SEROLOGICAL SCREEN AND TREAT TRIAL FOR *PLASMODIUM VIVAX*: A PROOF-OF-CONCEPT TRIAL IN EASTERN INDONESIA

Sponsorship:

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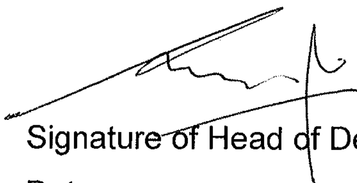

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Signature of Principal Investigator

Date 21th August 2019

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1. TITLE OF RESEARCH PROTOCOL

Serological screen and treat trial for *P. vivax*: a proof-of-concept trial in eastern Indonesia

2. INVESTIGATORS AND INSTITUTIONS

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Funding: Australian Government National Health and Medical Research Council

3. Study Synopsis

Study title	SEROLOGICAL SCREEN AND TREAT TRIAL FOR P. VIVAX: A PROOF-OF-CONCEPT TRIAL IN EASTERN INDONESIA
Regulatory Status	Investigational – individually randomised phase IIb proof-of-concept trial
Investigational Product and Route	Multi-antigen sero-diagnostic test for measurement of *P. vivax* antibodies in plasma from finger stick as a means to detect hypnozoite carriers for treatment
Study Objectives	***Primary objective:*** To determine the efficacy of a Serological Screening and Treatment (SSAT) intervention for the prevention of recurrent *P. vivax* malaria. ***Secondary objectives:*** (I) To evaluate the performance of a point-of-care (POC) anti-*P. vivax* antibody detection test relative to Luminex (MagPix). (II) To evaluate safety of high dose PQ administration in schoolchildren. (III) To evaluate the accuracy of Sahli's method and Standard G6PD (SD Biosensor Inc., Suwon-si, Gyeonggi-do, Republic of Korea) relative to HemoCue for haemoglobin measurement. (IV) To estimate the sensitivity and specificity of a microscopic diagnosis of malaria by blood sample from skin (ankle) relative to standard finger stick microscopic and PCR. (V) To measure duration of gametocyte in the blood samples of the skin of the ankle and finger prick. (VI) To estimate the sensitivity and specificity of magneto-optical hemozoin detection by Gazelle® (Hemex Health, USA) relative to standard finger stick microscopic and

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PCR.
(VII) To analyse hemoglobinopathies in schoolchildren using HemeChip by Gazelle (Hemex Health, USA)

Primary study endpoint: the proportional reduction of P. vivax incidence by PCR in children serologically screened relative to those receiving routine care during 9 months of active follow-up.

Secondary endpoints:

(I) Difference in the time-to recur of P. vivax by PCR in SSAT and control arms.
(II) Difference in the number of recurrent P. vivax by PCR in SSAT vs. control arms.
(III) Difference in the incidence of recurrent symptomatic P. vivax by LMF in SSAT vs control arms.
(IV) Seroconversion rate before and after intervention in SSAT and control arms.
(V) Sensitivity and specificity of POC antibody detection test vs. gold standard Luminex assay.
(VI) Adverse event (AE) and Severe Adverse Event (SAE) of high dose PQ in schoolchildren.
(VII) Hb level in Sahli’s method, Standard G6PD (SD Biosensor Inc., ROK), and Gazelle® (Hemex Health, USA), in comparison with HemoCue (HemoCue AB, Angelholm, Sweden).
(VIII) Sensitivity and specificity of microscopic examination to detect parasitemia from the shallow skin vasculature of the ankle (light microscopy-skin/LMS) compared to standard microscopic (light microscopy-finger/LMF) and PCR.
(IX) Mean duration time of gametocyte in LMS and LMF
(X) Sensitivity and specificity of magneto-optical hemozoin detection (MOD) compared to standard malaria detection and PCR.
(XI) Hemoglobinopathy rate in schoolchildren
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<tr><td>Study Site</td><td>Malaka regency, East Nusatenggara province, Indonesia.</td></tr>
<tr><td>Study Duration</td><td>January 2020 to January 2021</td></tr>
<tr><td>Number of Participants, Randomisation, and Treatment</td><td>
A total of 800 elementary schoolchildren and their households living at Malaka, West Timor.

Randomization and Treatment:

• Participants will be randomized into two groups: (1) intervention group (SSAT; n=400) and (2) routine care group (n=400). All participants will be tested for presence of antibodies to a validated panel of P. vivax antigens and
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	standard finger stick microscopic. • In the SSAT arm at enrollment, only children who are *Pv* seropositive and/or LMF *Pv*/*Po* positive receive supervised high-dose primaquine (1mg/kg for 7 days) regardless of their symptoms. All blood slides will be processed and read directly after blood collection. Then treatment will follow if positive. Sero-positive children, on the other hand, will commence treatment after the result is available (approximately 1 week). Symptomatic or asymptomatic LMF positive for *Pf*/*Pm* will be treated according to current national guidelines. • In the control arm at enrollment, only children who are symptomatic and LMF Pv/Po positive will receive supervised high-dose primaquine (1mg/kg for 7 days). • In both arms at every other timepoint, symptomatic LMF positive children will receive treatment in accordance with national guidelines (unsupervised). • In both arms at the final timepoint, LMF will be conducted on all children and if positive will be treated according to national guidelines. • As blood schizontocides, DHA-PP for 3 days will be given according to body weight (national guidelines).
Inclusion and Exclusion Criteria	**Inclusion:** • resident of study area and attending selected elementary school in Grade 1-5 • no evidence of health condition that would interefere with study participation • assent of child and documented parental informed consent **Exclusion:** • G6PD deficiency as determined by SD Biosensor quantitative determination of <70% G6PD activity (male: <4 U/g Hb, female: <6 U/g Hb). • Haemoglobin < 9 g/dL
Analysis plan and sample size calculation	The study is designed to show a superiority of SSAT vs. routine care for the prevention of recurrent *P. vivax* infections. The primary study endpoint will be the proportion of children with recurrent *P. vivax* by PCR during 9 months of follow-up. Secondary endpoints include time-to-first *P. vivax* recurrence as well as incidence of symptomatic

	P. vivax. SSAT intervention is expected to reduce incidence of *P. vivax* in comparison to standard care. With the previous prevalence rate of 20%, we will have a power of >90% to detect a significant difference with the sample size of 350 children per group. We will anticipate the exclusion of 15% by recruiting 400 children per group.
Lay Summary	This study evaluates an experimental serological diagnostic technique intended to identify people at high risk of having dormant malaria parasites in their liver. The findings will assess the ability of this sero test to identify those carriers. 800 children living in eastern Indonesia will be individually randomised to the experimental serologic test or routine care. Children in the serological diagnosis arm will be screened for the presence of antibodies to a previously validated panel of malaria antigens optimized for sensitivity to infection during the prior 9 months. Furthermore, they also will be screened by microscopy. If positive by either test, they will be treated for that malaria infection. Children assigned to routine care will be screened by microscopic examination and treated when they show or have history of symptoms in the last 3 days. After initial screening and treating according to diagnostic technique, all children will be actively followed for 9 months with PCR detection every 4 weeks. During 9 month follow up, all children becoming acutely ill and proven to be positive for malaria by microscopy will be treated, in addition, all asymptomatic children will be treated at the final time point. POC serology test will be performed at baseline and final timepoint on all children in both arms. The results from this POC serology test will not be used to inform diagnosis or treatment in any way at either of the timepoints. None of these blood samples will be collected by venopuncture but instead minimally invasive lancet devices will be used.
Sero-diagnostic test	Quantitative measurement of antibody titres to a panel of 8 specially selected *P. vivax* antigens in study subject plasma samples using a Luminex MAGPIX® bead array system. This testing will be done at the Eijkman Institute in Jakarta. The results will be generated in no

	more than 7 days.

4. Background and Rationale

In order to eliminate *P. vivax* within proposed timeframes (i.e. by 2030) it is essential to directly target the 'silent' hypnozoite reservoir sustaining *P. vivax* transmission. Modelling studies show that population mass-screening and treatment (MSAT) of parasite positive individuals will not have a persistent effect on *P. vivax* transmission even if screening is done by PCR (1). Cohort studies conducted in Thailand and Solomon Islands demonstrate that qPCR at a single timepoint detects only 25-30% of all individuals who subsequently have recurrent *P. vivax* infections in the following 10-12 months.

While MDA including an anti-hypnozoitocidal drug such a primaquine is predicted to be highly effective against *P. vivax*, this is logistically challenging: G6PD testing is required to prevent the potentially severe haemolysis associated with 8-aminoquinoline treatment in G6PD-deficient people and directly observed treatment (DOTs) is needed to assure treatment success. However, between 70 – 90% of people living in low- transmission and pre-elimination settings do not experience any *P. vivax* infections over a 12 months period and are thus highly unlikely to carry hypnozoites and would be exposed to the risks of primaquine treatment, without any of its benefits. In short, whilst MSAT misses up to 75% of all individuals requiring treatment (2), MDA "over-treats" up to 90% of the population.

Effective screening with a *P. vivax* sero-diagnostic test may address this gap. As all non-temperate *P. vivax* strains cause a primary infection followed by a primary relapse within 4 weeks to 9 months, a validated panel of serological exposure markers (SEMs) are expected to identify most individuals that potentially harbour hypnozoites (3). SSAT with our novel antigens is therefore predicted to be superior to routine diagnosis and treatment in preventing recurrent *P. vivax* infections and thus reducing *P. vivax* transmission.

Further to the idea of identifying silent and latent/subpatent infections, this project explores the possibility of the shallow vasculature of human skin sequesters and sustains infectious gametocytes of the plasmodia. Gametocytes are the only stage able to continue living inside the mosquito body to undergo a sexual reproduction. Therefore, anopheline feeding time is a critical phase for survival of

this species. However, a typical anopheline has a proboscis about 300 microns in length, in which its protrudable feeding parts are housed. Its feeding depth would certainly not exceed that reach and would probably be considerably shorter. Gametocytes must be near to the surface of the skin in order to infect anopheline mosquitoes (i.e., survive to reproduce). We know that microscopically sub-patent volunteers very often infect anophelines allowed to feed on their skin while being 5-times less likely to infect anophelines simultaneously allowed to membrane feed on a sample of venous blood (4). Other studies have reported very similar findings (5). Those studies corroborate earlier reports of sexual stage gametocytes in skin vasculature occurring at 3-fold higher numbers relative to peripheral blood (finger stick) (6). We hypothesize that gametocytes observed in finger stick samples of vasculature well below 300 microns (typically about 600 microns) rapidly transit that compartment on their way to longer-term sequestration in the microvasculature of the uppermost dermis, just below the epidermis. That is precisely where they need to be, and a protracted residence in that compartment may explain their virtually dormant metabolic state (7), much like that of latent hypnozoites in hepatic cells (8). Human hosts experiencing exceptional and fleeting states of infection like symptomatic patency may go on to host silent, stable, and durable infections of the shallow skin microvasculature by sexual plasmodia. Moreover, these sexual stage should be distributed in such a way to increase the odds of being taken up by the mosquito, i.e. feet and ankle, where anopheles shows the strong preference (9). There is also possibility they have circardian rhythm (10).

The current standard for the diagnosis of malaria in ill patients or healthy residents of endemic areas perform poorly at parasite counts below 50 per microliter blood (11,12). Nucleic acid-based diagnostic techniques offer relatively much greater sensitivity (i.e., from approx. 1/uL to 1/mL), but these assays cannot be done at point-of-care (a sophisticated laboratory and equipment are required), takes days or weeks to complete, requires highly specialized training, and imposes prohibitive direct costs (13). Malaria research leaders and communities identified and acknowledged the need for a point-of-care diagnostic tool with PCR-like sensitivity as a critical need (14,15). The simple, practical, and inexpensive approach to a bedside diagnosis within an hour would effectively empower mass screening and treatment as a means of interrupting malaria transmission in endemic communities, whereas today that practice is futile due to the weakness of diagnostic technology

and the epidemiological dominance of clinically silent sub-patent parasitemias (5). In search of point-of-care diagnostic test, potential of hemozoin as detection tool will also be explored. Previous studies employing magnetic field to capture hemozoin have demonstrated strong preference for gametocytes and increased sensitivity for detection of *P. vivax* asexual stages (16,17). This project will investigate the performance of a point-of-care diagnostic tool employing magneto-optical detection in ankle/feet area which can provide further evidence for the skin reservoir hypothesis.

Moreover, previous studies have demonstrated a higher rate of hemoglobinopathy in malarious areas due to evolutionary pressure (18). Apart from its controversial benefit against malaria, this trait brings substantial health problem to individuals carrying it. This project will investigate the rate of hemoglobinopathy in schoolchildren.

Lastly, radical cure of *P. vivax* is crucial part to stop malaria transmission, therefore compliance and safety monitoring of currently available hypnozoitocidal PQ is essential (19). This project will contribute evidence towards the development of guidelines for high dose PQ in Primary Health Center to establish its use in national scale. The utilisation of cheap and widely used Sahli's Hb measurement for such purpose will be evaluated as well.

5. Objectives and Endpoints

5.1. Primary objective: to determine the efficacy of a Serological Screening and Treatment (SSAT) intervention for the prevention of recurrent *P. vivax* malaria.

5.2. Secondary objectives:

1. To evaluate the performance of a point-of-care (POC) anti-*P. vivax* antibody detection test relative to Luminex (MagPix).
2. To evaluate safety of high dose PQ administration in schoolchildren.
3. To evaluate the accuracy of Sahli's method and Standard G6PD (SD Biosensor Inc., Deogyeong-daero, Korea) relative to HemoCue for haemoglobin measurement.

4. To estimate the sensitivity and specificity of a microscopic diagnosis of blood by sample from skin (ankle) relative to standard finger stick microscopic and PCR.
5. To measure duration of gametocyte in the blood samples of the skin of the ankle and finger prick.
6. To estimate the sensitivity and specificity of magneto-optical hemozoin detection by Gazelle® (Hemex Health, USA) relative to standard finger stick microscopic and PCR. To analyse hemoglobinopathies in schoolchildren using HemeChip by Gazelle (Hemex Health, USA)

Primary endpoint: the proportional reduction of *P. vivax* incidence by PCR in children serologically screened relative to those receiving routine care during 9 months of active follow-up.

Secondary endpoints:

(I) Difference in the time-to recur of *P. vivax* by PCR in SSAT and control arms.

(II) Difference in the number of recurrent *P. vivax* by PCR in SSAT vs. control arms.

(III) Difference in the incidence of recurrent symptomatic *P. vivax* by LMF in SSAT vs control arms.

(IV) Seroconversion rate before and after intervention in SSAT and control arms.

(V) Sensitivity and specificity of POC antibody detection test vs. gold standard Luminex assay.

(VI) Adverse event (AE) and Severe Adverse Event (SAE) of high dose PQ in schoolchildren.

(VII) Hb level in Sahli's method, Standard G6PD (SD Biosensor Inc., Deogyeong-daero, Korea), and Gazelle® (Hemex Health, USA), in comparison with HemoCue (HemoCue AB, Angelholm, Sweden).

(VIII) Sensitivity and specificity of microscopic examination to detect parasitemia from the shallow skin vasculature of the ankle (light microscopy-skin/LMS) compared to standard microscopic (light microscopy-finger/LMF) and PCR.

(IX) Mean duration time of gametocyte in LMS and LMF

(X) Sensitivity and specificity of magneto-optical hemozoin detection (MOD) compared to standard malaria detection and PCR.

(XI) Sensitivity and specificity of Standard G6PD (SD Biosensor, Inc., Deogyeong-daero, Korea Korea) compared to CareStart G6PD RDT (Access Bio. Inc., New Jersey, USA).

(XII) Hemoglobinopathy rate in schoolchildren

6. Methodology

6.1. Study site and Participants

The study will be conducted at mesoendemic area of Malaka regency (124º 38' 32.17" – 125º 5' 21.38" E and 9º 18' 7.19" – 9º 47'26.68" S), West Timor, Indonesia. Formerly known as part of Belu regency, Malaka regency was established in 2012. At north it is adjacent to Belu regency, at south Timor sea, at east Democratic Republic of Timor Leste, and at west South Central Timor and North Central Timor. This area has 20 Primary Health Center (Puskesmas) and one hospital. Most of these Puskesmas (14) reside in malaria endemic areas. The highest Annual Parasite Incidence (API) were reported from Puskesmas Alkani (21.43), Weoe (4.79), and Tunabesi (4.46) in 2018. Working area of Puskesmas Weoe includes 15,652 residents and 16 elementary schools, in contrast with Puskesmas Alkani which only has 6,111 residents and 4 elementary schools. Therefore, we propose to conduct the study at working area of Puskesmas Weoe.

6.2. Schools selection and demographic census

Before the start of the study, a serological survey will be conducted to select the schools. Blood samples will be collected from 20 randomly selected children from each school in Weoe for serological screening with Luminex. Only schools with sero-prevalence of 30-70% will be eligible for enrollment. Maximal number of selected schools will be 6-7, where 800 children will be individually randomized. Demographic census will be conducted during which name, date of birth/age, gender, village, hamlet, parents/guardian will be recorded (census form). Photograph will be taken from each participants to ensure the correct identification for treatment administration and follow up.

6.3. Study design and study overview

The study design is a randomized controlled trial with serological screening and treatment as the intervention. Selected schoolchildren will be allocated into two study arms: (1) serological screening and treatment (SSAT), and (2) routine care as control arm.

At enrolment, in the SSAT arm, individuals found *P. vivax* positive by either serological (Luminex) or Giemsa stained microscopic examination regardless of the symptoms will receive supervised treatment (direct observation) with high dose PQ (daily 1 mg/kg BW) for 7 days (*Po*=*Pv*). In the control arm, only symptomatic individuals found *P. vivax* positive by Giemsa stained microscopic examination will receive the same regimen (*Po*=*Pv*). In addition, in the treated children of both arms, dyhidroartemisinin-piperaquine (DHA-PP) will be given as blood schizontocide according to body weight. All other species (*P. falciparum, P. malariae*) found by Giemsa stained microscopic examination will be treated according to national guideline. Serological examination will be performed by Luminex (done at Eijkman, Jakarta) and point-of-care (POC) antibody detection using rapid test on site

Follow up will be perfomed monthly for 9 months. During this period, 400 µL of finger pricked blood samples will be collected from all children in both arms. These samples will be tested for malaria presence by PCR which will be done at EOCRU, Jakarta. However, children with clinical symptoms (body temperature of $\geq$37.5^{o}C and/or history of fever within 3 days), will be examined by Giemsa stained microscopy on site, and treated if positive (any species) according to national guideline (unsupervised).

At the last follow up, a mass blood survey will be conducted to both arms for *Pv* serological test, LMF, and PCR. Those found positive by LMF for any species will be treated regardless of their symptoms.

6.4. Inclusion and exclusion criteria

Inclusion:

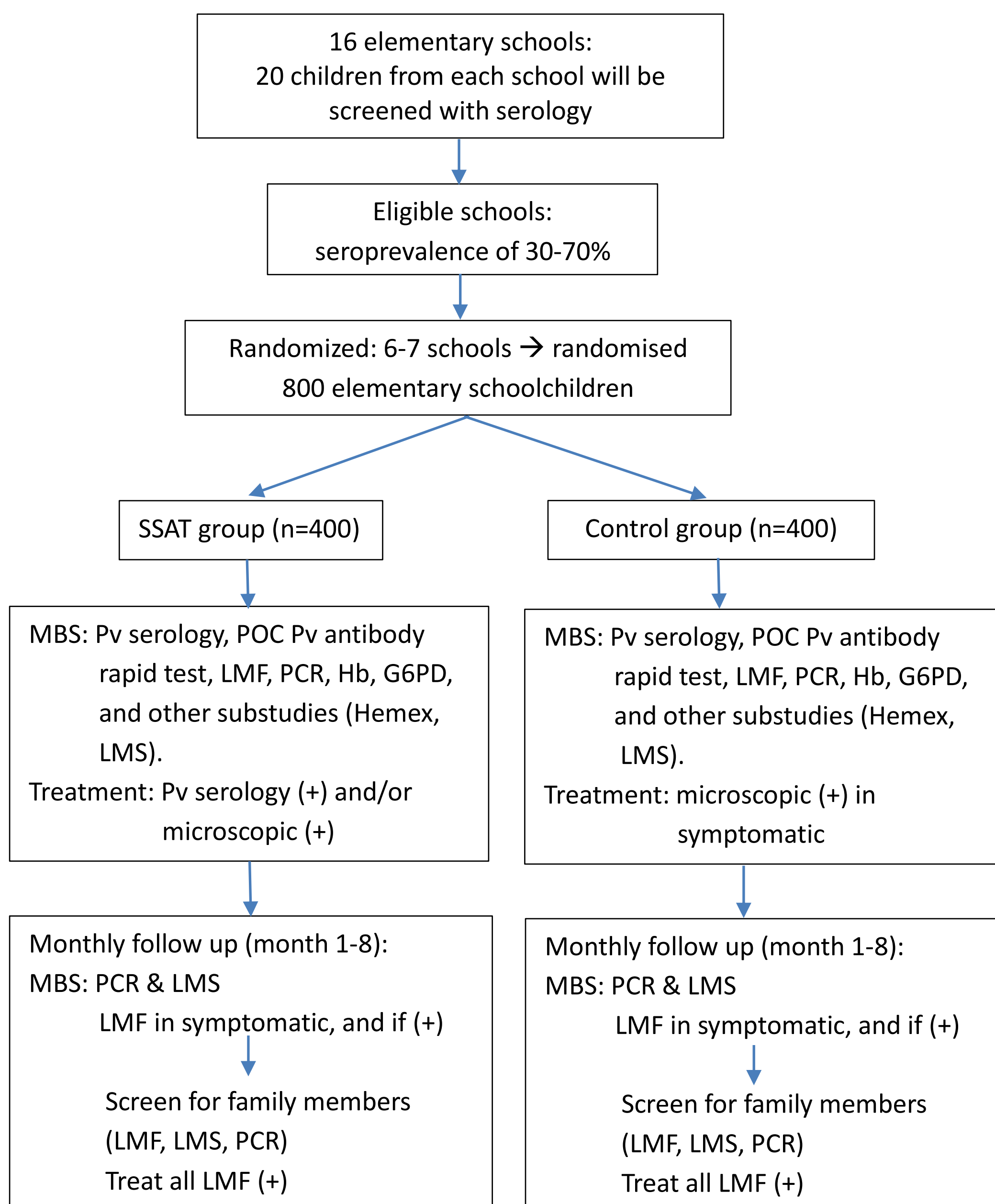
- resident of study area and attending selected elementary school in Grade 1-5
- no evidence of health condition that would interefere with study participation
- assent of child and documented parental informed consent

Exclusion:

- G6PD deficiency as determined by SD Biosensor quantitative determination of <70% G6PD activity (male: <4 U/g Hb, female: <6 U/g Hb).
- Haemoglobin < 9 g/dL as determined by HemoCue.

These subjects will be referred to PHC for treatment.

Figure 1. Study Framework



Staff of Primary Health Center (PHC) of Weoe will be gathered and explained about the study plan. They will be asked to assist our team in the field activity. Then, head and teachers of selected schools will be gathered and explained about the study plan. Finally, meetings which invite parents/ legal guardians of the selected children will be organized 2-3 weeks prior to the study to obtain informed consent from every child. During these meetings the study will be explained to parents/legal guardian of the schoolchildren. At the end of activity, there will be a discussion session. The explanation is arranged in a seminar form by the trained investigator team with ample time of question and answer session. At the end of discussion, informed consent form will be distributed for each parent. They have 1 week to consider whether they will participate in our study or not. The signed informed consent form will be collected by the class teacher and field team.

Trainings will be given for the personnel of PHC that involved in the study, school teachers and health care volunteers. Explanation will be given in details with standard operating procedure (SOP) provided on their duty of each group to facilitate the process of data and sample collection.

6.6. Enrolment

During enrolment, finger pricked blood samples will be collected from all participants. At this activity, body temperature will be recorded using infrared thermometers, body weight will be scaled, history of fever within 3 days and taking antimalarial drugs within last 2 weeks will be recorded. Finger pricked blood samples will be made into malaria blood smear and tested by POC Pv antibody rapid detection. A total of 400 µL will be collected into microtainer tube containing EDTA to be sent to field laboratory, and separated for various tests, e.g. serology (Luminex), PCR, Hb, G6PD, and Hemex.

All participants' blood samples will be tested for the presence of antibodies to a validated panel of *P. vivax* antigens (using a gold-standard laboratory test) at the Eijkman Institute for Molecular Biology, Jakarta. Blood samples will be shipped every 2 days, and the result will be reported to the field team within no more than 1 week.

On site, blood slides will be Giemsa stained (see 7.3) and assessed by microscopy with 1000x magnification. Screening for G6PD deficiency will be performed quantitatively by Standard G6PD (SD Biosensor, ROK) with the cut off of 4 U/g Hb (male) or 6 U/g Hb (female) on the same day of blood collection. Hb level will be measured using HemoCue and Hb Sahli. Other substudies (LMS, hemozoin detection, hemoglobinopathy) will also be conducted (see 6.10)

6.7. Follow up and end of study

First follow up will be conducted one month after the last dose of PQ treatment administration. Every visit, blood samples from finger prick and skin (LMS) will be taken. Unlike in the 16ecurrent process, malaria blood smear will be made only from participants with clinical symptoms suggestive for malaria. If positive, they will be treated. All treatment during follow up period will be provided by PHC staff according to national guideline (Appendix B table 1 & 3).

At the end of study (month-9 of the follow up), mass blood survey will be conducted to collect finger prick blood (LMF, Pv serological test, qPCR) and LMS. Seroconversion will be assessed. All LMF (+) will be treated as above.

All study subjects will be followed until the end of study (month 9) although they cannot fulfil the complete schedule.

6.8. Antimalarial treatment

Treatment will be provided based on body weight (Appendix B). Blood schizontocide for any species is 3-day DHA-PP (daily dose: 6-10 kg=1/2 tab, 11-17 kg=1 tab, 18-30 kg=1 ½ tab, 31-40 kg=2 tab). For *P. vivax* subjects, the administration of high dose primaquine will be started at the same day of DHA-PP treatment (see Table 2 appendix B for PQ dosage). Meal should be given prior to PQ administration daily. The total dose of PQ should be completed within 10 days as the window period. Subjects who does not complete the dose will be recorded, and still be followed until end of study. Monitoring of Hb level and hemoglobinuria for treated subjects will be done daily before and during treatment by Hb measurement using HemoCue (HemoCue AB, Angelholm, Sweden) and urine test (inspection and urinalysis) in order to detect hemolysis. Primaquine will be stopped if hemolysis

occur, the subject will be observed for daily vital sign, Hb level, and urine until recovery. If worsen, the subject will be referred to the hospital for further management, and given blood transfusion if necessary (Appendix E).

Primaquine for *P. falciparum* will be given as single dose 0.25 mg/kgBW (6-17 kg=1/4 tab, 18-30 kg=1/2 tab, 31-40 kg=3/4 tab). *P. ovale* will be treated as *P. vivax*. Mixed infection with *Pv* will be treated as *Pv*.

6.9. Adverse Event (AE) and Serious Adverse Event (SAE)

Adverse events (AE) are defined as any untoward and unintended reaction during the study period. AE will be identified and recorded in CRF by field team in collaboration with the teachers and primary health center attendants. These subjects will be given symptomatic treatment as necessary. Specific AE are black urine, gastro intestinal disturbances, blue lips and breathless.

Serious adverse events (SAE) is an AE which becomes serious and could endanger the life of subjects, cause hospitalization/prolong hospitalization, and disability to conduct normal life. The SAE will be recorded in SAE form and reported to PI, clinician coinvestigators, Ethic Committee, and DSMB within 24 hours. SAE' subjects will be treated in RSPP/RS Atambua until recover completely. Complete SAE report will be distributed within one month after the occurrence of SAE.

The observation of AE and SAE will be performed routinely according to the schedule of drug administration (7 days).

If subject is allergic to DHA-PP, second-line treatment (7 days quinine) will be provided by the team in close collaboration with local primary health center (11-17 kg: 3x1, 18-33 kg: 3x1½, 34-40 kg: 3x2). All treatments for AE/SAE which will be given either at the PHC or in hospital, should be reported to the investigator team and being documented in the database.

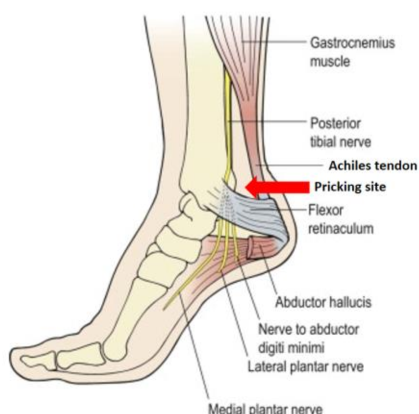
Treatment will be stopped immediately if any of these following occurs: 1) allergy to the antimalarial regimen being given, 2) Hb drop of more than 20%, 3) active hemolysis which is proven by urine test and Hb drop, 4) Hb drop with warning sign of MetHb (breathless, blue lip/cyanosis, drowsiness, lethargy, palpitation), 5) Any possible SAE related to antimalarial treatment. Hospitalisation is indicated for 2) to 5).

6.10. Gametocyte study

At enrollment, blood samples will also be taken from shallow vasculature of the skin from the ankle of all participants from both arms for microscopic examination (light microscopic-skin/LMS) (figure 2). Malaria status by LMS will be assessed post-hoc and will not indicate any treatment.

To determine longevity of these skin gametocytes, LMS samples will be taken at monthly follow up. Moreover, to explore any diurnal variation of this stage, we should obtain blood samples at night and during the day. Therefore, during follow up activity, house visit will be made to the malaria infected children with symptoms for collecting two times blood samples, i.e. 7-10 AM and 7-10 PM. In addition, household members will be asked to contribute their blood samples (LMF, LMS, and PCR). For the household members, LMF will be read on site to indicate treatment.

Figure 2. Location of ankle blood sampling



6.11. Other substudies

During enrollment, several diagnostic tests will be performed to all schoolchildren as substudies: magneto-optical detection of hemozoin/MOD (finger prick and skin), hemoglobinopathy screening by HemeChip (finger prick), and Hb Sahli.

6.12. Ethical clearance

The study protocol will be submitted to Ethic Committee Faculty of Medicine, University of Indonesia, the Oxford Tropical Diseases Research Ethics Committee (OXTREC), and Walter and Eliza Hall Institute Human Research Ethics Committee to obtain ethical clearance. Upon above approval, the protocol will be sent to the local government of Malaka regency to obtain the local permit.

7. Laboratory Methods

7.1. Blood Collection and Transportation

7.1.1. Finger-prick Blood Sample Collection

Blood samples will be drawn from fingertip using BD lancet. During enrolment, malaria blood smear, POC rapid *Pv* antibody detection, hemozoin detection, and hemoglobinopathy screening will be done directly on site. Then 400 µL blood will be collected into microtainer tube containing EDTA. The microtainer tubes will be placed into the ice box, and delivered in no more than 4 hours to the field laboratory for further process.

During follow up (month 1-month 8), only 400 µL of finger pricked blood will be collected into the microtainer. At month-9, malaria blood smear and POC Pv antibody detection will again be done on site, as an addition to the 400 µL microtainer blood.

7.1.2. Skin Blood Samples

To collect blood from skin of the ankle, a vacuum-assisted lancet (Genteel®) will be used with penetration depth of 600 µm. The selected location is shown in the Figure 2. An alternative site will be dorsal surface of the foot between second and middle toe. Thin blood smear will be done directly from the skin blood using microcapillary tube or micropippette. This almost completely painless procedure may repeated one or more times (up to 3 times) to sufficient blood volume.

7.2. Separation of Whole Blood Specimen and Shipment

This step will be done in the field laboratory. During enrolment, blood collected in the microtainer will be separated for quantitative G6PD screening test by Standard G6PD (SD Biosensor, ROK), Hb measurement by HemoCue and Sahli, serological test, and qPCR.

Ten microliters will be used for Standard G6PD (SD Biosensor), 30 µL for hemoglobin measurement (10 µL for HemoCue and 20 µL for Sahli). The remaining

blood will be centrifuged at 5000 RPM for 10 minutes at room temperature. Plasma (supernatant, yellow transparent top layer) will be transfered into new screwed cryogenic tubes. Tubes containing plasma for serological test and pellet for qPCR will be immediately stored in the -20°C freezer. Every 2 days, tubes containing plasma will be shipped to Jakarta for serological assay using cold-chain, and monitored for temperature during transportation. During follow up, blood will be separated into plasma (for serological analysis when needed) and pellet for qPCR to detect recurrence.

7.3. Blood smear Giemsa staining and microscopic reading

Blood films will be dried in room temperature overnight, and fixed with methanol (thin smear only) before it is stained using 3% Giemsa made by mixing the stock solution with buffer. The stain will be gently poured into the slides until they are totally covered. After 45-60 minutes, slides will be rinsed with water and allowed to dry and read under binocular microscope with 1,000 magnification (20).

WHO certified microscopist will read the slides in the field, and cross check will be done at Jakarta. Asexual stages and gametocytes will be counted separately. For LMF, parasites will be counted against leucocytes in the thick smear. Density will be recorded as the number of parasites found per 200 leucocytes. A conversion to number of parasites in microliter of blood will conducted under the assumption of one microliter of blood contains 8,000 leucocytes.

For LMS, parasites will be counted against RBC found in 20 HPF. Density will be recorded as number of parasites per 1 microliter. A conversion to number of parasites in microliter of blood will conducted under the assumption of one microliter of blood contains 5,000,000 RBC.

7.4. Serological Test

7.4.1. Gold-standard Luminex

This test will measure IgG antibodies titres to a panel of 8 specially selected *P. vivax* antigens in plasma samples and will be performed using a Luminex MAGPIX® bead array system. This test will be run in plate format containing blank (in duplicate), positive (singlicate), and negative (singlicate) controls. Blank contains only PBT(1x PBS, 1% BSA, 0.05% Tween-20 (Sterile filter the PBS-BSA prior to

adding Tween-20). A 2-fold serial dilution from 1/50 to 1/25,600 of positive controls will be run in singlicate. A 1/100 dilution of plasma sample will be run in each well.

7.4.2. Point-of-Care anti-*P. vivax* antibody detection test

This test will be done on site by finger prick. This laminar flow rapid diagnostic test will measure IgG antibodies titres to a fragment of the *P. vivax* RBP2b (reticulocyte binding protein 2b) antigen in whole samples. This test will require placing 15µL of blood and a buffer into a laminar flow cartridge. The test can be read after 10-15 minutes either by eye or with a specific reader (if quantification is desired).

7.5. Glucose-6-Phosphate Dehydrogenase (G-6-PDH) Screening Test

Quantitative G6PD screening test will be performed to all schoolchildren. Standard G6PD (SD Biosensor, ROK) will detect amount of G6PD enzyme in U/gHb. The result is shown as number of U/gHb. G6PD normal is defined as G6PD level >4 U/g Hb for male or >6 U/gHb for female.

7.6. Hemoglobin Level Measurement

Hemoglobin level will be measured in the field lab using HemoCue® (HemoCue AB, Angelholm, Sweden) as golden standard. After mix properly,10 µL blood will be transferred into the Hemocue microcuvette. Blood filled microcuvette will be inserted into the Hemocue Hb 301+ automated machine system (HemoCue AB, Angelholm, Sweden). The haemoglobin result will be then displayed after about 30 to 45 seconds in g/dL units. Result will be saved, and transferred to PC. Result will also be recorded in the Case Report Form manually. Additionally, Sahli's hemoglobinometer and Standard G6PD (SD Biosensor Inc., Deogyeong-daero, Korea) will be evaluated.

For Sahli's method, 20 µL blood will be transferred by micropipette into the tube containing 2 g% of HCl. The solution is left for 10 minutes, then diluted with distilled water drop by drop until the colour changes to matched the comparator in the Sahli's hemoglobinometer.

7.7. Gazelle® (Hemex Health, USA) test

This point-of-care test will be done on site during enrolment. It will detect the presence of malaria paramagnetic byproduct hemozoin using magneto-optical detection (MOD) principle. A pipette is used to drop 10uL from skin vasculature or 15uL of whole blood from finger prick into the cartridge bottom, and mixed with 85uL of Gazelle Diluent (mostly water). The cartridge is then manually inserted into the chamber in the Reader. Inside the cartridge, blood sample is sonicated, causing it to lyse the blood and release hemozoin. The magnetic field is used to align the hemozoin. The alignment will block the transmission of light which is proportional to the quantity of hemozoin in the sample. The malaria positive/negative (qualitative) test result is displayed on the Reader within approximately one minute. The result will be stored in the Reader’s memory which can be printed or transferred to a laptop or printer.

The machine will also identify hemoglobin type by electrophoresis on microchip. Twenty microliter of finger pricked blood sample will be inserted into the cartridge and read within 10 minutes.

7.8. qPCR Malaria Speciation

This step will be performed at Universities of Indonesia and Oxford Clinical Research Laboratory (UIOCRL), Jakarta. DNA will be extracted from 200 µL of red cell pellet using a commercially available kit. All blood samples will be screened for the presence of malaria parasites using Real-Time PCR targeting a genus-specific, conserved region of 18S rRNA. For all positive samples, speciation and quantification will be conducted using probe-based Real-Time PCR, which will amplify the multicopy gene 18S rRNA (21).

7.9. Genotyping

All samples from schoolchildren found to be qPCR-positive for *Plasmodium falciparum* or *Plasmodium vivax* will undergo genotyping using a targeted amplicon deep sequencing approach to genotype clones within individual infections, measure genetic relatedness, and discriminate new and existing infections. Each sample will undergo PCR-amplification of highly polymorphic genomic regions followed by next-generation sequencing (22,23).

7.10. Storage of the Specimens

Malaria stained blood smears will be stored in the UIOCRL, Jakarta. Blood samples will be stored in the -20°C freezer at UIOCRL, Jakarta until further process.

8. Data management and analysis

8.1. Data management

Qualitative and quantitative data will be collected during study period. Research team will visit selected elementary schools to conduct demographic census of study participants with the assistance of class teacher and cadres.

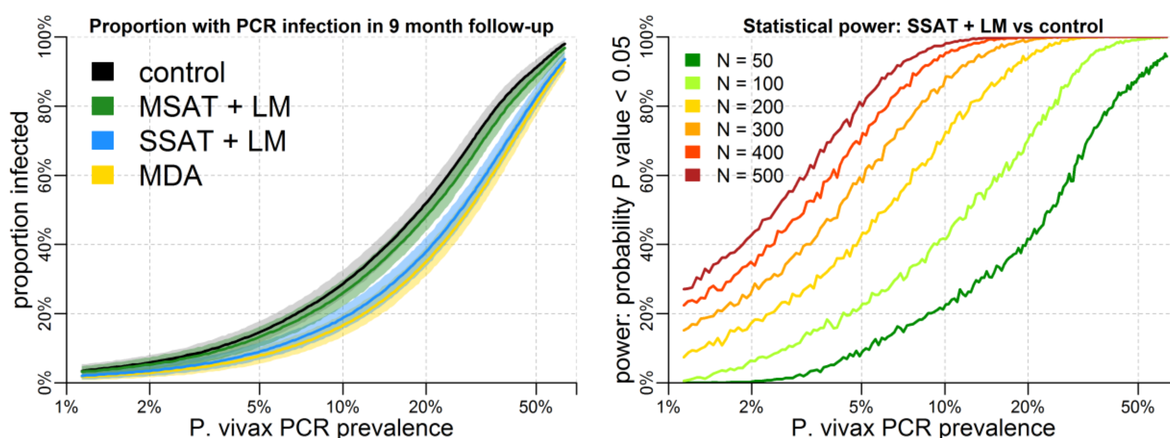
Body weight and temperature, history of fever, results of malaria examination and other substudies, anti-malarial treatment, AE, SAE (if any) will be recorded in Case Report Forms. CRF will only contain ID number of the subjects instead of their full name. Labelling of specimen will be given by adding activity number to the subject ID, e.g. QQxxx-0 (enrollment), QQxxx-1 (follow up 1), etc. (QQ=school initial, xxx=subject number)

After end of study, hard copy files will be stored for at least 5 years at UIOCRL. All CRFs will be transferred into electronic database. Only authorized individuals using secure, authorized computers may access this data management system.

8.2. Sample size consideration

Sample size is calculated based on the difference in the incidence of *P. vivax* infection between the intervention and control arm. The impact of the SSAT intervention is expected to reduce incidence of *P. vivax* in schoolchildren compared to control group. Our study in 2013 found *Pv* prevalence of ~20% by PCR (2). Different effect and sample sizes were simulated using a specific mathematical transmission model (24) and statistical power calculated. With the proposed sample size of 350 children per arm, we will have a power of >90% to detect a significant difference (Figure 3). Assumming 15% exclusion rate, we will recruite 400 children per arm.

Figure 3. Simulation of various sample size (n=50-500) to detect significant difference in the proportion of infected subjects during follow up period.



8.3. Data analysis

Plasmodium vivax incidence is defined as the total number of new genetically distinct *P. vivax* clones per child per detected during the follow up period. The analysis will use the comparison of two incidence rates between SSAT group and control group. For comparison, data will be entered as the number of recurrent *Pv* (numerators) and the total length of time people contributed in the cohort (person-time) as denominators. We will calculate the exact probabilities (Fisher's and Mid-P), the rate ratio with the exact confidence intervals and the measures of the impact of intervention. We will report the 95% of confidence interval for this comparison. Measures of the impact of intervention are computed for the prevented fractions in the exposed and in the population and the preventable fraction in the population.

As secondary endpoints, we will use Kaplan-Meier method to detect differences in the time-to-first recurrence of *Pv* by PCR in SSAT and control arms. The log-rank test is used to detect any difference between the two groups. Cox proportion hazard will be used to measure the effect size.

Multiple recurrences of *P. vivax* infections will be calculated during follow up. Number of events will be calculated, divided by the total length of time people

contributed in the cohort (person-time) as denominators. We will calculate the exact probabilities, rate ratio with the exact confidence intervals, and the measures of the impact of intervention using same tests as above.

Symptomatic recurrent *P. vivax* is defined as LMF positive with fever (>=37.5^{o}C) or history of fever in the last 3 days during follow up. The same statistical test will be performed to compare both groups.

Difference of seropositivity between the two arms before and after the intervention will be calculated using chi-square test with p value < 0.05 as limit of significance.

Sensitivity, specificity, positive predictive value, and negative predictive value of POC *Pv* antibody rapid test will be reported with Luminex as the golden standard.

Type and number of AE and SAE will recorded, and reported with total length of time people contributed in the cohort (person-time) as denominators.

Plasmodium gametocytes prevalence in LMF and LMS will be calculated as the number positive for gametocytes by each diagnostic method divided by the number of subject examined. Diagnostic performance will be derived using 2 × 2 contingency to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV). Results of qPCR detection will be used as the gold standard for diagnostic method evaluation. All statistics will be reported as absolute values with their 95% confidence interval (95% CI). To assess the significance of different results of LMF and LMS methods, we will apply McNemar's chi-square test on 2x2 contingency tables derived from the results of each detection method.

We will evaluate durability analysis by measuring population half-life of the existence of *Plasmodium* gametocyte detected by LMS samples. Gametocyte prevalence-based approach will use data on the appearance and disappearance of any circulating gametocytes according to the prevalence at month 0 and the prevalence at the time when they are fully cleared from skin vasculature.

Sensitivity, specificity, positive predictive value, and negative predictive value of hemozoin detection will be reported using microscopic Giemsa examination as golden standard.

Hemoglobin measurement using Sahli method and Standard G6PD will be compared to HemoCue by t test.

Hemoglobinopathy rate will be reported as descriptive value.

9. Ethical consideration

9.1. The subject risks

Blood samples collection will only bring minimal risk to the subjects. Only small volume of blood samples (~0.5 ml) will be drawn from the fingertip and using modern equipment which only cause small lesion on the incision site where the lancet or microtainer is introduced. A lancing device of the latest technology will be used to collect blood samples from the skin to collect sufficient blood volume with minimal pain. Blood sample collection will only be performed by trained staff of our investigator team to minimize the possibility of infection or other unlikely adverse events.

The risk of hemolysis in G6PD deficient subjects has been minimized by conducting G6PD screening to all schoolchildren and daily monitoring for hemolysis before and during PQ administration.

9.2. Benefit for study subjects

All positive individuals will receive standard antimalarial treatment by the PHC staff. A G6PD screening and Hb measurement will be performed to maximize the safety of subjects receving primaquine.

10. Expected application of results of the study

The study is expected to provide an improved screen and treat strategy to clear hypnozoites by the use of highly sensitive detection tools. The reduction of hypnozoites in the liver will lower the reservoirs of *Plasmodium vivax* which hopefully will bring down the transmission.

Moreover, this study may offer a highly sensitive and practical diagnostic procedure that detects these carriers allows treatment, effectively empowering an efficacious approach to mass screen and treat (MSAT) interventions. The malaria research community engaged in discovery of targets of chemotherapy or immunoprevention would be offered a whole new universe of possibilities with sequestered gametocytes in the upper vasculature of the dermis.

11. Study Insurance

The research will be appropriately covered by the Oxford University's insurances.

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12. Roles of Investigators

Inge Sutanto is Principal Investigator of this study. She is professor at Faculty of Medicine, University of Indonesia. She will provide scientific support, coordination and supervision of the study, and will participate in manuscript preparation.

Rintis Noviyanti is senior researcher at Eijkman Institute for Molecular Biology. She will be responsible for molecular diagnostic of Plasmodium. She will provide scientific support and will participate in manuscript preparation.

Ari Satyagraha is a senior researcher at Eijkman Institute for Molecular Biology. She will be responsible for G6PD analysis. She will provide scientific support and will participate in manuscript preparation

Ayleen Alicia Kosasih is the study coordinator of the study. She will assist with supervision of the study, scientific support, and will participate in manuscript preparation.

Lenny Ekawati is an public health scientist of Eijkman-Oxford Clinical Research Unit who will provide regular support in study design, data analysis, and will participate in manuscript preparation.

Iqbal Elyazar is statistician & epidemiologist of Eijkman-Oxford Clinical Research Unit who will provide regular support in study design, data analysis, and will participate in manuscript preparation.

Decy Subekti is laboratory manager of Eijkman-Oxford Clinical Research Unit who will provide regular support in laboratory, molecular work, and data analysis, and will participate in manuscript preparation.

Mulya Rahma Karyanti is academic staff at Department of Pediatrics, Faculty of Medicine, University of Indonesia. She will provide assistance in developing safety protocol, andShe will support the clinical aspect of this study, particularly in terms of safety.

Erni Juwita Nelwan is academic staff at Department of Internal Medicine, Faculty of Medicine, University of Indonesia. She will provide assistance in developing safety protocol, and support the clinical aspect of this study, particularly in terms of safety.

Instiaty is is academic staff at Department of Pharmacology and Theuraptics, Faculty of Medicine, University of Indonesia. She will provide assistance in developing treatment and safety protocol. She will also support the clinical aspect of this study, particularly in terms of safety.

Jeanne Rini Poespoprodjo is staff at Rumah Sakit Umum Daerah Kabupaten Mimika, Papua. She will provide scientific insight for the protocol and safety guideline of the participants.

J. Kevin Baird, head of Eijkman-Oxford Clinical Research Unit. He will provide scientific support and support in study design, data analysis, and will participate in manuscript preparation.

Shazia Ruybal Pesántez is post-doctoral researcher in the Population Health & Immunity Division, Walter & Eliza Hall Institute. She will provide assistance in data

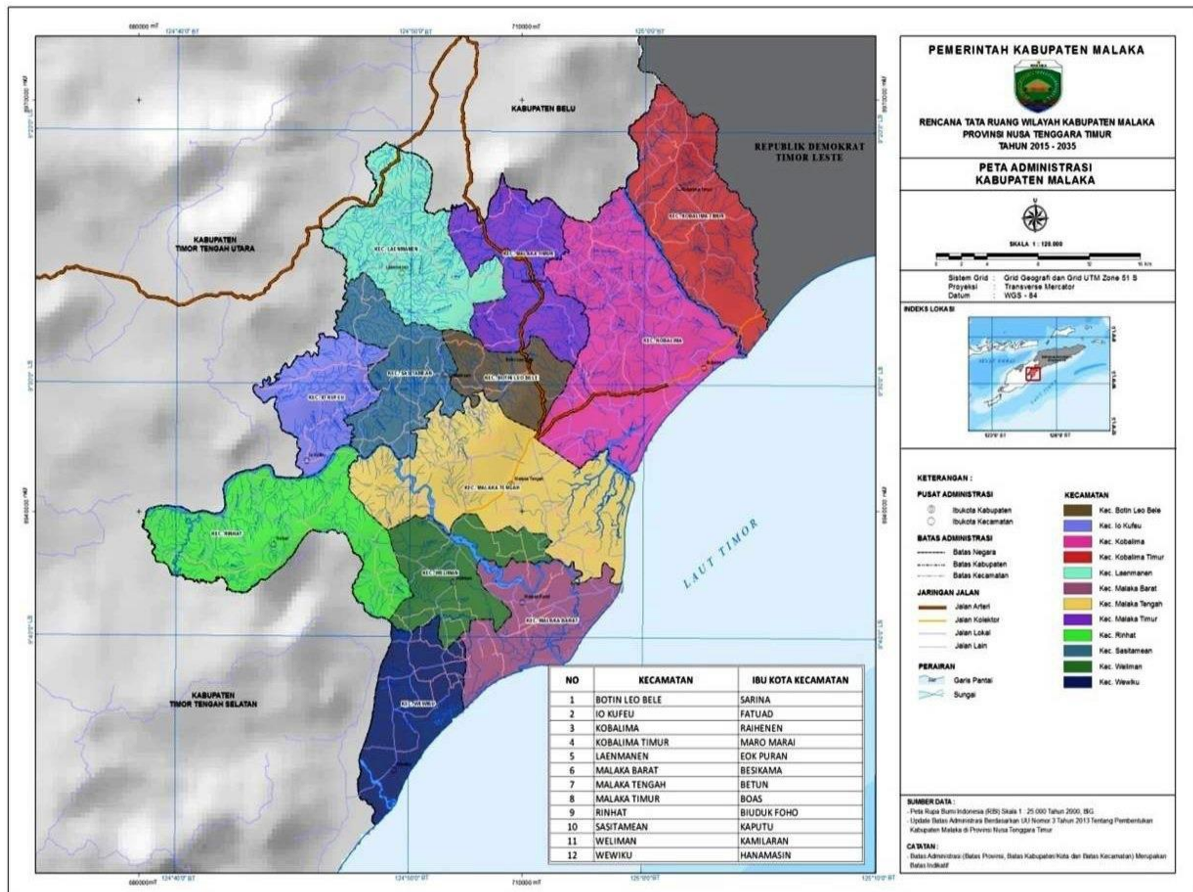
management, analysis of the molecular epidemiology, and will participate in manuscript preparation.

Leanne J. Robinson is Laboratory Head in the Population Health & Immunity Division, Walter & Eliza Hall Institute, Group Head of Vector Borne Diseases and Tropical Public Health, Burnet Institute, Adjunct Principal Research Fellow, Vector Borne Disease Unit, Papua New Guinea Institute of Medical Research. She will provide scientific support and support in study design, data analysis, and will participate in manuscript preparation.

Ivo Mueller is Laboratory Head and Co-Head of Population Health & Immunity Division, Walter & Eliza Hall Institute. He will provide scientific support and support in study design, data analysis, and will participate in manuscript preparation.

APPENDIXES

APPENDIX A. MAP OF STUDY SITE



NO	KECAMATAN	IBU KOTA KECAMATAN
1	BOTIN LEO BELE	SARINA
2	IO KUFEU	FATUAD
3	KOBALIMA	RAIHENEN
4	KOBALIMA TIMUR	MARO MARAI
5	LAENMANEN	EOK PURAN
6	MALAKA BARAT	BESIKAMA
7	MALAKA TENGAH	BETUN
8	MALAKA TIMUR	BOAS
9	RINHAT	BIUDUK FOHO
10	SASITAMEAN	KAPUTU
11	WELIMAN	KAMILARAN
12	WEWIKU	HANAMASIN

APPENDIX B. DRUG DOSAGE

Table 1. DHA-PP

DHA-PP will be given for any species. Same dosage will be given at the enrollment and during follow up.

Day	Drug	Daily dosage based on body weight						
		≤ 5 kg	6-10 kg	11-17 kg	18-30 kg	31-40 kg	41-59 kg	≥ 60 kg
1-3	DHA-PP	¼	½	1	1 ½	2	3	4

Table 2. High dose Primaquine (PQ)

Body weight (kg)	mg/tab	Tablet given/day	Actual dose given mg/kg BW	Total dose received (mg)
12	15	0,75	0,9375	6,5625
13	15	1	1,153846	8,076923
14	15	1	1,071429	7,5
15	15	1	1	7
16	15	1	0,9375	6,5625
17	15	1,25	1,102941	7,720588
18	15	1,25	1,041667	7,291667
19	15	1,25	0,986842	6,907895
20	15	1,5	1,125	7,875
21	15	1,5	1,071429	7,5
22	15	1,5	1,022727	7,159091
23	15	2	1,304348	9,130435
24	15	2	1,25	8,75
25	15	2	1,2	8,4
26	15	2	1,153846	8,076923
27	15	2	1,111111	7,777778
28	15	2	1,071429	7,5
29	15	2	1,034483	7,241379
30	15	2	1	7

31	15	2	0,967742	6,774194
32	15	2	0,9375	6,5625
33	15	2	0,909091	6,363636
34	15	2	0,882353	6,176471
35	15	3	1,285714	9
36	15	3	1,25	8,75
37	15	3	1,216216	8,513514
38	15	3	1,184211	8,289474
39	15	3	1,153846	8,076923
40	15	3	1,125	7,875
41	15	3	1,097561	7,682927
42	15	3	1,071429	7,5
43	15	3	1,046512	7,325581
44	15	3	1,022727	7,159091
45	15	3	1	7

Table 3. Low dose Primaquine

Single 0.25 mg/kg BW dose PQ will be given for *P. falciparum* or 14 days 0.25 mg/kg BW dose PQ for *P. vivax/P. ovale* infection any time during the study period.

Day	Species	Daily dosage based on body weight					
		≤ 5 kg	6-17 kg	18-30 kg	31-40 kg	41-59 kg	≥ 60 kg
1	*P. falciparum*	-	¼	½	¾	1	1
1-14	*P. vivax/P. ovale*	-	¼	½	¾	1	1

Table 4 Quinine dose

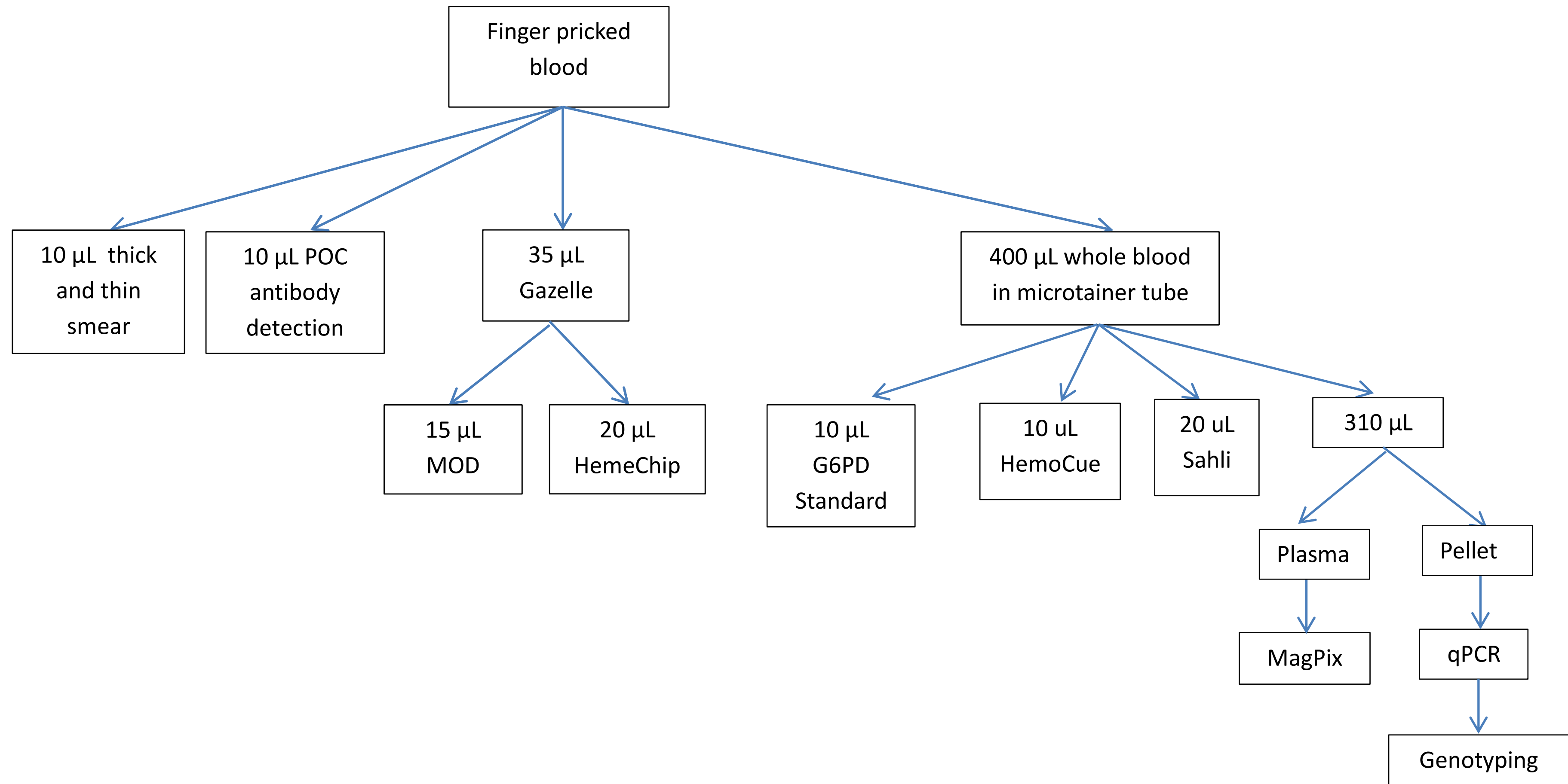
Day	Drug	Daily dosage based on body weight					
		≤ 5 kg	6-10 kg	11-17 kg	18-33 kg	34-40 kg	41-60 kg
1-7	Quinine	3 x 10 mg/kg BW	3 x ½	3 x 1	3 x 1½	3 x 2	3 x 2½

1 (1-14)	Primaquine	-	¼	½	¾	1	1

APPENDIX C. TIME FRAME

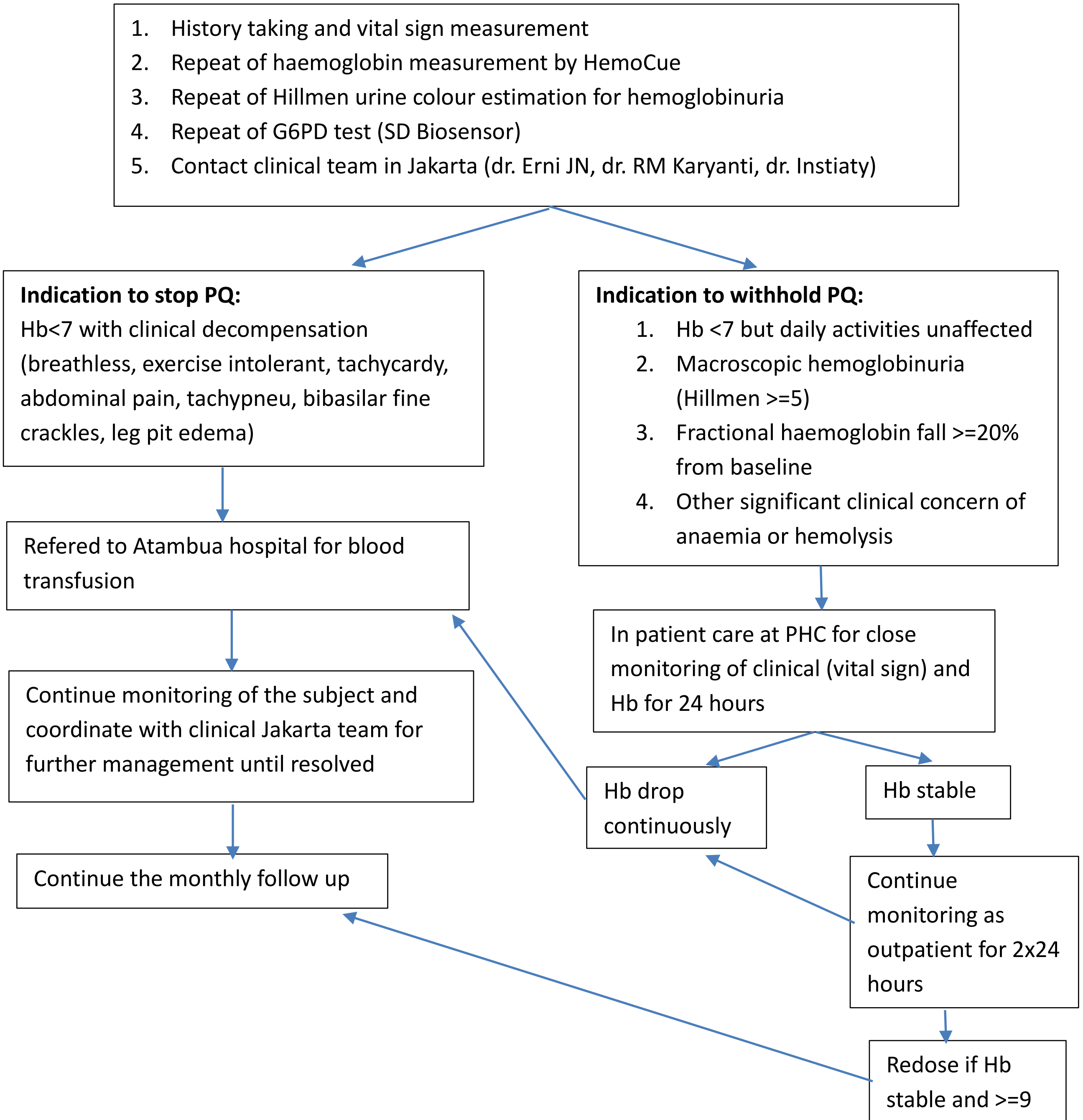
Activity	2019								2020												2021									
	V	VI	VII	VIII	IX	X	XI	XII	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	I	II	III	IV	V	VI	VII	VIII	IX	X
Protocol	x	x	x																											
Ethical review				x	x	x																								
Investigator meeting & trainings					x	x																								
Study approval						x	x																							
Site establishment						x	x																							
Socialization							x																							
Sero-positivity screening								x																						
School selection and randomization								x																						
Socialization, Informed Consent, and Training								x	x																					
Enrolment									x	x																				
Monthly sampling											x	x	x	x	x	x	x	x	x											
Family screening											x	x	x	x	x	x	x	x	x											
PCR & genotyping											x	x	x	x	x	x	x	x	x											
Data analysis																				x	x	x	x	x						
Publish findings																									x	x	x	x	x	x

APPENDIX D. SAMPLE HANDLING WORKFLOW DURING INITIAL SCREENING



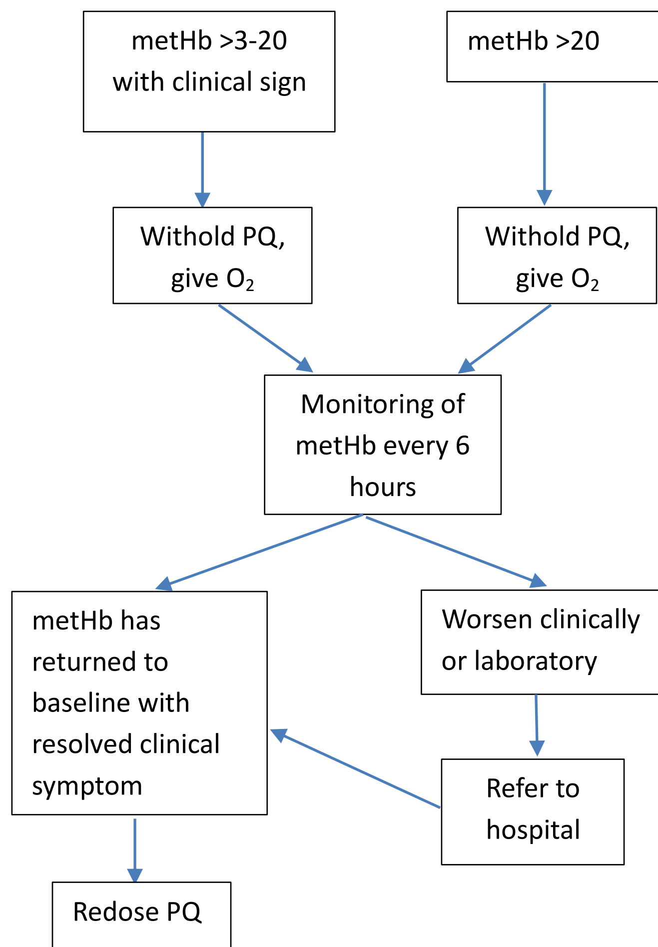
APPENDIX E. MANAGEMENT OF ACUTE HEMOLYSIS

Any clinical concern of acute hemolysis (sign of anaemia e.g. breathless, fatigue, pale, dark urine, clinical jaundice) or falling haemoglobin during 7 days of treatment should trigger the following:



APPENDIX F. MANAGEMENT OF METHEMOGLOBINEMIA

Any sign of metHb (dyspnea, headache, fatigue, weakness, dizziness, syncope) without sign of hemolysis should be followed by metHb measurement.



APPENDIX G. PENETRATION DEPTH OF GENTEEL® LANCING DEVICE

Contact Tip Color	Penetration Depth in mm
Blue	0.025
Yellow	0.66
Green	1.30
Clear	2.00
Orange	2.57
Violet	3.20

APPENDIX H. SCHEDULE OF PROCEDURES

	Day																Month								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	2	3	4	5	6	7	8	9	10
History of fever	x																x	x	x	x	x	x	x	x	x
Temperature taking	x																x	x	x	x	x	x	x	x	x
Body weight measurement	x																								
Finger prick samples & microtainer up to 400 µL	x																x	x	x	x	x	x	x	x	x
LMF	x																x	x	x	x	x	x	x	x	x
POC antibody detection test	x																								
Hemex test for hemozoin detection & hemoglobinopathy	x																								
SD Biosensor G6PD screening	x																								
HemoCue	x								d0	d1	d2	d3	d4	d5	d6	d7									
Sahli	x																								
MagPix	x																								
qPCR	x																x	x	x	x	x	x	x	x	x
Genotyping	x																x	x	x	x	x	x	x	x	x
Drug treatment																									
DHA-PPQ[1]									D1	D2	D3														
PQ[1]									D1	D2	D3	D4	D5	D6	D7										
Ankle prick	x																x	x	x	x	x	x	x	x	x
LMS	x																x	x	x	x	x	x	x	x	x
Hemex test for hemozoin detection	x																								
Urine color inspection[1]									d0	d1	d2	d3	d4	d5	d6	d7									
Urinalysis[1,2]									d0	d1	d2	d3	d4	d5	d6	d7									

[1]For microscopic positive subjects, treatment should be given promptly according to malaria species
[2]Macroscopic, chemistry (protein), microscopic (RBC)

APPENDIX I. RETREATMENT SCHEDULE ON ENROLMENT

LMF	Antimalarial drugs	Pv Serology	
		Positive	Negative
Pf	3d DHP	7d PQ (1 mg/kgBW)	1d PQ (0.25 mg/kg BW)
Pv	3d DHP + 7d PQ	No further treatment	No further treatment
Pm	3d DHP	7d PQ (1 mg/kgBW)	No further treatment
Po	3d DHP + 7d PQ	No further treatment	No further treatment
Mixed Pf&Pv	3d DHP + 7d PQ	No further treatment	No further treatment
Mixed Pf&Pm	3d DHP	7d PQ (1 mg/kgBW)	1d PQ (0.25 mg/kg BW)
Mixed Pv&Pm	3d DHP + 7d PQ	No further treatment	No further treatment

APPENDIX J. FORMS

CENSUS FORM

SEKOLAH : **KELAS :**

TANGGAL :

No	Nama	L/P	Tgl lahir / Usia	Nama Bapak	Nama Ibu	Desa	Dusun

FORM SCREENING

SEKOLAH : **KELAS :**

TANGGAL :

No	ID	Nama	L/P	Usia	BB	Suhu	Demam seminggu terakhir	Serologi	Mikroskopik

FORM FOLLOW UP

SEKOLAH :

ID : **KELAS:** **USIA:**

NAMA: **L/P**

Kohort	Tgl	BB	Suhu	Demam seminggu terakhir (Y/T)	LMF	LMS	qPCR
1							
2							
3							
4							
5							
6							
7							
8							
9							
Di luar jadwal							
Di luar jadwal							
Di luar jadwal							

FAMILY SCREENING

ID SUBJEK :

NAMA SUBJEK:

No	Nama anggota keluarga	ID	BB	Suhu	Demam seminggu terakhir (Y/T)	LMF	LMS	Filter paper
1						Malam:	Malam:	Malam:
						Siang:	Siang:	Siang:
2						Malam:	Malam:	Malam:
						Siang:	Siang:	Siang:
3						Malam:	Malam:	Malam:
						Siang:	Siang:	Siang:
4						Malam:	Malam:	Malam:
						Siang:	Siang:	Siang:
5						Malam:	Malam:	Malam:
						Siang:	Siang:	Siang:

CASE REPORT FORM
ID : NAMA: L/P
FAMILY SCREENING/SEKOLAH: G6PD: HASIL: *P. FALCIPARUM / P.VIVAX / P. MALARIAE / P. OVALE*

Hari	D-1	D-2	D-3	D-4	D-5	D-6	D-7	D-8	D-9	D-10	D-11	D-12	D-13	D-14
Tanggal														
DHP (jml tablet)														
Primakuin (jml tablet)														
Hb (D-1 sebelum minum obat & D-3)														
Urin (D-1 sebelum minum obat)														
Keluhan														
Alergi														
Pusing														
Sakit kepala														
Bibir kebiruan														
Keluhan di dada														
Mual														
Muntah														
Gangguan napsu makan														
Gangguan Buang Air Besar (BAB)														
Gangguan Buang Air Kecil (BAK)														
Gangguan tidur														
Tanda tangan pasien														
Tanda Tangan Petugas Pengawas Minum Obat														
Tanda Tangan Manajer Site/Wakil														