Reply to Reig et al.

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As Reig and co-authors state, the ARREST trial found that in adults with *Staphylococcus aureus* bacteraemia, 14 days' adjunctive rifampicin had no significant effect on the composite primary endpoint of death or microbiologically-confirmed failure or recurrence through 12 weeks.[1] However, contrary to their subsequent statements, rifampicin had no impact on treatment failure, only on recurrence, and the significant association between rifampicin and antibiotic-modifying adverse events and drug interactions was in the intention-to-treat population, not a sub-group.

A single trial rarely provides a completely definitive answer, especially in a clinically heterogenous infection like S. *aureus* bacteraemia. ARREST cannot exclude the possibility of a patient sub-group who might benefit from rifampicin. Reig et al assert that patients with complicated, deep-seated infections may benefit from rifampicin and suggest we enrolled too few such patients. However, just 130 (17%) participants had uncomplicated, intravenous catheter-related infections; the rest included 301 (40%) with a deep-seated focus (40 endocarditis) and 139 (18%) with no established focus, a sub-group with particularly poor outcomes.[2] Planned sub-group analysis found no significant interaction between the primary outcome and sub-groups defined by deep focus (P=0.10), endocarditis (P=0.13), or unestablished focus (P=0.30), at best weak evidence for rifampicin's benefit in complicated infections.

Indeed, 20 planned and exploratory sub-group analyses failed to identify benefits from rifampicin in any sub-group, with the possible exception of those treated initially with flucloxacillin alone, a finding of uncertain clinical relevance. As Reig et al note, the benefit was lost if vancomycin or another drug was added to flucloxacillin, or the sub-group was defined by any beta-lactam antibiotic. There are few clinically plausible explanations for these observations, leaving the possibility that when 20 sub-group analyses are conducted, one produces a p-value <0.05 by chance.

We accept that one important limitation of ARREST was the small number of participants with infected prosthetic devices, and we regret not having collected more information on those excluded because rifampicin was considered mandatory. The question of whether rifampicin benefits these patients, and other sub-groups articulated by Reig et al and no doubt many others who treat this common and serious infection, will only be answered by further well-conducted, adequately powered trials. Such trials are urgently needed to improve the treatment of this and many other life-threatening infectious diseases. However, our key point remains that ARREST has demonstrated

unequivocally that adjunctive rifampicin provides no overall benefit over standard antibiotic therapy in unselected adults with *S. aureus* bacteraemia.

402 words (max 400)

References:

1. Thwaites GE, Scarborough M, Szubert A, et al. Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2018; **391**(10121): 668-78.
2. Kaasch AJ, Barlow G, Edgeworth JD, et al. *Staphylococcus aureus* bloodstream infection: a pooled analysis of five prospective, observational studies. *J Infect* 2014; **68**(3): 242-51.