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China Trip Report

Project DIAMETER (Diagnostics for Malaria Elimination Toward Eradication)

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Abbreviations

AEIOU	Activity, Environment, Interaction, Object, and User
API	Annual Parasite Incidence
APMEN	Asia Pacific Malaria Elimination Network
CDC	Centers for Disease Control and Prevention
CFDA	China Food and Drug Administration
DBS	Dried blood spots
DIAMETER	Diagnostics for Malaria Elimination Toward Eradication
JOC	Jobs-Outcomes-Constraints
LAMP	Loop-mediated isothermal polymerase chain reaction
LOD	Limit of detection
MoH	Ministry of Health
NIPD	National Institute of Parasitic Diseases
NMEP	National Malaria Elimination Programme
NRCMI	New Rural Cooperative Medical Insurance
PCD	Passive case detection
PCR	Polymerase chain reaction
QA	Quality assurance
QC	Quality control
RACD	Reactive case detection
RDT	Rapid diagnostic test
SARS	Severe Acute Respiratory Syndrome
SOP	Standard Operation Procedure
TPP	Target product profile

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Introduction

Project DIAMETER

The goal of Project DIAMETER (Diagnostics for Malaria Elimination Toward Eradication) is to define the diagnostic needs unique to malaria elimination settings with sufficient clarity so that all stakeholders can act with confidence to develop, commercialize, and efficiently implement the most promising, cost-effective, and impactful technologies for malaria elimination.

Recent progress in malaria control has enabled countries to reduce malaria transmission rates. Existing diagnostic technologies—microscopy and rapid diagnostic tests (RDTs)—have played a critical role in this success by enabling many regions to achieve transmission rates near the threshold that defines the elimination phase. However, it is not clear whether these same tests are the most efficient and cost-effective tools to achieve accurate infection detection at low levels of parasitemia, which is critical to achieving elimination goals. Furthermore, there is a lack of clarity and agreement on the use scenarios, target product profiles (TPPs), standardized methods of assay validation, and market potential for the malaria diagnostic tools best suited for cost-effective detection in elimination settings. The resulting ambiguity hinders the development of new infection-detection technologies as well as strategic application of existing and nearly ready tools.

PATH has developed a rigorous approach to identifying the most promising solutions to diagnostic challenges in low-resource settings. This involves aggregating and analyzing user needs, market needs, and technical requirements to generate the comprehensive evidence base necessary to inform product development, commercialization, and strategic program operations. Thus, through extensive field research and collaboration with malaria-elimination experts, the DIAMETER team will evaluate and hone the use scenarios and TPPs for infection detection in elimination settings. To this end, stakeholder interviews will be conducted in a selection of countries in Asia, Africa, and South America that are nearing malaria elimination. Information gathered will be collated to inform product development of new diagnostics and areas where further research is required. This report presents findings from stakeholder interviews conducted in China in September 2013.

Malaria in China

Historically, China is one of the malaria-endemic countries in the Western Pacific Region. In ancient Chinese, malaria was described as the miasma (literally the *Dirty Qi*). Since 1949, malaria has been identified by the Chinese Government as one of the top five parasitic diseases that tremendously affect the social-economic development in mainland China. Approximately 70 to 80 percent of the total counties in the 24 provinces/municipalities/autonomous regions were

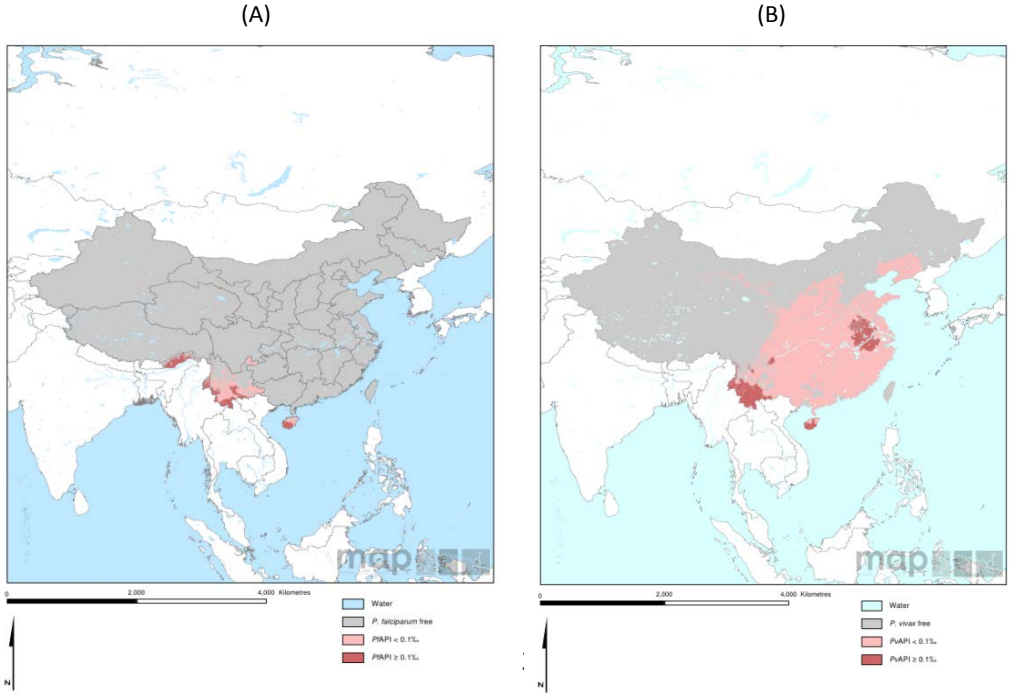
malaria endemic, and there were over 30 million cases and about a one percent fatality rate in 1950.[1,2]

Despite major malaria outbreaks in the 1960s and 1970s, China has seen a steady decrease in the number of malaria cases, especially over the past three decades of economic boom. Local malaria surveillance was established in the 1980s in endemic provinces of China; however, malaria surveillance in the different provinces was independent and not aligned very well, and the data analysis was difficult at nationwide level. After the infamous outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003, China has put great effort into improving its public health system infrastructures and launched a national online infectious disease reporting system soon after. Malaria is on the category B list of notifiable diseases to be reported according to the Law of Communicable Diseases Prevention and Control of China.

In 2012, 2,718 malaria cases were reported in China. China has a population of 1.38 billion, and of this, approximately 58% of the people live in areas with no risk of malaria transmission; 42% live in areas of low risk (1–10 cases per 10,000 people). Less than 0.2 million people lived in high-transmission areas (≥ 10 cases per 10,000 people) in China in 2012, while this figure was 13.5 million in 2011.[3]

Endemic malaria in China is caused by two types of parasites: *Plasmodium falciparum* (*Pf*) and *Plasmodium vivax* (*Pv*). With the geographical difference and varying climate in China, *Pf* is endemic in the warmer southern region with year-round transmission, while *Pv* is distributed throughout southern and central China with some transmission evidence in northern China during summer season (Figure 1). Currently Yunnan, which lies along China's southern border with Myanmar, and Hainan (before 2009; no local *pf* case has been reported in Hainan since 2010), an island in the South China Sea, are the only two provinces in China where there is endemic *Pf* transmission.[4]

Figure 1. The spatial limits of *Plasmodium falciparum* (A) and *Plasmodium vivax* (B) malaria transmission in 2010 in China.[5,6]



Methods

In order to capture a complete picture of the current state of malaria elimination in each country, Project DIAMETER combines thorough desk research on malaria control and elimination efforts with theory-driven qualitative research targeting the opinions and actions of key players within the country's malaria program.

Desk research

Prior to initiating in-country research, a literature review of relevant documents was undertaken. This desk research helped the team define priority areas for further research, as well as provide context around China's existing malaria program strategies and goals. The preliminary literature review also informed the development of the in-country research tools and key informant list.

Qualitative research

We identified key informants who are working in the malaria elimination network from China's national, provincial, and local health systems. Due to China's vast size and its varying situations on malaria transmission, we chose only Yunnan and Jiangsu to do field research, as these are two representative provinces which are constantly highlighted in China malaria reports. Yunnan borders Myanmar, and faces both local malaria transmission and importation, especially the *P. falciparum*. Jiangsu was malaria endemic historically, and with its large number of migrant workers returning from African nations, malaria importation has become a significant issue.

Nine interviews were completed. A list of interviewees is provided in Appendix A. Interview guides and observation checklists were developed in advance to encourage systematic and uniform data-collection techniques within the tenets of Contextual Inquiry methodology and using a hybrid of two frameworks—Jobs-Outcomes-Constraints (JOC) and Activity, Environment, Interaction, Object, and User (AEIOU)—to organize concepts. Contextual Inquiry approaches qualitative data collection with the objective of describing how actors, objects, and rules influence and are influenced by the larger system in which they exist. This method exposes tacit knowledge that informants may not be aware of and encourages the informant (rather than the reviewer) to prioritize concepts.

Interview guides and observational checklists were used for each category of key informants: thought leaders, implementers, and clinic and laboratory staff. The data-collection tools were developed using a hybrid JOC-AEIOU framework, prompting the interviewees to describe the main elements of the system (AEIOU) within which they work, and then define the barriers to successfully achieving the intended objectives (JOC).

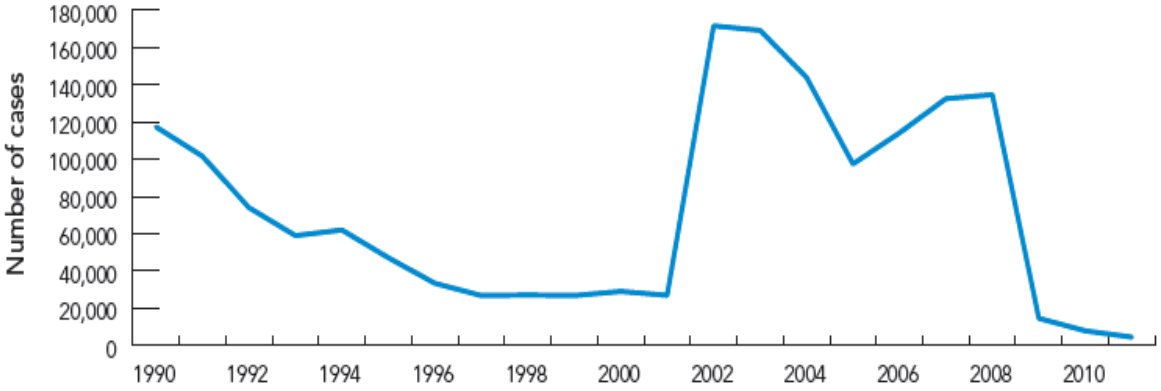
Following data collection, key concepts from each interview and observation visit were summarized by the research team, mapped to the corresponding use scenarios and settings, and aggregated across all nine interviews. A spreadsheet mapping key concepts to use scenarios and settings is included as Appendix B.

Results

China malaria control and elimination programs

China's first malaria control program was established in 1955, soon after it was revealed that with the most conservative estimate at least seven million cases were identified in China in 1954, with devastating effects in rural areas. Cases of malaria decreased by more than 80 percent during the 1990s due to intensive malaria-control activities. Prior to the implementation of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2000, China had experienced dramatic declines in the number of malaria cases from millions per year to only 29,039 reported cases. However, in the early 2000s, China saw a sharp rise of malaria cases, which possibly resulted from cross-border importation, poor surveillance, and the reemergence of *P. vivax* in central provinces Henan, Hubei, Jiangsu, and, remarkably, in Anhui (Figure 2).

Figure 2. Reported malaria cases in China (1990–2011).[4]



After seeing these setbacks in malaria control work during 2000–2005, the Chinese Ministry of Health (MoH) published the *China National Malaria Control Programme (2006–2015)* in 2006. The strategies in this document were formulated to accelerate malaria control in China in pursuit of the goals outlined below.

By 2010:

1. Control malaria in all endemic counties, except those at the border areas of Yunnan and mountainous areas of Hainan (control defined as an incidence <1/1,000), and
2. Achieve basic elimination in 70 percent of all endemic counties, except those at the border areas of Yunnan and mountainous areas of Hainan (basic elimination defined as incidence <1/10,000).

By 2015:

1. Control malaria in the border areas of Yunnan and mountainous areas of Hainan,
2. Achieve basic elimination in all other counties, and
3. Eliminate *falciparum* malaria in Hainan Province.

A near-term evaluation was conducted in 2009 to assess the implementation of this 2006 program, and 2008 data indicated that it achieved most of the 2010 goals ahead of target. Based on the significant success achieved since 2006, and the confidence that China can achieve more, it was determined that national malaria strategy should be revised to include the ambitious goal of elimination.

In May 2010, the China MoH officially launched a national campaign on malaria elimination, *China Malaria Elimination Action Plan for 2010–2020*, with an overall goal: by 2015, local transmission of malaria should be eliminated except for partial border areas in Yunnan Province; and by 2020, malaria elimination should be achieved nationwide.

This 2010 Action Plan is the current China National Malaria Elimination Programme (NMEP). In this document, counties in China were stratified into four types (Types I–IV) based on the malaria epidemic reports of 2006–2008 (Table 1).

Table 1. County classification based on malaria endemicity.

Classification	Malaria Endemicity	Definition
Type I	Higher malaria incidence	Presence of reported local case(s) in the last three years, with all three years having an annual incidence ≥1/10,000.
Type II	Lower malaria incidence	Presence of confirmed local case(s) in the last three years, and at least in one year the annual incidence < 1/10,000 and > 0.
Type III	Potential malaria transmission	No local case for at least three years, only imported cases.
Type IV	Historically and currently malaria-free	Non-malaria-epidemic areas.

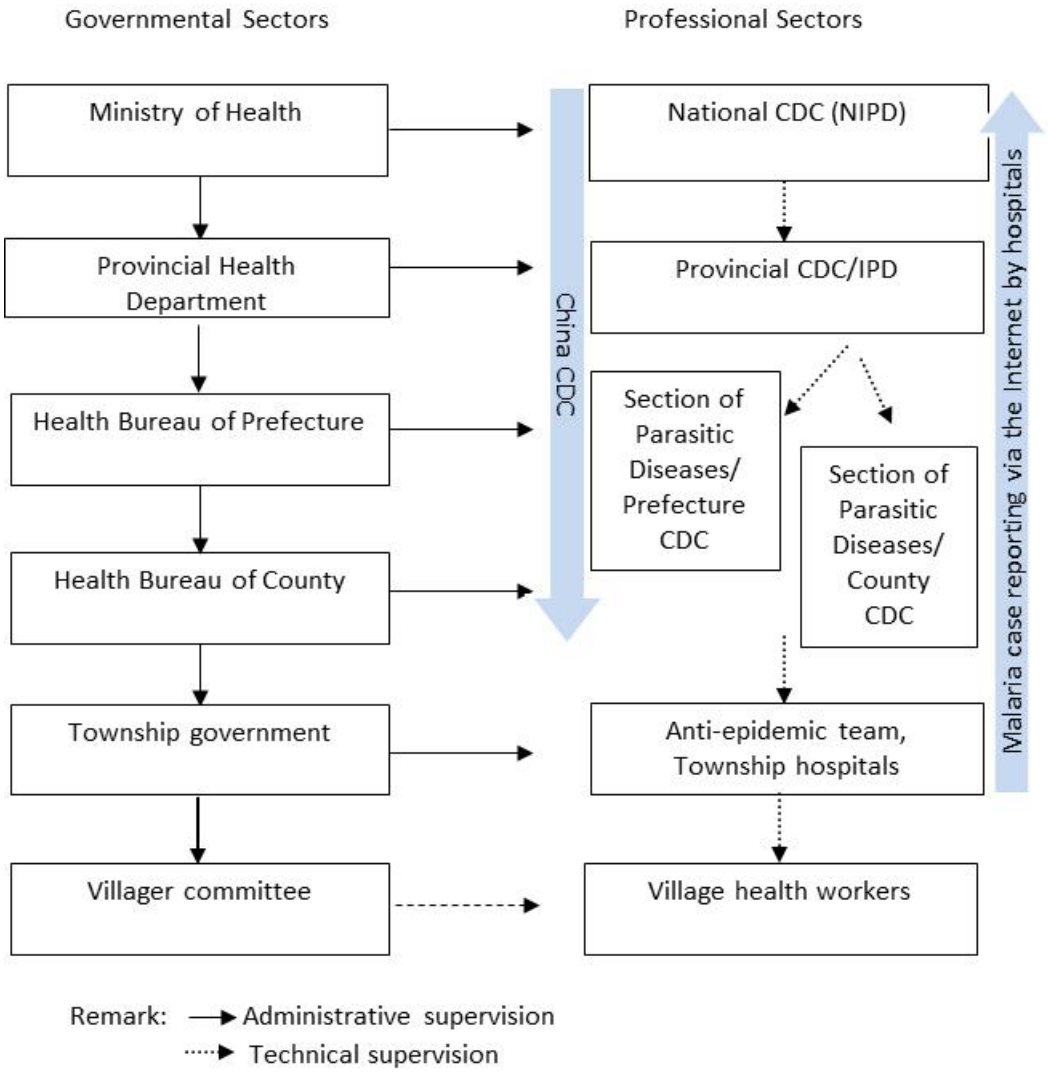
Varying levels of strategies are taken in these different stratifications. In Type I counties, the integrated interventions of case management and vector control will be scaled up to reduce the incidence; in Type II counties, addressing any possible malaria cases and active foci will be the main strategies to interrupt local transmissions; in Type III counties, the capabilities of malaria surveillance and response will be emphasized to prevent malaria reintroduction; and in Type IV counties, the key point is to save lives of imported cases through early diagnosis and appropriate treatment. Uniquely, China is implementing a "1-3-7" strategy: one day to report a case, three days to confirm and classify the case, and seven days to conduct a local response and prevent any onward transmission.

Health system structure for malaria in China

To implement the malaria-elimination strategy and to achieve the national malaria-elimination goal, the Chinese MoH works in partnership with the Chinese Centers for Disease Control and Prevention (China CDC), which is the primary government agency working in the fields of disease control and prevention, public health management, and provision of service. China CDC

has four-tier structures from top down as national, provincial, prefectural to county levels; however, China's current NMEP is designed to have three tiers: national [China National Institute of Parasitic Diseases (NIPD)], provincial CDC or IPD, and local (prefecture and county) CDC. Each CDC works closely with the health bureau of equivalent level, responsible for local malaria strategy implementation that conforms to national goals. Hospitals and other health care providers are also important components in malaria work. Since 2004, when China instituted an internet-based disease-reporting system, hospitals/clinics even at most township levels have had facilities that allow for timely malaria case reporting and response (Figure 3).

Figure 3. A schematic of the Chinese health system.



There are staff who are dedicated to malaria-elimination work at both national and provincial levels, while at lower levels, a person may have other duties besides malaria-related work. Responsibilities for each setting are as follows:

- NIPD: be responsible for research on strategies and measures for nationwide malaria elimination; organize and implement overall work plans, and provide technical guidance, staff training and quality control for malaria elimination throughout the country; collect, archive, and ensure the quality of national malaria data; organize inspection, examination, supervision of malaria-elimination work across China.
- Provincial CDC or IPD: develop and implement provincial malaria-elimination plans in accordance with the national malaria-elimination plan while also taking local situation into consideration; provide staff training and quality control for all aspects of malaria-related work in the province; review, analyze, and provide feedback on malaria data collected in the province.
- Local CDC: conduct surveillance as required by the surveillance plan, and collect, archive, and report surveillance data to provincial CDC or IPD; provide training and technical support to medical institutions in its administrative area; review, analyze, and report local malaria data, and be responsible for quality-assurance activities for areas under its administration.
- Township hospital/clinic: assist local CDC in the implementation of malaria-elimination strategy as required.

Malaria diagnostic tests used in China

Malaria cases are normally found in the villages of rural countryside. All villages are covered by one to two village doctors, but the government cannot provide enough financial support to the village doctors to ensure the conduct of essential activities. A significant level of under-diagnosis and under-reporting occurs at the village level due to inadequate skills and lack of incentive. With the implementation of the New Rural Cooperative Medical Insurance (NRCMI) in China, people are encouraged to go to township and/or county hospitals to see doctors, so malaria diagnosis generally takes place at county- or lower-level settings.

In China, all suspected malaria cases are required to be definitively diagnosed with microscopy, RDTs, or polymerase chain reaction (PCR), and all reported cases currently receive parasite-based diagnosis (i.e., microscopy or RDTs). Confirmed cases are further classified as *Pv*, *Pf*, *P. malariae* (*Pm*), *P. ovale* (*Po*) and mixed infection.

As malaria importation is the focus for China, there are interests in looking for diagnostics tools to differentiate the imported cases and local cases, or trace the parasite origin. Currently, only sophisticated molecular diagnostics tools such as PCR are available in certain laboratories for research, and it is not practical to roll out in field application.

Microscopy

Microscopic diagnosis is the gold standard and the most frequently used approach for malaria detection in China, and microscopy has the coverage in all hospitals to the township level in Type

I and Type II counties and to the county level in Type III and Type IV counties. Microscopy is preferred by some people (mostly the experienced microscopist) over RDTs, as the visible parasites are more convincing than the positive lines to them. Cost of microscopic diagnosis is about RMB 1–5 Yuan/slide ($0.16–0.82USD), which is perceived as a cost-efficient method by some people.

Two blood slides are taken if a febrile patient is suspected to have malaria. All slides are to be kept for re-examination by higher-level CDC as described below.

- County CDC: to re-examine all positive slides and at least ten percent of randomly selected negative slides in the county.
- Prefecture CDC: to re-examine all positive slides and at least three percent of randomly selected negative slides in the prefecture.
- Provincial CDC: to re-examine all positive slides and at least one percent of randomly selected negative slides in the province.
- National CDC: to conduct annual quality assessment of microscopic skills on each province.

However, microscopic skills are not well maintained at the township level, especially in those regions where malaria cases are rare and staff have less opportunity to experience the real malaria case. There are concerns about malaria awareness and attitude as microscopists at lower-level settings are often generalists responsible for other tasks. To illustrate the quality of microscopy: In 2010, the Yunnan Institute of Parasitic Diseases reread 11,589 slides previously reported as negative for malaria for microscopy quality control. Eighty-four slides (0.73 percent) were false negative, which is even higher than the slide positivity rate of 0.51 percent for the whole province.[7]

China National CDC aims to retain at least one “expert” microscopist at county level, and it holds an annual malaria microscopy skills and knowledge competition to build staff’s motivation and camaraderie. The contestants are from provincial and local CDC, as well as the township hospitals all over China. Based on WHO criteria of malaria microscopist assessment and China national malaria technical guide, the competition involves tests of contestants’ microscopical skills such as blood smear preparation, slide staining and reading, plasmodium specie identification and microscope operating and maintaining, as well as malaria diagnosis theoretical knowledge examination. Fifty-eight contestants from 17 provinces (23 contestants from township level, 21 county level, and 14 provincial level) took part in the first competition in 2008, and the average score was 68 out of 100, with 13 (22 percent) contestants scoring under the qualifying 60. It was observed that the contestants from Global Fund-supported regions, which basically meant they were malaria-endemic areas, performed much better than those from places where malaria transmission was low.[8]

Rapid diagnostic tests

RDTs are viewed as a back-up tool for malaria microscopic diagnosis where facilities, manpower, and skills are unavailable, often in remote villages, in high-incidence counties, and for emergencies. RDTs are not widely used in China, although it was approved as a malaria-

confirmation tool.[9] So far, only five types of malaria RDT products are in the China Food and Drug Administration (CFDA) online database,[10] namely the Wondfo Pf (HRPII), Wondfo Pf (pfLDH)/Pan (panLDH), Zhongshan Bio-Tech Pf (HRPII), Zhongshan Bio-Tech Pf /Pv (LDH), and Binax (USA) NOW Malaria Test (HRPII). Wondfo dominates the malaria RDT domestic market in China. RDT procurement has historically been driven mostly from Global Fund, mainly with products from foreign companies and predominantly for research and pilot studies in the field. Wondfo is one of the two domestic companies supplying RDTs in the market, with a much lower price compared to foreign products (RMB 5–10 Yuan vs. 10–70 Yuan; 0.82–1.65 USD vs. 1.65–11.52 USD).

With the pulling out of Global Fund in China, some hospitals and CDC have experienced RDT stockouts. If the China government funds step in and support procurement of malaria RDTs in the future, it is anticipated that the government bidding system will prefer products from domestic manufacturers; however, there are not many players on the market, and domestic product quality is a concern as well.

CFDA regulation on malaria RDT registration requires that clinical trials be conducted in China, but it is getting more difficult to find proper clinical samples in China, although it is agreed that preserved blood samples can be used in the trial. With some foreign companies interested in getting into this market, Chinese companies are looking to get into other markets outside of China, especially within Africa.

There are two different opinions on the utility of malaria RDTs: some think RDTs (with high quality and adequate sensitivity) are useful for malaria elimination since they are easy to use and can serve as a complement or even a replacement to microscopy, especially in the low-level, high-risk settings such as rural counties, townships, and villages where the maintenance of microscopic skills is a challenge. Others think RDTs are a weak solution and not cost-effective for China because of the huge population and the complexity of the malaria situation—let alone the short shelf life and the inadequate sensitivity, as well as poor *vivax* detection and post-treatment false positives (HRP2 types) of the currently available RDTs.

Polymerase chain reaction

Provincial CDC runs PCR for malaria diagnosis monitoring and quality assurance (QA) work, as well as for research. China National CDC has issued a PCR Standard Operation Procedure (SOP) on malaria diagnosis, which works well with *Pf* but is not sensitive to *Po*. PCR is conducted using dried blood spots (DBS) or blood samples taken in township or higher-level hospitals/health care centers. Provincial CDC is required to re-examine the slides of all suspected, clinical, and/or laboratory-confirmed positive cases from those counties with incidence <1/10,000 in three consecutive years, and run PCR detection on those deemed negative samples after re-examination. If a provincial CDC has no facilities or capabilities to conduct PCR, NIPD will provide assistance and guidance to accomplish the case confirmation.

In some counties with advanced facilities, they may have the capability and relevant staff with appropriate training background to operate PCR.

Malaria diagnostic scenarios in China

China CDC set up *National Technical Protocols for Malaria Elimination* in 2011 after publication of the elimination action plan, requiring each province to establish, adapt, and adjust their malaria strategies and technical protocols according to their own malaria situation and tendency.

Three aspects are included in diagnosis basis for a malaria case: epidemiology (recent histories on traveling, blood transfusion, and infection); symptoms (typical and atypical, patients triaged based on the severity of complication); and laboratory detection (parasite, antigen-antibody, and gene identification). Patients are classified into four groups: suspected case, clinical case, confirmed case, and asymptomatic carrier.

Passive case detection

Passive case detection (PCD) is used in China to identify a malaria case, especially in the rural countryside. A patient with fever in the village may go to see a village doctor, who generally has three years of basic medical training in *Weixiao* (a vocational training school in health care). Village doctors may respond to the patient differently depending on where the village is and the local malaria incidence situation. Village doctors in Type I counties are supposed to act more vigilantly, and when they suspect malaria infection, they would test using RDTs if they have stock, and prepare blood smears (one thin and one thick blood film) and send to township (community) hospitals to do microscopic examination. Village doctors in Type I counties also are required to keep the log of malaria patient registration sheet for future inspection. Village doctors in other counties normally refer a patient to the township/county hospital if a suspected malaria case emerges.

Township/county hospitals are where the malaria cases get diagnosed in a laboratory. There are one to two microscopy generalists in each township hospital in charge of routine blood smear and examination, and currently malaria microscopic examination capabilities have the coverage in all hospitals to the township level in Type I and Type II counties and to the country level in Type III and Type IV counties. In malaria high-incidence regions or during an emergency situation, RDTs may be used as a complement method to microscopy where the skills are not very well maintained or manpower is in short supply. A laboratory technician is required to collect blood samples (national protocols: two DBS or 2ml anticoagulant blood) from all cases (suspected case, clinical case, or confirmed case) and send the samples from all positive cases to provincial lab to conduct PCR detection.

Malaria PCD is integrated in China's notifiable diseases reporting system with a "1-3-7" strategy. Most township hospitals and all county CDCs have had web-based reporting systems installed. When a malaria case is identified, it should be reported online or a reporting card sent to county CDC if internet access is unavailable within one day of detection. County CDCs check the reporting system daily, start a case investigation within three days of receiving the case report, and recheck the slides and confirm or correct the primary diagnosis. Within seven days, county CDCs conduct a local response and prevent any onward transmission.

Constraints

Microscopy is the main primary test and is viewed as the gold standard method for malaria at all levels. However, the microscopic skills at lower levels, such as township/community levels, where the most malaria are supposed to be encountered and identified, are not satisfactory. Year-round frequent technical trainings are organized by provincial CDCs and county CDCs for the lower-level settings, which has been one of their main tasks. For example, Jiangsu IPD provides four to six rounds of trainings each year for county CDCs. However, as malaria prevalence is decreasing, fewer health care professionals have the opportunity to see a real malaria case and this makes it extremely difficult to maintain the microscopic skills at all regions/levels. On the other hand, poor pay to lower-level microscopists discourages them from maintaining their motivation and from putting efforts into maintaining their skills. Some interviewees indicated that maintaining microscopy skills requires significant resources, and it would be impractical and cost-inefficient to invest in the microscopic skill training at the township/community levels. They believe there should be spaces in these settings for good-quality malaria RDTs.

RDTs are perceived as a secondary or back-up option for malaria detection. They are only used widely in remote areas with high malaria incidence or in situations where microscopy capabilities are insufficient. At some township hospitals, RDTs are used as a screening tool and blood smears are conducted afterwards on RDT-positive cases to confirm the diagnosis. RDTs were mostly purchased by the Global Fund and used for operational research but not in primary use. Currently, malaria RDTs are not adequately available on the market in China, which may be because of few manufacturers, CFDA rigid regulation, poor sensitivity for *Pv* and low density, and confusion resulting from HRP2 persistence and/or other complexity of the RDTs. Another concern about RDTs is their apparently high cost. Poor stability of RDTs was also mentioned by some interviewees, as notable wastage caused by expired stocks has been observed in the past, which may get more sensitive to the government following the Global Fund pull-out. As aforementioned, microscopy is favored for its parasite visual evidence; RDT is subordinate, and there are no clear guidelines for RDT use in China.

Importation of malaria is a big problem in China, and it is a priority for the China CDC to determine the origin of parasites. Current practice is to determine parasite origin by epidemiology questionnaire, and genotyping and fingerprinting using molecular analytical methods such as PCR is implemented only for research purposes—typically at the provincial level and sometimes at the better county-level facilities.

Feedback we gathered from the field on follow-up of a malaria-positive case varied. A patient who needs hospitalization is easy to track down and take blood for treatment effectiveness testing, and township hospitals may keep contact with patients by telephone and ask them to come back in two to four weeks for a follow-up test, but this mostly happens only to patients who are local. For those populations who are transient (often along the borders), mobility and language barriers add difficulties to case follow-up; therefore, often no follow-up tests are performed on these people.

Another constraint in PCD is the sample transport to county CDCs and provincial CDCs. Positive slides and blood samples are required to be sent to county and provincial CDCs, and in most

places there are dedicated staff taking care of sample transport. However, in the rural areas, county CDCs may reach out to township to fetch the samples, or they may use some unreliable channels, such as local bus drivers, to transfer the packages.

Proactive case detection

There are several situations that require proactive case detection: hotspots in which a population-wide malaria screening is conducted and followed by treatment of positive cases, and hotpops in which a certain population (e.g., the border-crossers and/or migrant workers) is screened to identify the asymptomatic parasite carriers and eliminate parasite reservoir.

Due to the vast area and population in China, it is really challenging to set one unique protocol for proactive case detection. Individual provinces establish their own strategies for proactive malaria detection.

The Jiangsu IPD set up this scheme for proactive survey: During malaria high season (May to October), in malaria historically endemic areas, the county CDC chooses two villages from one township to conduct family visits. Microscopic check or RDT screening is required to be performed on at least 200 people in each village, and DBS on filter paper is sent to the provincial laboratory (Jiangsu IPD) to conduct molecular (gene) diagnostics. All counties are required to do at least one active investigation every two years prior to receiving an elimination certificate.

Hotpops survey in Jiangsu is conducted among the migrant workers who travel to Africa, as Jiangsu is the number-one province that exports construction industry in Africa. The main approach is anti-malaria advocacy and education using TV and other public media. The county CDC also collaborates with the Entry-Exit Inspection and Quarantine Bureau to deliver educational materials to migrant workers when they pass through customs, and advocates for free check-ups for migrant workers who have fever. Anti-malaria education is even integrated with AIDS-prevention education programs in some areas.

In Yunnan, they call the proactive survey a ‘top down survey’, which is led by the county CDC. The frequency of proactive survey varies according to malaria seasons or agriculture seasons when migrant workers cross the border. At the Yingjiang County CDC, they conduct four proactive surveys every 36 months, and increase the frequency to eight times per month during malaria high season. Villages are chosen based on the recent reporting rates (too high or too low, and close proximity to recent cases) and the size of the migration population who crosses the border during harvesting season. One blood slide is taken for proactive survey. Normally, the township hospitals and village doctors provide assistance with people tracking and locating during proactive survey.

<u>Constraints</u>

The most frequently mentioned issue with proactive case detection is the difficulties tracking and locating people, especially the migrants. All Chinese who travel to Africa will go through Middle East or Europe, so that makes it very difficult to position a border screening system for malaria. In Yunnan, it is too expensive to cover all routes across the borders.

A patient receives anti-malaria drugs only when it is confirmed by microscopy or RDT, as there is concern of drug resistance derived from presumptive treatment; therefore, there is delayed time to get treatment.

Reactive infection detection

Once a malaria-positive case (index case) is identified, either by passive or active detection, a reactive measure is triggered to identify and treat any asymptomatic parasite carriers associated with the index case and eliminate parasite reservoir at some location and/or among some population.

If a malaria-positive case is identified passively or through proactive measures, a family visit is conducted during case investigation. Besides vector investigation and control and malaria education and awareness advocacy, DBS on filter paper is prepared from all of the patient's family members and neighbors who had febrile history in the past two weeks, and microscopic examination or RDTs is conducted on this blood. If two or more malaria-infected cases are identified, all villagers go through microscopy or RDT detection. If the index case is identified among people returning from malaria-endemic areas/countries, a snowball sampling method is employed to identify other imported cases and amplify the scope of screening (e.g., by identifying the people the patient traveled with and the neighbors and close contact of this patient).

In Yunnan, blood smears and RDTs are used during reactive case detection (RACD). In remote villages, investigators may take microscopes with them to prevent loss to follow-up. Otherwise, they make two slides at the village, and then stain and dry later when they get back to the county laboratory.

Molecular diagnostics is seen by some interviewees as the best method for reactive detection because of its sensitivity, accuracy, and high throughput. In Jiangsu, they rely on PCR at theIPD. Blood is collected in village, residential settlement, or work place and taken back to the provincial malaria laboratory.

<u>Constraints</u>

Reactive detection is based on a chain referral sampling, and the case number of the "snowball" waiting for screening may grow quite large; workload is tiresome to malaria field staff, and microscopy is less preferred. The sampling number is often compromised as a result.

Reactive detection is supposed to capture the asymptomatic parasite carriers who normally have low density of parasites. The limit of detection (LOD) of the diagnostics tool is seen as insufficient. RDT is considered a less favorable diagnostics tool, as it is not good for subpatent cases. PCR and other molecular diagnostics tools are seen as a better fit for reactive detection; however, these methods are perceived to be complicated and only staff with enough training can use them.

During reactive detection, it is sometimes difficult to locate villagers as they may be out for work, and some villagers do not want to participate by giving blood, as they are symptom-free or

asymptomatic. Loss to follow-up issues can be mediated with mass drug administration (MDA) approach, but MDA seems not rolled out in all places.

Similar to proactive detection, delayed treatment is another problem within malaria reactive detection. If additional cases are identified through RACD, they often have to wait at least seven days or longer to get the confirmation and receive drugs.

Quality assurance (QA) and quality control (QC)

QA and QC of malaria diagnostics are conducted for staff training, slide re-examination, and/or PCR testing by higher-level CDCs in order to maintain and monitor microscopic skills at all levels in the health system. The national CDC provides training to the provincial CDC once a year, and the provincial CDC to the county CDC (also slide re-examination on all positive and at least one to three percent of negative slides), the county CDC to township hospitals (also slide re-examination on all positive and at least ten percent of negative slides). Microscopic skill is the main indicator to assess the quality of malaria diagnostics in China. A malaria-positive slide gets at least three to four examinations under microscopes at different levels and a number of negative slides also get checked for false negatives. PCR is used only in the provincial CDCs or some county CDCs with advanced facilities for research or as a complement to malaria diagnostics QA/QC.

Constraints

In some places, there is a desire to push malaria molecular testing to all county-level facilities. However, PCR needs to be standardized and operated by trained staff, and some people consider PCR too expensive to conduct on negative samples. Loop-mediated isothermal polymerase chain reaction (LAMP) is seen as an alternative, but the IP challenges block its way to the market.

Summary

The malaria surveillance and reporting system is robust in China. Since the implementation of NMEP in China in 2010, the epidemiology of malaria has changed dramatically. However, importation of malaria is becoming a great challenge to China's elimination strategy. It is widely understood in China that prompt and accurate diagnosis is the key to eliminating malaria. Microscopy is the primary tool to detect malaria in most situations, and great efforts are invested in maintaining satisfactory microscopic skills at all levels of the health system. RDT as a back-up tool for malaria detection is used in the lowest settings where microscopic skills are compromised, but the concern about quality and perceived higher costs of RDT make universal use in China prohibitive. PCR and other molecular diagnostics tools are used at the provincial level and occasionally at the county level, mainly for QA/QC and for research. With its progress on malaria elimination, China would be a great candidate for a malaria diagnostics adjustment case study on its solution to the evolving technical and financial climates.

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Appendix A: List of interviewees

Date/Place	Interviewees	Role/Title
September 23 China IPD (National CDC) High level	Xiaonong Zhou	Director of National Institute of Parasitic Diseases (NIPD), Shanghai
	Ning Xiao	Deputy Director of National Institute of Parasitic Diseases (NIPD), Shanghai
	Zhigui Xia	Deputy (Acting) Chief, NIPD Malaria Department, Shanghai
	Junhu Chen	Vice Chief, Key Laboratory of Parasite and Vector Biology, NIPD, Shanghai
September 23 Jiangsu IPD (Provincial CDC) High-mid level	Desheng Tong	Lab Technician/Microscopist, Jiangsu IPD Clinic
	Qi Gao	Director, Jiangsu IPD
September 24 Jiangsu IPD	Shuisen Zhou	Chief, NIPD Malaria Department, Shanghai/ WHO GMP consultant, Geneva
September 25 Jiangsu IPD	Jun Cao	Chief, Malaria Department, Jiangsu IPD

Date/Place	Interviewees	Role/Title
September 28 Yingjiang County CDC Mid-level	Yingxue Lin	Malaria Department, Yingjiang County CDC
	Xiangrui Guo	Malaria Department, Yingjiang County CDC
	Guocui Yu	Microscopist, Malaria Department, Yingjiang County CDC
	Lifei Chen	Malaria Department, Yingjiang County CDC
	Jiayuan Shen	Malaria Department, Yunnan Provincial IPD
September 29 Rende private hospital (township level) Low level	Tide Wang	Owner of Rende Hospital (Private)
	Fugui Xu	Doctor, Rende Hospital (Private)
	Guotao Xin	Pharmacist, Rende Hospital (Private)
September 29 Nongdao township hospital Low level	Mr. Guo	Head of Nongdao Township Hospital
	Dr. Guo	Malaria Department, Nongdao Township Hospital
	Menglan Qin	Microscopist, Nongdao Township Hospital
Yunnan Provincial CDC High-mid level	Hui Liu	Chief of Yunnan IPD (YIPD) Malaria Clinical Department

Appendix B: Use scenarios for malaria diagnostic tests in China

Use Scenario	Setting	Inputs				Outcomes	Constraints
		Diagnostics	Process	Human Resources	Infrastructure/Supplies		
Passive Case Detection (PCD)	Village clinic -- (low-level infrastructure in Type I counties may have access to malaria rapid diagnostic test [RDT] kits)	Type I counties: RDT (if available), one thin and one thick slide, dried blood spot (DBS) Other counties: refer patients to township/county hospitals	Type I counties: • Patient presents to village clinic • Village doctor performs RDT tests if available • Village doctor prepares two slides (one thin and one thick) and sends to township hospital to do microscopic examination • Village doctor takes DBS on filter paper and sends to township hospital • Village doctor keeps the log of malaria patient registration sheet for future inspection Other counties: • Village doctor refers patient to township/county hospitals	• A village doctor generally has three years of basic medical training in a health care vocational school	Type I counties: • Supply of slides, sharps, filter paper, and waste disposal • RDT (maybe) • Notebook/table for record keeping	• Treat patient if RDT available and positive • Slides and DBS prepared and sent to township hospital • Refer patient to township/county hospitals • Record information in register	RDT constraints: • Frequent RDT stockouts • RDT with poor sensitivity for vivax and low density malaria • Wastage casued by expired shelf life/stability of RDT • No clear guidelines for RDT use • Difficulty in interpreting RDT results • Government bidding system favors RDT products from domestic manufacturers but currently only one player on the market Other constraints: • Awareness and attitude of village doctors
	Township hospital -- (low-to-mid level infrastructure, Type I & II counties with malaria microscopy coverage)	Type I & II counties: Mainly by microscopy and alternatively by RDT (if available) Other counties: Microscopy and/or RDT if available, otherwise, prepare slides and DBS on filter paper, and send to county CDC to perform lab tests	Type I & II counties: • Patient goes or is referred to township hospital • Doctor prescribes a lab test • Lab technician examines slides prepared by village doctor if the patient is referred to township hospital, or prepares slides and performs microscopy test or RDT test if available • Lab technician takes DBS on filter paper or 2ml anticoagulant blood, keeps frozen • If internet-based reporting systems available, township hospital reports positive case to the online China infectious disease reporting system, otherwise sends the reporting card to county CDC Other counties: • Conduct the same process as Type I & II counties if there are microscopy and/or RDT available • Otherwise, lab technician prepares slides and takes DBS on filter paper, and sends to county CDC to perform lab tests. County CDC gives lab test results back to township hospital. • If internet-based reporting systems available, township hospital reports positive case to the online China infectious disease reporting system, otherwise phones up county CDC and sends in the reporting card	• Doctors, nurses, and lab technicians with three years of basic medical training in a health care vocational school, and a very few may have university level training • Anti-epidemic team responsible for local infectious diseases monitoring and reporting	• Dozens of beds • Basic clinical lab • Microscopy (Type I & II counties) • RDT (maybe) • Computer and internet access	• Patients treated if results positive • Positive cases reported online or by phone/reporting card, and county CDC informed within one day • Slides, DBS, or blood samples prepared, read, and transported to county CDC • Transfer severe patient to county hospital • Records of household information and travel history, previous infection history, species	• Weak microscopy skills at township level • Difficulty in maintaining microscopy skills • Perceived higher cost of RDT test against microscopy • Microscopy is favored over RDT for its parasite visual evidence • Difficult to determine the origin of parasites • Awareness and attitude of township staff • RDT constraints as listed above • Mobility and language barriers of the population along the borders add difficulties to case follow-up • Sample transport to county CDC sometimes by unreliable channels, such as local bus drivers
	County hospital/CDC -- (mid-level infrastructure)	Mainly by microscopy, and occasionally by RDT	• Patient goes or is referred to county hospital/CDC • Doctor prescribes a lab test • Lab technician performs microscopy test • Lab technician takes DBS on filter paper or 2ml anticoagulant blood, keeps frozen • Case reported via online China infectious disease reporting system • County CDC prepares case investigation and reactive infection detection	• Most doctors, nurses and lab technicians at county level have university level medical training • In county hospital, an anti-epidemic team responsible for infectious diseases monitoring and reporting • In county CDC, there is a malaria specific team/department who is responsible to case investigation, reactive infection detection, IRS, surveillance, training and quality-assurance activities for areas under its administration. This team includes microscopist, epidemiologist, medical doctors.	• Dozens to hundreds of beds at county hospitals • Clinical lab • Microscopy • Some counties have PCR capacities • Computer and internet access	• Patients treated appropriately • County CDC re-examines slides and confirms the case, and checks the integrity of online reporting data within three days • County CDC conducts a local response and prevents any onward transmission within seven days • Positive slides sent to provincial CDC to re-exam, negative slides kept at county CDC	• Microscopy skills and malaria awareness may poor at county hospital if the local incidence is low • Difficult to determine the origin of parasites • Difficult to follow up the transient patient
	Provincial CDC -- (high-level infrastructure)	Microscopy: (most for re-examination of positive slides from county CDC) Polymerase chain reaction (PCR): for research or complicated case confirmation RDT may be used for evaluation	• Provincial CDC seldom sees patients directly coming in	• Most staff at provincial CDC have educational background at university and/or postgraduate level. There is a malaria department that develops and implements provincial malaria-elimination plans in accordance with the national malaria-elimination plan by taking local situation into consideration.	• Research laboratory equipped with advanced facilities: PCR, microscopy, centrifuge, -80 degree freezer • Computer and internet access	• Strategy for provincial malaria elimination plan • Review, analyze, and provide feedback on malaria data collected in the province • Staff training and quality control for all aspects of malaria-related work in the province	• Difficult to coordinate multiple department collaboration for importation case identification and tracking • Poor pay to lower-level microscopists discourages them from maintaining their motivation and from putting efforts into maintaining their skills • Tight budget on malaria work
	National Center for Disease Control and Prevention (CDC) -- (high-level infrastructure)	Microscopy: for assessing microscopy skills in each province PCR: for research or complicated case confirmation RDT may be used for evaluation	• Hardly has malaria patients directly coming in	• Most staff at National CDC (China Institute of Parasitic Diseases, IPD) have education background at university and/or postgraduate level. Malaria is one of the components of IPD	• Research laboratory equipped with advanced facilities: PCR, microscopy, centrifuge, -80 degree freezer • Computer and internet access	• Review, analyze, and ensure the quality of national malaria data • Be responsible for research on strategies and measures for nationwide malaria elimination • Organize and implement overall malaria work plans • Organize inspection, examination, supervision of malaria-elimination work across China	• Decrease of malaria disease burden in China results in overall shrinking of resources and declining awareness • No feasible tools to differentiate the imported cases from local cases, or to trace the parasite origin in practice

Use Scenario	Setting	Inputs				Outcomes	Constraints
		Diagnostics	Process	Human Resources	Infrastructure/Supplies		
Proactive Case Detection	Hotspots -- organized by county CDC	Microscopy, RDT, and PCR	• **[Jiangsu Province]:** During malaria high season (May to October), in malaria historically endemic areas, the county CDC chooses two villages from one township to conduct family visits. Microscopic check or RDT screening is required to be performed on at least 200 people in each village, and DBS on filter paper is sent to the provincial laboratory (Jiangsu IPD) to conduct molecular (gene) diagnostics. All counties are required to do at least one active investigation every two years prior to receiving an elimination certificate.	• County CDC organizes proactive case detection with village doctor and township hospital assistance • County CDC sends blood sample to provincial CDC to perform PCR (gene) tests	• RDT • Microscope and consumables • Notebook/formatted table for record keeping • Blood drawing kits • PCR (provincial CDC)	• Persons testing positive are treated • Positive case triggers expanded range of screening (reactive case detection)	• Difficulty in tracking and locating people, especially the border-crossers • Delayed treatment
	Hotpops -- organized by county CDC	Microscopy, RDT, and PCR	• **[Jiangsu Province]:** Hotpops survey is conducted among the migrant workers, mainly in the construction industry in Africa. The main approach is anti-malaria advocacy and education. The county CDC also collaborates with the Entry-Exit Inspection and Quarantine Bureau to deliver educational materials when they pass through customs, and advocates for free check-ups for migrant workers who have fever.	• County CDC combines proactive case detection with malaria education and advocacy, with other departments' support • County CDC sends blood sample to provincial CDC to perform PCR (gene) tests	• RDT • Microscope and consumables • Education materials • Notebook/formatted table for record keeping • Blood drawing kits • PCR (provincial CDC)	• Persons testing positive are treated • Positive case triggers expanded range of screening (reactive case detection)	• Difficulty in tracking and locating people, especially the border-crossers • Delayed treatment
Reactive Case Detection (RACD)	Index case from a rural village or a work place (such as construction site)	Microscopy or RDT or PCR (Jiangsu)	• Family/contact visit to the index case • Vector investigation and control and malaria education and awareness advocacy • RDT tests (if available) performed or two slides examined on family members/close contacts and those with fevers • DBS on filter paper prepared from family members/close contacts and those with fevers • If two or more malaria-infected cases are identified, all villagers/co-workers go through microscopy or RDT detection	• County CDC organizes family/contact visit and reactive case detection (RACD) with village doctor and township/community hospital assistance	• RDT if available • Devices and consumables for microscopy examination (only if the village is not remotely located), or only slides prepared and taken back to county CDC to do microscope examination • Notebook/formatted table for record keeping • [Jiangsu] Draw blood and take filter paper back to provincial lab to perform PCR tests	• Snowball sampling: expand scope of detection if new positive case emerged • Turnover of test results may take seven days or longer, so a positive case needs to wait	• Difficult to perform microscopy in field • Microscopy is not best solution for RACD while supply of RDT is often inadequate • Need lower limit of detection (LOD) for lower density of parasite infection • Workload may be tiresome and sampling number therefore compromised as a result • RDT is not good for subpatent cases • PCR/molecular tools fit best but need well-trained staff with expertise • Villagers may not be collaborative (out for work or reluctant to give blood) • Delayed treatment
	Index case from a travelling group (such as migrant workers or people returning from malaria-endemic areas/countries)	Microscopy or RDT or PCR (Jiangsu)	• Visit the company that provides export of labor service if the index case is a returning worker to track those who were travelling in the same group • Talk to the employer who hires the migrant worker to get his/her background and group information • Perform RDT or microscopy tests, or take blood from group and close contacts • Expand scope of screening if new case identified	• County/Provincial CDC organizes RACD with support from township/community hospital, and collaboration from employers	• RDT if available • Consumables for blood drawing • Slides prepared and taken back to CDC lab to do microscope examination • Notebook/formatted table for record keeping • [Jiangsu] Draw blood and take filter paper back to provincial lab to perform PCR tests	• Snowball sampling: expand scope of detection if new positive case emerged • Turnover of test results may take seven days or longer, so a positive case needs to wait	• Difficult to perform microscopy in field • Microscopy is not the best solution for RACD while supply of RDT is often inadequate • Need lower LOD for lower density of parasite infection • Workload may be tiresome and sampling number therefore compromised as a result • RDT is not good for subpatent cases • PCR/molecular tools fit best but need well-trained staff with expertise • Difficult to reach all people in the group, and they may not be collaborative (continue to travel to other places or reluctant to give blood) • Delayed treatment
Quality Assurance (QA) and Quality Control (QC)	National level	Microscopy and PCR	• China IPD conducts regular assessment on provincial microscopy skills and PCR capacities, by re-examing randomly selected slides and re-testing blind samples	• National malaria lab	• Microscopy and PCR	• China IPD conducts assessment on every province once a year	• PCR needs to be standardized and operated by trained staff • PCR is expensive
	Provincial level	Microscopy and PCR	• Provincial malaria department re-examines all positive and 1-3% of negative slides throughout the province (submitted by county CDC and township/county hospitals).	• Microscopist in provincial malaria lab	• Microscopy and PCR	• Provincial malaria department re-examines all positive and 1-3% of negative slides throughout the province (submitted by county CDC and township/county hospitals).	• PCR is difficult to roll out to county level • Other molecular tests may be hampered by technology barrier, performance, and IP issues
	County level	Microscopy	• County malaria department re-examines all positive and 10% of negative slides throughout the county (submitted by township/county hospitals).	• Microscopist in county malaria lab	• Microscopy	• County malaria department re-examines all positive and 10% of negative slides throughout the county (submitted by township/county hospitals).	