Delamanid susceptibility testing of Mycobacterium tuberculosis using the resazurin microtitre assay and the BACTEC™ MGIT™ 960 system—authors’ response

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Sir,

Imkamp et al.1 raise some interesting points in their comments for which we thank them. Indeed, drug susceptibility testing (DST) of delamanid is challenged by a certain instability of the compound when stored in liquid solution. We observed a loss of activity after 6 months of storage in DMSO at −20°C. As long as the compound was stored for less than half a year, the instability did not impact our DST results either in MGIT or in the resazurin microtitre assay or with the agar proportional method. Otsuka provides a separate stabilizer upon request that is not included in the delamanid powder. We did not use it and were able to yield reproducible and repeatable MIC results with the pure substance alone.2

The comments of Imkamp et al.1 raise a very important aspect regarding the establishment of DST for the new anti-mycobacterial drugs in high-prevalence countries. In multiple countries with high prevalence rates of resistant forms of TB, delamanid, bedaquiline, linezolid and clofazimine are currently being introduced in anti-MDR-TB regimens. While most countries with emerging MDR-TB have successfully implemented DST of first-line drugs, fluoroquinolones and injectables with technical assistance from the Supranational Reference Laboratory Network (SRLN; http://www.stoptb.org/wg/gli/srln.asp) of the WHO, to our knowledge, none of the countries is testing the susceptibility of MDR-TB isolates to the new groups C and D2 of second-line anti-TB agents.3,4 We recently reported an MDR-TB case with double resistance to both new drugs delamanid and bedaquiline.5 In our technical experiments for the standard protocol of DST in MGIT we have observed clinical Mycobacterium tuberculosis isolates with resistance to delamanid although they were never exposed to the drug.2 The previously described mechanism of cross-resistance of clofazimine and bedaquiline leads to the conclusion that with the intensified use of clofazimine following the roll-out of short-term MDR treatment, resistance to bedaquiline will emerge.6 All this underlines the urge of implementation of DST for all drugs in regions where rates of MDR-TB are high.7 The implementation should be supported by WHO policies in the very short-term and facilitated by the manufacturing companies by simplified access to the test compounds. In this respect we are grateful to Imkamp et al.1 for their call to simplify access to test substances, which should, however, be extended to all manufacturers of anti-TB drugs. While bedaquiline is accessible in quantities of up to 40 mg per year only after registration and approval by the US NIH AIDS Reagent Program (https://www.aidsreagent.org/reagentdetail.cfm?oi_and_hcv&sid=99), delamanid is provided by Otsuka Novel Products GmbH (Munich, Germany) upon signature of a material transfer agreement (MTA). MTAs are common practice to regulate exchange of substances covered by patents and, despite imposing certain restrictions, protect both parties. This is particularly important in high-prevalence countries where laboratory capacities are currently under development towards international standards with enormous efforts and technical input from the SRLN and many other stakeholders. It must be guaranteed by the manufacturers that all national and supranational reference laboratories get access to test substances and protocols for DST of all anti-TB drugs. We also believe that anti-TB drugs should be introduced into new markets always together with validated DST protocols and with the implementation of responsible antibiotic stewardship programmes in order to prevent uncontrolled emergence of new resistances.

Transparency declarations
None to declare.

References