Reply to Arya and Agarwal

To the Editor—We recognize and share the concerns expressed by Arya and Agarwal on the issue of drug quality in the treatment of visceral leishmaniasis (VL) [1], but dismiss this as a possible explanation for the observed high relapse rate in our study and, more generally, we favor a different approach to cope with this issue.

As Arya and Agarwal accurately point out, we have previously described the first case of a "substandard" miltefosine medicine from Bangladesh that did not contain any of its active ingredient, miltefosine [2]. This product was manufactured locally for the Bangladeshi elimination program for VL, but has been replaced now in Bangladesh by the originator product Impavido manufactured by Paladin Labs. The product that was and is being used in the Nepali VL elimination program, and thus was used throughout the reported cohort study, is the same quality-controlled originator product by Paladin Labs. Moreover, following our clinical finding of increased relapse rates in miltefosine-treated Nepali VL patients, we performed additional quality checks using liquid chromatography coupled to tandem mass spectrometry on the batch of miltefosine capsules used by the patients in our study, which confirmed that these capsules contained the exact declared amount of miltefosine. This is further corroborated by representable pharmacokinetic profiles of miltefosine in our patients, as illustrated in our publication [3]. All in all, the increase in relapse rates for VL in Nepal as reported

by us cannot be due to low quality of the miltefosine drug in use in Nepal.

Additionally, the storage conditions for miltefosine are less strict than depicted by Arya and Agarwal: Miltefosine is not light-sensitive, does not need to be stored cooled, and remains stable in hot and humid environments (ICH climatic zone IV), with a validated shelf-life of 5 years when kept in the original alu-foil blister packages.

The role of simple detection methods to assess drug quality in the field, as suggested by Arya and Agarwal, remains dubious. Indeed, we have previously developed a simple colorimetric assay that can be used in the field to detect and quantify miltefosine content in pharmaceutical preparations [4]. However, use and implementation of such a point-of-care test would only spot some bad apples, but would not uproot the general problem of poor-quality medicines. Priority should thus be given to actions that would prevent the production and distribution of such products, by implementing, strengthening, and enforcing good drug regulatory oversight in low- and middle-income countries and by making procurement policies more transparent [5, 6]. Without good regulatory oversight, simple detection methods can be helpful to monitor the problem of poor-quality drugs but will not be able to solve the issue.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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.

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