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Systematic review

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The recent Cochrane Collaboration review by Jacquerioz and Croft on drugs to prevent malaria in travellers is a welcome evaluation of randomised controlled trials of malaria chemoprophylaxis in non-immune individuals. The goal of the systematic review was to evaluate the efficacy, safety and tolerability of atovaquone-proguanil, doxycycline and mefloquine (the three priority regimens for malaria prophylaxis) compared with each other, with the defunct combination chloroquine-proguanil, doxycycline and mefloquine (the three priority regimens for malaria prophylaxis) compared with each other, with the defunct combination chloroquine-proguanil, and with primaquine (considered in some countries to be a candidate for chemoprophylaxis of travellers’ malaria).

This systematic review is particularly valuable for the fact that the stringent selection process meant that only scientifically rigorous trials were included. The authors used appropriate search terms and strategies in screening the chosen databases (the Cochrane Infectious Diseases Group Specialised Register, the Cochrane Central Register of Controlled Trials, the Cochrane Library, Medline, Embase, Lilacs, Biosis and the metaRegister of Controlled Trials). They also contacted malaria drug experts and pharmaceutical companies and hand-searched conference proceedings.

The authors did not find sufficient evidence to allow a comparison of the efficacy of the drugs, and so their focus narrowed to the tolerability of antimalarials used in chemoprophylaxis. For the evaluation of tolerability, primaquine was dropped from the comparators, again because of insufficient evidence. The systematic review could, in essence, be renamed as a systematic review on the tolerability of currently used drugs for preventing malaria in travellers.

Despite the rigorous and appropriate searches, only eight trials (with a total of 4240 randomised participants,
including 1098 soldiers) met the inclusion criteria. No serious adverse events occurred in any of the included studies. This fact should have been highlighted in the abstract. The authors concluded there is little quality evidence on the tolerability of antimalarial drugs, that atovaquone-proguanil and doxycycline are best tolerated and that mefloquine has more adverse effects than other regimens (with the exception of chloroquine-proguanil). These core findings of the review, together with the data presented on moods, mirror exactly the findings of the four-arm double-blind study of malaria chemoprophylaxis published in 2003.\(^1\) Jacquerioz and Croft are to be commended for the scientific rigour applied to the selection of studies included in the review, but this rigour is lost when they report on their search for case reports of deaths in the literature. The authors found case reports of 22 deaths "associated with mefloquine," but they do not put these cases into context. They fail to indicate the number of mefloquine users (as denominator data), which is estimated to be well in excess of 35 million, which would make mefloquine a very safe drug indeed! They do not indicate how many lives were saved, in terms of malaria cases prevented, by the use of mefloquine prophylaxis for high-risk malaria endemic areas. Furthermore, they do not cite an International Society of Travel Medicine congress abstract\(^2\) presenting a database analysis of suicide that showed no excess of suicide in mefloquine users compared with high background incidence in male populations worldwide.

The review should have focused exclusively on controlled clinical studies. If case report data are used and these tend to be sensational and anecdotal, then powerful record linkage analyses also need to be cited, as these provide an evidence-based analysis. Two such analyses were not unduly negative for mefloquine users.\(^3\,\^{4}\) The sections at the beginning of the article showing registration details of drugs are more appropriate as appendices and detract from the core review.

The authors rightly call for more malaria chemoprophylaxis trials with a focus on non-immune travelers and an emphasis on women and children rather than soldiers, and they raise the subject of bias. Gender aspects are assuming great importance,\(^5\) and the excess poor tolerability of mefloquine in women warrants further evaluation. Prospective controlled studies are complex and expensive and require financial support, but a multiarm study can still be independent if research grants are provided and an academic institution assumes the role of sponsor rather than the drug companies. Innovative use of record linkage databases can evaluate research questions without bias. Ultimately the common goal is to provide accurate data to travel medicine practitioners so that malaria chemoprophylaxis guidelines are based on evidence rather than anecdote.

**Competing interests:** PS has received research grants, consultancy fees and speaker’s honoraria from GlaxoSmithKline and F. Hoffmann-La Roche

**References**