Randomised controlled trial

Monthly malaria chemoprevention shows potential in an area of very high, perennial malaria transmission

10.1136/ebmed-2015-110173

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Commentary on: Bigira V, Kapisi J, Clark TD, *et al*. Protective efficacy and safety of three antimalarial regimens for the prevention of malaria in young Ugandan children: a randomized controlled trial. *PLoS Med* 2014;11:e1001689.

Context

New approaches are needed for malaria control where the burden has remained high despite scaled up coverage of long-lasting insecticide-treated nets (LLIN) and prompt access to artemisinin-based combination therapies (ACTs).[1] Bigira and colleagues evaluated three regimens for chemoprevention of malaria in young children in eastern Uganda, in an area of very high year-round malaria transmission and high resistance to antifolate drugs, including sulfadoxine-pyrimethamine (SP) and sulfamethoxazole.

Methods

Children between 6 and 24 months of age were randomised to receive daily trimethoprim-sulfamethoxazole (TS), monthly SP, monthly dihydroartemisinin-piperaquine (DP) or no intervention. All study participants were given LLINs. Follow-up continued to 36 months of age. The primary outcome was incidence of uncomplicated malaria, treated with artemether-lumefantrine (AL).

Findings

Between 6 and 24 months of age, children without chemoprevention experienced almost seven malaria episodes per person-year, despite apparently high LLIN use. Monthly SP provided no protection against clinical malaria and possibly increased incidence of moderate–severe anaemia: protective efficacy (PE) −70% (95% CI −184% to −2%). Daily TS reduced clinical malaria by 28% (95% CI 7% to 44%) despite antifolate resistance. Monthly DP reduced clinical malaria by 58% (95% CI 45% to 67%) and possibly moderate–severe anaemia: PE 47% (95% CI 1% to 72%). Self-reported adherence was high but the reliability of this was unclear. There were no significant differences in incidence of complicated malaria or hospitalisation, although numbers were low. Between 24 and 36 months of age, children experienced close to 11 episodes per person-year, regardless of prior intervention group.

Commentary

A 58% reduction in malaria incidence in an area of such high burden reflects an important potential public health impact. However, efficacy is lower than expected given the regularity of dosing and the high efficacy of DP. Monthly DP given as directly observed therapy reduced clinical malaria by 96% among Ugandan school children.[2] This suggests adherence to monthly DP was not optimal under trial conditions, which is a concern. Lack of reliable information on adherence may also undermine the finding that piperaquine did not affect the QTc interval, although other studies have partly allayed these concerns.[3] ACTs such as DP are not ideal for chemoprevention because the artemisinin component is eliminated rapidly, leaving the partner drug as monotherapy soon after administration. New regimens specifically for chemoprevention are needed.

Chemoprevention requires carefully supervised delivery. This is because suboptimal adherence could accelerate development of resistance to the drugs used, if either incomplete courses are taken, or drugs are not readministered each month and concentrations fall below subtherapeutic levels. However, in areas of very high incidence, drug pressure on ACTs will be large even in the absence of chemoprevention: after the intervention period, children received 11 courses of AL per person-year. Well-administered chemoprevention may avoid these issues and help prolong the life of ACTs used for treatment. Community-based health workers may be one means to improve adherence, increase coverage outside the context of a trial, and may be more cost-effective per dose administered, as for monthly seasonal malaria chemoprevention.[4]

Implications for practice

Chemoprevention is currently recommended for children under 5 years old in areas of high and seasonal malaria transmission and in infants in areas with high malaria transmission and low SP resistance.[5 6] Adapting chemoprevention to areas with high, year-round transmission and/or high SP resistance could have a substantial impact. Additional research in this area is crucial to inform future changes in practice. Further studies are needed to evaluate adherence and delivery, the safety and pharmacokinetics of repeated treatments and selection for resistant parasites.

Despite exceptionally high transmission, the burden of clinical and complicated malaria was higher in the postintervention period in this study. Providing chemoprevention to a wider age range could potentially increase impact further. If monthly chemoprevention is given for longer, there may be more scope for rebound morbidity later in life, concerns also faced by preventive approaches including malaria vaccines.

While it is unclear how widely year-round chemoprevention will be appropriate, it will be most cost-effective in areas with very high incidence: control policy needs to be tailored to local epidemiology. Focusing on fewer areas may also limit the impact of chemoprevention on resistance. This will require policymakers to have accurate and regularly updated information on malaria epidemiology and drug resistance markers.

Contributors MC wrote the first draft of the commentary. PGTW revised the draft. Both the authors approved the final version.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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