# Adjunctive rifampicin to reduce early mortality from *Staphylococcus aureus* bacteraemia: the ARREST RCT

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**Declared competing interests of authors:** Alexander Szubert reports grants from National Institute for Health Research (NIHR) and the Medical Research Council (MRC) during the conduct of the study. Robert Tilley reports personal fees from NIHR Clinical Research Network outside the submitted work. Peter Wilson reports personal fees from 3M Advisory Panel, Roche Drug Safety Monitoring Board and Merck Sharp & Dohme Corp. (MSD; Hoddesdon, UK) outside the submitted work. Achyut Guleri reports receiving fees from Novartis as a member of advisory boards and speaker panels, and consultancy fees from Astellas (Chertsey, UK), AstraZeneca (Cambridge, UK), MSD and Schering-Plough (Hoddesdon, UK); he also received support to attend scientific conferences, including accommodation and travel payments from Becton Dickinson (Winnersh Triangle, UK), Carefusion UK (Winnersh Triangle, UK), Janssen-Cilag (High Wycombe, UK) and MSD. Paul R Chadwick reports non-financial support from Novartis (Frimley, UK), and grants and personal fees from NIHR outside the submitted work. Bernadette Young reports grants from the Wellcome Trust outside the submitted work. M Estee Török reports grants from Academy of Medical Sciences/The Health Foundation, grants from Medical Research Council (MRC), grants from NIHR Cambridge Biomedical Research Centre, grants from MRC/Department of Biotechnology Partnership Grant, and personal fees from Oxford University Press outside the submitted work. Martin J Llewelyn reports personal fees from Pfizer (Walton Oaks, UK) outside the submitted work and is a member of the panel that develops the European Society of Clinical Microbiology and Infectious Diseases/Infectious Diseases Society of America clinical practice guideline on *Staphylococcus aureus* bacteraemia.

Published October 2018
DOI: 10.3310/hta22590

# Scientific summary

## The ARREST RCT

Health Technology Assessment 2018; Vol. 22: No. 59
DOI: 10.3310/hta22590

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# Scientific summary

## Background

*Staphylococcus aureus* bacteraemia is a common and serious infection, with an associated mortality of approximately 25%. Once *S. aureus* enters the bloodstream, it can disseminate to infect almost any organ of the body, but it most commonly affects the bones, joints and heart valves. Despite the infection's severity, the evidence guiding optimal antibiotic therapy is weak, as < 1500 patients have been included in 16 randomised controlled trials investigating *S. aureus* bacteraemia treatment. Therefore, which antibiotics are most effective, their route of administration and duration, and whether or not antibiotic combinations are better than single agents, are unknown. It was hypothesised here that adjunctive rifampicin would reduce bacteriologically confirmed failure/recurrence or death by enhancing early *S. aureus* killing, sterilising infected foci/blood faster and reducing the risks of dissemination and metastatic infection.

## Objectives

The primary objective of the trial was to investigate the impact of adjunctive rifampicin on bacteriologically confirmed failure/recurrence or death through 12 weeks from randomisation.

Secondary objectives included evaluating the impact of rifampicin on all-cause mortality up to 14 days from randomisation, clinically defined failure/recurrence or death, toxicity [serious or grade 3 or 4 adverse events (AEs) or modification of any treatment due to drug interactions], emergence of resistance, and duration of bacteraemia; and assessing the cost-effectiveness of adjunctive rifampicin for *S. aureus* bacteraemia in the NHS.

## Methods

### *Design*

Parallel-group, randomised (1 : 1), blinded, placebo-controlled multicentre trial.

### *Setting*

A total of 29 large acute NHS trusts. Patients were identified through the clinical microbiology laboratory and the infectious diseases/microbiology consult service at each centre.

### *Participants*

Inclusion criteria were as follows:

- adult inpatients (aged ≥ 18 years)
- *S. aureus* (meticillin susceptible or resistant) grown from at least one blood culture
- < 96 hours of active antibiotic therapy for the current infection, not including rifampicin, and excluding any stat doses
- patient or legal representative provided written informed consent.

Exclusion criteria were as follows:

- infection not caused by *S. aureus* alone in the opinion of the infection specialist (e.g. *S. aureus* considered a blood culture contaminant, or polymicrobial culture with another organism likely to be contributing clinically to the current infection)
- sensitivity results already available and demonstrate rifampicin-resistant *S. aureus*
- infection specialist, in consultation with the treating physician, considers rifampicin is contraindicated for any reason
- infection specialist, in consultation with the treating physician, considers rifampicin treatment is mandatory for any reason
- infection specialist suspects active infection with *Mycobacterium tuberculosis*
- previously randomised in the ARREST (Adjunctive Rifampicin to Reduce Early mortality from *STaphylococcus aureus* bacteraemia) trial for a prior episode of *S. aureus* bacteraemia.

Incapacitated adults were eligible provided that they had an appropriate legal representative to provide consent.

### *Interventions*

Eligible patients were randomised to standard intravenous (i.v.) antibiotic therapy of the attending physician's choice plus either 14 days of placebo or rifampicin (900 mg/24 hours if $\geq$ 60 kg; 600 mg/24 hours if $<$ 60 kg). Rifampicin could be administered via i.v. or oral route depending on patient status and either once or twice daily.

### *Follow-up*

All participants were followed up on days 3, 7, 10, 14, weekly until discharge, and the final assessment took place at 12 weeks post randomisation.

### *Sample size*

A total of 770 patients were recruited, providing 80% power to detect a 30% relative reduction in bacteriological failure/death from 35% to 25%, an absolute difference of 10% corresponding to an number needed to treat of 10 patients, assuming 10% loss to follow-up by 12 weeks (two-sided alpha = 0.05).

### *Health economics*

Cost and health outcomes for patients with *S. aureus* bacteraemia were evaluated using data from the ARREST trial. Costs considered were those incurred by the NHS and encompassed antibiotic therapy, admissions to secondary care (including investigations and procedures undertaken while hospitalised) and consultations with health-care providers after hospital discharge from first admission. Health outcomes were measured as quality-adjusted life-years (QALYs), calculated from EuroQol-5 Dimensions, three-level version, responses collected in the trial and imputed to account for missingness. Costs and QALYs were measured only for 84 days (i.e. 12 weeks), the maximum duration of active follow-up. The analyses used a regression approach to explore determinants of costs and QALYs on baseline covariates, including treatment group, which allowed for a cost-effectiveness analysis to be conducted. Decision uncertainty was accounted for through probabilistic modelling.

## Results

### *Baseline characteristics*

Between December 2012 and October 2016, 758 eligible participants from 29 UK hospitals were randomised: 370 to rifampicin and 388 to placebo. A total of 495 (65.3%) were men and the median [interquartile range (IQR)] age was 65 years (50–76 years). In addition, the median Charlson Comorbidity Index score was 2 (IQR 0–3) and 70 (9.2%) participants were in an intensive care unit. The mean C-reactive protein level was

164 mg/l (standard error 3.7 mg/l). A total of 127 (16.8%) participants had consent provided by a legal representative owing to incapacity, and 485 (64.0%) infections were community acquired, with only 132 (17.4%) nosocomial. In addition, 47 (6.2%) infections were caused by meticillin-resistant *Staphylococcus aureus* (MRSA). No patients were known to have rifampicin-resistant *S. aureus* bacteraemia at randomisation. The initial focus was deep in 301 (39.7%) participants [including 33 (4.4%) participants with endocarditis and 14 (1.8%) with infected prostheses]. The initial focus was as a result of infected central/peripheral lines in 130 (17.2%) participants, 138 (18.2%) were associated with skin/soft tissue infections, and another type of focus was identified in 49 (6.5%) and not established in 139 (18.3%). At randomisation, participants had received a median of 62 hours (IQR 42–75 hours) of active antibiotics.

### Follow-up

A total of 22 (2.9%) participants withdrew consent and at the 12-week visit, only 39 (5.1%) participants had unknown vital status and 65 (8.6%) participants were not assessed for signs/symptoms of *S. aureus* infection (including consent withdrawals).

A total of 744 (98.2%) participants had the blinded trial drug, of whom 96 (12.7%) participants had the drug intravenously and 595 (78.5%) participants had 900 mg of the drug daily, at a median of 68 hours (IQR 48–85 hours) after starting active antibiotics for the current infection. The trial drug was continued for a median of 12.6 days (IQR 6.0–13.2 days) for the participants receiving rifampicin and 13.0 days (11.3–13.5 days) for the participants receiving the placebo ($p < 0.0001$; primarily because of antibiotic-modifying AEs and drug–drug interactions, see below). The percentage of participants reporting missing any doses ranged from 9.5% to 16.2% but did not differ between the randomised groups (global $p = 0.72$).

A substantial variety of 'backbone' active antibiotics were used, although flucloxacillin was given to 619 (81.7%) participants and vancomycin or teicoplanin was given to 380 (50.1%) participants at some point in the primary treatment course. The numbers of antibiotics used [median 3 (IQR 2–4)] and the duration of anti-staphylococcal treatment [median 29 days (IQR 18–45 days)] was similar between groups. A total of 32 (8.6%) participants in the rifampicin group versus 52 (13.4%) participants in the placebo group used open-label rifampicin ($p = 0.04$), which was initiated at a median of 14 days (IQR 7–18 days) after randomisation. A total of 159 participants in the placebo group versus 142 participants in the rifampicin group had a deep focus, which was drained/removed in 35 (22.0%) participants and 29 (20.4%) participants, a median of 5 days (IQR 2–12 days) and 3 days (IQR 1–6 days) from randomisation, respectively.

### Primary end point

By 12 weeks, 62 out of 370 (16.8%) participants in the rifampicin group versus 71 out of 388 (18.3%) participants in the placebo group experienced bacteriological failure/recurrence or died [absolute risk difference (RD) –1.4%, 95% confidence interval (CI) –7.0% to 4.3%; hazard ratio (HR) 0.96, 95% CI 0.68 to 1.35; $p = 0.81$]. Comparing rifampicin with placebo, there were 4 (1.1%) and 5 (1.3%) bacteriological failures ($p = 0.82$), 3 (0.8%) and 16 (4.1%) bacteriological recurrences ($p = 0.01$), and 55 (14.9%) and 50 (12.9%) deaths without bacteriological failure/recurrence, respectively ($p = 0.30$).

### Secondary end points

Clinically defined failure/recurrence or death occurred in 76 (20.5%) participants in the rifampicin group versus 86 (22.2%) participants in the placebo group (RD –1.4%, 95% CI –7.4% to 4.7%; HR 0.97, 95% CI 0.71 to 1.32; $p = 0.84$). Comparing the rifampicin and placebo groups, there were 23 (6.2%) versus 25 (6.4%) failures ($p = 0.97$), 8 (2.2%) versus 23 (5.9%) recurrences ($p = 0.01$), and 45 (12.2%) versus 38 (9.8%) deaths without clinically defined failure/recurrence, respectively (competing risks $p = 0.22$). By 12 weeks, 56 (15.1%) participants in the rifampicin group versus 56 (14.4%) participants in the placebo group died (RD 1.0%, 95% CI –4.3% to 6.2%; HR 1.10, 95% CI 0.76 to 1.60; $p = 0.60$). A total of 25 (6.8%) participants in the rifampicin group versus 17 (4.4%) participants in the placebo

group died before 2 weeks (HR 1.60, 95% CI 0.86 to 2.95; $p = 0.13$). A total of 14 deaths in the rifampicin group and 16 deaths in the placebo group were adjudicated definitely as being *S. aureus* related, 14 deaths and 12 deaths were probably *S. aureus* related, and 8 deaths and 4 deaths were possibly *S. aureus* related, respectively. A total of 18 and 23 deaths were not attributed to *S. aureus* (remainder unattributable) (overall $p = 0.64$). There was no difference in longer-term (post week 12) survival between the groups ($p = 0.69$). There was no evidence that the duration of bacteraemia was significantly shorter in those randomised to the rifampicin group (global $p = 0.66$). Two (0.5%) participants in the rifampicin group developed new rifampicin-resistant *S. aureus* bacteraemia 7 and 42 days after randomisation ($p = 0.24$). Of these, one participant developed resistance on day 7 (followed by rifampicin discontinuation on day 11 and bacteriological failure on day 14) and the other participant developed resistance on day 42 (prescribed 14 days of rifampicin; bacteriological recurrence on day 42).

### Safety

By 12 weeks, 101 (27.3%) participants in the rifampicin group versus 94 (24.2%) participants in the placebo group experienced 112 and 116 serious adverse events (HR 1.21, 95% CI 0.92 to 1.61; $p = 0.17$), respectively. Two participants in the rifampicin group with pre-existing liver disease experienced non-fatal hepatic failure. A total of 129 (34.9%) participants in the rifampicin group versus 131 (33.8%) participants in the placebo group experienced 209 and 193 grade 3/4 AEs (HR 1.12, 95% CI 0.88 to 1.43; $p = 0.36$), respectively. Most notable was a trend towards more renal grade 3/4 AEs with rifampicin, which occurred in 19 (5.1%) participants in the rifampicin group and 9 (2.3%) participants in the placebo group ($p = 0.053$), of whom 17 and 6 participants, respectively, had acute kidney injury. A total of 63 (17.0%) participants in the rifampicin group versus 39 (10.1%) participants in the placebo group experienced 89 and 52 antibiotic-modifying AEs (subdistribution HR 1.78, 95% CI 1.20 to 2.65; $p = 0.004$), respectively. Gastrointestinal disorders (24 vs. 8 participants, respectively; $p = 0.003$) and renal/urinary disorders (8 vs. 1 participants, respectively; $p = 0.02$) were more common in the rifampicin group than the placebo group. A total of 24 (6.5%) participants in the rifampicin group versus 6 (1.5%) participants in the placebo group experienced drug interactions ($p = 0.0005$), of which 13 and 4 led to discontinuation of trial drug ($p = 0.03$), 14 and 3 led to grade 1/2 AEs ($p = 0.006$), and 5 and 2 to grade 3/4 AEs ($p = 0.27$), respectively.

### Health economics

It was found that an episode of *S. aureus* bacteraemia costs, on average, £12,197 over 12 weeks. The cost categories that contributed the most to costs were length of stay (primary hospital admission and readmissions) and the procedures undertaken in hospital. Baseline determinants of higher episode costs were nosocomial *S. aureus* bacteraemia (costs 41% higher), a deep primary focus of infection (costs 43% higher), endocarditis (costs 65% higher), high neutrophil count ($> 9 \times 10^9$/l, costs 33% higher), and whether or not the patient was comatose (costs 32% higher). Age, sex, body mass index, Charlson Comorbidity Index score and meticillin resistance did not affect costs.

Analysis indicates that adjunctive rifampicin may save 10% of episode costs, with larger savings happening after 14 days. Despite not being statistically significant, this result is consistent with the small reduction in recurrences that probably drives shorter hospital stays. It is, however, important to note that the costs of rifampicin toxicity and drug–drug interactions were not included in this analysis.

As expected in this population of acutely ill patients, very low values of the EuroQol-5 Dimensions (EQ-5D) score were observed at baseline (mean EQ-5D score of 0.10). Determinants of QALYs in the sample were baseline EQ-5D score (0.0064 QALYs lost for every 0.1 decrease in baseline EQ-5D), higher age (up to 0.044 QALY loss), Charlson Comorbidity Index score (up to 0.024 QALY loss) and coma (mean QALY loss of 0.020). After adjustment, the effect of rifampicin on total QALYs was positive (0.004 QALY) but not statistically significant (standard error 0.004 QALY).

## Conclusions

Adjunctive rifampicin does not reduce mortality from *S. aureus* bacteraemia, but it may reduce the risk of disease recurrence. This trial suggests that this effect had no impact on short- or long-term mortality, but it may reduce costs. However, rifampicin significantly complicates other drug treatment. Therefore, it was considered that adjunctive rifampicin provides no overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

## Trial registration

This trial is registered as ISRCTN37666216, EudraCT 2012-000344-10 and Clinical Trials Authorisation 00316/0243/001.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

# Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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### This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/104/25. The contractual start date was in July 2012. The draft report began editorial review in November 2017 and was accepted for publication in July 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.



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