trachomatis. The authors believe that this was mediated by interactions with a host cell target involved in resisting infection.

In the current scenario of increasing incidence of drug-resistant tuberculosis, any promising new drug should be carefully evaluated. Ivermectin and moxidectin are the only clinically tested members of the avermectin family, representing a new chemical entity in the antituberculosis armamentarium. The in vitro bactericidal activity of the avermectins against both drug-susceptible and drug-resistant M. tuberculosis clinical isolates, their mycobacterial specificity, their potential new mode of action and the extensive pre-clinical and clinical literature make this family of drugs attractive for future studies. Here, we find common ground with the closing statement of Muhammed Ameen and Drancourt: ‘Additional studies are required to precisely determine the potential of ivermectin as an antituberculous drug’.

**Acknowledgements**

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**Transparency declarations**

None to declare.

**Table 1.** MIC (mg/L) of ivermectin in broth and agar media

<table>
<thead>
<tr>
<th>M. tuberculosis strain</th>
<th>Broth&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Agar&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>H37Rv</td>
<td>8</td>
<td>&gt;40</td>
</tr>
<tr>
<td>CDC 1551</td>
<td>4–8</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Erdman</td>
<td>8–16</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

<sup>a</sup>MIC determination was performed as described in Lim et al.<sup>1</sup>

<sup>b</sup>MIC determination was performed as described in Muhammed Ameen and Drancourt.<sup>2</sup>

**References**


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**Keywords:** tuberculosis, antituberculosis drugs, antiparasitics

**Comment on: Measurements of the in vitro anti-mycobacterial activity of ivermectin are method-dependent**

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**Keywords:** tuberculosis, antituberculosis drugs, antiparasitics

Sir,

Ramón-García et al.<sup>1</sup> rightly point to the limitations of current antimycobacterial assays performed in axenic culture medium, either broth<sup>1–2</sup> or agar. <sup>1–3</sup> It is interesting to note, as our colleagues did,<sup>1</sup> that the only undisputed results regarding ivermectin and bacteria have been obtained for *Chlamydia trachomatis*<sup>4</sup> in cell culture. These observations may suggest further testing of ivermectin and mycobacteria using cell culture assays, as mycobacteria, including *Mycobacterium tuberculosis*, are intracellular pathogens.<sup>5</sup> However, the major point we disputed in our study was that the MICs reported by our colleagues<sup>1–2</sup> and ourselves<sup>3</sup> are far above the concentration reported in patients treated with ivermectin for parasitoses. The fact is that a concentration of ivermectin in the order of magnitude of the MIC (in mg/L) has never been achieved in patients. The only issue would be to demonstrate an intracellular concentration of ivermectin above the intracellular MIC for mycobacteria, including *M. tuberculosis*. Therefore, we do agree with our colleagues that it is time to...
develop a new generation of in vitro assays, based on cultured cells. Demonstrating an antituberculous activity of ivermectin would be good news in the current era of extended and totally resistant tuberculosis.

Transparency declarations
None to declare.

References

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Measurements of the in vitro anti-mycobacterial activity of ivermectin are method-dependent—authors’ response

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Keywords: tuberculosis, avermectins, antituberculosis drugs, ivermectin

Sir,

Discovering and developing new drugs for treating tuberculosis (TB) is a complex and challenging endeavour and very few drugs have been found that are clinically effective. To be effective, drugs must enter the plasma and move to disperse tissues in which mycobacterial cells reside, both intracellularly and extracellularly. Furthermore, mycobacterial cells residing in these environments are in different physiological states, and therefore likely to have associated differences in drug susceptibilities. It is clear that no single drug in our limited TB drug pool can effectively reach and kill all mycobacterial subpopulations. Discarding potential TB drugs based only on plasma indices or intracellular activity, as Muhammed Ameen and Drancourt propose, might be a relevant selection criterion if large numbers of clinically tested drugs with activity in vitro were available; however, this is currently not the case for TB drugs. Given this situation, we cannot afford to ignore active drug candidates that have been used clinically for other purposes.

Ivermectin is approved for human use in many countries to treat onchocerciasis, lymphatic filariasis, strongyloidiasis and scabies. Muhammed Ameen and Drancourt emphasize that effective dosage levels for these conditions are unusually low and would not be effective for TB treatment. Ivermectin is typically administered once a month at a standard dose of 12 mg (maximal concentration in plasma of ~50 ng/mL). However, very little is known about the safety and tolerability of ivermectin at higher doses or after more frequent administration. A study in healthy volunteers showed that doses 10 times higher (120 mg) were safe and correlated with higher plasma concentrations (~0.25 μg/mL). In fact, the more severe reactions observed in the treatment of onchocerciasis and lymphatic filariasis with ivermectin are most likely to be secondary immunological effects triggered by the death of the parasite. Thus, higher ivermectin dosages should be explored for TB treatment. Furthermore, we have recently demonstrated that synergistic drug combinations could allow the use of drugs that normally do not inhibit Mycobacterium tuberculosis at clinically relevant concentrations. Exploring the synergistic interactions of ivermectin with current anti-TB drugs could allow its use in combinatorial therapies for multidrug-resistant and extensively drug-resistant TB at dosages lower than the MICs of the individual drugs.

In summary, our recent discovery showing direct in vitro anti-mycobacterial activity of the avermectins represents only a first step in the long, complex and challenging process of TB drug selection and development. Determining whether ivermectin, or other avermectins, could supplement the current TB armamentarium would require a highly interdisciplinary and comprehensive drug development approach.

Transparency declarations
None to declare.

References