Title: Status of randomised and non-randomised clinical trials assessing safety, efficacy, effectiveness of malaria control interventions in groups at increased risk of malaria disease and death

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Introduction:

Notably, the clinical profile of malaria disease varies according to epidemiological region and *Plasmodium* species, it is imperative to tailor control strategies towards groups at increased risk of adverse outcomes of malaria. This review summarises current evidence on safety, efficacy, and effectiveness of chemoprevention as a malaria control intervention, with the contents presented here focusing on selected highly mobile and hard-to-reach risk groups.

Methods:

A systematic search was performed to identify clinical trials or reviews from: MEDLINE (PubMed), Embase, Web of Science, CINAHL Plus, The Cochrane Library databases, and the WHO Global Health Library/WHO Library (WHOLIS) reporting safety and efficacy of malaria control interventions between January 1947 and January 2021. Summary statistics and measures of efficacy extracted and analyzed for each identified risk group (PROSPERO registration: CRD42021267637).

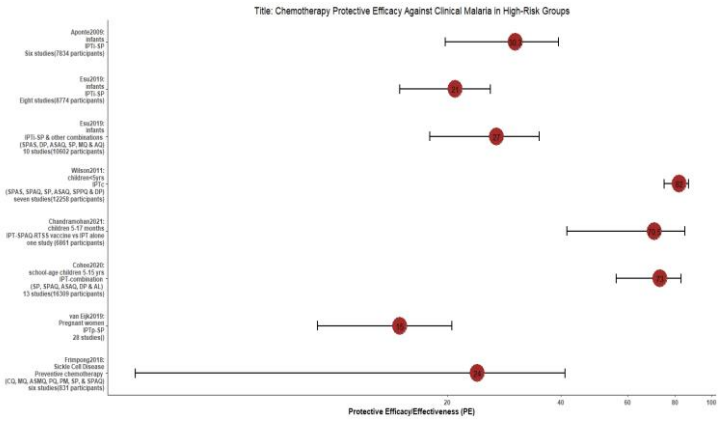

Fig1: Summary Protective Efficacy (PE) of malaria chemoprevention in selected high-risk groups

Author/ Year or CT Registration	Risk group	Treatment	Outcome	Estimate	Comment
Soto 1998 & 1999, 2006, Ohrt 1997, Michel 2010, Walsh 2004, Croft 1997 & Elmes 2008	Military personnel/ troops	PQ, CQ, AP, MQ, DX, DX+CQ, TQ , MQ & DP as chemoprophylaxis	Protective Efficacy (PE) against Clinical malaria	Range across studies: 88% -100%	Highly mobile risk group, reached via institution
NCT04041973	Forest goers/ dwellers	AL	Efficacy of AL against forest malaria	Ongoing	Evaluating chemoprophylaxis in Cambodia
NCT04094727	Nomadic (cattle herders & agricultural workers)	AL	Effectiveness of presumptive treatment	pending	Use or chemoprevention and enhance vector control in Namibia
Lwin 2012	Cross-border settings	IPT-DP	PE against all cause clinical malaria	Monthly 98% (95% CI: 96 - 99%) & twice monthly 86% (95% CI: 81-90%)	Evaluating IPT in Thailand-Myanmar border

Results:

Classical preventive chemotherapy strategies: intermittent preventive treatment for infants (IPTi), pregnancy (IPTp), seasonal malaria chemoprevention (SMC) and mass drug administration (MDA), remained safe and effective in preventing clinical malaria, anaemia, and death. Further studies on pharmacokinetics, safety and efficacy of chemoprevention treatment are needed in specific high-risk groups beyond young children and pregnant women; for example, obese/overweight individuals, individuals with renal impairment, and malnourished children and including migrant workers, agricultural and plantation workers, forest goers or dwellers and other nomadic populations, to inform new policy guidelines. Adopting a chemoprevention treatment strategy for individuals with sickle cell disease and for children under five years admitted with severe (malaria) anaemia or receiving blood transfusion, reduced risk of morbidity and mortality in these groups.

Table1: Limited clinical studies on selected mobile & hard-to-reach groups

Risk group	Vector control					Chemoprevention					Vaccine
	ITN	IRS	Larviciding	Topical repellents	ITclothings	IPT	SMC	MDA	Chemo-prophylaxis	Pre-referral treatment	
Occupational characteristics											
Migrants/Refugees (including internally displaced persons-IDP/Migrant contract workers											
Military/Troops											
Miners (Mining workers)											
Airline crew members											
Construction/oil & gas workers											
Plantation workers (Rubber Tappers, Banana & plantains/ Rice/Sugar Cane Farmers)											
Socio-economic characteristics											
Forest Goers/Dwellers											
Nomadic Populations (cattle herders...)											
Poor and Rural communities											
People in Prisons/Enforced Segregation											
Epidemiological characteristics											
Imported/Non-Immune/traveller's/Tourists											
Residents in endemic settings (disrupted health systems/ humanitarian crisis)											
Environmental/geographical characteristics											
Rural communities											
Urban Dwellers (Urban malaria)											
Cross-border Communities											

: Very important ; somewhat important ; minimal importance or not feasible

*DEET: N, N diethyl-m-toluamide ** DEET not recommended for infants < 2months old*
ITN: Insecticide treated nets, IRS: Indoor residual spraying, IPT: Intermittent preventive therapy, SMC: Seasonal malaria chemoprevention, MDA: Mass drug administration

Fig2: Multipronged strategies to target mobile & hard-to-reach risk groups

Conclusions:

The growing rate of SP resistant and multi-drug resistant P. falciparum warrants new safe and effective anti-malaria regimens across high-risk groups including neglected population as elderly >60 years, migrants and mining workers, non-immune pregnant women, immunocompromise pregnant women/young children and splenectomised or functionally asplenic travellers. New regimens for SMC should be evaluated incorporating the RTS, S/AS01E vaccine.

Abbreviations: *AS: Artesunate, AQ:Amodiaquine, AM-PQP: Arterolane maleate-piperaquine phosphate, AP: Atovaquone+Proguanil SP: Sulfadoxine-Pyrimethamine, DP: Dihydroartemisinin-piperaquine, DX: Doxycycline, DX+CQ: Doxycyclin+Chloroquine, AL: Artemether-Lumefantrine, ASAQ: Artesunate-Amodiaquine, AZ: Azithromycin, MQ: Mefloquine, ASMQ: Artesunate, PQ: Primaquine, CQ: chloroquine, SPAS: Sulfadoxine-pyrimethamine +Artesunate, SPAQ: Sulfadoxine-pyrimethamine +Amodiaquine, MQSP: Mefloquine + Sulfadoxine-pyrimethamine, SPPQ: Sulfadoxine-pyrimethamine+Primaquine*