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Project title : Molecular and in vitro surveillance of artemisinin combination therapy (ACT) partner drug efficacy in the Greater Mekong Subregion (MIVS-ACT)

INITIATIVE 5% SIDA, TUBERCULOSE, PALUDISME

Overall objective	To inform *P. falciparum* treatment policies in the Greater Mekong Subregion by providing timely high quality information on the efficacy of antimalarial drugs using rapid genotypic and phenotypic assessments.			
	Intervention logic	**Objectively verifiable indicators of achievement**	**Sources and means of verification**	**Risks and assumptions**
Specific objective(s)	**1) To define the prevalence and distribution of genetic markers of resistance to partner drugs in artemisinin-based combination therapies (ACTs).** In the context of increasing artemisinin resistance (ART-R) in the Greater Mekong Subregion (GMS), efficacy of the partner drugs becomes the most important determinant of ACT efficacy. Therefore, resistance to partner drugs must be assessed rapidly throughout the region to ensure that an optimal antimalarial treatment strategy is implemented.	- Numbers of specimens tested & results reported stratified by country (target: 12000-15000 specimens tested across GMS from 2014-2018) - Proportion of results reported within target turn-around times (target: ≥80% results reported within 3 months of delivery of specimens)	- Laboratory logs & databases - Report dates & records - Country &/or programme-wise periodic report	**Risks:** Low sample numbers due to reduced malaria cases (medium); political instability in specific regions of interest could prevent project implementation (low) **Assumptions:** Programmatic partners will use the output of ths project for malaria control policy/activity; overall research project approved by respective ethics committees; *kelch13* genotyping will be performed through other concurrent projects
	2) To validate molecular markers of resistance with *in vitro* testing of selected isolates from across GMS. *In vitro* phenotyping is required to confirm parasite susceptibility to ACTs and to aid in the selection combinations with greatest likely therapeutic efficacy.	- Numbers of specimens tested & results reported stratified by country (target: 200-400 specimens tested across GMS over project duration)	- Laboratory logs & databases	**Risk:** Lower than expected field isolates tested due to impossibility of culture adaptation caused by intrinsic parasite factors (low) **Assumption:** Field isolates will be collected and processed by trained staff to ensure sample quality
	3) To build sustainable capacity and improve quality of genotypic and phenotypic assessments of antimalarial resistance. As targeted malaria elimination campaigns and/orintensifiedmalaria control prograammes are implemented across GMS and elsewhere, the activities proposed here will need to be sustained beyond the duration of this project.	- Numbers of labs participating in proficiency testing for genotyping (target: ≥1 lab per country) - Formal cross-validation of *in vitro* assays (target: ≥1-2 labs with demonstrated capacity to perform *in vitro* assays)	- Proficiency Testing reports - Training records	**Risks:** Loss of trained technical capacity due to turnover of human resources (low) **Assumptions:** Laboratories performing malaria parasite genotyping tests will participate in the PT scheme; laboratories aiming to perform *in vitro* phenotyping have the required laboratory infrastructure in place
	4) To validate the feasibility of near-real time molecular surveillance to guide policy implementation in resource-limited settings. Strategies similar to that proposed here will be needed in other endemic regions advancing towards malaria elimination.	- Proportion of results reported within target turn-around times (target: ≥80% results reported within 3 months of delivery of specimens) - Proportion of fit-for-purpose samples collected (target: analysable data obtained from ≥90% specimens)	- Laboratory logs & databases - Report dates & records	**Risks:** Conclusions and recommendations derived from proposed project results are only applicable in pre-elimination settings (low) **Assumptions:** Successful implementation of the proposed project
Expected result(s)	**1a) Genetic Markers - Baseline assessment:** A baseline assessment is needed as a starting point to identify geospatial trends in drug efficacy.	- Numbers of specimens tested & results reported stratified by country (target: 2000-3000 specimens from 2014-2015) - Proportion of results reported within target turn-around times (target: ≥80% results reported within 3 months of delivery)	- Laboratory logs & databases	**Risk:** Low transmission of malaria in some zones selected for sampling by models (medium) **Assumption:** Quality of archived samples is fit for purpose
	1b) Genetic Markers - Prospective assessment: Data from prospective testing is needed to update maps with new data and to inform treatment strategies.	- Numbers of specimens tested & results reported stratified by country (target: average of 600-800 samples analysed per country per year, total 10 000 - 12 000 specimens) - Proportion of results reported within target turn-around times (target: ≥80% results reported within 3 months of delivery of specimens)	- Laboratory logs & databases	**Risk:** Low sample numbers due to reduced malaria cases (medium) **Assumption:** Quality of collected samples is fit for purpose
	1c) Maps and reports: Rapidly generated and disseminated maps of prevalence and modelled geospatial trends would help guide and prioritize interventions to specific geographic locations.	- Published prevalence & modelled maps (target: maps updated within 1 month of data reception) - Country &/or programme-wise periodic report submitted at mutually agreed time-points (target: ≥ 90% reports delivered at agreed time-points)	- Report dates & records - Web-based prevalence & modelled maps	**Risks:** Low geographic coverage of sampling locations (low) **Assumptions:** Genotyping results will be mapped and modelled within target turn-around times; uptake of reports and maps by beneficiary organisations
	Intervention logic	**Objectively verifiable indicators of achievement**	**Sources and means of verification**	**Risks and assumptions**
	2) In vitro ACT drug susceptibility profiles: In vitro testing provides a quantitative measure of drug resistance from the qualititative information obtained by genotyping. 50-100 specimens per year.	- Numbers of specimens tested & results reported (target: ≥50 specimens tested per year)	- Laboratory logs & databases	**Risk:** Failure of culture-adaptation of isolates due to intrinsic parasite factors (low) **Assumptions:** Adequate numbers of samples with acceptable quailty are collected

Expected result(s) (contd.)	**3) Transfer of in vitro assay techniques to partner labs:** *In vitro* assays need to be implemented in selected labs to supplement information generated from *in vivo* and molecular marker studies	- Results of cross-validation experiments (target: training and cross-validation completed in ≥1 partner lab within Year 1 of project)	- Training logs - Cross-validation report	**Risks:** Loss of trained technical capacity due to turnover of human resources (low) **Assumption:** Required laboratory infrastructure already exists
	4) Proficiency testing scheme: Profiency Testing (PT) schemes promote quality improvement and provide independent validation of results.	- Numbers of labs participating in the PT scheme (target: ≥1 lab per country) - PT scores of labs (target: ≥1 lab per country with demonstrated capacity to perform molecular testing)	- Report dates & records - PT reports	**Risk:** None identified **Assumption:** Uptake of PT scheme by laboratories performing molecular assays for detection of resistance markers
Activities	Pre-launch activities - Protocol submission for ethics approval to local Ethics Committees and/or Insititutional Review Boards - Selection of specimens for baseline assessment			**Risks:** Signficant delay in obtaining ethics approval **Assumption:** Protocol will be approved by all concerned Ethics Boards
	Training and quality assurance - Training for field personnel in sample collection, logging, shipping, processing - Training and quality assurance of drug susceptibility testing using in vitro assays - Preparation of specimens for use in proficency testing - Proficiency testing of molecular assays and cross-validation of *in vitro* assays			**Risks:** Loss of trained technical capacity due to turnover of human resources (low) **Assumption:** Required laboratory infrastructure already exists; laboratories participating in PT scheme will provide results in a timely manner
	Specimen collection, management and processing - Sample collection and shipment - Specimen tracking and logistics - DNA extraction from dried blood spots			**Risk:** Low sample numbers due to reduction in malaria prevalence (medium) **Assumptions:** Sampling locations will provide optimal coverage for prevalence/modelled maps; adequate numbers of samples with acceptable quality are collected
	Molecular assays for markers of resistance - Pfmdr1 copy-number measurement - Single nucleotide polymorphisms of Pfmdr1 or other markers of resistance identified during project implementation			**Risk:** Low sample numbers due to reduction in malaria prevalence (medium) **Assumption:** Sampling will be performed at multiple locations providing optimal coverage for prevalence/modelled maps
	Mapping and modelling - Data management and mapping - Data modelling ('Smart surveillance') - Data visualisation and interpretation			**Risk:** Reduction in malaria cases and/or logistical infeasiblity in zones targeted for sampling (medium) **Assumption:** Cross-verification of sampling locations based on two independent models
	In vitro phenotyping of field isolates - Culture adaptation of field isolates - Assay set up and drug susceptibility testing (including assay validation and/or cross-validation)			**Risks:** Failure to adapt field isolates to culture due to intrinsic parasitologic factors (low) **Assumptions:** Assays have been (cross-) validated across any/all implementing laboratories; samples with acceptable quality are collected
				Preconditions Currently ongoing or planned activities for targeted malaria elimination or intensified malaria control will continue within the GMS.