiza City

MTPR- Malaria Test Positivity Rate

OR- Odds Ratio

PAR-Population at Risk

PCR- Polymerase Chain Reaction

PL-Preventive Line

PPR- Parasite Prevalence Rate

RDTs- Rapid Diagnosis Tests

SSD-Statistically Significant Differences

TPLs- Three Preventive Lines

WHO- World Health Organization

YJC- Yingjiang County

YNC -Yunnan Province of China

Declarations

Ethics approval and Consent to participate

For the routine data of malaria case and vector of the pilot project, Ethics Committee of Yunnan Institute of Parasitic Disease (YIPD, China) and the Health Department of KSR II of Myanmar approved the access and collection. Malaria parasite prevalence tested by using CLIP-PCR was as a part of this study, the Ethics Committee of YIPD approved the study [Reference number: YIPD-EC-2017(4) and YIPD-EC-2019(4)]. All participants were informed in native language and the written informed consent was obtained from individual before the two dried blood spots were collected. There was no any personal information has been appeared in this article.

Consent for publication

Not applicable.

Availability of supporting data

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

X-D S and H-Z Z conceived and designed this project. Z-R L and S-G L organized and supervised the field implementation, Z-R L, S-G L, X-D S, X-R G, JY, PT, Q-Y C, X-Y S, C-L D, K-X D, H-W C and Y-B D performed the field works and collected data. ZZ and H-R P tested the PCR examination. Z-R L and X-D S analyzed the data wrote the paper. All authors read and approved the final manuscript.

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Figures

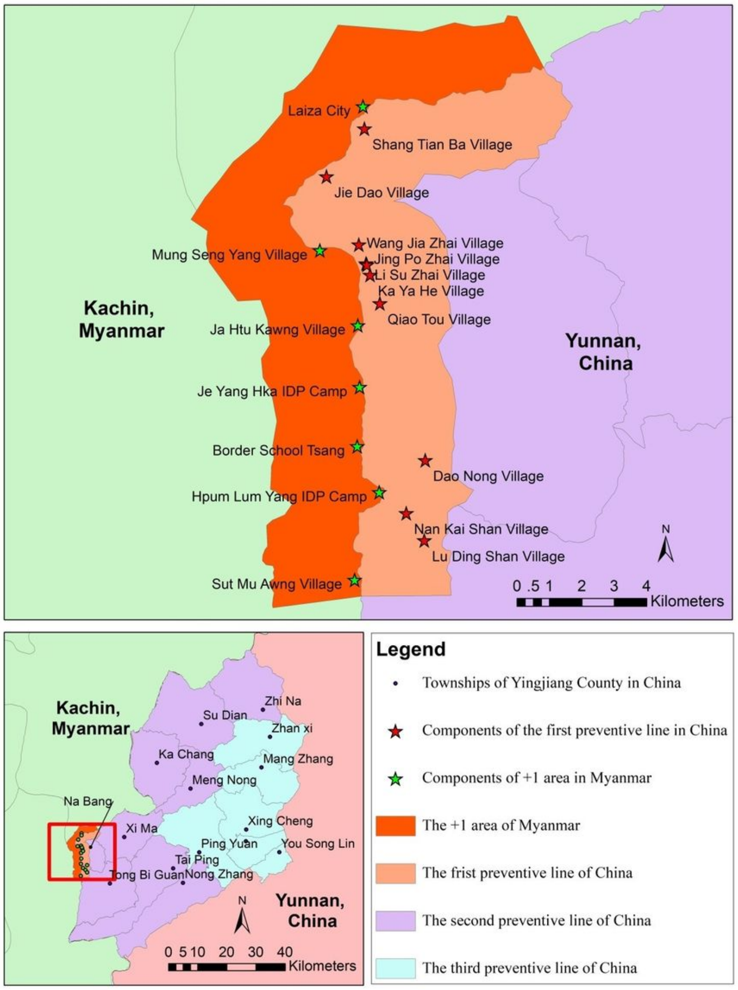

Figure 1

The map of study area of Pilot project on 3+1 malaria strategy. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

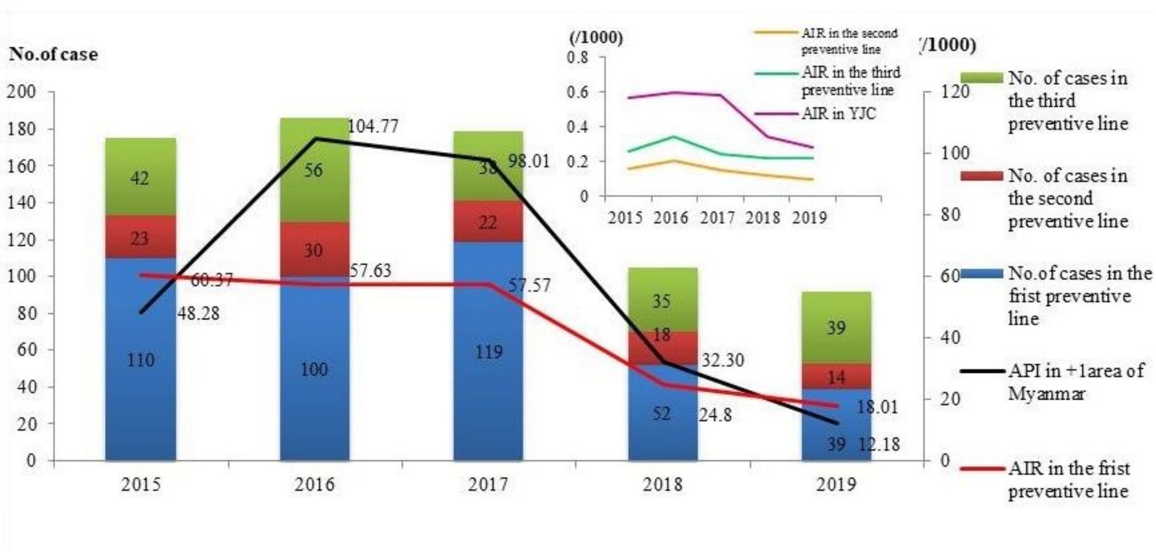

Figure 2

The trend of annual parasite incidence in +1 area of Myanmar, and the annual importation rate and cases composition in Yingjiang Country of China from 2015 to 2019. Note: 1) API=annual parasite incidence 2) AIR=annual importation rate

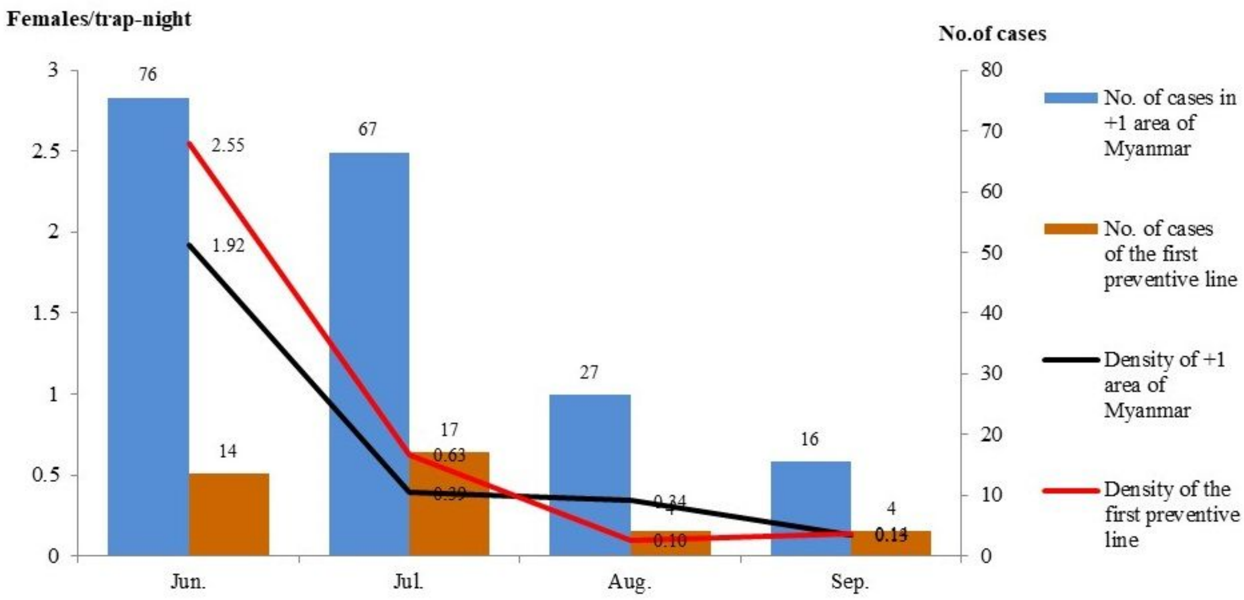

Figure 3

The trend of average monthly density of A. minimus and No. of monthly malaria cases in June to September in 2018 and 2019. Note: All house indoor residual spraying in the middle of June.

Supplementary Files

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- SupplementaryMaterial.docx