Reply to Nevin

We agree with Nevin [1] that the post-marketing surveillance methodology of our article [2] has similarities with the analysis published in 1998 by Vanhauwere and colleagues [3]. We appropriately referenced the aforementioned paper in our publication. Our methodology however, differs in that we separately analyzed maternal, paternal, and both-parent exposure to mefloquine, and the time period for our study was significantly longer (1986–2010) [2]. Furthermore, for comparison, we provided background rates for pregnancy outcomes in the general population.

We disagree that the use of this methodology should limit the usefulness of our data. Pregnant women are routinely excluded from clinical trials. For many medications that are initially contraindicated in pregnancy, the use of drug safety databases constitutes an important tool for assessing safety during pregnancy. Our analysis provides physicians and patients with information for the evaluation of benefit and risk in women of childbearing potential exposed to mefloquine.

Our main outcome measures were descriptive birth defect reporting prevalence and types of malformations. We also provided limited data on fetal loss and reviewed all literature on this subject including the references that Nevin cites in his letter and other references that he omitted to mention. Fetal loss or miscarriage is difficult to quantify in any population due to ascertainment bias [4], and epidemiological data from previous studies show varying results: a Thai study reported an increased risk of miscarriage in 159 mefloquine prophylaxis users [5], whereas a second larger study in Malawi showed no increase in stillbirths in women receiving mefloquine prophylaxis (n = 1032) [6].

Nevin refers to the use of sulfadoxine-pyrimethamine as intermittent treatment in the developing world for pregnant women. This is a separate topic that we did not address. Our paper is concerned with malaria prophylaxis in pregnant women from industrialized countries who cannot defer travel to malaria-endemic areas.

Dr Nevin's other letter [7] suggests a biological mechanism linking mefloquine to pregnancy loss. This proposed mechanism warrants further inquiry but because it is a hypothesis, based on non-clinical data, it should be interpreted with caution in the human context.

Various factors, such as age and exposure to malaria, could contribute to the loss of pregnancy in women traveling to endemic areas. A large study from Denmark showed that the risk of spontaneous abortion in women aged 20–24

is 8%–9%, rising with age to 74.7% in women aged >45 years [8]. Exposure to malaria further increases the risk of fetal loss. A recent analysis found that a single episode of *Plasmodium falciparum* or *Plasmodium vivax* malaria could cause miscarriage [9].

Malaria in women of childbearing potential needs to be prevented. The recent data on imported malaria in the US report 41 cases in pregnant women in 2010, the majority traveling to Africa and not using a chemoprophylaxis [10]. In 2011, the Food and Drug Administration reclassified mefloquine from pregnancy category C to category B. The Centers for Disease Control and Prevention recommends mefloquine prophylaxis in all trimesters of pregnancy for women who cannot defer travel to high-risk, malaria-endemic areas [11].

Note

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All 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.

Patricia Schlagenhauf,[1] William A. Blumentals,[2] Pia Suter,[2] Loredana Regep,[2] Gabriel Vital-Durand,[2] Martin T. Schaerer,[2] Margarita Suarez Boutros,[2] Hans-Georg Rhein,[2] and Miriam Adamcova[2]

[1]University of Zurich Centre for Travel Medicine, World Health Organization Collaborating Centre on Travel and Health, Institute for Social and Preventive Medicine, Zurich, and [2]F. Hoffmann-La Roche, Basel, Switzerland

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Correspondence. Professor Patricia Schlagenhauf, PhD, University of Zurich Centre for Travel Medicine, WHO Collaborating Centre for Travellers' Health, Institute for Social and Preventive Medicine, Hirschengraben 84, 8001 Zurich, Switzerland (pat@ifspm.uzh.ch).

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