This is a repository copy of Comment on: Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant Streptococcus pneumoniae: analysis of Phase 3 clinical trial data.

White Rose Research Online URL for this paper: http://eprints.whiterose.ac.uk/91371/

Version: Accepted Version

Article:

https://doi.org/10.1093/jac/dkv212

Reuse
Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher’s website.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.
Title: Comment on: Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant Streptococcus pneumoniae: analysis of Phase 3 clinical trial data.

Author: Andrew Kirby*, The University of Leeds and Leeds Teaching Hospitals NHS Trust. Old Medical School, Leeds General Infirmary, Leeds, LS1 3EX, UK. E-mail: a.kirby@leeds.ac.uk. Telephone: 0113 3923929

Corresponding author: Andrew Kirby

Running title: S. pneumoniae azithromycin MICs and clinical outcome.
Comment on: Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant *Streptococcus pneumoniae*: analysis of Phase 3 clinical trial data.

Zhanel *et al.* report that *Streptococcus pneumoniae* azithromycin MICs ≥2mg/L, compared to <0.5mg/L, predict worse outcomes in azithromycin treated *S. pneumoniae* respiratory tract infections.¹ This relationship between MIC and outcome is not a linear dose (MIC) response relationship. Whilst an MIC ≥2mg/L predicts worse outcomes, outcomes are no different if the *S. pneumoniae* MIC is 2-8mg/L, ≥16 or ≥ 64mg/L. The absence of a linear dose (MIC) response relationship is not explained and raises the possibility that the MIC is not causally related to outcomes.² Defining if an MIC is causally related to outcome is important to ensure the maximal benefit from azithromycin treatment can be obtained. Given this non-linear dose response relationship I suggest further analysis is required to understand the study findings. Specifically, an analysis of individual patient factors should be completed. It may be that patient factors e.g. age, co-morbidities, previous episodes of respiratory tract infection or macrolide treatment, are associated with both treatment failure and azithromycin MICs. A study by Moreno *et al.* supports this possible explanation, they showed nosocomial acquisition of a *S. pneumoniae* infection was a risk factor for macrolide (erythromycin) resistance.³ Data from Holmes *et al.* has also shown that raised MICs are not always causally related to outcomes. Holmes *et al.* investigated outcomes from *Staphylococcus aureus* bacteraemia in relation to vancomycin MICs.⁴ A multivariate analysis determined that raised vancomycin MICs were associated with poorer clinical outcomes, even in the absence of vancomycin treatment. Might a raised *S. pneumoniae* azithromycin MIC also be a predictor of a poorer outcome, but not one related to a reduced efficacy of azithromycin treatment? A multivariate analysis is required to determine if patient factors may explain the observed association between azithromycin resistance and outcome in the treatment of *S. pneumoniae* respiratory tract infection. Such analyses have been completed for penicillin treated *S. pneumoniae* respiratory tract infections. One such analysis by Pallares *et al.* showed that after adjusting for co-morbidities the odds ratio for mortality in patients with penicillin-resistant, compared to penicillin sensitive strains, was 1.0.⁵ If patient factors do explain the association between MICs of ≥2mg/L and clinical failure, MIC criteria defining resistance for azithromycin treatment of *S. pneumoniae* respiratory tract infections may be unhelpful in predicting an individuals risk of treatment failure.

Transparency declarations: None to declare

References


