Reply to Lauhio et al

To the Editor—We thank Lauhio et al for bringing up a noteworthy point [1] in our recent study [2] showing that the long-term use of doxycycline is not a risk factor for colonization with travel-acquired extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-PE), a result recently confirmed by Ruppe et al [3]. This finding is especially relevant from the viewpoint that doxycycline is one of the 3 alternatives officially recommended for antimalarial prophylaxis and it is considered effective in all malaria-endemic regions [4]. With the concerns on mefloquine
use [5], doxycycline may become more widely used, also providing a more affordable alternative to the third prophylactic regimen, atovaquone-proguanil.

Lauhio et al inquired about the dosing and regimen of doxycycline in our study. The volunteers were prescribed doxycycline hyclate 100 mg once daily for prophylaxis, starting 1 day before arrival in a malaria-endemic region, to be continued throughout the stay and for 4 weeks after leaving the area, all in accordance with current recommendations [4]. Ninety-six percent of our volunteers reported regular intake of the antimalarial (data not shown).

By disrupting the colonization resistance provided by each traveler’s own microbiota [6, 7], antibiotics make space for newcomers. As a manifestation of this, we found antibiotics to be an independent risk factor for colonization with travel-acquired ESBL-PE [2]. Interestingly, however, even if doxycycline as an antibiotic is expected to kill members of the intestinal microbiota sensitive to this drug [8], in our study, doxycycline did not differ from other antimalarials with respect to the risk of acquiring ESBL-PE [2]. It is interesting to cogitate further on this.

If most intestinal bacteria were already resistant to doxycycline at baseline, this drug would only have a limited effect on the intestinal microbiota, and could thus be considered quite safe. If, however, most of the intestinal bacteria were doxycycline sensitive, the drug could be expected to have a significant impact on the microbiota. Whether this would predispose to ESBL-PE would depend on a number of factors, such as the doxycycline sensitivity of the strains. Reports on the influence of long-term doxycycline on gut microbiota are somewhat controversial [8, 9].

Our data showing no differences between the 3 antimalarial subgroups should not be exploited beyond our focus on ESBL-PE to indicate lack of risk for contracting other resistant bacteria; strains resistant to various non-β-lactam antibiotics (doxycycline and others) were not covered separately. This point is nicely exemplified by a previous study [10] in which 22% of returning travelers had ESBL-PE, yet another 27% carried non-ESBL-PE strains resistant either to ciprofloxacin, gentamicin, or third-generation cephalosporins. It is essential to note, however, that despite missing a multitude of other changes, exploring the acquisition of ESBL-PE offers a pertinent model of the risk factors and travel-related changes in the microbiota. As for doxycycline, its effect on the selection of travel-acquired microbes calls for further research.

### Notes

**Potential conflict of interest.** A. K. has received lecture fees from Baxter, Crucell, Glaxo SmithKline (GSK), Pfizer, and PauVax and fees for participation in meetings in travel medicine from GSK, Crucell, and Janssen. T. L. reports no potential conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

### References


Correspondence: Anu Kantele, MD, PhD, Inflammation Center, Clinic of Infectious Diseases, University of Helsinki and Helsinki University Hospital, POB 348, FI-00029 HUS, Helsinki, Finland (anu.kantele@hus.fi)."