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1 **Title:** Comment on: Clinical cure rates in subjects treated with azithromycin for community-acquired
2 respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant
3 *Streptococcus pneumoniae*: analysis of Phase 3 clinical trial data.

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8 **Running title:** *S. pneumoniae* azithromycin MICs and clinical outcome.

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29 **Comment on: Clinical cure rates in subjects treated with azithromycin for community-acquired**
30 **respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant**
31 ***Streptococcus pneumoniae*: analysis of Phase 3 clinical trial data.**

32 Zhanel *et al.* report that *Streptococcus pneumoniae* azithromycin MICs $\geq 2\text{mg/L}$, compared to
33 $< 0.5\text{mg/L}$, predict worse outcomes in azithromycin treated *S. pneumoniae* respiratory tract
34 infections.¹ This relationship between MIC and outcome is not a linear dose (MIC) response
35 relationship. Whilst an MIC $\geq 2\text{mg/L}$ predicts worse outcomes, outcomes are no different if the *S.*
36 *pneumoniae* MIC is 2-8mg/L, ≥ 16 or $\geq 64\text{mg/L}$. The absence of a linear dose (MIC) response
37 relationship is not explained and raises the possibility that the MIC is not causally related to
38 outcomes.² Defining if an MIC is causally related to outcome is important to ensure the maximal
39 benefit from azithromycin treatment can be obtained. Given this non-linear dose response
40 relationship I suggest further analysis is required to understand the study findings. Specifically, an
41 analysis of individual patient factors should be completed. It may be that patient factors e.g. age, co-
42 morbidities, previous episodes of respiratory tract infection or macrolide treatment, are associated
43 with both treatment failure and azithromycin MICs. A study by Moreno *et al.* supports this possible
44 explanation, they showed nosocomial acquisition of a *S. pneumoniae* infection was a risk factor for
45 macrolide (erythromycin) resistance.³ Data from Holmes *et al.* has also shown that raised MICs are
46 not always causally related to outcomes. Holmes *et al.* investigated outcomes from *Staphylococcus*
47 *aureus* bacteraemia in relation to vancomycin MICs.⁴ A multivariate analysis determined that raised
48 vancomycin MICs were associated with poorer clinical outcomes, even in the absence of vancomycin
49 treatment. Might a raised *S. pneumoniae* azithromycin MIC also be a predictor of a poorer outcome,
50 but not one related to a reduced efficacy of azithromycin treatment? A multivariate analysis is
51 required to determine if patient factors may explain the observed association between azithromycin
52 resistance and outcome in the treatment of *S. pneumoniae* respiratory tract infection. Such analyses
53 have been completed for penicillin treated *S. pneumoniae* respiratory tract infections. One such
54 analysis by Pallares *et al.* showed that after adjusting for co-morbidities the odds ratio for mortality
55 in patients with penicillin-resistant, compared to penicillin sensitive strains, was 1.0.⁵ If patient
56 factors do explain the association between MICs of $\geq 2\text{mg/L}$ and clinical failure, MIC criteria defining
57 resistance for azithromycin treatment of *S. pneumoniae* respiratory tract infections may be
58 unhelpful in predicting an individuals risk of treatment failure.

59 **Transparency declarations:** None to declare

60 **References**

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