Diagnosis, treatment and detection strategy

Conceptual document and strategic path

Background Document for Session 5

Document for guidance

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1

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3 Contents

1 Background

There is a need to translate the Framework for Malaria Elimination (1) into an operational language and to guide countries in finding the most efficient way to implementation activities that may lead to the elimination of malaria.

Responding to this need, PAHO wants to promote a stepwise approach in which diagnosis, with the consequent treatment is the first step, followed by reactive case detection. This approach (now called DTD strategy) arises from the T3 strategy (2) and goes beyond it to meet the needs of the new Framework for Malaria Elimination and the new Surveillance Manual (currently in draft). The concept of time will be critical in an intervention based on Test, Treat and Track aiming at elimination.

1.1 Test and Treat

The T3 strategy promotes that each suspected malaria case must be treated, ensuring that universal diagnosis and treatment is available for all populations to reduce morbidity and mortality (2). From a public health point of view, the goal of treatment is to reduce transmission of the infection to others by reducing the infectious reservoir, and to prevent the emergence and spread of resistance to antimalarial medicines (3). Two manuals were developed to support these 2 components: “Universal access to malaria diagnostics testing operational manual”(4) and the “Guidelines for the Treatment of Malaria”(5).

1.2 Track

The Track component of the T3 strategy refers to the need that every malaria case should be tracked in a surveillance system. To guide countries in this process, WHO released in 2012 two manuals to help endemic countries to strengthen their malaria surveillance: “Disease Surveillance for Malaria Control”, for countries engaged in malaria control, and “Disease Surveillance for Malaria Elimination” for countries conducting elimination programmes (2, 6). The differences on surveillance in a control and elimination context were clarified.

The Framework for Malaria Elimination launched in 2017 and the new Malaria Surveillance, Monitoring and Evaluation manual (now in draft) states that “ACD is **always** conducted during epidemiological investigation of **new cases and foci**” in low and very low transmission settings. Active case detection when triggered by a case is then called Reactive Case Detection (RCD) (1).

The rational of the RCD is that, at low transmission intensity, malaria cases are highly aggregated. This is the situation in the Americas where the malaria transmission is not homogenous geographically neither demographically (7). Where there is a case, there might be more. In this context, the identification of new cases from one index case is a strategy that might reduce and interrupt the transmission in a focus. RCD is an important component of the elimination strategy in areas of low transmission and it is related to the concept of focus investigation as mentioned above (1).

During RCD, household members, neighbours and other contacts of the index case diagnosed through passive case detection are diagnosed and the positive cases treated (8, 9). The type of RCD will depend on the local epidemiology, the health service coverage, on how the case was identified, the potential connections and who is going to be tested. RCD usually is conducted with vector control activities and education/participation of the community in the context of focus investigation, classification and response. However, RCD can be conducted alone when the malaria foci is known and vector control measures are in place.

The efficiency of RCD will vary based on transmission dynamics, the diagnostic methods used and on how it is conducted. Several countries use RCD in America, Africa and Asia. However, there are no clear indications about the most effective way of implementing it. In 2016, a systematic review on RCD included 7 studies conducted in Zambia, Senegal, Swaziland, Thailand and India (10). Authors concluded that household members had 5 times more chance to have malaria than their neighbours. The average contacts screened to detect one case varied from 2 to 216, concluding that the benefits of RCD were not clear taking into consideration the efforts and resources invested. However, these studies used different diagnostic methods, in different epidemiological contexts, different parasites, different radius of action, and 3 out of 4 studies didn’t specify the timing when the RCD was

conducted. A study conducted in Brazil looked at the efficacy of RCD for P. Vivax comparing different radius, different timing and different diagnostics methods (microscopy and PCR). PCR detected more than double the number of infections than microscopy. More cases were detected in household members than in neighbours located at less than 3 km from the index case when the RCD was conducted at day 0 and 30. However, at day 60 and 180 the positivity rates were similar among the household members and the neighbours (8). Information about cost-effectiveness of RCD is not available.

1.3 Time

Time is a key factor to reduce malaria mortality, particularly due to *P. falciparum*. Time is critical to interrupt the transmission, avoiding the generation and dissemination of gametocytes from the index case. Malaria elimination requires surveillance systems that can **rapidly** detect and respond to individual cases.

WHO promotes prompt diagnosis and treatment in the first 24-48h from onset of symptoms (3, 11). The new Malaria Surveillance, Monitoring and Evaluation operational manual set the target of notifying a case within one day from diagnosis, conduct case investigation within 3 days and focus investigation and response within 7 days.

China, one of the countries that made an important progress on the reduction of malaria (from more than 26,000 in 2008 to 2,716 in 2012 of which only 243 were transmitted locally) developed a malaria elimination program described as the **1,3,7 Strategy**, making emphasis in the timelines of activities in order to seek out infections and interrupt transmission (12). The 1,2,3 Strategy (which corresponds to the notification, case investigation and focus investigation and response as in the Malaria surveillance manual) also established clear procedures to conduct RCD for each malaria case detected with rapid diagnostic tests (RDT) and PCR. If from the focus investigation it is believed that the area cannot support transmission (no vectors) the RCD was carried out in demographic contacts (household/co-workers) with health education. If the area had vectors, the RCD was more intense (up to 200 neighbours) and vector control activities were conducted.

Sri Lanka, another country that recently eliminated malaria focussed its efforts on early diagnosis, detection and RCD.

1.4 Diagnosis, Treatment and Detection strategy

Based on the WHO recommendations and the successful experiences of some countries in the path towards malaria elimination, PAHO is proposing the Diagnosis, Treatment and Detection (DTD) Strategy with the aim to provide countries with more tools to implement the T3 concept, emphasizing the importance of time, the concept of "surveillance as intervention" and providing operational guidance to implement additional efforts to promptly detect new cases in the community.

The key message of the DTD strategy is to prioritize the process of "diagnosis- treatment - investigation - response" as the core elements of the elimination strategy (and the prevention of reestablishment of transmission). The authorities, health workers and others stakeholders need to optimize this process at the local level. Every case of malaria should be diagnosed and treated in the shortest possible time, and every case (in settings with few cases) or cluster cases (in settings with many cases) should trigger a basic action to detect other possible related cases.

DTD reminds that actions do not stop after testing and treating a case, but continue searching for possible contacts of the case, contributing to the interruption of the transmission. **Diagnose-Treat and Detect** more cases. Diagnosis, treatment and detection must be imbedded in all components of the program: from access to diagnosis and treatment, case management policies and the monitoring and evaluation plan where the percentages of cases detected, treated and the response in the stipulated time must be key indicators of the program.

To make DTD operational at large scale the 3 actions of diagnosis, treatment and detection must be translated in concrete activities in the field. Secondly, they must be able to be followed and monitored. Thirdly, they need to be easy to understand at local level. Therefore, the communication component is an essential part of the strategy.

Finally, DTD brings a unique message that can be applicable in the different scenarios of the endemic countries. The concept of **Diagnose-Treat and detect** more cases in a timely manner should be done in all countries. However, the ways to do it will be different based on the different contexts.

2 Aim and objectives of the strategy

2.1 Aim

To detect, diagnose and treat all malaria cases promptly, to reduce morbidity and mortality and reduce and eventually stop the transmission.

2.2 Objetives

- To place the Diagnosis- Treatment - Investigation – Response in the **centre of the malaria programs**.
- To highlight the importance of a **local and routine** process of Diagnosis, Treatment and Detection as a main component of the strategies aiming to control and eliminate malaria in the Americas.
- To **guide countries on the implementation** of the DTD strategy, ensuring that the programmatic, strategic and policy framework is in place.

3 Description of the strategy

The DTD strategy has 3 main components aiming that each malaria case or cluster of cases have (i) access to diagnosis as soon as possible, (ii) receive prompt and appropriate treatment and (iii) generates a response which always includes RCD (BOX 1, Figure 1, Table 1 and Table 2). The strategy focuses on a basic programmatic action, departing from a strong network of diagnosis and treatment followed by detection adapted to the local epidemiological context. These 3 components must be seen as a continuum in the path towards malaria elimination and need to be clearly stablished at the local health services level.

BOX 1

Main components of the DTD strategy

Diagnosis:	Every suspected malaria case must be **diagnosed** using microscopy or RDT within the first 48h from onset of symptoms.
Treatment:	Every confirmed case must receive appropriate **treatment** based on the national protocols, starting the same day of the diagnosis.
Detection:	Every case or cluster cases should trigger a basic action to promptly **detect** and treat other possible related cases within 7 days.

3.1 Diagnosis

Each suspected malaria case must be diagnosed using microscopy or RDT within the first 48h from onset of symptoms. The rational is to reduce morbidity and mortality (particularly due to *P. Falciparum*) and to interrupt transmission (particularly due to P. Vivax). In the context of low transmission where few cases are detected each year, the target of diagnosing a case within 48h from onset of symptoms might be unrealistic and a more flexible target (always in the first 7 days from onset of symptoms) might be accepted (Annex 1).

Since malaria is a human disease, without proper diagnosis, there is no knowledge of its epidemiology and distribution, no way to stratify the risk, no proper treatment of patients, no guidance for vector control and no surveillance. The knowledge of the epidemiology of malaria is dialectic linked with the diagnosis. Surveillance and

stratification are the natural extension of a proper network of diagnosis. Access to diagnosis remains a challenge in the malaria endemic areas in the Americas.

Assuming that diagnosis and treatment is the anchor of a successful program, attention should be made on the determinants of access and the quality (coverage and effectiveness) of the services. Universal access to diagnosis means that the coverage of the health services must reach all the population in the area and that there are not financial constrains to seek care. The extension and improvement in the quality of formal health care system needs to be promoted when possible. When the formal care services are not available, community volunteers, mobile services and active case detection needs to be considered.

Universal access to diagnosis must be guarantee independently of the number of cases the country is experiencing. A combination between microscopy and RDT might help to reach all areas and to adjust to the work load, understanding that the microscopy is still the gold standard.

All fever cases in endemic areas need to be tested for malaria. Atypical symptoms and asymptomatic cases need to be tested as well if there is a connection/suspicion of malaria.

3.2 Treatment

All positive cases must receive appropriate treatment based on the national protocols, starting the same day of the diagnosis results. The rational is as well to reduce morbidity and mortality (particularly due to P. Falciparum) and to interrupt transmission (due to P. Vivax and P. falciparum).

Personnel from the formal health care are responsible to provide treatment. When the coverage of the health facilities doesn't reach the entire population, efforts must be done on the extension of the network. As this takes time, countries need to consider allowing community volunteers to provide treatment and avoid delays which may cause the continuation of the transmission.

3.3 Detection

Every case or cluster cases should trigger a basic action to promptly detect and treat other possible related cases within 7 days. The local health services must be organised in a way that they can respond in the expected time. Each malaria case should be investigated, a RCD of his/her contacts must be conducted and all positive must be treated. The level and extension of the RCD will be dictated by the epidemiological situation.

A case investigation must ideally be conducted within 3 days from the diagnosis. Establishing the procedures to investigate a case (or cluster of cases) within an expected time is key. The detail of the case investigation and the team in charge of the investigation will vary depending on the coverage of the health services and the number of cases the locality is presenting.

Irrespective of whether the case is classified as local or imported, a RCD will be conducted at least among the household members of the index case (symptomatics or asymptomatics). The same person/team that diagnose the index case and started the case investigation can/should conduct the RCD without waiting for a larger team from the higher level to arrive. In a context of limited resources and high number of malaria cases, less labour intense approaches can be followed. For example, asking the patient to bring to the malaria services any contact that could have malaria or taking into consideration clusters of cases and high-risk areas to conduct the RCD.

The RCD must be conducted using RDT or microscopy, but aiming getting results and provide treatment on the field or ASAP. When conducting the RCD, the health personnel should take advantage of this opportunity to sensitize about malaria prevention and the use of mosquito nets (LLITN) or indoor residual spraying (IRS).

In a context where only few malaria cases occur, the case investigation, focus investigation and response must be done in a more intensive and detailed way. Several rounds of RCD can be planned at day 7, 30, 60 and 180 (the later if *P.Vivax*). PCR could be used if available to detect low parasitemias.

RCD is one component of the response to new cases and foci. In addition to RCD, vector control activities are also a key component of the integrated response to malaria foci. As mention in the Framework for Malaria Elimination(1), "optimal coverage of ITN/IRS should be ensured and maintained in strata that are both receptive and vulnerable". Malaria programs need to ensure appropriate coverage of LLITN or IRS which need to be maintained to avoid rebound of malaria transmission. Although vector control activities are part of the response, they are not necessary included in the basic DTD strategy because of operational reasons. **DTD must be a set of actions operationally feasible to be executed in the shortest time by the basic local team.** Considering that different actors are in charge of the diagnosis, treatment and vector control activities, and the place where they are based, starting the response with RCD might avoid delays. Later, a more extensive focus investigation and response can be conducted with the support of the ETV team, ensuring that the population living in a malaria focus is protected by LLITN or IRS. Without proper diagnosis and surveillance there is no proper guidance for vector control.

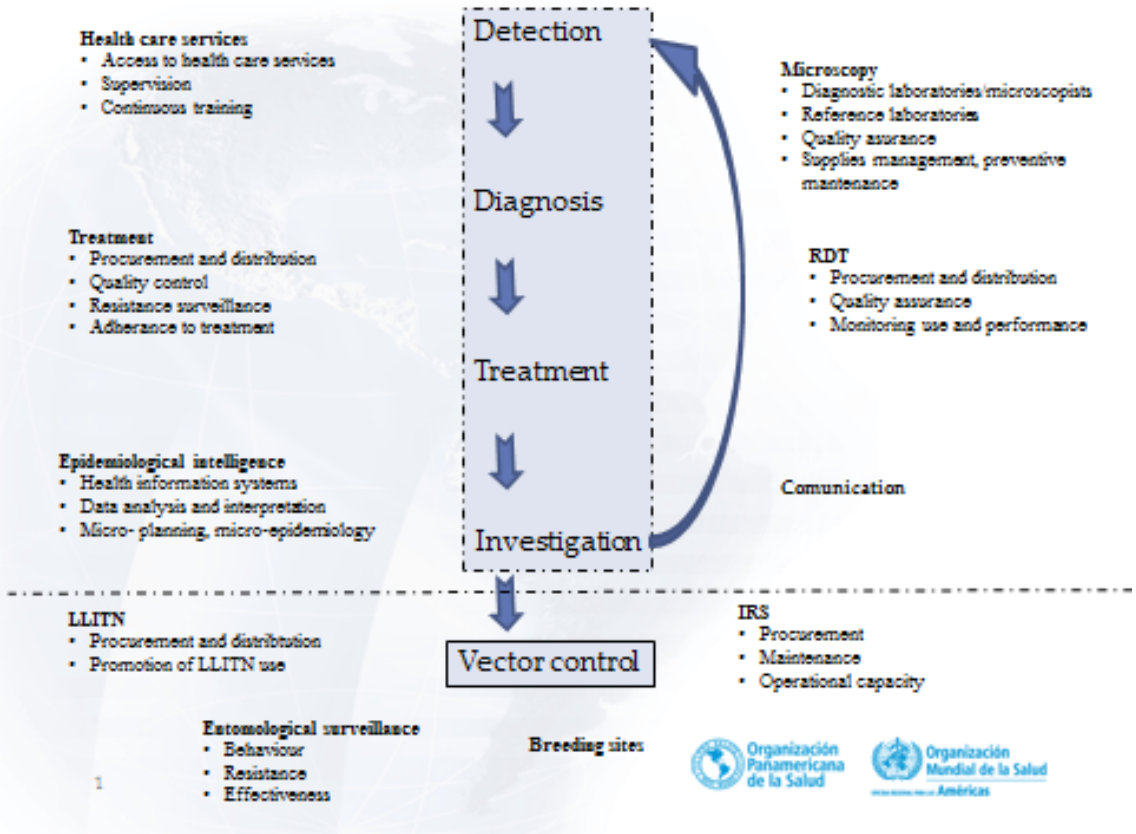

Figure 1. Chart flow DTD

Table 2. Components of the DTD strategy

Component	Action	Rational
Diagnose: within the first 2 days from the onset of symptoms (or within the first 7 days if few cases of malaria)	Diagnosis of suspect cases with microscopy or RDT	1. Reduction of the complications and death due to severe malaria, particularly from P. Falciparum. 2. Interruption of malaria transmission, particularly due to P. Vivax. P. *falciparum* gametocytes appear in the first 7-14 days from the first asexual cycle, generally after several days from onset of symptoms. *P. vivax* gametocytes appear in the 2-3 days from the first asexual cycle, generally right after the onset of symptoms (Annex 1).
Treatment: starts on the same day of the diagnosis	Start treatment including primaquine	
Case investigation: within the first 3 days from the diagnosis	Case is investigated and classified as indigenous, introduced or imported	1. Indigenous and introduced cases show active transmission. The classification of a case as locally acquired (indigenous and introduced) or imported will determine the response, the condition of elimination or the re-establishment of the transmission. 2. More than 72h to classify a case may involve a late response, allowing that other cases not diagnosed complete the incubation period and the generation of gametocytes or that the mosquitos' extrinsic incubation period is finalized.
Reactive case detection	Reactive case detection on household members and neighbours of the index case	1. Evidence of clustered local transmission, particularly in low transmission settings. 2. The new Malaria Surveillance, Monitoring and Evaluation manual (now in draft) states that "ACD is always conducted during epidemiological investigation of new cases and foci". 3. To avoid the infection of mosquitos from the same generation of cases than the index case, perpetuating the transmission. Those cases could already be in the community or might be in the incubation period. 4. Prevent the second generation of cases form the index case. Once mosquitos are infected, a 10 days extrinsic incubation period is needed to become infective. Once these mosquitos infect a human, 15 more days will be needed to complete the incubation period and become a second generation of cases. 5. If a case is classified as imported, the goal is to find other imported cases that shared with the index case the origin of the infection. Introduced cases should not be found until the 10 days extrinsic incubation period and the 15 days intrinsic incubation period are complete.

Table 2. How, when and who must implement the different components of the DTD strategy

	WHAT	**WHEN**	**HOW**	**WHO**
Diagnose	Few and many cases Diagnose febrile/atypical cases with microscopy and RDT	**2 days** from onset of symptoms (or within the first 7 days if few cases) (Annex 1)	Microscopy or RDT in health units, community agents, community volunteers, mobile points or active case detection	Health facility staff, microscopists, community agents, community volunteers
Treat	Few and many cases Start treatment	**Same day** of the diagnosis	Prescription of treatment according to national protocols	Health facility staff, microscopists, community agents, community volunteers
Case Investigation	Case classification Few cases Detailed case investigation (classified as imported, introduced or indigenous) Many cases Case classification as imported or locally acquired (specifying place of probable infection)	**3 days** from the diagnosis	Few cases (where?) Starts from the diagnosis, finished with the field visit Many cases (where?): Starts from the diagnosis and treatment	Few cases Starts with the diagnostic team and finishes with the epidemiology team. Many cases: Diagnostic team (Health facility staff, microscopists, community agents, community volunteers)
Reactive case detection	Case detection of febriles and asymptomatics around the index case. Consider co-workers. Few cases Several rounds within the first 7 days from the index case diagnosis, 30, 60 and 180 days (the later if P. Vivax) Many cases, no outbreak One round within the first 7 days. Many cases, outbreak One round within the first 7 days. Repeat rounds based on resources.	Few cases Start within the first 7 days from the index case diagnosis. Continue with rounds. Many cases, no outbreak One round within the first 7 days Many cases, outbreak One round within the first 7 days. Repeat rounds based on resources.	Few cases Microscopy or RDT. PCR when available*. Household members and neighbours. Define radius based on context. Many cases, no outbreak Microscopia or RDT. Household members Many cases, outbreak Microscopy or RDT. Household members and neighbours. Define radius based on context.	Few cases Response team: laboratory, Health facility staff, microscopists, community agents, community volunteers, ETV team. Many cases: Community agents, community volunteers, “visitadores de malaria “.

*Exceptional(1).

4 Approaches to operationalize the DTD strategy

At the national level: Development of the political, normative and technical capacity necessary to support the "diagnosis, treatment, investigation, response" at local level. Ensure that the supportive elements for the implementation of the "diagnosis, treatment, investigation, response" are in place, such as the integration of health services, diagnostic quality assurance systems, supply chain, drug resistance, RDT management, data management, notification processes, data analysis, provision and distribution of LLIN among others. Conceptualize the local process based on diagnosis as the core action and as essential input of analysis and decision-making at national level**.**

At the local level: Establish the operational model (health care network / surveillance) necessary for the "diagnosis-response" processes to be completed within the required times. It is proposed to develop a local, dynamic, micro-planning exercise, aimed at implementing the process of "diagnosis - treatment - investigation and response" at micro-operative areas (focus, cluster of foci).

5 Communication strategy

The DTD strategy needs to be clearly understood at local and national level, by all stakeholders. Providers need to be sensitized about malaria elimination and the importance of diagnosing and detecting more cases in the community. Users need to be aware about the situation of malaria and the importance of seeking care to get treatment and to reduce the transmission in the community. The continued use of LLITN/IRS should also be part of the message to stop the transmission of malaria.

6 DTD immersed in the monitoring & evaluation strategy of the malaria programs

If DTD becomes the core intervention of the malaria program, its importance needs to be reflected on the malaria monitoring & evaluation framework and the malaria related information processes. The Framework for Malaria Elimination and the GTS already recommends the inclusions of some key indicators related with the DTD process. A systematic monitoring and evaluation of the strategy must be ensured to guide the routine decisions in the field.

7 Plan for the development and implementation of the DTD strategy

a) Develop a technical document directed to sensitize the MoH, NMP and partners about the importance of using early detection, investigation and response as a core intervention in the National Plan and present key actions toward the implementation of this approach at country level:
    a. “Early detection, investigation and response” as a core strategy and documented evidence pointing to its impact on malaria control/elimination in the Americas.
    b. Problem areas impeding adoption of this strategy in the Americas.
    c. Operational and policy solutions to barriers in diagnosis and treatment of malaria.
    d. Details about supervision processes and key indicators for monitoring the strategy.
    e. Communication strategy aimed at field workers/MOH staff/others.

b) Review and update law and guidelines to guarantee malaria diagnosis and treatment by primary care and community health workers or alternatives for prompt diagnosis and treatment in remote areas
    a. Establish the problem by review of existing laws in MOH in all endemic countries regarding staffing.
    b. Review existing WHO/PAHO guidelines on health systems strengthening and recommendations.
    c. Propose policy solutions to problem areas found

    d. Produce a document/resolution for consideration of the PAHO directing council
c) Distribute the documents to the MoHs and Webex sessions to promote the approach
d) Workshops in selected countries for orientation of the malaria elimination/ control efforts, malaria elimination program structure and processes with special emphasis on “early detection, investigation and response” as a key intervention.
e) Support the countries on the updating of national guidelines and strategic plans including DTD strategy as core intervention:
    a. Relevant indicators (time between detection and confirmation, detection and investigation, detection and response, investigation and response operations)
    b. Supervision process.
    c. Communication campaign within the health system to include it as a key intervention.

Operational questions which need more work

1. How early is early for detecting and treating *P. vivax*?
2. When to start case investigations, how many cases per week/month such that it is not burdensome given the human resources available?
3. Defining “Response” viz a viz risk area – what interventions constitute response according to geographical area and actual malaria epidemiology/risk?

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Annex1. **Brief note on gametocytes**

P. Falciparum has an incubation period between 9-14 days. Mature gametocytes (responsible of the transmission of the parasite from the reservoir to the mosquitos) appear in blood between 7-15 days from the finalization of the first asexual cycle. Without treatment targeting mature gametocytes, those can stay in blood for 3-4 weeks, and therefore, infecting mosquitos. In the case of P. Vivax, mature gametocytes appear earlier (between 2-3 days from the first asexual cycle) and therefor its capacity to infect mosquitos (13).

The detection of gametocytes in blood will depend on the diagnostic method and the parasite density (13, 14). Submicroscopic parasitemia (detected by PCR but not from microscopy) is associated with the age of the patient, his/her immunity and the treatment received (15, 16). The infectivity of P. falciparum and P. Vivax submicroscopic infections has been reported in several studies conducted in Colombia, Burkina Faso, Thailand and USA (15, 17-19). Contrary to what we might believe, low transmission areas have a higher prevalence of submicroscopic infections (15, 16).

In low transmission areas with high treatment coverage such as the Americas, the WHO recommends the use of transmission blocking chemotherapy (primaquine) to the treatment of P. Falciparum. In the case of infections for P. Vivax or P.Ovale, the treatment includes 14 days of primaquine to eliminate hypnozoites and to avoid relapses. (7, 11).