TACTs similar to those of the ACTs. Most importantly, in regions of southeast Asia with relevant ACT resistance (Cambodia, Thailand, and Vietnam), 42-day PCR-corrected efficacies were 98% (95% CI 94–100) for dihydroartemisinin–piperaquine plus mefloquine versus a dismal 48% (39–56) for dihydroartemisinin–piperaquine. The study was limited by a lack of blinding and by a relative lack of paediatric participants, who are the highest risk group for malaria worldwide, but who make up a small proportion of malaria cases in areas with ACT resistance.

These new results suggest that TACTs might replace ACTs. The addition of mefloquine to dihydroartemisinin–piperaquine rescued the regimen from unacceptably poor efficacy, and mefloquine might additionally restrict selection of resistance to piperaquine. If safety and tolerability remain acceptable in follow-up studies, use of optimally dosed and formulated TACTs to treat *P falciparum* malaria might soon be appropriate in regions with artemisinin resistance. However, most cases of *P falciparum* malaria occur in regions without established artemisinin resistance. Should TACTs be implemented in these regions? On the one hand, TACTs might delay the development of resistance to multiple antimalarials, a vital benefit.[10] On the other hand, despite promising initial results, adding another drug to established regimens will likely add to challenges regarding tolerability, toxicity, and drug interactions, especially considering known concerns for the partner drugs mefloquine and amodiaquine.[11] On the ground, there might be little enthusiasm for changing highly efficacious regimens because implementing any policy change is difficult. Thus, this study offers promise for TACTs in regions with artemisinin resistance, but whether we should implement TACTs in other areas is uncertain. In any event, TACTs should be seen as a stopgap; novel combination therapies to treat malaria are greatly needed.

I declare no competing interests.

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Reducing malaria transmission with reactive focal interventions

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A massive scale-up of investments in malaria control resulted in an estimated 663 million lives saved in sub-Saharan Africa between 2000 and 2015,[1] and 11 countries have been certified malaria-free in the current millennium.[2] Unfortunately, progress has stalled recently, and increases in malaria incidence were observed in several endemic countries.[3] Continuing with business as usual is likely to jeopardise gains made in the past 20 years, and slow the progress towards elimination goals. Innovative and targeted measures are required to complement universal coverage with basic vector control and case management interventions, especially as heterogeneity in case incidence increases with declining transmission.

In the last mile to achieving elimination, malaria transmission and the appearance of asymptomatic and clinical infections become increasingly focal. Targeted reactive approaches, such as reactive case detection (RACD), are likely to form efficient interventions to eliminate infections and prevent onward transmission.[4] Supporting research on the effectiveness and operational

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feasibility of various forms of reactive focal strategies is required.[5]

In the low *Plasmodium falciparum*-endemic area of northeastern Namibia, Michelle Hsiang and colleagues[6] report in *The Lancet* an innovative approach to test two such interventions: reactive focal mass drug administration (rfMDA), implemented as presumptive treatment with artemether-lumefantrine, and reactive focal vector control (RAVC) by indoor residual spraying of the insecticide pirimiphos-methyl. The cluster-randomised trial was done in 56 census enumeration area clusters. The study applied a two-by-two factorial design that allowed rfMDA to be compared with RACD (rapid diagnostic testing and treatment with artemether-lumefantrine), RAVC to be compared with no RAVC, and rfMDA plus RAVC to be compared with RACD only. An intention-to-treat analysis was done, and the primary outcome was the cluster-level cumulative incidence of autochthonous malaria cases.

Testing an intervention in a low-transmission setting means that finding a sufficient number of cases to demonstrate effectiveness is difficult. Nevertheless, the study[6] provided evidence that rfMDA and RAVC are both effective in reducing the incidence of malaria (rfMDA *vs* RACD, adjusted incidence rate ratio 0·52 [95% CI 0·16–0·88], p=0·009; and RAVC *vs* no RAVC, 0·48 [0·16–0·80], p=0·002), and that combining both interventions could be beneficial (rfMDA plus RAVC *vs* RACD only, 0·26 [0·10–0·68], p=0·006).

Simultaneously, this study[6] also highlights the difficulty inherent in demonstrating the effectiveness of interventions in a real-world setting.[7] The study period,[6] which was originally planned for 2 years, had to be limited to 1 year because of unforeseen operational challenges resulting from an increase in malaria cases in the first year. The observed outcomes are thus short-term results, and the sustainability of the achieved coverage and resulting effects are yet to be determined. Longer-term evaluations are essential, as effectiveness might reduce over time because of epidemiological fluctuations and health system constraints;[7,8] and studies[9] in other settings have found the effect of targeting hotspots to be transient. This requires long-term commitment from funding agencies, stamina from researchers and implementers, and acceptance from the scientific community that generating comprehensive results requires time.

An imbalance in the baseline characteristics across the study arms[6] could be adjusted for, thanks to a robust study design that measured the relevant indicators. However, the absence of buffer zones between implementation clusters could have led to a contamination effect that reduced the observed effectiveness of RAVC in this study. Furthermore, RAVC by indoor residual spraying of an insecticide has a residual effect that lasts for months (unlike RACD and rfMDA) and might therefore prevent onward transmission from future importations. The effectiveness of RAVC requires further investigation in longer running trials, as it could become a cornerstone of malaria elimination strategies.

The study[6] in Namibia was implemented as a trial, and hence with substantial external support. A high coverage (>80%) was achieved for all interventions. Case management, though not discussed in detail in the manuscript, could well have been better (in terms of coverage and quality) than in a non-study context. Most importantly, the study team invested substantial time and effort in working with local authorities to improve the completeness and timeliness of the passive surveillance system. As modelling suggests that the effectiveness of RACD (and probably also rfMDA) depends strongly on the quality of the passive surveillance system,[10] these interventions might not work equally as well outside of a trial setting. Additionally, the frequency of malaria importation from higher endemic areas, mosquito ecology and behaviour, and the presence of other malaria species (most notably *Plasmodium vivax*) could influence the effectiveness of the interventions tested in Namibia.

The limitations and challenges in the study by Hsiang and colleagues[6] do not diminish the relevance of their findings. Challenges with RACD due to high levels of subpatent infections not detected by conventional diagnostic tools have been found elsewhere.[11] Bold but evidence-supported actions are required to accelerate progress towards malaria elimination wherever possible. The presented evidence on rfMDA and RAVC, alone or in combination, should encourage larger scale implementation of these strategies in other settings, accompanied by well designed, long-term evaluations.

NC reports grants from the Bill & Melinda Gates Foundation. MWH declares no competing interests.

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Antiplatelet strategies in ageing patients with acute coronary syndromes

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Older patients who present with a non-ST-segment elevation acute coronary syndrome (NSTE-ACS) are at particular risk of recurrent ischaemic events, but also of bleeding complications.[1] Choosing the optimal dual antiplatelet strategy for the ageing patient with ACS can thus present a dilemma in daily practice. Should dual antiplatelet therapy in an older patient include the less potent P2Y12 inhibitor clopidogrel, thus minimising bleeding risk, or should a more potent P2Y12 inhibitor such as ticagrelor or prasugrel be used to avoid recurrent ischaemic events? In addition, the ideal dual antiplatelet therapy duration for these patients remains unclear. Unfortunately, guidelines do not contain specific age-tailored advice, reflecting the conflicting and suboptimal evidence from primary clinical studies.[1–5]

Additional guidance for treating older NSTE-ACS patients now comes from the POPular AGE trial by Marieke Gimbel and colleagues,[6] reported in *The Lancet*. In this study, 1002 patients with NSTE-ACS, aged 70 years or older (64% male and 36% female), were randomly assigned to either clopidogrel or one of the two more potent P2Y12 inhibitors, ticagrelor or prasugrel, for 1 year after their acute event. 475 (95%) patients received ticagrelor in the ticagrelor or prasugrel group; therefore, the results show a comparison between clopidogrel and ticagrelor. The primary outcome, any bleeding requiring medical intervention, was significantly lower in the clopidogrel group (88 [18%] of 500 patients) than in the ticagrelor group (118 [24%] of 502; hazard ratio [HR] 0·71, 95% CI 0·54–0·94; p=0·02). The reduction in bleeding risk with clopidogrel was not only driven by fewer minor bleedings, but also by a lower risk of major bleeding. There were also five fatal bleedings in the ticagrelor group versus none in the clopidogrel group. Net clinical benefit, a coprimary endpoint, including bleeding and ischaemic outcomes, was similar for both treatment groups (p=0·03 for non-inferiority). Although five stent thromboses occurred with clopidogrel versus none with ticagrelor, there were no differences in myocardial infarction or cardiovascular death. Overall, the study showed that in NSTE-ACS patients, aged 70 years or older, clopidogrel can decrease bleeding risk in a clinically