ISSN 2096-7071
CN 10-1629/R1

CHINA CDC WEEKLY

Vol. 3 No. 17 Apr. 23, 2021

中国疾病预防控制中心周报

THE WORLD MALARIA DAY ISSUE

ISSN 2096-7071

China CDC Weekly

Editorial Board

Editor-in-Chief George F. Gao

Deputy Editor-in-Chief Liming Li Gabriel M Leung Zijian Feng

Executive Editor Feng Tan

Members of the Editorial Board

Xiangsheng Chen	Xiaoyou Chen	Zhuo Chen (USA)	Xianbin Cong
Gangqiang Ding	Xiaoping Dong	Mengjie Han	Guangxue He
Xi Jin	Biao Kan	Haidong Kan	Qun Li
Tao Li	Zhongjie Li	Min Liu	Qiyong Liu
Jinxing Lu	Huiming Luo	Huilai Ma	Jiaqi Ma
Jun Ma	Ron Moolenaar (USA)	Daxin Ni	Lance Rodewald (USA)
RJ Simonds (USA)	Ruitai Shao	Yiming Shao	Xiaoming Shi
Yuelong Shu	Xu Su	Chengye Sun	Dianjun Sun
Hongqiang Sun	Quanfu Sun	Xin Sun	Jinling Tang
Kanglin Wan	Huaqing Wang	Linhong Wang	Guizhen Wu
Jing Wu	Weiping Wu	Xifeng Wu (USA)	Yongning Wu
Zunyou Wu	Fujie Xu (USA)	Wenbo Xu	Hong Yan
Hongyan Yao	Zundong Yin	Hongjie Yu	Shicheng Yu
Xuejie Yu (USA)	Jianzhong Zhang	Liubo Zhang	Rong Zhang
Tiemei Zhang	Wenhua Zhao	Yanlin Zhao	Zhijie Zheng (USA)
Maigeng Zhou	Xiaonong Zhou		

Advisory Board

Director of the Advisory Board Jiang Lu

Vice-Director of the Advisory Board Yu Wang Jianjun Liu

Members of the Advisory Board

Chen Fu	Gauden Galea (Malta)	Dongfeng Gu	Qing Gu
Yan Guo	Ailan Li	Jiafa Liu	Peilong Liu
Yuanli Liu	Roberta Ness (USA)	Guang Ning	Minghui Ren
Chen Wang	Hua Wang	Kean Wang	Xiaoqi Wang
Zijun Wang	Fan Wu	Xianping Wu	Jingjing Xi
Jianguo Xu	Jun Yan	Gonghuan Yang	Tilahun Yilma (USA)
Guang Zeng	Xiaopeng Zeng	Yonghui Zhang	

Editorial Office

Directing Editor	Feng Tan			
Managing Editors	Lijie Zhang	Yu Chen	Peter Hao (USA)	
Senior Scientific Editors	Ning Wang	Ruotao Wang	Shicheng Yu	Qian Zhu
Scientific Editors	Weihong Chen	Xudong Li	Nankun Liu	Qi Shi
	Xi Xu	Qing Yue	Xiaoguang Zhang	Ying Zhang

Cover Photo: Artemisia annua, known as sweet wormwood, is a Chinese herb that produces artemisinin, which is a medication used to treat malaria. The ancient malaria characters "疟" (at the top left corner) were recorded on an oracle bone in the Shang dynasty from 1600 to 1046 BC (Photographer: Hexin Tan from Naval Medical University).
This week's issue was organized by Guest Editor Xiao-nong Zhou.

Preplanned Studies

A Case Study on the Disease Burden and Influencing Factors of Imported Malaria Patients in a County-Level Hospital — Guangxi Zhuang Autonomous Region, China, 2016–2019

Qiuli Xu[1]; Kangming Lin[1]; Shenning Lu[1]; Lei Duan[1]; Hongrang Zhou[2]; Xuejiao Ma[1]; Bei Wang[1]; Ning Xiao[1,#]

Summary

What is already known on this topic?

Imported malaria cases endanger people's health and potentially cause local re-transmission, and they may also cause economic loss on patients' families and society as a whole.

What is added by this report?

This is the first report to focus on the disease burden of a case study incurred by the imported malaria. The results indicated that the median direct medical cost was 2,904.4 CNY and the median indirect cost was 242.0 CNY for a patient's hospitalization. The economic cost was related to age, time between onset and diagnosis, and days of stay in hospital.

What are the implications for public health practice?

This study analyzed the main causes based on both direct and indirect economic loss of imported malaria cases to provide general information for the evaluation of the disease burden of imported malaria patients and shed light on the rational allocation of medical resources.

Although no locally transmitted malaria cases have been reported in China since 2017, the number of imported cases still remained high in recent years. From 2017 to 2019, China has reported 8,202 imported malaria cases and 33 deaths (*1*–*4*). Imported malaria not only puts the health and safety of local residents at risk, but also takes an economic toll on the patients' families and the communities (*5*). This paper assessed the disease burden of imported malaria patients and possible determinants based on economic loss, which aims to inform policymaking and promote rational allocation of medical resources in China during the elimination and post-elimination stage. The study targeted imported malaria patients who visited the People's Hospital of Shanglin County (a designated hospital for malaria diagnosis and treatment) in Guangxi Zhuang Autonomous Region from January 1, 2016 to December 31, 2019 to calculate the economic cost during stay in the hospital and explore influencing factors through univariate analysis and multiple linear regression. The median of direct medical cost was 2,904.4 CNY and the median of indirect cost was 242.0 CNY. Univariate analysis showed that the direct cost was related to days of stay in hospital, and there was no significant difference in indirect cost among groups. Multiple linear regression analysis indicated total economic burden depended on the patients' age, interval between onset and diagnosis, and days of stay in hospital. Therefore, standardized treatment leading to normal hospital stay and enhanced health education on malaria prevention can effectively reduce the economic loss of imported malaria patients.

Guangxi Zhuang Autonomous Region is located in the south of China where malaria was historically highly prevalent. A total of 3,195 malaria cases were reported in Guangxi from 2010 to 2019, of which 3,193 were imported cases. Most imported malaria cases were *P. falciparum* infection, which accounted for 72.3% (2,310/3,193), followed by *P. ovale* 13.9% (444/3,193). According to the report, the medical information of 3,159/3,193 (98.94%) patients was obtained, in which 70.7% (2,233/3,159) were treated in Shanglin County medical institutions and the local CDC (*6*). Therefore, Shanglin County was selected as the study site.

The disease burden evaluation of imported malaria patients in this study was comprised of direct cost and indirect cost. Direct cost contains hospitalization expenses, while indirect cost refers to economic loss caused by work delays during the treatment. The formula for indirect cost in this study was as follows: indirect costs = hospitalized days × Shanglin County GDP per person/365. Based on the *Statistical Bulletin of National Economic and Social Development of Shanglin County in 2019*, the GDP per capita of the county is 22,086 CNY, and the average daily GDP per

capita is 60.5 CNY (22,086.0/365).

In this study, the People's Hospital of Shanglin was selected as the target institution. The case information of all imported malaria patients treated in the hospital from January 1, 2016 to December 31, 2019 was collected through medical records investigation for further analysis, excluding data with logic errors and incomplete information. Considering the impact of price growth and other factors on hospitalization costs in different years, the hospitalization costs from 2016 to 2018 were standardized by consulting the Consumer Price Index (CPI) of Guangxi from 2017 to 2019 (*7*–*9*) and taking the hospitalization costs in 2019 as the baseline. For example, hospitalization expenses in 2016 (standardized) = hospitalization expenses in 2016 × (1 + 2017's CPI) × (1 + 2018's CPI) × (1 + 2019's CPI). The case information included the patient's gender, age, infected *Plasmodium* species, interval between onset and diagnosis, days of stay in hospital, hospitalization cost, and the cost of each item, etc.

The data were recorded in Excel and statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC, USA). Descriptive statistical analysis was used to describe the general characteristics of the patients. Since direct costs, indirect costs, and total costs did not meet the normal distribution, the quantitative data were analyzed by means, median, and Q1 and Q3. Wilcoxon rank sum test was carried out for comparison between two groups, and Kruskal-Wallis one-way ANOVA test was conducted for comparison between multiple groups. Through square root transformation, the total economic burden satisfied the normal distribution, and multiple linear regression analysis was performed step-by-step to screen independent variables using test level $\alpha = 0.05$.

The results showed that 537 imported malaria cases were collected from the People's Hospital of Shanglin, including 527 males and 10 females. The median age was 40 years, with patients aged 20–49 years accounting for 77.1% (414/537), and each patient was hospitalized for 4 days. The median direct cost was 2,904.4 CNY, accounting for 92.3% of the total expenditures (2,904.4/3,146.4), with the cost of laboratory tests, drug products, and examination as the top three costs. The median indirect cost was 242.0 CNY, accounting for 7.7% of the total economic burden (242.0/3,146.4) (Figure 1). Univariate analysis showed that direct expenses were only related to days of stay in the hospital and that the direct cost of

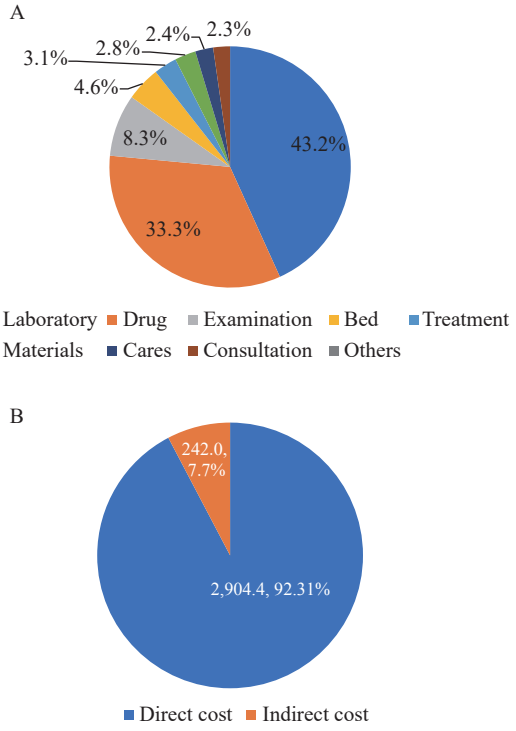

FIGURE 1. Composition of economic costs of imported malaria patients in Shanglin County, Guangxi Zhuang Autonomous Region from 2016 to 2019. (A) Proportion of direct costs of imported malaria patients. (B) Proportion of the total economic burden of imported malaria patients.

hospital stay ≥4 days group was higher than that of hospital stay <4 days group (Table 1). There was no significant difference in indirect cost among the groups (Table 1). Multiple linear regression analysis of the total economic burden showed that total cost was highly related to age, days of stay in hospital, and onset-diagnosis time (Table 2).

DISCUSSION

The total economic burden of a malaria case was about 3,146.4 CNY, which was 14.2% of the local per capita GDP, bringing a major economic burden to families of the patients. Most malaria inpatients in the People's Hospital of Shanglin were males aged 20–49 years, which was consistent with the characteristics of most imported malaria cases being migrant workers (*10*). Among the direct costs of malaria-related treatment, the costs of laboratories, drugs, and examinations were relatively high, which may be caused by the frequent examination of blood routine, blood biochemistry, urine routine, and other indicators for malaria diagnosis, disease progress, and drug side effects. Although antimalarial drugs were free of

TABLE 1. The average medical costs of imported malaria patients in Shanglin County, Guangxi Zhuang Autonomous Region, 2016–2019.

Indicator	Total, n(%)	Direct cost					Indirect cost				
		Mean	Median	(Q1, Q3)*	Z/χ^2 value	*P* value	Mean	Median	(Q1, Q3)*	Z/χ^2 value	*P* value
Gender											
Female	527(98.1)	3,030.8	2,895.4	(2,408.9, 3,459.2)	1.11	0.26	244.6	242.0	(181.5, 302.5)	1.2	0.23
Male	10(1.9)	3,178.1	3,309.0	(2,748.9, 3,560.6)			260.2	242.0	(242.0, 302.5)		
Age (years)					4.29	0.12				3.2	0.20
<20	2(0.4)	2,576.2	2,576.2	(2,428.8, 2,723.6)			211.8	211.8	(181.5, 242.0)		
20–49	414(77.1)	3,014.9	2,861.0	(2,414.3, 3,444.6)			242.7	242.0	(181.5, 302.5)		
≥50	121(22.5)	3,104.7	3,056.7	(2,407.6, 3,556.8)			253.0	242.0	(181.5, 302.5)		
Onset-diagnosis days (days)					0.80	0.42				1.4	0.18
≤1	289(53.8)	2,993.6	2,895.4	(2,433.9, 3,284.1)			237.2	242.0	(181.5, 242.0)		
>1	248(46.2)	3,080.0	2,935.9	(2,390.6, 3,524.1)			254.0	242.0	(181.5, 302.5)		
Length of stay (days)					−10.07	<0.01				–	–
<4	186(34.6)	2,540.9	2,559.5	(2,060.0, 2,874.7)			–	–	–		
≥4	351(65.4)	3,294.5	3,129.9	(2,693.4, 3,690.9)			–	–	–		
Species classification					2.16	0.71				3.7	0.45
P. falciparum	328(61.1)	3,101.2	2,916.2	(2,433.9, 3,494.0)			252.0	242.0	(181.5, 302.5)		
P. ovale	176(32.8)	2,931.5	2,920.3	(2,380.7, 3,443.3)			232.4	242.0	(181.5, 302.5)		
P. vivax	17(3.2)	2,800.0	2,713.8	(2,219.6, 3,462.6)			249.1	242.0	(181.5, 302.5)		
Mixed-infection	9(1.7)	3,081.1	2,895.4	(2,754.1, 3,500.2)			235.3	242.0	(181.5, 242.0)		
P. malariae	7(1.3)	2,930.8	3,140.1	(2,802.6, 3,245.0)			233.4	242.0	(242.0, 242.0)		

* Q1, known as the "Smaller Quartile", is equal to the 25% of all values in the sample, from smallest to largest. Q3, known as the "higher fourth quantile", is equal to the 75% of all values in the sample, from smallest to largest.

TABLE 2. Multiple linear regression results of total cost of imported malaria patients in Shanglin County, Guangxi Zhuang Autonomoums Region, 2016–2019.

Variable	β	Standard error	Standard β	*t* value	*P* value
Intercept	1,822.8	151.3	0	12.1	<0.01
Age	7.7	3.3	0.1	2.4	0.02
Length of stay	268.6	17.7	0.5	15.1	<0.01
Onset-diagnosis interval (days)	−3.3	1.5	−0.1	−2.2	0.03

charge, other drugs for related symptoms and supportive treatment drugs were required during hospitalization. The differential diagnosis of malaria and other diseases often required B-scan ultrasound, electrocardiogram, X ray and other examinations.

Univariate analysis showed that longer stays in the hospital affected the direct cost of hospital stay as the hospital stay ≥4 days group had higher costs than the hospital stay <4 days group. The differences in indirect costs between groups were not statistically significant, which means that the differences in hospitalization days between groups were not statistically significant. For univariate analysis, both age and onset-diagnosis interval were included as categorical variables, while continuous variables were included for multiple linear regression, which could explain the difference in results. Multiple linear regression analysis showed that age, longer stay, and the onset-diagnosis interval affected the total cost. The interval between onset and diagnosis might affect the severity of the patient's illness. The longer the time spent from onset to treatment for diagnosis, the worse the patient will become, leading to an increase in economic costs. The length of the hospital stay might be related to the severity of the patient's symptoms and various indicators of the body of patients. As the hospital stay was extended, the total costs of various items including bed fee, medical consultation fee, and nursing fee

would rise accordingly, thus causing higher hospital costs.

This study was subject to some limitations. First, the direct economic burden included direct medical expenses and direct non-medical expenses. Because imported malaria cases were scattered and there were little direct non-medical burden data available through the field investigations, the study did not include direct non-medical expenses, such as meals, accommodation, and transportation for patients and their families. Second, it was found in a survey in Shanglin County that only 6.7% (2/30) of the imported malaria patients had a caretaker to take care of them all day in the hospital. Therefore, the indirect economic burden in this study only took into account for patients who missed work due to illness. Finally, the relatively poor balance between groups contributed to poor comparability between groups, such as gender grouping.

In conclusion, the economic burden of imported malaria patients in Guangxi Zhuang Autonomous Region was affected by age, the length of hospitalization, and the interval between onset and diagnosis. Therefore, by advocating reasonable medical treatment behavior and standardizing hospitalization, discharge, and the length of hospitalization, the treatment costs of imported malaria patients could be effectively reduced. In addition, one of the most crucial strategies and approaches to reducing the malaria disease burden is to strengthen health education and personal self-protection for people who travel abroad to endemic areas so as to reduce the chance of malaria infection, mitigate the threat of malaria importation, and consolidate the achievements of malaria elimination.

Funding: Supported by the National Key Research and Development Program of China (No. 2016YFC1200502) and the WHO Biennial Cooperative Project (No. 2012/269948-0).

doi: 10.46234/ccdcw2021.096

Corresponding author: Ning Xiao, xiaoning@nipd.chinacdc.cn.

[1] National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention; Chinese Center for Tropical Diseases Research; WHO Collaborating Centre for Tropical Diseases; National Center for International Research on Tropical Diseases, Ministry of Science and Technology; Key Laboratory of Parasite and Vector Biology, Ministry of Health, Shanghai, China; [2] Qingpu District Center for Disease Control and Prevention, Shanghai, China.

Submitted: February 26, 2021; Accepted: April 21, 2021

REFERENCES

1. Zhang L, Feng J, Zhang SS, Xia ZG, Zhou SS. The progress of national malaria elimination and epidemiological characteristics of malaria in China in 2017. Chin J Parasitol Parasit Dis 2018;36(3):201-9. http://www.jsczz.cn/CN/Y2018/V36/I3/2. (In Chinese).
2. Zhang L, Feng J, Zhang SS, Xia ZG, Zhou SS. Epidemiological characteristics of malaria and the progress towards its elimination in China in 2018. Chin J Parasitol Parasit Dis 2019;37(3):241 – 7. http://dx.doi.org/10.12140/j.issn.1000-7423.2019.03.001. (In Chinese).
3. Zhang L, Feng J, Xia ZG, Zhou SS. Epidemiological characteristics of malaria and progress on its elimination in China in 2019. Chin J Parasitol Parasit Dis 2020;38(2):133 – 8. http://dx.doi.org/10.12140/j.issn.1000-7423.2020.02.001. (In Chinese).
4. Xiao N, Xu QL, Feng J, Xia ZG, Duan L, Wang DQ, et al. Approaching malaria elimination in China. China CDC Wkly 2020;2(17):293 – 7. http://dx.doi.org/10.46234/ccdcw2020.075.
5. Xu QL, Zhou HR, Qian MB, Wang DQ, Xiao N. Research progress on economic burden of malaria. Chin J Parasitol Parasit Dis 2020; 38(6):749 – 52. http://dx.doi.org/10.12140/j.issn.1000-7423.2020.06.012. (In Chinese).
6. Li J, Wei SJ, Zhang WW, Lin KM, Yan H, Feng XY. Analysis of malaria epidemiological characteristics in Guangxi in 2010-2019. Chin J Parasitol Parasit Dis 2020;38(5):589 – 94. http://dx.doi.org/10.12140/j.issn.1000-7423.2020.05.010. (In Chinese).
7. Guangxi Zhuang Autonomous Region Bureau of Statistics. Statistical bulletin of national economic and social development of Guangxi Zhuang autonomous region, 2017. http://tjj.gxzf.gov.cn/tjsj/tjgb/ndgmjjhshfz/t2382810.shtml. [2018-4-16]. (In Chinese).
8. Guangxi Zhuang Autonomous Region Bureau of Statistics. Statistical bulletin of national economic and social development of Guangxi Zhuang autonomous region, 2018. http://tjj.gxzf.gov.qqgb/t2381649.shtml. [2019-4-10]. (In Chinese).
9. Guangxi Zhuang Autonomous Region Bureau of Statistics. Statistical bulletin of national economic and social development of Guangxi Zhuang autonomous region, 2019. [2020-3-17]. http://tjj.gxzf.gov.cn/tjsj/tjgb/ndgmjjhshfz/t2382864.shtml. (In Chinese).
10. Liu YB, Hsiang MS, Zhou HY, Wang WM, Cao YY, Gosling RD, et al. Malaria in overseas labourers returning to China: an analysis of imported malaria in Jiangsu Province, 2001–2011. Malar J 2014;13:29. http://dx.doi.org/10.1186/1475-2875-13-29.

Preplanned Studies

Challenges of Sustaining Malaria Community Case Management in 81 Township Hospitals along the China-Myanmar Border Region — Yunnan Province, China, 2020

Wei Ding[1]; Shenning Lu[1]; Qiuli Xu[1]; Xuejiao Ma[1]; Bei Wang[1]; Jingbo Xue[1]; Xiaodong Sun[2]; Jianwei Xu[2]; Chris Cotter[3]; Duoquan Wang[1,#]; Yayi Guan[1]; Ning Xiao[1]

Summary

What is already known on this topic?

The health workforce at township hospitals in the China-Myanmar border region has played a key role in sustaining Community case management of malaria (CCMm), while few studies have investigated their performance and challenges.

What is added by this report?

Sustaining CCMm in the region was subject to the following major challenges: insufficient training on malaria diagnosis and testing, lacking necessary and timely treatment for patients, and risks of instability among the malaria workforce.

What are the implications for public health practice?

These challenges called for the national and provincial authorities to provide regular trainings and intensive supervision to strengthen malaria diagnosis and treatment capacity in the region and to set up incentive mechanisms and individual career development paths to sustain the workforce.

Through years of malaria elimination efforts, China has been on track for the World Health Organization (WHO)'s malaria-free certification after reporting 3 consecutive years of 0 indigenous case since 2017 (*1*). Sustaining the elimination efforts in the border region of Yunnan Province is critical as it shares a long borderline with Myanmar without natural barriers and faced malaria importation and the risk of re-establishment due to mutual business and population movement (*2–4*). Community case management of malaria (CCMm) promotes the early detection, prompt testing, and appropriate treatment of malaria in communities. To consolidate the efforts, this study assessed the status of CCMm in 81 township hospitals of 6 border counties in Yunnan in 2020 by investigating the knowledge and practice of health workforce and their challenges in the delivery of malaria diagnostic and treatment services through a structured questionnaire. The results showed that the CCMm was satisfactory for case recognition and testing by rapid diagnostic tests (RDTs), while both training on malaria diagnosis and providing necessary treatment for patients were insufficient, and risks of instability in the malaria workforce existed. It is recommended to provide regular training and intensive supervision for the malaria workforce to identify strategies to sustain the workforce.

The study was conducted from July to December 2020. All relevant malaria health staff (568) of all township hospitals (81) from 6 counties (Yingjiang, Tengchong, Cangyuan, Longling, Longchuan, and Lushui) was included in the study. The 6 counties were selected out of 18 total border counties by having a higher number of imported malaria cases in the border region between January 1, 2017 and December 31, 2019 according to the data from China Information System for Disease Control and Prevention (CISDCP).

The questionnaire was generated using an online survey tool Wenjuanxing (WJX, https://www.wjx.cn/, in Chinese) and was pretested among 32 health staff in Tengchong County and Simao County. The finalized questionnaire was delivered to the targeted respondents by a mobile application and administrated by the field investigators of local CDCs. Written informed consent was obtained from each respondent. Results were collected by WJX and analyzed by Microsoft Office Excel (version 2019; Microsoft Corp, Beijing, China).

The average age of the respondents was 32.15±8.40 years and 53.7% (305/568) were aged between 30–50 years; 88.4% (502/568) had bachelor's degree or junior college degree in medicine. Among all the respondents, 44.7% (254/568) were physicians responsible for the diagnosis and treatment of malaria, 26.4% (150/568) were lab technicians responsible for testing the malaria suspects, and 28.9% (164/568) were public health

doctors responsible for reporting infectious diseases and conducting epidemiological investigations.

Most physicians (94.9%, 241/254) would suspect malaria if any patient presented symptoms including chills, fever, and shivering. However, half (50%, 127/254) of the respondents had not received any training on diagnosis and treatment of malaria over the past 3 years, and nearly one-third (33.1%, 84/254) of respondents had never had a patient with malaria infection during their practice. In addition, 53.5% of respondents did not provide malaria treatment in local hospitals (Table 1).

Most lab technicians had knowledge of (96.7%, 145/150) and were capable (90.7%, 136/150) of using RDTs, while 55.3% (83/150) of them were not adequately trained for preparing blood films, and 47.3% (71/150) could not identify *Plasmodium* species through microscopy. Only 50.7% (76/150) were trained on microscopy examination of *Plasmodium* during the past 3 years (Table 2).

Among the 164 public health doctors, 29.3% (48/164) reported a lack of regular review of blood films by local county CDCs. Over a quarter (28.7%, 47/164) mentioned shortages of necessary anti-malarial drugs in their hospitals. Almost every respondent (99.4%, 163/164) was engaged in the malaria health education activities, while the promotion via official WeChat account only made up for 26.2% (43/174). In addition, 68.3% (112/164) reported "no change" in terms of the number of malaria health staffs during the last 3 years. Inadequate training (70.7%, 116/164) and professional movement (59.8%, 98/164) stood out as 2 major challenges (Table 3).

DISCUSSION

This study assessed the knowledge and practices of the physicians, lab technicians, and public health doctors who worked at the township hospitals in border counties in Yunnan and the challenges during their work on malaria. Positive findings from the study included the following: local township health staff at the Yunnan border area was relatively young and well educated; physicians were vigilant in recognizing the

TABLE 1. Physicians' knowledge and practice of malaria diagnosis and treatment in the 81 township hospitals of 6 border counties, Yunnan Province, 2020.

Variable	Yingjiang, n (%)	Tengchong, n (%)	Cangyuan, n (%)	Longling, n (%)	Longchuan, n (%)	Lushui, n (%)	Total, n (%)
Knowledge of malaria symptoms							
Yes	49 (98.0)	71 (94.7)	17 (77.3)	46 (97.9)	21 (95.5)	37 (97.4)	241 (94.9)
No	1 (2.0)	4 (5.3)	5 (22.7)	1 (2.1)	1 (4.6)	1 (2.6)	13 (5.1)
Trained in last 3 years							
Yes	37 (74.0)	28 (37.3)	7 (31.8)	28 (59.6)	10 (45.5)	17 (44.7)	127 (50.0)
No	13 (26.0)	47 (62.7)	15 (68.2)	19 (40.4)	12 (54.6)	21 (55.3)	127 (50.0)
Recognize high-risk groups							
Returnees	49 (98.0)	72 (96.0)	18 (81.8)	43 (91.5)	19 (86.4)	32 (84.2)	223 (87.8)
Migrants	43 (86.0)	67 (89.3)	16 (72.7)	44 (93.6)	18 (81.8)	32 (84.2)	220 (86.6)
Women	11 (22.0)	16 (21.3)	4 (25.0)	13 (27.7)	9 (40.9)	9 (23.7)	62 (24.4)
Children	13 (26.0)	22 (29.3)	7 (43.8)	15 (31.9)	8 (36.4)	11 (29.0)	76 (29.9)
Others	1 (2.0)	4 (5.3)	4 (25.0)	2 (4.3)	0 (0.0)	1 (2.6)	12 (4.7)
Provided treatment							
Yes	31 (62.0)	35 (46.7)	15 (68.2)	23 (48.9)	8 (36.4)	6 (15.8)	118 (46.5)
No	19 (38.0)	40 (53.3)	7 (31.8)	24 (51.1)	14 (63.6)	32 (84.2)	136 (53.5)
Last malaria patient received							
Never	11 (22.0)	13 (17.3)	9 (40.9)	21 (44.7)	10 (45.5)	20 (52.6)	84 (33.1)
<5 years ago	19 (38.0)	23 (30.7)	5 (22.7)	8 (17.0)	6 (27.3)	3 (7.9)	64 (25.2)
5–10 years ago	14 (28.0)	23 (30.7)	3 (13.6)	10 (21.3)	3 (13.6)	8 (21.1)	61 (24.0)
>10 years ago	6 (12.0)	16 (21.3)	5 (22.7)	8 (17.0)	3 (13.6)	7 (18.4)	45 (17.7)
Total	50 (19.7)	75 (29.5)	22 (8.7)	47 (18.5)	22 (8.7)	38 (15.0)	254 (100.0)

TABLE 2. Lab technicians' knowledge and practice on malaria testing including use of rapid diagnostic tests (RDTs) in the 81 township hospitals of 6 border counties, Yunnan Province, 2020.

Variable	Yingjiang, n (%)	Tengchong, n (%)	Cangyuan, n (%)	Longling, n (%)	Longchuan, n (%)	Lushui, n (%)	Total, n (%)
Know about RDTs							
Yes	33 (100.0)	32 (94.1)	20 (95.2)	28 (100.0)	16 (100.0)	16 (88.9)	145 (96.7)
No	0 (0)	2 (5.9)	1 (4.8)	0 (0)	0 (0)	2 (11.1)	5 (3.3)
Be able to use RDTs							
Yes	33 (100.0)	29 (85.3)	20 (95.2)	26 (92.9)	16 (100.0)	12 (66.7)	136 (90.7)
No	0 (0)	5 (14.7)	1 (4.8)	2 (7.1)	0 (0)	6 (33.3)	14 (9.3)
Use RDTs in daily work							
Always	11 (33.3)	13 (38.2)	4 (19.1)	19 (67.9)	4 (25. 0)	0 (0)	51 (34.0)
Sometimes	22 (66.7)	16 (47.1)	15 (71.4)	7 (25.0)	11 (68.8)	10 (55.6)	81 (54.0)
Never	0 (0.0)	5 (14.7)	2 (9.5)	2 (7.1)	1 (6.3)	8 (44.4)	18 (12.0)
Blood film preparation							
Skillful	15 (45.5)	13 (38.2)	8 (38.1)	10 (35.7)	5 (31.3)	8 (44.4)	59 (39.3)
Not skillful	13 (39.4)	20 (58.8)	13 (61.90)	18 (64.3)	10 (62.5)	9 (50.0)	83 (55.3)
No	5 (15.2)	1 (2.9)	0 (0)	0 (0)	1 (6.3)	1 (5.6)	8 (5.3)
Received microscopy training							
Yes	16 (48.5)	16 (47.1)	7 (33.3)	19 (67.9)	5 (31.3)	13 (72.2)	76 (50.7)
No	17 (51.5)	18 (52.9)	14 (66.7)	9 (32.1)	11 (68.8)	5 (27.8)	74 (49.3)
Microscopy ability							
Can identify species	16 (48.5)	18 (52.9)	6 (28.6)	7 (25.0)	3 (18.8)	5 (27.8)	55 (36.7)
Cannot identify species	10 (30.3)	11 (32.4)	11 (52.4)	18 (64.3)	10 (62.5)	11 (61.1)	71 (47.3)
No	7 (21.2)	5 (14.7)	4 (19.1)	3 (10.7)	3 (18.8)	2 (11.1)	24 (16.0)
RDTs stock outs in last 1 year							
Yes	1 (3.0)	1 (2.9)	1 (4.8)	1 (3.6)	1 (6.3)	0 (0)	5 (3.3)
No	32 (97.0)	33 (97.1)	20 (95.2)	27 (96.4)	15 (93.8)	18 (100)	145 (96.7)
Total	33 (22.0)	34 (22.7)	21 (14.0)	28 (18.7)	16 (10.7)	18 (12.0)	150 (100.0)

malaria patients; and almost all lab technicians knew and were able to use RDTs. Challenges were also identified in three aspects. First, there was insufficient training on malaria diagnosis and testing. The results showed that lab technicians had a low proficiency in preparing blood films and public health doctors regarded lacking adequate training for malaria as one of their major challenges in work. The findings were consistent with the previous studies (*5*–*7*) that suggested that training the malaria workforce was urgently required to sustain the malaria diagnosis and treatment capacity in the post-elimination era. Second, there was a lack of necessary treatment for patients. Only 46% of the interviewed physicians confirmed providing the necessary treatments to patients that had been diagnosed with malaria, which might partially be linked to a shortage of antimalarials. Nevertheless, delayed treatment would threaten the life of severe malaria patients and might leave untreated patients become indirect infection sources that lead to a secondary infection from imported cases. Finally, there were risks of instability among the local malaria workforce. Although the movement of malaria health staff was not obvious, 59.8% and 36.0% of the public health doctors regarded the instability (movement) of staff and the aging of experienced staff as challenges. According to our follow-up interviews, with the elimination of malaria, fewer cases were received in local township hospitals (some hospitals have even not received any malaria patients in the past 3 years), which might explain the shift of the malaria workforce. On the other hand, experienced staff tends to get into upper-level medical facilities once they accumulate enough experiences at the township level and this would contribute to losses of the experienced malaria workforce.

TABLE 3. Public health doctors' knowledge and practice on malaria case management and the challenges in the 81 township hospitals of 6 border counties, Yunnan Province, 2020.

Variable	Yingjiang, n (%)	Tengchong, n (%)	Cangyuan, n (%)	Longling, n (%)	Longchuan, n (%)	Lushui, n (%)	Total, n (%)
Review of blood films							
Yes	21 (72.4)	30 (73.2)	12 (80.0)	28 (90.3)	7 (41.2)	18 (58.1)	116 (70.7)
No	8 (27.6)	11 (26.8)	3 (20.0)	3 (9.7)	10 (58.8)	13 (41.9)	48 (29.3)
Assist in case investigation							
Perform case survey	19 (65.5)	28 (68.3)	10 (66.7)	29 (93.6)	12 (70.6)	22 (71.0)	120 (73.2)
Provide case information	7 (24.1)	11 (26.8)	5 (33.3)	2 (6.5)	3 (17.7)	7 (22.6)	35 (21.3)
Others	1 (3.4)	2 (4.9)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1.8)
No	2 (6.9)	0 (0)	0 (0)	0 (0)	2 (11.8)	2 (6.45)	6 (3.7)
Assist in foci response							
Fill in registration form	21 (72.4)	27 (65.8)	7 (46.7)	28 (90.3)	7 (41.2)	26 (83.87)	116 (70.7)
Survey of companions	5 (17.2)	7 (17.1)	2 (13.3)	2 (6.5)	4 (23.5)	2 (6.45)	22 (13.4)
Vector investigation	0 (0)	0 (0)	2 (13.3)	0 (0)	0 (0)	0 (0)	2 (1.2)
Vector control	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.9)	0 (0)	1 (0.6)
Health education	1 (3.5)	8 (19.5)	4 (26.7)	1 (3.2)	2 (11.8)	1 (3.23)	17 (10.4)
No	2 (6.9)	0 (0)	0 (0)	0 (0)	3 (17.7)	2 (6.5)	7 (4.3)
Antimalarials in stock							
Yes	20 (69.0)	34 (82.9)	10 (66.7)	30 (96.8)	9 (52.9)	14 (45.2)	117 (71.3)
No	9 (31.0)	7 (17.1)	5 (33.3)	1 (3.2)	8 (47.1)	17 (54.8)	47 (28.7)
Health education							
Provide leaflets in hospital	21 (72.4)	29 (70.7)	15 (100.0)	27 (87.1)	14 (82.4)	24 (77.4)	130 (79.3)
Malaria Day campaign	18 (62.1)	39 (95.1)	11 (73.3)	26 (83.9)	9 (52.9)	22 (71.0)	125 (76.2)
Promotion in villages	22 (75.9)	28 (68.29)	11 (73.3)	21 (67.7)	13 (76.5)	24 (77.4)	119 (72.6)
Promotion via WeChat	5 (17.2)	14 (34.15)	4 (26.67)	15 (48.4)	2 (11.8)	3 (9.7)	43 (26.2)
No	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.2)	1 (0.6)
Movement of malaria staff							
Increase	10 (34.5)	7 (17.1)	5 (33.3)	0 (0)	3 (17.7)	5 (16.1)	30 (18.3)
Reduce	4 (13.8)	1 (2.4)	0 (0)	2 (6.5)	1 (5.9)	5 (16.1)	13 (7.9)
No change	15 (51.7)	31 (75.6)	10 (66.7)	28 (90.3)	9 (52.9)	19 (61.3)	112 (68.3)
Unknown	0 (0)	2 (4.9)	0 (0)	1 (3.2)	4 (23.5)	2 (6.5)	9 (5.5)
Malaria-related work							
Radical treatment	9 (31.0)	21 (51.2)	6 (40.0)	21 (67.7)	5 (25.4)	8 (25.8)	70 (42.7)
Insecticide spray	26 (89.7)	23 (56.1)	14 (93.3)	20 (64.5)	13 (76.5)	22 (71.0)	118 (72.0)
Promote nets use	23 (79.3)	31 (75.6)	11 (73.3)	20 (64.5)	16 (94.12)	23 (74.2)	124 (75.6)
Distribute antimalarials	17 (58.6)	31 (75.6)	11 (73.3)	28 (90.3)	12 (70.6)	23 (74.2)	122 (74.4)
Challenges							
Staff shifting	17 (58.6)	22 (53.7)	8 (53.3)	20 (64.5)	7 (41.2)	24 (77.4)	98 (59.8)
Aging of experienced staff	10 (34.5)	17 (41.5)	6 (40.0)	8 (25.8)	5 (29.4)	13 (41.9)	59 (36.0)
Lack motivation	9 (31.0)	8 (19.5)	1 (6.7)	8 (25.8)	4 (23.5)	9 (29.0)	39 (23.8)
Heavy workload	14 (48.3)	20 (48. 8)	12 (80.0)	9 (29.0)	4 (23.5)	17 (54.8)	76 (46.3)
Inadequate training	21 (72.4)	28 (68.3)	9 (60.0)	24 (77.4)	13 (76.5)	21 (67.7)	116 (70.7)
Others	1 (3.5)	2 (4.9)	1 (6.7)	0 (0)	0 (0)	0 (0)	4 (2.4)
Impacted by COVID-19							
Yes	6 (20.7)	14 (34.2)	4 (26.7)	5 (16.1)	1 (5.9)	7 (22.6)	37 (22.6)
No	23 (79.3)	27 (65.9)	11 (73.3)	26 (83.9)	16 (94.1)	24 (77.4)	127 (77.4)
Total	29 (17.7)	41 (25.0)	15 (9.1)	31 (18.9)	17 (10.4)	31 (18.9)	164 (100.0)

According to the WHO framework of malaria elimination (*8*), maintaining the malaria technical expertise and sustaining financial and political commitment at national and subnational levels are among the key points for countries to prevent re-establishment of malaria transmission. In this regard, it is necessary for local government of the border region to sustain their current efforts, with additional focus on training the local health workforce; increasing supervision on malaria testing and treatment; strengthening the capacities on risk identification; and sustaining the local malaria workforce through certain strategies such as include the stability of malaria workforce as a key performance indicator in health facilities. Yunnan's malaria diagnostic reference laboratory has improved the standardization of blood examination in the province since its establishment in 2012 (*7*). It is recommended to reinforce its function in the training of lab technicians and supervision of the quality on slide preparation. Raising the malaria awareness of the public and the targeted groups is also recommended. As most malaria patients admitted in hospitals were the returning laborers who worked in construction sites, lumbering and mine industry (*9*), we encourage local health facilities to increase use of social applications such as WeChat [the most widely used mobile social application in China, which has proven improvement in efficiency of public health education (*10*)] for disseminating information on malaria prevention among the general public and targeted groups including the laborers and the related companies to provide tailored information.

The study was subject to at least two limitations: First, selection of the study groups might not capture all relevant information. For instance, the performance of case notification was not assessed because the duty falls into different positions across hospitals, and those who are responsible for case notification might not be covered in the study. Second, the respondents were subject to potential recall bias. The answers of the respondents were not capable of being cross verified as the study did not cover patients or the hospitals' administrators.

In conclusion, the CCMm in Yunnan border townships has performed satisfactorily in terms of case detection and testing by RDTs, whereas training on both malaria case diagnosis and treatment is insufficient and the risk of workforce instability exists. It is recommended to provide regular training and intensive supervision to strengthen the malaria diagnosis and treatment capacity in the region and to set up incentive mechanisms and individual career development path to sustain the workforce.

Funding: the UNICEF/UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases (TDR) Small Grant (WHO Reference 2021/1104003-0) and the program of the Chinese Center for Tropical Diseases Research (No. 131031104000160004).

doi: 10.46234/ccdcw2021.097

[#] Corresponding author: Duoquan Wang, wangdq@nipd.chinacdc.cn.

[1] National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention (Chinese Center for Tropical Diseases Research); NHC Key Laboratory of Parasite and Vector Biology; WHO Collaborating Centre for Tropical Diseases; National Center for International Research on Tropical Diseases, Shanghai, China; [2] Yunnan Institute of Parasitic Diseases, Puer, Yunnan, China; [3] Malaria Elimination Initiative, Institute for Global Health Sciences, University of California, San Francisco, CA, USA.

Submitted: March 02, 2021; Accepted: April 21, 2021

REFERENCES

1. Feng J, Zhang L, Huang F, Yin JH, Tu H, Xia ZG, et al. Ready for malaria elimination: zero indigenous case reported in the People's Republic of China. Malar J 2018;17(1):315. http://dx.doi.org/10.1186/s12936-018-2444-9.
2. Feng J, Tu H, Zhang L, Xia ZG, Zhou SS. Vital surveillances: imported malaria cases—China, 2012–2018. China CDC Wkly 2020;2(17):277 – 84. http://dx.doi.org/10.46234/ccdcw2020.072.
3. Zhu GD, Cao J. Challenges and countermeasures on Chinese malaria elimination programme during the coronavirus disease (COVID-19) outbreak. Chin J Schisto Control 2020;32(1):7 – 9. http://dx.doi.org/10.16250/j.32.1374.2020036. (In Chinese).
4. Wang DQ, Cotter C, Sun XD, Bennett A, Gosling RD, Xiao N. Adapting the local response for malaria elimination through evaluation of the 1-3-7 system performance in the China-Myanmar border region. Malar J 2017;16(1):54. http://dx.doi.org/10.1186/s12936-017-1707-1.
5. Xian Y, Wang ML, Shao T, Hu T, He ZF, Liu CY, et al. Analysis on the evolution and trend of malaria prevention and control policies in China. Chin J Health Pol 2017;10(3):70 – 4. http://dx.doi.org/10.3969/j.issn.1674-2982.2017.03.012. (In Chinese).
6. Wang JZ, Feng J, Li XS, Li SG, Wang XJ, Yang DH, et al. Analysis of imported malaria in Tengchong City, Yunnan Province during 2016-2019. Chin J Parasitol Parasit Dis 2020;38(4):435 – 9. http://dx.doi.org/CN/Y2020/V38/I4/435. (In Chinese).
7. Xu YC, Deng Y, Zhang CL, Chen MN, Liu H, Xue JB, et al. Analysis of the quality of review and laboratory diagnosis of malaria cases in Yunnan Province in 2017. J Pathogen Biol 2018;13(10):1103 – 8. http://dx.doi.org/10.13350/j.cjpb.181010. (In Chinese).
8. Global Malaria Programme. A framework for malaria elimination. Geneva: WHO, 2017. https://www.who.int/malaria/publications/atoz/9789241511988/en/.
9. Jiang T, Yang LL, Wang SQ, Wu XF, Wang TY, Li YL, et al. Epidemiological and clinical characteristics of 623 malaria inpatients in Tengchong, Yunnan Province. China J Infect Dis 2017;35(7):420 – 1. http://dx.doi.org/10.3760/cma.j.issn.1000-6680.2017.07.009. (In Chinese).
10. Wang LP, Huang LC, Xu H, Yang J, Shen JJ. Application of a WeChat public account in health education and health promotion. Chin J Health Edu 2017;33(7):669 – 71. http://dx.doi.org/10.16168/j.cnki.issn.1002-9982.2017.07.024. (In Chinese).

Vital Surveillances

Malaria Deaths — China, 2011–2020

Li Zhang[1]; Hong Tu[1]; Shuisen Zhou[1]; Zhigui Xia[1]; Jun Feng[1,2,#]

ABSTRACT

Introduction: The malaria deaths (MDs) caused by imported *Plasmodium falciparum* has become a great challenge. This article analyzed MDs in China in 2011–2020 to provide evidence-based data for further strategies and interventions adjustment.

Methods: Individual data via the National Notifiable Disease Reporting System (NNDRS) in 2011–2020 were collected. The *Plasmodium* species, case classification, temporal and spatial distribution, and source of MDs were analyzed to explore MD characteristics. The Parasitic Diseases Information Reporting Management System (PDIRMS) of MDs in 2013–2020 which explored clinical symptom and treatment was also collected and analyzed.

Results: A total of 165 MDs with a mortality rate of 0.5% were recorded in the NNDRS from 2011 to 2020. Among them, 164 (99.4%) died due to imported malaria cases, 1 (0.6%) died of indigenous case reported in Yunnan in 2013. The number of MDs showed a decreasing trend from 2011 (n=30) to 2020 (n=6). The MDs consisted of 160 (97.0%) *P. falciparum* cases, 1 (0.6%) mixed infection case, and 4 (2.4%) clinical diagnosed cases. The MDs were mainly reported in Guangdong (n=18, 10.9%), Sichuan (n=17, 10.3%), Beijing (n=15, 9.1%) and Henan (n=15, 9.1%). The PDIRMS had reported 121 MDs from 2013–2020, and 46.3% (n=56) of MDs exhibited severe brain damage, and most of the patients (n=95, 78.5%) were administrated by artemisinin combination therapy injection form.

Conclusions: The total MDs decreased in China, and a delay in diagnosis and treatment is the main causes of MDs. Therefore, two actions are needed to prevent MDs, including improving health education for key populations such as migrant workers who come to and return from endemic regions and maintaining malaria diagnosis and treatment capabilities of clinicians in medical facilities.

INTRODUCTIONS

China has eliminated indigenous malaria and reached this milestone for 4 consecutive years since 2017 (*1–2*). However, with globalization and economic integration, an increasing number of people come to or return from Africa and Southeast Asia, which also make imported malaria as a major challenge to malaria post-elimination stage in China (*3–5*). Severe malaria infections, or even fatalities, that are mainly caused by imported *Plasmodium falciparum* (*P. falciparum*), would be catastrophic if diagnosis and treatment could not be carried out promptly.

Therefore, the objective of this study was to characterize the epidemiological status of malaria deaths (MDs) and the clinical symptoms and treatments for deaths from 2011 to 2020, aiming to provide evidence-based data that could support the adjustment of appropriate control strategies and activities during the malaria post-elimination stage in China.

METHODS

Data from 31 provincial-level administrative divisions (PLADs) via the National Notifiable Disease Reporting System (NNDRS) were collected and carefully reviewed from January 1, 2011 to December 31, 2020. The NNDRS, which was set up in 2004 after the severe acute respiratory syndrome (SARS) outbreak, is a standardized platform that provides healthcare systems nationwide with the ability to detect, analyze, prevent, and respond to any communicable diseases in the country. The clinically diagnosed cases referred to individuals with malaria-related symptoms [fever (axillary temperature ≥ 37.5 °C), chills, severe malaise, headache, or vomiting] at the time of examination, and laboratory-confirmed cases referred to clinical cases confirmed by microscopy, polymerase chain reaction (PCR), or rapid diagnostic tests (RDT) in the laboratory, and both types of cases were included in this analysis. The clinical symptoms and treatments of all MDs from 2013 to 2020 were collected from the Parasitic Diseases Information Reporting Management System (PDIRMS). Data from Hong Kong, Macao, and

Taiwan were excluded in this study. Individual information including *Plasmodium* species, case classification, source of death cases, intervals from onset to diagnosis, intervals from onset to death, and treatment were used to analyze MD characteristics. The statistical analysis was evaluated by trend chi-squared tests (SPSS, version 21.0, IBM Corp.), and $P<0.05$ was considered as statistical significance.

RESULTS

A total of 165 MDs with a fatality rate of 0.54% were recorded in the NNDRS from 2011 to 2020 (Table 1). Among them, 164 (99.4%) MDs were due to imported malaria cases, and 1 death was an indigenous case (2013 in Yunnan). The number of MDs decreased from 2011 (n=30) to 2020 (n=6), a result which was statistically significant (evaluated by trend chi-squared test, $\chi^2=322.153$, $P<0.001$). The MDs consisted of 160 (97.0%) *P. falciparum* cases, 1 (0.6%) mixed infection case (2012 in Xinjiang), and 4 (2.4%) clinically-diagnosed cases. Most of the MDs (n=143, 86.7%) were reported in 22 endemic PLADs, and others (n=22, 13.3%) were reported in 5 non-endemic PLADs. The MDs were mainly reported in Guangdong (n=18, 10.9%), Sichuan (n=17, 10.3%), Beijing (n=15, 9.1%), and Henan (n=15, 9.1%) (Table 2). The distribution of MDs has been shrunken for reported cases from 14 PLADs in 2011 to 3 PLADs in 2020. The highest number of MDs was observed in the age group of 46 to 50 (n=32, 19.4%), followed by the age group of 40 to 45 (n=29, 17.6%). The highest number of MDs occurred in 2011 (n=30, 18.2%). The temporal distribution showed that MDs was reported throughout the whole year and monthly distribution showed that the highest number of MDs was reported in January (n=27, 16.4%) and February (n=23, 13.9%) (Figure 1). The MDs (n=156, 94.5%) were reported in hospitals and CDCs (n=9, 5.5%). In addition, the MDs were mainly reported by facilities at the prefecture level (n=95, 57.6%), at the provincial level (n=54, 32.7%), and at the county level (n=16, 9.7%). The average medium of interval from onset to diagnosis was 7 days, and the average medium of interval from onset to death was 8 days. Most of the MDs were from people of Chinese nationality (n=162, 98.2%).

The MDs due to imported cases were from 30 countries and 2 continents. Among them, 150 cases (90.9%) were from Africa and mainly from Central (n=59, 35.8%) and West Africa (n=47, 28.5%), including Angola (n=27, 16.4%), Nigeria (n=17, 10.3%), and Mozambique (n=10, 6.1%) (Table 3). For the MDs from Southeast Asia, they were mainly from Myanmar (n=8, 4.8%), Cambodia (n=1, 0.6%), and Indonesia (n=1, 0.6%).

TABLE 1. Malaria cases, deaths, and case-fatality rate reported in China (2011–2020).

Year	Total cases	Deaths	
		Total deaths	Case-fatality rate (%)
2011	4,450	30	0.67
2012	2,714	15	0.55
2013	4,137	21	0.51
2014	3,081	24	0.78
2015	3,277	21	0.64
2016	3,320	15	0.45
2017	2,861	7	0.24
2018	2,678	7	0.26
2019	2,674	19	0.71
2020	1,086	6	0.55
Total	30,278	165	0.54

The PDIRMS showed that among 121 MDs reported from 2013 to 2020, 46.3% (n=56) of them exhibited severe brain damage and 19.0% of them exhibited (n=23) severe liver and kidney damage. Most of the patients (n=95, 78.5%) were administrated by artemisinin combination therapy injection form.

DISCUSSION

Malaria mortality has declined over the past decades in China. The findings in this study revealed that most of the deaths were identified as imported malaria cases in returning migrant workers from Africa, and the findings were similar to a previously reported study (*6*). This result was consistent with expectations as *P. falciparum* was widespread in Africa, and Central and West Africa were the main source regions of imported deaths, which were regions with high disease burden of malaria mortality as reported by the World Health Organization (WHO) (*7*).

The interval from onset to diagnosis was 7 days in this study, which was longer than that reported in other non-endemic countries, whose median diagnosis delays were 4 or more days (*8*). Reasons that are likely to cause delays from onset to diagnosis are as follows. First, the patients failed to recognize the harm of malaria to the human body, which led to poor

TABLE 2. Malaria deaths in 31 provincial-level administrative divisions (PLADs) in China (2011–2020).

PLADs	Malaria endemicity	Total cases	Deaths		Proportion of deaths (%) in the whole country
			Total	Case-fatality rate (%)	
Guangdong	Endemic	1,686	18	1.07	10.9
Sichuan	Endemic	2,163	17	0.79	10.3
Henan	Endemic	1,903	15	0.79	9.1
Beijing	Non-endemic	769	15	1.95	9.1
Shandong	Endemic	1,702	13	0.76	7.9
Fujian	Endemic	880	11	1.25	6.7
Hunan	Endemic	1,298	9	0.69	5.5
Anhui	Endemic	1,645	8	0.49	4.8
Jiangsu	Endemic	2,797	7	0.25	4.2
Hubei	Endemic	1,248	7	0.56	4.2
Yunnan	Endemic	5,415	6	0.11	3.6
Liaoning	Endemic	460	6	1.30	3.6
Guangxi	Endemic	3,193	5	0.16	3.0
Chongqing	Endemic	290	5	1.72	3.0
Shanghai	Endemic	409	4	0.98	2.4
Hebei	Endemic	456	3	0.66	1.8
Jilin	Non-endemic	131	3	2.29	1.8
Zhejiang	Endemic	1,723	2	0.12	1.2
Xinjiang*	Endemic	63	2	3.17	1.2
Inner Monglian	Non-endemic	33	2	6.06	1.2
Shannxi	Endemic	606	1	0.17	0.6
Jiangxi	Endemic	399	1	0.25	0.6
Gansu	Endemic	203	1	0.49	0.6
Shanxi	Endemic	119	1	0.84	0.6
Hainan	Endemic	99	1	1.01	0.6
Tianjing	Non-endemic	92	1	1.09	0.6
Ningxia	Non-endemic	40	1	2.50	0.6
Qinghai	Non-endemic	17	0	0.00	0.0
Tibet	Endemic	30	0	0.00	0.0
Guizhou	Endemic	340	0	0.00	0.0
Heilongjiang	Non-endemic	69	0	0.00	0.0
Total	NA	30,278	165	0.54	100

* Xinjiang includes Xinjiang Uygur Autonomous Region and the Xinjiang Production and Construction Corps.

awareness of medical treatment. After the appearance of symptoms such as chills and fever, patients did not pay attention on them. They often obtained infusions in small clinics and even self-administered medication to relieve symptoms, which could lead to delays in diagnosis and treatment, worsen conditions, and even death. These factors were found in some MDs reported recently in Beijing, Sichuan, Shanghai, Jiangsu, and Shandong (*9*–*13*).

Second, the clinicians had insufficient experience in the diagnosis and treatment of malaria, and some of them did not take the initiative to ask the patient's epidemiological history, so patient who had symptoms of *P. falciparum* could not be promptly diagnosed. Third, low-level hospitals for first visits were also main factors influencing malaria deaths. In this study, 47.9% of MDs were first diagnosed in county-level hospitals or below, which need to be strengthened on capacity

TABLE 3. Source of imported malaria cases contributing to deaths reported in China, 2011–2020.

Regions	Country	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
Africa		25	12	19	25	20	11	7	6	19	6	150
Southeast Africa		2	6	7	9	4	4	0	2	3	2	38
	Mozambique	1	0	3	3	0	2	0	0	0	1	10
	Uganda	0	0	2	1	3	1	0	0	1	1	9
	Tanzania	0	2	0	4	0	0	0	1	0	0	7
	Zambia	1	1	0	1	0	0	0	0	1	0	4
	Madagascar	0	2	0	0	1	0	0	0	0	0	3
	Malawi	0	1	0	0	0	0	0	0	1	0	2
	South Sudan	0	0	0	0	0	1	0	1	0	0	2
	Kenya	0	0	1	0	0	0	0	0	0	0	1
	Egypt	0	0	1	0	0	0	0	0	0	0	1
West Africa		9	2	4	7	6	2	3	4	7	3	47
	Nigeria	5	1	1	2	1	1	2	2	1	1	17
	Guinea	1	0	2	1	2	0	0	0	0	2	8
	Côte d'Ivoire	0	0	0	1	1	0	0	1	3	0	6
	Sierra Leone	0	1	0	0	1	0	1	1	2	0	6
	Ghana	1	0	0	2	0	1	0	0	1	0	5
	Benin	1	0	1	1	0	0	0	0	0	0	3
	Mali	1	0	0	0	0	0	0	0	0	0	1
	Mauritania	0	0	0	0	1	0	0	0	0	0	1
Central Africa		13	3	7	7	10	5	4	0	9	1	59
	Angola	8	1	6	2	4	1	2	0	3	0	27
	Cameroon	0	0	0	2	5	0	0	0	1	0	8
	Equatorial Guinea	3	0	1	0	0	1	0	0	2	0	7
	Democratic Republic of the Congo	0	0	0	0	1	3	2	0	0	0	6
	Republic of Congo	1	1	0	1	0	0	0	0	2	1	6
	Gabon	1	0	0	2	0	0	0	0	0	0	3
	Chad	0	1	0	0	0	0	0	0	0	0	1
	The Central African Republic	0	0	0	0	0	0	0	0	1	0	1
South Africa		0	1	0	1	0	0	0	0	0	0	2
	South Africa	0	1	0	1	0	0	0	0	0	0	2
Africa (Other regions)		1	0	1	1	0	0	0	0	0	0	3
Asia		3	3	1	1	1	0	0	1	0	0	10
Southeast Asia		3	3	1	1	1	0	0	1	0	0	10
	Myanmar	3	3	1	0	0	0	0	1	0	0	8
	Indonesia	0	0	0	1	0	0	0	0	0	0	1
	Cambodia	0	0	0	0	1	0	0	0	0	0	1
Unknown source		2	2	0	0	0	0	0	0	0	0	4
Total		30	17	20	26	21	10	7	7	19	6	164

building, particularity for malaria diagnosis and treatment. A study by Tu et al. has also proved this point by learning the experience and lessons on 16 MDs reported in China (*14*). Finally, most patients who were infected with *P. falciparum* were diagnosed with malaria abroad in private clinics had previously

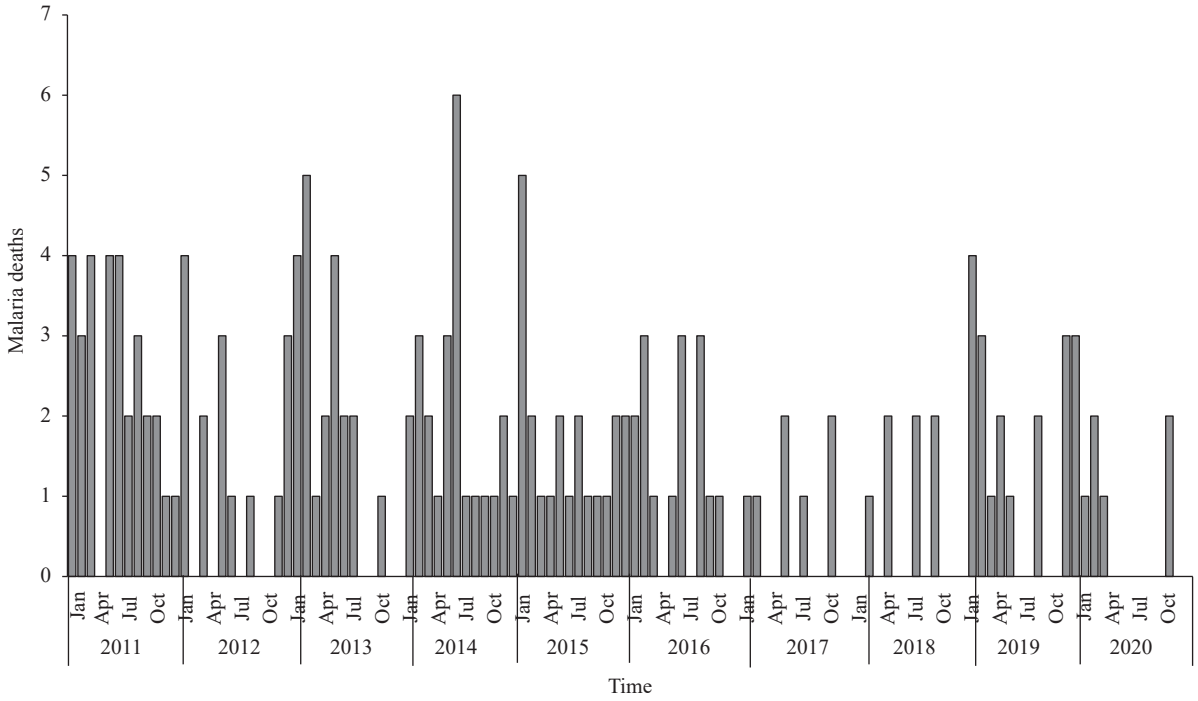

FIGURE 1. Temporal distribution of malaria deaths (MDs) in China, 2011–2020.

received improper treatments such as aspirin, which added the risk of recurrence of *P. falciparum* when they returned from African countries. This was similar to *P. vivax* and *P. ovale*. For example, in 2014, 78.6% of all imported *P. vivax* and *P. ovale* in Guangxi were individuals who had been given aspirin instead of antimalarial agents (*15*).

The results indicated that MDs occurred in returning migrant workers from January and February because most of the migrant population came back from abroad at this period due to the Chinese Spring Festival, and delays in diagnosis and treatment were the main causes of MDs. Since imported *P. falciparum* was now reported in every PLAD in China, timely detection, proper treatment, and deaths prevention caused by imported *P. falciparum* were major challenges faced by post-elimination stage in China. Therefore, some strategies and interventions should be carried out as follows: 1) health education through cooperation with customs and CDCs for the targeted populations such as migrant workers who come to and return from endemic regions; 2) maintain malaria diagnosis and treatment capabilities of clinicians in medical facilities above county levels, especially in the COVID-19 prevention and control process since both malaria and COVID-19 harbored the same clinical symptom at the initial onset stage; and 3) improve the ability to treat severe malaria cases. Expert panels at the national and provincial level could use these recommendations derived from tracking the reasons for MDs and provide suggestions for preventing MDs caused by imported malaria.

The study was subject to some limitations. Not all MDs were well recorded with the exact epidemiological information in 2011–2020. The study still has 5 unknown MDs imported from abroad. In addition, not all MDs were confirmed in the laboratory as 4 clinically diagnosed cases were found in this study.

Acknowledgement: Provincial and county-level CDCs in China.

Conflict of interest: No conflicts of interest were reported.

Funding: The key techniques in collaborative prevention and control of major infectious diseases in the Belt and Road (2018ZX10101002-004)

doi: 10.46234/ccdcw2021.098

Corresponding author: Jun Feng, fengjun@nipd.chinacdc.cn.

[1] National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention (Chinese Center for Tropical Diseases Research); NHC Key Laboratory of Parasite and Vector Biology; WHO Collaborating Centre for Tropical Diseases; National Center for International Research on Tropical Diseases, Shanghai, China; [2] School of Global Health, Chinese Center for Tropical Diseases Research, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Submitted: March 16, 2021; Accepted: April 19, 2021

REFERENCES

1. Feng J, Zhang L, Huang F, Yin JH, Tu H, Xia ZG, et al. Ready for malaria elimination: zero indigenous case reported in the People's Republic of China. Malar J 2018;17(1):315. http://dx.doi.org/10.1186/s12936-018-2444-9.
2. Feng J, Zhou SS. From control to elimination: the historical retrospect of malaria control and prevention in China. Chin J Parasitol Parasit Dis 2019;37(5):505 – 13. http://dx.doi.org/10.12140/j.issn.1000-7423.2019.05.001.
3. Feng J, Xia ZG, Vong S, Yang WZ, Zhou SS, Xiao N. Preparedness for malaria resurgence in China: case study on imported cases in 2000-2012. Adv Parasitol 2014;86:231 – 65. http://dx.doi.org/10.1016/B978-0-12-800869-0.00009-3.
4. Feng J, Tu H, Zhang L, Xia ZG, Zhou SS. Vital surveillances: imported malaria cases —China, 2012–2018. Chin CDC Wkly 2020;2(17):277 – 84. http://dx.doi.org/10.46234/ccdcw2020.072.
5. Feng J, Xiao HH, Xia ZG, Zhang L, Xiao N. Analysis of malaria epidemiological characteristics in the People's Republic of China, 2004-2013. Am J Trop Med Hyg 2015;93(2):293 – 9. http://dx.doi.org/10.4269/ajtmh.14-0733.
6. Zhang Q, Geng QB, Sun JL, Zhang ZK, Lai SJ, Zhou S, et al. Epidemiological analysis of the deaths of malaria in China, 2005-2014. Chin J Prev Med 2016;50(4):302 – 5. http://dx.doi.org/10.3760/cma.j.issn.0253-9624.2016.04.004. (In Chinese).
7. World Health Organization. World malaria report 2020. Geneva: World Health Organization. 2020. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2020.[2020-11-30].
8. Bastaki H, Carter J, Marston L, Cassell J, Rait G. Time delays in the diagnosis and treatment of malaria in non-endemic countries: a systematic review. Travel Med Infect Dis 2018;21:21 – 7. http://dx.doi.org/10.1016/j.tmaid.2017.12.002.
9. Song YG, Ji AP, Wang F, Ren J. Epidemiological and clinical features of imported malaria cases in Beijing. Chin Trop Med 2013;13(2):198 – 200,203. http://dx.doi.org/10.13604/j.cnki.46-1064/r.2013.02.029. (In Chinese).
10. Xu GJ, Kang Y, Lai Q, Lei Y. Death due to imported falciparum malaria: 4 cases. Chin J Parasitol Parasit Dis 2006;24(3):165. http://dx.doi.org/10.3969/j.issn.1000-7423.2006.03.023. (In Chinese).
11. Li Y, Zou PP, Lu L, Jin LF. One death due to imported falciparum malaria in Fengxian of Shanghai. Chin J Parasitol Parasit Dis 2010;28(2):88. (In Chinese).
12. Jia CY, Yang WZ, Wang WM, Tang Y. Analysis of two cases of malaria death in Huai'an. Chin Trop Med 2018;18(7):675 – 7. http://dx.doi.org/10.13604/j.cnki.46-1064/r.2018.07.11. (In Chinese).
13. Liu SZ, Ji FY, Li XK, Dou XJ. A case of malaria death in Qingdao, 2018. Chin Trop Med 2019;19(6):600 – 2. http://dx.doi.org/10.13604/j.cnki.46-1064/r.2019.06.25. (In Chinese).
14. Tu H, Feng J, Zhang L, Zhang SS, Xia ZG, Zhou SS. The analysis of deaths due to malaria in China, 2016. Chin Trop Med 2018;18(7):650 – 3. http://dx.doi.org/10.13604/j.cnki.46-1064/r.2018.07.05. (In Chinese).
15. Lin KM, Wei HY, Jiang WK, Li J, Zhang WW, Wei SJ, et al. Malaria in the Guangxi Zhuang Autonomous Region in China: a twelve-year surveillance data study. Am J Trop Med Hyg 2017;97(4):1163 – 9. http://dx.doi.org/10.4269/ajtmh.16-0260.

Vital Surveillances

Antimalarial Drug Resistance Surveillance in China, 2016–2020

Fang Huang[1,#]; Hui Liu[2]; He Yan[1]; Shuisen Zhou[1]; Zhigui Xia[1]

ABSTRACT

Introduction: Antimalarial drug resistance, especially artemisinin resistance, has been a global threat to reduce morbidity and mortality and to eliminate malaria. Antimalarial drug resistance surveillance could provide evidence for the efficacy of a national drug policy for treatment of all reported malaria cases.

Methods: The therapeutic efficacy of dihydroartemisinin-piperaquine (DHA-PPQ) and chloroquine (CQ) for the treatment of uncomplicated *Plasmodium falciparum* and *Plasmodium vivax* infection, respectively, was evaluated by enrolling patients between 2016 and 2020. Surveillance of molecular markers involved collecting blood samples by passive or active detection and amplifying the drug resistance genes *Pfcrt*, *Pfmdr1*, *Pfdhfr*, *Pfdhps*, and *PfK13*.

Results: DHA-PPQ and CQ were effective for the treatment of *P. falciparum* and *P. vivax* infections, with cure rates > 90% and 100%, respectively. Among the 2,492 samples, the *Pfcrt* wild-type CVMNK was the most frequent haplotype (70.1%, 1,747/2,492), while 19.4% (484/2,492) displayed the triple mutant haplotype CVIET. In total of 228 isolates with sequencing in *Pfdhfr* and *Pfdhps*, high mutant prevalence of 98.7% and 95.2% were detected, respectively. A total of 54 non-synonymous mutations in the *PfK13* propeller domain were confirmed with a prevalence of 3.5% (87/2,483), and the most common mutation was A578S, with a proportion of 16.1% (14/87), followed by Q613E (6.9%, 6/87).

Conclusion and Implications for Public Health Practice: DHA-PPQ and CQ, the first line drugs for *P. falciparum* and *P. vivax* treatment, showed efficacy in China. Molecular markers showed high levels of polymorphism and resistance, which revealed an early warning of drug resistance in imported cases.

INTRODUCTION

Great progress on malaria elimination has been achieved in China, and thousands of imported malaria cases annually remain a key focus in malaria elimination and the post-elimination phase in China (*1–2*). In 2012, China established the malaria diagnosis reference laboratory network focusing on malaria diagnosis, treatment, and surveillance, which covered national, provincial, and county levels (*3*). According to the World Health Organization (WHO) malaria surveillance reference manual in the elimination stage, the antimalarial drug resistance surveillance network in China was established in 2016 and covered 8 provincial-level administrative divisions (PLADs) with more imported malaria cases or a high risk of malaria re-transmission including the following: Yunnan, Henan, Zhejiang, Shandong, Shanghai, Hunan, Sichuan, and Guangxi. This network depended on the malaria diagnosis reference laboratories and the Chinese Infectious Disease Reporting System (CIDRS), the largest web-based communicable diseases reporting system to provide diagnostic and treatment support and case information for drug resistance surveillance (*2*).

Up to now, *P. falciparum* has developed resistance to nearly all antimalarial drugs, including artemisinin and its derivatives (*4*). Antimalarial resistance surveillance is designed to monitor the efficacy against any *Plasmodium* spp. of the recommended first and second line drugs, and any new medicine or drug that is to be evaluated before being introduced into the national drug policy (*5*). Therapeutic efficacy studies (TES) remain the gold standard for assessing the efficacy of antimalarial drug, and integrated drug efficacy studies (iDES) will be introduced in low malaria transmission or malaria elimination areas, where surveillance capacity is strong enough to ensure all the data on malaria cases can be used to generate information on drug efficacy. Currently, molecular markers involved in *P. falciparum* resistance against antimalarial drugs have been confirmed (Table 1): chloroquine (CQ) resistance markers of *P. falciparum* CQ-resistance transporter (*Pfcrt*), multidrug resistance gene of *P. falciparum* multidrug resistance gene 1 (*Pfmdr1*), and *P.*

TABLE 1. Haplotypes of *Pfcrt*, *Pfmdr1*, *Pfdhfr*, and *Pfdhps* genes conferring resistance to antimalarial drugs in *Plasmodium falciparum* isolates.

Genes	Regions and countries (n)	Haplotype	Number	Prevalence	Drug	Chemical family
Pfcrt (n=2,492)	Eastern Africa (145), Western Africa (957), Central Africa (733), Southern Africa (619), North Africa (2), Other regions (36)	Wild type (CVMNK)	1,747	70.1%	Chloroquine	4-Aminoquinolines
		CV**IET**	484	19.4%		
		CVMN**T**	120	4.8%		
		CV M/**I** N/**E** K/**T**	74	3.0%		
		Others [*]	67	2.7%		
Pfmdr1 (n=617)	Eastern Africa (20), Western Africa (185), Central Africa (165), Southern Africa (247)	Wild type (NYD)	307	49.8%	Amodiaquine Lumefantrine	4-Aminoquinolines Amino-alcohols
		N**F**D	124	20.1%		
		YFD	82	13.3%		
		N Y/**F** D	42	6.8%		
		YYD	31	5.0%		
		Others [†]	31	5.0%		
Pfdhfr (n=228)	Angola (158), Equatorial Guinea (70)	Wild type (ANCSI)	3	1.3%	Pyrimethamine	Antifolates
		A**IRN**I	160	70.2%		
		A**ICN**I	55	24.1%		
		Others [§]	10	4.4%		
Pfdhps (n=228)	Angola (158), Equatorial Guinea (70)	Wild type (SAKAA)	11	4.8%	Sulfadoxine	Antifolates
		S**G**KAA	153	67.1%		
		S**GE**AA	25	11.0%		
		AGKAA	24	10.5%		
		Others [¶]	15	6.6%		

[*] CVM**E**K; **S**VMN**T**; CV**I**N**T**; CV**I**KK; **S**V**I**NK; CV**IKT**; CVM**K** K/**T**; C/**S** VMN K/**T**; CV M/**I** N/**E**/**D** K/**T**.
[†] **Y**Y**Y**; N**FY**; N/**Y** **F**D; N/**Y** YD; **Y** Y/**F** D; N/**Y** Y/**F** D; N/**Y** **Y** D/**Y**.
[§] AN**RN**I; A**IRN**I; A**IRNL**.
[¶] **A**AKAA.

falciparum dihydrofolate reductase (*Pfdhfr*) and *P. falciparum* dihydropteroate synthase (*Pfdhps*) conferring resistance to pyrimethamine and sulfadoxine (SP), respectively. Point mutations in *PfK13* propeller region have been confirmed to be associated with artemisinin resistance (*6*). Since 2008, TES and molecular markers surveillance, 2 primary tools for monitoring antimalarial drug resistance, have been implemented in China for several years (*7*–*9*). The aim of this study was to investigate the efficacy of first line drugs for malaria treatment in Yunnan Province and characterize the drug resistance genes in the imported *P. falciparum* isolates from 2016 to 2020 in order to produce a systematic picture of antimalarial resistance to guide drug policy.

METHODS

TES and iDES were conducted to evaluate dihydroartemisinin-piperaquine (DHA-PPQ) for *P. falciparum* treatment and CQ for *P. vivax* treatment in Yunnan Province between 2016 and 2020. Patients with malaria infection, including symptomatic and asymptomatic cases confirmed in a malaria reference laboratory by passive or active case detection, were included, with the exception of patients with severe malaria who were also treated with other medicines for severe complications. Patients were followed-up from the first day of treatment (Day 0) to the specified last day of the follow-up period when appropriate for the infecting species was identified and the treatment was administered (Figure 1). Treatment outcome was determined following the WHO guidelines for therapeutic efficacy monitoring including early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF), and adequate clinical and parasitological response (ACPR) (*5*).

The haplotypes and polymorphisms of *Pfcrt*, *Pfmdr1*, *Pfdhfr*, *Pfdhps*, and *PfK13* (propeller domain) were genotyped by sequencing the samples collected from imported malaria cases from different sub-regions of Africa, Asia, and Oceania between 2012 and 2019.

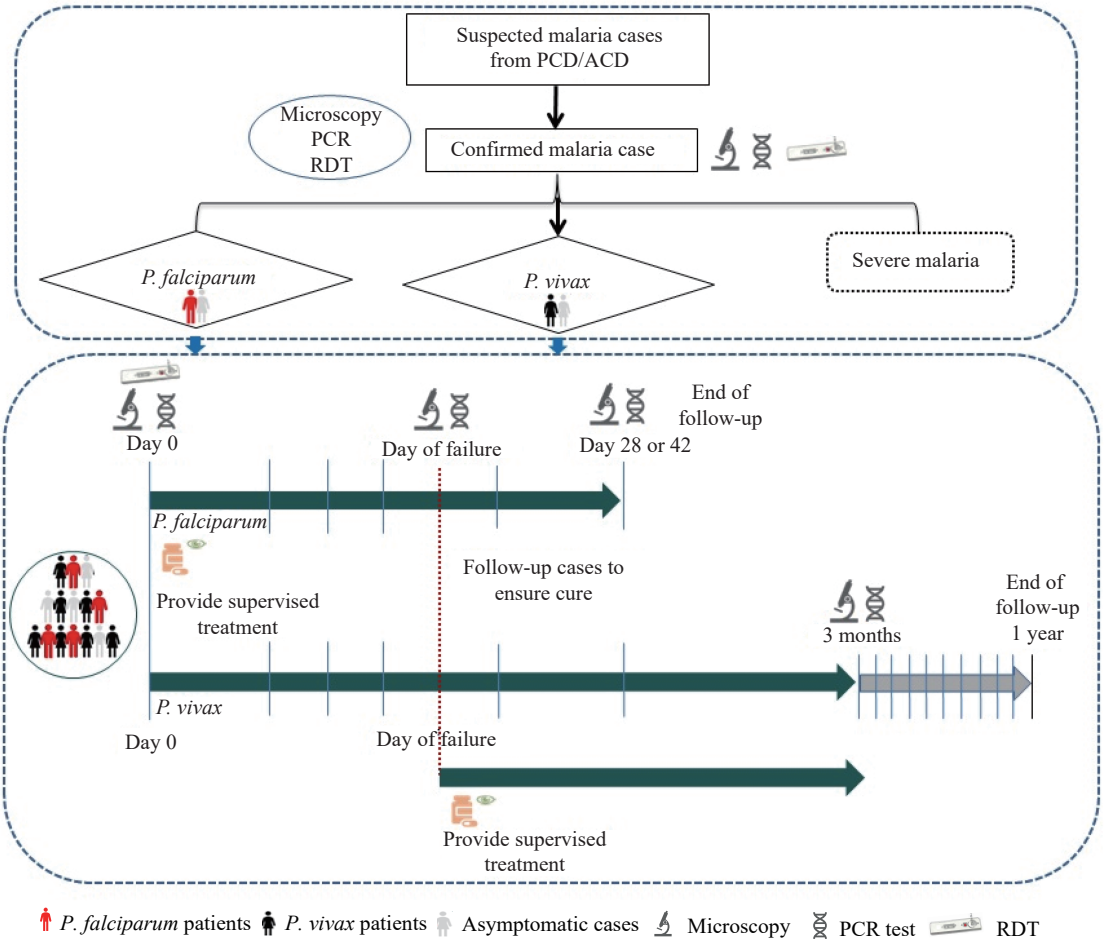

FIGURE 1. Flowchart of iDES in case detection, treatment, and follow-up integration in the routine malaria surveillance system in China between 2016–2020.
Abbreviations: PCD=passive case detection; ACD=active case detection; PCR=polymerase chain reaction; RDT=rapid diagnosis test.

The sequence data were aligned and compared with the reference sequences from PlasmoDB (http://www.plasmodb.org).

RESULTS

A total of 60 participants were enrolled and received observed treatment with DHA-PPQ or CQ between 2016 and 2020. The outcome of DHA-PPQ efficacy was adjusted and corrected using a nested polymerase chain reaction (PCR) assay. Overall, 39 participants with *P. falciparum* infection completed the 42 days of follow-up and 1 was lost to follow-up. The average ACPR rate for DHA-PPQ in 2016 (9/10), 2017 (15/16), and 2018 (12/13) was 92.0% (minimum: 90.0%; maximum: 93.8%) (Table 1). In 2017, 1 patient showed recurrent parasite infection after DHA-PPQ treatment and was originally determined as treatment failure but corrected to *P. vivax* infection by PCR amplification. In addition, 3 out of 39 patients (7.7%) were still positive on Day 3 by microscopy detection, which indicated that the time of parasite clearance was delayed and was an early warning of antimalarial drug resistance. The iDES was initiated in Yunnan Province in 2020. A total of 19 imported *P. vivax* patients were recruited and finished the 28 days of follow-up. Among them, 2 participants were lost and end of follow-up. The cure rate of CQ for *P. vivax* treatment in Yunnan Province was 100.0% (17/17).

Pfcrt gene was sequenced in 2,492 *P. falciparum* isolates imported from Africa. The most prevalent haplotype was the wild type (70.1%, 1,747/2,492). A total of 8 mutant haplotypes including single, double, and triple mutant types were detected, and another 4 mixed mutant haplotypes were observed simultaneously (Table 2). The triple mutant haplotype CV**IET** (19.4%, 484/2,492) was the most common mutant type, followed by the single mutant haplotype

TABLE 2. Treatment outcome of therapeutic efficacy studies (TES) and integrated drug efficacy studies in Yunnan Province, 2016–2020.

Item	TES of DHA-PIP for *P. falciparum* treatment			iDES of CQ for *P. vivax* treatment	Total
	2016	2017	2018	2020	
ETF	1	2*	1	0	4
LCF	0	0	0	0	0
LPF	0	0	0	0	0
ACPR	9	14	12	19	55
PCR-corrected ACPR	9	15	12	19	56
LFU *	0	0	1	2	3
Total	10	16	13	21	60
No. of Day3 (+)	0	3	1	NA	

Abbreviations: ETF=early treatment failure; LCF=late clinical failure; LPF=late parasitological failure; ACPR=adequate clinical and parasitological response; LFU=lost to follow-up. DHA-PPQ=dihydroartemisinin–piperaquine; CQ=chloroquine; NA=not available.
* One patient in 2017 who showed treatment failure after DHA-PPQ treatment was confirmed to have *P. vivax* infection, using PCR amplification, and the outcome was changed to PCR-corrected ACPR.

CVMNT (4.8%, 120/2,492).

There were 617 *P. falciparum* isolates collected from Southern Africa (n=247), Western Africa (n=185), Central Africa (n=165), and Eastern Africa (n=20) for *Pfmdr1* gene sequencing. The *Pfmdr1* wild type NYD was common (49.8%, 307/617). Point mutations were identified in codons 86 and 184, and the D1246Y mutation was absent. In addition, 2 single and 3 double mutant haplotypes were identified. The single mutant haplotype NFD was the highest prevalent mutation (20.1%, 124/617). The double mutant haplotype YFD (13.3%, 82/617) was more common than the haplotypes of YYY (0.5%, 3/617) and NFY (0.2%, 1/617). The mixed mutant haplotypes were detected. Among them, N Y/F D was the main one and detected in 42 isolates (Table 2).

Pfdhfr and *Pfdhps* were genotyped in 70 *P. falciparum* samples from Equatorial Guinea and 158 from Angola. Most of them revealed high mutant prevalence and only 3 contained the *Pfdhfr* wild type ANCSI (Table 2). A total of 5 mutant haplotypes were identified and the most prevalent was the triple mutant haplotype AIRNI (70.2%, 160/228), followed by AICNI (24.1%, 55/228). No mixed mutant haplotype in the *Pfdhfr* gene. There were 8 isolates in *Pfdhps* wild type SAKAA (4.8%, 11/228). In addition, 1 single mutant (AAKAA), 2 double mutants (SGEAA and AGKAA), 2 triple mutants (AGKAS and SGEGA), and 1 mixed mutant haplotype were identified. The haplotype SGKAA with single mutant was common, with a prevalence of 67.1% (153/228), while the haplotypes SGEAA (11.0%, 25/228) and AGKAA (10.5%, 24/228) with double mutant were relatively less prevalent.

A total of 2,483 samples were collected including 941 from western Africa, 746 from central Africa, 666 from southern Africa, 120 from eastern Africa, 4 from northern Africa, and 6 from Asia and Oceania. Of all the successful sequencing samples, 2,344 isolates were wild type, 87 isolates carried *PfK13* non-synonymous (NS) mutations, and 26 synonymous mutations were detected in 52 samples (Table 3). The mutant alleles A578S was detected in 14 isolates (0.6%, 14/2,483), which was the most frequent *PfK13* mutation. Q613E variant was carried by 6 samples, which was the second-most frequent mutation; 74.1% (40/54) and 65.4% (17/26) of the NS and synonymous mutations were identified in one sample each. There were 11 samples carried *PfK13* mutations associated with artemisinin resistance consisting of C580Y, R561H, R539T, M476I, and P553L. C469C variants were detected in 10 isolates with the highest prevalence of synonymous mutation.

DISCUSSION

Antimalarial drug resistance is an obstacle for malaria elimination worldwide, especially as the emergence of artemisinin resistance in the Greater Mekong Subregion has been an urgent regional public health concern (*10–11*). In this study, DHA-PPQ was efficacious with a high cure rate in Yunnan Province, although it has been used as the first-line drug for the treatment of *P. falciparum* for more than 10 years in China. *P. vivax* resistance to CQ has also been identified in Southeast Asia and part of Africa (*12*). A total of 17 imported *P. vivax* patients fully completed the follow up in iDES with 100% efficacy. According

TABLE 3. Numbers and proportion of non-synonymous and synonymous mutations in the *PfK13* gene detected in imported *P. falciparum* isolates collected during 2012–2019.

Non-synonymous mutations in *PfK13*			Synonymous mutations in *PfK13*		
Variant	**n**	**Proportion**	**Variant**	**n**	**Proportion**
A578S	14	16.1%	C469C	10	19.2%
Q613E	6	6.9%	R471R	6	11.5%
C580Y	3	3.4%	V589V	4	7.7%
M579I	3	3.4%	A676A	3	5.8%
N664D	3	3.4%	T478T	3	5.8%
C580F	2	2.3%	Y493Y	3	5.8%
D464N	2	2.3%	A627A	2	3.8%
N694K	2	2.3%	G496G	2	3.8%
P441S	2	2.3%	N664N	2	3.8%
R539T	2	2.3%	Others †	17	32.7%
R561H	2	2.3%			
R575T	2	2.3%			
R622I	2	2.3%			
V589I	2	2.3%			
Others*	40	46.0%			
Total	**87**	**100.0%**		**52**	**100.0%**

* Others refer to the other non-synonymous mutations and one isolate of each variant, including A481T, A569T, A578T, A621S, A626T, C469F, C469F, D462N, D464E, D584V, D648N, D648Y, E556K, F434Y, F662C, G665S, I634T, I646K, I683R, K503E, K610R, K658Q, L457S, L488V, L619E, L663V, M476I, M562I, N629S, P443R, P553L, P574L, Q613H, R575K, T437N, T474I, V589A, V603E, V650F, V692L.

† Others refer to the other synonymous mutations and one isolate of each variant, including A557A, G454G, G533G, G638G, K610K, L492L, P443P, R417R, R575R, S477S, T535T, T573T, T685T, V487V, V510V, V666V, Y502Y.

to the latest guideline of antimalarial drugs policy in China, the first-line treatment drug for *P. falciparum* and *P. vivax* infections in China were artemisinin-based combination therapies (ACTs) and CQ plus primaquine, respectively. Although there was no evidence for DHA-PPQ and CQ resistance emerging in China, continued antimalarial drug resistance surveillance focus on the imported cases by designated public hospitals at the provincial level should be strengthened in the post-elimination stage.

Drug resistance is the main cause of clinical treatment failure. Therefore, characterization of the drug resistance markers is an important way to reveal the drug resistance and treatment failure. In the recent 20 years, the CQ resistance of *P. facliparum* decreased along with the wild type of *Pfcrt* increasing caused by the termination of the use of CQ when its resistance spread widely in Africa in the 1990s (*13*). In this study, the *Pfcrt* wild type was the most common haplotype, and the mutant prevalence was rising. *Pfmdr1* mutations were observed in codons 86 and 184 in this study, although the wild type (49.8%) was the majority. SP resistance genes *Pfdhfr* and *Pfdhps* displayed high mutant prevalence of 98.7% and 95.2%, respectively. SP, the only choice for the intermittent preventive treatment in infants (IPTi) remain in use in Africa. This study indicated most of the imported *P. falciparum* cases in China showed high-level SP resistance. High polymorphisms of *PfK13* propeller region were revealed and 54 non-synonymous mutations and 26 synonymous mutations were detected, with low prevalence of 3.5% and 2.1%, respectively. The A578S mutation was detected in 14 isolates, which was the most frequent mutation in the *PfK13* propeller domain in the isolates from Africa (*14*). A few patients carrying *PfK13* mutations associated with artemisinin resistance still showed sensitivity to antimalarials based on the individual information collected from CIDRS, but the systematic efficacy study data were absent. However, the risk of the importation of artemisinin resistance should be particularly concerning.

The study was subject to at least two limitations. First, TES and iDES were only implemented in Yunnan Province and the sample size was small. Further study will be extensively rolled out in the eight

key provinces and then nationwide in the future. Second, *plasmepsin II*/*III* (*pm2*/*3*), another molecular marker associated with PPQ resistance (*15*), the partner drug of DHA, was not involved in this study.

Acknowledgements: Staff members of the provincial CDC involved in the national antimalarial drug resistance network; all the malaria patients recruited in TES/iDES; and the participants who provided blood samples for this study.

Conflicts of interest: No competing interests.

Funding: The Natural Science Foundation of Shanghai (No. 18ZR1443400), the Fifth Round of Three-Year Public Health Action Plan of Shanghai (No. GWV-10.1-XK13), and the National Important Scientific & Technological Project (2018ZX10101 002–002).

doi: 10.46234/ccdcw2021.099

[#] Corresponding author: Fang Huang, huangfang@nipd.chinacdc.cn.

[1] National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention, Chinese Center for Tropical Diseases Research, WHO Collaborating Center for Tropical Diseases, National Centre for International Research on Tropical Diseases, NHC Key Laboratory of Parasite and Vector Biology (National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention), Shanghai, China; [2] Yunnan Institute of Parasitic Diseases, Puer, China.

Submitted: March 16, 2021; Accepted: April 20, 2021

REFERENCES

1. Feng XY, Levens J, Zhou XN. Protecting the gains of malaria elimination in China. Infect Dis Poverty 2020;9(1):43. http://dx.doi.org/10.1186/s40249-020-00661-y.
2. Zhang L, Feng J, Zhang SS, Xia ZG, Zhou SS. The progress of national malaria elimination and epidemiological characteristics of malaria in China in 2017. Chin J Parasitol Parasit Dis 2018; 36(3): 201-9. https://d.wanfangdata.com.cn/periodical/zgjscxyjscbzz201803001. (In Chinese).
3. Yin JH, Yan H, Huang F, Li M, Xiao HH, Zhou SS, et al. Establishing a China malaria diagnosis reference laboratory network for malaria elimination. Malar J 2015;14(1):40. http://dx.doi.org/10.1186/s12936-015-0556-z.
4. White NJ. Antimalarial drug resistance. J Clin Invest 2004;113(8):1084 – 92. http://dx.doi.org/10.1172/JCI21682.
5. WHO. Methods for surveillance of antimalarial drug efficacy. Geneva: World Health Organization. 2009. https://www.who.int/malaria/publications/atoz/9789241597531/en/.
6. WHO. Malaria surveillance, monitoring & evaluation: a reference manual. Geneva: World Health Organization. 2009. https://www.who.int/malaria/publications/atoz/9789241565578/en/.
7. Huang F, Tang LH, Yang HL, Zhou SS, Sun XD, Liu H. Therapeutic efficacy of artesunate in the treatment of uncomplicated *Plasmodium falciparum* malaria and anti-malarial, drug-resistance marker polymorphisms in populations near the China-Myanmar border. Malar J 2012;11(1):278. http://dx.doi.org/10.1186/1475-2875-11-243.
8. Huang F, Tang L, Yang H, Zhou S, Liu H, Li J, Guo S. Molecular epidemiology of drug resistance markers of Plasmodium falciparum in Yunnan Province, China. Malar J 2012;11(1):243. http://dx.doi.org/10.1186/1475-2875-11-278.
9. Liu H, Yang HL, Tang LH, Li XL, Huang F, Wang JZ, et al. *In vivo* monitoring of dihydroartemisinin-piperaquine sensitivity in *Plasmodium falciparum* along the China-Myanmar border of Yunnan Province, China from 2007 to 2013. Malar J 2015;14(1):47. http://dx.doi.org/10.1186/s12936-015-0584-8.
10. van der Pluijm RW, Imwong M, Chau NH, Hoa NT, Thuy-Nhien NT, Thanh NV, et al. Determinants of dihydroartemisinin-piperaquine treatment failure in *Plasmodium falciparum* malaria in Cambodia, Thailand, and Vietnam: a prospective clinical, pharmacological, and genetic study. Lancet Infect Dis 2019;19(9):952 – 961. http://dx.doi.org/10.1016/S1473-3099(19)30391-3.
11. WHO. Artemisinin resistance and artemisinin-based combination therapy efficacy. Geneva: World Health Organization; 2018. https://www.who.int/publications/i/item/status-report-on-artemisinin-resistance-and-act-efficacy.
12. Ferreira MU, Nobrega de Sousa T, Rangel GW, Johansen IC, Corder RM, Ladeia-Andrade S, Gil JP. Monitoring *Plasmodium vivax* resistance to antimalarials: Persisting challenges and future directions. Int J Parasitol Drugs Drug Resist 2021;15:9 – 24. http://dx.doi.org/10.1016/j.ijpddr.2020.12.001.
13. Djimdé A, Doumbo OK, Cortese JF, Kayentao K, Doumbo S, Diourté Y, et al. A molecular marker for chloroquine-resistant falciparum malaria. N Engl J Med 2001;344(4):257 – 63. http://dx.doi.org/10.1056/NEJM200101253440403.
14. Kamau E, Campino S, Amenga-Etego L, Drury E, Ishengoma D, Johnson K, et al. K13-propeller polymorphisms in *Plasmodium falciparum* parasites from sub-Saharan Africa. J Infect Dis 2015;211 (8):1352 – 5. http://dx.doi.org/10.1093/infdis/jiu608.
15. Witkowski B, Duru V, Khim N, Ross LS, Saintpierre B, Beghain J, et al. A surrogate marker of piperaquine-resistant *Plasmodium falciparum* malaria: a phenotype-genotype association study. Lancet Infect Dis 2017;17(2):174 – 83. http://dx.doi.org/10.1016/S1473-3099(16)30415-7.

Commentary

Time to Integrate Malaria and Neglected Tropical Diseases Control and Elimination

Dirk Engels[1,2,#]; Fang Huang[2,3]; Xiao-nong Zhou[2,3,4]

Traditionally, malaria has always been considered one of the tropical diseases. This only has changed in the late 1990s, with the World Health Organization (WHO) profiling HIV, tuberculosis (TB), and malaria as priority "poverty-related" killing diseases (*1*). This has led to the creation of the Global Fund to Fight AIDS, Tuberculosis, and Malaria (*2*), that has mobilized substantial resources to advance the control of all three diseases, even if mostly in a siloed manner.

Around the same time, efforts were undertaken to solicit international attention for an entire group of other tropical diseases, currently still affecting over 1.7 billion people worldwide, that had been left "neglected" (*3*). The global response that was mounted to advance the control/elimination of neglected tropical diseases (NTDs) — that are more disabling than killing diseases — was based on a different logic. It profiled NTDs as a group of diseases that 1) together represented a similar burden as HIV, TB, or malaria; 2) were treatable or preventable by similar interventions that could be delivered as integrated packages; and 3) were entrenched in poverty as no other diseases, urging the international community to prioritize the deployment of development efforts focused on the poorest sections of society.

Both global strategies have worked well, even though with vastly different levels of resources.

Impressive global progress has been made in the fight against malaria over the last two decades. The malaria case incidence rate (cases per 1,000 population at risk) has decreased from 80 in 2000 to 57 in 2019, a reduction of almost 30%. The mortality incidence rate (deaths per 100,000 population at risk) was reduced from 25 in 2000 to 10 in 2019, or a reduction of 60%. As a result, the global number of deaths due to malaria has fallen from 736,000 in 2000 to 409,000 in 2019, a decrease of over 40%. Over the same period, the number of countries with fewer than 100 indigenous malaria cases increased from 6 to 27, with 21 countries — including China — reporting zero indigenous malaria cases for at least three consecutive years, and 10 of these countries being certified malaria-free by the WHO (*4*). In 2019, an estimated 3.0 billion USD was spent globally on malaria control and elimination (*5*).

Interventions for NTDs, especially large-scale preventive treatments for lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, and trachoma, have scaled up massively over the last decade with over a billion people reached yearly from 2015 to 2019. This has led, at the end of 2020, to already 600 million fewer people needing interventions for NTDs and 42 countries having eliminated at least one NTD. A complex disease such as sleeping sickness has been brought to the verge of elimination, elimination of visceral leishmaniasis is close to being achieved in South-East Asia, and the global number of reported cases of Chagas disease has decreased by 40% between 2011 and 2019. During the same period, 90 million people have been freed from the risk of vector transmission of Chagas disease, and universal blood screening for the disease implemented at 100% in Latin-America (*6*–*7*). The yearly amount of Overseaos Development Aid (ODA) funding has been estimated to be in the order of 300 million USD per year since 2014, leveraging a contribution in medicines donated by the pharmaceutical sector with a value of approximately 1.5 billion USD per year (*8*–*9*).

Despite good progress, both program areas face challenges. The global gains in combating malaria have levelled off in recent years. The emergence of resistance to insecticides and medicines is threatening malaria control and elimination (*10*), and the quest for novel technological solutions is hardly coping with the need. Redistributing resources toward control or elimination-specific interventions, such as diagnosis and treatments, vector control, preventive treatments in pregnant women and children, and strengthening surveillance systems to identify and investigate foci, may produce economic efficiencies (*5*). Hence the increasing awareness that something more fundamentally preventive needs to be done, and new program and policy interventions to be developed, such as integrated vector management along with

community involvement (*11*).

Likewise, notwithstanding the good progress in scaling up of NTD interventions, progress for NTDs such as leprosy and Guinea worm disease has been stagnating. Thanks to progress in R&D and implementation research interventions for NTDs such as Buruli ulcer, scabies, rabies, and yaws are now ready to be scaled up towards 2030, but considerable challenges remain in terms of affordable access to the required quantities of commodities and for technological solutions like novel diagnostics across the NTD spectrum. The need for novel tools and strategies is especially critical for five or six NTDs that remain relatively orphaned (*12*). These needs will not be fulfilled if the current siloed approach and funding logic in global health is maintained — hence the increasing awareness for the need to find synergies with other diseases and health areas in terms of implementation and R&D and the need for "development solutions" to limit the transmission of NTDs. The latter are particularly important for dengue and other *Aedes*-transmitted diseases, for which there are no other options than supportive treatment and vector control.

The above challenges provide an incentive for an integrated approach to interventions that are common to both disease areas, as illustrated by the recent convergence between the Zika virus outbreak and emerging evidence of pyrethroid resistance and loss of efficacy of long-lasting insecticidal nets (LLINs) in malaria control, that has prompted WHO to strongly advocate for integrated vector control in 2017 (*13*–*14*).

The recent coronavirus disease 2019 (COVID-19) pandemic has provided a further stark reminder that technological advancements are undeniably a big part of the solution (*15*), but not the only solution. It is equally important to reduce the risk or force of disease transmission, whether it be airborne, vector-borne, water-borne, food-borne, or zoonotic. This can only be achieved by acting simultaneously on human, animal, and environmental health through One Health approach, in an integrated manner.

An additional argument in favour of integration is surveillance. With an ever-increasing risk of emerging diseases, but also an increasing number of diseases that are on the verge of elimination and may resurge, it is important to put cost-effective surveillance methods in place. An integrated approach can greatly contribute to this, as illustrated by the example of sleeping sickness surveillance while doing rapid diagnosis of malaria in a primary healthcare setting (*16*).

The current state of advancement in technology has undoubtedly made integrated approaches more feasible. The recent epidemics of chikungunya, Ebola virus disease, and especially COVID-19 have shown that new technological solutions can rapidly be developed based on existing platforms, if will and resources are available.

Multi-disease solutions clearly have the potential to provide better return on investment. And opportunities for integration or convergence of malaria and NTD interventions exist, such as 1) environmental improvement aimed at control of transmission of multiple diseases (*17*); 2) the setting up of integrated entomological and disease surveillance and response systems; 3) potential integration of WHO-recommended preventive therapies for malaria* with preventive treatment activities against NTDs, and potentially with other programs such as HIV, female genital schistosomiasis and cervical cancer prevention and treatment programs (*18*); and 4) the development of new or improved tools with dual- or multi-disease utility such as new formulations of ivermectin targeting residual outdoor transmission of malaria, onchocerciasis, lymphatic filariasis and scabies, or multiplex diagnostics, both for differential diagnosis (of fevers for example) or surveillance

In conclusion, the COVID-19 pandemic has made the world realize that a more systemic approach to solutions is required (*19*), if we wish to "build back better" in a sustainable way (*20*). In this endeavour, it would be wrong to focus on epidemics only, let alone on airborne epidemics only. Inequity in health across the disease spectrum needs to be considered. Furthermore, along with battered global economies, there is likely to be less ODA funding available in the foreseeable future. It will be important to try and go further with less being available. Integrated approaches may help to achieve this, and a more integrated approach to the control and elimination of malaria and NTDs may provide an iconic example of how this could be done.

doi: 10.46234/ccdcw2021.100

[#] Corresponding author: Dirk Engels, engelsd54@gmail.com.

[1] Secretariat, Uniting Forum To Combate NTDs, Geneva, Switzerland;

* such as intermittent preventive treatment of pregnant women (IPTp), intermittent preventive treatment of infants (IPTi), and seasonal malaria chemoprevention (SMC).

[2] NHC Key Laboratory for Parasite and Vector Biology, National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention, Shanghai, China; [3] Chinese Center for Tropical Diseases Research; WHO Collaborating Centre for Tropical Diseases; [4] School of Global Health, Chinese Center for Tropical Diseases Research, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Submitted: April 19, 2021; Accepted: April 22, 2021

REFERENCES

1. World Health Organization. Global report for research on infectious diseases of poverty. 2012. https://www.who.int/tdr/capacity/global_report/en/. [2021-04-01].
2. Kerouedan D. Enjeux politiques de l'evaluation du Fonds mondial de lutte contre le sida, la tuberculose et le paludisme. Med Trop 2010; 70:19 – 27.
3. Engels D, Zhou XN. Neglected tropical diseases: an effective global response to local poverty-related disease priorities. Infect Dis Poverty 2020;9(1):10. http://dx.doi.org/10.1186/s40249-020-0630-9.
4. World Health Organization. World malaria report 2020. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2020. [2021-04-01].
5. Shretta R, Liu J, Cotter C, et al. Malaria elimination and eradication. In: Holmes KK, Bertozzi S, Bloom BR, et al., editors. Major Infectious Diseases. 3rd ed. Washington, DC: The International Bank for Reconstruction and Development/The World Bank. 2017.
6. World Health Organization. Neglected Tropical Diseases progress dashboard 2011–2020. Geneva: WHO. https://www.who.int/teams/control-of-neglected-tropical-diseases/overview/progress-dashboard-2011-2020. [2021-04-01].
7. Uniting to Combat Neglected Tropical Diseases. Progress on the London Declaration on NTDs. West Sussex: Uniting to Combat NTDs. https://unitingtocombatntds.org/progress/. [2021-04-01].
8. World Health Organization. Investing to overcome the global impact of neglected tropical diseases: Third WHO report on neglected tropical diseases. Geneva: WHO. http://apps.who.int/iris/bitstream/handle/10665/152781/9789241564861_eng.pdf;jsessionid=61384725EE69B73645557869AE9FDF2A?sequence=1. [2021-04-1].
9. Cohen JP, Silva L, Cohen A, Awatin J, Sturgeon R. Progress report on neglected tropical disease drug donation programs. Clin Ther 2016;38(5):1193 – 204. http://dx.doi.org/10.1016/j.clinthera.2016.02.031.
10. The malERA Refresh Consultative Panel on Insecticide and Drug Resistance. malERA: an updated research agenda for insecticide and drug resistance in malaria elimination and eradication. PLoS Med 2017;14(11):e1002450. http://dx.doi.org/10.1371/journal.pmed.1002450.
11. Hemingway J. The role of vector control in stopping the transmission of malaria: threats and opportunities. Philos Trans R Soc Lond B Biol Sci 2014;369(1645):20130431. http://dx.doi.org/10.1098/rstb.2013.0431.
12. World Health Organization. Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases 2021–2030. 2020. https://www.who.int/publications/i/item/9789240010352. [2021-04-01].
13. Alonso P, Engels D, Reeder J. Renewed push to strengthen vector control globally. Lancet 2017;389(10086):2270 – 1. http://dx.doi.org/10.1016/S0140-6736(17)31376-4.
14. World Health Organization. Global vector control response 2017–2030. 2017. https://www.who.int/vector-control/publications/global-control-response/en/. [2021-04-01].
15. Renu N. Technological advancement in the era of COVID-19. SAGE Open Med 2021;9:20503121211000912. http://dx.doi.org/10.1177/20503121211000912.
16. Lumbala C, Matovu E, Sendagire H, Kazibwe AJN, Likwela JL, Mavoko HM, et al. Performance evaluation of a prototype rapid diagnostic test for combined detection of gambiense human African trypanosomiasis and malaria. PLoS Negl Trop Dis 2020;14(4):e0008168. http://dx.doi.org/10.1371/journal.pntd.0008168.
17. Engels D. Fighting NTDs in burundi. 2021. https://rstmh.org/news-blog/blog/fighting-ntds-in-burundi. [2021-04-01].
18. Engels D, Hotez PJ, Ducker C, Gyapong M, Bustinduy AL, Secor WE, et al. Integration of prevention and control measures for female genital schistosomiasis, HIV and cervical cancer. Bull World Health Organ 2020;98(9):615 – 24. http://dx.doi.org/10.2471/BLT.20.252270.
19. Horton R. Offline: COVID-19 is not a pandemic. Lancet 2020;396(10255):874. http://dx.doi.org/10.1016/S0140-6736(20)32000-6.
20. Ehrenberg N, Ehrenberg JP, Fontes G, Gyapong M, Rocha EMM, Steinmann P, et al. Neglected tropical diseases as a barometer for progress in health systems in times of COVID-19. BMJ Glob Health 2021;6(4):e004709. http://dx.doi.org/10.1136/bmjgh-2020-004709.

Copyright © 2021 by Chinese Center for Disease Control and Prevention

All Rights Reserved. No part of the publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior permission of *CCDC Weekly*. Authors are required to grant *CCDC Weekly* an exclusive license to publish.

All material in *CCDC Weekly* Series is in the public domain and may be used and reprinted without permission; citation to source, however, is appreciated.

References to non-China-CDC sites on the Internet are provided as a service to *CCDC Weekly* readers and do not constitute or imply endorsement of these organizations or their programs by China CDC or National Health Commission of the People's Republic of China. China CDC is not responsible for the content of non-China-CDC sites.

The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 3 No. 17 Apr. 23, 2021

Responsible Authority

National Health Commission of the People's Republic of China

Sponsor

Chinese Center for Disease Control and Prevention

Editing and Publishing

China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN

ISSN 2096-7071
CN 10-1629/R1