Annals of the American Thoracic Society

Dear Prof. Cooke,

Re: *Carriage and transmission of macrolide resistance genes in patients with chronic respiratory conditions and their close contacts*

The use of macrolide antibiotics to prevent pulmonary exacerbations in those with chronic respiratory diseases continues to increase. While long-term treatment with macrolides in chronic respiratory disease appears to be safe and effective, the potential for increased carriage and dissemination of antibiotic resistance is a potential concern. This has been highlighted in a number of clinical guidelines and manuals for long-term macrolide use, including: Prevention of COPD exacerbations: an ERS/ATS guideline, 2017; GINA Guidelines for difficult-to-treat & severe asthma, 2019; and Bronchiectasis: The EMBARC Manual 2017.

In our study, we hypothesised that the carriage of macrolide resistance genes, and associated resistance genes under co-selection, would be more frequent within the oropharyngeal microbiota of recipients of long-term azithromycin for chronic respiratory conditions, compared to azithromycin-naïve patients. We further hypothesised that any differences in resistance carriage between recipient and non-recipient patients would be reflected in resistance carriage rates in patient close contacts, suggesting a potential route for person to person transmission of resistance genes. We assessed carriage of ten macrolide-associated resistance genes in oropharyngeal swabs from 52 individuals with chronic respiratory conditions (44 cystic fibrosis, 8 asthma), of whom 35 were receiving long-term azithromycin. In each case, an additional oropharyngeal swab was assessed from a close co-habiting contact.

In an important extension of our current understanding, we found long-term azithromycin in patients with chronic respiratory conditions to be associated with increased abundance of associated resistance genes within the oropharyngeal microbiota. Azithromycin exposure was not, however, associated with increased resistance gene carriage frequency. A significant association was identified between carriage of *erm*(F) in patients receiving AZM and carriage by close contacts. However, *erm*(F) carriage was not significantly higher in close contacts of AZM patient compared to non-AZM patients.

This work is not under consideration for publication by any other journal and no author has any relevant conflict of interest. We thank you in advance for your consideration of our work.

Yours sincerely,

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