



## CORRESPONDENCE

### Comment on: Randomized controlled trial of a traditional preparation of *Artemisia annua* L. (Annual Wormwood) in the treatment of malaria

In the article on a clinical trial of a traditional preparation of *Artemisia annua* by Mueller et al. (2004) the authors conclude that 'Monotherapy with tea preparations from *Artemisia annua* can, therefore, not be recommended as a treatment option for malaria because of recrudescence, as well as concerns about possible resistance development against artemisinin'.

However, the outcome measure used (parasite clearance at day 7) was unnecessarily stringent. WHO (1996) proposed new clinical outcome measures for endemic areas, where 'adequate clinical response' was defined as the absence of fever at day 14, irrespective of parasitaemia, or absence of parasitaemia at day 14, irrespective of body temperature (without first meeting criteria for early or late treatment failure). This is more pragmatic in a situation where reinfection occurs rapidly, and many patients harbour malaria parasites asymptotically. A low parasitaemia in the absence of symptoms is clinically insignificant in such circumstances, but would nevertheless have been judged as a treatment 'failure' in this trial.

Mueller et al. (2004) also found that the infusion of *A. annua* was more effective than chloroquine, which is often still recommended as a first-line drug in spite of high levels of resistance, because the alternatives are unaffordable. Even a full course of oral quinine, when it is available, may be unaffordable in the poorest parts of rural Africa. In such situations, it might be better to recommend local cultivation and use of artemisinin-rich *A. annua* varieties, than continued use of chloroquine. Some non-governmental organizations (NGOs), such as Anamed (<http://www.anamed.net>), are already advocating such an approach.

Mueller et al. (2004) showed that *Artemisia annua* tea was better tolerated than oral quinine, with much less tinnitus and nausea. Outside of the trial situation, compliance with *Artemisia annua* may be better than with quinine, especially if the herb is cheap and readily available. Furthermore, as the dose of *Artemisia annua* given was safe, it may be

possible to increase the dose in the tea in an attempt to reduce recrudescence rates.

The authors raise concerns about the possible development of resistance to artemisinin. However, artemisinin levels in the plasma remain at an antiparasitodal level for about four hours after administration of the tea, and thereafter the artemisinin is eliminated rapidly (Räth et al., 2004). Therefore, parasites will be exposed to subtherapeutic concentrations for only a very short time (in comparison, for example, to sulfadoxine-pyrimethamine, which remains at subtherapeutic levels in the plasma for up to 37 days). Furthermore, *Artemisia annua* contains many compounds other than artemisinin, some of which also have antimalarial activity, and act synergistically with it (Willcox et al., 2004). There is no evidence of resistance to artemisinin in China, although *Artemisia annua* teas have been used there for over 2000 years.

We consider the findings of Mueller et al. (2004) to be very encouraging, and believe that research on the traditional preparations of *Artemisia annua* should continue. We agree that future trials should consider combinations of *Artemisia annua*, either with other drugs or with other antimalarial plants, with the aim of reducing recrudescence rates. Future trials in endemic areas should measure clinical as well as parasitological outcomes.

### Conflicts of interest statement

The authors are members of the *Artemisia annua* Task Force of the Research Initiative for Traditional Antimalarial Methods (RITAM).

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