Author's response to reviews

Title: Successful MDR-TB treatment regimens including Amikacin are associated with high rates of hearing loss

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Editor-in-Chief
BMC Infectious Diseases
BioMed Central
236 Gray's Inn Road
London WC1X 8HB
United Kingdom

Re: Submission of the manuscript entitled “High rates of hearing loss in patients treated for MDR-TB”

Dear Editor,

We are submitting the manuscript entitled “High rates of hearing loss in patients treated for MDR-TB” for consideration for publication in your prestigious journal.

Despite extensive TB control efforts implemented over the last two decades, multi drug resistant tuberculosis (MDR-TB) is an increasing global problem. The overwhelming burden of MDR-TB is in resource-poor countries, where co-infection with HIV is common. Co-infection was associated with 100% mortality, but with greater awareness and earlier diagnosis and treatment, the survival rate has increased up to 50%. Fluoroquinolones and aminoglycosides are considered to be the critical potent drugs that constitute MDR-TB treatment that may have helped reduce the mortality rate.

Hence World Health Organization guideline recommends a minimum of 8 months of aminoglycosides use. Despite their widespread use, they have substantial toxicity, causing, in particular, irreversible hearing loss. Their optimal dosage and treatment duration for the treatment of MDR-TB are limited and are particularly scarce in patients co-infected with MDR-TB and HIV. We analyzed the effects of amikacin-based regimens on the clinical outcomes of MDR-TB patients and the risk factors associated with the development of hearing loss.
Our study shows that although high rates of clinical success are achieved with amikacin use in MDR-TB, it is accompanied by a high incidence of hearing loss close to 70%, the highest that has been documented.

Moreover, our results suggested that both good clinical outcomes and hearing loss are strongly associated with higher amikacin dosages and longer administration durations. This property of AGs has been demonstrated in vitro for MDR-TB strains but our results are the first to support the conclusion that the bactericidal effect of AGs on MDR-TB isolates in vivo is also concentration-dependent. We are the first group to confirm that amikacin dosage and amikacin duration are independently associated with the development of hearing loss, but also that they have a strong interaction with each other, in MDR-TB treatment.

Our results also show that despite the vast majority of our patients receiving an adequate dosage per weight and renal function as per the World Health Organization, there was still a high incidence of ototoxicity, suggesting that these recommended dosages may not apply to every population. We did not find any association between hearing loss and HIV infection, regardless of anti-retroviral therapy use or CD4 cell count.

All authors have seen and approved the manuscript. They have all contributed significantly to the work. The manuscript has not been previously published nor is it being considered for publication elsewhere.

The changes made in the revision include: addition of the all email addresses of the authors on the ‘Title Page’ and moving ‘Competing Interest’, ‘Author’s Contribution’ and ‘Acknowledgements’ section after the ‘Conclusion’ section.

Please do not hesitate to contact me for any further information.

Sincerely,

[Signature]

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Sincerely,
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