PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Accuracy of LightCycler® SeptiFast for the detection and identification of pathogens in the blood of patients with suspected sepsis: a PROSPERO systematic review protocol
AUTHORS	Paul Dark, Claire Wilson, Bronagh Blackwood, Danny McAuley, Gavin D Perkins, Ronan McMullan, Simon Gates, Geoffrey Warhurst

VERSION 1 - REVIEW

REVIEWER	John Simpson, Professor of Respiratory Medicine, Newcastle University, UK Statement of competing interests. I currently hold a grant on which 3 of the authors are named. I have previously been co-author on manuscripts with one of the authors.
REVIEW RETURNED	13/10/2011

RESULTS & CONCLUSIONS	The first 3 questions in the panel above are hard to answer because the paper is describing a protocol to be used in future work. Therefore there are no results, but the 'result' of the work presented in the manuscript is certainly credible.
GENERAL COMMENTS	The authors seek to address the important issue of whether the SeptiFast technique performs adequately against the 'standard' of blood culture in sepsis. The authors make a clear case for why more rapid, accurate microbiological assessment in sepsis is required. The methods described are comprehensive and robust, and the breadth of expertise makes it likely that the aims of the project will be achieved. The systematic review, as presented, will make an important contribution to the field. I have only a few minor comments/queries. 1. The authors may wish to expand their plans for obtaining all unpublished data (or justify their current strategy in more detail). In addition to checking clinical trial registries, what plans do they have for trying to identify data held by the manufacturer, or by competitors, that have not been published? 2. The authors touch upon the issue of how to interpret results in patients who have already received antibiotics, but their plans could perhaps be expanded slightly. The utility of blood culture is obviously recognised to be reduced by prior administration of antibiotics, whereas PCR may still detect signal in this context. How will the authors classify positive PCR (in the context of a negative blood culture whilst on antibiotics)? The answer to this question is implied in the manuscript but should be made explicit. 3. One potential concern for such a review is that numbers of patients from studies fulfilling the (commendably stringent) criteria

	may be small. The authors might wish to discuss this potential limitation and consider including other PCR-based strategies (or justify further why they wish to limit the analysis to SeptiFast). 4. To help readers unfamiliar with SeptiFast, the authors should consider listing the organisms detectable in the kit (so that readers can place in context studies where blood cultures have grown organisms not incorporated in the kit). A final practical point is that the inclusion of abstracts in all languages is most welcome, but the authors might wish to convince readers that they have suitable back up for medical translation in all languages.

VERSION 1 – AUTHOR RESPONSE

Comments in reply to Professor Simpson (Reviewer):

We thank Professor Simpson for his careful reading of our manuscript and his challenging comments that we will try to address in turn.

1. The authors may wish to expand their plans for obtaining all unpublished data (or justify their current strategy in more detail). In addition to checking clinical trial registries, what plans do they have for trying to identify data held by the manufacturer, or by competitors, that have not been published?

We have edited the section on “Other resources” to try to explain in more detail how we intend to discover and obtain unpublished data. In addition, we have moved the section “Search terms/search strategy” above “Other resources” for clarity.

SeptiFast is a unique technology designed by Roche Diagnostics and there are no other manufacturers/competitors of this precise technology. We have already sourced the reported data underpinning the CE-mark in 2006, which was presented in the public domain by Roche at the time and which was freely available on the internet as a non-peer reviewed PDF presentation.

2. The authors touch upon the issue of how to interpret results in patients who have already received antibiotics, but their plans could perhaps be expanded slightly. The utility of blood culture is obviously recognised to be reduced by prior administration of antibiotics, whereas PCR may still detect signal in this context. How will the authors classify positive PCR (in the context of a negative blood culture whilst on antibiotics)? The answer to this question is implied in the manuscript but should be made explicit.

We agree with Professor Simpson that the issue of “false” results is very important and challenging when comparing diagnostic tests that do not measure the same biomarker (pathogen DNA vs. culturable organisms in this study) in the setting of a complex syndrome (sepsis in this case). We believe that the precise extent of this issue will only be revealed by reviewing the details of the relevant papers uncovered. It is possible, for instance, that some of these studies will have been designed to exclude patients receiving antibiotics for this very reason – although we cannot be sure at this stage. It is also possible that investigators will have created different definitions of “true positivity” in sepsis. By applying our (“blood culture”) reference standard definition (albeit with some limitations) to all datasets reviewed, we can overcome the much greater limitation created by such variability – as this is what limits potential index test users in understanding how the test performs. In using blood culture results as the reference standard for true positivity, we effectively increase the sample size of the ‘interpretable’ validation dataset, because blood culture is mandated internationally in suspected

sepsis. In doing so, we accept that this may underestimate the performance of the test (i.e. it will produce some false-negative PCR results, but we prefer this to wrongly categorising false positive PCRs as true positives). Also in terms overall robustness, its easier to argue for blood cultures, as we have done previously (NIHR-HTA study currently recruiting) as the reference standard than some other definition, synthesised or adopted by the authors. We have tried to incorporate this vision, succinctly, in the section “Reference Standard”.

3. One potential concern for such a review is that numbers of patients from studies fulfilling the (commendably stringent) criteria may be small. The authors might wish to discuss this potential limitation and consider including other PCR-based strategies (or justify further why they wish to limit the analysis to SeptiFast).

We have had the opportunity to pilot our Medline search strategy and we have found at least 21 studies (about 10% of total returned), involving the assessment of a number of thousand test comparisons with blood culture in the setting of suspected sepsis, despite our stringent criteria – at least at abstract review and before more formal appraisal. We are confident that these data will allow systematic review and, hopefully data synthesis, to try to understand the test performance in this setting internationally. However, we do acknowledge that a small number of CE-marked tests are emerging in new clinical studies that could be candidate competitors in the future – unfortunately, there is a paucity of studies to allow systemic review now. We have now indicated this situation and alluded directly to such technologies in the manuscript in the introduction section. Together we feel our approach is justified at this time. In addition, only CE-marked commercially available tests are considered evaluable. Other molecular tests that are not widely available to clinical diagnostic labs are not necessarily standardised and are hence either not clearly reproducible or sufficiently accessible to potential test users to justify inclusion at this stage.

4. To help readers unfamiliar with SeptiFast, the authors should consider listing the organisms detectable in the kit (so that readers can place in context studies where blood cultures have grown organisms not incorporated in the kit). A final practical point is that the inclusion of abstracts in all languages is most welcome, but the authors might wish to convince readers that they have suitable back up for medical translation in all languages.

We have incorporated the organism panel as a new Table 1 and re-numbered the other Tables.

We have excellent access to a large and varied modern language Faculty in Manchester, incorporating Masters programs in Translation and Interpretation. We are already realising this access by translating one German and one Spanish paper resulting from the initial Medline pilot. We have agreed with our Humanities academic colleagues appropriate honoraria for these services.