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Comment on: Efficacy and safety of tigecycline: a systematic review and meta-analysis

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Sir,

In the September 2011 issue of the *Journal of Antimicrobial Chemotherapy*, Yahav *et al.*¹ published a systematic review and meta-analysis of 15 randomized clinical trials (RCTs) that compared tigecycline with other antibiotics for the treatment of severe infections. The overall 30 day mortality was estimated

to be higher with tigecycline compared with other regimens [relative risk (RR) 1.29, 95% confidence interval (CI) 1.02–1.64]; therefore, the authors recommend that clinicians should avoid tigecycline monotherapy in the treatment of severe infections and reserve it as a last-resort drug.

The authors performed a test of heterogeneity between studies. Given that the test result was not significant at 5%, they decided to pool all the RRs by using a fixed-effect meta-analysis model. Unfortunately, this is a common practice in meta-analysis, which usually leads to very misleading results. First of all, the pooled RR as well as its standard error are sensitive to the estimation of the between-studies standard deviation (SD).² SD is difficult to estimate with a small number of studies. On the other hand, it is very well known that the significant test of heterogeneity lacks statistical power to detect values of SD greater than zero.³ In addition, the statistically non-significant results of this test cannot be interpreted as evidence of the homogeneity of the results among all RCTs included.⁴

The profile likelihood of the SD in a random-effect model is an alternative method to analyse the evidence of heterogeneity in the RCTs included in the review;³ Figure 1 presents this type of analysis. In the left panel we have the profile likelihood of SD, which summarizes the support from the RCTs for different values of SD. The broken lines are the 95% CI for SD (0–0.538). Clearly, a value of SD=0 has the maximum support; however, values of SD greater than zero (e.g. SD=0.1) might be considered as being reasonably supported by the data of

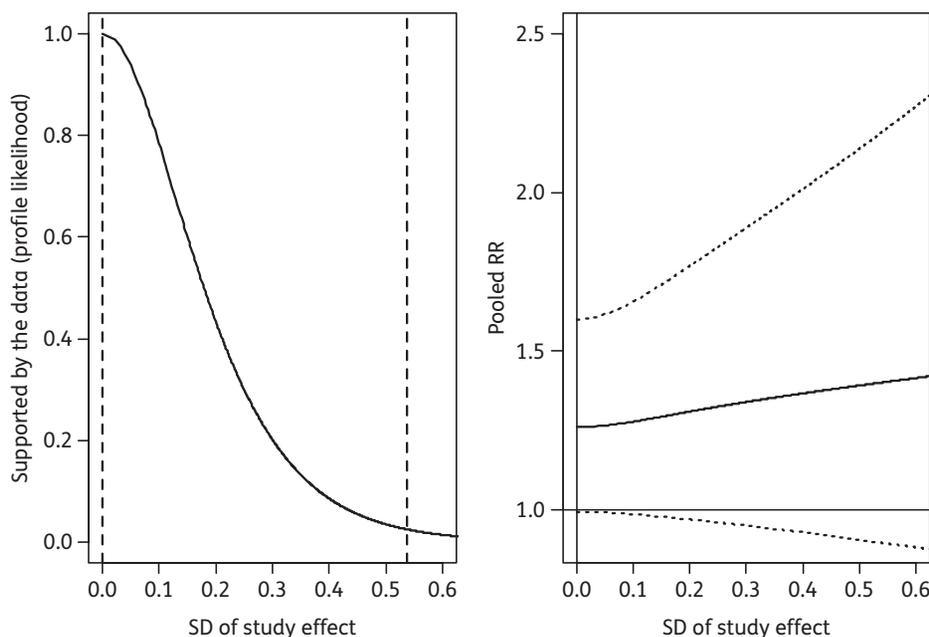


Figure 1. Meta-analysis sensitivity plot. Left panel: profile likelihood of the SD of between-study effects. The y-axis represents support from the data of the studies included in the meta-analysis (0=no support; 1=maximum support). The broken lines are the 95% CI of the SD of this variability parameter. Right panel: the y-axis is the pooled RR and the x-axis is the SD of between-study effects. The broken lines are the 95% CI of the RR for different values of the SD of between-study effects.

the RCTs. In the right panel we show how the pooled RR and its 95% CI change for different values of SD. For example, for SD=0.1 the pooled RR (95% CI) is 1.28 (0.987–1.656), which is not statistically significant. This sensitivity analysis shows that SD=0 is not a robust choice as an estimate, since small non-zero values of SD, which are well supported by the data, can have a strong influence on the conclusions. Therefore, a sharp conclusion based on SD=0 is misleading in this context.

The decision to pool studies with SD=0 is based on the assumption that the studies are identical, which is incorrect, mainly from a clinical point of view. For example, the RCT of hospital-acquired pneumonia presents a total mortality rate of 62.5%, while the mortality rates of the other studies are between 2.1% and 13.2%. That clearly casts doubt on the simplistic assumption of the homogeneity of the studies. In addition, the correlation between the RR of the studies and the total mortality rates in the logarithmic scale is -0.72 , which indicates that the meta-analysis should include an adjustment for the total mortality rate.⁵

Lastly, the authors do not present any predictive quantities in the meta-analysis. The predictive summary statistics are considered the most important quantities in a meta-analysis.⁶ The main reason is that these quantities are associated with the future use and the potential clinical use of the meta-analysis results. In the context of few therapeutic options for treating infections due to multidrug-resistant pathogens, this is a very important issue to solve in this tigecycline meta-analysis. By using the authors' fixed-effects model, the 95% predictive interval for the RR is 0.971–1.641, which predicts that a future comparative study might have an RR <1. However, six studies included in the meta-analysis cannot be predicted from the model presented by the authors [complicated skin and skin structure infections ($n=2$), complicated intra-abdominal infections, diabetic foot infection with osteomyelitis, community-acquired pneumonia and methicillin-resistant *Staphylococcus aureus* infections]. This clearly indicates the inconsistency between the data and the model used for the meta-analysis.

In summary, the main conclusion presented by the authors that the overall mortality was higher with tigecycline compared with other regimens is, at least, misleading.

A suitable statistical analysis, which accounts for the complexity of the clinical evidence, should be presented for application of the published results in clinical practice.

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Transparency declarations

D. C. is an adviser of Pfizer (formerly Wyeth) Laboratories Argentina for antibiotics and he has participated in several experimental and observational studies with tigecycline (Tygacil®). P. E. V.: none to declare.

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