Artemisinin-based combination therapies (ACTs) and herbal drugs crosstalk: facts and perspectives

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Sir,

For the past decades, antimalarial drugs have been used according to recommendations established and adopted by most of the malaria endemic countries in the tropics. However, traditional remedies mainly made from plants remain extensively used against malaria and fever in general. Thus, traditional medicine has been integrated to primary health care policies (World Health Organization, 2002) or at least authorized. Since traditional medicines combine long-standing and evolving practices based on indigenous beliefs, their surveillance is particularly challenging and this compromises practical application of national policies. To tackle this issue, a better surveillance of herbal medications is essential but this can not be achieved without thorough plant knowledge. Differences observed in the way local populations make use of them undoubtedly clearly reflect their wide range of virtues (Ariey *et al.*, 2003; Penali *et al.*, 2007; Ramisiray, 1901; Randrianarivelojosia *et al.*, 2003; Rasoanaivo *et al.*, 1992). Unfortunately, although an extensive literature related to conventional drugs performance is already available, very little is known about safety and efficacy of plant-based remedies, even the most common ones.

Malaria control strategies in the tropics progressively turn towards the use of artemisinin-containing drugs, called ACTs for artemisinin-based combination therapies (World Health Organization, 2006). From the peculiar situation of Madagascar on, this letter reports main issues encountered when calibrated medications like ACTs are confronted to the use of empiric medicinal plants piloted by traditional practice. First of all, an unavoidable imbalance exists between intakes of ACTs and herbal remedies in Madagascar. The competition between these two medicines actually starts as early as their respective accessibility to local communities. Indeed, while medicinal plants are easily available within the village, from informal markets, as well as from supermarkets or convenience stores, ACTs remain essentially delivered by health facilities. Herbal drugs are commonly used as self-medication or prescribed by traditional healers to treat a broad range of illness (Novy, 1997; Rakotobe *et al.*, 1993; Ramisiray, 1901). So-called antimalarial plants are then administrated to treat malaria symptoms including fever, headache, fatigue, etc. (Novy, 1997; Penali *et al.*, 2007; Randrianarivelojosia *et al.*, 2003; Rasoanaivo *et al.*, 1992) or to enhance the activity of standard antimalarial drugs (Ramanitrahasimbola *et al.*, 2004). Since such intakes can not easily stay under the control of the medical staff prescribing treatments in case of malaria attack, they are susceptible of being taken by patients prior, during or after their ACT regimen without any reliable evidence. As mentioned above, the safety and the intrinsic activity of herbal preparations often remain unknown and in particular no (or few) data are available when they are associated to other active principles. Some observations have been reported about severe or fatal adverse events following herbal remedies intake anyway in Madagascar. To cite few, sudden death in a child was reported following the administration of *Crotalaria* sp. (Fabaceae) infusion as "tambavin-jaza" (childhood remedy) (Boiteau, 1968). Several cases of renal failure have been detected in hospital among patients taking *Lantana camara* (Verbenaceae) (Ramialiharisoa, unpublished) and among children taking "tambavin-jaza" (Andriamanjatoarinohatra, 1987). A skin rash was observed in a malaria infected patient following the administration of the "antimalarial" *Strychnos myrtoides* (Loganiaceae) decoction during a clinical trial (Ranaivoravo & Randrianarivelojosia, unpublished). This suggests that association of herbal drugs with antimalarials might present risks for the patient to develop adverse events, and such events could be excessively attributed to ACT.

From this review emerges a fundamental constraint. Whether an adverse effect has to be attributed to medicinal plants or to ACT itself (when simultaneously taken) is still a matter of debate. On the top of that, intrinsic activity and clinical efficacy of plants have to be demonstrated. If they crosstalk with ACT or not has not been investigated neither. Therefore, do we have to consider the intake of herbal drugs as an exclusion criterion during clinical trials? Even though patients would be willing to advert medical staff of any episode of herbal intake, this information is compro-

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mised anyway by two major satellite features. First is the impossibility to get accurate and reliable plant identifications when only based on patient interviews. Second is related to the cultural strength wrapping traditional medicine in general. Since traditions are deeply rooted in Malagasy societies and so are they in most African communities, herbal-based remedies are massively spread. Such practices are supported by strong social values and often ruled by secrecy, so that the exact nature of the plant taken and the frequency of intakes remain challenging even though critical to estimate. All the aspects related to the use of herbal remedies reported herein converge to that statement: in-depth studies of medicinal plants are definitely required to ensure an accurate pharmacovigilance of the conventional antimalarial drugs. Since national policies in the tropics recommend ACTs as first line drug for treating malaria, efforts have to be particularly focused on investigating the effects of herbal intakes in this context. This means that any plant-based intake, even preparations not supposed to act as a remedy like (traditional) tea, have to be documented during the follow-up of ACT-treated patients. Moreover, pharmacovigilance programmes have to be developed according to an active multi-site form in which the behaviour of ACTs in combination with local herbal drugs would be assessed in both rural and urban areas.

Up to date, concomitant intake of herbal medicines can not be due to compromise ACT efficacy and should not constitute an exclusion criterion in clinical studies. Nevertheless, it possibly makes analyses and interpretations more complex, for a more accurate final result though. For research purposes, volunteers could be discouraged from taking any herbal medicines once enrolled in an ACT study, instead of being excluded. The less complex study design is, the more accurate results reading is. Beyond toxicity risks, there is an obvious crosstalk existing between calibrated modern medicines, like ACTs, and empiric traditional remedies, made from plant. Improvement and development of in vitro methods to assess and predict the nature of these interactions are then crucial for a better control and a more efficient establishment of new antimalarial treatment strategies.

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