Rapid detection of health-care-associated bloodstream infection in critical care using multipathogen real-time polymerase chain reaction technology: a diagnostic accuracy study and systematic review

Geoffrey Warhurst,^{1,2,3*} Graham Dunn,⁴ Paul Chadwick,⁵ Bronagh Blackwood,⁶ Daniel McAuley,⁶ Gavin D Perkins,⁷ Ronan McMullan,⁸ Simon Gates,⁷ Andrew Bentley,^{3,9} Duncan Young,¹⁰ Gordon L Carlson^{1,3} and Paul Dark^{1,3,11}

- ¹Infection, Injury and Inflammation Research Group, Salford Royal NHS Foundation Trust, Manchester Academic Health Sciences Centre (MAHSC), University of Manchester, Salford, UK
- ²Faculty of Environment and Life Sciences, University of Salford, Manchester Academic Health Sciences Centre (MAHSC), Salford, UK
- ³Institute of Inflammation and Repair, Faculty of Medical and Human Sciences, Manchester Academic Health Sciences Centre (MAHSC), University of Manchester, Salford, UK
- ⁴Centre for Biostatistics, Institute of Population Health, Faculty of Medical and Human Sciences, Manchester Academic Health Sciences Centre (MAHSC), University of Manchester, Salford, UK

 ⁵Microbiology Department, Salford Royal NHS Foundation Trust, Manchester Academic Health Sciences Centre (MAHSC), University of Manchester, Salford, UK
⁶Centre for Infection and Immunity, Queen's University Belfast, Belfast, UK
⁷Clinical Trials Unit, Medical School, Warwick University, Coventry, UK
⁸Medical Microbiology, Royal Victoria Hospital, Belfast, UK

 ⁹Intensive Care Unit, University Hospital of South Manchester NHS Foundation Trust, Manchester Academic Health Sciences Centre (MAHSC), Manchester, UK
¹⁰Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK
¹¹Intensive Care Unit, Salford Royal NHS Foundation Trust, Manchester Academic

Health Sciences Centre (MAHSC), University of Manchester, Salford, UK

*Corresponding author

Declared competing interests of authors: Geoffrey Warhurst, Paul Dark, Ronan McMullen and Daniel McAuley have received research funding from the Technology Strategy Board to develop point-of-care diagnostics for sepsis. Paul Chadwick has received lecture honoraria from Novartis and funding from Pfizer and AstraZeneca to support local and regional research meetings in Clinical Microbiology.

Published May 2015 DOI: 10.3310/hta19350

Plain English summary

Rapid detection of health-care-associated bloodstream infection in critical care

Health Technology Assessment 2015; Vol. 19: No. 35 DOI: 10.3310/hta19350

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

Plain English summary

Infection is a major cause of illness and death in patients admitted to NHS hospitals, and improving prevention and treatment of infection are among the highest priorities of the Department of Health. Life-threatening infections often occur in critically ill patients, who are particularly vulnerable. Early therapy with the correct antibiotic is the key to effective treatment, but current techniques for identifying the specific bacteria responsible involve trying to grow the organism in an incubator (culture). This process takes up to 5 days, and during this time patients are treated by 'educated guesswork' involving prescription of powerful 'broad-spectrum' antibiotics, usually reserved for hard-to-treat infections. These drugs are effective against a wide range of organisms but their use, unfortunately, encourages development of multiresistant bacteria, for example meticillin-resistant *Staphylococcus aureus*, which is becoming a major problem.

New molecular techniques that detect minute amounts of bacterial deoxyribonucleic acid in a patient's blood within a few hours have the potential to provide much more rapid and precise diagnosis and treatment of bloodstream infection. This technology is currently being marketed commercially, but independent studies are needed to be sure that these techniques are sufficiently accurate to justify their routine clinical use. A large clinical trial of this technology has been undertaken by a team of clinicians and scientists in over 1000 patients suspected of having bloodstream infection from four large critical care NHS services in the north-west of England. Following permission from patients and their families, blood from each patient was analysed by the molecular test and by conventional blood culture. Before commencing the study, it was agreed with an independent ethics committee and a National Institute for Health Research Trial Steering Committee, which included patient representatives, that the results of blood culture, but not of the molecular test, would be used to guide care for patients in this study because we did not know how the new molecular test would perform.

Comparison of the results of the two tests showed that the molecular test was able to detect bloodstream organisms twice as often as conventional culture, suggesting that the new test might uncover more infections in patients. However, on occasion, the molecular test missed some important infections compared with conventional culture and, therefore, is not ready for routine introduction to frontline NHS care. The reasons for these results are currently being carefully investigated by the project team, as they were able to store extra clinical blood samples, with permission from each patient, allowing them to perform additional scientific investigations that will help them uncover how to improve the molecular test. This means that when a better molecular test is developed, the team will be able to rerun this study quickly on the stored samples without the need for further patient blood sampling allowing rapid transfer from laboratory scientific discovery to help deliver the safest care for patients being treated within the NHS.

© Queen's Printer and Controller of HMSO 2015. This work was produced by Warhurst *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. 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.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

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

Editorial contact: nihredit@southampton.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 08/13/16. The contractual start date was in May 2010. The draft report began editorial review in November 2013 and was accepted for publication in December 2014. 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. 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.

© Queen's Printer and Controller of HMSO 2015. This work was produced by Warhurst *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. 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).

Editor-in-Chief of *Health Technology Assessment* and NIHR Journals Library

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

NIHR Journals Library Editors

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

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

Dr Martin Ashton-Key Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Professor Aileen Clarke Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick, UK

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Peter Davidson Director of NETSCC, HTA, UK

Ms Tara Lamont Scientific Advisor, NETSCC, UK

Professor Elaine McColl Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

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

Professor Geoffrey Meads Professor of Health Sciences Research, Faculty of Education, University of Winchester, 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 Institute of Child Health, UK

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

Please visit the website for a list of members of the NIHR Journals Library Board: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: nihredit@southampton.ac.uk