Author's response to reviews

Title: Use of an automated blood culture system (BD BACTECTM) for diagnosis of prosthetic joint infections: easy and fast

Authors:

    Angela M Minassian (angela.minassian@ouh.nhs.uk)
    Robert Newnham (robert.newnham@ouh.nhs.uk)
    Elizabeth Kalimeris (elizabeth.kalimeris@ouh.nhs.uk)
    Philip Bejon (pbejon@well.ox.ac.uk)
    Bridget L Atkins (bridget.atkins@ouh.nhs.uk)
    Ian CJW Bowler (ian.bowler@ouh.nhs.uk)

Version: 3 Date: 31 March 2014

Author's response to reviews: see over
Dear Editors

Re: Use of an automated blood culture system (BD BACTEC™) for diagnosis of prosthetic joint infections: easy and fast – responses to reviewers’ comments

1,2 Angela M Minassian, 1 Robert Newnham, 1 Elizabeth Kalimeris, 1,2 Philip Bejon, 1,2 Bridget L Atkins, 1 Ian CJW Bowler
1 Department of Microbiology, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, UK; 2 Bone Infection Unit, Nuffield Orthopaedic Centre, Windmill Road, Oxford OX3 7LD, UK

Thank you for your correspondence inviting us to re-submit a revised version of the above manuscript, in response to comments from the reviewers. Below is a point-by-point response to each of the reviewers’ valid comments.

I confirm that all authors have approved the revised version of the manuscript.

We look forward to hearing from you as to whether it may now be acceptable for publication.

Yours faithfully,

Angela Minassian (on behalf of the co-authors)
Reviewer's report - responses

Title: Use of an automated blood culture system (BD BACTECTM) for diagnosis of prosthetic joint infections: easy and fast

Version: 2 Date: 23 February 2014

Reviewer: Carolyn C Hemsley

Reviewer's report:

No major compulsory revisions

Minor compulsory revisions:

The numbers in the second paragraph of the results section need to be checked. Line 150 - can the authors add the percentage in bracket.

Added (now line 152)

Line 151 the number 79 must be incorrect please can the authors check this. Should this be 40?

The reviewer is correct and the correction has been made (now line 153)

The authors should check the percentages stated for gold standard neg and gold standard positive in the boxes in Figure 1. They are the wrong way round

The reviewer is correct and the percentages have been amended accordingly in the revised figure 1

Discretionary revisions:

The authors state that they did not include any bacteriological component to the definition of gold standard with their reasons. There is no comment on what percentage of patients had histology sent although given that 16 of 22 with frank pus did not have cultures not all patients had histology routinely sent. Please can the authors state how many patients had histology sent alongside the cultures. Although sending paired histology may be recommended it many institutions it may not always be sent by the surgical team

We have added the following line to page 7 “RESULTS”, second paragraph, line 145-146:

“53 of the 79 “gold standard infection” cases (67.1%) met the histological criteria for infection, 1 was equivocal, 6 were negative and 19 had no histological analysis performed”.

Table 1 and figure 1 show that there were 7 patients with positive cultures and 236 patients with negative cultures (2 or more samples with identical organisms and
antibiograms) who did not have either positive histology or clinical gold standard features. Did all these patients have negative histology? Could there be any bias because of lack of histology because none was sent?

We have added the following to page 9, paragraph 2, line 191-195:

“189 of the 236 (80.1%) culture-negative cases were also negative for histological criteria, 10 (4.2%) were equivocal and 37 (15.7%) had no samples sent for histological analysis. The remaining 7 “gold standard negative” cases were culture-positive but all of these were negative by histological and clinical criteria. 4 of these 7 grew a Propionibacterium, 4 a CNS, and 1 a Bacillus spp”.

There is therefore no bias due to lack of histological analysis.

With reference to Butler Wu paper where they suggested that significant growth of propioni often had negative histology, can the authors comment on the organisms from the 7 culture positive but gold standard negative patients. Was histology available for these patients? What were the organisms in theses 7 patients. Were these then considered to be ‘true’ pathogens or ignored?

The paragraph added to page 9, paragraph 2, line 191-195 (see last response) answers this question: 4 of the 7 “gold-standard negative” culture-positive cases grew a Propionibacterium, 4 grew a CNS, and 1 a Bacillus spp.

These were considered to be contaminants as the cases did not fulfil the gold-standard definition for PJI.

Lines 206 and 207 are not completely clear on this point wrt propioni and histological features

This has been clarified by the addition of the following to Page 10, paragraph 2, lines 213-214, regarding the 16 cases of suspected PJI where Propionibacteria spp. were identified:

“Only 2 of these 16 patients had “gold standard infection”; both fulfilled clinical and histological criteria and were detected by BACTEC™ at 3 and 8 days”.

The following has also been added to the discussion, pages 11-12, lines 249-255:

“Interestingly, Butler-Wu et al., found that only 40% of significant cases of PJI secondary to Propionibacteria spp. fulfilled histological criteria for infection (≥ 5 neutrophils/high-power field). While 4 of our 7 culture-positive cases that were “gold-standard negative” for infection (and therefore negative by histological criteria) grew a Propionibacterium, both of our “gold standard positive” cases of Propionibacterium, were in fact positive for histological as well as clinical criteria of infection. However, these small numbers limit further interpretation”
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests
Reviewer's report - responses

Title: Use of an automated blood culture system (BD BACTECTM) for diagnosis of prosthetic joint infections: easy and fast

Version: 2 Date: 15 February 2014

Reviewer: Werner Zimmerli

Reviewer's report:

This is a prospective single-center laboratory study on the role of the BD BACTECTM instrumented blood culture system for the diagnosis of periprosthetic joint infection (PJI). The prevalence of PJI in the population of 322 patients undergoing revision arthroplasty was 24.5%. The aim of the study was to evaluate the duration of incubation required for the diagnosis of PJI using the BD BACTECTM system. This is a clinically relevant question, since prolonged incubation up to 14 days, as it is currently suggested for the microbiological diagnosis of PJI, is time-, labor- and money-consuming. The manuscript is scientifically sound, and well-written. The analysis is based on a well-accepted solid gold standard definition for PJI. Thus, there are only minor criticisms.

Specific comments.

1. Lines 33-34. In the Abstract, the gold standard definition of PJI looks less strict than it has actually been used in the study. It doesn’t mention that not all clinical criteria were accepted. Indeed, only 2 very strict clinical criteria were accepted, namely “sinus tract” and “pus around device”. Thus, the sentence should be changed to “The gold standard definition for PJI was the presence of at least one histological criterion, the presence of a sinus tract or purulence around the device.”

   The sentence has been changed accordingly in the abstract: Page 2, paragraph 2, lines 33-34.

2. Lines 103-107. To my knowledge, the use of glass bead treatment of tissue specimens (beadmill processing) is rather the exception. Therefore, it could be that the excellent sensitivity and the rapid growth were due to the beadmill processing, not to the BD BACTECTM incubation. The authors should comment on this technical step.

   We agree with the reviewer and therefore the following has been added to the discussion, page 12, paragraph 2, lines 256-262, with an additional reference (11):

   “It is possible that the excellent sensitivity of BACTECTM and rapid growth observed over the study period were in part due to vortexing with sterile beads, rather than to the BD BACTECTM incubation per say. The use of a beadmill has previously been shown to be highly effective in the microbiological identification of PJI, using multiple peri-prosthetic samples, with inoculation onto solid and liquid media. Prolonging culture incubation from 7 to 14 days also failed to increase the sensitivity of this method (11). No studies have yet compared the efficacy of BACTECTM with and without prior beadmill processing”.
3. Lines 153-154. Polymicrobial infection is rather rare in patients with PJI. In this study, 21 patients (26.6%) had mixed infection. Since about the same number of patients had a sinus tract (line 146: 22 patients), it would be of interest, whether only patients with a sinus tract had mixed infection.

The following has been added to the results section, page 7, paragraph 3, lines 156-158:
“Of those with mixed cultures, 4/21 (19.0%) had a sinus, compared to 14/45 (31.1%) of those with single cultures (P=0.383, Fisher’s exact 2-sided test)”. Hence there was no evidence that the presence of a sinus tract was more likely to occur in those with mixed infection.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician