

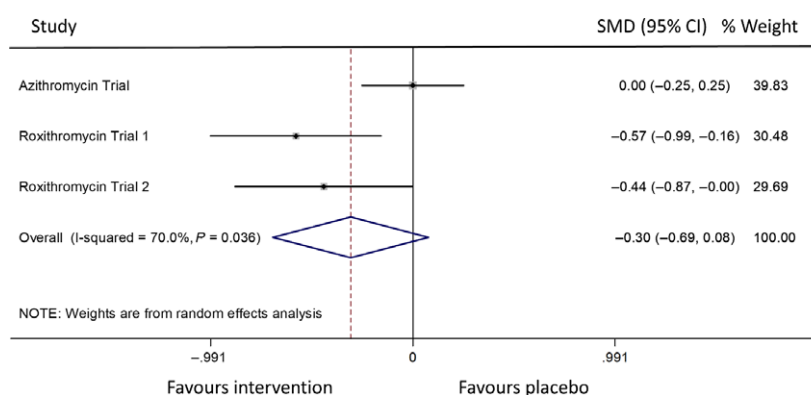
## Response to letter about ‘Lack of an effective drug for abdominal aortic aneurysm’

Dear Sir,

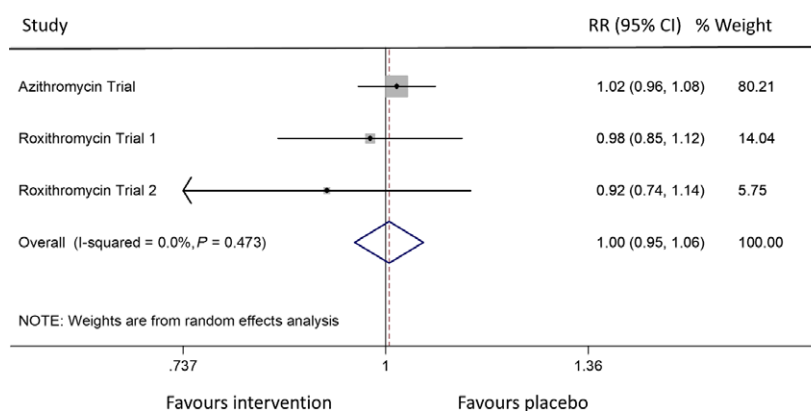
We thank Yu and colleagues for their letter [1] about our recent review [2].

We agree there was substantial heterogeneity in the design of the past abdominal aortic aneurysm

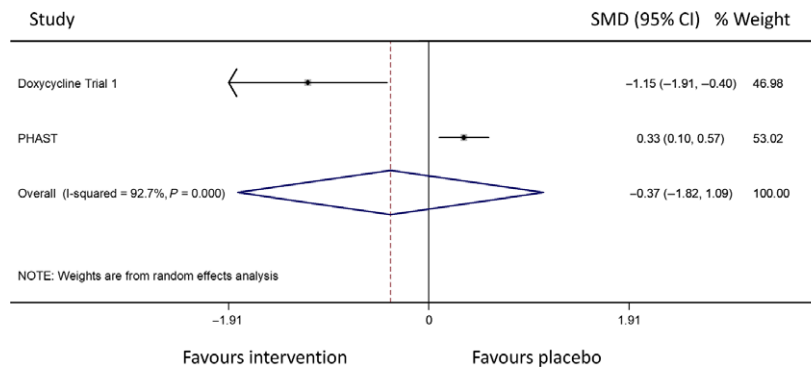
(AAA) drug trials, particularly those testing antibiotics. Whilst Yu *et al.* have focused on  $I^2$ , it should be noted that this describes the dispersion of effect sizes and does not completely describe the heterogeneity between studies. The included antibiotic trials had many methodological variations, such as



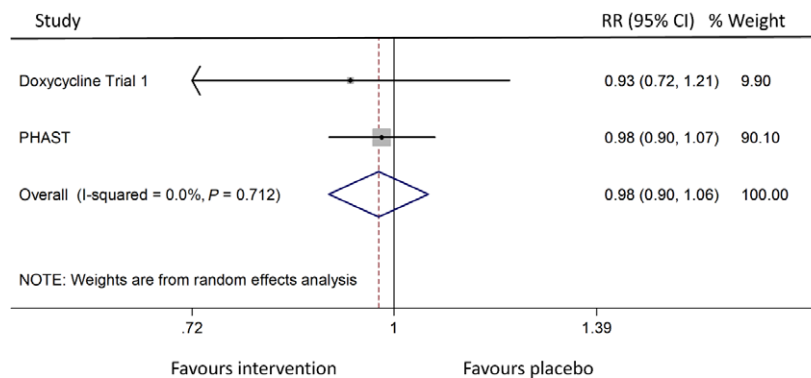
**Fig. 1** Effect of macrolides antibiotics on AAA growth. The SMD is the mean difference in AAA growth rate (mm/year) between participants who were prescribed macrolide antibiotics and participants who were prescribed placebo, standardized to one standard deviation difference. The summary SMD was estimated from inverse-variance weighted meta-analysis. Box areas are inversely proportional to the variance of the SMD, and horizontal lines illustrate 95% confidence intervals. No significant effect was found ( $P = 0.119$ ).



**Fig. 2** Effect of macrolide antibiotics on AAA events. Effect of macrolide antibiotics on clinical events (AAA repair or AAA rupture) reported as relative risk (RR), and 95% confidence interval (CI) for participants prescribed antibiotics or placebo. Box areas are inversely proportional to the variance of the RR, and horizontal lines illustrate 95% CI. No significant effect was found ( $P = 0.852$ ).



**Fig. 3** Effect of tetracycline antibiotics on AAA growth. The SMD is the mean difference in AAA growth rate (mm/year) between participants who were prescribed tetracycline antibiotics and participants who were prescribed placebo, standardized to one standard deviation difference. The summary SMD was estimated from inverse-variance weighted meta-analysis. Box areas are inversely proportional to the variance of the SMD, and horizontal lines illustrate 95% confidence intervals. No significant effect was found ( $P = 0.623$ ).



**Fig. 4** Effect of tetracycline antibiotics on AAA events. Effect of tetracycline antibiotics on clinical events (AAA repair or AAA rupture) reported as relative risk (RR), and 95% confidence interval (CI) for participants prescribed antibiotics or placebo. Box areas are inversely proportional to the variance of the RR, and horizontal lines illustrate 95% CI. No significant effect was found ( $P = 0.545$ ).

different sample sizes, durations of antibiotic administration and follow-up protocols, as outlined in Tables 1 and 2 of our review [2].

The rationale for four of the five antibiotic trials was that *chlamydomphilia pneumonia* was pathogenic in AAA [2]. Since all the antibiotics tested are commonly prescribed to treat this organism, it was logical to combine the five trials in a meta-analysis despite the study heterogeneity. Yu and colleagues suggested subanalyses separately analysing the macrolide and tetracycline antibiotics. These analyses show similar findings to the main analysis with neither group of antibiotics significantly

reducing AAA growth or limiting AAA events (Figures 1–4).

Yu and colleagues highlight the high  $I^2$  for the meta-analyses that examined the effect of the antibiotics on AAA growth (illustrated in Figure 1 of our review [2] and also present for the sensitivity analyses on AAA growth: Figures 1 and 3). The  $I^2$  for the meta-analyses examining the effect of antibiotics on AAA events were, however, zero (Figure 2 of our review [2]; and sensitivity analyses Figures 2 and 4). Since the clinical value of any AAA drug will be evaluated in its efficacy to prevent clinically important events, such as AAA rupture

and repair, we feel our conclusion that antibiotics are not an effective approach to treating most AAAs is valid.


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#### Conflict of interest statement

JG is supported by grants from the National Health and Medical Research Council, Townsville Hospital and Health Service Study, Education and Research Trust Fund, James Cook University and Queensland Government. JG holds a Practitioner Fellowship from the National Health and Medical Research Council (1117601) and a Senior Clinical Research Fellowship from the Queensland Government. JVM holds an Advance Queensland Mid-Career Fellowship from the Queensland Government. TPS holds a

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#### References

- 1 Yua X, Weia X, Caob X. Regarding, "Lack of an effective drug therapy for abdominal aortic aneurysm". *J Intern Med* 2020; **288**: 155.
- 2 Golledge J, Moxon JV, Singh TP, Bown MJ, Mani K, Wanhainen A. Lack of an effective drug therapy for abdominal aortic aneurysm. *J Intern Med* 2020; **288**: 6–22.

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