Surveillance template protocol for *pfhrp2/pfhrp3* gene deletions

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Disclaimers

1. This recommended template protocol has been developed by WHO to guide surveillance for *pfhrp2/3* gene deletions in malaria endemic countries; however, WHO cannot accept any responsibility or liability for the conduct of studies by third parties that follow the protocol.
2. Studies conducted by third parties pursuant to the protocol cannot be considered "WHO studies". Appropriate approval(s) at local and/or national level should be obtained prior to the start of any such study.

Title	
Surveillance site(s)	Site 1: Name, city, district and province Site 2: Name, city, district and province Site 3: Name, city, district and province *(Add more sites as needed or include just counties and add annex with health facilities list)*
Protocol submission date	dd/mmm/yyyy
Protocol number	Unique protocol number/version number
Principal investigator	Name: Degree: Institution: Address: street, city, postal code, country Tel: Email:
Co-investigators (insert additional name(s) if needed)	Name: Degree: Institution: Address: street, city, postal code, country Tel: Email:
Participating institutions (insert additional institution(s) if needed)	Name: Complete postal address: street, city, postal code, country Tel: Email:
Planned survey dates	From mmm/yyyy to mmm/yyyy
Sponsor	Complete postal address: street, city, postal code, country Tel: Email:

Project summary

Surveillance objectives	This surveillance activity is intended to determine whether the local prevalence of mutations in the *P. falciparum hrp2/3* genes causing false negative RDTs has reached a threshold that might require a local or national change in diagnostic strategy. The specific objectives are to: 1. Measure the prevalence of suspected false-negative HRP2 RDT results among symptomatic patients attending public health facilities with *P. falciparum* infection detected by microscopy or a pf-pLDH RDT; 2. Detect the parasite density and frequency of *pfhrp2/3* gene deletions in that cohort; 3. Determine the predictive value of false-negative HRP2 RDT results for *pfhrp2/3* gene deletions in different settings; 4. Identify provinces in which the prevalence of *pfhrp2/3* gene deletions causing false negative *P. falciparum* RDTs is at or above 5%, warranting a change in RDTs.
Surveillance site	Pre-selected public health facilities representing the spectrum of transmission and geographical diversity across the country
Target population	Individuals seeking care for febrile illness at health facilities
Survey type	Cross-sectional, multi-site
Primary output measures	1. Prevalence of suspected false-negative HRP2 RDT results among symptomatic patients with *P. falciparum* malaria. 2. Prevalence of *pfhrp2/3* gene deletions among symptomatic falciparum patients with a false-negative HRP2 RDT result 3. Prevalence of *pfhrp2/3* gene deletions causing false negative HRP2 RDTs amongst all symptomatic *P. falciparum* confirmed cases.
Secondary output measures (optional)	1. Parasite density, as measured by quantitative PCR and/or microscopy, in patients with suspected false-negative HRP2 RDT results.
Sample size	A sample size of 370 confirmed *P. falciparum* cases per sampling domain (37 per health facility) is recommended to quantify whether or not the prevalence of *pfhrp2* deletion is above 5%. Once the sample of 370 *P. falciparum* cases have been enrolled then molecular confirmation of *pfhrp2* deletions amongst suspected false negative *P. falciparum* cases should ensue.
Sampling method	In at least 10 pre-selected health facilities per sampling domain eg. province at risk, a cross-sectional survey will measure the suspected and confirmed prevalence of *pfhrp2/3* gene deletions causing false-negative HRP2 RDT results. 37 *P. falciparum* confirmed cases should be included in each health facility.

Data collection

1. Identify provinces to be included in the study.
2. Select at least 10 health facilities per province for testing (facility sample size may vary depending on logistical and budgetary constraints). Any facility where RDTs are being used is eligible; however, microscopy services are not a requirement.
3. Test all individuals presenting with suspected malaria using both a WHO-recommended HRP2 RDT and a non-HRP2 method (e.g., pf-pLDH RDT (separate single or multiple test line RDT) or quality – assured microscopy in the health facility and collect minimum two dried blood spots (DBS).
4. Record demographic and clinical history details and all test results
5. Administer antimalarial therapy based on results from (either) RDT and/or microscopy and according to national guidelines.
6. Send minimum of two DBS from all Pf patients with negative HRP2 RDT and positive pf-pLDH RDT or microscopy for molecular +/-- serological analysis.[1]
7. Surveillance activity can stop once 370 individuals with confirmed *P. falciparum* malaria (ideally ~37/site across the 10 sites in the province) have been recorded as having *P. falciparum* in step 4.
8. Supplemental data collection options are described in Appendix 1.
9. Discard all RDTs, microscopy slides and DBS after survey results finalized and reported

Statistical and analytic plan

The prevalence of suspected false-negative HRP2 RDT results and *pfhrp2/3* gene deletions will be established at the sampling domain (e.g. provincial level), with 95% confidence intervals (CI) estimated for all point estimates. If desired, point estimates and 95% CIs can be weighted according to relative facility size or patient flows. Differences between point estimates across sociodemographic characteristics and transmission levels, or other collected variables can be determined using X^2 and/or logistic regressions, as desired.

[1] Use of the DBS for any purpose other than surveillance for *pfhrp2/3* deletions and/or long-term storage of the DBS would require patient consent/assent and protocol review by an ethical review board