Re treatment for the prevention of relapses in cases of *P.vivax*

1 Introduction

1.1 Rationale

Vivax malaria is still an important public health problem in the Americas [1]. Globally only around 4 % of all the malaria cases are caused by *P. vivax* but outside of Africa the proportion of *P. vivax* cases is 41 %. In the Americas 69 % of the cases are caused by *P. vivax*. For the elimination of malaria in the Americas proper strategies for the elimination of *P. vivax* need to be implemented.

A large part of the cases of malaria in the Americas is concentrated in specific risk groups who share common characteristics of having low social economic status and living in areas of difficult access. They are small scale miners, loggers, amerindians, populations in areas of conflict, peasants, harvesters of forest products and inhabitants of the periphery of urban areas of the Amazon region.

Another common aspect of the risk groups is their difficulty to adhere to the currently used schemes for first line treatment for *P. vivax* that per se, due to its long duration is already difficult to complete. The end result is an epidemiological situation where *P. vivax* malaria is probably maintained by a frequent number of relapses[2]. It is therefore essential to look for alternatives to increase the adherence and to maximize the effectiveness of the first line treatment.

This document (proposal) aims to provide conceptual and operational elements to analyze the utility of vivax re- treatment strategies as a part of more comprehensive intervention to reduce the relapse rate in order to decrease its burden and speed the elimination of malaria in the Americas.

It has to be made emphatically clear that the adequate framing of the problem, presupposes and includes an improvement of all the aspects that are important for the successful treatment of malaria cases, trained personnel, drug quality, early diagnosis and treatment, patient information, patient follow up, epidemiological surveillance according to WHO latest recommendations[3].

1.2 The context and importance of relapses for the control and elimination of *P. vivax*

P. vivax relapses are an important part of the burden of malaria and their minimization should be a priority for elimination of the disease. The number of relapses per individual vivax infection vary a lot but are of universal occurrence. Taking into consideration the lack of adherence to Primaquine or the insufficient dosages used in some countries we can make crude estimates of the size of the burden. In Tropical areas, if 60% of the patients are correctly treated with Cq plus Pq and 40% do not take the correct Pq scheme; using low end estimates of relapse we would have around 20% of the correctly treated relapsing in one year ; 12% of the total plus 40% of the not correctly treated 16% a total of 26% of relapses in one year. Since it seems that the percentages of relapses are even higher it indicates that there is a high probability that more than one quarter of the *P. vivax* cases are relapses that have an important impact in the perpetuation of the transmission. In areas with more than 50% of relapses most of the *P. vivax* cases will be relapses.

Manojit Roy, modeling data from NW India has estimated that with 31% relapse rate, a rate in line to the actual rates, anti relapse treatment of 65% of the infected would result in elimination in 10 years.[4]
A detailed study of the dynamics of *P. vivax* in the Peruvian Amazon[5] have encountered that 76% of the participants experienced one or more recurrent infections in two years follow up.
In Oaxaca, Mexico, secondary episodes occurred in 23.4% of all primary cases. There were limitations in the study that did not allow to discriminate relapse from new infections [15].

1.3 Limitations of the treatment with Primaquine

To achieve a radical cure (cure and prevention of relapse), a 14-day course of primaquine is required. Use of primaquine is recommended in all transmission settings. For frequent relapsing *P. vivax*, total doses of 3.5 mgbase/kg (0.25 mg/kg/day) are required for temperate settings and 7 mg base/kg (0.5 mg/kg/day) for tropical settings. Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach; it should always be taken with food.

Primaquine treatment targeting has important limitations:

- The efficacy of the treatment is related to its long duration with a certain dosage level. Short treatments and low doses are ineffective.
- It does not always kill all the hypnozoites therefore it does not avoid all the possible relapses.
- Primaquine should not be administered to anyone with G6PD deficiency in whom it causes hemolytic anemia.
- Primaquine is contraindicated in pregnancy, because the glucose-6-phosphate dehydrogenase status of the fetus would be unknown.

There are also frequent problems in the management of vivax cases that are summarized in the table bellow with and indication of possible solutions. (ref)

Figure 1: Problems in the management of vivax cases

Confounder	Ambiguity	Solution
Noncompliance to prescribed therapy	Adequacy of dose	Supervise of therapy
Emesis of dose	Adequacy of dose	Supervise of therapy and readminister vomited doses
Parasite tolerance	Resistance vs. tolerance	Determine baseline susceptibility or use 30-mg regimen
Chloroquine resistance	Recrudescence vs. relapse	Relapse can be discounted if recurrence is <1 month after the end of therapy; or use an alternative therapy (e.g. quinine)
Reinfection	Reinfection vs. relapse	Evaluate repatriated traveler or, if necessary, evacuate to an area where malaria is not endemic

1.4 Epidemiological and parasitological aspects of *P. vivax* relapse

There are some important epidemiological and parasitological aspects of relapse that are important to realize in order to design a strategy for the minimization of relapse within the current limitations that exist

- The number of sporozoites that are inoculated influence the number and the synchronicity of the relapses.

- There are evidences that a high proportion of the individuals that have had *P.vivax* do have latent hypnozoites that can be activated.
- Infections, including malaria; vivax or falciparum are factors that initiate episodes of relapse.
- In tropical areas the phenotypes present are both of short and long latency.
- In the natural infections it is common the presence of different *P. vivax* genotypes and in addition the relapses facilitate the recombination of genotypes.
- In endemic areas with multiple new infections the relapses can be caused by parasites that are distinct genetically to the previous infection, having been inoculate in a previous episode of vivax and being activated by the current infection[6].
- The decrease of vivax prevalence would decrease the number of "generations" of hypnozoites present in the liver. It has been demonstrated that the hypnozoites in the liver can be from different infections. The decrease in their numbers would potentially increase the efficacy of the future treatments with Primaquine[7].

1.5 Review of interventions targeting relapse

The strategy of targeting patients with previous vivax infection has been used for the elimination of Plasmodium vivax. In Brazil it was used in the "Bromeliad Malaria" in the South. The final push towards elimination was guided by serology. All individuals with a positive serology were retreated[8].

The Mexican malaria program adopted a combination of strategies to deal with the problem of relapse. In line with the results from epidemiological studies of repeated cases and households, the administration of a Single Dose Treatment (Tratamiento de Dosis UnicaTDU) was designed for all individuals living in the households where malaria had been detected, with the following scheme: one monthly dose for three months, followed by no treatment for three months, and then a monthly dose repeated for the next three months, and consecu- tively following this same scheme over a period of three years[9]. The scheme was referred to as TDU 3x3x3 (Scheme 1). The promoters of this scheme considered that TDU 3x3x3 was able to not only make parasites disappear from the blood during the following 24 hours, but it could also cover possible *P. vivax* relapses[9]. In according with the developers of the intervention, the objective of that treatment was to rapidly eliminate the parasitemias of typical fever cases and atypical (sub-clinical and sub-microscopic) fever cases, to eliminate the parasitemias of asymptomatic infections and to prevent parasitemias due to *P. vivax* relapses. Based on the knowledge that relapses from *P. vivax* strains in Mexico and Central America can occur up to three years later, consequently the treatment was extended to cover a three-year period[9]. The decision was made to include all households with confirmed transmission from the three prior years. Main concern about this policy was the use of incomplete treatments of Cq and Pq during the first and the subsequent courses of treatment. Recently the national malaria program in Mexico has suspended the use of 3x3x3 and presumptive malaria treatment ("tratamiento supresivo").

The Chinese National Program has implemented a strategy based on massive treatment of individuals in areas of seasonal malaria, done in the period preceding the malaria season. The strategy is described in detail in[10]. MDA in China was combined with re-locating the previous year's vivax cases and re-treating them with primaquine during the spring [16], this extensive use of primaquine has apparently lowered the amount of vivax malaria in China and it is considered unclear if this type of strategy could be applied in other areas of the world with different populations having a greater prevalence of G6PD deficiency. The use of retreatment is also mentioned in relation to the response of an outbreak in 2006, "*..In other areas, people with a history of infection during the past year and their families and neighbors were given pretransmission season treatment with chloroquine and primaquine for the radical cure, or 'spring treatment' of P. vivax malaria*[17]

By informal communication (Professor Gao Qi) the results of 2 relevant studies done in China in 1965 and 1966. the numbers showed in both studies approximately 1500 vivax patients treated either with standard of care (CQ + 8 days PQ at 22.5 mg daily) and the new intervention (same plus another course of 8 days PQ at 22.5 mg daily given just before the next malaria transmission season). The data showed a decrease of 50% in the intervention group receiving the repeated radical cure with PQ, and according to him these two studies were the basis to adopt this specific way of administering primaquine in some provinces of China.

In some studies conducted in China in 1960s with retreatment schemes of primaquine, an impact proportional to the amount to medicine used was found. When the total dose of primaquine was increased from 90 mg per person to 135 mg per person, with time between two doses being 15 days, the relapse rates decreased by 10.3% to 2.2% (Table 1 & 2 in Appendix 2) in 6 months. Comparable control group for 135 mg total dose showed a relapse rate of 11.8% at the end of 6 months. In another population level study conducted, the results were ambiguous. (Treatment scheme and regimen and other details still to be translated) (Tables 3 & 4 in Appendix 1).

2 Re treatment for the prevention of relapses in cases of *P.vivax*

2.1 Proposed strategy

Since in Tropical areas early relapses are common a second treatment right before the timing for the first relapses would decrease the occurrence of early relapses and also decrease the burden of hypnozoites in the liver. The liver can harbor hypnozoites from the current infection and from previous infections.

All *P. vivax* malaria cases in adults and children (see exceptions below) would receive a second course of treatment with the same complete treatment of chloroquine and primaquine, when they complete 30 days after the conclusion of the initial treatment (45 days after diagnosis) (60 days after treatment could be an alternative): Chloroquine at a total dose of 25 mg base/kg bw (initial dose of 10 mg base/kg, followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day and 14 days of Primaquine at 0.25 mg/kg bw per day. The second course of treatment will be offered to all the asymptomatic patients that received *P. vivax* treatment 45 days before irrespective of the compliance to the initial scheme. Symptomatic people at the moment of the second treatment will be previously tested with microscopy of RDT and in case of positivity treated according to the result for *P. vivax* or *P. falciparum* malaria. Symptomatic people with negative test will also receive the second course of treatment.

In according with WHO recommendations for tropical, frequent-relapsing *P.vivax*, in areas with high frequency of relapses, scheme of first and second course of treatment (re treatment) with higher doses of primaquine (0.5 mg/ kg bw per day) could be considered as an alternative scheme.

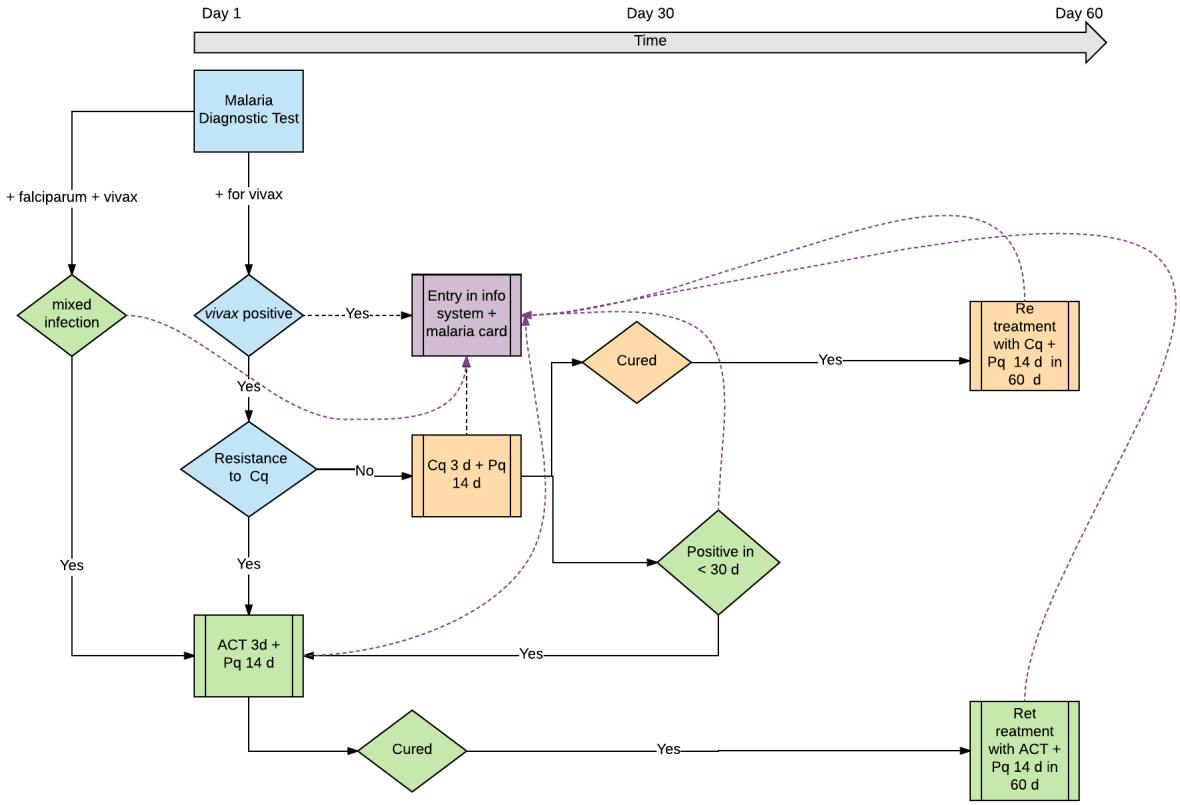
Exceptions for re-treatment:

- Women who are pregnant or breastfeeding (unless the child is aged >6 months and known not to be G6PD deficient)
- Infants aged <6 months
- People with G6PD deficiency
- People that refer have had reactions to the initial treatment

The timing of the re treatment should, if possible, be based on evidence about the locally observed timing of relapses. If no data is available 45 days after the beginning of treatment could be selected as a starting point (need references for the timing from different Latin American countries). In a study in Rondonia the mean time of the first relapse was 87.5 days.(Factors associated with recurrent Plasmodium vivax malaria in Porto Velho, Rondonia, Brasil, 2009)[6]. It seems that the timing of the first relapse varies geographically and it is recommended that the implementers should use the most appropriate time frame for their specific epidemiological setting based on the available information.

The safety and efficacy of primaquine against relapse when combined with any of the recommended ACTs for chloroquine-resistant P. vivax has not been established except with dihydroartemisinin-piperaquine.

Figure 2. Management of *P. vivax* cases with re-treatment



2.2 Considerations about re-treatment and G6PDd

The strategy of re treatments has the advantage of treating patients already exposed to primaquine, since they were treated before during the first course of treatment, and who did not present hemolysis due to

G6PD deficiency or other adverse reaction to treatment. However it should be considered that minor side effects could have occurred and not been detected before the second treatment. Proper patients counselling should be mandatory especially for the first course of treatment.

2.3 Re treatment of positivity within 30 days (recrudescence)

When vivax was treated with Quinine early relapses where observed approximately 3 to 4 weeks after the beginning of the treatment [6]. In Thailand approximately 50% of the vivax cases treated with Artesunate relapse within 28 days.

At the operational level it is reasonable to consider that individuals that have taken a full appropriate dose of Cq associated with Pq that are positive after treatment before 30 days should be considered possible cases of resistance to Cq and should be treated with a combination of ACT and a full 14 days treatment with Pq [11].

There are two options for the choice of ACT. The most simple option is to use the same combination being used for *P. falciparum*. The most effective, preferable option, is to use ACTs with long half life companion drugs [12] . The longer life of the companion drug would protect the individuals for relapses during their presence in the blood in effective dosages and in addition would prevent reinfection.

Two companion drug that has longer half life are Mefloquine and Piperaquine. The longer half life would also function as Post Treatment Prophylaxis, suppressing reinfections of both vivax and falciparum for a certain period of time (depending of the dose, pharmacokinetics properties of the drug and parasite susceptibility) [13].

Re-treatment policy should be also implemented in case of *P. vivax* malaria treatment with ACT. As well as with Cq, a second complete course of treatment, in this case with ACT + Pq would be administered 45 – 60 day (TBD) after the beginning of the treatment.

2.4 Pros and cons analysis of re treatment

Pros

- Individual benefits: less incapacity, anemia in children, suffering, etc
- Collective benefits: Reduce transmission associated to relapses and reduce risk of transmission reestablishment in elimination settings.
- Reduce the number of cases of malaria by *P. vivax* (by reducing the relapses, responsible for between 10 to 60 % of the cases depending on the strains and adherence to Pq)
- The introduction of re-treatment as a programmatic measure, could increase sensitization of heath team (at all levels) on the importance of relapses (primaquina dosification, prescription, adherence, role of relapses in perpetuation of transmission)
- Improve the tracking of patients, cluster of cases and hot spots with *P. vivax* malaria (T3)
- Could be complemented with other elements of a comprehensive strategy to improve *P. vivax* malaria management that includes the use of ACT in suspected cases of resistance
- Easily adapted to seasonal and work related malaria by *P. vivax*

Cons

- Operational issues: more effort to find patients, consumption of resources and working hours *(counterargument : high relapses rate, with recommended active and passive case detection and follow up efforts generates more operational efforts)*
- Ethical questions because the treatment of people than don't need it. (*similar situation with the use of Pq for P. falciparum, but in P. vivax re treatment is being used to treat a clinical condition which is the possible presence of hypnozoites)(Consider and argument that P. vivax case shouldn't be considered completed cured with the first course of treatment because uncertainly about the complete elimination of hypnozoites . Because the evidence of persistence of hypnozoites after the current P.* vivax schemes, *"complete P. vivax treatment" should require a second course of treatment)*
- The expectation that there will be a second treatment may reduce adherence to the first course of treatment. Adherence problem can also be an issue on the second course of treatment. (*It is a general problem of all treatments of vivax not specifically - A counterargument may be that even adherence might be better since the person is not nauseated and sick from P. vivax symptoms)*
- More risk of adverse effects that with only one course of treatment (*No because the patients have had the same scheme before - it is re treatment with the same scheme*). Minor side effects during the first course of treatment could not be noticed or reported by the patient who will be exposed to a second course.

2.5 Operational aspects for re treatment

During the administration of the first course of treatment patients need to be properly oriented about the necessity of the second course of treatment and an appointment with a defined date for the administration of the retreatment must be agreed. According to the local conditions, the health services can identify different alternatives to operationalize the administration of the second course of treatment: implementation of a card for follow-up (malaria card), telephone notification to the cases to return to the second course of treatment, text messages by mobile telephony, active search of cases in locations where the low number of cases allows.

In situations of low number of cases where the local health care model allows, the monitoring of *P vivax* cases for re-treatment could help to promote a greater dedication of the local team to work with more depth on hot spots and the characterization of clusters of malaria cases, contributing to the understanding of local transmission dynamics.

In epidemiological setting where malaria is predominantly seasonal or work related, the seasonal or working schedule could be used as guide to when to re treat in order to impact the transmission. This is particularly interesting for the case of malaria in the Brazil Nut harvesters in the Amazon or for Miners entering and exiting mining areas where they had only access to self treatment. In such circumstances, people who have had malaria in the previous season could be easily captured for re-treatment administration upon entering or leaving the transmission zone

Malaria card: Even in the countries where the malaria information system stores individual data from all the patients diagnosed and treated, the information is not readily available to the individuals delivering the malaria services in the field. When a health professional or a community health worker has to treat a patient, frequently it does not have immediate access to the history of malaria of the individual.

For the increase in the impact of the proposal of re treatment the previous history of malaria is an important information. A malaria card containing information about the latest episodes and their treatment

facilitates the management of the re treatment of cases. The card can also be used as a research tool to measure the quality of the malaria data base and for inference of proxies of early relapses.

Efforts to increase the adherence

Since all the different treatments of *P. vivax* that target hypnozoites are currently of long duration it is crucial to maximize the adherence. WHO recommends that Primaquine should always be taken with food. The improvement of the adherence should include, whenever possible, the use of directly observed treatment (DOT). Directly observed treatment should be important in urban areas and in rural areas where the access to services is easy, like in small villages with malaria health workers or treatment services and mandatory in some settings. In rural areas with increasing difficulties of access adaptations to a full DOT should be made. It should be emphasized that the strictly supervised treatment should not compromise the full treatment. When the implementation of supervision is no adequate, the full treatment should be given to the patients with strong counseling about the need to complete the full course. Semi-supervised treatment strategies can be an alternative approach in some settings.

The treatment can be optimized with the use of graphical prescriptions and pre packaged blistered treatment with appropriated dosages for different weight/age groups. Graphical material and radio spots should be developed and used to explain the crucial importance for the adherence to full treatment. The use of images should be stimulated in areas with low literacy rate. Professional advice of communication specialists is necessary for the development of the material. It should be done in a dialectical relationship with the community, with their participation in the different steps of the development. A system of control of ”cure” would also be a plus, helping to evaluate the level of adherence, creating a stronger link with the patients and possibly unraveling some of the causes of non adherence potentially remediable. The use of cell phones to contact the patients could be an alternative in many situations.

Programmes may be reluctant to strongly promote full adherence for fear of inadvertently encouraging continuation of therapy in patients experiencing symptoms of acute haemolytic anaemia. Patients should be advised of the possible risks and informed that they should stop the drug if they become ill or their urine becomes red or black [14] .

3 Road map for implementation of Re-treatment policy

GMP comments on the proposed scheme (re-treatment for all *P. vivax* cases) is that it should be considered as research project with careful evaluation in terms of efficacy in comparison with the recommended standard of care in the country.

1. Development of technical document for analysis by TAG (meeting in June 2017)
2. Final technical document with recommendations
3. Elaboration of protocol and planning pilot implementation
   Since the main objective of the change of strategy is the collective impact on the burden of *P. vivax* in the population, it is proposed to pilot it at the population level using municipalities. The incidence of the disease and of the relapses as outcomes at municipal level. Comparisons can be made in time, before and after the intervention and between municipalities with and without the intervention.
4. Implementation in demonstrative areas
   - Selection of demonstrative areas
   - Training

- Implementation of adjustments in information system
- Retreatment implementation
- Evaluation

5. Evaluation by TAG. General recommendation to countries
6. Implementation at a higher scale

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5 Appendix

RESULTS FROM SOME STUDIES IN CHINA (CIRCA 1960s)

Table 1: Dose Regimens by Group Type

Group type	Group number	Experimental protocol	Dose for one regimen (adults, mg)				Double regimen (Days between regimens)
			Primaquine (base value)			Chloroquine (base value)	
			Daily dosage	# days medicated	Total amount		
Experimental group	1	135mg Primaquine double regimen	22.5	6	135	600	15
	2	112.5mg Primaquine double regimen	22.5	5	112.5	600	15
	3	90mg Primaquine double regimen	30	3	90	600	15
Control group	4	135mg Primaquine single regimen	22.5	8	180	600	-
	5	135mg Primaquine single regimen	30	3	90	600	-
	6	600 mg Chloroquine double regimen	-	-	-	600	20

Table 2: Results- Relapse Rates by month by therapy regimens

Group type	Group number	Number of cases	Relapse rate after taking medication by month (%, cumulative)					
			1	2	3	4	5	6
Experimental group	1	137	0	0	0	0	2.2	2.2
	2	125	0	0	0	0	1.6	3.2
	3	126	0	0.8	1.6	4	5.6	10.3
Control group	4	153	0.7	2	3.3	6.5	8.5	11.8
	5	68	0	1.5	4.4	13.2	25	32.4
	6	136	1.5	11.8	25	39.7	52.9	66.2

Table 3: Number of malaria cases by month in XXX county, China in 3 years.

Year	Number people surveyed	Number people falling ill	Illness rate (%)	Number people falling ill by month											
				Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec
1959	974	425	43.6	0	1	2	10	38	69	176	105	21	3	0	0
1960	974	600	61.6	0	3	6	21	54	103	266	112	21	5	4	5
1961	1029	219	21.3	8	21	27	25	25	18	34	27	21	6	7	-

Table 4: Results from blood surveys conducted before and after retreatment with antimalarials

Age group	Early May (before antimalarials)			Early August			Early October		
	Number tested	Number Positive	%	Number tested	Number Positive	%	Number tested	Number Positive	%
0-14	155	76	49	143	64	44.7	142	73	51.4
15 years and up	154	25	16.2	168	18	10.7	193	26	13.5
All ages	309	101	32.7	311	82	16.4	335	99	29.5

Table 2	[unlabeled]						
Treatment program/plan	Number of "carrier" cases treated	Observation period (number months)	Relapse rate (%)		Reaction rate (%)		Break between two treatments
			Protozoan disease	Symptoms	Cyanosis	General	
Primaquinoline 21(	71	3	0	0	19	26	4
Primaquinoline 18(	193	3	0.5	0	1	15	1
Primaquinoline 12(	91	5	3.3	0	0	2	half
Primaquinoline 21(	83	4 and a half	6	1.2	1.2	17	-
	carrier means, you can detect parasite in the blood sample						