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

Guy E Thwaites, 1,2* Matthew Scarborough, 1 Alexander Szubert,³ Pedro Saramago Goncalves,⁴ Marta Soares, 4 Jennifer Bostock, 5 Emmanuel Nsutebu,⁶ Robert Tilley,⁷ Richard Cunningham,⁷ Julia Greig,⁸ Sarah A Wyllie,⁹ Peter Wilson, 10 Cressida Auckland, 11 Janet Cairns, 3 Denise Ward,³ Pankaj Lal,¹² Achyut Guleri,¹³ Neil Jenkins, 14 Julian Sutton, 15 Martin Wiselka, 16 Gonzalez-Ruiz Armando, 17 Clive Graham, 18 Paul R Chadwick, 19 Gavin Barlow, 20 N Claire Gordon, 1 Bernadette Young,¹ Sarah Meisner,²¹ Paul McWhinney,²² David A Price,²³ David Harvey,²⁴ Deepa Nayar,²⁵ Dakshika Jeyaratnam,²⁶ Timothy Planche,²⁷ Jane Minton,²⁸ Fleur Hudson,³ Susan Hopkins,²⁹ John Williams,³⁰ M Estee Török,³¹ Martin J Llewelyn,³² Jonathan D Edgeworth³³ and A Sarah Walker^{1,3} on behalf of the UK Clinical Infection Research Group

¹Nuffield Department of Medicine, University of Oxford, Oxford, UK

²Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

³Medical Research Council Clinical Trials Unit, University College London, London, UK

⁴Centre for Health Economics, University of York, York, UK

⁵Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

⁶Tropical and Infectious Diseases Unit, Royal Liverpool University Hospital, Liverpool, UK

⁷Department of Microbiology, Plymouth Hospitals NHS Trust, Plymouth, UK

⁸Department of Infectious Diseases, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

⁹Microbiology Department, Portsmouth Hospitals NHS Trust, Portsmouth, UK

- ¹⁰Centre for Clinical Microbiology, University College London Hospital NHS Foundation Trust, London, UK
- ¹¹Microbiology Department, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
- ¹²Microbiology Department, Aintree University Hospital NHS Foundation Trust, Liverpool, UK
- ¹³Microbiology Department, Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool, UK
- ¹⁴Department of Infectious Diseases and Tropical Medicine, Heart of England NHS Foundation Trust, Birmingham, UK
- ¹⁵Department of Microbiology and Virology, University Hospital Southampton NHS Foundation Trust, Southampton, UK
- ¹⁶Department of Infection and Tropical Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK
- ¹⁷Microbiology Department, Darent Valley Hospital, Dartford, UK
- ¹⁸Microbiology Department, North Cumbria University Hospitals NHS Trust, Cumbria, UK
- ¹⁹Microbiology Department, Salford Royal NHS Foundation Trust, Salford, UK
- ²⁰Department of Infection, Hull and East Yorkshire Hospitals NHS Trust, Hull, UK
- ²¹Microbiology Department, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK
- ²²Microbiology Department, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK
- ²³Department of Infectious Diseases, Newcastle Upon Tyne Hospital NHS Foundation Trust, Newcastle, UK
- ²⁴Microbiology Department, Wirral University Teaching Hospital NHS Foundation Trust, Birkenhead, UK
- ²⁵Microbiology Department, County Durham and Darlington NHS Foundation Trust, Durham, UK
- ²⁶Department of Microbiology, King's College Hospital NHS Foundation Trust, London, UK
- ²⁷Department of Infectious Diseases and Tropical Medicine, St George's University Hospitals NHS Foundation Trust, London, UK
- ²⁸Department of Infectious Diseases, Leeds Teaching Hospitals NHS Trust, Leeds, UK
- ²⁹Infectious Diseases Unit, Royal Free London NHS Foundation Trust, London, UK
- ³⁰Department of Infectious Diseases, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK
- ³¹Department of Medicine, University of Cambridge, Cambridge, UK
- ³²Department of Infectious Diseases, Brighton and Sussex Medical School, Brighton, UK
- ³³Department of Immunology, Infectious and Inflammatory diseases, King's College London, London, UK

^{*}Corresponding author gthwaites@oucru.org

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

Plain English summary

The ARREST RCT

Health Technology Assessment 2018; Vol. 22: No. 59

DOI: 10.3310/hta22590

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Plain English summary

Staphylococcus aureus is a germ that can cause serious infections, particularly when it gets into the bloodstream. Doctors use an antibiotic to cure *S. aureus*, but sometimes the antibiotic does not succeed in curing the infection and sometimes the infection comes back.

The ARREST (Adjunctive Rifampicin to Reduce Early mortality from *STaphylococcus aureus* bacteraemia) trial tested whether or not giving 2 weeks of an extra antibiotic, called rifampicin, in addition to the standard antibiotic, would help people who were ill owing to *S. aureus* blood infections. The aim was to find out if rifampicin could cure more people, possibly faster than without the extra antibiotic, and to see whether it caused fewer or more side effects. The aim was also to see if the germ that causes the infection became resistant to rifampicin.

In total, 770 patients from the UK aged 18–100 years participated. The participants all received the same standard antibiotic that they would have received if they had not joined the study. In addition, 370 patients received 2 weeks of rifampicin and 388 patients received 2 weeks of placebo (dummy).

The ARREST study found that people who had rifampicin in addition to standard antibiotic treatment did no better overall than people who had just standard antibiotic treatment, in terms of how successful their treatment was. People in the group who had rifampicin were no more likely to have serious or severe side effects than those in the group who had placebo. There was some evidence that rifampicin reduced the risk that the infection would come back again, but this did not reduce the overall deaths. In addition, *S. aureus* from only two people's blood developed resistance to rifampicin.

The results suggest that people with *S. aureus* blood infections are unlikely to benefit from adding rifampicin to standard antibiotic treatment. The study included a wide range of patients with *S. aureus* blood infections, so the results apply widely.

HTA/HTA TAR

Health Technology Assessment

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

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the Health Technology Assessment journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

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.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

© Queen's Printer and Controller of HMSO 2018. This work was produced by Thwaites et al. under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

NIHR Journals Library Editor-in-Chief

Professor Tom Walley Director, NIHR Evaluation, Trials and Studies and Director of the EME Programme, UK

NIHR Journals Library Editors

Professor Ken Stein Chair of HTA and EME Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andrée Le May Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals)

Professor Matthias Beck Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont Scientific Advisor, NETSCC, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Wellbeing Research, University of Winchester, UK

Professor John Norrie Chair in Medical Statistics, University of Edinburgh, UK

Professor John Powell Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk