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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.<sup>1</sup> 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  $2\text{--}8\text{mg/L}$ ,  $\geq 16$  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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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**

- 61 1- Zhanel GG, Wolter KD, Calciu C, et al. Clinical cure rates in subjects treated with azithromycin  
62 for community-acquired respiratory tract infections caused by azithromycin-susceptible or  
63 azithromycin-resistant *Streptococcus pneumoniae*: analysis of Phase 3 clinical trial data. J  
64 Antimicrob Chemother 2014;69:2835-40.
- 65 2- Hill AB. The environment and disease: Association or causation? Proceed Roy Soc Medicine  
66 1965;58:295-300.
- 67 3- Moreno S, Garcia-Leoni ME, Cercenado E, et al. Infections caused by erythromycin-resistant  
68 *Streptococcus pneumoniae*: incidence, risk factors, and response to therapy in a prospective  
69 study. Clin Infect Dis 1995;20:1195-200.

- 70 4- Holmes NE, Turnidge JD, Munckhof WJ, et al. Antibiotic choice may not explain poorer  
71 outcomes in patients with *Staphylococcus aureus* bacteremia and high vancomycin minimum  
72 inhibitory concentrations. J Infect Dis 2011;204:340–7.
- 73 5- Pallares R, Linares J, Vadillo M, et al. Resistance to penicillin and cephalosporin and mortality  
74 from severe pneumococcal pneumonia in Barcelona, Spain. New England Journal of  
75 Medicine 1995;333:474–80.