The task for the clinical expert is to provide a midpoint estimate together with a range for the variables shown in Tables 1 and 2. We would like this estimate provided in terms of a single positive test result. Tables 1 and 2 differ in that the Table 1assumes that the results from standard blood culture process are concordant with the positive test result, whereas Table 2 assumes that the results from the standard blood culture process are negative. It is acknowledged that blood culture results would not be known when the result from the rapid test becomes available, but it was believed that formulating the question in this manner would make the task easier for the clinician, and these data can be weighted by rates of true positives and false positives by the researchers.

Illustrative examples are provided. For example, If you believed that the information provided by a positive SeptiFast result would produce a net average reduction in ICU length of stay of 0.1 days compared with not having the information from SeptiFast then -0.1 would be entered into the top left cell. Were it believed that a positive MALDI-TOF MS test would be associated with a net average reduction of 0.001 in 30-day mortality then -0.001 would be entered into the bottom right cell. If it is believed that the answers differ for subgroups, such as children and neonates, people who are immunocompromised, those with recent antibiotic use, and people with suspected health care acquired infection and suspected community acquired infection, then please duplicate the tables with appropriate data.

In order to aid clinical judgement data that may be considered useful is contained following Table 2 although the generalisability of the data to treatment in England in 2015 needs to be assessed. These data have been split into two categories, data obtained from systematic reviews, and additional data. The data from the systematic reviews were identified either through the review of diagnostic accuracy undertaken by ScHARR or by a review undertaken by the NICE Guideline Development Group when constructing the draft guidelines on antimicrobial stewardship.

The additional data has been sourced from studies identified within the cost effectiveness searches undertaken by ScHARR. These were supplemented by citation searching. As such, the results cannot be classed as derived from a systematic review.

Table 1: Template to be completed by the clinical expert. Assuming that the result from the blood culture process is positive and in agreement with the test

	LightCycler SeptiFast Test MGRADE	SepsiTest	IRIDICA BAC BSI	MALDI-TOF MS
Average net effect on ICU length of stay				
Average net effect on hospital length of stay				
Average net effect on the cost of antimicrobials				
Net effect on 30-day mortality				

Table 2: Template to be completed by the clinical expert. Assuming that the result from the blood culture process is negative

	LightCycler SeptiFast Test MGRADE	SepsiTest	IRIDICA BAC BSI
Average net effect on ICU length of stay			
Average net effect on hospital length of stay			
Average net effect on the cost of antimicrobials			
Net effect on 30-day mortality			

Information that may be considered useful:

Data from systematic reviews

- From an RCT[1] the mean time to SeptiFast result was 15.9 hours compared with 38.1 hours for blood culture plus MALDI-TOF MS. No data from RCTs on the timings of a result being known were available for SepsiTest or IRIDICA BAC BSI. The same RCT [1] reports the mean time spent in ICU as 34 days for the SeptiFast and 32 days for blood culture plus MALDI-TOF MS. This was not statistically significant.

- An RCT[2] of de-escalation of antimicrobials recruiting 116 patients with severe sepsis reported statistically significantly greater rates of superinfection in the de-escalation group (27% vs 11%; p-value = 0.03) and in the mean number of antibiotic days (9 vs 7.5; p-value = 0.03). There was a non-statistically significant increase in median duration of ICU stay (9 days vs 8 days; p-value = 0.71) in the de-escalation arm

Additional data

- A paper[3] reports the implementation of an evidence-based intervention that integrated MALDI-TOF MS, rapid antimicrobial susceptibility testing, and near–real-time antimicrobial stewardship practices. Comparison of results before and after were made. The mean hospital

length of stay after blood stream infection onset in the pre-intervention group survivors (n = 100) was 9.9 versus 8.1 days in the intervention group (n=101; p-value=.01). Within a multivariate model receiving active antibiotic therapy at 48 hours was associated with a hazard ratio for discharge of 2.90 (95% CI 1.15-7.33; p-value = 0.02) and the intervention was associated with a hazard ratio for discharge of (95% CI 1.01-1.88; p-value = 0.04). Total hospitalisation costs was $45,709 in the pre-intervention cohort vs $26,162 in the intervention.

- A further paper reporting a pre–post quasi-experimental study analysed the impact of MALDI-TOF MS with an antimicrobial stewardship team.[4] The intervention (n = 256) decreased time to organism identification (84.0 vs 55.9 hours, p-value < .001), and improved time to effective antibiotic therapy (30.1 vs 20.4 hours, p-value = .021), optimal antibiotic therapy (90.3 vs 47.3 hours, p-value < .001) and length of ICU stay (14.9 vs 8.3 days, p-value = .014) compared with pre-intervention (n=245). 30-day all-cause mortality was lower in the intervention arm compared with pre-intervention (12.73 vs 20.3%. p-value = .021) as was length of hospitalisation (14.2 vs 11.4 days, p-value = .066)

- An Italian observational, propensity matched analysis[5] comparing a retrospective cohort with a prospective cohort (using SeptiFast) in haematological patients – typically acute myeloid leukaemia. Propensity matching was undertaken for: definitive blood culture; positive blood cultures; negative blood cultures; (and patients with positive SeptiFast and patients with negative SeptiFast results. No differences were observed in the length of stay or in changes in management. The mortality difference in the original propensity score matching was not significant 8.24 vs 13.48 p = 0.39). However, in a more stringently matched group SeptiFast was reported to have better mortality rates (3.13% compared with 14.71% p-value =0.04). There were lower costs (€431; p-value = 0.05) in the prospective cohort compared with the retrospective cohort.

- One study[6] aimed to evaluate the economic impact of SeptiFast via a cost-minimisation study. 48 patients were in the SeptiFast group with 54 in control. The paper concluded that there was a 94.6% chance of cost savings associated with use of SeptiFast when samples were run per batch. A large proportion of these savings were from reduced ICU length of stay although this could be heavily confounded by the demographic and clinical data of the SeptiFast and control groups. For example, there were 20 patients with heart surgery in the control and 2 in the SeptiFast group, and 4 polytrauma / head injuries in the control group compared with 20 in the SeptiFast group.

- A prospective, observational trial in 2 German university hospitals, 1 Spanish, 1 American and 1 Italian tertiary hospital compared the use of SeptiFast with Blood Culture.[7] This study estimated that if SeptiFast had been used then there would have been 22.8 days reduction in inadequate treatment per 100 tests. The results for those in ICU alone were taken and it was estimated that the SeptiFast could have presented 5 mortalities from 221 investigated sepsis episodes within 30 days of discontinuing antimicrobial treatment.[8]. However, the data relating inadequate treatment to mortality were taken from studies published in 2000 or earlier.[9,10]

- A study in Texas compared the outcomes of 112 patients with antibiotic-resistant Gram-negative bacteraemia, during January 2009 – November 2011 with 157 patients during February 2012 to June 2013 post intervention following the introduction of an intervention (MALDI-TOF MS and antimicrobial stewardship).[11] Time to initiation of active treatment was 90 hours pre-intervention and 32 hours post intervention ($p<0.001$). There were 33 (21%) and 10 (9%) all-cause mortalities observed in the pre-intervention cohort and the intervention cohort respectively. In multivariate logistic regression the intervention was a significant predictor of survival (OR=0.28, 0.12-0.71; p-value =0.008). A significant reduction in average total hospital costs was observed from $78,991 to $52,693.

- A paper by Martiny *et al.*,[12] reports that the use of MALDI-TOF MS resulted in the modification of in treatment in 21/157 adults and 1/40 paediatrics

- A Spanish retrospective matched cohort study[13] attempted to determine the attributable mortality and excess length of stay associated with inadequate empirical antimicrobial therapy between 1997 – 2006. Therapy was considered inadequate when no effective drug against the isolated pathogen(s) was included in the empirical antibiotic treatment within the first 24 hours of admission to the ICU, or the doses and pattern of administration were not in accordance with current medical standards. From 87 matched pairs 59 (67.8%) died in the inadequate group compared with 25 (28.7%) in the control group. Removing pairs with nosocomial infection still showed a 31.4% excess in mortality (65.7% vs 34.3%). In those without a nosocomial infection there was a significant reduction in the length of stay in ICU associated with adequate treatment (7 vs 9 days; p-value = 0.02)

- Using a generalised linear model, adjusted for confounders, Zilberberg *et al.*,[14] estimated that the excess length of hospitalisation was 7.7 days (95% CI 0.6-13.5) and attributable costs were $13,398 (95% CI $1,060-$26,736) when a patient had inadequate antifungal treatment. Inadequate antifungal treatment was defined as treatment delay of ≥24 hours from Candidemia onset or inadequate dose of antifungal agent active against the pathogen.

- Arnold *et al*.,[15] attempted to estimate from 167 consecutive patients the costs of inappropriate treatment of Candidemia, which was defined as delayed antifungal therapy >24 hours from culture collection. 22 patients had appropriate therapy, 145 did not. Length of stay was shorter in the appropriately treated group (7 vs 10.4 days; p-value = 0.037) and the costs were lower ($15,832 vs $33,021; p-value <0.001)

- Morrell *et al*.,[16] retrospectively analysed 157 consecutive patients over a 4-year period with a candida bloodstream infection of which 50 (32%) died during hospitalisation. The number of people without a delay in antifungal treatment (>12 hours) was 9, whilst 148 patients had delayed treatment. Adjusted odds ratio associated with delay in antifungal treatment was 2.09 (95% CI 1.53-2.84). Delay in antifungal treatment was also associated with a longer duration within ICU (9.4 days vs 0.4 days; p-value = 0.019).

References

1. Tafelski S., Nachtigall I., Adam T., Bereswill S., Faust J., Tamarkin A. *et al*. Randomized controlled clinical trial evaluating multiplex polymerase chain reaction for pathogen identification and therapy adaptation in critical care patients with pulmonary or abdominal sepsis. *J Int Med Res* 2015.PM:25911587

2. Leone M., Bechis C., Baumstarck K., *et al*. De-escalation versus continuation of 34 empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized 35 noninferiority trial. *Intensive Care Medicine* 2014; 40:1399-408.

3. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Land GA *et al*. Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. *Archives of Pathology & Laboratory Medicine* 2013; 137(9):1247-1254.

4. Huang A.M., Newton D., Kunapuli A., Gandhi T. Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. *Clinical Infectious Diseases* 2013; 57(9):1237-1245.

5. Mancini N., Sambri V., Corti C., Ghidoli N., Tolomelli G., Paolucci M. *et al*. Cost-effectiveness of blood culture and a multiplex real-time PCR in hematological patients with suspected sepsis: an observational propensity score-matched study. *Expert Review of Molecular Diagnostics* 2014; 14(5):623-632.http://dx.doi.org/10.1586/14737159.2014.916212

6. Alvarez J., Mar J., Varela-Ledo E., Garea M., Matinez-Lamas L., Rodriguez J. *et al*. Cost analysis of real-time polymerase chain reaction microbiological diagnosis in patients with septic shock. *Anaesthesia and Intensive Care* 2012; 40(6):958-963.

7. Lehmann L.E., Alvarez J., Hunfeld K.-P., Goglio A., Kost G. Potential clinical utility of polymerase chain reaction in microbiological testing for sepsis. *Critical Care Medicine* 2009; 37(12):3085-3090.

8. Lehmann L.E., Herpichboehm B., Kost G., Kollef M., Stuber F. Cost and mortality prediction using polymerase chain reaction pathogen detection in sepsis: evidence from three observational trials. *Critical Care* 2010; 14(5):R186.

9. Ibrahim E.H., Sherman G., Ward S., Fraser V.J., Kollef M.H. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000; 118(1):146-155.

10. Kollef M.H., Sherman G., Ward S., Fraser V.J. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999; 115(2):462-474.

11. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Peterson LE *et al*. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. *Journal of Infection* 2014; 69(3):216-225.

12. Martiny D., Debaugnies F. Impact of rapid microbial identification directly from positive blood cultures using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on patient management. *Clinical Microbiology & Infection* 2013; 19(12):E568-E581.

13. Garnacho-Montero J., Ortiz-Leyba C., Herrera-Melero I., Aldabo-Pallas T., Cayuela-Dominguez A., Marquez-Vacaro JA. *et al*. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study. *Journal of Antimicrobial Chemotherapy* 2008; 61(2):436-441.http://jac.oxfordjournals.org/content/61/2/436.abstract

14. Zilberberg M., Kollef M., Arnold H., Labelle A., Micek S., Kothari S. *et al*. Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: a retrospective cohort study. *BMC Infectious Diseases* 2010; 10(1):150.http://www.biomedcentral.com/1471-2334/10/150

15. Arnold HM., Micek ST., Shorr AF., Zilberberg MD., Labelle AJ., Kothari S. *et al*. Hospital Resource Utilization and Costs of Inappropriate Treatment of Candidemia. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 2010; 30(4):361-368.http://dx.doi.org/10.1592/phco.30.4.361

16. Morrell M., Fraser V., Kollef M.H. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrobial Agents and Chemotherapy* 2005; 49(9):3640-3645.