

**Doctoral Project Title:** Safety and efficacy of methylene blue based combination therapy against malaria: RCT

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**Description:** Malaria remains the most important parasitic disease and is globally responsible for 200-300 million disease episodes and 0.6-1 million deaths per year. The international Roll-Back Malaria Initiative (RBM) aims to eliminate malaria country by country until the longterm goal of malaria eradication will be achieved. Malaria combination therapy, in particular artemisinin-based combination therapy (ACT), has become the gold standard for treatment in every country. However, ACT is only partly effective against the gametocytes of *P. falciparum* and thus in reducing transmission, including transmission of resistant strains. Thus, adding a gametocytocidal drug to an ACT has become an interesting intervention in programs where the aim is elimination.

Methylene blue (MB) is the first synthetic drug ever used against malaria (late 19th century). MB has been revitalised in the treatment of malaria in recent years. In a series of clinical studies conducted mainly in West Africa, it was shown that using MB in combination with other malaria drugs was very safe and quite effective in children with uncomplicated falciparum malaria. It appears thus likely that it will have benefits in comparison with primaquine (PQ), the gametocytocidal drug currently recommended to be added to ACT. Moreover, adding MB to an ACT may protect it from development of resistance. Thus, it is planned to conduct a randomised controlled trial (RCT) comparing MB-ACT with PQ-ACT for safety and efficacy outcomes in patients with falciparum malaria. Moreover, MB may also be effective against *P. vivax* and could be a potential replacement of PQ, the only registered drug which works against the hypnozoites of *P. vivax*. In this regard, a pilot study which will for the first time use a MB-based combination therapy will be planned in a country where vivax malaria is endemic.

The objective of the study is to investigate the safety and efficacy of MB-based combination therapy in patients with uncomplicated falciparum and vivax malaria in comparison to PQbased combination therapy.

This will be a mono- or multi-centre RCT conducted in collaboration with partner organisations in malaria endemic countries.