NICE National Institute for Health and Care Excellence

Diagnostics Assessment Programme

Procalcitonin testing for Diagnosing and monitoring sepsis (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay)

Committee Papers

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Contents:

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National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Sepsis: Procalcitonin testing for diagnosing and monitoring (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay)

This overview summarises the key issues for the Diagnostics Advisory Committee's consideration. It includes a brief description of the topic, a description of the analytical structure and model, a discussion of the analytical difficulties, and a brief summary of the results. It is not a complete summary of the diagnostics assessment report, and it is assumed that the reader is familiar with that document. This overview contains sections from the original scope and the diagnostics assessment report, as well as referring to specific sections of these documents.

1 Background

1.1 Introduction

BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific) was selected by the Medical Technologies Advisory Committee (MTAC) for the Diagnostics Assessment Programme to develop recommendations on its use in the NHS. Four other technologies (ADVIA Centaur BRAHMS PCT assay [Siemens Healthcare Diagnostics], Elecsys BRAHMS PCT assay [Roche Diagnostics], LIAISON BRAHMS PCT assay [DiaSorin] and VIDAS BRAHMS PCT assay [bioMérieux]), were identified during the scoping phase and included in the assessment.

The purpose of this assessment is to evaluate the clinical- and cost-effectiveness of using procalcitonin testing with standard clinical practice to guide antibiotic therapy in the following two populations:

- Adults and children presenting to the emergency department with suspected bacterial infection.
- Adults and children with confirmed or highly suspected sepsis in intensive care settings.

Provisional recommendations on the use of these technologies will be formulated by the Diagnostics Advisory Committee at the Committee meeting on 25 February 2015.

1.2 The conditions

Systemic inflammatory response syndrome, bacterial infection and sepsis

Systemic inflammatory response syndrome (SIRS) is a life-threatening illness caused by the body overreacting to an infectious or non-infectious insult. Sepsis is the presence of SIRS in addition to a documented or presumed infection. If sepsis is not treated it can progress to severe sepsis or septic shock and can lead to multiple organ failure and death. Severe sepsis occurs when sepsis progresses to sepsis-induced organ dysfunction. That is, when the body's response to infection interferes with the functioning of vital organs, such as the heart, kidneys, lungs or liver.

Septic shock occurs in severe cases of sepsis, and is defined as sepsis-induced hypotension (low blood pressure) persisting despite adequate fluid resuscitation. Septic shock prevents organs from receiving enough oxygenated blood. Complications of septic shock can include:

- respiratory failure
- heart failure

- kidney injury or failure
- abnormal blood clotting.

Definitions of sepsis have been published by the following societies:

- The American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference Committee (Bone et al. 1992)
- 2001 SCCM / ESICM / ACCP / ATS / SIS International Sepsis Definitions Conference (Levy et al. 2003)
- The German Sepsis Society (Reinhart et al. 2010).

In the UK there are estimated to be 30,000 cases of severe sepsis each year, and it is one of the most common reasons for admission to an intensive care unit, accounting for almost one third of all cases. Sepsis, especially when treatment is delayed, has a mortality rate of 40%, rising to approximately 60% if septic shock develops.

Bacterial infections are the most common cause of sepsis; however it can also be caused by viral and fungal infections. The most common type of suspected bacterial infection to present to the emergency department is respiratory tract infection. Lower respiratory tract infection includes acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease or asthma and pneumonia, and is a major cause of morbidity and mortality in children and adults. In addition to the lungs, the most common sites of infection leading to sepsis are the urinary tract, abdomen and pelvis. Other sources of infection leading to sepsis include skin infections (such as cellulitis), post-surgical infections and infections of the nervous system (such as meningitis or encephalitis). Sepsis can also be caused by a condition known as neutropenia, in which the number of white blood cells in the blood is low. This is called neutropenic sepsis and people having anticancer treatment, particularly chemotherapy, can be at risk.

Everybody is potentially at risk of developing sepsis from minor infections, but some people are at higher risk, such as people who:

- are very young or very old
- have a weakened immune system
- have just had surgery, have severe injuries or large burns
- are on mechanical ventilation
- have intravenous drips or catheters.

Sepsis is a particular risk for people already in hospital for another serious illness.

1.3 Patient issues and preferences

No specific patient issues relating to procalcitonin testing for the diagnosis and monitoring of sepsis were identified during scoping.

Depression, post-traumatic stress disorder, and functional disability are common in survivors of critical illness (Jackson et al. 2007). Further, older adults who have survived severe sepsis are more likely to develop cognitive and/or physical problems than older adults who are hospitalised for other reasons (Iwashyna et al. 2010).

1.4 Diagnostic and care pathways

Diagnosis of sepsis

The diagnostic work-up of sepsis is described in several guidelines:

- Prevention and management of neutropenic sepsis in cancer patients NICE clinical guideline 151 (2012)
- Bacterial Sepsis in Pregnancy The Royal College of Obstetricians and Gynaecologists Green-Top Guideline 64a (2012)
- Bacterial Sepsis following Pregnancy The Royal College of Obstetricians and Gynaecologists Green Top Guideline 64b (2012)

- Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012.

In addition, a NICE clinical guideline Sepsis: the recognition, diagnosis and management of severe sepsis is currently in development with an estimated publication date of July 2016.

Diagnostic criteria for sepsis are listed in the Surviving Sepsis Campaign guidelines (adapted from Levy et al. 2003). In summary, regular observations of all vital signs should be taken and recorded, kidney and liver function tests should be performed, inflammatory biomarkers and serum lactate should be measured. These guidelines state a diagnosis of sepsis should be based on infection, documented or suspected, plus some of the following:

- General variables: temperature of greater than 38.3°C or less than 36°C; heart rate greater than 90 beats per minute; rapid breathing; altered mental status; significant oedema; high blood sugar in the absence of diabetes.
- Inflammatory variables: low or high white blood cell count or more than 10% immature forms; raised plasma C-reactive protein; raised plasma procalcitonin.
- Haemodynamic and tissue perfusion variables: low blood pressure; raised blood lactate (a concentration of equal to or greater than 4 mmol per litre suggests tissue hypoperfusion).
- Organ dysfunction variables: low blood oxygen; reduced urine output; increased creatinine levels (indicating impaired kidney function); coagulation abnormalities; absent bowel sounds; reduced platelet count; raised plasma bilirubin levels.

The Surviving Sepsis Campaign guidelines also make the following specific recommendations relating to the diagnosis of sepsis:

- At least 2 sets of blood cultures should be collected (aerobic and anaerobic) before antimicrobial therapy is initiated if such cultures do not

cause significant delay (more than 45 minutes) in the start of antimicrobial administration.

- Cultures of other sites such as wounds, urine, cerebrospinal fluid, respiratory secretions or other body fluids that may be the source of infection should be obtained before initiation of antimicrobial therapy, if doing so does not cause significant delay in the start of antimicrobial administration.
- Imaging studies such as CT or X-ray should be performed in order to confirm a potential source of infection.
- Assays to diagnose systemic fungal infection should be used if available and invasive candidiasis is suspected.

The Surviving Sepsis Campaign guidelines recommend care 'bundles' which should be initiated during the diagnostic work-up of a patient. The 3-hour bundle should be completed within 3 hours:

- measure lactate levels
- obtain blood cultures prior to administration of antibiotics
- administer broad spectrum antibiotics
- administer 30 millilitres per kilogram crystalloid for hypotension or lactate equal to or greater than 4 mmol per litre.

The 6-hour bundle should be completed within 6 hours:

- apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure equal to or greater than 65 mmHg
- in the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate equal to or greater than 4 mmol per litre:
  - Measure central venous pressure
  - Measure central venous oxygen saturation
- re-measure lactate if initial lactate was elevated.

Management and treatment of sepsis

The treatment of sepsis varies based on the initial infection, the organs affected and the extent of tissue damage. If sepsis is detected early enough it may be possible for patients to be treated with antibiotics in an outpatient setting. If sepsis is severe the patient is normally admitted to the intensive care unit and treated with empiric intravenous antibiotics.

Recommendations on the management of severe sepsis and septic shock are made in the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock; 2012 and are summarised below. All patients with severe sepsis or septic shock will require initial resuscitation, antimicrobial therapy, source control and fluid therapy. Some patients may require additional treatment with vasopressors, inotropic therapy, corticosteroids and other supportive therapy.

Initial resuscitation

Protocol led, quantitative resuscitation (also known as haemodynamic optimisation) of patients with sepsis-induced tissue hypoperfusion should be carried out and within the first 6 hours the following thresholds should be met:

- Central venous pressure: 8 to 12 mmHg
- Mean arterial pressure: equal to or greater than 65 mmHg
- Urine output: equal to or greater than 0.5 ml/kg per hour
- Central venous or mixed venous oxygen saturation: 70% or 65%, respectively.

Antimicrobial therapy

Intravenous empiric antimicrobials should be administered within the first hour of recognition of septic shock and severe sepsis. The initial antimicrobial therapy should include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis.

Antimicrobials should be reassessed daily for potential de-escalation. Procalcitonin or similar biomarkers can be measured to assist the clinician in deciding whether to stop empiric antimicrobial treatment in patients who were initially suspected of having sepsis but have no subsequent evidence of infection. Empiric combination therapy should not be administered for more than 3 to 5 days and de-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.

The duration of therapy should typically be 7 to 10 days, however longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteraemia with Staphylococcus aureus, some fungal and viral infections or immunological deficiencies.

Source control

A rapid diagnosis of the specific site of infection should be made and source control measures undertaken (for example, drainage of abscess, removal of infected necrotic tissue, removal of a potentially infected device).

Fluid therapy

Crystalloids should be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock. When patients require substantial amounts of crystalloids then albumin should be used for fluid resuscitation.

Haemodynamic support and adjunctive therapy

Vasopressors should be used to target a mean arterial pressure of 65 mmHg. Inotropic therapy should be administered if the patient experiences myocardial dysfunction or ongoing signs of hypoperfusion. If haemodynamic stability is not achieved through use of fluid resuscitation and vasopressor therapy, intravenous corticosteroids should be used.

Other supportive therapy

Other supportive therapy may include administration of blood products, mechanical ventilation for sepsis-induced acute respiratory distress syndrome,

sedation, analgesia and neuromuscular blockade, glucose control, renal replacement therapy, deep vein thrombosis prophylaxis, stress ulcer prophylaxis, oral or enteral feeding.

Special considerations for paediatric patients

Definitions of sepsis, severe sepsis, and septic shock are similar to adult definitions but depend on age-specific heart rate, respiratory rate and white blood cell count cut-off values. Special considerations for managing sepsis in paediatric patients are described in the Surviving Sepsis Campaign guidelines and in the American College of Critical Care Medicine guidelines on Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock.

Diagnosis of bacterial infection

Infections, such as pneumonia, may be caused by bacteria or viruses. Viral pneumonia tends to have a mild course of disease and antibiotic treatment is inappropriate. Bacterial pneumonia can be treated with antibiotics. However, many patients, especially children are treated with antibiotics without the causative agent being known. Therefore, rapid and accurate determination of the presence or absence of bacterial infection is important to reduce unnecessary exposure to antibiotics.

The care pathway relating to pneumonia is described in the NICE clinical guideline Diagnosis and management of community- and hospital-acquired pneumonia in adults (CG191, 2014). Recommendations from this guideline on the use of tests to diagnose community-acquired pneumonia in people presenting to hospital include:

- Do not routinely offer microbiological tests to patients with low-severity community-acquired pneumonia.
- For patients with moderate or high-severity community-acquired pneumonia:
  - take blood and sputum cultures and

- consider pneumococcal and legionella urinary antigen tests.

The NICE clinical guideline on Feverish illness in children (CG160, 2013) makes a research recommendation relating specifically to procalcitonin. The guideline development group recommended that a UK study of the performance characteristics and cost-effectiveness of procalcitonin versus C-reactive protein in identifying serious bacterial infection in children with fever without apparent source be carried out. This research recommendation was made in 2007 and evidence was not updated and reviewed in the 2013 guideline update.

The NICE clinical guideline on Antibiotics for early-onset neonatal infection (CG149, 2012) also makes a research recommendation relating to procalcitonin. The guideline development group recommend further research to provide evidence on the clinical and cost effectiveness of laboratory investigations used individually or in combination to exclude early-onset neonatal infection in babies receiving antibiotics for suspected infection. During the development of this guideline no evidence was found relating to the use of procalcitonin testing for the identification of asymptomatic babies who should receive antibiotic treatment. Limited low quality evidence was found relating to babies with symptoms about to start antibiotics. The guideline development group considered that procalcitonin assessments were insufficiently useful to accurately rule in or rule out early-onset neonatal infection in babies about to start antibiotic treatment and chose not to recommend the use of this test.

Management and treatment of bacterial infection

The NICE clinical guideline on pneumonia: Diagnosis and management of community- and hospital-acquired pneumonia in adults (CG191, 2014), makes the following recommendations:

- Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours to all patients with community-acquired pneumonia who are admitted to hospital.
- Offer a 5-day course of a single antibiotic to patients with low-severity community-acquired pneumonia.
- Consider extending the course of the antibiotic for longer than 5 days as a possible management strategy for patients with low-severity community-acquired pneumonia whose symptoms do not improve as expected after 3 days.
- Consider a 7- to 10-day course of antibiotic therapy for patients with moderate- or high-severity community-acquired pneumonia.
- Consider measuring a baseline C-reactive protein concentration in patients with community-acquired pneumonia on admission to hospital, and repeat the test if clinical progress is uncertain after 48 to 72 hours.

During the development of the pneumonia guideline, evidence was gathered on the use of procalcitonin testing to determine whether or not to initiate antibiotics and to guide the duration of therapy in patients who have been appropriately treated with antibiotics. The guideline development group, however, did not make any recommendations on the use of procalcitonin.

1.5 The population

The populations covered in this assessment are

- Children and adults presenting to the emergency department with suspected bacterial infection
- Children and adults in an intensive care unit with suspected or confirmed sepsis.

2 The technologies

Procalcitonin is a 116 amino acid precursor to calcitonin (a hormone which lowers the concentration of calcium in the blood when it rises above the

normal value). Procalcitonin is an indirect marker of infection. It is released into the circulation in response to pro-inflammatory stimuli, especially those that are bacterial in origin. Procalcitonin testing may be used to assist clinicians in making a diagnosis of bacterial infection (which can cause sepsis), and to guide decisions on the initiation of antibiotics. Procalcitonin levels are usually low in people with viral infections, chronic inflammatory disorders or autoimmune processes.

Thermo Fisher Scientific holds a patent for the use of procalcitonin as a biomarker for sepsis. However, several other companies have licensed the use of procalcitonin and its antibodies. All commercial quantitative BRAHMS PCT assays use the same 'sandwich ELISA' principle to quantify procalcitonin by forming antibody-procalcitonin-antibody complexes. The main difference between these assays is the mechanism of detection of these antibody-procalcitonin-antibody complexes.

There are 5 automated quantitative BRAHMS PCT assays available in the UK: the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific), the VIDAS BRAHMS PCT (bioMérieux), the ADVIA Centaur BRAHMS PCT (Siemens Healthcare Diagnostics), the Elecsys BRAHMS PCT (Roche Diagnostics), and the LIAISON BRAHMS PCT (DiaSorin). These assays have all been standardised using the BRAHMS PCT LIA assay (the original manual procalcitonin assay that is not in widespread use in the UK). It is claimed that these assays are technically similar but adapted for use on different analysers. Published data are available which suggest a good correlation between the assays (Schuetz et al. 2009, Hausfater et al. 2010, Lloyd et al. 2012, Sanders et al. 2011, and de Wolf et al. 2009).

2.1 BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific)

The BRAHMS PCT Sensitive Kryptor assay is an automated immunofluorescent sandwich assay for the determination of procalcitonin in

human serum and plasma. The measurement principle is based on TRACE™ Technology (Time-Resolved Amplified Cryptate Emission), which measures the signal that is emitted from an immunocomplex with time delay. It is indicated for use with the BRAHMS Kryptor, BRAHMS Kryptor compact and BRAHMS Kryptor compact PLUS analysers. The assay has a measuring range of 0.02 to 5000 nanograms per millilitre, a functional assay sensitivity of 0.06 nanograms per millilitre, and an analytical sensitivity of 0.02 nanograms per millilitre. The time to result is 19 minutes.

2.2 Elecsys BRAHMS PCT (Roche Diagnostics)

The Elecsys BRAHMS PCT is an automated electrochemiluminescent immunoassay (ECLIA) for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with the detection of light emission by a photomultiplier. The assay is indicated for use on the Elecsys, Modular and Cobas e analysers (Roche). It has a measuring range of 0.02 to 100 nanograms per millilitre, a functional sensitivity of 0.06 nanograms per millilitre and an analytical sensitivity of less than 0.02 nanograms per millilitre. The time to result is 18 minutes.

2.3 VIDAS BRAHMS PCT (bioMérieux)

The VIDAS BRAHMS PCT is an automated Enzyme-Linked Fluorescent Assay (ELFA) for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with a final fluorescent detection. It is indicated for use with the VIDAS and miniVIDAS analysers (bioMérieux). It has a measuring range of 0.05 to 200 nanograms per millilitre, a functional detection limit of 0.09 nanograms per millilitre and an analytical detection limit of 0.05 nanograms per millilitre. The time to result is 20 minutes.

2.4 ADVIA Centaur BRAHMS PCT (Siemens Healthcare Diagnostics)

The ADVIA Centaur BRAHMS PCT is an automated chemiluminescent assay for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with the detection of light emission as the final step. It is indicated for use with the ADVIA Centaur/XP and ADVIA Centaur CP analysers (Siemens). It has a measuring range of 0.02 to 75 nanograms per millilitre, a functional sensitivity of less than 0.05 nanograms per millilitre and an analytical sensitivity of less than 0.02 nanograms per millilitre. The time to result is 26 to 29 minutes, depending on the selected analyser.

2.5 LIAISON BRAHMS PCT (DiaSorin)

The LIAISON BRAHMS PCT is a sandwich chemiluminescent immunoassay for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with the detection of light emission by a photomultiplier. The assay is indicated for use with the LIAISON analyser (DiaSorin). It has a measuring range of 0.1 to 500 nanograms per millilitre, a functional sensitivity of less than 0.24 nanograms per millilitre and an analytical sensitivity of less than 0.032 nanograms per millilitre.

2.6 The comparator

The comparator used in this assessment is treatment decisions based on standard clinical practice without procalcitonin testing.

3 The evidence

This section summarises data from the diagnostics assessment report compiled by the External Assessment Group (EAG).

3.1 Clinical effectiveness

Methods

The EAG conducted a systematic review of the evidence on the clinical effectiveness of the use of procalcitonin testing with standard clinical practice to guide antibiotic therapy for the treatment of:

- Patients with confirmed or highly suspected sepsis in intensive care settings
- people presenting to the emergency department with suspected bacterial infection.

Details of the systematic review can be found starting on page 33 of the diagnostics assessment report. Studies were included if they contained information on the following:

- Adults or children with confirmed or highly suspected sepsis, in whom antibiotic therapy is indicated, who are being treated in intensive care units; or, adults or children presenting to the emergency department with suspected bacterial infection.
- Treatment decisions based on standard clinical practice with laboratory procalcitonin testing (using any of the 5 tests included in the scope) compared with treatment decisions based on standard clinical practice without procalcitonin testing.
- At least one of the following outcomes:
  - antibiotic exposure (initiation/duration of antibiotic therapy)
  - resource use (number of hospital admissions, length of hospital or intensive care unit stay, costs)
  - adverse clinical outcomes (for example, Sequential Organ Failure Assessment [SOFA] scores, in-hospital mortality, condition-specific outcomes), antibiotic-related adverse events.

Included studies were randomised controlled trials (RCTs), or controlled clinical trials (CCTs) where no RCTs were available. Where no controlled trials (RCTs or CCTs) were available, studies assessing the change in diagnostic accuracy associated with the addition of procalcitonin testing to standard diagnostic work-up were sought. Studies that assessed the diagnostic accuracy of procalcitonin testing alone, or that used culture alone as the reference standard were excluded.

Studies were also excluded if:

- They were only in immunosuppressed neutropenic patients or neonates on chemotherapy, immunosuppressant drugs or transplant programmes.
- They were studies of point-of-care procalcitonin tests, which did not provide a quantitative estimate of procalcitonin levels.

Overview of included studies

Based on the searches and inclusion screening, 36 publications of 18 studies were included in the review; 8 studies were conducted in intensive care unit settings and 10 studies were conducted in emergency department settings.

As shown in table 1, the majority (12) of the included studies measured procalcitonin levels using the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific). Two studies measured procalcitonin levels using the VIDAS BRAHMS PCT (bioMérieux). The remaining 4 studies used quantitative procalcitonin assays, but did not specify the assay manufacturer.

Twelve studies were conducted in Europe (predominately Switzerland), 3 were conducted in China, and 1 was conducted in Brazil; no UK studies were identified. Two studies (conference abstracts) did not specify location.

Nine studies reported receiving some support from assay manufacturers, including supply of assay platforms and/or kits; 5 studies were fully supported by public funding and 4 studies did not report any information on funding.

The methodological quality of all included studies was appraised using the Cochrane Risk of Bias Tool. Three studies were judged as high risk of bias and 1 as low risk of bias. All other studies were judged as unclear risk of bias because insufficient information was reported to make a judgement on one or more bias domains.

Table 1: Overview of included studies

Study	Assay	Location	Funding	Bias
Adults/ICU				
Annane (2013)	Sensitive Kryptor	France	Industry	Unclear
Bouadma (2010)	Sensitive Kryptor	France	Industry	Unclear
Deliberato (2013)	Vidas	Brazil	Not stated	High risk
Layios (2012)	Vidas	Belgium	Not stated	Unclear
Liu (2013)	Not specified	China	Public	Unclear
Nobre (2005)	Sensitive Kryptor	Switzerland	Industry	High risk
Qu (2012)	Not specified	China	Public	Unclear
Stolz (2009)	Sensitive Kryptor	Switzerland	Mixed	Unclear
Adults/ED				
Christ-Crain (2004)	Sensitive Kryptor	Switzerland	Mixed	Unclear
Christ-Crain (2006)	Sensitive Kryptor	Switzerland	Industry	Unclear
Drozdov (2014)	Sensitive Kryptor	Switzerland	Public	Unclear
Roh (2013)	Not specified	Not reported	Not stated	Unclear
Roh (2010)	Not specified	Not reported	Not stated	Unclear
Schuetz (2009)	Sensitive Kryptor	Switzerland	Mixed	Unclear
Stolz (2007)	Sensitive Kryptor	Switzerland	Mixed	High risk
Tang (2013)	Sensitive Kryptor	China	Public	Low risk
Children/ED				
Baer (2013)	Sensitive Kryptor	Switzerland	Mixed	Unclear
Esposito (2011)	Sensitive Kryptor	Italy	Public	Unclear
Abbreviations: ICU – intensive care unit; ED – emergency department				

Results - Intensive care unit settings

The results of the systematic review of studies in patients with confirmed or highly suspected sepsis in intensive care unit settings can be found starting on page 44 of the diagnostics assessment report. Results are also summarised in table 2 on page 25 of this overview document.

Eight RCTs provided data on the effectiveness of using procalcitonin testing with standard clinical practice to guide antibiotic therapy in intensive care unit settings. All studies were conducted in adult populations. No studies conducted in paediatric intensive care unit settings met the inclusion criteria for the review. Four studies were conducted in adults with confirmed or highly suspected sepsis, in whom antibiotic therapy is indicated. One study included adults who were being treated in an intensive care unit for suspected bacterial infection, or who developed sepsis during their stay. Two studies included adults being treated in intensive care unit settings who were considered to be at increased risk of developing sepsis (1 study in adults with acute pancreatitis and 1 study in adults with ventilator-associated pneumonia). The final study included adults who were being treated for suspected bacterial infections in intensive care unit settings. This was the only study to assess the effectiveness of using procalcitonin testing with standard clinical practice to guide the initiation of antibiotic treatment. All of the other studies assessed the effectiveness of using procalcitonin testing with standard clinical practice to decide when to discontinue antibiotic treatment.

All studies assessing discontinuation used procalcitonin algorithms with multiple decision thresholds to guide antibiotic discontinuation in the intervention arm. Final treatment decisions always remained at the discretion of the treating clinician. The details of the procalcitonin algorithm varied between studies, however, all included a component which ‘strongly encouraged’ or ‘encouraged’ discontinuation of antibiotics when the procalcitonin level was less than 0.25 nanograms per millilitre, and/or ‘encouraged’ discontinuation of antibiotics when the procalcitonin level was less than 0.5 nanograms per millilitre. Discontinuation studies reported measuring procalcitonin at baseline and daily or every 2 days until discontinuation, discharge or death.

Antibiotic duration

Four of the 7 studies assessing discontinuation reported data to allow the calculation of mean difference in the duration of antibiotic therapy between study arms. Three of these studies found that the inclusion of a procalcitonin algorithm in the clinical decision making process resulted in a statistically significant reduction in the mean duration of antibiotic therapy. The fourth study found that the procalcitonin algorithm was associated with a trend towards reduction in the duration of antibiotic therapy, which was not statistically significant. The summary effect estimate indicated that the addition of a procalcitonin algorithm to the clinical decision making process was associated with a statistically significant reduction in the duration of antibiotic therapy, weighted mean difference −3.19 days (95% confidence interval [CI]: −5.44 to −0.95). However, between study heterogeneity was high. Only 2 of these 4 studies were conducted in populations with suspected or confirmed sepsis. Of the other 2 studies, 1 was conducted in patients with acute pancreatitis and the other was conducted in patients with suspected bacterial infection and those who developed sepsis whilst in the intensive care unit. When the meta-analysis was restricted to the 2 studies conducted in populations with suspected or confirmed sepsis, the summary effect estimate still indicated that the addition of a procalcitonin algorithm to the clinical decision making process was associated with a statistically significant reduction in the duration of antibiotic therapy, weighted mean difference −1.20 days (95% CI: −1.33 to −1.07).

Three further studies assessed the effectiveness of using procalcitonin testing with standard clinical practice to decide when to discontinue antibiotic treatment, but reported the outcome as median duration of antibiotic therapy. Two of these studies were conducted in people with suspected or confirmed sepsis and results indicated that adding a procalcitonin algorithm to the clinical decision making process had no statistically significant effect on the duration of antibiotic treatment. The third study was conducted in adults with ventilator associated pneumonia and found that inclusion of a procalcitonin

algorithm in the clinical decision making process was associated with a statistically significant reduction in the median duration of antibiotic therapy from 15 to 10 days.

Full results on antibiotic duration can be found on pages 44 to 47 of the diagnostics assessment report.

Duration of hospital stay

All 7 studies assessing discontinuation reported information on the duration of hospital stay. Four studies reported data to allow the calculation of mean difference in the duration of hospital stay between study arms. Two of these studies found that the inclusion of a procalcitonin algorithm in the clinical decision making process resulted in a statistically significant reduction in the mean duration of hospital stay. One study found that inclusion of a procalcitonin algorithm was associated with a trend towards reduction in the duration of hospital stay, which was not statistically significant. The fourth study, which included people with suspected bacterial infection and those who developed sepsis whilst in the intensive care unit, indicated that the inclusion of a procalcitonin algorithm did not reduce the duration of hospital stay. This result may be related to the less clinically severe spectrum of clinical presentations represented.

The summary effect estimate indicated that the addition of a procalcitonin algorithm to the clinical decision making process was associated with a statistically significant reduction in the duration of hospital stay, weighted mean difference −3.85 days (95% CI: −6.78 to −0.92). However, between study heterogeneity was high. Only 2 of these 4 studies were conducted in populations with suspected or confirmed sepsis. Of the other 2 studies, 1 was conducted in patients with acute pancreatitis and 1 was conducted in patients with suspected bacterial infection and those who developed sepsis whilst in the intensive care unit. When the meta-analysis was restricted to the 2 studies conducted in populations with suspected or confirmed sepsis, the summary effect estimate indicated that the addition of a procalcitonin algorithm to the

clinical decision making process was associated with a greater reduction in duration of hospital stay, weighted mean difference −4.32 days (95% CI: −6.50 to −2.14).

The 3 remaining studies reported median duration of hospital stay. Two of these studies were conducted in people with suspected or confirmed sepsis and 1 was conducted in people with ventilator associated pneumonia. All reported results indicating that the addition of a procalcitonin algorithm had no statistically significant effect on the duration of hospital stay.

Full results on the duration of hospital stay and the duration of intensive care unit stay can be found on pages 48 to 52 of the diagnostics assessment report.

Duration of intensive care unit stay

Six of the 7 studies assessing discontinuation reported information on the duration of intensive care unit stay. Four studies reported data to allow the calculation of mean difference in the duration of intensive care unit stay between study arms. Two of these studies found that the inclusion of a procalcitonin algorithm in the decision to discontinue antibiotics resulted in a statistically significant reduction in the mean duration of intensive care unit stay. One study found that the procalcitonin algorithm was associated with a trend towards reduction in the duration of intensive care unit stay, which was not statistically significant. As with duration of hospital stay, the fourth study, which included both people with a less severe spectrum of disease (suspected bacterial infection and those who developed sepsis whilst in the intensive care unit), indicated that the inclusion of a procalcitonin algorithm in the clinical decision making process did not reduce the duration of intensive care unit stay.

The summary effect estimate indicated that the inclusion of a procalcitonin algorithm in the decision to discontinue antibiotics was associated with a trend towards decreased duration of intensive care unit stay, which did not reach

statistical significance, weighted mean difference −2.03 days (95% CI: −4.19 to 0.13). However, between study heterogeneity was high. Only 2 of these 4 studies were conducted in populations with suspected or confirmed sepsis. Of the other 2 studies, 1 was conducted in patients with acute pancreatitis and 1 was conducted in patients with suspected bacterial infection and those who developed sepsis whilst in the intensive care unit. When the meta-analysis was restricted to the 2 studies conducted in populations with suspected or confirmed sepsis, the summary effect estimate indicated that the inclusion of a procalcitonin algorithm in the decision to discontinue antibiotics was associated with a statistically significant reduction in the duration of intensive care unit stay, weighted mean difference −2.31 days (95% CI: −3.97 to −0.65).

The 2 remaining studies reported median duration of intensive care unit stay. Both of these studies were conducted in people with suspected or confirmed sepsis and both reported results indicating that adding the procalcitonin algorithm had no statistically significant effect on the duration of intensive care unit stay.

Adverse clinical outcomes

All 8 studies conducted in intensive care unit settings reported some data on adverse clinical outcomes. Five studies reported 28-day all-cause mortality. All reported no statistically significant difference in mortality rates between participants in the intervention group (decision to discontinue antibiotics based on procalcitonin algorithm plus clinical judgement) and those in the control group (decision to discontinue antibiotics based on clinical judgement alone). The summary relative risk was 0.98 (95% CI: 0.76 to 1.27). This finding was consistent when the meta-analysis was restricted to studies conducted in people with suspected or confirmed sepsis; relative risk 1.07 (95% CI: 0.54 to 2.12). One study also reported mortality at 60 days and found no statistically significant difference between the intervention and control groups; relative risk 1.15 (95% CI: 0.89 to 1.48). One further study, conducted in people with

apparent septic shock, assessed mortality at 5 days and found no statistically significant difference between the intervention and control groups; relative risk 1.0 (95% CI:0.25 to 4.04).

Four studies reported in-hospital mortality and all reported no statistically significant difference in mortality rates between participants in the intervention and control groups. The summary relative risk was 0.75 (95% CI: 0.49 to 1.16). This finding was consistent when the meta-analysis was restricted to studies conducted in people with suspected or confirmed sepsis; relative risk 0.78 (95% CI: 0.45 to 1.35).

Three studies reported intensive care unit mortality. Two of these studies assessed the effects of using a procalcitonin algorithm with standard clinical practice to guide discontinuation of antibiotics, and were conducted in people with confirmed or suspected sepsis. Both reported no statistically significant difference in the intensive care unit mortality rate between the intervention and control groups. The remaining study assessed the effects of using a procalcitonin algorithm with standard clinical practice to decide whether or not to initiate antibiotic treatment and was conducted in people with suspected bacterial infection. This study also found no statistically significant difference in the intensive care unit mortality rate between the intervention and control groups. The summary relative risk derived from all 3 studies was 0.87 (95% CI: 0.55 to 1.37). This finding was consistent when the meta-analysis was restricted to studies conducted in people with suspected or confirmed sepsis; relative risk 0.59 (95% CI: 0.27 to 1.28).

Four studies reported rates of infection relapse or recurrence, and all found no statistically significant difference in infection relapse or recurrence rates between participants in the intervention group and those in the control group. The summary relative risk was 1.37 (95% CI: 0.77 to 2.44). This finding was consistent when the meta-analysis was restricted to the 3 studies conducted in people with suspected or confirmed sepsis; relative risk 1.89 (95% CI: 0.47 to 7.59).

A variety of other general and disease-specific adverse clinical outcomes were reported by one or more studies. These included multi-drug-resistant infection, sepsis-related mortality, multiple organ dysfunction syndrome, ventilator associated pneumonia-related clinical deterioration, duration of mechanical ventilation, and Sequential Organ Failure Assessment [SOFA] scores at various time points. No study reported a statistically significant difference between the intervention and control groups for any adverse clinical outcome assessed. None of the included studies reported antibiotic-related adverse events.

Full results for adverse clinical outcomes can be found on page 53 to 60 of the diagnostics assessment report.

Table 2: Summary of results for adults in the intensive care unit

Outcome	No. of studies	Weighted mean difference (95% CI)	Summary
Duration of antibiotic therapy (days)	4	−3.19 (−5.44 to −0.95)	Statistically significant reduction with procalcitonin
Duration of antibiotic therapy (people with suspected or confirmed sepsis only) (days)	2	−1.20 (−1.33 to −1.07)	
Duration of hospital stay (days)	4	−3.85 (−6.78 to −0.92)	
Duration of hospital stay (people with suspected or confirmed sepsis only) (days)	2	−4.32 (−6.50 to −2.14)	
Duration of ICU stay (days)	4	−2.03 (−4.19 to 0.13)	Non-significant trend towards reduction with procalcitonin
Duration of ICU stay (people with suspected or confirmed sepsis only) (days)	2	−2.31 (−3.97 to −0.65)	Statistically significant reduction with procalcitonin
Outcome	**No. of studies**	**Relative risk (95% CI)**	**Summary**
All-cause mortality (28 day)	5	0.98 (0.76 to 1.27)	No statistically significant difference between groups
All-cause mortality (28 day) (people with suspected or confirmed sepsis only)	2	1.07 (0.54 to 2.12)	
In hospital mortality	4	0.75 (0.49 to 1.16)	
In hospital mortality (people with suspected or confirmed sepsis only)	3	0.78 (0.45 to 1.35)	
ICU mortality	3	0.87 (0.55 to 1.37)	
ICU mortality (people with suspected or confirmed sepsis only)	2	0.59 (0.27 to 1.28)	
Infection relapse/recurrence (ICU population)	4	1.37 (0.77 to 2.44)	
Infection relapse/recurrence (ICU population, people with suspected or confirmed sepsis only)	3	1.89 (0.47 to 7.59)	
Abbreviations: CI – confidence intervals; ICU – intensive care unit			

Results - Emergency department

The results of the systematic review of studies in people presenting to the emergency department with suspected bacterial infections can be found starting on page 62 of the diagnostics assessment report. Results are also summarised in tables 3 and 4 on pages 34 to 35 of this overview document.

Ten RCTs provided data on the effectiveness of using procalcitonin testing with standard clinical practice to guide antibiotic therapy in emergency department settings. Two studies were conducted in children and the remainder were conducted in adults. Most studies were conducted in people with respiratory presentations. Of the adult studies, 2 were conducted in people with lower respiratory tract infection, 3 were conducted in people with community acquired pneumonia, 1 included people with chronic obstructive pulmonary disease exacerbations, 1 included people with suspected asthma exacerbations, and 1 was conducted in people with urinary tract infection. Of studies conducted in children, 1 included children with lower respiratory tract infection and 1 included children with community acquired pneumonia.

With the exception of 2 studies published as abstracts, all studies used procalcitonin algorithms with multiple decision thresholds to guide antibiotic treatment in the intervention arm. Final treatment decisions remained at the discretion of the treating clinician. The details of the procalcitonin algorithm varied between studies, however, all algorithms (both initiation and discontinuation) discouraged antibiotic use where the procalcitonin level was less than 0.25 nanograms per millilitre. The most frequently reported algorithm for both initiation and discontinuation of antibiotics was:

- procalcitonin less than 0.1 nanograms per millilitre, antibiotics strongly discouraged;
- procalcitonin 0.1 to 0.25 nanograms per millilitre, antibiotics discouraged;
- procalcitonin 0.25 to 0.5 nanograms per millilitre, antibiotics encouraged;

- procalcitonin greater than 0.5 nanograms per millilitre, antibiotics strongly encouraged.

Reported timings for the measurement of procalcitonin were similar. All studies that reported timings included a baseline measurement. Three studies reported that repeat measurements were taken at 3 days and 5 days, or 3 days, 5 days, and 7 days. Three studies reported that repeat measurements were taken at 4 days, 6 days and 8 days, or every 2 days until discontinuation. Four studies noted that procalcitonin measurements were repeated at between 6 hours and 24 hours if antibiotic treatment was initially withheld.

Eight of the studies conducted in emergency department settings used the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific) to measure procalcitonin levels, and 2 used an un-specified quantitative procalcitonin assay.

Antibiotic initiation

Seven studies, conducted in adults presenting to the emergency department with suspected bacterial infections, assessed the effectiveness of using procalcitonin testing with standard clinical practice to guide the initiation of antibiotic treatment. All of these studies found that the addition of a procalcitonin algorithm was associated with a reduction in antibiotic use. The summary relative risk was 0.77 (95% CI: 0.68 to 0.87).

Two studies conducted in children presenting to the emergency department reported contradictory results for the proportion of patients in the intervention and control groups who received antibiotic treatment. The study conducted in children with community acquired pneumonia found that using a procalcitonin algorithm with standard clinical practice to decide whether to initiate antibiotic treatment was associated with a statistically significant reduction in antibiotic use, relative risk 0.85 (95% CI: 0.79 to 0.91). Subgroup analyses indicated that the procalcitonin algorithm was associated with a greater reduction in antibiotic use for children with mild community acquired pneumonia (relative

risk 0.69 [95% CI: 0.59 to 0.80]) than for children with severe community acquired pneumonia (relative risk 0.96 [95% CI: 0.92 to 1.01]).

In contrast the study conducted in children with lower respiratory tract infection (including community acquired pneumonia and non-community acquired pneumonia lower respiratory tract infection) reported a trend towards increased antibiotic use when procalcitonin levels were included in decision making, relative risk 1.12 (95% CI: 0.94 to 1.35). Subgroup analyses indicated that, for children presenting with non-community acquired pneumonia lower respiratory tract infection, the addition of a procalcitonin algorithm was associated with a statistically significant increase in antibiotic use (relative risk 2.71 (95% CI: 1.46 to 5.01). But for children presenting with community acquired pneumonia the addition of a procalcitonin algorithm was associated with a trend towards reduction in antibiotic use (relative risk 0.92 [95% CI: 0.79 to 1.08]). When data from the 2 studies on children presenting with community acquired pneumonia were combined the summary relative risk was 0.86 (95% CI: 0.80 to 0.93).

Full results on antibiotic initiation and antibiotic duration can be found on pages 62 to 67 of the diagnostics assessment report.

Antibiotic duration

Six studies, conducted in adults, assessed the effectiveness of using procalcitonin testing with standard clinical practice to decide when to discontinue antibiotic treatment. Of these, 2 reported data to allow the calculation of mean difference in the duration of antibiotic therapy between study arms. Both of these studies found that the inclusion of a procalcitonin algorithm in the clinical decision making process resulted in a statistically significant reduction in the mean duration of antibiotic therapy. The summary effect estimate indicated that the addition of a procalcitonin algorithm was associated with reduction in the duration of antibiotic therapy, which did not reach statistical significance, weighted mean difference −4.49 days (95% CI: −9.59 to 0.61). However, these studies included patients who did not receive

antibiotics in their estimates of mean duration. Therefore an additional meta-analysis was conducted, excluding participants who did not receive antibiotic treatment. The summary effect estimate for patients who received antibiotic treatment (that is, weighted mean difference conditional upon receipt of antibiotics) was 1.48 days (95% CI: −13.64 to 16.59).

Four studies, conducted in adults reported median duration of antibiotic therapy, or mean with no estimate of variance. The results of these studies were consistent with the 2 studies included in the meta-analysis, indicating that adding a procalcitonin algorithm to the clinical decision making process was associated with a reduction in the duration of antibiotic therapy.

Only one of the studies conducted in children reported data on duration of antibiotic therapy. This study found that adding a procalcitonin algorithm to the clinical decision making process was associated with a statistically significant reduction in the duration of antibiotic therapy, mean difference −1.8 days (95% CI: −3.1 to −0.5).

Duration of hospital stay

Six studies, conducted in adults, reported data on duration of hospital stay. The intervention arms of 5 of these studies used procalcitonin algorithms in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment. In 1 study the decision on whether or not to initiate antibiotic therapy was considered. Only 2 studies reported data to allow the calculation of mean difference in the duration of hospital stay between study arms and neither found a statistically significant difference between groups. The summary effect estimate indicated that addition of a procalcitonin algorithm was associated with a trend towards reduction in the duration of hospital stay, weighted mean difference −0.80 days (95% CI: −2.37 to 0.78).

Four studies reported median duration of hospital stay, or mean with no estimate of variance. Two of these studies, both conducted in people with

community acquired pneumonia, reported results indicating that the procalcitonin algorithm was associated with a reduction in the duration of hospital stay; mean duration 9.2 days in the procalcitonin group and 14.6 days in the control group; mean duration 14.6 days in the procalcitonin group and 16 days in the control group. The remaining 2 studies, 1 conducted in people with lower respiratory tract infection and 1 conducted in people with chronic obstructive pulmonary disease exacerbations, found that use of a procalcitonin algorithm did not affect the median duration of hospital stay.

Both of the studies conducted in children assessed the effectiveness of including a procalcitonin algorithm in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment. Both reported data to allow the calculation of mean difference in the duration of hospital stay between study arms. When data on children presenting with community acquired pneumonia were combined the summary effect estimate indicated that the use of a procalcitonin algorithm was associated with a small reduction in the duration of hospital stay (weighted mean difference −0.74 days [95% CI: −1.17 to −0.31]).

One study reported data on duration of intensive care unit stay. This study was conducted in adults with chronic obstructive pulmonary disease exacerbations and assessed the effectiveness of adding a procalcitonin algorithm to the information used to decide whether or not to initiate antibiotic treatment. It reported no statistically significant difference in the mean duration of intensive care unit stay between the study groups (mean difference −0.40 [95% CI: −1.06 to 0.26]).

Full results on duration of hospital stay can be found on pages 68 to 72 of the diagnostics assessment report.

Adverse clinical outcomes

All 10 studies conducted in emergency department settings reported data on adverse clinical outcomes. Two studies in adults reported hospital re-

admission rates. One study was in people with acute asthma exacerbations and the other was in people with urinary tract infection. Both studies found no statistically significant difference in re-admission rates between the group with procalcitonin test results and the group without. Two other studies, in adults with acute asthma exacerbations and in adults with chronic obstructive pulmonary disease exacerbations, also reported no statistically significant difference in the rate of secondary emergency department visits between the procalcitonin test group and the control group.

Six studies reported all-cause mortality at various time points, ranging from 14 days to 6 months. Five of these studies used procalcitonin algorithms to decide whether to initiate antibiotic treatment and to decide when to discontinue antibiotic treatment. In 1 study, only the decision on whether to initiate antibiotic therapy was considered. All studies reported no statistically significant difference in mortality rates between participants in the intervention group and those in the control group. The summary relative risk was 0.95 (95% CI: 0.71 to 1.27). When data from the 2 studies reporting mortality at 6 months were pooled the summary relative risk was 0.85 (95% CI: 0.46 to 1.59). Neither of the 2 emergency department studies conducted in children reported mortality data.

Four studies reported data on rates of admission to the intensive care unit. Three of these studies used procalcitonin algorithms to decide whether to initiate antibiotic treatment and to decide when to discontinue antibiotic treatment. In 1 study only the decision on whether or not to initiate antibiotic therapy was considered. All studies found no statistically significant difference between groups in intensive care unit admissions. The summary relative risk was 0.79 (95% CI: 0.59 to 1.05). Neither of the 2 emergency department studies conducted in children reported any information on intensive care unit admissions.

Two studies, conducted in adults, reported inconsistent results with respect to rates of infection relapse or recurrence. One study, in adults with urinary tract

infection, found no statistically significant difference in relapse or recurrence rates between participants in the intervention group and those in the control group. The second study, in adults with lower respiratory tract infection, found that inclusion of a procalcitonin algorithm in both the information used to guide initiation and discontinuation of antibiotics was associated with a statistically significant reduction in infection relapse or recurrence rates (relative risk 0.57 [95% CI: 0.36 to 0.92]). One study, conducted in children with community acquired pneumonia, reported very low rates of infection relapse or recurrence and a trend towards lower rates in the procalcitonin group (relative risk 0.23 [95% CI: 0.04 to 1.34]).

One study, conducted in adults with lower respiratory tract infection, reported numbers of participants experiencing antibiotic-related adverse events. This study found that including a procalcitonin algorithm in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment was associated with a reduction in antibiotic-related adverse events, (relative risk 0.71 [95% CI: 0.58 to 0.86]). This finding is consistent with the reduced rate of antibiotic prescribing and mean duration of antibiotic therapy reported by this study.

Both studies conducted in children reported numbers of participants experiencing antibiotic-related adverse events. Results for the subgroup of children with community acquired pneumonia indicated that using a procalcitonin algorithm to decide whether to initiate antibiotic treatment and when to discontinue antibiotic treatment was associated with a reduction in antibiotic-related adverse events (relative risk 0.37 [95% CI: 0.04 to 3.49]). When data for all participants in both studies were included in the meta-analysis, the summary relative risk was 0.40 (95% CI: 0.06 to 2.78).

A variety of other general and disease-specific adverse clinical outcomes were reported by one or more studies. These included composite adverse outcome measures, need for steroids, need for mechanical ventilation, and complications from pneumonia. No study reported a statistically significant

difference between the intervention and comparator groups for any adverse clinical outcome assessed.

Full results on adverse clinical outcomes can be found on pages 73 to 78 of the diagnostics assessment report.

Table 3: Summary of results for adults in the emergency department

Outcome	**No. of studies**	**Weighted mean difference (95% CI)**	**Summary**
Duration of antibiotics (days)	2	−4.49 (−9.59 to 0.61)	Non-significant reduction with procalcitonin
Duration of antibiotics (conditional upon receipt of antibiotics) (days)	2	1.48 (−13.64 to 16.59)	No statistically significant difference between groups
Duration of hospital stay (days)	2	−0.80 (−2.37 to 0.78)	Non-significant reduction with procalcitonin
Duration of ICU stay	1	−0.40 (−1.06 to 0.26)	No statistically significant difference between groups
Outcome	**No. of studies**	**Relative risk (95% CI)**	**Summary**
Initiation of antibiotics	7	0.77 (0.68 to 0.87)	Statistically significant reduced risk with procalcitonin
All-cause mortality	6	0.95 (0.71 to 1.27)	No statistically significant difference between groups
All-cause mortality (6 months)	2	0.85 (0.46 to 1.59)	
ICU admission	4	0.79 (0.59 to 1.05)	Non-significant trend towards reduced risk with procalcitonin
Antibiotic related adverse effects	1	0.71 (0.58 to 0.86)	Statistically significant reduced risk with procalcitonin
Rate of relapse/recurrence in adults with LRTI	1	0.57 (0.36 to 0.92)	
Abbreviations: CI – confidence intervals; ICU – intensive care unit; LRTI – lower respiratory tract infection			

Table 4: Summary of results for children in the emergency department

Outcome	**No. of studies**	**Weighted mean difference (95% CI)**	**Summary**
Duration of antibiotics (days)	1	−1.80 (−1.30 to −0.50)	Statistically significant reduction with procalcitonin
Duration of hospital stay for children with CAP	2 *	−0.74 (−1.17 to −0.31)	
Outcome	**No. of studies**	**Relative risk (95% CI)**	**Summary**
Initiation of antibiotics in children with CAP	2 *	0.86 (0.80 to 0.93)	Statistically significant reduced risk with procalcitonin
Initiation of antibiotics in children with mild CAP	1	0.69 (0.59 to 0.80)	
Initiation of antibiotics in children with severe CAP	1	0.96 (0.92 to 1.01)	Non-significant trend towards reduced risk with procalcitonin
Initiation of antibiotics in children with non-CAP LRTI	1	2.71 (1.46 to 5.01)	Statistically significant increased risk with procalcitonin
Antibiotic side effects in children with CAP	2	0.37 (0.04 to 3.49)	No statistically significant difference between groups
Rate of relapse/recurrence in children with CAP	1	0.23 (0.04 to 1.34)	
* one study provided data on 2 subgroups (mild and severe CAP) Abbreviations: CAP – community acquired pneumonia; CI – confidence intervals; LRTI – lower respiratory tract infection			

3.2 Costs and cost effectiveness

The External Assessment Group (EAG) conducted a search to identify existing economic evaluations of people with sepsis or bacterial infection receiving care in emergency departments or intensive care units. The EAG also constructed a de novo economic model to assess the cost effectiveness of using procalcitonin testing with standard clinical practice compared with standard clinical practice alone.

Systematic review of cost effectiveness evidence

The EAG conducted a search for relevant economic evaluations on adults and children presenting to or being treated at emergency departments and intensive care units with sepsis or bacterial infection. Details are reported on pages 80 to 92 of the diagnostics assessment report. Two studies (3 publications) were considered eligible for inclusion in the systematic review.

One study (Michaelidis et al. 2013) considered procalcitonin testing in 2 separate scenarios. The first analysis was based on adults presenting to an outpatient clinic with an acute respiratory tract infection and judged by their physicians to require an antibiotic prescription. The second analysis was based on adults presenting to an outpatient clinic with an acute respiratory tract infection prior to any decision to initiate antibiotic therapy. Procalcitonin guided antibiotic therapy was both more costly and more effective than usual care without procalcitonin guided treatment, leading to incremental cost effectiveness ratios of $118,828 and $575,249 per quality adjusted life year (QALY) gained for the first and second analyses respectively.

The second study (Smith et al. 2013) considered the cost-effectiveness of procalcitonin guided antibiotic therapy versus standard care in community acquired pneumonia in a hospital setting. Analysis indicated that procalcitonin guided antibiotic therapy is both more costly and more effective compared with standard care alone. For patients with low risk community acquired pneumonia, procalcitonin guided antibiotic initiation is likely to be cost-effective for willingness to pay values above $90,000 per QALY gained. For the same patients, procalcitonin used to guide antibiotic initiation and monitoring is likely to be cost-effective for willingness to pay values above $40,000 per QALY gained. For patients with high-risk community acquired pneumonia this is $170,000 per QALY gained (using procalcitonin for both initiating and monitoring antibiotic use).

Economic analysis

The External Assessment Group developed a de novo economic model designed to assess the cost effectiveness of procalcitonin testing in addition to standard clinical practice compared with standard clinical practice alone for:

- adults with confirmed or highly suspected sepsis in an intensive care unit setting
- adults with suspected bacterial infection presenting to the emergency department
- children with suspected bacterial infection presenting to the emergency department.

Children with confirmed or highly suspected sepsis in an intensive care unit setting were not considered due to the lack of clinical evidence.

Model structure

Two decision tree models were constructed;

- One in the intensive care unit setting which incorporated discontinuation of antibiotics only (figure 1).
- One in the emergency department setting which incorporated both initiation and discontinuation of antibiotics (figure 2).

The structures of both models start with a decision node that denotes the use of procalcitonin testing in addition to standard clinical practice or standard clinical practice alone. The key endpoints are: (i) alive with antibiotic related complications, (ii) alive without antibiotic related complications and (iii) death. The time horizon is 6 months (183 days), divided into an initial short-term (28 days) phase and a subsequent phase lasting 155 days. The 6 month time horizon and the initial phase of 28 days were adopted to be consistent with the outcomes reported in the studies included in the clinical effectiveness systematic review.

Figure 1: Decision tree for intensive care unit setting

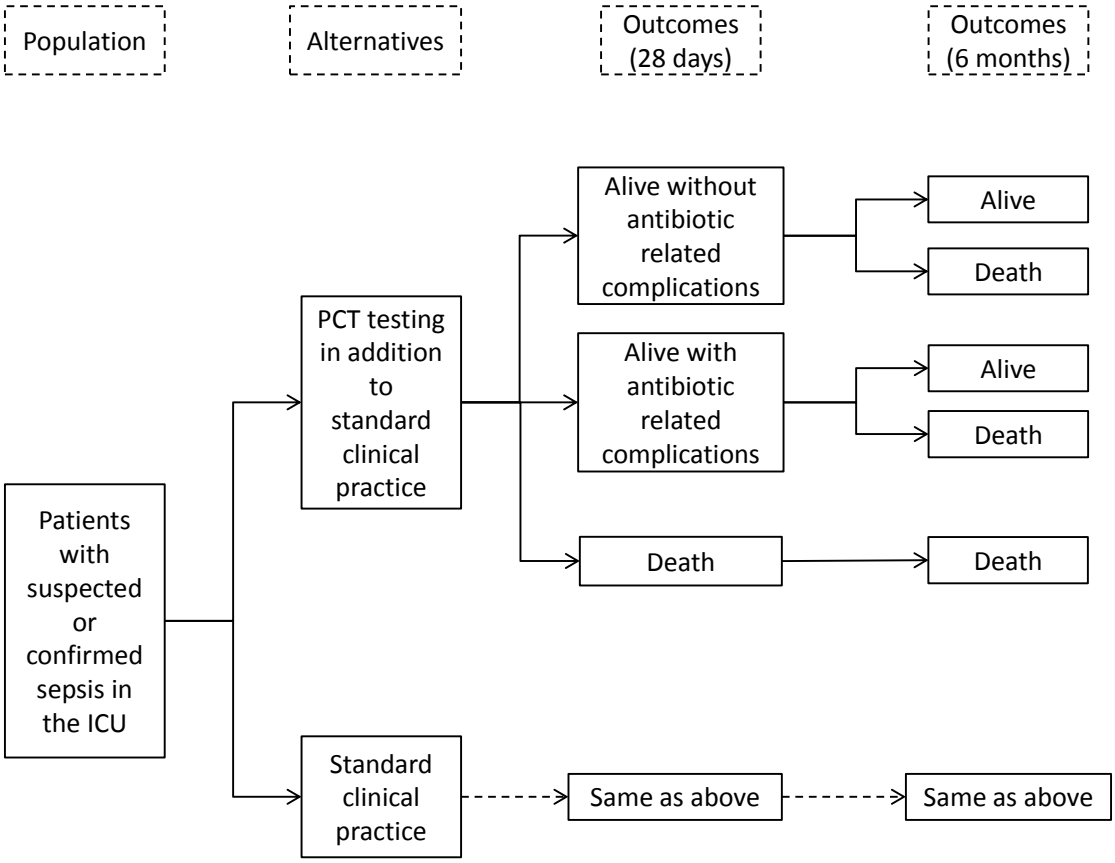
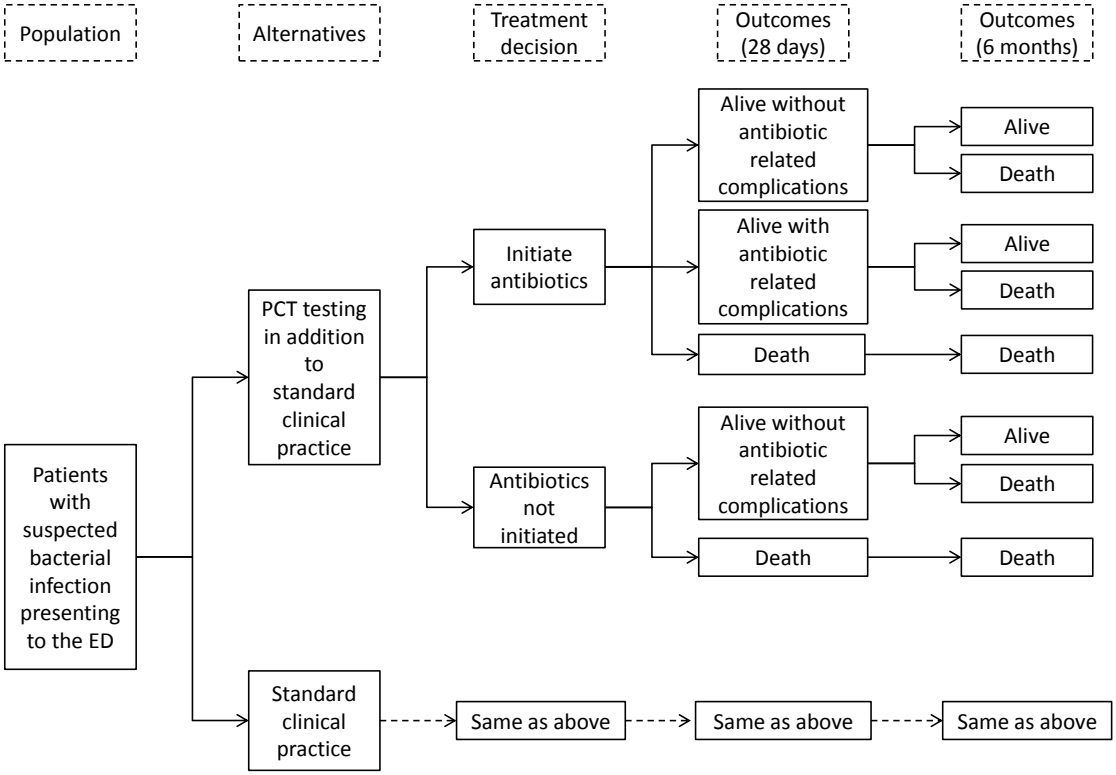


Figure 2: Decision tree for the emergency department setting



Model inputs

The EAG populated the model using data derived from the clinical effectiveness review, published literature and routine sources of cost data. A 'lower clinical extreme' and a 'higher clinical extreme' was specified for each population and setting. For these 'clinical extremes' different baseline values are used for mortality, duration of antibiotic therapy, probability of initiation of antibiotic treatment (emergency department setting only), length of hospital stay and/or length of intensive care unit stay, while applying the same relative risk or mean difference estimates for both clinical extremes. The baseline mortality probabilities and mortality relative risks used in the model are summarised in table 5. Justification for the choice of each estimate is provided on page 99 of the diagnostics assessment report.

Table 5: All-cause mortality

Parameter	Period	Estimate	Source
Baseline probability for all-cause mortality			
Children in ED Lower clinical extreme	28 days	<0.001	Office for National Statistics (2014)
Children in ED Lower clinical extreme	6 months	<0.001	
Children in ED Higher clinical extreme	28 days	<0.001	
Children in ED Higher clinical extreme	6 months	<0.001	
Adults in ED Lower clinical extreme	28 days	0.062	Christ-Crain (2004)
Adults in ED Lower clinical extreme	6 months	0.121	Roh (2013)
Adults in ED Higher clinical extreme	28 days	0.072	Christ-Crain (2006)
Adults in ED Higher clinical extreme	6 months	0.121	Roh (2013)
Adults in ICU Lower clinical extreme	28 days	0.169	Bouadma (2010)
Adults in ICU Lower clinical extreme	6 months	0.222	Bouadma (2010), Christ-Crain (2004), Roh (2013)
Adults in ICU Higher clinical extreme	28 days	0.182	Qu (2012)
Adults in ICU Higher clinical extreme	6 months	0.225	Christ-Crain (2006), Qu (2012), Roh (2013)
Relative risk for all-cause mortality			
Children in ED	28 days	0.950	meta-analysis
Children in ED	6 months	0.950	meta-analysis
Adults in ED	28 days	0.980	meta-analysis
Adults in ED	6 months	0.850	meta-analysis
Adults in ICU	28 days	0.980	meta-analysis
Adults in ICU	6 months	0.980	meta-analysis
Abbreviations: ED – emergency department; ICU – intensive care unit			

Resource use

Resource use consisted of duration of hospital stay (days), intensive care unit stay (days) and antibiotic treatment duration (days). The estimates were retrieved from studies identified in the systematic review and are presented in table 6. Justification for the choice of each estimate is provided on page 104 of the diagnostics assessment report.

Table 6: Resource use

Parameter	Estimate	Source
Baseline duration of antibiotic therapy		
Children in ED Lower clinical extreme [a]	9.600	Baer (2013)
Children in ED Higher clinical extreme [a]	11.512	Baer (2013)
Adults in ED Lower clinical extreme [a]	15.386	Christ-Crain (2004)
Adults in ED Higher clinical extreme [a]	13.073	Christ-Crain (2006)
Adults in ICU Lower clinical extreme	9.900	Bouadma (2010)
Adults in ICU Higher clinical extreme	16.060	Qu (2012)
Baseline probability for antibiotic initiation		
Children in ED Lower clinical extreme	0.167	Baer (2013)
Children in ED Higher clinical	0.790	Baer (2013)
Adults in ED Lower clinical extreme	0.832	Christ-Crain (2004)
Adults in ED Higher clinical extreme	0.987	Christ-Crain (2006)
Relative risks for antibiotic initiation		
Children in ED	0.970	meta-analysis
Adults in ED	0.770	meta-analysis
Length of hospital stay		
Children in ED Lower clinical extreme; total	2.300	Baer (2013)4
Children in ED Lower clinical extreme; % in ICU	[redacted]	Prof E Carrol (05/11/2014, personal communication)
Children in ED Higher clinical extreme; total	5.010	Esposito (2011)
Children in ED Higher clinical extreme; % in ICU	[redacted]	Prof E Carrol (05/11/2014, personal communication)
Adults in ED Lower clinical extreme; total	11.200	Christ-Crain (2004)
Adults in ED Lower clinical extreme; ICU	3.700	Stolz (2007)
Adults in ED Higher clinical extreme; total	13.000	Christ-Crain (2006)
Adults in ED Higher clinical extreme; ICU	3.700	Stolz (2007)
Adults in ICU Lower clinical extreme; total	26.400	Bouadma (2010)
Adults in ICU Lower clinical extreme; ICU	14.400	Bouadma (2010)
Adults in ICU Higher clinical extreme; total	33.000	SIGN (2008)
Adults in ICU Higher clinical extreme; ICU	23.000	SIGN (2008)
Mean difference in length of hospital stay		
Children in ED; total	−0.620	meta-analysis
Adults in ED; total	−0.800	meta-analysis
Adults in ED; ICU	−0.400	Stolz (2007)
Adults in ICU; total	−4.200	meta-analysis
Adults in ICU; ICU	−1.620	meta-analysis

[a] Conditional on initiation of antibiotic therapy

Abbreviations: ED – emergency department; ICU – intensive care unit

Costs

Data for the cost analyses were drawn from routine NHS sources and discussions with manufacturers of procalcitonin tests. Table 7 gives an overview of the unit prices and their sources

Table 7: Unit prices

	Unit price (£)	Source
Antibiotic treatment ICU setting/day (adults)	£12.90	British National Formulary (2014)
Antibiotic treatment ED setting/day (children)	£3.99	
Antibiotic treatment ED setting/day (adults)	£2.20	
Hospital stay/day (children)	£819.56	National Schedule of Reference Costs, Department of Health (2012)
Hospital stay/day (adults)	£819.56	
ICU stay/day (children)	£1,493.98	
ICU stay/day (adults)	£1,168.45	
ED stay/day (children)	£124.41	
ED stay/day (adults)	£124.41	
Abbreviations: ED – emergency department; ICU – intensive care unit		

An average unit price for the procalcitonin test was calculated based on the list prices of the tests (excluding the VAT) and with no discounts assumed. Overhead costs including capital, service and maintenance, and calibration costs were included (table 8).

Table 8: Total cost per test

Name of test	Manufacturer	Listed price/test
ELECSYS® BRAHMS PCT	Roche	£12.15
ADVIA Centaur BRAHMS PCT	Siemens	£16.81
VIDAS BRAHMS PCT	bioMérieux	£12.80
B.R.A.H.M.S PCT KRYPTOR	Thermo Fisher Scientific	£12.38[a]
Average price/test		£13.54
Overhead costs		
Capital costs/test		£0.10
Service or maintenance costs /test		£0.07
Calibration costs		£0.08
Total overhead cost/test		£0.26
Total average cost/test		£13.79
[a] Prices in Euros were converted to British Pounds where 1 Pound = 1.2521 Euros		

Health related quality of life and QALY decrements

Searches were undertaken to locate relevant utility value studies on adults and children presenting to or being treated at emergency departments and intensive care units with sepsis or bacterial infection (full details are reported on page 94 of the diagnostics assessment report).

For adults being treated in the intensive care unit, a utility of score of 0.53 was used for the initial short-term phase, and a utility of 0.68 was used for the subsequent phase (Drabinksi et al.). In a scenario analysis the utility value of 0.68 was replaced with the 3.5 year utility value of 0.64 (Cuthbertson et al.) which was judged to provide the most representative long-term utilities for the UK population.

No utility values for adults presenting to the emergency department with suspected infection were identified in the systematic review. Therefore, utility values for adults presenting to their primary care clinician with lower respiratory tract infection were used; 0.70 for the initial short-term phase and 0.86 for the subsequent phase (Oppong et al.). For children presenting to the emergency department, a constant base utility of 0.99 was assumed (utility for local infection) (Bennett et al.).

To incorporate antibiotic related adverse events in adults being treated in the intensive care unit, a disutility of 0.046 for being on antibiotic treatment was used (Oppong et al.). Although this disutility might be higher for people being treated in the intensive care unit, due to the intravenous route of antibiotic administration, it was conservatively assumed that this disutility is equal for all settings and populations. It was also conservatively assumed that there is no disutility for staying in hospital.

Base-case results

The following assumptions were applied in the base case analysis:

- The duration of hospital stay retrieved from the review of clinical effectiveness includes days in hospital after infection relapse or recurrence.
- Relative risks for all-cause mortality for children presenting to the emergency department are assumed to be equal to those for adults presenting to the emergency department (as no data were found in the literature for children).
- There is no disutility for the hospital stay.
- The baseline utility for children presenting to the emergency department was constant over time.
- The disutility for being on antibiotic treatment was equal for all settings and populations.
- Procalcitonin testing used for initiation of antibiotics in the emergency department and discontinuation of antibiotics in the intensive care unit was used to calculate the average number of tests per day.
- There are no costs associated with antibiotic related adverse events.
- There are no differences in disease specific complications between the group with procalcitonin testing and the group without procalcitonin testing.
- There are no differences in long-term costs and effects between the group with procalcitonin testing and the group without procalcitonin testing.

The base case analyses (presented on page 114 of the diagnostics assessment report) indicate that procalcitonin testing with standard clinical practice dominates standard clinical practice alone for all populations, that is, it was both cost saving and more effective (table 9). The cost savings ranged from £368 for children with suspected bacterial infection presenting to the emergency department (lower clinical extreme) to £3,268 for adults with confirmed or highly suspected sepsis in an intensive care unit setting (lower clinical extreme). The use of procalcitonin testing with standard clinical practice to guide antibiotic therapy resulted in only a small QALY gain. For adults with suspected bacterial infection presenting to the emergency department this was 0.005 for the lower and higher clinical extremes and for

adults with confirmed or highly suspected sepsis in the intensive care unit setting it was 0.001 for both clinical extremes. For children with suspected bacterial infection presenting to the emergency department, the QALY gains were less than 0.001 for both clinical extremes.

Table 9: Results for base case analysis

Population	Scenario	Change in costs (£)	Change in QALYs	ICER
Children ED	Low risk	−368	<0.001	Dominant
Children ED	High risk	−581	<0.001	Dominant
Adults ED	Low risk	−662	0.005	Dominant
Adults ED	High risk	−715	0.005	Dominant
Adults ICU	Low risk	−3,268	0.001	Dominant
Adults ICU	High risk	−2,862	0.001	Dominant
Abbreviations: ED – emergency department; ICU – intensive care unit; QALY – quality adjusted life year; ICER – incremental cost effectiveness ratio				

Cost-effectiveness acceptability curves (shown in Appendix 7 on page 272 of the diagnostics assessment report) illustrate that, for any willingness to pay threshold ranging from £0 to £60,000 per QALY gained, procalcitonin testing always has a higher probability of being cost-effective than standard clinical practice. For a willingness to pay threshold of £20,000 the probability of procalcitonin testing with standard clinical practice being cost effective over standard clinical practice alone is:

- 85% and 98% respectively for both the lower and higher clinical extremes for children with suspected bacterial infection presenting to the emergency department;
- 88% for adults with suspected bacterial infection presenting to the emergency department (both clinical extremes);
- 97% and 95% respectively for the lower and higher clinical extremes for adults with confirmed or highly suspected sepsis in an intensive care unit setting.

Analysis of alternative scenarios

The following scenario analyses were performed to assess the impact of assumptions on the estimated outcomes:

- Assume no difference in mortality (relative risk of 1)
- Assume an increased cost of £50 per test
- Assume no overhead costs for the tests
- Alternative utility value for adults on the intensive care unit
- Assume no disutility for being on antibiotic treatment
- Assume no difference in duration of antibiotic treatment
- Assume no difference in hospital stay (including intensive care unit stay)
- Assume lower prices for hospital and intensive care unit stay
- Assume that procalcitonin testing in the emergency department was solely used to initiate antibiotic treatment (not to discontinue antibiotic treatment).

The scenario analyses that assumed no difference in hospital stay had a substantial impact on all analyses. For all analyses procalcitonin guided treatment became more costly (incremental costs varied between £7 for adults in the intensive care unit and £25 for children in the emergency department) and remained more effective (QALY gain varied between less than 0.001 for children in the emergency department and 0.007 for adults in the intensive care unit) compared with standard clinical practice alone. For children presenting to the emergency department with suspected bacterial infection, this resulted in an ICER of £287,076 per QALY gained for the lower clinical extreme and £35,219 per QALY gained for the higher clinical extreme compared with standard clinical practice alone. For adults in both settings (and both clinical extremes), the ICER varied between £3,390 and £3,948 per QALY gained compared with standard clinical practice alone.

None of the other scenario analyses resulted in substantial changes to the base case ICERs, and use of procalcitonin testing with standard clinical

practice remained cost effective compared with standard clinical practice alone.

Sensitivity analyses

One-way sensitivity analyses were performed for all stochastic input parameters between the 95% confidence intervals.

The one-way sensitivity analysis for the relative mortality risk for adults with suspected bacterial infection presenting to the emergency department, showed that when using the upper bound of the 95% confidence interval, (1.590; base case value: 0.850) procalcitonin guided treatment was less costly (£772) and less effective (QALY loss: 0.025) compared with standard clinical practice, leading to savings per QALY lost of £30,469 (lower clinical extreme) and £30,446 (higher clinical extreme).

None of the other one-way sensitivity analyses resulted in substantial changes to the base case ICERs, and use of procalcitonin testing with standard clinical practice remained cost effective compared with standard clinical practice alone.

4 Issues for consideration

Clinical effectiveness

- There is a lack of data on the clinical effectiveness of using procalcitonin levels or algorithms with standard clinical practice to guide antibiotic treatment decisions in children. The systematic review of clinical effectiveness identified 8 RCTs in adults in an intensive care setting, 8 RCTs in adults in an emergency department setting, and 2 RCTs in children in an emergency department setting. No studies of children with confirmed or highly suspected sepsis in intensive care settings were identified. Both studies of children in an emergency department setting included children presenting with respiratory symptoms. It is uncertain, therefore, whether the use of procalcitonin levels in algorithms used to

guide antibiotic treatment decisions in children with confirmed or highly suspected sepsis in the intensive care unit is clinically- or cost-effective.

- In the emergency department setting, all but one of the adult studies, and both of the studies in children were conducted in people presenting with respiratory symptoms. It is therefore unclear whether the findings for the emergency department setting would be generalisable to adults or children with suspected bacterial infections in other sites. The external assessment group identified an additional RCT, conducted in young children (aged 1 to 36 months) presenting to the emergency department with fever of unknown origin. This study did not meet the inclusion criteria for the review because it used a qualitative procalcitonin assay. The study reported that the use of procalcitonin testing with standard clinical practice had no effect on antibiotic exposure or hospitalisation rates compared with standard clinical practice alone.
- The majority of the included studies measured procalcitonin levels using the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific) or the VIDAS BRAHMS PCT assay (bioMérieux). It is unclear whether results of the analyses would be similar for the procalcitonin assays for which no relevant clinical data were identified (Elecsys BRAHMS PCT assay [Roche Diagnostics], ADVIA Centaur BRAHMS PCT assay [Siemens Healthcare Diagnostics], LIAISON BRAHMS PCT assay [DiaSorin]). However, the evidence included in the systematic review does not suggest a difference in effect between the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific) or the VIDAS BRAHMS PCT assay (bioMérieux). All the procalcitonin assays included in the scope use the same monoclonal anti-procalcitonin antibody, under licence from Thermo Fisher Scientific. The main difference between the assays is the methods of detection. In addition, all assays included have been standardised using the BRAHMS PCT LIA assay. This was the original manual procalcitonin assay which was not included in this assessment as it is not in widespread use in the UK. With regards to the technical performance characteristics of different

procalcitonin assays, a study provided by Siemens Healthcare Diagnostics shows good agreement in the procalcitonin levels measured in clinical samples between the Roche Elecsys PCT assay and the BRAHMS PCT Sensitive Kryptor assay (r = 0.987) and between the Siemens ADVIA Centaur PCT assay and the BRAHMS PCT Sensitive Kryptor assay (r= 0.977).

Cost effectiveness

- It is uncertain whether the data included in this assessment are generalisable to UK settings. None of the studies included in the systematic review component of the assessment were conducted in the UK. As the assessment considers the effectiveness of using procalcitonin testing with standard clinical practice to inform decisions on antibiotic treatment, differences in the behaviour and routine practice of clinicians in different countries and health care settings may influence the effectiveness of procalcitonin testing. For example, resource use (length of hospital stay) and the exact application of the test (number of tests) may be setting dependent. Hospital stay was one of the main influential parameters on the model results. This parameter was investigated in a scenario analysis which assumed no difference in hospital stay between the intervention group and control group. Procalcitonin guided treatment was found to be more costly and also more effective than standard clinical practice without procalcitonin testing (incremental costs varied between £7 and £25; incremental QALY gains varied between less than 0.001 and 0.007). For children presenting to the emergency department with suspected bacterial infection, this resulted in an ICER of £287,076 for the lower clinical extreme and £35,219 for the higher clinical extreme. For adults in both settings (and both clinical extremes), the ICER varied between £3,390 and £3,948.
- The model was restricted to a 6 month time horizon due to a lack of evidence on long term outcomes relating to the use of procalcitonin testing with standard clinical practice compared with standard clinical practice alone. It is uncertain whether the addition of a procalcitonin algorithm to

standard clinical practice would impact on long term clinical outcomes and costs. It is possible that procalcitonin guided treatment may affect the long term impact of short term survival differences. It may also impact on the costs and effects arising from reduced antibiotic resistance (due to decrease antibiotic use and treatment duration).

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Bacterial sepsis may be more difficult to identify in pregnant women, young children, older people and people with a mental health problem. People with cancer are at risk of neutropenic sepsis.

6 Implementation

Due to the time critical nature of diagnosing and initiating treatment of sepsis and bacterial infections, results from procalcitonin testing would need to be available quickly. Therefore, laboratories would need to analyse samples immediately rather than waiting to run a batch of samples. In addition, the use of the procalcitonin assay may require the implementation of local protocols to aid clinicians with the interpretation of procalcitonin results.

7 Authors

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January 2015

Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Kleijnen Systematic Reviews Ltd in collaboration with Erasmus University Rotterdam and Maastricht University:

Westwood ME, Ramaekers BLT, Whiting P, Tomini F, Joore MA, Armstrong N, Ryder S, Stirk L, Severens JL, Kleijnen J. Procalcitonin (PCT) testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: A systematic review and cost-effectiveness analysis. A Diagnostic Assessment Report. Kleijnen Systematic Reviews Ltd, 2014.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope:

- BioMérieux UK Ltd
- Roche Diagnostics
- Siemens Healthcare Diagnostics
- Thermo Fisher Scientific

Other commercial organisations:

- Imutest Limited
- Spectral Platforms

Professional groups and patient/carer groups:

- British Infection Association
- Children's Cancer and Leukaemia Group
- Department of Health

- Department of Microbiology, North West London Hospitals NHS Trust and Ealing Hospital NHS Trust
- Dudley Group NHS Foundation Trust
- Group B Strep Support
- Healthcare Improvement Scotland
- Imperial College NHS Trust
- Intensive Care Society
- Meningitis Research Foundation
- MRSA Action UK
- NHS England
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- UK Sepsis Trust
- Welsh Government

Research groups:

- Integrated Medicines Ltd
- Manchester Centre for Health Economics, The University of Manchester

Associated guideline groups:

- National Clinical Guidelines Centre

Others:

- British In Vitro Diagnostics Association (BIVDA)

Appendix B: Glossary of terms

C-reactive protein

A protein which is produced by the liver and rises when there is inflammation throughout the body

Empiric antibiotic

An antibiotic given to a person before a specific microorganism or source of the potential infection is known. It is usually a broad-spectrum antibiotic and the treatment may change if the microorganism or source is confirmed.

Immunoassay

A test used to detect the presence or quantity of a protein such as a hormone or an enzyme, based on its ability to act as an antigen a chemical reaction.

Relative risk

A statistical method that is used to make a comparison of the risk of a particular event for different groups of people.

Sepsis

A life-threatening systematic inflammatory response caused by the presence of an infectious agent (i.e. bacterial, viral, fungal or parasitic).

Severe sepsis

A septic infection that is associated with signs of organ dysfunction, damage and altered cerebral function. Most patients with severe sepsis require treatment in intensive care units and severe sepsis can lead to death.

Septic shock

Sepsis-induced hypotension persisting despite adequate fluid resuscitation

Serum lactate

A laboratory test to measure the amount of lactate in the blood; high levels indicate lactic acidosis, a marker of hypoxia

Systemic Inflammatory Response Syndrome

A life-threatening condition which arises from a severe systemic response to either an infectious or non-infectious insult

Procalcitonin (PCT) testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: A systematic review and cost-effectiveness analysis

A Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

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Westwood ME, Ramaekers BLT, Whiting P, Tomini F, Joore MA, Armstrong N, Ryder S, Stirk L, Severens JL, Kleijnen J. Procalcitonin (PCT) testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: A systematic review and cost-effectiveness analysis. A Diagnostic Assessment Report. Kleijnen Systematic Reviews Ltd, 2014.

Contributions of authors

Marie Westwood and Penny Whiting planned and performed the systematic review and interpretation of evidence. Manuela Joore, Bram Ramaekers and Florian Tomini planned and performed the cost-effectiveness analyses and interpreted results. Nigel Armstrong contributed to planning and interpretation of cost-effectiveness analyses, acquisition of input data and conducted model peer review. Steve Ryder contributed to acquisition of model input data. Lisa Stirk devised and performed the literature searches and provided information support to the project. Jos Kleijnen and Johan Severens provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively. All parties were involved in drafting and/or commenting on the report.

Academic in confidence information is marked [redacted] and commercial in confidence information is marked [redacted].

Total word count: 73,045

ABSTRACT

Background

Determination of the presence or absence of bacterial infection is important to guide appropriate therapy and reduce antibiotic exposure. Procalcitonin is an inflammatory marker that is produced in response to bacterial infections but does not usually rise significantly with viral or non-infectious inflammation. It has been suggested as a marker for bacterial infection.

Objectives

To assess the clinical- and cost-effectiveness of adding procalcitonin (PCT) testing to the information used to guide antibiotic therapy in adults and children:

1. with confirmed or highly suspected sepsis in intensive care settings.
2. presenting to the emergency department with suspected bacterial infection.

Methods

Twelve databases were searched to June 2014. Randomised controlled trials (RCTs) were assessed for quality using the Cochrane Risk of Bias tool. Summary relative risks (RR) and weighted mean differences (WMDs) were estimated using random effects models. Heterogeneity was assessed visually using forest plots and statistically using the I^2 and Q statistics and investigated through subgroup analysis.

In a de novo health economic analysis, the cost-effectiveness of PCT testing in addition to current clinical practice was compared with current clinical practice using a decision tree with a six months' time horizon.

Results

Eighteen RCTs (36 reports) were included in the clinical effectiveness review.

Intensive care unit (eight studies)

PCT algorithms were associated with reduced antibiotic duration (WMD -3.19 days, 95% CI: -5.44 to -0.95, I^2 95.2%; four studies), hospital stay (WMD -3.85 days, 95% CI: -6.78 to -0.92, I^2 75.2%; four studies) and a trend towards reduced ICU stay (WMD -2.03 days, 95% CI: -4.19 to 0.13, I^2 81.0%; four studies). There were no differences for adverse clinical outcomes (mortality, infection relapse/recurrence, mechanical ventilation, multi-organ dysfunction syndrome, SOFA score).

Emergency department (10 studies)

PCT algorithms were associated with a reduction in the proportion of adults (RR was 0.77, 95% CI: 0.68 to 0.87; seven studies) and children (RR 0.86 (95% CI: 0.80 to 0.93) receiving antibiotics,

reduced antibiotic duration (two studies), reduced hospital stay in children (WMD -0.74 days, 95% CI: -1.17 to -0.31; two studies), a trend towards reduced stay in adults (WMD -0.80 days, 95% CI: -2.37 to 0.78; two studies) and a reduction in antibiotic-related adverse events in adults and children. Duration of ICU stay, hospital re-admission, secondary ED visits, and adverse clinical outcomes (mortality, infection relapse/recurrence, mechanical ventilation, need for steroids, complications of pneumonia) showed no differences between groups.

Cost-effectiveness

The base case analyses indicated that PCT testing was cost-saving for (i) adults with confirmed or highly suspected sepsis in an ICU setting (ii) adults with suspected bacterial infection presenting to the ED; and (iii) children with suspected bacterial infection presenting to the ED. Cost savings ranged from £368 to £3,268. Moreover, PCT-guided treatment resulted in a small QALY gain (ranging between <0.001 and 0.005). Cost-effectiveness acceptability curves showed that PCT-guided treatment has a probability of 84% or higher of being cost-effective for all settings and populations considered (at willingness to pay thresholds of £20,000 and £30,000 per QALY).

Conclusions

The addition of a PCT algorithm to the information used to guide antibiotic treatment may reduce antibiotic exposure in adults being treated for suspected or confirmed sepsis in ICU settings and in adults presenting to the ED with respiratory symptoms and suspected bacterial infection, without any adverse consequences for clinical outcome. The use of a PCT algorithm may also be associated with reductions hospital and ICU stay. Very limited data suggest that similar effects may apply for children presenting to the ED with respiratory symptoms and suspected bacterial infection.

PCT testing may be cost-effective in the UK. However, although the economic model indicates that there is little decision uncertainty, not all uncertainties are reflected in the model outcomes. This 'scenario uncertainty' includes the generalisability of the results to the UK setting given that the effectiveness and resource use parameters were based on non-UK trials. Therefore, it is important to note that the results of the economic assessment should be interpreted with caution.

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LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

ACB	Association of Clinical Biochemists
ARTI	acute respiratory tract infection
CADTH	Canadian Agency for Drugs and Technologies in Health
CAP	community-acquired pneumonia
CCT	controlled clinical trial
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CV	co-efficient of variation
DARE	Database of Abstracts of Reviews of Effects
DTA	diagnostic test accuracy
ED	emergency department
EED	Economic Evaluations Database
ESICM	European Society of Intensive Care Medicine
FN	false negative
FP	false positive
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HALex	Health And Limitation index
HES	Hospital Episode Statistics
HQIP	Health Quality Improvement Partnership
HRQoL	Health-Related Quality of Life
HSROC	hierarchical summary receiver operating characteristic
HTA	Health technology Assessment
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
INAHTA	International Network of Agencies for Health Technology Assessment
INR	international normalised ratio
IQR	interquartile range
ITT	intention to treat
LIA	luminescence immunoassay
LILACS	Latin American and Caribbean Health Sciences Literature
LR+	positive likelihood ratio
LR-	negative likelihood ratio
LRTI	lower respiratory tract infection
LY	life year

MODS	multiple organ dysfunction syndrome
NA	not applicable
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NPV	negative predictive value
NR	not reported
ONS	Office for National Statistics
PCT	procalcitonin
PICU	paediatric intensive care unit
PSA	probabilistic sensitivity analysis
PSI	Pneumonia Severity Index
PTT	prothrombin time
QALY	Quality-Adjusted Life Year
RCT	randomised controlled trial
ROC	receiver operating characteristic
RR	relative risk
SCI	Science Citation Index
SCCM	Society of Critical Care Medicine
SIGN	Scottish Intercollegiate Guidelines Network
SIRS	systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
SROC	summary receiver operating characteristic
SSC	Surviving Sepsis Campaign
TN	true negative
TP	true positive
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
WMD	weighted mean difference

GLOSSARY

Cost-effectiveness analysis	An economic analysis that converts effects into health terms and describes the costs for additional health gain.
Decision modelling	A mathematical construct that allows the comparison of the relationship between costs and outcomes of alternative healthcare interventions.
False negative	Incorrect negative test result – number of diseased persons with a negative test result.
False positive	Incorrect positive test result – number of non-diseased persons with a positive test result.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.
Index test	The test whose performance is being evaluated.
Likelihood Ratio (LR)	Likelihood ratios describe how many times more likely it is that a person with the target condition will receive a particular test result than a person without the target condition.
Markov model	An analytic method particularly suited to modelling repeated events, or the progression of a chronic disease over time.
Meta-analysis	Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.
Meta-regression	Statistical technique used to explore the relationship between study characteristics and study results.
Opportunity costs	The cost of forgone outcomes that could have been achieved through alternative investments.
Publication bias	Bias arising from the preferential publication of studies with statistically significant results.
Quality of life	An individual's emotional, social and physical well-being and their ability to perform the ordinary tasks of living.
Quality-adjusted life year (QALY)	A measure of health gain, used in economic evaluations, in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.
Receiver Operating Characteristic (ROC) curve	A graph which illustrates the trade-offs between sensitivity and specificity which result from varying the diagnostic threshold.
Reference standard	The best currently available method for diagnosing the target condition. The index test is compared against this to allow calculation of estimates of accuracy.
Sensitivity	Proportion of people with the target disorder who have a positive test result.
Specificity	Proportion of people without the target disorder who have a negative test result.
True negative	Correct negative test result – number of non-diseases persons with a negative test result.
True positive	Correct positive test result – number of diseased persons with a positive test result.

PLAIN ENGLISH SUMMARY

Procalcitonin (PCT) testing to guide antibiotic therapy: A systematic review and cost-effectiveness analysis

We wanted to see whether PCT could be used to decide whether to start and when to stop antibiotic treatment. Procalcitonin is an inflammatory marker that is produced when you have a bacterial infection but does not usually increase with viral infections or other types of inflammation. We looked at two groups of patients: adults and children with sepsis (blood poisoning) in the intensive care unit (ICU) and adults and children with possible bacterial infections in emergency departments (ED). The evidence is current to June 2014.

We included eighteen randomised controlled trials, eight in ICUs and 10 in EDs. None of the ICU studies included children but two of the ED studies were conducted in children. All studies compared guidance on when to start or stop antibiotic therapy that included PCT testing to guidance that did not.

Guidance that includes PCT testing reduces the amount of antibiotics used, is likely to reduce hospital stay and may reduce ICU stay. There are no adverse effects of PCT testing such as hospital re-admission, mortality, infections, mechanical ventilation, need for steroids or organ function. PCT testing is likely to be cost saving for adults with sepsis in an ICU setting and adults and children with possible bacterial infection in emergency departments.

SCIENTIFIC SUMMARY

Background

This assessment is concerned with the value of procalcitonin (PCT) in managing antibiotic therapy in two distinct populations: adults and children with known or highly suspected sepsis who are being treated in ICUs and adults and children who present to the ED with suspected bacterial infection. Rapid and accurate determination of the presence or absence of bacterial infection is important to guide appropriate therapy and to reduce unnecessary exposure to antibiotics. Reduction of antibiotic exposure is increasingly a priority for the NHS, in the context of efforts to conserve the effectiveness of existing drugs.

Procalcitonin is a 116 amino acid precursor to calcitonin. Normal serum or plasma levels of PCT in healthy adults are ≤0.05 ng/mL. Procalcitonin can be produced by a variety of cell types in response to inflammatory stimuli, especially of bacterial origin. It does not usually rise significantly with viral or non-infectious inflammation and so has the potential to be used as a marker of bacterial infection. All methods for the quantification of PCT are based on immunoassay and there are currently a number of CE marked automated assays available in the UK.

Objectives

The overall objectives of this project are to assess the clinical- and cost-effectiveness of adding procalcitonin (PCT) testing to the information used to guide antibiotic therapy in the following two populations

1. Adults and children with confirmed or highly suspected sepsis in intensive care settings.
2. Adults and children presenting to the emergency department with suspected bacterial infection.

For each of these populations we defined the following research questions:

- How does initiation of antibiotic therapy differ when PCT test results are added to the information available to treating clinicians?
- How does duration of antibiotic therapy and length of hospital/ICU stay differ when PCT test results are added to the information available to treating clinicians?
- How do clinical outcomes (e.g. septic shock, Sequential Organ Failure Assessment (SOFA) scores, in-hospital mortality) differ when PCT test results are added to the information available to treating clinicians?

- Does the addition of PCT testing to current clinical practice, to determine whether to initiate and when to discontinue antibiotic therapy represent a cost-effective use of National Health Service (NHS) resources?

Methods

Assessment of clinical effectiveness

Twelve databases, including MEDLINE and EMBASE, research registers and conference proceedings were searched to June 2014. Search results were screened for relevance independently by two reviewers. Full text inclusion assessment, data extraction, and quality assessment were conducted by one reviewer and checked by a second. Randomised controlled trials (RCTs) were assessed for quality using the Cochrane Risk of Bias tool. Analysis was stratified by objective. Summary relative risks (RR) and weighted mean differences (WMDs) were estimated using random effects models. Heterogeneity was investigated visually using forest plots and statistically using the I^2 and Q statistics. Observed heterogeneity was assessed using subgroup analysis.

Assessment of cost-effectiveness

In a de novo health economic analysis the short-term cost-effectiveness of PCT testing in addition to current clinical practice compared with current clinical practice without PCT was assessed for: (i) adults with confirmed or highly suspected sepsis in an ICU setting (ii) adults with suspected bacterial infection presenting to the ED; (iii) children with suspected bacterial infection presenting to the ED. Children with confirmed or highly suspected sepsis in an ICU setting were not considered due to the lack of data on clinical effectiveness in this population.

The structure of the decision tree starts with one decision node that denotes the use of PCT or current clinical practice without PCT. The key endpoints are: (i) alive with antibiotic related complications, (ii) alive without antibiotic related complications and (iii) death. The time horizon is six months (183 days), divided into an initial short-term (28 days) phase and a subsequent phase lasting 155 days (see Figures 23 and 24). The mean expected costs, life years (LYs), duration of antibiotic treatment and QALYs are calculated separately for both strategies.

Given the variation within the patient groups of interest, a ‘lower clinical extreme’ and a ‘higher clinical extreme’ is specified for each population and setting. For these ‘clinical extremes’ different baseline values are used for the mortality probability and resource use parameters while applying the same relative risk or mean difference estimates for both clinical extremes.

One-way sensitivity analyses were performed for all stochastic input parameters between the 95% confidence intervals. Scenario analyses were performed to assess the impact of assumptions on the estimated outcomes.

Results

Clinical effectiveness

Eighteen parallel group RCTs (36 reports) were included in the clinical effectiveness review. Studies were generally of unclear quality due to limitation in reporting. Twelve of the included studies measured plasma/serum PCT levels using the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA), two studies measured plasma/serum PCT levels using the VIDAS BRAHMS PCT (bioMérieux, Marcy l'Etoile, France) and four studies used quantitative PCT assays, but did not specify the assay manufacturer.

Three[1-3] of the 18 studies were judged at high risk of bias, one as low risk of bias,[4] and all other studies were judged at unclear risk of bias as insufficient information was reported to make a judgement on one or more bias domains.

Adults and children with confirmed or highly suspected sepsis in intensive care settings

Eight studies (12 reports), all conducted in adults, evaluated patients with sepsis in the intensive care unit (ICU) setting. Populations in ICU studies included adults with confirmed or highly suspected sepsis (four studies), adults being treated for suspected bacterial infection and those who developed sepsis during their ICU stay (one study), adults with acute pancreatitis (one study), adults with ventilator acquired pneumonia (VAP) (one study), and adults being treated for suspected bacterial infections (one study).

PCT algorithms were associated with a reduction in antibiotic duration (WMD -3.19 days, 95% CI: -5.44 to -0.95, I^2 95.2%; four studies). Uncertainty around this effect was reduced when the analysis was restricted to studies conducted in populations with suspected or confirmed sepsis (WMD -1.20 days, 95% CI: -1.33 to -1.07, two studies). Data on resource use indicated that PCT algorithms were associated with a reduction in the duration of hospital stay (WMD -3.85 days, 95% CI: -6.78 to -0.92, I^2 75.2%; four studies) and a trend towards a reduction in the duration of ICU stay (WMD -2.03 days, 95% CI: -4.19 to 0.13, I^2 81.0%; four studies). Uncertainty around these effect estimates was also reduced when the analysis was restricted to studies conducted in populations with suspected or confirmed sepsis (duration of hospital stay WMD -4.32 days, 95% CI: -6.50 to -2.14, two studies; duration of ICU stay WMD -2.31 days, 95% CI: -3.97 to -0.65, two studies). There were no differences between intervention groups for any adverse clinical outcomes assessed including

mortality at various time points, infection relapse/recurrence, mechanical ventilation, multi-organ dysfunction syndrome (MODS) and SOFA score. No study reported data on antibiotic-related adverse events.

Adults and children presenting to the emergency department with suspected bacterial infection

Ten studies (16 publications), eight in adults and two in children, evaluated patients presenting to the ED with suspected bacterial infections. One study was conducted in adults with UTI,[5] all others included adults or children with respiratory presentations.

PCT algorithms were associated with a reduction in the proportion of adults receiving antibiotics (RR was 0.77, 95% CI: 0.68 to 0.87; seven studies), the proportion of children with community acquired pneumonia (CAP) receiving antibiotics (RR 0.86 (95% CI: 0.80 to 0.93), and in the duration of antibiotic therapy in adults (two studies) and children (one study). However, the observed reduction in duration of antibiotic therapy appeared to be driven by the inclusion in the analysis of participants who did not receive any antibiotic therapy. Four further studies reported data in a form that could not be included in the meta-analysis; all found that PCT algorithms were associated with a reduction in the duration of antibiotic therapy in adults and children. PCT algorithms were associated with a trend towards reduction in the duration of hospital stay (WMD -0.80 days, 95% CI: -2.37 to 0.78; two studies), the effect of PCT on duration of hospital stay was inconsistent across the six adult studies reporting this outcome. PCT algorithms were associated with a small reduction in the duration of hospital stay in children (WMD -0.74 days, 95% CI: -1.17 to -0.31; two studies). There was no difference between intervention groups for duration of ICU stay, hospital re-admission, or secondary ED visits. Adverse clinical outcomes including mortality at various time points, infection relapse/recurrence, composite measures of adverse outcomes, mechanical ventilation, need for steroids, and complications of pneumonia generally showed no differences between intervention groups. Data from one study in adults and two in children indicated that PCT algorithms were associated with a reduction in antibiotic-related adverse events.

Assessment of cost-effectiveness

Base case analysis

The base case analyses indicated that PCT dominates current clinical practice for all populations in that it was both cost saving and more effective. The cost saving ranged from £368 for children with suspected bacterial infection presenting to the ED (lower clinical extreme) to £3,268 adults with confirmed or highly suspected sepsis in an ICU setting (lower clinical extreme). PCT testing resulted in only a small QALY gain. For adults with suspected bacterial infection presenting to the ED this was 0.005 for the lower and higher clinical extremes and for adults with confirmed or highly suspected

sepsis in the ICU setting it was 0.001 respectively for both clinical extremes. For children with suspected bacterial infection presenting to the ED, the QALY gains were less than 0.001 for both clinical extremes. The differences between the lower and higher clinical extremes were small for all settings and populations.

Cost-effectiveness acceptability curves showed that PCT-guided treatment has a probability of 84% or higher of being cost-effective for all settings and populations considered (at willingness to pay thresholds of £20,000 and £30,000 per QALY).

Sensitivity and scenario analyses

The one-way sensitivity and scenario analyses indicated that the base case outcomes were robust. Only one sensitivity analyses showed a relevant change in the incremental outcomes. This was the one-way sensitivity analysis for the relative mortality risk for adults with suspected bacterial infection presenting to the ED. This analysis showed that when using the upper bound of the 95% confidence interval PCT-guided treatment was less costly and less effective compared with current clinical practice, leading to savings of £30,469 (lower clinical extreme) and £30,446 (higher clinical extreme) per QALY lost. This indicates that PCT-guided treatment is cost-effective based on a threshold of £30,000, i.e. that a QALY lost is accepted given the obtained savings for PCT-guided treatment. The scenario analyses that assumed no difference in hospital stay had a substantial impact on all analyses. For all analyses PCT-guided treatment became more costly and remained more effective (instead of dominating current clinical practice). For the children presenting to the ED, this resulted in an ICER of £287,076 for the lower clinical extreme and £35,219 for the higher clinical extreme. For adults in both settings and both clinical extremes the ICER varied between £3,390 and £3,948.

Conclusions

Implications for service provision

The addition of a PCT algorithm to the information used to guide antibiotic treatment may reduce antibiotic exposure in adults being treated for suspected or confirmed sepsis in ICU settings and in adults presenting to the ED with respiratory symptoms and suspected bacterial infection, without any adverse consequences for clinical outcome. In ICU settings, the PCT algorithm was primarily used to inform decisions on when to discontinue antibiotic treatment, where as in ED settings the primary application was decisions on whether or not to initiate antibiotic treatment. The use of a PCT algorithm may also be associated with reductions hospital and ICU stay. Very limited data suggest that similar effects may apply for children presenting to the ED with respiratory symptoms and suspected bacterial infection, in particular the subgroup with CAP. No evidence was identified

on the effectiveness using a PCT algorithm to guide antibiotic treatment for children with suspected or confirmed sepsis in the ICU.

Available evidence suggests that the addition of PCT testing to current clinical practice leads to cost savings and a very small QALY gain and thus dominates current practice. Hence PCT testing potentially represents a cost-effective use of NHS resources for adults with confirmed or highly suspected sepsis in an ICU setting, adults with suspected bacterial infection presenting to the ED and children with suspected bacterial infection presenting to the ED. However, although the economic analysis indicates that there is little decision uncertainty, not all uncertainties can be captured in the parameters and thus be reflected in the outcomes of the economic assessment. This 'scenario uncertainty' includes the generalisability of the results to the UK setting. Therefore, it is important to note that the results of the economic assessment should be interpreted with caution. This applies in particular to the ED setting as another generalisability issue arises: the applicability of the presented outcomes to other patients than patients with respiratory symptoms. The paucity of evidence on long-term outcomes might further add to uncertainty.

Suggested research priorities

Further studies are needed to assess the effectiveness of adding PCT algorithms to the information used to guide antibiotic treatment in children with suspected or confirmed sepsis in ICU settings. Additional research is needed to examine whether the outcomes presented in this report are fully generalisable to the UK setting and whether the outcomes found for the ED setting are also applicable for other patients than patients with respiratory symptoms. Finally, although it is only likely to add to the gain in effectiveness and/or cost savings for PCT-guided treatment, it would be of relevance to examine long-term costs and effects of PCT-guided treatment, including its potential impact on antibiotic resistance.

1. OBJECTIVE

The overall objectives of this project are to assess the clinical- and cost-effectiveness of adding procalcitonin (PCT) testing to the information used to guide antibiotic therapy in the following two populations:

1. Adults and children with confirmed or highly suspected sepsis in intensive care settings.
2. Adults or children presenting to the emergency department with suspected bacterial infection.

For each of these populations we defined the following research questions:

- For adults and children with confirmed or highly suspected sepsis who are being treated in intensive care unit (ICU) settings, how does initiation of antibiotic therapy differ when PCT test results are added to the information available to treating clinicians?
- How does duration of antibiotic therapy and length of hospital/ICU stay differ when PCT test results are added to the information available to treating clinicians?
- How do clinical outcomes (e.g. septic shock, Sequential Organ Failure Assessment (SOFA) scores, in-hospital mortality) differ when PCT test results are added to the information available to treating clinicians?
- Does the addition of PCT testing to current clinical practice, to determine whether to initiate and when to discontinue antibiotic therapy represent a cost-effective use of National Health Service (NHS) resources?

2. BACKGROUND AND DEFINITION OF THE DECISION PROBLEM(S)

2.1 Population

This assessment is concerned with the value of PCT in managing antibiotic therapy in two distinct populations: adults and children with known or highly suspected sepsis who are being treated in ICUs and adults and children who present to the ED with suspected bacterial infection.

For the ICU setting, the assessment focuses primarily on people with confirmed or highly suspected sepsis; this is because sepsis is a common and serious problem amongst patients being treated in ICUs.[6] Sepsis is defined as probable or documented infection together with systemic manifestations of infection (sometimes described as systemic inflammatory response syndrome (SIRS)), severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction, and septic shock is defined as severe sepsis with hypotension which is not reversed by fluid resuscitation.[7, 8] Bacteria are the most common cause of sepsis, however, systemic viral and fungal infections can also occur. SIRS can also occur as a result of non-infectious challenge to the immune system and it is important for clinicians to be able to rapidly distinguish between infectious and non-infectious causes, as well as between different agents of infection, in order to guide appropriate therapy.

The most recent UK Hospital Episode Statistics (2012-2013) recorded 69,036 finished consultant episodes related to sepsis.[9] In addition, a recently published analysis of the 2001-2010 Office of National Statistics mortality data found that, during this period, 4.7% of all deaths recorded in England were 'definitely directly associated with sepsis.'[10] Ninety-nine per cent of deaths definitely associated with sepsis had at least one of the ICD-10 codes A40 (sepsis due to pneumonia), A41 (other sepsis), or P36 (sepsis of new-born due to streptococcus group B) on the death certificate, however, only 8.6% of deaths definitely associated with sepsis in 2010 had a sepsis-related condition as the underlying cause of death.[10] Only 7.0% of deaths definitely associated with sepsis did not occur in hospital.[10] Incidence of sepsis is particularly high in patients admitted to ICUs. A large retrospective analysis of 56,673 admissions of adult patients to ICUs in England Wales and Northern Ireland, between 1995 and 2000, found that 27.1% met the criteria for severe sepsis with the first 24 hours of admission.[6] Thirty-five per cent of these patients died before discharge from the ICU and 47% died in hospital.[6] Patients with severe sepsis accounted for 45% of intensive care bed days and 33% of hospital bed days used by all ICU admissions.[6] These data indicate that sepsis is a substantial healthcare problem with a high mortality rate, representing a major clinical challenge and associated with high resource use. Improving the management of sepsis, in particular in ICU settings is therefore an important healthcare goal.

For the emergency department setting, the assessment considers a broader population, which includes people presenting with any suspected bacterial infection. This is because discussions at scoping suggested that inclusion of a broader population would be more clinically appropriate in this setting and that presentation to the ED with symptoms consistent with sepsis would be relatively uncommon. The most recent UK Hospital Episode Statistics (2012-2013) recorded a first ED diagnosis of 'infectious disease' in 141,308 out of a total of 18.3 million ED presentations; 'septicaemia' was recorded as the first ED diagnosis for 24,850 presentations.[11] The most common type of suspected bacterial infection to present to the ED is respiratory tract infection.[12] A study of common medical presenting problems in the children's ED department found that the two most common presenting problems were breathing difficulty (31%) and febrile illness (20%).[13] LRTI (acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease or asthma and pneumonia) is a major cause of morbidity and mortality in children and adults. Pneumonia is the main cause of childhood mortality worldwide and accounts for 9% of deaths in children aged less than five years in Europe. Community acquired pneumonia is diagnosed in 5-12% of adults presenting to the GP with LRTI of whom 22-42% are admitted to hospital. Mortality in hospital is between 5-14%.[14] Many cases of pneumonia are caused by viruses and have a mild course and so antibiotic treatment is inappropriate; a bacterial cause of pneumonia has been shown in 33-70% of cases. However, most children with pneumonia are treated with antibiotics without the causative agent being known.[15] LRTIs account for almost 10% of worldwide morbidity and mortality and as much as 75% of all antibiotic prescriptions are for respiratory tract infections.[16] Rapid and accurate determination of the presence or absence of bacterial infection is important to guide appropriate therapy and to reduce unnecessary exposure to antibiotics. Reduction of antibiotic exposure is increasingly a priority for the NHS, in the context of efforts to conserve the effectiveness of existing drugs. The Department of Health has set out actions to slow the development and spread of antimicrobial resistance in the UK Five Year Antimicrobial Resistance Strategy 2013 to 2018.[17] One of the aims of the strategy is to conserve and steward the effectiveness of existing antimicrobials by ensuring antibiotics are used responsibly and less often. NICE public health guidance (PHG89), 'Antimicrobial resistance – changing risk-related behaviours,' is currently under development.[18]

2.2 Intervention technologies and comparator

Procalcitonin is a 116 amino acid precursor to calcitonin. In normal metabolism, calcitonin is produced solely by the C cells of the thyroid medulla and neuroendocrine cells in the lungs. Normal serum or plasma levels of PCT in healthy adults are ≤0.05 ng/mL.[19] Procalcitonin can also be produced by a variety of cell types in response to inflammatory stimuli (including systemic infection) and can be very high (>10 ng/mL) in sepsis, severe sepsis and septic shock.[19] PCT modulates the

immune response through induction of cytokine production and by affecting the migration of monocytes and parenchymal cells to the site of inflammation. A summary of the characteristics and clinical applications of PCT, produced by the Association for Clinical Biochemistry (ACB), lists the clinical uses of PCT measurement as:

- Diagnosis of bacterial infections of the lower respiratory tract and sepsis
- Monitoring progression of sepsis and response to antibiotic treatment
- Informing initiation, change or discontinuation of antibiotic therapy for sepsis

whilst cautioning that PCT can also be raised following surgery, trauma or severe burns, or in cases of severe pancreatitis, severe liver damage, severe multi-organ dysfunction syndrome, and severe fungal or viral infections.[19] The ACB document also notes that particular care is needed when interpreting PCT levels in neonates, as PCT levels can exceed 10 ng/mL in neonates in the absence of infection.[19]

All methods for the quantification of PCT are based on immunoassay and there are currently a number of CE marked automated assays available in the UK.

2.2.1 Thermo Fisher Scientific BRAHMS PCT Sensitive Kryptor assay

The BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA), sometimes also referred to as the BRAHMS PCT Kryptor assay, is an automated immunofluorescent sandwich assay for the determination of PCT in human serum and plasma. It is indicated for use with the BRAHMS Kryptor, BRAHMS Kryptor compact and BRAHMS Kryptor compact PLUS analysers. The assay has a measurement range of 0.02-5000 ng/mL, a functional assay sensitivity of 0.06 ng/mL, and an analytical sensitivity of 0.019 ng/mL. The time to result is 19 minutes.[20, 21]

A number of other companies have licensed the use of procalcitonin and its antibodies from Thermo Fisher Scientific. The main difference between these assays is the mechanism of detection of the antibody-PCT-antibody complexes.

All of the commercial assays have been standardised using the BRAHMS PCT luminescence immunoassay (LIA) (the original manual PCT assay). This assay was designed to be used in conjunction with a luminometer and results are calculated based on relative light units. The assay has a measurement range of 0.1-500 ng/mL, an analytical sensitivity of approximately 0.1 ng/mL, and a functional sensitivity of 0.3 ng/mL. The BRAHMS PCT LIA is not included in this assessment as it is no longer in widespread use in the UK. A more sensitive version of the assay (BRAHMS PCT Ultrasensitive Kryptor) is currently used for research purposes, not for sales. This version of the

assay has a lower functional assay sensitivity than the BRAHMS Sensitive Kryptor assay, allowing measurement of very low procalcitonin quantities in healthy individuals. The BRAHMS PCT Ultrasensitive Kryptor assay is also not included in this assessment, as it is not currently being marketed.

2.2.2 Roche Elecsys BRAHMS PCT

The Elecsys BRAHMS PCT assay (Roche Diagnostics GmbH, Mannheim, Germany) is an electrochemiluminescent immunoassay for the determination of PCT in human serum and plasma. The assay is indicated for use on the Elecsys, Modular and Cobas e analysers. It has a measurement range of 0.02-100 ng/mL, a functional sensitivity of 0.06 ng/mL and an analytical sensitivity of <0.02 ng/mL. The time to result is 18 minutes.[21, 22]

2.2.3 Siemens ADVIA Centaur BRAHMS PCT

The ADVIA Centaur BRAHMS PCT assay (Siemens Healthcare Diagnostics Ltd., Camberley, UK) is a chemiluminescent assay for the determination of PCT in human serum and plasma. The assay is indicated for use with the ADVIA Centaur/XP and ADVIA Centaur CP analysers. It has a measurement range of 0.02-75.00 ng/ml, a functional sensitivity of <0.05 ng/ml and an analytical sensitivity of <0.02 ng/ml. The time to result is 26-29 minutes, depending on which analyser is used.[21]

2.2.4 bioMérieux VIDAS BRAHMS PCT

The VIDAS BRAHMS PCT (bioMérieux, Marcy l'Etoile, France) is an Enzyme-Linked Fluorescent Assay for the determination of PCT in human serum and plasma. It is indicated for use with the VIDAS and miniVIDAS analysers. It has a measurement range of 0.05-200 ng/mL, a functional detection limit of 0.09 ng/mL and an analytical detection limit of 0.05 ng/mL. The time to result is 20 minutes.[23]

2.2.5 DiaSorin LIAISON BRAHMS PCT

The LIAISON BRAHMS PCT assay (DiaSorin S.p.A., Saluggia, Italy) is a sandwich chemiluminescent immunoassay for the determination of PCT in human serum and plasma. The assay is indicated for use with the LIAISON analyser. It has a measurement range of 0.1-500 ng/mL, a functional sensitivity of <0.24 ng/mL and an analytical sensitivity of <0.032 ng/mL. This assay is not currently marketed in the NHS. However, it will be included in the assessment so that, should the marketing situation change, any relevant data will have been evaluated.[24]

The ACB document states that PCT is not recommended as a routine screening test for infection, e.g. as part of an emergency department admission profile,[19] i.e. it is not useful to rule out infection where there is a low pre-test probability. This proposition is supported by data from a randomised controlled trial, conducted in children (aged 1 to 36 months) presenting to the emergency

department with fever of unknown origin, which compared diagnosis based on standard investigations, as directed by the attending physician, with and without information on the results of PCT testing.[25] This study found no difference in the overall rates of antibiotic use or hospitalisation between the groups.[25] When only patients without bacterial infection or neutropenia identified by other emergency department investigations (UTI, pneumonia, bacterial meningitis and neutropenia <500 $x10^6$/L excluded) were considered, there were still no differences between groups in either rate of antibiotic use or rate of hospitalisation; the researchers calculated that if all patients in this group with a PCT indicative of moderate risk of infection had been treated with antibiotics, the rate of antibiotic use would have increased by 24%.[25] An alternative diagnostic application would be in differentiating patients with sepsis from those who have systemic inflammatory response syndrome (SIRS) without infection, i.e. diagnosing sepsis where there is a high pre-test probability. A recent systematic review and meta-analysis of 30 studies assessing procalcitonin for the diagnosis of sepsis in critically ill patients reported summary estimates of sensitivity and specificity of 77% (95% CI: 72 to 81%) and 79% (95% CI: 74 to 84%).[26] The reference standard for determination of sepsis was defined as microbiological confirmation, or one or more of the following: white blood cells in a normally sterile body fluid; perforated viscus; radiographic evidence of pneumonia and production of purulent sputum; syndrome associated with high risk of infection.[26] This level of sensitivity does not suggest that a negative PCT test results alone would be adequate to rule out bacterial infection in high risk population; the study authors concluded that whilst 'procalcitonin is a helpful biomarker for early diagnosis of sepsis in critically ill patients, the results of the test must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment.'[26] This is in line with the ACB document, which states that: 'PCT results should be used to assist and guide clinicians towards a diagnosis or treatment strategy, but they should not be used to replace clinical judgement; treatment should not be withheld on the basis of PCT test results.'[19]

In order to provide information on the effectiveness of PCT testing, when used in an appropriate context alongside other clinical information, this assessment summarises data from clinical trials comparing the management of patients with probable or confirmed sepsis (ICU setting) or infection (ED setting) based on standard practice plus PCT testing to management based on standard practice alone. Thus, the comparator for this assessment was antimicrobial management based on standard clinical practice, without PCT testing. Any multi-component (i.e. not solely based on the results of a single biochemical or microbiological test) definition of standard clinical practice reported by the identified studies was considered relevant for inclusion.

2.3 Care pathway

2.3.1 Sepsis

Diagnosis and monitoring

There is currently no NICE clinical guideline covering the diagnosis and management of sepsis in general; NICE clinical guideline CG151 addresses the specific issue of prevention and management of neutropenic sepsis in cancer patients;[27] neutropenic sepsis is outside the scope of this assessment. A new NICE guideline, 'Sepsis: The recognition, diagnosis and management of severe sepsis', is currently under development and publication is expected in July 2016.[28] There is also an ongoing study by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD), commissioned by the Health Quality Improvement Partnership (HQIP), which aims to 'identify and explore avoidable and remediable factors in the process of care for patients with known or suspected sepsis.'[29] This study will examine organisational issues, systems and processes, recognition or early signs of sepsis, appropriate management of established severe infection, communication with families and carers, and use of the 'acute' end of life pathway and ceilings of treatment; publication is expected in autumn 2015.

Comprehensive guidance on the diagnosis and management of sepsis is provided by the Surviving Sepsis Campaign (SSC), a joint collaboration of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM).[7] This guideline was last up-dated in 2012 and is currently undergoing revision. The guideline was developed following the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system; the quality of evidence was rated as high (A) to very low (D) and recommendations were classified as strong (1) or weak (2).[30]

The SSC guideline specifies the presence of some the following criteria, alongside the presence of proven or suspected infection, for the diagnosis of sepsis:[7, 8]

- Clinical criteria – fever >38.3° C, hypothermia <36° C, heart rate >90 bpm or >2 SD above the age-specific normal range, tachypnea, altered mental status, significant oedema or positive fluid balance (>20 mL/kg over 24 hrs), hyperglycaemia (plasma glucose >7.7 mmol/L) in the absence of diabetes.
- Inflammatory markers – white blood cell count >12,000 μL^{-1} or <4,000 μL^{-1}, normal white blood cell count with >10% immature forms, plasma C-reactive protein or PCT level >2 SD above the age-specific normal range.

- Haemodynamic status – arterial hypotension (systolic blood pressure <90 mm Hg, mean arterial pressure <70 mm Hg, or decrease in systolic blood pressure >40 mm Hg in adults or <2 SD below the age-specific normal range.
- Organ dysfunction signs – arterial hypoxemia (PaO_2/FiO_2 <300), acute oliguria (<0.5 mL/kg/hr for ≥2 hrs despite adequate fluid resuscitation, creatinine increase >44.2 µmol/L, coagulation abnormalities (INR >1.5 or PTT >60 s), ileus (absent bowel sounds), thrombocytopenia (platelet count <100,000 μL^{-1}), hyperbilirubinemia (plasma total bilirubin >70 µmol/L).
- Tissue perfusion status – hyperlactatemia (>1 mmol/L), decreased capillary refill or mottling.

Definitions of sepsis in children are similar to adult definitions but depend on age-specific heart rate, respiratory rate and white blood cell count cut-off values. Special considerations for managing sepsis in paediatric patients are described in the SSC guidelines.[7]

The SSC guideline includes the specific recommendation (GRADE 1C – strong recommendation, low or very low quality evidence) that blood (and urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids, as appropriate) cultures should be taken before initiating antimicrobial therapy, provided that this does not significantly delay (>45 min) the start of antimicrobial therapy.[7] It should be noted that, although the guideline includes elevated PCT in the list of criteria indicative of sepsis (see above), no specific recommendation is made for its use in the diagnosis of sepsis.

Treatment

The SSC guideline provides the following recommendations on antimicrobial therapy:[7]

- 'The administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (GRADE 1B – strong recommendation, moderate quality evidence) and severe sepsis without septic shock (GRADE 1C – strong recommendation, low or very low quality evidence) should be a goal of therapy.'
- 'Initial empiric anti-infective therapy should include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis.' (GRADE 1B – strong recommendation, moderate quality evidence).
- 'Combination empirical therapy for neutropenic patients with severe sepsis' (GRADE 2B – weak recommendation, moderate quality evidence) 'and for patients with difficult-to-treat,

multidrug resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp' (GRADE 2B – weak recommendation, moderate quality evidence). 'For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteraemia' (GRADE 2B – weak recommendation, moderate quality evidence). 'A combination of beta-lactam and macrolide for patients with septic shock from bacteraemic *Streptococcus pneumoniae* infections' (GRADE 2B – weak recommendation, moderate quality evidence).

- 'Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known' (GRADE 2B – weak recommendation, moderate quality evidence).
- 'Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteraemia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia' (GRADE 2B – weak recommendation, low or very low quality evidence).
- 'Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin' (GRADE 2B – weak recommendation, low or very low quality evidence).
- 'Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of non-infectious cause' (ungraded recommendation).

The SSC guideline also includes a recommendation (GRADE 2C – weak recommendation, low or very low quality evidence) for the use of PCT or similar biomarkers to aid the clinician in discontinuation of empiric antibiotics, where there is no subsequent evidence of infection.[7]

2.3.2 Suspected bacterial infection in the ED

Diagnosis and monitoring

The only available NICE guideline relevant to the workup of suspected bacterial infection in the ED is on the Diagnosis and management of community- and hospital-acquired pneumonia in adults.[14]

These guidelines recommend that the following:

- Assess people with a clinical diagnosis of community-acquired pneumonia at presentation to hospital to determine whether they are at low, intermediate or high risk of death using their CURB65 score[31].

- Put in place processes to allow diagnosis and treatment of community-acquired pneumonia within four hours of presentation to hospital.

NICE clinical guideline CG160, on the assessment and management of feverish illness in children under five years,[32] included a research recommendation for a UK study on the performance characteristics and cost-effectiveness of procalcitonin versus C-reactive protein in identifying serious bacterial infection in children with fever of unknown origin. However, it should be noted that, whilst the guideline included a systematic review of studies assessing the diagnostic accuracy of these biomarkers, this review did not appear to have considered RCTs comparing the effectiveness of diagnostic strategies with and without PCT testing. Although the guideline cites later studies by the same authors, it does not include the RCT described above (pg. 4, Index test Section). [25]

Treatment

The NICE guidelines on pneumonia make the following recommendations regarding antibiotic treatment:

- Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours, to all patients with community-acquired pneumonia admitted to hospital.

Low-severity community-acquired pneumonia

- Offer a five day course of a single antibiotic to patients with low-severity community-acquired pneumonia.
- Consider amoxicillin in preference to a macrolide or tetracycline for patients with low-severity community-acquired pneumonia. Consider a macrolide or tetracycline for patients who are allergic to penicillin.
- Consider extending the course of the antibiotic for longer than five days as a possible management strategy for patients with low-severity community-acquired pneumonia whose symptoms do not improve as expected after three days.
- Explain to patients with low-severity community-acquired pneumonia treated in the community, and when appropriate their families or carers, that they should seek further medical advice if their symptoms do not begin to improve within three days of starting the antibiotic, or earlier if their symptoms are worsening.
- Do not routinely offer patients with low-severity community-acquired pneumonia:
    - a fluoroquinolone
    - dual antibiotic therapy.

Moderate- and high-severity community-acquired pneumonia

- Consider dual antibiotic therapy with amoxicillin and a macrolide (such as clarithromycin) for patients with moderate-severity community-acquired pneumonia.
- Consider dual antibiotic therapy with a beta-lactamase stable beta-lactam (such as co-amoxiclav) and a macrolide (such as clarithromycin) for patients with high-severity community-acquired pneumonia.
- Consider a 7- to 10-day course of antibiotic therapy for patients with moderate- or high-severity community-acquired pneumonia.

Monitoring

- Consider measuring a baseline C-reactive protein concentration in patients with community-acquired pneumonia on admission to hospital, and repeat the test if clinical progress is uncertain after 48 to 72 hours.

This guideline also includes the following research recommendation:

- In patients hospitalised with moderate- to high-severity community-acquired pneumonia, does using C-reactive protein monitoring in addition to clinical observation to guide antibiotic duration safely reduce the total duration of antibiotic therapy compared with a fixed empirical antibiotic course?

This assessment summarises the evidence on the use of PCT testing to determine whether or not to initiate antibiotics and to guide the duration of therapy in patients who have been appropriately treated with antibiotics.

3. ASSESSMENT OF CLINICAL EFFECTIVENESS

A systematic review was conducted to summarise the evidence on the clinical effectiveness of adding PCT testing to the information used to guide antibiotic therapy for the treatment of confirmed or highly suspected sepsis in ICU settings and the clinical effectiveness of adding PCT testing to the information used to guide antibiotic therapy in people presenting to the ED with suspected bacterial infection. Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[33] and the NICE Diagnostic Assessment Programme manual.[34]

3.1 Systematic review methods

3.1.1 Search strategy

Development of search strategies followed the recommendations of the Centre for Reviews and Dissemination guidance for undertaking reviews in health care[33] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[35] Strategies were based on PCT assays and target conditions (sepsis or bacterial infection); initial searches included a sensitive filter for RCTs.[36] Because initial searches identified no RCTs for the paediatric ICU population and only one RCT for the paediatric ED population, searches were re-run without a study design filter and limited to the paediatric population.

Candidate search terms were identified from target references, browsing database thesauri (e.g. MEDLINE MeSH and Embase Emtree), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches were used to generate test sets of target references, which informed text mining analysis of high-frequency subject indexing terms using EndNote reference management software. Strategy development involved an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search dates were determined in consultation with clinical specialist members of the Assessment Subgroup.

No restrictions on language or publication status were applied. Date restrictions were determined in consultation with clinical specialist members of the Assessment Subgroup, based on expert advice on the earliest appearance of literature of PCT diagnostic testing. Searches took into account generic and other product names for the intervention. The main Embase strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the CADTH Peer Review Checklist.[37] Search strategies were developed specifically for each database and keywords were adapted according to the configuration of each database.

Full search strategies are reported in Appendix 1.

Rapid appraisal searches

To assess the scope and scale of the literature, and to identify candidate search terms, a rapid appraisal of the literature was conducted.

The following databases were searched for relevant studies from database inception date to June 2014:

- The Cochrane Library:
    - Cochrane Database of Systematic Reviews (CDSR): up to Issue 4 of 12, April 2014
    - Database of Abstracts of Reviews of Effects (DARE): up to Issue 1 of 4, January 2014
    - Health Technology Assessment (HTA) Database: up to Issue 1 of 4, January 2014
    - NHS Economic Evaluation Database (NHS EED): up to Issue 1 of 4, January 2014
- PROSPERO (Internet): up to 9.4.14 (http://www.crd.york.ac.uk/prospero/)
- National Institute for Health and Care Excellence (NICE) Guidance (Internet): up to 8 April 2014 (http://www.nice.org.uk/)
- NIHR Health Technology Assessment (HTA) Programme (Internet): up to 8 April 2014 (http://www.hta.ac.uk/)
- US Food & Drug Administration (FDA) (Internet): up to 8 April 2014 (http://www.fda.gov/)
- Guidelines International Network (G-I-N) (Internet): up to 9 April 2014 (http://www.g-i-n.net/)
- National Guidelines Clearinghouse (NGCH) (Internet): up to 9 April 2014 (http://www.guideline.gov/index.aspx)
- Medicines and Healthcare Products Regulatory Agency (MHRA) (Internet): up to 9 April 2014 (http://www.mhra.gov.uk/index.htm)
- The Medion Database up to 2014/5/4 (Internet): up to 9 April 2014 (http://www.mediondatabase.nl/)

RCT searches

The following databases were searched for relevant studies from 1995 to June 2014:

- Embase (OvidSP): 1995 - 27 June 2014
- MEDLINE (OvidSP): 1995 - June Week 3 2014

- MEDLINE In-Process Citations and Daily Update (OvidSP): 1995 – 27 June 2014
- PubMed (http://www.ncbi.nlm.nih.gov/pubmed): 1995 – 14 July 2014
- CINAHL (Cumulative Index to Nursing & Allied Health Literature) (EBSCO): 1995 – 25 June 2014
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): 1995 - Issue 5 of 12, May 2014
- Science Citation Index (SCI) (Web of Science): 1995 – 27 June 2014
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet): 1995 – 1 July 2014 (http://regional.bvsalud.org/php/index.php?lang=en)
- NIHR Health Technology Assessment Programme (Internet): up to 1 July 2014 (http://www.nets.nihr.ac.uk/programmes/hta)

Completed and on-going trials were identified by searches of the following resources (1995-present):

- NIH ClinicalTrials.gov: up to 14 July 2014 (http://www.clinicaltrials.gov/)
- Current Controlled Trials: up to 14 July 2014 (http://www.controlled-trials.com/)
- WHO International Clinical Trials Registry Platform (ICTRP) : up to 14 July 2014 (http://www.who.int/ictrp/en/)

Paediatric population searches

The following databases were searched for relevant studies from 1995 to August/September 2014:

- Embase (OvidSP): 1995 – 29 August 2014
- MEDLINE (OvidSP): 1995 - August Week 3 2014
- MEDLINE In-Process Citations and Daily Update (OvidSP): 1995 – 29 August 2014
- PubMed (http://www.ncbi.nlm.nih.gov/pubmed): 1995 – 2 September 2014
- CINAHL (Cumulative Index to Nursing & Allied Health Literature) (EBSCO): 1995 – 27 August 2014
- Science Citation Index (SCI) (Web of Science): 1995 – 29 August 2014
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) (http://regional.bvsalud.org/php/index.php?lang=en): 1995 – 2 September 2014

Electronic searches were undertaken for abstracts and poster presentations of studies of procalcitonin from the following conferences:

- Royal College of Paediatrics and Child health (RCPCH) meetings: 2009-2014 (https://www.escmid.org/research_projects/eccmid/past_eccmids/)
- ECCMID (European Congress of Clinical Microbiology and Infectious Diseases): 2009-2014 (https://www.escmid.org/research_projects/eccmid/past_eccmids/
- International Symposium on Intensive Care and Emergency Medicine: 2009-2014 (http://ccforum.com/supplements/)

3.1.2 Inclusion and exclusion criteria

Population

1. Adults and children with confirmed or highly suspected sepsis, in whom antibiotic therapy is indicated, who are being treated in intensive care units.
2. Adults and children presenting to the emergency department with suspected bacterial infection.

Studies of neonates or immunosuppressed neutropenic patients on chemotherapy, immunosuppressant drugs or transplant programmes were excluded.

Intervention/Index test

Treatment decisions based on laboratory-based PCT testing, using any of the tests currently available to the UK NHS as described in Section 2.2, in addition to standard practice (as reported in individual studies).

Point-of-care tests, which do not provide a quantitative estimate of PCT levels, were excluded.

Comparator

Treatment decisions based on standard practice (as reported in individual studies), without PCT testing.

Outcomes

Antibiotic exposure (initiation/duration of antibiotic therapy), resource use (number of hospital admissions, length of hospital/ICU stay, costs), adverse clinical outcomes (e.g. SOFA scores, in-hospital mortality, condition-specific outcomes), antibiotic-related adverse events.

Study design

Randomised controlled trials (RCTs), or controlled clinical trials (CCTs) where no RCTs were available. Where no controlled trials (RCTs or CCTs) were available for a specified population, studies assessing the change in diagnostic accuracy associated with the addition of PCT testing to standard diagnostic work-up were sought. On the advice of clinical specialist members of the Assessment Subgroup, such studies were required to use adjudication of infection by independent panel as the reference standard; microbiological testing alone was not considered adequate. Studies that assessed the diagnostic accuracy of PCT testing alone, or that used culture alone as the reference standard were excluded.

3.1.3 Inclusion screening and data extraction

Two reviewers (MW and PW) independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full paper screening stage are presented in Appendix 5.

The principal investigators of completed trials (identified through searches of clinical trials registries) that appeared to meet our inclusion criteria but for which no publication was identified, were contacted and asked to provide publication details or un-published data. Details of ongoing trials and trials for which data were requested are reported in Appendix 2

Studies cited in materials provided by the manufacturers of PCT assays were first checked against the project reference database, in EndNote X6; any studies not already identified by our searches were screened for inclusion following the process described above.

Data were extracted on the following: setting (ICU or ED); age group (adults or children); study details; inclusion and exclusion criteria; participant characteristics (demographic characteristics, primary presentation and co-morbidities); details of the PCT assay used; details of the intervention PCT algorithm (decision thresholds for PCT levels and any clinical criteria); details of the standard care comparator; outcome measures (measures of antibiotic exposure (e.g. initiation and/or duration of antibiotics), resource use (e.g. duration of hospital stay, duration of ICU stay, secondary presentations) and adverse clinical outcomes (e.g. mortality, relapse/re-infection, SOFA score). Data were extracted by one reviewer, using a piloted, standard data extraction form and checked by a second (MW and PW); any disagreements were resolved by consensus. One Chinese language paper

was extracted by PW in consultation with a native speaker.[38] Full data extraction tables are provided in Appendix 3.

3.1.4 Quality assessment

The methodological quality of included RCTs was assessed using the Cochrane Risk of Bias Tool.[39] Risk of bias assessments were undertaken by one reviewer and checked by a second reviewer; any disagreements were resolved by consensus or discussion with a third reviewer. No studies of other designs were included in the review. The results of the risk of bias assessments are summarised and presented in tables and graphs in the results of the systematic review (Section 3.2.2) and are presented in full, by study, in Appendix 4.

3.1.5 Methods of analysis/synthesis

The results of studies included in this review are summarised by population/setting, (see Section 1) i.e. studies providing information studies providing information on the effectiveness of adding PCT testing to the information used to guide antibiotic therapy for the treatment of confirmed or highly suspected sepsis in ICU settings (Section 3.2.3), and studies providing information on the effectiveness of adding PCT testing to the information used to guide antibiotic therapy in people presenting to the ED with suspected bacterial infections (Section 3.2.4). Within each section, studies on adults and children are described separately. In addition, results are structured to illustrate the effects of PCT algorithms on antibiotic exposure, resource use and costs and adverse clinical outcomes.

Where more than one study reported the same outcome measure for clinically similar populations, meta-analysis was used to calculate summary effect estimates (relative risk (RR) for dichotomous outcomes and weighted mean difference (WMD) for continuous outcomes) together with 95% CIs, using DerSimonian and Laird random effects models.[40] Forest plots are used to display results from individual studies and summary estimates to allow visual assessment of heterogeneity. Heterogeneity was assessed statistically using the I^2 statistic.[41] Observed heterogeneity was explored using subgroup analyses.

3.2 Results of the assessment of clinical effectiveness assessment

The initial literature searches of bibliographic databases for RCTs identified 2,919 references. After initial screening of titles and abstracts, 146 were considered to be potentially relevant and ordered for full paper screening; of these 35 were included in the review.[1-4, 38, 42-71] Additional searches of bibliographic databases for non-RCTs conducted in paediatric populations yielded an additional 515 references. After initial screening of titles and abstracts, 14 were considered to be potentially

relevant and ordered for full paper screening; none of these met the criteria for inclusion in the review (see Appendix 5). All potentially relevant studies cited in documents supplied by the test manufacturers had already been identified by bibliographic database searches. One additional publication was obtained through contact with the authors,[5] after searches had identified the study protocol.[51] Figure 1 shows the flow of studies through the review process, and Appendix 4 provides details, with reasons for exclusions, of all publications excluded at the full paper screening stage.

3.2.1 Overview of included studies

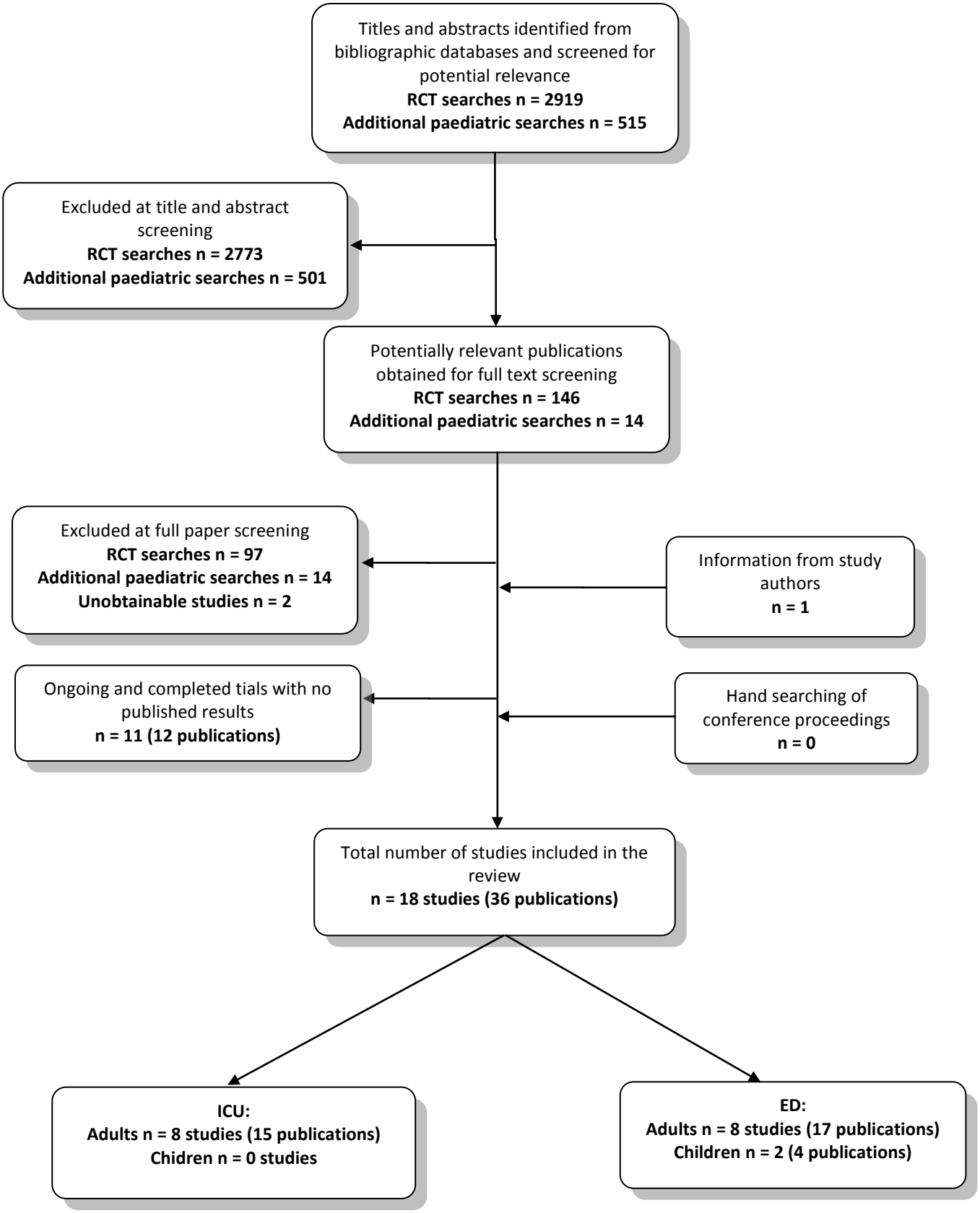
Based on the searches and inclusion screening described above (Sections 3.1.1 and 3.1.2), 36 publications[1-5, 38, 42-71] of 18 studies[1-5, 38, 42, 44, 46, 47, 49, 53, 54, 57-60, 63] were included in the review; the results section of this report cites studies using the primary publication and, where this is different, the publication in which the referenced data were reported. Eight studies were conducted in ICU settings[1, 2, 38, 42, 46, 54, 57, 63] and all of these studies included only adult participants; we did not identify any studies conducted in paediatric ICU settings that met the inclusion criteria for this review. Ten studies were conducted in ED settings, of which eight included only adults[3-5, 47, 49, 58-60] and two included only children.[44, 53]

The majority (12) of the included studies measured plasma/serum PCT levels using the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA). [2-5, 42, 44, 46, 47, 49, 53, 60, 63] Two studies measured plasma/serum PCT levels using the VIDAS BRAHMS PCT (bioMérieux, Marcy l'Etoile, France).[1, 54] The remaining four studies used quantitative PCT assays, but did not specify the assay manufacturer;[38, 57-59] two of these studies were published as conference abstracts only,[58, 59] and one was a Chinese language publication.[38]

Twelve of the 18 included studies were conducted in Europe (predominately Switzerland), [2, 3, 5, 42, 44, 46, 47, 49, 53, 54, 60, 63] three were conducted in China,[4, 38, 57] and one was conducted in Brazil;[1] no UK studies were identified. The two studies that were published as conference abstracts did not specify location.[58, 59] Nine of the 18 included studies reported receiving some support from assay manufacturers, including supply of assay platforms and/or kits; [2, 3, 42, 44, 46, 47, 49, 60, 63] five studies were fully supported by public funding[4, 5, 38, 53, 57] and four studies did not report any information on funding.[1, 54, 58, 59]

Full details of the characteristics of study participants, study inclusion and exclusion criteria, and intervention and comparator, and detailed results are reported in the data extraction tables presented in Appendix 3 (Tables a, b, c and d).

Figure 1: Flow of studies through the review process



3.2.2 Study quality

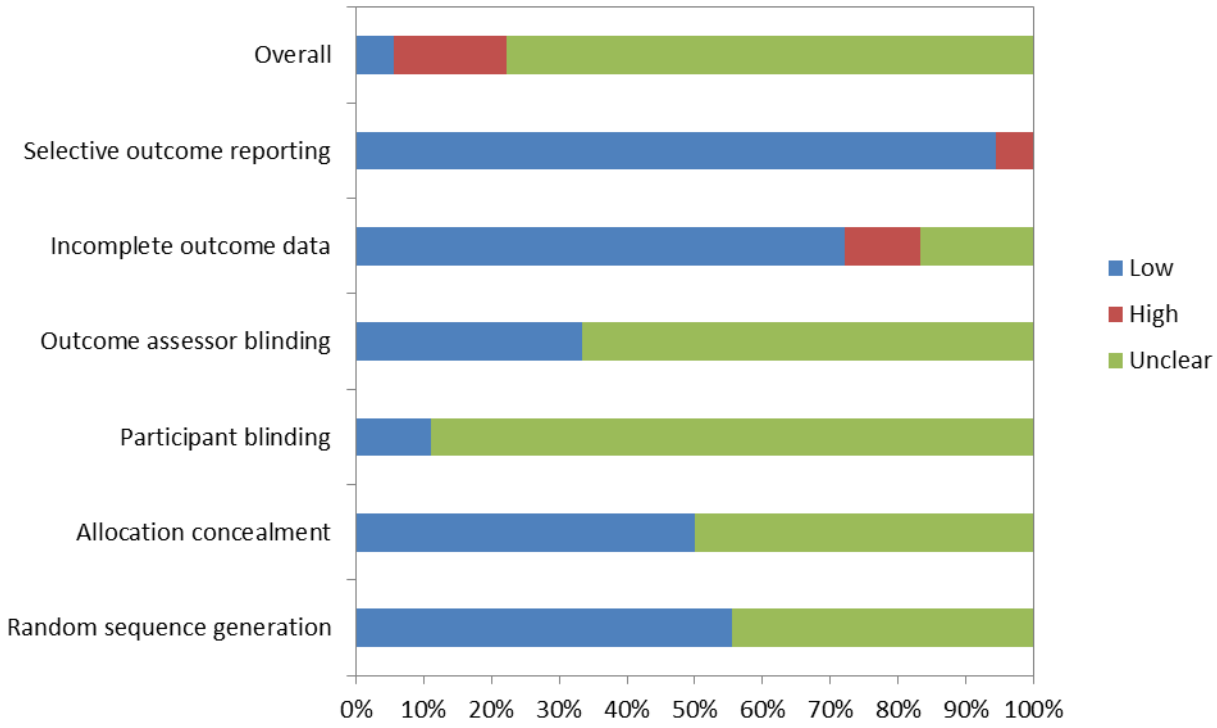
Studies were generally of unclear quality due to limitation in reporting. Three[1-3] of the 18 studies were judged at high risk of bias, one as low risk of bias,[4] and all other studies were judged at unclear risk of bias as insufficient information was reported to make a judgement on one or more bias domains (Figure 2; Table 2).

Two studies were judged at high risk of bias for incomplete outcome data. Both trials reported intention to treat (ITT) and per-protocol analyses and showed considerable variation in results for the two analyses suggesting that the relative large numbers of withdrawals (37% and 14%) may have introduced bias into the results. A further trial was judged at high risk of bias for selective outcome reporting[3] as a single outcome (antibiotic exposure) was reported in multiple different formats which could have resulted in confusion and a suggestion of a greater beneficial effect than was actually found. All other trials were judged at low risk of bias for selective outcome reporting. Where reported, methods used to randomise participants and conceal treatment allocation were appropriate, however around half of trials did not provide sufficient information on these processes. Given the nature of the intervention, it was not possible to blind study personnel. Very few studies provided details on participant blinding – only two studies provided this information, in both studies this was judged to be appropriate.[4, 42] Details on outcome assessor blinding was also rarely reported. Six studies reported information on outcome assessor blinding, in all studies this was judged to be appropriate.[1, 3, 4, 42, 53, 60] There were no clear differences in study quality based on setting (ICU versus ED) or population (adults versus children). Full details of the risk of bias assessments for individual trials, including the support for judgements, are provided in Appendix 4.

Table 1: Risk of bias in included trials

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Adults/ICU							
Annane(2013)[42]	☺	?	☺	☺	☺	☺	?
Bouadma(2010)[46]	☺	☺	?	?	☺	☺	?
Deliberato(2013)[1]	?	?	?	☺	☹	☺	☹
Layios(2012)[54]	?	?	?	?	☺	☺	?
Liu(2013)[38]	☺	?	?	?	☺	☺	?
Nobre(2005)[2]	☺	☺	?	?	☹	☺	☹
Qu(2012)[57]	?	?	?	?	?	☺	?
Stolz(2009)[63]	?	☺	?	?	☺	☺	?
Adults/ED							
Christ-Crain(2004)[49]	☺	?	?	?	☺	☺	?
Christ-Crain(2006)[47]	?	☺	?	?	☺	☺	?
Drozdov(2014)[5]	☺	☺	?	?	☺	☺	?
Roh(2013)[59]	?	?	?	?	?	☺	?
Roh(2010)[58]	?	?	?	?	?	☺	?
Schuetz(2009)[60]	☺	☺	?	☺	☺	☺	?
Stolz(2007)[3]	?	?	?	☺	☺	☹	☹
Tang(2013)[4]	☺	☺	☺	☺	☺	☺	☺
Children/ED							
Baer(2013)[44]	☺	☺	?	?	☺	☺	?
Esposito(2011)[53]	☺	☺	?	☺	☺	☺	?

Figure 2: Risk of bias across included trials



3.2.3 Effectiveness of adding PCT testing to the information used to guide antibiotic therapy for the treatment of confirmed or highly suspected sepsis in ICU settings.

Study details

Eight RCTs,[1, 2, 38, 42, 46, 54, 57, 63] reported in 12 publications, [1, 2, 38, 42, 43, 46, 50, 54-57, 63] provided data on the effectiveness of adding PCT testing to the information used to guide antibiotic therapy in ICU settings. All studies were conducted in adult populations. Four studies fully matched the participant inclusion criteria for this review (adults with confirmed or highly suspected sepsis, in whom antibiotic therapy is indicated, who are being treated in ICUs).[1, 2, 38, 42] A further study included adults who were being treated in an ICU for suspected bacterial infection, or who developed sepsis during their ICU stay.[46] Two additional studies that included adults being treated in ICU settings, who were considered to be at increased risk of developing sepsis, were also included; one study included adults with acute pancreatitis[57] and the other included adults with ventilator-associated pneumonia (VAP).[63] The final study included adults who were being treated for suspected bacterial infections in ICU settings.[54] This was the only study, conducted in an ICU setting, to assess the effectiveness of adding PCT testing to the information used to guide the initiation of antibiotic treatment, reflecting the lower level of symptom severity in the included population.[54] All of the other studies conducted in ICU settings assessed the effectiveness of adding PCT testing to the information used to decide when to discontinue antibiotic treatment.[1, 2, 38, 42, 46, 57, 63]

All studies used PCT algorithms with multiple decision thresholds to guide antibiotic treatment in the intervention arm, with final treatment decisions always remaining at the discretion of the treating clinician. The details of the PCT algorithm varied between studies, however, all discontinuation algorithms included a component which strongly encouraged/encouraged discontinuation of antibiotics when the PCT level was <0.25 ng/mL,[2, 38, 42, 46, 63] and/or encouraged discontinuation of antibiotics when the PCT level was <0.5 ng/mL.[1, 42, 46, 54, 57, 63] Discontinuation studies reported measuring PCT at baseline and daily[2, 38, 46, 57, 63] or every two days[1, 42] until discontinuation, discharge or death. The study which assessed the effectiveness of adding PCT testing to the information used to guide the initiation of antibiotic treatment used similar thresholds; initiation of antibiotic treatment was strongly discouraged when PCT levels were <0.25 ng/mL, less strongly discouraged when PCT levels were between 0.25 ng/mL and 0.5 ng/mL, less strongly recommended when PCT levels were between 0.5 and 1.0 ng/mL and strongly recommended when PCT levels were >1.0 ng/mL.[54] This study stated that PCT levels were measured when infection was suspected.[54] Full details of all PCT algorithms are reported in Appendix 3b. All studies compared the intervention, a PCT algorithm combined with clinical decision making, to decisions about antibiotic treatment based

on standard clinical decision making without PCT levels; full details of the standard clinical decision making comparator are reported in Appendix 3b.

Four of the studies conducted in ICU settings used the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA) to measure PCT levels,[2, 42, 46, 63] two used the VIDAS BRAHMS PCT assay (bioMérieux, Marcy l'Etoile, France),[1, 54] and two used an un-specified quantitative PCT assay.[38, 57]

Antibiotic exposure

The only study, conducted in an ICU setting, to assess the effectiveness of adding PCT testing to the information used to guide the initiation of antibiotic treatment found no significant difference in the proportion of participants who were prescribed antibiotics; RR 1.24 (95% CI: 0.89 to 1.71).[54]

Four[2, 38, 46, 57] of the seven[1, 2, 38, 42, 46, 57, 63] studies that assessed the effectiveness of adding PCT testing to the information used to decide when to discontinue antibiotic treatment reported data to allow the calculation of mean difference in the duration of antibiotic therapy between study arms. Three of these studies found that the inclusion of a PCT algorithm in the clinical decision making process resulted in a statistically significant reduction in the mean duration of antibiotic therapy;[38, 46, 57] the fourth study found that the PCT algorithm was associated a trend towards reduction in the duration of antibiotic therapy, which was not statistically significant[2] (see Table 2). The summary effect estimate, derived from these four studies, indicated that the addition of a PCT algorithm to the clinical decision making process was associated with a statistically significant reduction in the duration of antibiotic therapy, weighted mean difference (WMD) -3.19 days (95% CI: -5.44 to -0.95), however, between study heterogeneity was high (I^2 95.2%), (see Figure 3). The study with the largest effect size was conducted in adults with severe acute pancreatitis, mean difference -5.17 days (95% CI: -6.41 to -3.93, (see Table 2 and Figure 3).[57] Of the remaining three studies included in the meta-analysis two conducted in populations with suspected or confirmed sepsis.[2, 38] and one included both people with suspected bacterial infection and those who developed sepsis whilst in the ICU.[46] When the meta-analysis was restricted to the two studies conducted in populations with suspected or confirmed sepsis,[2, 38] the summary effect estimate still indicated that the addition of a PCT algorithm to the clinical decision making process was associated with a statistically significant reduction in the duration of antibiotic therapy, weighted mean difference (WMD) -1.20 days (95% CI: -1.33 to -1.07), (see Figure 4). One of these studies used the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA)[2] and the other used the VIDAS BRAHMS PCT assay (bioMérieux, Marcy l'Etoile, France);[38] there was no clear difference in effect between the two studies. Three further studies assessed the effectiveness of adding PCT testing to the information used to decide

when to discontinue antibiotic treatment, but reported the outcome as median (IQR) duration of antibiotic therapy, with *p* values for the between group comparison.[1, 42, 63] Two of these studies were conducted in people with suspected or confirmed sepsis and reported results indicating that adding a PCT algorithm to the clinical decision making process had no statistically significant effect on the duration of antibiotic treatment (see Table 2).[1, 42] The remaining study was conducted in adults with VAP and found that, in these patients, inclusion of a PCT algorithm in the clinical decision making process was associated with a statistically significant reduction in the median duration of antibiotic therapy from 15 to 10 days (see Table 2).[63]

The study by Bouadma et al, which included both people with suspected bacterial infection and those who developed sepsis whilst in the ICU, was the only ICU study to report duration of antibiotic therapy stratified by clinical diagnosis (UTI, community acquired pneumonia (CAP), VAP, infection with positive blood culture, and intra-abdominal infection).[46] The inclusion of a PCT algorithm in the clinical decision making process was associated with a statistically significant reduction in the duration of antibiotic therapy for people with UTI (mean difference -7.1 days (95% CI: -12.1 to-2.1)), CAP (mean difference -5.0 (95% CI: -6.5 to -3.5)), or VAP (mean difference -2.1 (95% CI: -3.9 to -0.3)), but not for people with infection and positive blood cultures (mean difference -3.0 (95% CI: -6.0 to 0.0)), or intra-abdominal infections (mean difference -2.7 (95% CI: -7.7 to 2.3)).[46] Full results, including all clinical subgroup data are presented in Appendix 3c and d.

Figure 3: Duration of antibiotic therapy

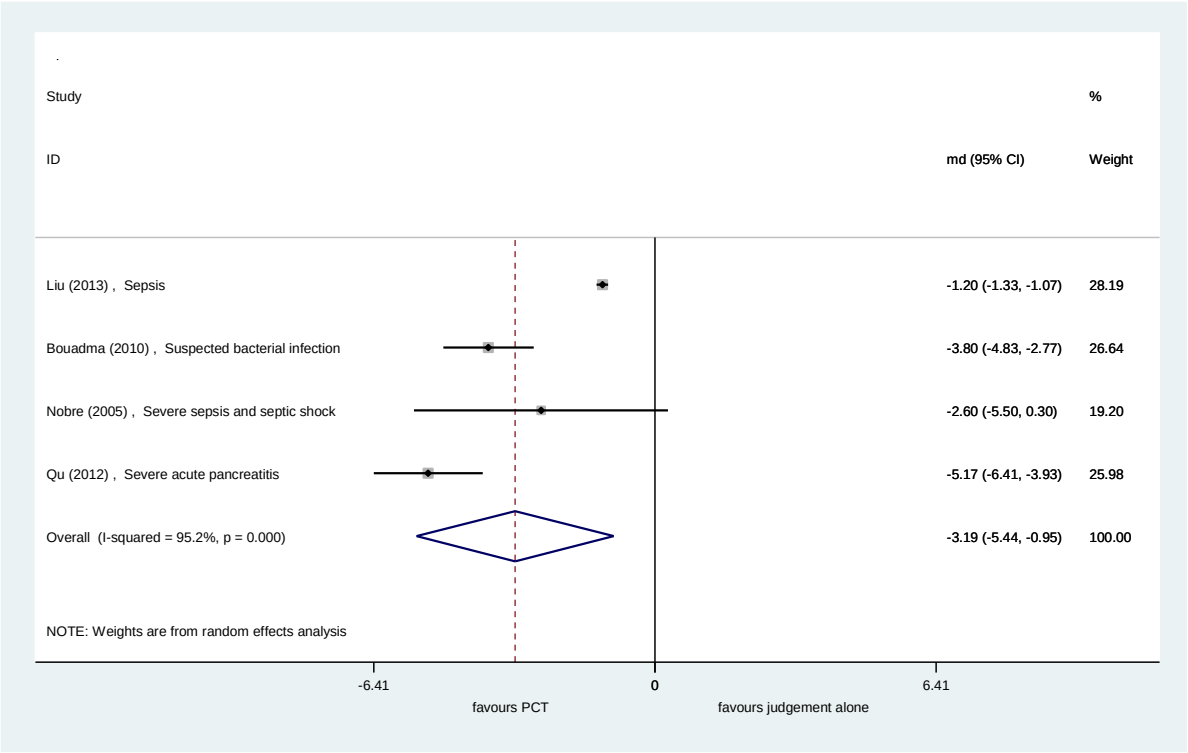


Figure 4: Duration of antibiotic therapy (studies which included only people with suspected or confirmed sepsis)

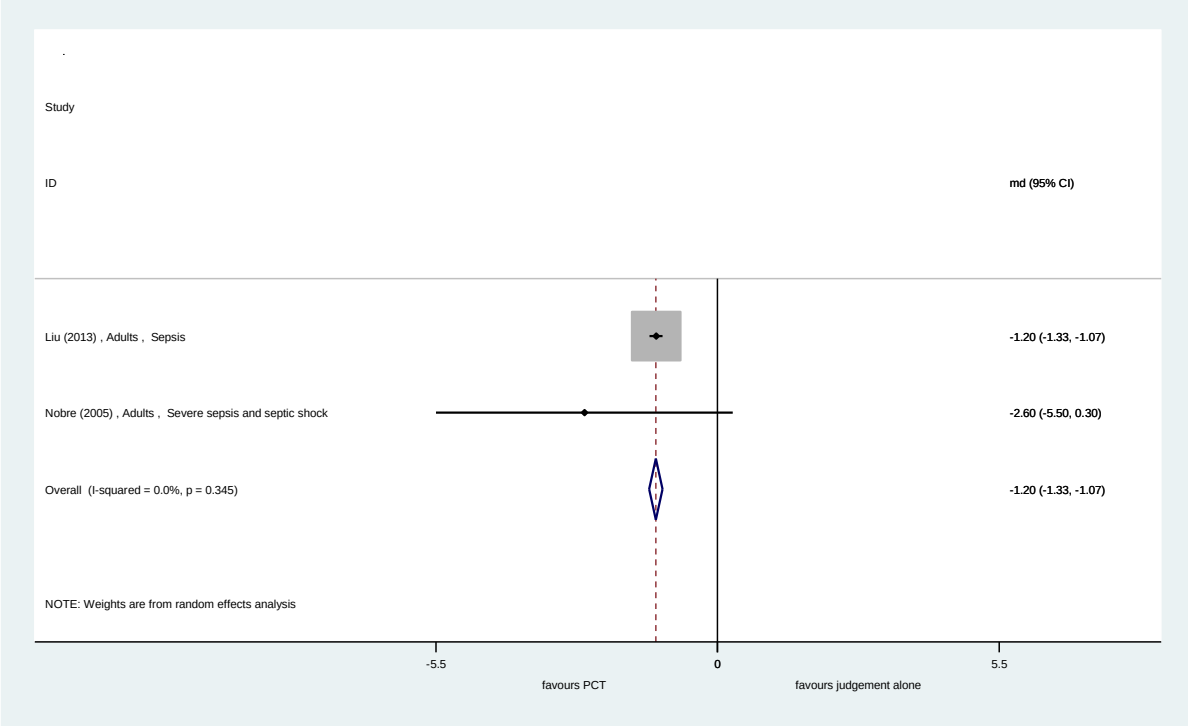


Table 2: Effects on antibiotic exposure of adding PCT testing to standard care in the ICU

Duration of antibiotics (days)				
Study Details	**Population**	**PCT-based algorithm**	**Clinical judgement alone**	**Effect Estimate**
		Median IQR or Mean (sd) *(number of participants)**		**Mean difference at follow-up (CI) or p value**
Annane(2013)[42]	Adults with apparent septic shock (SIRS and acute dysfunction of at least one organ) and no clear source of infection	5 (2, 5) (*30)*	5 (3, 5)*(28)*	p-value=0.52
Bouadma(2010)[46]	Adults with suspected bacterial infection or who developed sepsis in the ICU	**6.1 (6) (*307)***	**9.9 (7.1) *(314)***	**-3.80 (-4.83, -2.77)**
Deliberato(2013)[1]	Adults with suspected or confirmed sepsis	10 (3, 39) (*20)*	11 (2, 45) *(31)*	p-value=0.44
Liu(2013)[38]	Adults with suspected bacterial sepsis	**8.1 (0.3) (*42)***	**9.3 (0.3) *(40)***	**-1.20 (-1.33, -1.07)**
Nobre(2005)[2]	Adults with suspected severe sepsis or septic shock, or who developed sepsis in the ICU	6 (2, 33) (*39)*	9.5 (3, 34) *(40)*	**-2.6 (-5.5, 0.3)**
Qu(2012)[57]	Adults with severe acute pancreatitis	**10.89 (2.85) (*35)***	**16.06 (2.48) *(36)***	**-5.17 (-6.41, -3.93)**
Stolz(2009)[63]	Adults with VAP	10 (6, 16) *(50)*	15 (10, 23) (*51)*	p-value=0.038

Data sets included in the meta-analysis are marked in bold

Resource use and costs

Seven of the studies conducted in ICU settings reported data on resource use and costs outcomes.[1, 2, 38, 42, 46, 57, 63] All of these studies assessed the effectiveness of adding PCT testing to the information used to decide when to discontinue antibiotic treatment. All seven studies reported information on both the duration of hospital stay and six reported data on the duration of ICU stay.[1, 2, 38, 42, 46, 57]

Four studies reported data to allow the calculation of mean difference in the duration of hospital stay between study arms.[2, 38, 46, 57] Two of these studies found that the inclusion of a PCT algorithm in the clinical decision making process resulted in a statistically significant reduction in the mean duration of hospital stay[38, 57] and one study found that the PCT algorithm was associated a trend towards reduction in the duration of hospital stay, which was not statistically significant[2] (see Table 3). The results of study by Bouadma et al, which included both people with suspected bacterial infection and those who developed sepsis whilst in the ICU, indicated that the inclusion of a PCT algorithm in the clinical decision making process did not reduce the duration of hospital stay for these patients (mean difference 0.3 days (95% CI: -3.26 to 2.66)); this may be related to the less clinically severe spectrum of clinical presentations represented.[46] The summary effect estimate, derived from these four studies, indicated that the PCT algorithm was associated with a statistically significant reduction in the duration of hospital stay, weighted mean difference (WMD) -3.85 days (95% CI: -6.78 to -0.92), however, between study heterogeneity was high (I^2 75.2%) (see Figure 5). As with duration of antibiotic therapy, the largest effect size was derived from the study conducted in adults with severe acute pancreatitis, mean difference -7.15 days (95% CI: -9.16 to -4.34, (see Table 3 and Figure 5).[57] Two of the remaining three studies included in the meta-analysis were conducted in populations with suspected or confirmed sepsis,[2, 38] and one included both people with suspected bacterial infection and those who developed sepsis whilst in the ICU.[46] When the meta-analysis was restricted to studies conducted in people with suspected or confirmed sepsis[2, 38] the PCT algorithm appeared to be associated with a greater reduction in duration of hospital stay, WMD -4.32 days (95% CI: -6.50 to -2.14), (see Figure 6). One of these studies used the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA)[2] and the other used the VIDAS BRAHMS PCT assay (bioMérieux, Marcy l'Etoile, France);[38] there was no clear difference in effect between the two studies. Three further studies assessed the effectiveness of adding PCT testing to the information used to decide when to discontinue antibiotic treatment, but reported duration of hospital stay as median (IQR), with *p* values for the between group comparison.[1, 42, 63] Two of these studies were conducted in people with suspected or confirmed sepsis[1, 42] and one was conducted in people with VAP[63]; all reported results indicating that the PCT algorithm had no statistically significant effect on the duration of hospital stay (see Table 3).

Four studies reported data to allow the calculation of mean difference in the duration of ICU stay between study arms.[2, 38, 46, 57] Two of these studies found that the inclusion of a PCT algorithm in the decision to discontinue antibiotics resulted in a statistically significant reduction in the mean duration of ICU stay[38, 57] and one study found that the PCT algorithm was associated a trend towards reduction in the duration of hospital stay, which was not statistically significant[2] (see Table 3). As with duration of hospital stay, the results of the study by Bouadma et al indicated that the inclusion of a PCT algorithm in the decision to discontinue antibiotics did not reduce the duration of ICU stay for these patients with a less severe spectrum of disease (mean difference 1.5 days (95% CI: -0.88 to 3.88)).[46] The summary effect estimate, derived from these four studies, indicated that the inclusion of a PCT algorithm in the decision to discontinue antibiotics was associated with a trend towards decreased duration of ICU stay, which did not reach statistical significance, WMD -2.03 days (95% CI: -4.19 to 0.13), however, between study heterogeneity was high (I^2 81.0%), (see Figure 7). The largest effect size was again derived from the study conducted in adults with severe acute pancreatitis, mean difference -3.72 days (95% CI: -4.99 to -2.45, (see Table 3 and Figure 6).[57] Two of the remaining three studies included in the meta-analysis were conducted in populations with suspected or confirmed sepsis,[2, 38] and one included both people with suspected bacterial infection and those who developed sepsis whilst in the ICU.[46] When the meta-analysis was restricted to studies conducted in people with suspected or confirmed sepsis[2, 38] the summary effect estimate indicated that the inclusion of a PCT algorithm in the decision to discontinue antibiotics was associated with a statistically significant reduction in the duration of ICU stay, WMD -2.31 days (95% CI: -3.97 to -0.65), (see Figure 8). One of these studies used the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA)[2] and the other used the VIDAS BRAHMS PCT assay (bioMérieux, Marcy l'Etoile, France);[38] there was no clear difference in effect between the two studies. Two further studies assessed the effectiveness of adding PCT testing to the information used to decide when to discontinue antibiotic treatment, but reported duration of ICU stay as median (IQR), with *p* values for the between group comparison.[1, 42] Both of these studies were conducted in people with suspected or confirmed sepsis[1, 42] and both reported results indicating that adding the PCT algorithm had no statistically significant effect on the duration of ICU stay (see Table 3).

The study by Qu et al conducted in people with severe acute pancreatitis reported that the inclusion of a PCT algorithm in the decision to discontinue antibiotics was associated with a statistically significant reduction in the mean total cost of hospitalisation, mead difference -$3412 (95% CI: -4613 to -2211).[57]

No study reported clinical subgroup data for resource use and costs outcomes.

Figure 5: Duration of hospital stay

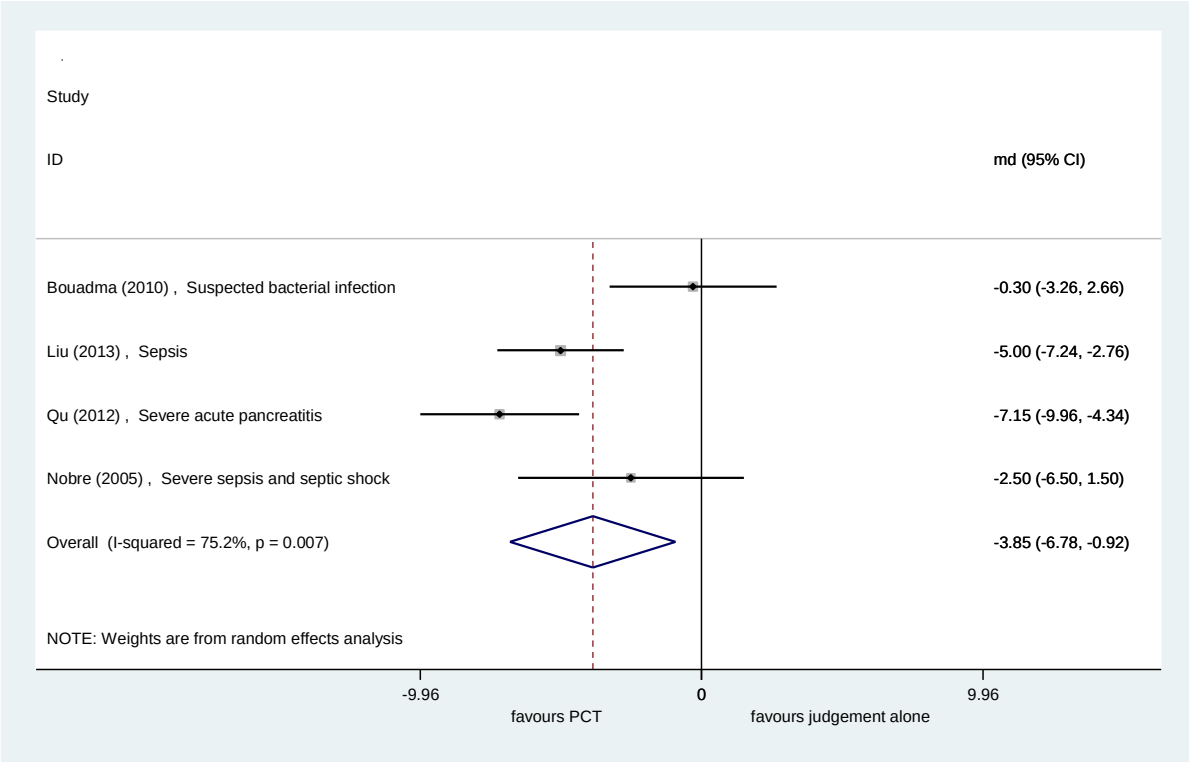


Figure 6: Duration of hospital stay (studies which included only people with suspected or confirmed sepsis)

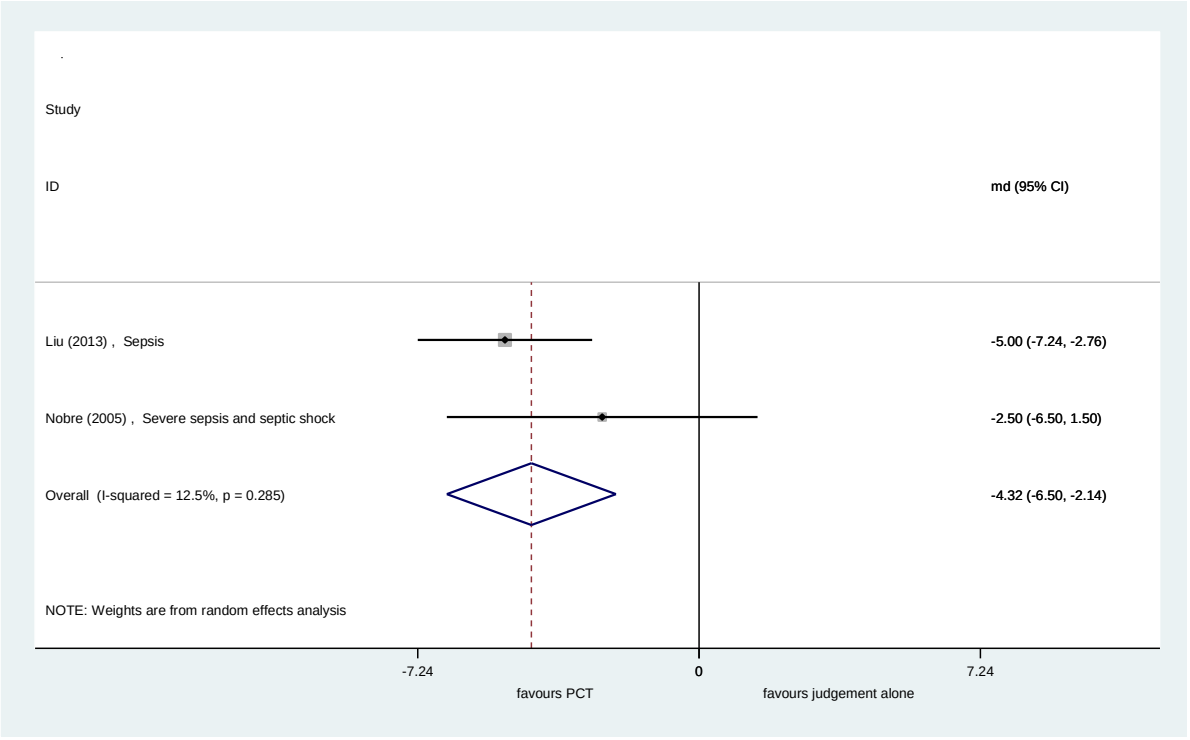


Figure 7: Duration of ICU stay

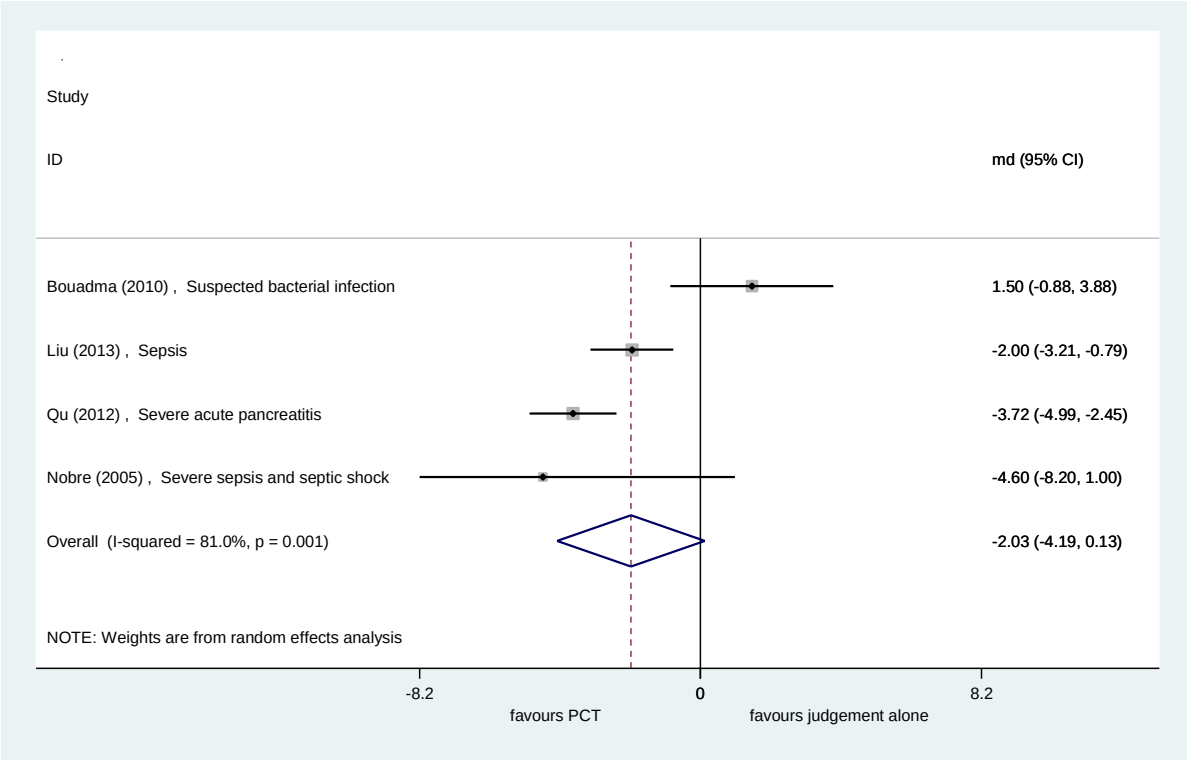


Figure 8: Duration of ICU stay (studies which included only people with suspected or confirmed sepsis)

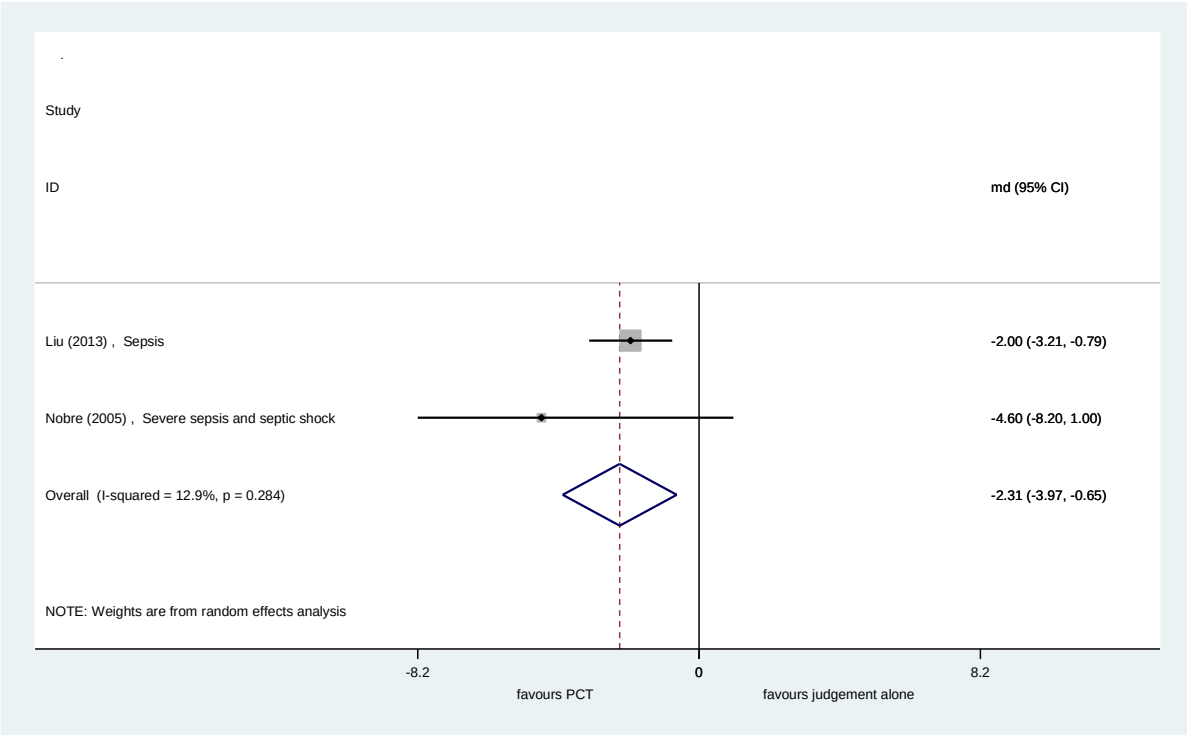


Table 3: Effects on resource use and costs of adding PCT testing to standard care in the ICU

Study Details	Population	PCT-based algorithm	Clinical judgement alone	Effect Estimate
		Median IQR or Mean (sd) *(number of participants)**		Mean difference at follow-up (CI) or p value
Duration of hospital stay (days)				
Annane(2013)[42]	Adults with apparent septic shock (SIRS and acute dysfunction of at least one organ) and no clear source of infection	27 (9, 49) (*30)*	33 (11, 69) *(28)*	p-value=0.22
Bouadma(2010)[46]	Adults with suspected bacterial infection or who developed sepsis in the ICU	**26.1 (19.3) (*307)***	**26.4 (18.3) *(314)***	**-0.3 (-3.26, 2.66)**
Deliberato(2013)[1]	Adults with suspected or confirmed sepsis	11 (3, 547) (*20)*	11 (2, 228) *(31)*	p-value=0.70
Liu(2013)[38]	Adults with suspected bacterial sepsis	**27 (4.9) (*42)***	**32 (5.4) *(40)***	**-5.0 (-7.24, -2.76)**
Nobre(2005)[2]	Adults with suspected severe sepsis or septic shock, or who developed sepsis in the ICU	17 (3, 96) (*39)*	23.5 (5, 44) *(40)*	**-2.5(-6.5, 1.5)**
Qu(2012)[57]	Adults with severe acute pancreatitis	**16.66 (4.02) (*35)***	**23.81 (7.56) (*36)***	**-7.15 (-9.16, -4.34)**
Stolz(2009)[63]	Adults with VAP	26 (7, 21) *(51)*	26 (16.8, 22.3) *(50)*	p-value=0.153
Duration of ICU stay (days)				
Annane(2013)[42]	Adults with apparent septic shock and no clear source of infection	22 (8, 42) (*30)*	23 (10, 60) *(28)*	p-value=0.58
Bouadma(2010)[46]	Adults with suspected bacterial infection	**15.9 (16.1)**	**14.4 (14.1)**	**1.5 (-0.88, 3.88)**
Deliberato(2013)[1]	Adults with suspected or confirmed sepsis	3.5 (1, 57) (*20)*	3 (1, 28) *(31)*	p-value=0.60
Liu(2013)[38]	Adults with suspected bacterial sepsis	**12 (2.9) (*42)***	**14 (2.7) *(40)***	**-2.0 (-3.21, -0.79)**
Nobre(2005)[2]	Adults with suspected severe sepsis or septic shock, or who developed	4 (1, 21) (*39)*	7 (1, 91) *(40)*	**-4.6 (-8.2, 1)**

Study Details	Population	PCT-based algorithm	Clinical judgement alone	Effect Estimate
		Median IQR or Mean (sd) *(number of participants)**		**Mean difference at follow-up (CI) or p value**
	sepsis in the ICU			
Qu(2012)[57]	Adults with severe acute pancreatitis	11.1 (2.94) (*35)*	14.8 (2.49) *(36)*	**-3.72 (-4.99, -2.45)**
Costs (total cost of hospitalisation in U.S. dollars)				
Qu(2012)[57]	Adult with severe acute pancreatitis	24401 (2631) (*35)*	27813 (2529) *(36)*	-3412 (-4613, -2211)

Data sets included in the meta-analyses are marked in bold

Adverse clinical outcomes

All eight studies conducted in ICU settings reported some data on adverse clinical outcomes.[1, 2, 38, 42, 46, 54, 57, 63] Three of these studies explicitly stated that they aimed to investigate whether the use of PCT in decision making can reduce antibiotic exposure, without adversely affecting clinical outcomes;[2, 46, 63] one of which specified a non-inferiority design for mortality and reported a Kaplan Meyer survival curve.[46]

Five studies reported 28-day all-cause mortality, and all reported no statistically significant difference in mortality rates between participants in the intervention group (decision to discontinue antibiotics based on PCT algorithm + clinical judgement) and those in the control group (decision to discontinue antibiotics based on clinical judgement alone), (see Table 4).[2, 38, 46, 57, 63] The summary RR derived from these five studies was 0.98 (95% CI: 0.76 to 1.27), (see Figure 9). This finding was consistent when the meta-analysis was restricted to studies conducted in people with suspected or confirmed sepsis,[2, 38] RR 1.07 (95% CI: 0.54 to 2.12). One study also reported mortality at 60 days and found no statistically significant difference between the intervention and control groups, RR 1.15 (95% CI: 0.89 to 1.48).[46] One further study, conducted in people with apparent septic shock, assessed mortality at five days and found no statistically significant difference between the intervention and control groups, RR 1.0 (95% CI:0.25 to 4.04).[42]

Four studies reported in-hospital mortality and, as with all-cause mortality, all reported no statistically significant difference in mortality rates between participants in the intervention and control groups, (see Table 4).[1, 2, 42, 63] The summary RR derived from these five studies was 0.75 (95% CI: 0.49 to 1.16), (see Figure 10). This finding was consistent when the meta-analysis was restricted to studies conducted in people with suspected or confirmed sepsis, [1, 2, 42] RR 0.78 (95% CI: 0.45 to 1.35).

Three studies reported ICU-mortality.[1, 42, 54] Two of these studies assessed the effects of the addition of a PCT algorithm to the information used to guide discontinuation of antibiotics, and were conducted in people confirmed or suspected sepsis;[1, 42] both reported no statistically significant difference in the ICU-mortality rate between the intervention and control groups, (see Table 4). The remaining study assessed the effects of adding a PCT algorithm to the information used to decide whether or not to initiate antibiotic treatment and was conducted in people with suspected bacterial infection;[54] this study also found no statistically significant difference in the ICU-mortality rate between the intervention and control groups, (see Table 4). The summary RR derived from all three studies was 0.87 (95% CI: 0.55 to 1.37), (see Figure 11). This finding was consistent when the

meta-analysis was restricted to studies conducted in people with suspected or confirmed sepsis,[1, 42] RR 0.59 (95% CI: 0.27 to 1.28).

Four studies reported rates of infection relapse/recurrence, and all found no statistically significant difference in mortality rates between participants in the intervention group (decision to discontinue antibiotics based on PCT algorithm + clinical judgement) and those in the control group (decision to discontinue antibiotics based on clinical judgement alone), (see Table 4).[1, 2, 38, 46] The summary RR derived from these four studies was 1.37 (95% CI: 0.77 to 2.44), (see Figure 12). This finding was consistent when the study by Bouadma et al, which included both people with suspected bacterial infection and those who developed sepsis whilst in the ICU, was excluded from the meta-analysis, RR 1.89 (95% CI: 0.47 to 7.59).

A variety of other general and disease-specific adverse clinical outcomes were reported by one or more studies, see Table 4. These included multi-drug-resistant infection,[46] sepsis-related mortality,[2] multiple organ dysfunction syndrome (MODS),[57] VAP-related clinical deterioration,[63] duration of mechanical ventilation,[42, 54] SOFA score at various time points.[42, 46, 54] No study reported a statistically significant difference between the intervention and comparator groups for any adverse clinical outcome assessed. None of the included studies reported antibiotic-related adverse events.

No study reported clinical subgroup data for adverse clinical outcomes.

Figure 9: All-cause mortality (28 day)

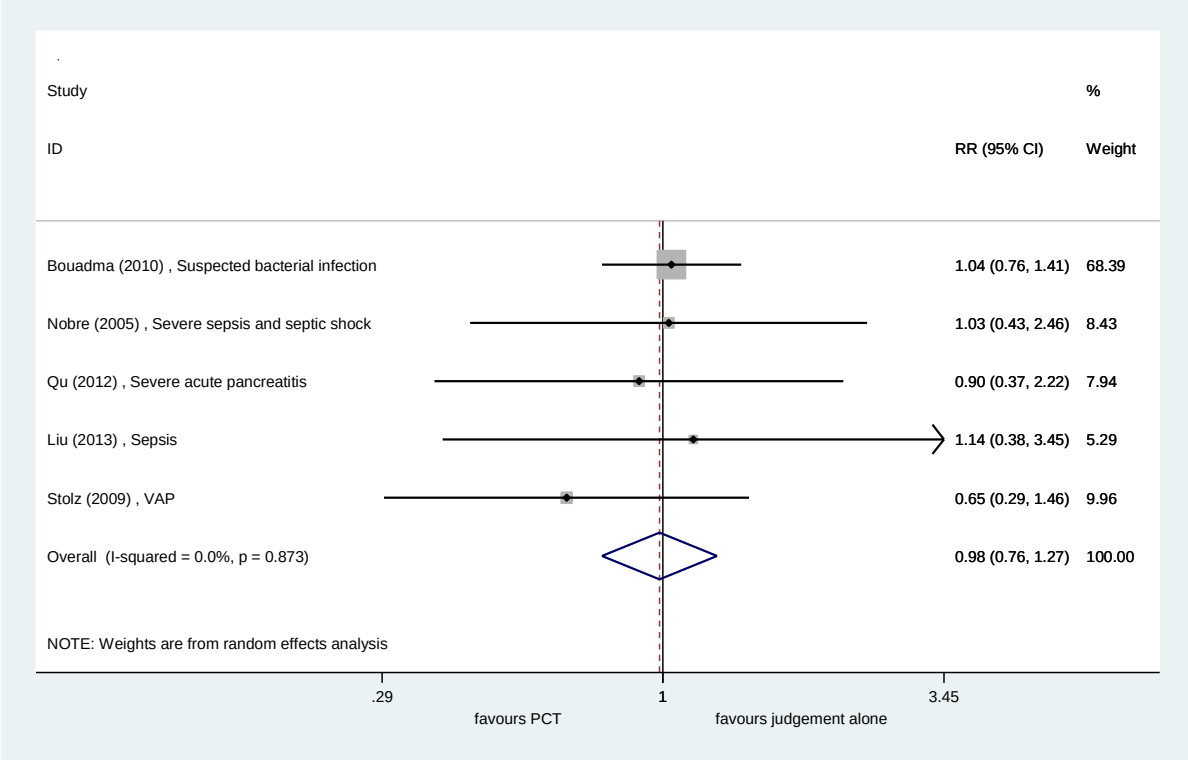


Figure 10: In-hospital mortality

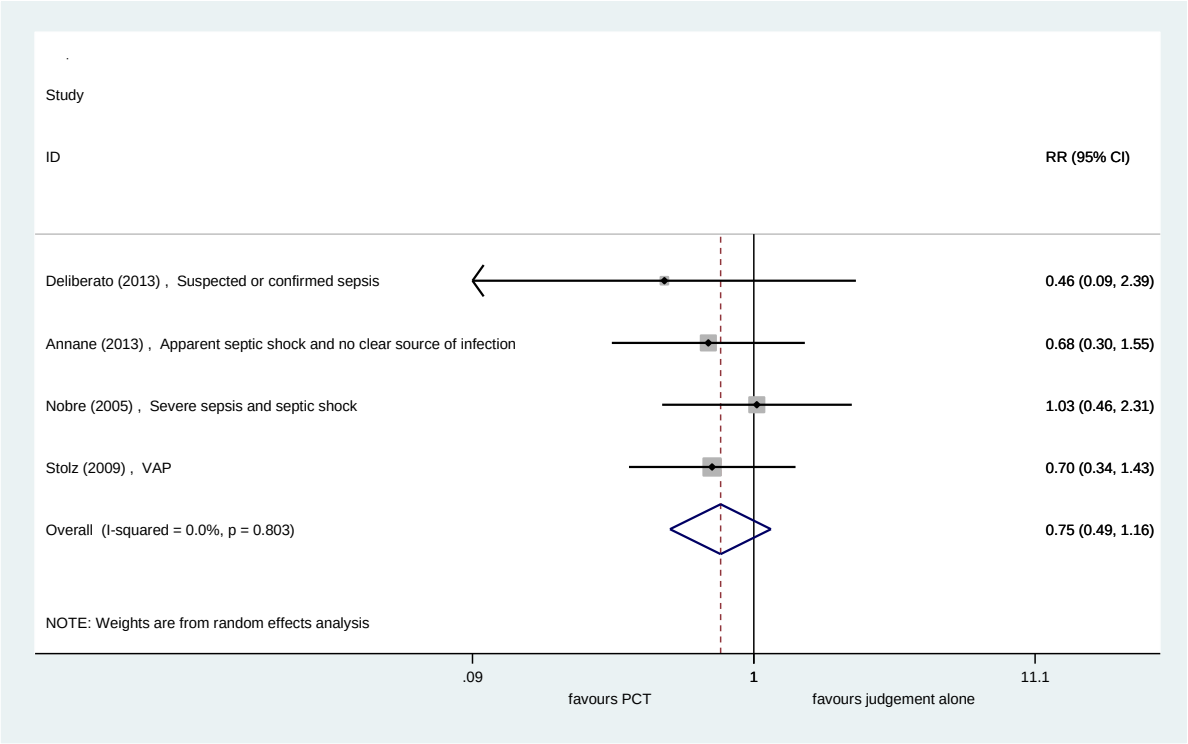


Figure 11: ICU mortality

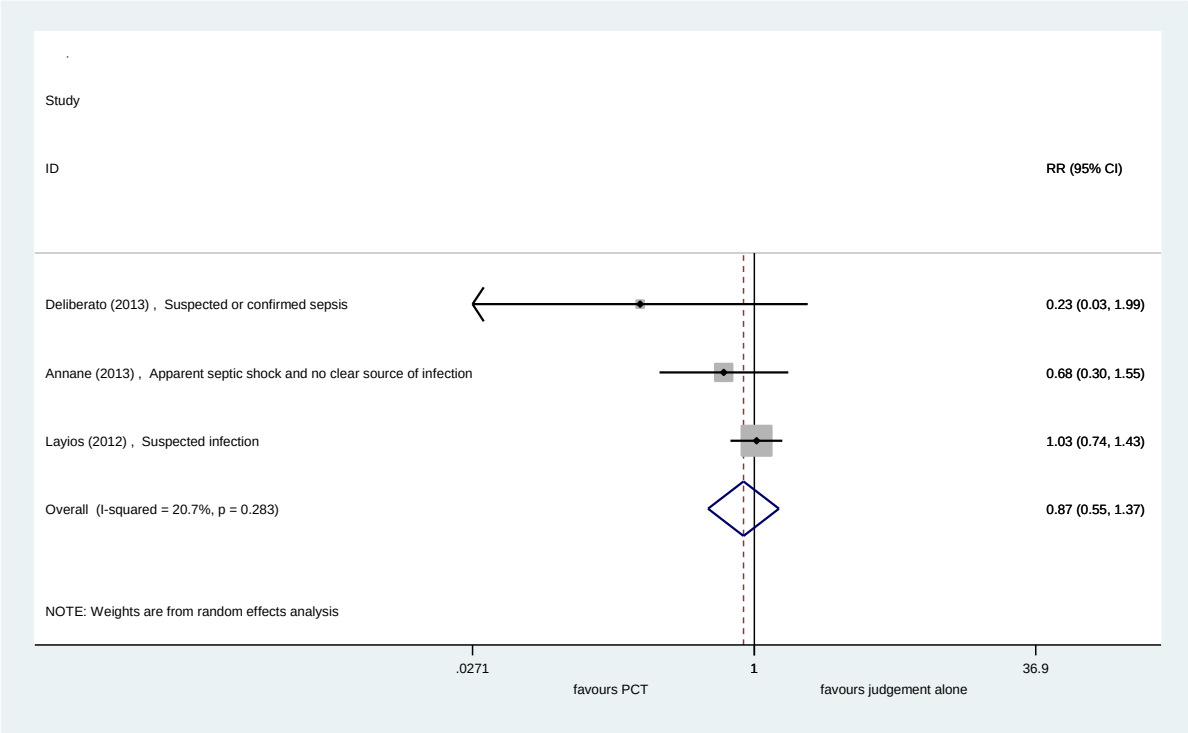


Figure 12: Infection relapse/recurrence (ICU population)

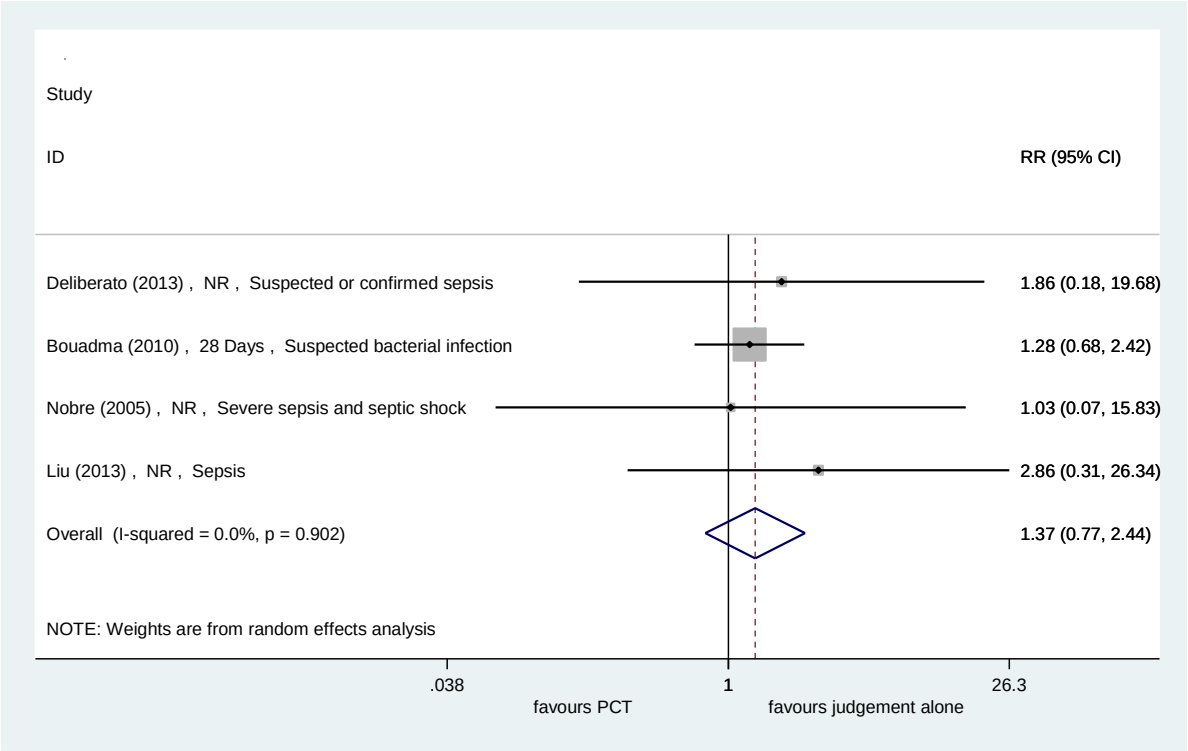


Table 4: Effects on adverse clinical outcomes of adding PCT testing to standard care in the ICU

Study Details	Population	PCT based algorithm	Clinical judgment alone	RR (95% CI)
		Number of patients with event/number patients	Number of patients with event/number patients	
All-cause mortality (28 day)				
Bouadma (2010)[46]	Adults with suspected bacterial infection or who developed sepsis in the ICU	**65/307**	**64/314**	**1.04 (0.76, 1.41)**
Liu (2013)[38]	Adults with suspected bacterial sepsis	**6/42**	**5/40**	**1.13 (0.39, 3.22)**
Nobre (2005)[2]	Adults with suspected severe sepsis or septic shock, or who developed sepsis in the ICU	**8/39**	**8/40**	**1.03 (0.44, 2.38)**
Qu (2012)[57]	Adults with severe acute pancreatitis	**7/35**	**8/36**	**0.91 (0.38, 2.16)**
Stolz (2009)[63]	Adults with VAP	**8/51**	**12/50**	**0.67 (0.31, 1.45)**
In-hospital mortality				
Annane (2013)[42]	Adults with apparent septic shock (SIRS and acute dysfunction of at least one organ) and no clear source of infection	**7/31**	**10/30**	**0.69 (0.31, 1.53)**
Deliberato (2013)[1]	Adults with suspected or confirmed sepsis	**2/42**	**4/39**	**0.52 (0.12, 2.28)**
Nobre (2005)[2]	Adults with suspected severe sepsis or septic shock, or who developed sepsis in the ICU	**9/39**	**9/40**	**1.03 (0.47, 2.25)**
Stolz (2009)[63]	Adults with VAP	**10/51**	**14/50**	**0.71 (0.36, 1.42)**
ICU-mortality				
Annane(2013)[42]	Adults with apparent septic shock (SIRS and acute dysfunction of at least one organ) and no clear source of infection	**7/31**	**10/30**	**0.69 (0.31, 1.53)**
Deliberato(2013)[1]	Adults with suspected or confirmed sepsis	**1/42**	**4/39**	**0.31 (0.05, 1.87)**

Study Details	Population	PCT based algorithm	Clinical judgment alone	RR (95% CI)
		Number of patients with event/number patients	Number of patients with event/number patients	
Layios(2012)[54]	Adults with suspected bacterial infection	**56/258**	**53/251**	**1.03 (0.74, 1.43)**
Infection relapse/recurrence				
Bouadma(2010)[46]	Adults with suspected bacterial infection or who developed sepsis in the ICU	**20/307**	**16/314**	**1.27 (0.68, 2.38)**
Deliberato(2013)[1]	Adults with suspected or confirmed sepsis	**2/42**	**1/39**	**1.55 (0.21, 11.19)**
Liu(2013)[38]	Adults with suspected bacterial sepsis	**3/42**	**1/40**	**2.22 (0.34, 14.34)**
Nobre(2005)[2]	Adults with suspected severe sepsis or septic shock, or who developed sepsis in the ICU	**1/39**	**1/40**	**1.03 (0.11, 9.44)**
Other adverse clinical outcomes				
Annane(2013)[42] **Outcome definition** All-cause mortality (5 day)	Adults with apparent septic shock (SIRS and acute dysfunction of at least one organ) and no clear source of infection	3/31	3/31	1 (0.25, 4.04)
Bouadma(2010)[46] **Outcome definition** All-cause mortality (60 day)	Adults with suspected bacterial infection or who developed sepsis in the ICU	92/307	82/314	1.15 (0.89, 1.48)
Bouadma(2010)[46] **Outcome definition** Multi-drug-resistant infection	Adults with suspected bacterial infection or who developed sepsis in the ICU	55/307	52/314	1.08 (0.77, 1.52)
Nobre(2005)[2] **Outcome definition** Sepsis-related mortality	Adults with suspected severe sepsis or septic shock, or who developed sepsis in the ICU	3/39	2/40	1.44 (0.3, 6.85)
Qu(2012)[57] **Outcome definition** Multi-organ dysfunction syndrome	Adults with severe acute pancreatitis	24/35	25/36	0.99 (0.73, 1.34)
Stolz(2009)[63] **Outcome definition**	Adults with VAP	5/51	7/50	0.72 (0.26, 2.01)

Study Details	**Population**	**PCT based algorithm**	**Clinical judgment alone**	**RR (95% CI)**
		Number of patients with event/number patients	**Number of patients with event/number patients**	
VAP-related clinical deterioration				
Study Details	**Population**	**PCT based algorithm**	**Clinical judgment alone**	**Effect Estimate**
		Median IQR or Mean (sd) (CI) ***(number of participants)***		**Mean difference at follow-up (CI) or p value**
Annane(2013)[42] **Outcome definition** Mechanical ventilation (days)	Adults with apparent septic shock (SIRS and acute dysfunction of at least one organ) and no clear source of infection	11 (5, 25) (*30)*	1 4 (8, 25) *(28)*	p-value=0.56
Layios(2012)[54] **Outcome definition** Mechanical ventilation (days)	Adults with suspected bacterial infection	9.3 (4.9) (*258)*	9.1 (5.4) *(251)*	p-value=0.42
Annane(2013)[42] **Outcome definition** SOFA score (day 5)	Adults with apparent septic shock and no clear source of infection	8 (5, 9) (*30)*	8 (7, 11) *(28)*	p-value=0.61
Bouadma(2010)[46] **Outcome definition** SOFA score (day 28)	Adults with suspected bacterial infection or who developed sepsis in the ICU	1.5 (3) (*307)*	0.9 (2.4) *(314)*	0.6 (0, 1.1)
Layios(2012)[54] **Outcome definition** SOFA score (maximum during ICU stay)	Adults with suspected bacterial infection	9.3 (4.9) (*258)*	9.1 (5.4) *(251)*	p-value=0.42

Data sets included in the meta-analyses are marked in bold

3.2.4 Effectiveness of adding PCT testing to the information used to guide antibiotic therapy in people presenting to the ED with suspected bacterial infections.

Study details

Ten RCTs,[3-5, 44, 47, 49, 53, 58-60] reported in 16 publications,[4, 5, 44, 45, 47-49, 51-53, 58-62, 72] provided data on the effectiveness of adding PCT testing to the information used to guide antibiotic therapy in ED settings. Two studies were conducted in children,[44, 53] and the remainder were conducted in all adult populations.[3-5, 47, 49, 58-60] The presenting characteristics of participants varied between studies, however, all but one[5] were conducted in people with respiratory presentations. Two of the adult studies were conducted in people with a primary diagnosis of LRTI,[49, 60] three were conducted in people with CAP,[47, 58, 59] one included people with chronic obstructive pulmonary disease (COPD) exacerbations,[3] one included people with suspected asthma exacerbations,[4] and the final study was conducted in people with UTI.[5] Of the two studies conducted in children, one included children with LRTI (including CAP and non-CAP LRTI)[44] and the other included children with CAP.[53] All but one of the studies conducted in emergency department settings assessed the effectiveness of adding PCT testing to the information used to guide the initiation of antibiotic treatment,[3, 4, 44, 47, 49, 53, 58-60] and six of these studies also assessed the effectiveness of adding PCT testing to the information used to guide the discontinuation of antibiotic treatment.[44, 47, 53, 58-60] The study conducted in adults with UTI only considered the discontinuation application.[5] This study divided participants into outpatients and those admitted to hospital; for the outpatient population the PCT algorithm informed an initial decision on the fixed length of antibiotic prescription, whereas, for hospitalised participants, the PCT algorithm informed the decision on when to discontinue antibiotics in a manner similar to other studies included in this assessment.[5] Data reported in this section are un-published subgroup data for the hospitalised participants and were supplied as a personal communication (22 October 2014) by a study author (Dr Werner Albrich, Division of Infectious Diseases and Hospital Epidemiology, Kantonsspital St. Gallen, Switzerland); results for the full study population are reported in Appendix 3c and d.[5]

With the exception of two studies published as abstracts,[58, 59] all studies used PCT algorithms with multiple decision thresholds to guide antibiotic treatment in the intervention arm, with final treatment decisions always remaining at the discretion of the treating clinician. The details of the PCT algorithm varied between studies, however, all algorithms (both initiation and discontinuation) discouraged antibiotic use where the PCT level was <0.25 ng/mL; this decision threshold was also used by the two studies published as abstracts; these two studies did not report the timing of PCT measurements.[58, 59] Four studies used the same initiation algorithm: PCT <0.1 ng/mL, antibiotics strongly discouraged; PCT 0.1-0.25 ng/mL, antibiotics discouraged; PCT 0.25-0.5 ng/mL, antibiotics

encouraged; PCT >0.5 ng/mL, antibiotics strongly encouraged,[44, 47, 49, 60] and three of these used the same thresholds to guide discontinuation decisions.[47, 49, 60] Two further studies used a similar initiation algorithm, without the upper threshold (PCT >0.5 ng/mL, antibiotics strongly encouraged).[3, 4] Reported timings for the measurement of PCT were similar; all studies that reported timings included a baseline measurement, [3, 4, 44, 47, 49, 60] three studies reported that repeat measurements were taken at days three and five[44] or days three, five and seven,[5, 60] and three studies reported that repeat measurements were taken at days four, six and eight[47, 49] or every two days until discontinuation.[53] Four studies noted that PCT measuements were repeated at between 6 and 24 hours if antibiotic treatment was initially witheld.[4, 47, 49, 60] Full details of all PCT algorithms are reported in Appendix 3b. All studies compared the intervention, a PCT algorithm combined with clinical decision making, to decisions about antibiotic treatment based on standard clinical decision making without PCT levels; full details of the standard clinical decision making comparator are reported in Appendix 3b.

Eight of the studies conducted in ED settings used the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA) to measure PCT levels,[3-5, 44, 47, 49, 53, 60] and two used an un-specified quantitative PCT assay.[58, 59]

Antibiotic exposure

Seven studies, conducted in adults presenting to the ED with suspected bacterial infections, assessed the effectiveness of adding PCT testing to the information used to guide the initiation of antibiotic treatment,[3, 4, 47, 49, 58-60] All of these studies reported the proportion of patients, in the intervention and control groups, who received antibiotic treatment and all found that adding a PCT algorithm to the information used to decide whether or not to initiate antibiotic treatment was associated with a reduction in antibiotic use, see Table 5 and Figure 13. The summary RR, derived from these seven studies was 0.77 (95% CI: 0.68 to 0.87), (see Figure 13). Where studies reported data for clinical subgroups, a reduction in antibiotic use associated with the PCT algorithm was observed for all groups: severe acute exacerbations of COPD;[49] COPD exacerbations, CAP and acute bronchitis;[60] differing severities of asthma (mild, moderate, severe and critical).[4] One study reported data indicating that the reduction in antibiotic use associated with the PCT algorithm increased with decreasing severity of asthma (critical asthma RR 0.90 995% CI: 0.74 to 1.1), mild asthma RR 0.47 (95% CI: 0.31 to 0.71)), see Appendix 3c.[4] Clinical subgroup data are reported in full in Appendix 3c.

Both of the two studies conducted in children presenting to the ED also reported the proportion of patients, in the intervention and control groups, who received antibiotic treatment.[44, 53] However, these two studies reported contradictory results. The study by Esposito et al, conducted in children

with CAP, found that adding a PCT algorithm to the information used to decide whether or not to initiate antibiotic treatment was associated with a statistically significant reduction in antibiotic use, RR 0.85 (95% CI: 0.79 to 0.91).[53] Subgroup analyses, by severity of CAP, indicated that the PCT algorithm was associated with a greater reduction in antibiotic use for children with mild CAP (RR 0.69 (95% CI: 0.59 to 0.80)) than was the case for children with severe CAP (RR 0.96 (95% CI: 0.92 to 1.01)), see Appendix 3c.[53] In contrast the study by Baer et al, conducted in children with LRTI (including CAP and non-CAP LRTI) reported a trend towards increased antibiotic use when PCT levels were included in decision making, RR 1.12 (95% CI: 0.94 to 1.35),[44] see Table 5. The Baer study also reported data on antibiotic initiation stratified by clinical subgroup (CAP and non-CAP LRTI). These data indicated that, for children presenting with non-CAP LRTI, adding a PCT algorithm to the information used to decide whether or not to initiate antibiotic treatment was associated with a statistically significant increase in antibiotic use (RR 2.71 (95% CI: 1.46 to 5.01), whereas, for children presenting with CAP the PCT algorithm was associated with a trend towards reduction in antibiotic use (RR 0.92 (95% CI: 0.79 to 1.08), see Table 5.[44] When data from the Esposito study were combined with data from the CAP subgroup of the Baer study the summary RR was 0.86 (95% CI: 0.80 to 0.93), see Figure 14; pooling data for the whole population of both studies resulted in a summary RR of 0.97 (95% CI: 0.67, 1.40).

Six studies, conducted in adults presenting to the ED, assessed the effectiveness of adding PCT testing to the information used to decide when to discontinue antibiotic treatment.[5, 47, 49, 58-60] However, only two reported data to allow the calculation of mean difference in the duration of antibiotic therapy between study arms.[47, 49] Both of these studies found that the inclusion of a PCT algorithm in the clinical decision making process resulted in a statistically significant reduction in the mean duration of antibiotic therapy,[47, 49] see Table 5. The summary effect estimate, derived from these two studies, indicated that the addition of a PCT algorithm to the clinical decision making process was associated with reduction in the duration of antibiotic therapy, which did not reach statistical significance, WMD -4.49 days (95% CI: -9.59 to 0.61), (see Figure 15). Four studies, conducted in adults, assessed the effectiveness of adding PCT testing to the information used to decide when to discontinue antibiotic treatment, but reported the outcome as median (IQR) duration of antibiotic therapy, with *p* values for the between group comparison,[5, 60] or mean no estimate of variance.[58, 59] The results of these studies were consistent with the two studies included in the meta-analysis, indication that adding a PCT algorithm to the clinical decision making process was associated with a reduction in the duration of antibiotic therapy in all populations considered, see Table 5. Where studies reported data for clinical subgroups, the observed reduction in duration of antibiotic use associated with use of a PCT algorithm was generally consistent across groups,

(severe acute exacerbations of COPD,[49] and COPD exacerbations, CAP and acute bronchitis)[60] however, effects were less clear cut due to smaller numbers of patients, see Appendix 3d. All studies that reported data on the duration of antibiotic treatment included patients with a zero duration (i.e. those who did not receive antibiotics) in their estimates of mean/median duration and hence are not strictly applicable to assessing the effectiveness of using PCT algorithms to inform the decision on when to discontinue antibiotics. We therefore conducted an additional meta-analysis, excluding participants who did not receive antibiotic treatment (see Appendix 8). The summary effect estimate for patients who received antibiotic treatment (i.e. WMD conditional upon receipt of antibiotics) was 1.48 days (95% CI: -13.64 to 16.59), based on data from two studies;[47, 49] The conditional data from one of these studies was consistent with PCT testing being associated with a decrease in the duration of antibiotic therapy (mean difference -6.23 days (95% CI: -7.54 to -4.92),[49] whilst analysis of conditional data from the second study resulted in a reversal of the observed effect and indicated that PCT testing was associated with an increase in the duration of antibiotic therapy (mean difference 9.18 days (95% CI: 7.75 to 10.61)).[47]

Only one of the studies conducted in children presenting to the ED reported data on duration of antibiotic therapy; this study found that adding a PCT algorithm to the clinical decision making process was associated with a statistically significant reduction in the duration of antibiotic therapy, mean difference -1.8 days (95% CI:-3.1 to -0.5).[44] Subgroup analyses from this study indicated that this reduction was only apparent for children with CAP (mean difference -3.4 days (95% CI: -4.9 to -1.7)); for children with non-CAP LRTI, there was no apparent difference in the duration of antibiotic therapy when a PCT algorithm was used (mean difference was 0.8 days (95% CI: -0.5 to 2.0)), see Appendix 3d.[44]

Figure 13: initiation of antibiotics in adults

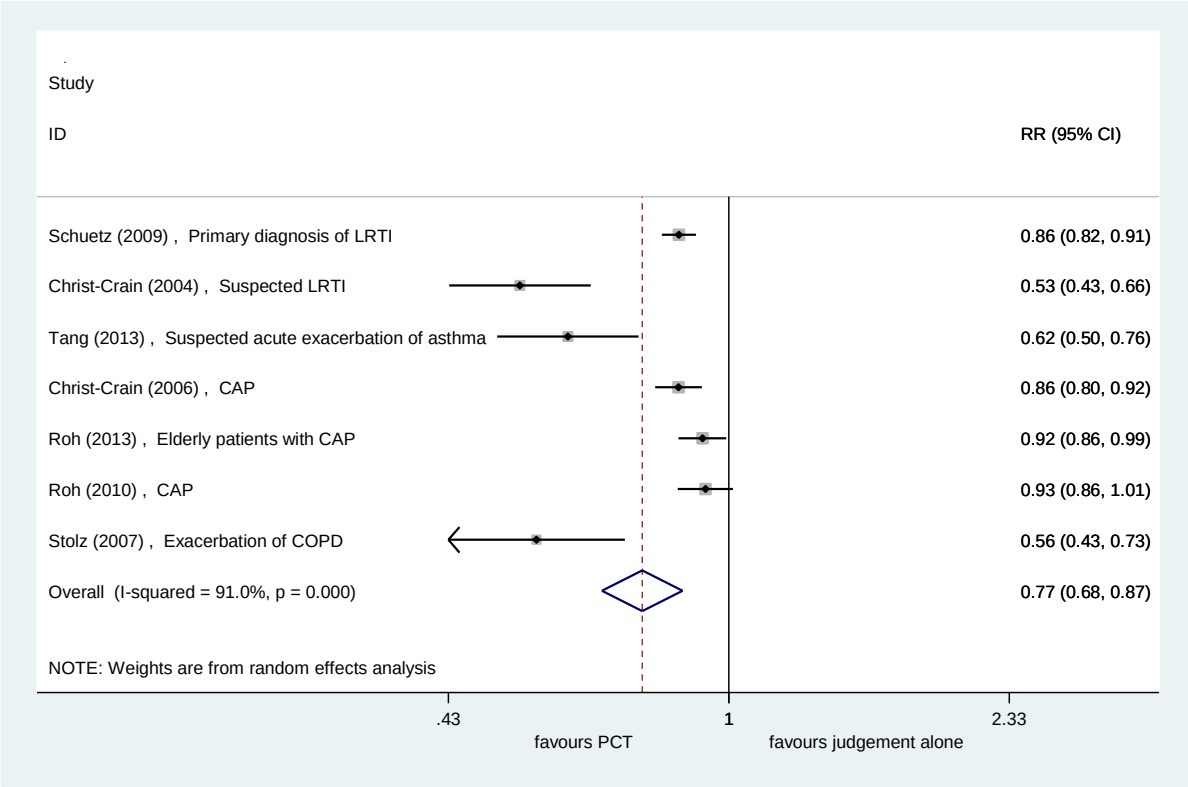


Figure 14: Initiation of antibiotics in children with CAP

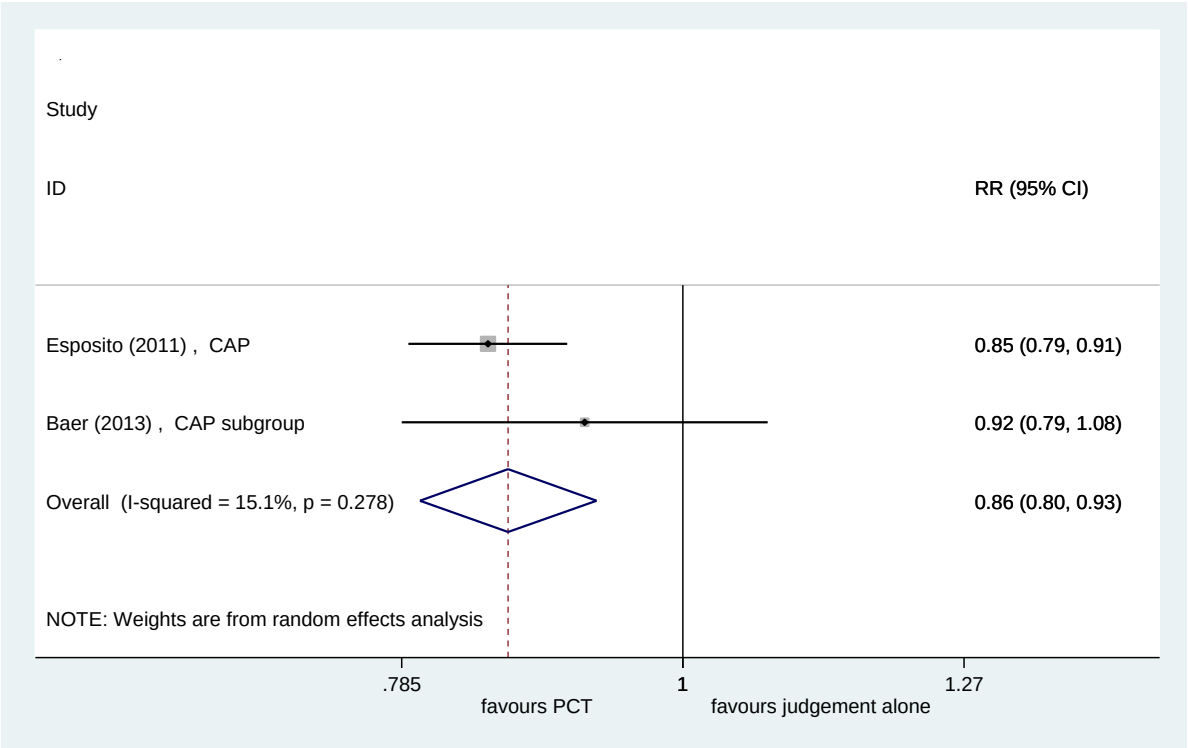


Figure 15: Duration of antibiotics in adults

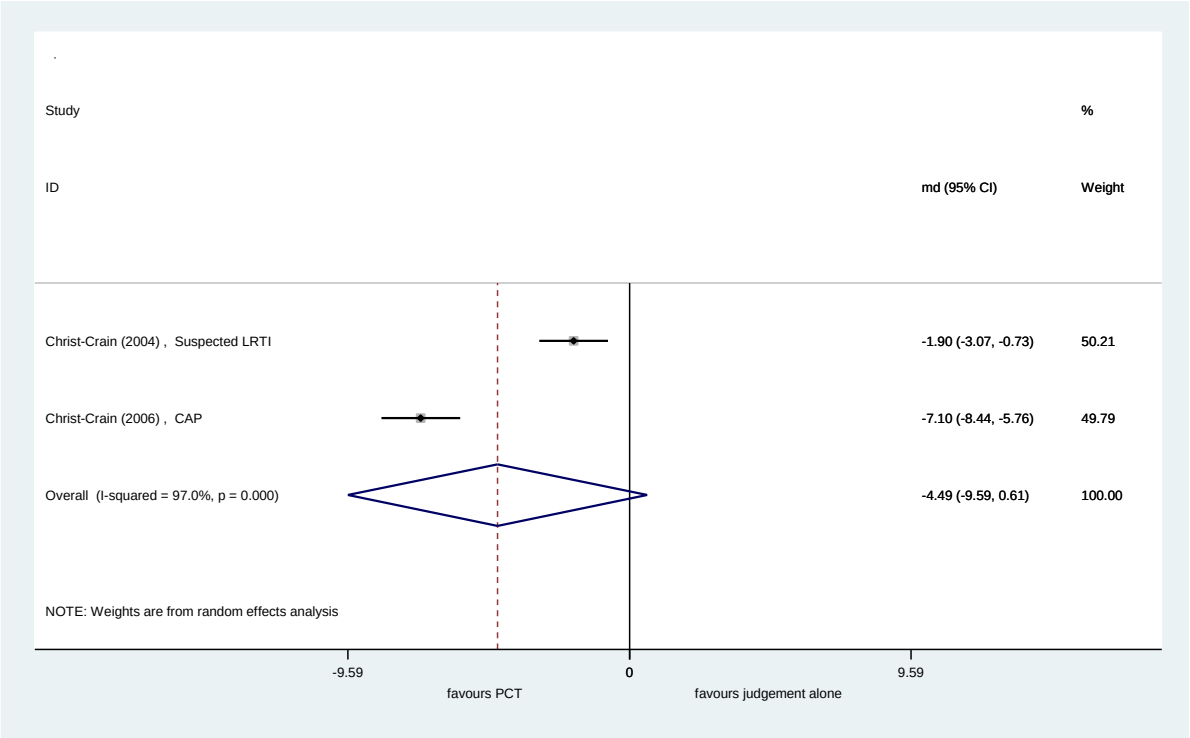


Table 5: Effects on antibiotic exposure of adding PCT testing to standard care in the ED

Study Details	Population	PCT based algorithm	Clinical judgment alone	RR (95% CI)
		Number of patients with event/number patients	Number of patients with event/number patients	
Initiation of antibiotics				
Christ-Crain(2004)[49]	Adults with suspected LRTI	**55/124**	**99/119**	**0.54 (0.43, 0.66)**
Christ-Crain(2006)[47]	Adults with CAP	**128/151**	**149/151**	**0.86 (0.8, 0.92)**
Roh(2010)[58]	Adults with CAP	**55/60**	**61/62**	**0.93 (0.86, 1.01)**
Roh(2013)[59]	Elderly adults with CAP	**73/80**	**83/84**	**0.92 (0.86, 0.99)**
Schuetz(2009)[60]	Adults with LRTI	**506/671**	**603/688**	**0.86 (0.82, 0.91)**
Stolz(2007)[3]	Adults with exacerbations of COPD	**41/102**	**76/106**	**0.56 (0.43, 0.73)**
Tang(2013)[4]	Adults with suspected acute exacerbation of asthma	**59/128**	**95/127**	**0.62 (0.5, 0.76)**
Baer(2013)[44]	Children with LRTI	104/168	93/169	1.12 (0.94, 1.35)
Baer(2013)[44]	Children with non-CAP LRTI	27/60	10/62	2.71 (1.46, 5.01)
Baer(2013)[44]	Children with CAP	**77/108**	**83/107**	**0.92 (0.79, 1.08)**
Esposito(2011)[53]	Children with CAP	**131/155**	**155/155**	**0.85 (0.79, 0.9)**
Duration of antibiotics				
Christ-Crain(2004)[49]	Adults with suspected LRTI	**10.9 (3.6) (*124)***	**12.8 (5.5) (*119)***	**-1.90 (-3.07, -0.73)**
Christ-Crain(2006)[47]	Adults with CAP	**5.8 (5.3) (*151)***	**12.9 (6.5) (*151)***	**-7.10 (-8.44, -5.76)**
Drozdov(2014)[5]*	Adults hospitalised with UTI	[redacted]	[redacted]	[redacted]
Roh(2010)[58]	Adults with CAP	9.2 (*60)*	14.6 *(62)*	p-value=<0.001
Roh(2013)[59]	Elderly adults with CAP	11.2 (*80)*	14.6 *(84)*	p-value=<0.05
Schuetz(2009)[60]	Adults with LRTI	5 (1, 8) (*671)*	9 (6, 11) *(688)*	NR
Baer(2013)[44]	Children with LRTI	4.5 (*168)*	6.3 *(169)*	-1.8 (-3.1, -0.5)

Data sets included in the meta-analyses are marked in bold; * subgroup data supplied by personal communication from Dr Werner Albrich, Division of Infectious Diseases and Hospital Epidemiology, Kantonsspital St. Gallen, Switzerland, 22/10/2014

Resource use and costs

All of the studies conducted in ED settings reported data on one or more resource use or costs outcome.[3-5, 44, 47, 49, 53, 58-60]

Six studies, conducted in adults presenting to the ED with various respiratory conditions, reported data on the effect on duration of hospital stay of adding a PCT algorithm to information used to guide antibiotic treatment, see Table 6.[3, 47, 49, 58-60] The intervention arms of five of these studies used PCT algorithms in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment,[47, 49, 58-60] and in the remaining study only the decision on whether or not to initiate antibiotic therapy was considered.[3] Only two studies reported data to allow the calculation of mean difference in the duration of hospital stay between study arms and neither found a statistically significant between group difference.[47, 49] The summary effect estimate, derived from these two studies, indicated that the PCT algorithm was associated with a trend towards reduction in the duration of hospital stay, weighted mean difference (WMD) -0.80 days (95% CI: -2.37 to 0.78), (see Figure 16). Four further studies assessed the effectiveness of adding PCT testing to the information used to guide antibiotic treatment, but reported duration of hospital stay as mean number of days with no estimate of variance,[58, 59] or median (IQR), with *p* values for the between group comparison.[3, 60] Two of these studies, both conducted in people with CAP[58, 59] reported results indicating that the PCT algorithm was associated with a reduction in the duration of hospital stay (mean duration 9.2 days in the PCT group and 14.6 days in the control group,[58] and mean duration 14.6 days in the PCT group and 16 days in the control group[59]), see Table 6. The remaining two studies, one conducted in people with LRTI[60] and one conducted in people with COPD exacerbations[3] found that use of a PCT algorithm did not affect the median duration of hospital stay, see Table 6. This finding was consistent for all three clinical subgroups (COPD exacerbations, CAP and acute bronchitis) of the LRTI study, see Appendix 3d.[60]

Both of the studies conducted in children presenting to the ED with respiratory conditions assessed the effectiveness of including a PCT algorithm in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment, and both reported data to allow the calculation of mean difference in the duration of hospital stay between study arms, see Table 6.[44, 53] When data from the subgroup of children with CAP from the Baer study[44] were combined with the Esposito study[53] the summary effect estimate indicated that the use of a PCT algorithm was associated with a small reduction in the duration of hospital stay (WMD -0.74 days (95% CI: -1.17 to -0.31)), see Figure 17; this effect was reduced when a summary estimate was calculated using the whole population of both studies (WMD -0.62 days 995% CI: -1.18 to -0.07)).

One ED study reported data on duration of ICU stay.[3] This study was conducted in adults with COPD exacerbations and assessed the effectiveness of adding a PCT algorithm to the information used to decide whether or not to initiate antibiotic treatment; there was no statistically significant difference in the mean duration of ICU stay between the study groups (mean difference -0.40 (95% CI: -1.06 to 0.26).

Two studies, one assessing the effectiveness of adding a PCT algorithm to the information used to decide whether or not to initiate antibiotic treatment in adults with acute asthma exacerbations,[4] and the other assessing the effectiveness of adding a PCT algorithm to the information used to decide when to discontinue antibiotic treatment in adults with UTI,[5] reported hospital re-admission rates. Both studies found no statistically significant between group difference in re-admission rates, see Table 6. Similarly, two studies, both assessing the effectiveness of adding a PCT algorithm to the information used to decide whether or not to initiate antibiotic treatment, in adults with acute asthma exacerbations[4] and adults with COPD exacerbations,[3] both found no statistically significant between group difference in the rate of secondary ED visits, see Table 6.

Two studies by Christ-Crain et al, both assessing the effectiveness including a PCT algorithm in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment, reported that use of the PCT algorithm was associated with reductions in antibiotic costs, see Table 6.[47, 49] These findings are consistent with the reduced rate of antibiotic prescribing and mean duration of antibiotic therapy reported by these two studies and described in *Antibiotic Exposure* section, above.

Figure 16: Duration of hospital stay for adults presenting to the ED

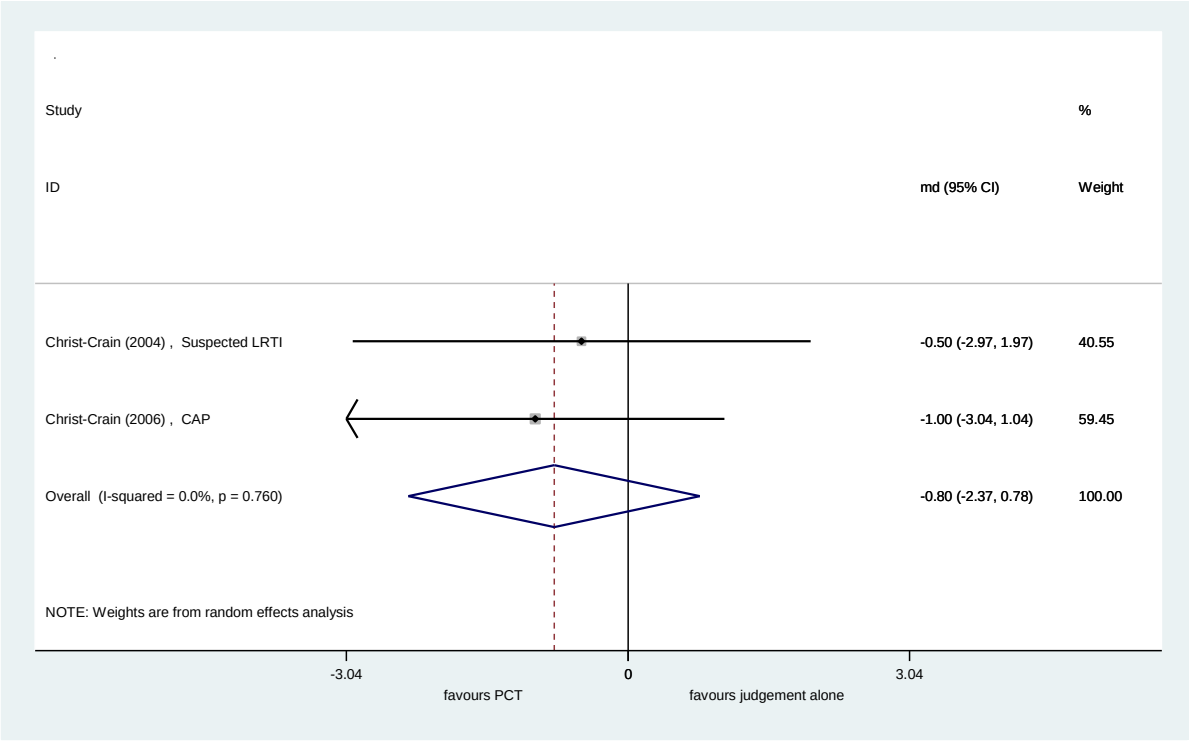


Figure 17: Duration of hospital stay for children with CAP

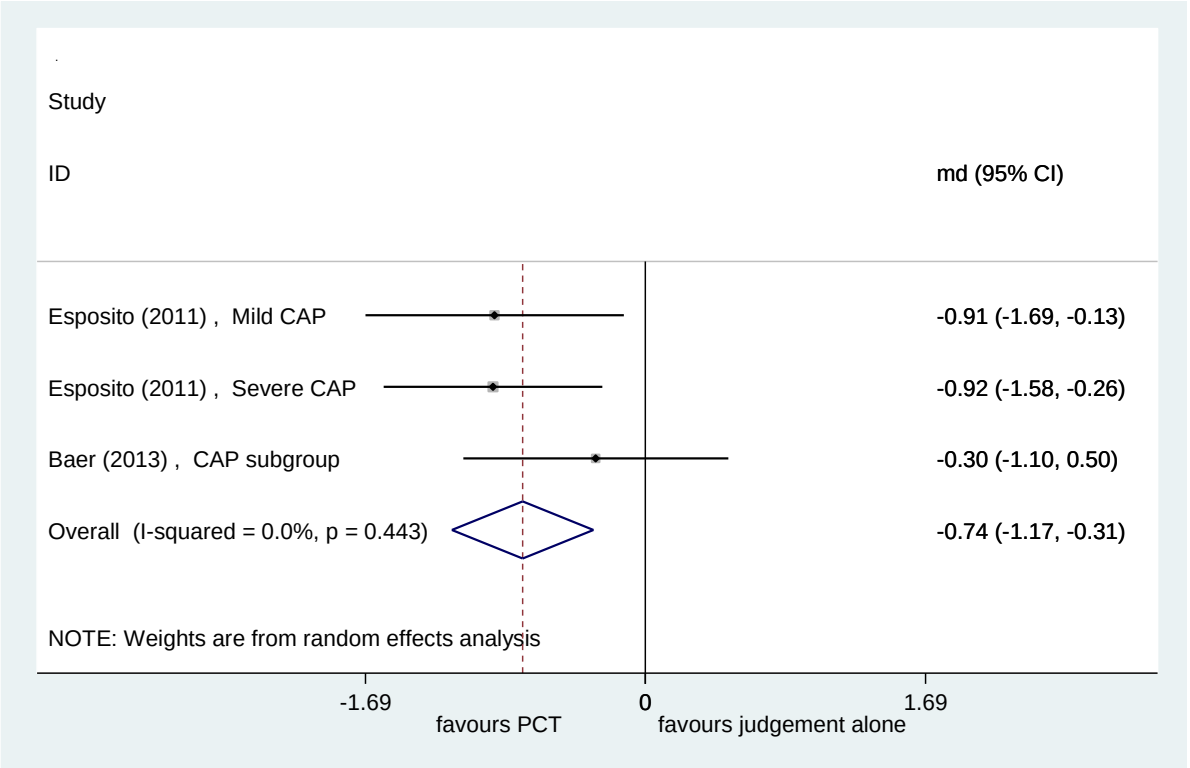


Table 6: Effects on resource use and costs of adding PCT testing to standard care in the ED

Study Details	Population	PCT-based algorithm	Clinical judgement alone	Effect Estimate
		Median IQR or Mean (sd) *(number of participants)**		Mean difference at follow-up (CI) or p value
Duration of hospital stay (days)				
Christ-Crain (2004)[49]	Adults with suspected LRTI	**10.7 (8.9) (*124*)**	**11.2 (10.6) (*119*)**	**-0.50 (-2.97, 1.97)**
Christ-Crain (2006)[47]	Adults with CAP	**12 (9.1) (*151*)**	**13 (9) (*151*)**	**-1.0 (-3.04, 1.04)**
Roh(2010)[58]	Adults with CAP	9.2 *(60)*	14.6 *(62)*	p-value≤0.001
Roh(2013)[59]	Elderly adults with CAP	14.6 *(80)*	16 *(84)*	p-value≥0.05
Schuetz(2009)[60]	Adults with LRTI	8 (4, 12) (*671)*	8 (4, 12) *(688)*	NR
Stolz(2007)[3]	Adults with COPD exacerbation	9 (1, 15) (*102)*	10 (1, 15) *(106)*	p-value=0.960
Baer (2013)[44]	Children with LRTI	2.6 *(168)*	2.7 *(169)*	-0.1 (-0.8, 0.5)
Baer (2013)[44]	Children with non-CAP LRTI	2.5 *(60)*	2.3 *(62)*	0.3 (-0.8,1.2)
Baer (2013)[44]	Children with CAP	**2.6 *(108)***	**2.9 *(107)***	**-0.3 (-1.1, 0.5)**
Esposito (2011)[53]	Children with mild CAP[$]	**4.7 (2.88) *(76)***	**5.61 (1.99) *(79)***	**-0.91 (-1.69, -0.13)**
Esposito (2011)[53]	Children with severe CAP[$]	**5.01 (2.43) *(79)***	**5.93 (1.7) *(76)***	**-0.92 (-1.58, -0.26)**
Duration of ICU stay (days)				
Stolz (2007)[3]	Adults with COPD exacerbation	3.3 (2.7) (*102)*	3.7 (2.1) *(106)*	-0.40 (-1.06, 0.26)
Hospital re-admission				
Drozdov(2014)[5]*	Adults hospitalised with UTI	[redacted]	[redacted]	[redacted]
Tang(2013)[4]	Adults with suspected acute exacerbation of asthma	5/128	8/127	0.64 (0.23, 1.82)
Secondary ED visit				

Study Details	Population	PCT-based algorithm	Clinical judgement alone	Effect Estimate
		Median IQR or Mean (sd) *(number of participants)**		**Mean difference at follow-up (CI) or p value**
Stolz(2007)[3]	Adults with COPD exacerbation	18/102	22/106	0.85 (0.49, 1.48)
Tang(2013)[4]	Adults with suspected acute exacerbation of asthma	6/128	9/127	0.68 (0.26, 1.79)
Antibiotic costs (U.S. dollars)				
Christ-Crain (2004)[49]	Adults with suspected LRTI	96.3 (172.8) (124)	202.5 (250.6) (119)	-106.2 (-160.5, -51.9)
Christ-Crain (2006)[47]	Adults with CAP	100 (33, 186) (*151)*	190 (133, 337) *(151)*	NR

Data sets included in the meta-analyses are marked in bold; * subgroup data supplied by personal communication from Dr Werner Albrich, Division of Infectious Diseases and Hospital Epidemiology, Kantonsspital St. Gallen, Switzerland, 22/10/2014; $ data for both subgroups included in the meta-analysis, to represent the whole study population

Adverse clinical outcomes

All ten studies conducted in ED settings reported data on at least one adverse clinical outcome. [3-5, 44, 47, 49, 53, 58-60] Five of these studies explicitly stated that they aimed to investigate whether the use of PCT in decision making can reduce antibiotic exposure,[3, 5, 44, 47, 60] and three further specified that they aimed to investigate whether a reduction in antibiotic exposures can be achieved without adversely affecting clinical outcomes.[3, 47, 60]

Six studies reported all-cause mortality at various time points, ranging from 14 days to six months. [3, 47, 49, 58-60] The intervention arms of five of these studies used PCT algorithms in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment,[47, 49, 58-60] and in the remaining study only the decision on whether or not to initiate antibiotic therapy was considered.[3] All studies reported no statistically significant difference in mortality rates between participants in the intervention group (antibiotic treatment decisions based on PCT algorithm + clinical judgement) and those in the control group (antibiotic treatment decisions based on clinical judgement alone), (see Table 7). Where studies reported data for clinical subgroups (acute COPD exacerbations,[49] and COPD exacerbations, CAP and acute bronchitis[60]), this finding was consistent across all subgroups, see Appendix 3c. The summary RR derived from all six studies reporting mortality data was 0.95 (95% CI: 0.71 to 1.27), I^2 0%, (see Figure 18). When data from the two studies reporting follow-up (6 months) mortality[3, 59] were pooled the summary RR was 0.85 (95% CI: 0.46 to 1.59).

Neither of the two ED studies conducted in children reported mortality data.[44, 53]

Four studies reported data on rates of admission to the ICU.[3, 47, 49, 60] The intervention arms of three of these studies used PCT algorithms in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment,[47, 49, 60] and in the remaining study only the decision on whether or not to initiate antibiotic therapy was considered.[3] As was the case for all-cause mortality, all studies found no statistically significant between group differences in ICU admissions (see Table 7) and this finding was consistent for clinical subgroups, where reported (see Appendix 3c).[49] The summary RR derived from these four studies was 0.79 (95% CI: 0.59 to 1.05), (see Figure 19).

Neither of the two ED studies conducted in children reported any information on ICU admissions.[44, 53]

Two ED studies, conducted in adults reported inconsistent results with respect to rates of infection relapse/recurrence. One study, conducted in adults hospitalised with UTI found no statistically

significant difference in relapse/recurrence rates between participants in the intervention group (decision to discontinue antibiotics based on PCT algorithm + clinical judgement) and those in the control group (decision to discontinue antibiotics based on clinical judgement alone), (see Table 7).[5] The second study, conducted in adults with LRTI, found that inclusion of a PCT algorithm in both the information used to guide initiation and discontinuation of antibiotics was associated with a statistically significant reduction in infection relapse/recurrence rates (RR 0.57 (95% CI: 0.36 to 0.92)),[60] see Table 7.

One ED study, conducted in children with CAP, reported very low rates of infection relapse/recurrence and a trend towards lower rates in the PCT group (RR 0.23 (95% CI: 0.04 to 1.34)), see Table 7.

One ED study, conducted in adults with LRTI, reported numbers of participants experiencing antibiotic-related adverse events.[60] This study found that including a PCT algorithm in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment was associated with a reduction in antibiotic-related adverse events, (RR 0.71 (95% CI: 0.58 to 0.86)).[60] This finding is consistent with the reduced rate of antibiotic prescribing and mean duration of antibiotic therapy reported by this study and described in *Antibiotic Exposure* section, above.[60]

Both of the ED studies conducted in children reported numbers of participants experiencing antibiotic-related adverse events.[44, 53] Results from the study by Esposito et al, conducted in children with CAP,[53] and from the subgroup of children with CAP from the study by Baer et al,[44] indicated that including a PCT algorithm in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment was associated with a reduction in antibiotic-related adverse events, see Table 7. The summary RR derived from these two data sets was 0.37 (95% CI: 0.04 to 3.49), see Figure 20; when data for all participants in both studies were included in the meta-analysis, the summary RR was 0.40 (95% CI: 0.06 to 2.78).

A variety of other general and disease-specific adverse clinical outcomes were reported by one or more studies, see Table 7. These included composite adverse outcome measures,[47, 60] need for steroids,[4, 60] need for mechanical ventilation,[4] and complications from pneumonia.[44] No study reported a statistically significant difference between the intervention and comparator groups for any adverse clinical outcome assessed.

Figure 18: All-cause mortality in adults presenting to the ED (any time point)

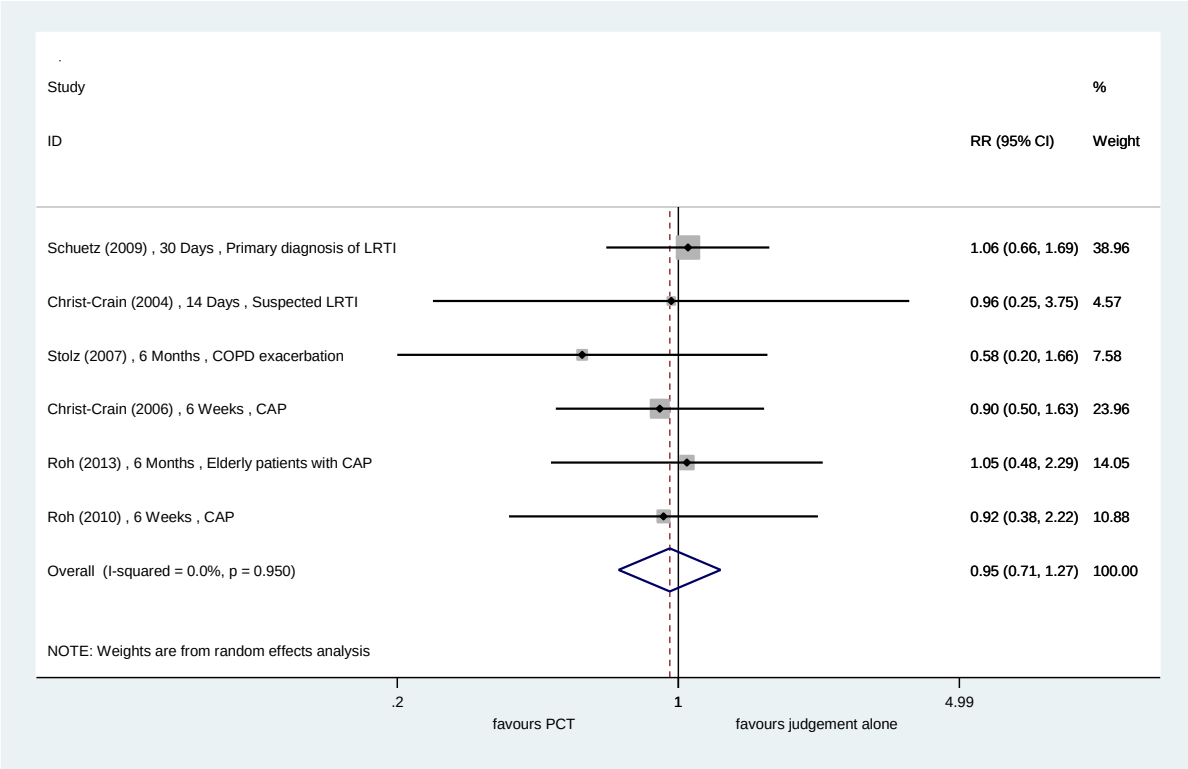


Figure 19: ICU admission for adults presenting to the ED

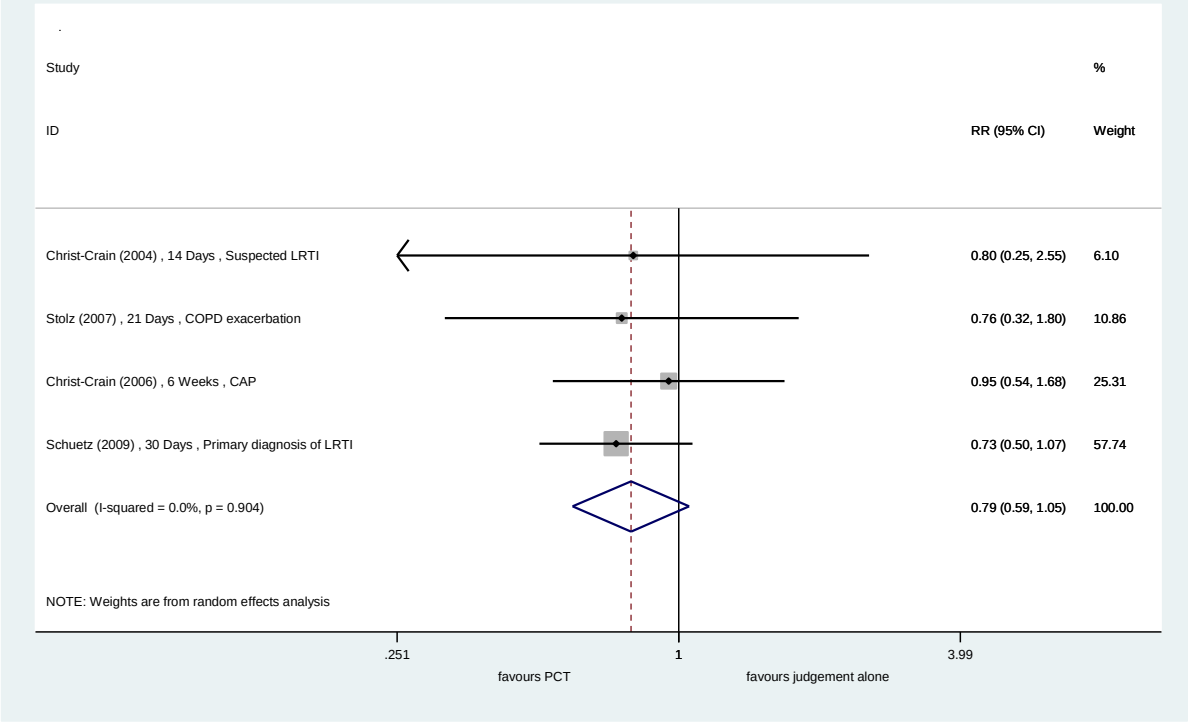


Figure 20: Antibiotic side effects in children with CAP presenting to the ED

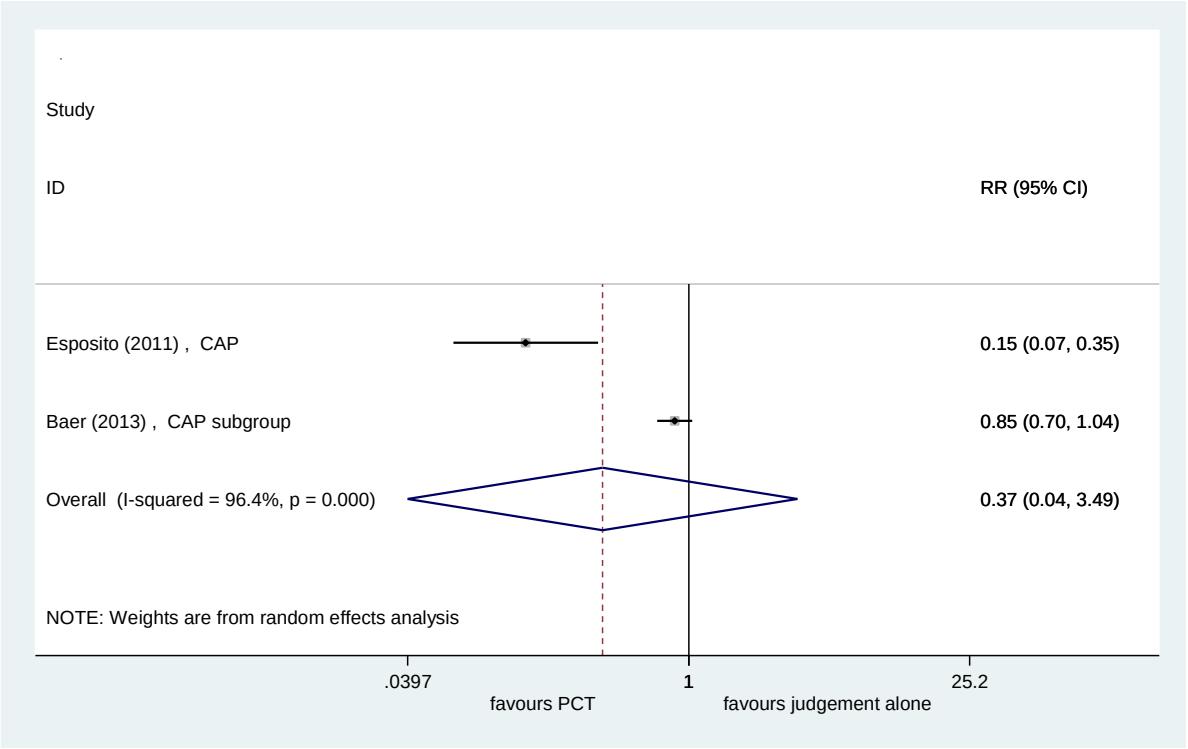


Table 7: Effects on adverse clinical outcomes of adding PCT testing to standard care in the ED

Study Details	Population	PCT based algorithm	Clinical judgment alone	RR (95% CI)
		Number of patients with event/number patients	Number of patients with event/number patients	
All-cause mortality				
Christ-Crain(2004)[49]	Adults with suspected LRTI	**4/124**	**4/119**	**0.96 (0.27, 3.46)**
Christ-Crain(2006)[47]	Adults with CAP	**18/151**	**20/151**	**0.9 (0.5, 1.62)**
Roh(2010)[58]	Adults with CAP	**8/60**	**9/62**	**0.92 (0.39, 2.17)**
Roh(2013)[59]	Elderly adults with CAP	**11/80**	**11/84**	**1.05 (0.49, 2.24)**
Schuetz(2009)[60]	Adults with LTRI	**34/671**	**33/688**	**1.06 (0.66, 1.68)**
Stolz(2007)[3]	Adults with COPD exacerbation	**5/102**	**9/106**	**0.6 (0.22, 1.66)**
ICU admission				
Christ-Crain(2004)[49]	Adults with suspected LRTI	**5/124**	**6/119**	**0.81 (0.27, 2.46)**
Christ-Crain(2006)[47]	Adults with CAP	**20/151**	**21/151**	**0.95 (0.54, 1.67)**
Schuetz(2009)[60]	Adults with LTRI	**43/671**	**60/688**	**0.74 (0.51, 1.07)**
Stolz(2007)[3]	Adults with COPD exacerbation	**8/102**	**11/106**	**0.77 (0.33, 1.79)**
Infection relapse/recurrence				
Drozdov(2014)[5]*	Adults hospitalised with UTI	[redacted]	[redacted]	[redacted]
Schuetz(2009)[60]	Adults with LTRI	25/671	45/688	0.57 (0.36, 0.92)
Esposito(2011)[53]	Children with CAP	1/155	6/155	0.23 (0.04, 1.34)
Antibiotic side effects				
Schuetz(2009)[60]	Adults with LTRI	133/671	193/688	0.71 (0.58, 0.86)
Baer(2013)[44]	Children with LRTI	56/168	57/169	0.99 (0.73, 1.33)
Baer(2013)[44]	Children with non-CAP LRTI	14/60	6/62	2.30 (0.98, 5.42)
Baer(2013)[44]	Children with CAP	**42/60**	**51/62**	**0.85 (0.70, 1.04)**
Esposito(2011)[53]	Children with CAP	**6/155**	**39/155**	**0.16 (0.07, 0.37)**

Study Details	Population	PCT based algorithm	Clinical judgment alone	RR (95% CI)
		Number of patients with event/number patients	Number of patients with event/number patients	
Other adverse clinical outcomes				
Christ-Crain(2006)[47] **Outcome definition** Composite adverse outcome (death, recurrence, relapse, or persistence of clinical, laboratory, and radiologic signs of CAP)	Adults with CAP	24/151	27/151	0.89 (0.54, 1.46)
Schuetz(2009)[60] **Outcome definition** Composite adverse outcome (death, ICU admission, recurrence, re-hospitalisation, or disease-specific complication)	Adults with LTRI	103/671	130/688	0.81 (0.64, 1.03)
Stolz(2007)[3] **Outcome definition** Need for steroids	Adults with COPD exacerbation	89/102	93/106	0.99 (0.9, 1.1)
Tang(2013)[4] **Outcome definition** Need for steroids (repeat need or dose increase)	Adults with suspected acute exacerbation of asthma	6/128	9/127	0.68 (0.26, 1.79)
Tang(2013)[4] **Outcome definition** Need for mechanical ventilation	Adults with suspected acute exacerbation of asthma	8/128	9/127	0.89 (0.36, 2.17)
Baer(2013)[44] **Outcome definition** Complications from pneumonia or other LRTI	Children with LRTI	38/168	33/169	1.16 (0.77, 1.74)

Data sets included in the meta-analyses are marked in bold; * subgroup data supplied by personal communication from Dr Werner Albrich, Division of Infectious Diseases and Hospital Epidemiology, Kantonsspital St. Gallen, Switzerland, 22/10/2014

4. ASSESSMENT OF COST-EFFECTIVENESS

This chapter explores the cost-effectiveness of adding PCT test results to the information available to clinicians treating 1) patients with confirmed or highly suspected sepsis in intensive care settings and; 2) patients presenting to the ED with suspected bacterial infection. More specifically, the following research questions will be addressed:

1. In the ICU, does the addition of PCT testing to current clinical practice, to determine whether to initiate and when to discontinue antibiotic therapy, in adults and children with confirmed or highly suspected sepsis who are being treated, represent a cost-effective use of NHS resources?
2. In the ED, does the addition of PCT testing to current clinical practice, to determine whether to initiate and when to discontinue antibiotic therapy, in adults and children presenting with suspected bacterial infection, represent a cost-effective use of NHS resources?

4.1 Review of economic analyses of PCT assays

4.1.1 Search strategy

Searches were undertaken to locate relevant economic evaluations on adults and children presenting to or being treated at emergency departments and intensive care units with sepsis or bacterial infection.

Economic evaluations

The following databases were searched for relevant studies from 2005 to August 2014:

- NHS Economic Evaluation Database (NHS EED) (Wiley): 2005 - Issue 3 of 4, July 2014
- Health Economic Evaluation Database (HEED) (Wiley): 2005 – 20 August 2014 (http://onlinelibrary.wiley.com/book/10.1002/9780470510933)
- IDEAS via Research Papers in Economics (REPEC) (Internet): 2005 – 20 August 2014 (http://repec.org/)
- EconLIT (EBSCO): 2005 – 20 August 2014

4.1.2 Inclusion criteria

Studies reporting a full economic analysis, with (at least) one of the comparators including PCT testing and with survival and/or Quality-Adjusted Life Years (QALYs) as an outcome measure, were eligible for inclusion.

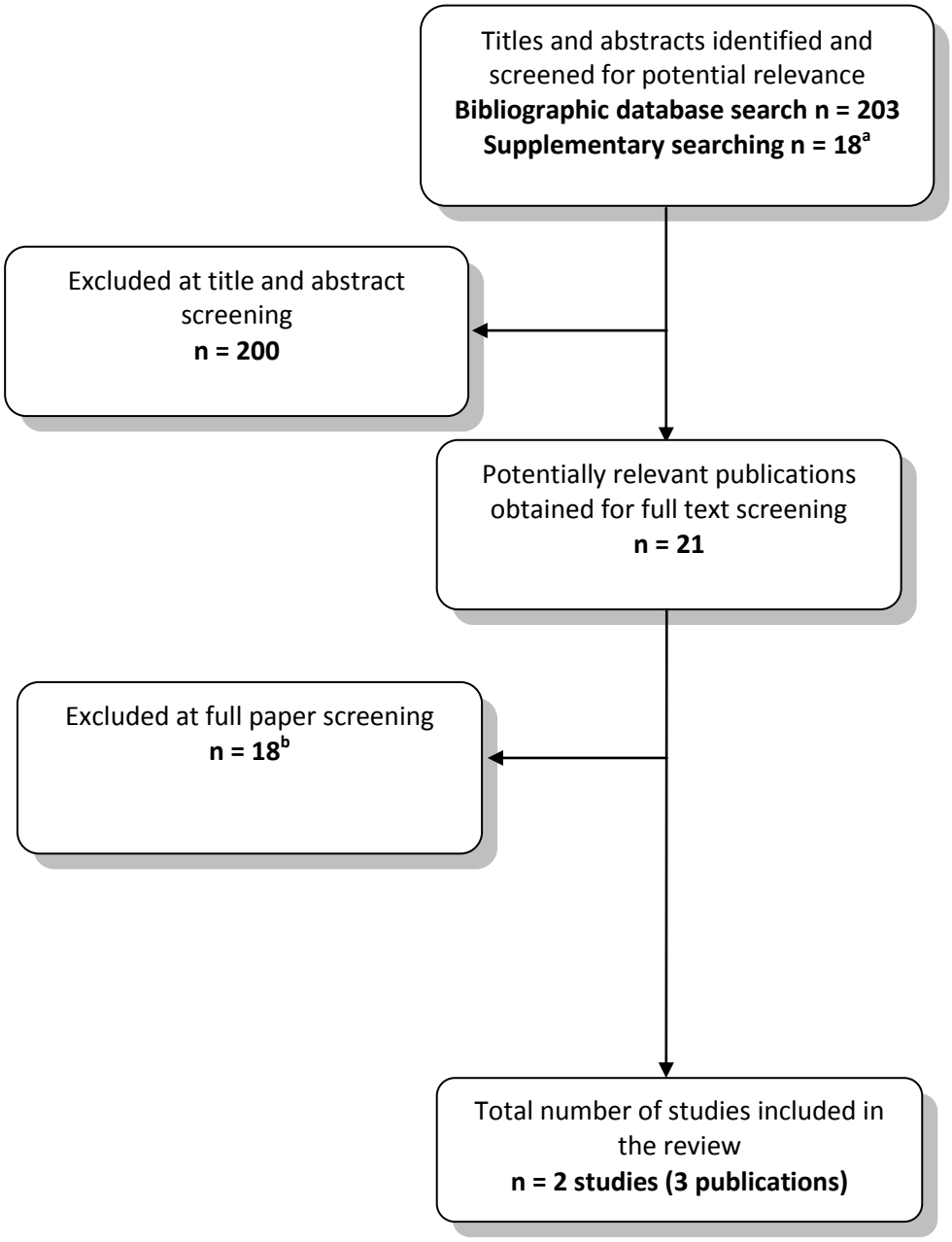
4.1.3 Quality assessment

Included studies were appraised using a quality checklist based on Drummond et al.[73]

4.1.4 Results

The literature search identified 221 records from bibliographic database searches and supplementary searching (e.g. reference/citation checking, additional database searches including the database search for the assessment of clinical effectiveness). The studies identified through supplementary searching also included one potentially relevant unpublished paper sent by bioMérieux. After title and abstract screening, 21 records were considered to be potentially relevant and after full text screening two studies (three publications) were considered eligible for inclusion (Figure 21). One study considered PCT testing for adult patients with acute respiratory tract infections (outpatient setting)[74, 75] and one considered PCT testing for adult patients with community-acquired pneumonia (in-hospital setting)[76]. These studies are described in more detail below and summarised in Table 8. The results of the quality assessment are shown in Table 9.

Figure 21: Flowchart (review of economic analyses)



[a] This includes one unpublished study (Bagshaw J,Clinical Strategic Marketing Manager bioMérieux UK Ltd, [personal communication] 02/10/2014)

[b] Reasons for exclusion: PCT-guided treatment was not considered as comparator (n=9), PCT implementation study (n=1), no comparison is performed (n=1), cost-minimisation study (n=6), cost-effectiveness study reporting other outcomes than QALYs and/or survival (n=1).

Michaelidis et al 2013[74, 75]

The study by Michaelidis and colleagues[74, 75] used a decision tree to analyse the cost-effectiveness of PCT-guided antibiotic therapy versus usual care for outpatient management of acute respiratory tract infections (ARTI) in adults. Two separate analyses were performed using data from two European RCTs separately.[77, 78] The first analysis is based on a study published by Briel et al[77] that considered all adults presenting to an outpatient clinic with an ARTI and judged by their physicians to require an antibiotic prescription. The second analysis was based on a study published by Bukhardt et al[78] that included all adults presenting to an outpatient clinic with an ARTI prior to any decision to initiate antibiotic therapy. PCT-guided antibiotic therapy was both more costly and more effective than care as usual without PCT-guided treatment (Table 8) leading to ICERs of $118,828 and $575,249 per QALY gained for the first and second analyses respectively.

Michaelidis and colleagues[75] also estimated the costs of antibiotic resistant infections attributable to an antibiotic prescription. It was estimated that these costs per antibiotic prescription (in the outpatient setting for management of ARTIs in adults) would range between $0 and $333 with a base case value of $43. These estimated costs of antibiotic resistance are not used in the economic evaluation. It is argued by the authors that these costs can be used as the willingness-to-pay per antibiotic prescription safely avoided and hence that PCT-guided antibiotic therapy would be cost-effective for adults presenting to an outpatient clinic with an ARTI and judged by their physicians to require an antibiotic prescription (probability of being cost-effective: 58%). Using this threshold PCT-guided antibiotic therapy would not be considered cost-effective for all adults presenting to an outpatient clinic with an ARTI prior to any decision to initiate antibiotic therapy (probability of being cost-effective: 3%).

Smith et al 2013[76]

The cost-effectiveness analysis by Smith and colleagues[76] (Table 8) used a decision tree to estimate the cost-effectiveness of PCT-guided antibiotic therapy versus usual care in community-acquired pneumonia (CAP). The analysis considered low-risk CAP patients (Pneumonia Severity Index (PSI) risk class of ≤ 3, or a CURB-65 score of ≤ 2 [CURB-65 is an acronym for five risk factors: **C**onfusion of new onset; Blood **U**rea nitrogen; **R**espiratory rate; **B**lood pressure and; aged **65** or older]) and high-risk CAP patients (PSI risk classes 4 or 5, or CURB-65 scores of ≥ 3). The base case analysis assumed no differences in clinical outcomes or hospital length of stay between the treatment strategies. This assumption was relaxed in the probabilistic sensitivity analysis (using a disutility of 0.2 for hospitalisation). This analysis indicated that PCT-guided antibiotic therapy is both more costly and effective compared with care without PCT-guided treatment and likely to be cost-effective for

willingness to pay values above $90,000 per QALY for low-risk patients using PCT for initiating antibiotic only, $40,000 per QALY when PCT is also used for monitoring antibiotic use for low-risk patients and for high-risk patients this is $170,000 per QALY (using PCT for both initiating antibiotic and monitoring antibiotic use).

4.1.5 Quality assessment and summary of studies in the cost-effectiveness review

Both studies used a short-term decision tree to assess the cost-effectiveness of PCT-guided antibiotic treatment compared to usual care for adults patients with ARTI (outpatient setting) and CAP (in-hospital setting) respectively. Quality assessment of the cost-effectiveness studies revealed caveats in justifications for choices that had been made (e.g. the viewpoint taken, choice of key parameters, exclusion of discounting and ranges for the probabilistic sensitivity analysis) and the description of the benefit valuation. Moreover, Smith et al[76] did not report outcomes per comparator, nor incremental QALYs (Table 9). The results of both cost-effectiveness studies indicated that PCT-guided treatment was more expensive than care as usual (incremental costs ranged between $10 and $54). Moreover, both analyses estimated higher QALYs for PCT-guided antibiotic treatment. For the study by Michaelidis et al[74, 75] this was probably due to a difference in antibiotic treatment duration and hence a difference in the duration of the disutility for antibiotic-associated side effects (estimated based on the EQ5D[79]). Although Smith et al[76] did not report the estimated QALYs, their analyses were likely to have estimated a QALY gain for PCT-guided treatment (given that PCT-guided treatment was more expensive and the ICERs were positive) due to a shorter hospital stay for PCT-guided treatment (disutility during hospital stay was based on the Health and Limitations Index; HALex[80]). In conclusion, depending on the setting, specific use of PCT tests (i.e. for initiating antibiotic and/or monitoring antibiotic use) and the patient population considered, the ICERs found in the literature ranged between $40,000 and $575,249 per QALY gained.

Table 8: Summary of included economic evaluations

	Michaelidis 2013[74, 75]	Smith 2013[76]
Population	Adult patients with ARTI.	Patients with CAP (stratified for low and high-risk patients).
Setting	Outpatient	In-hospital
Time horizon	ARTI treatment episode	Duration of the hospital stay.
Objective	To evaluate the cost-effectiveness of PCT-guided antibiotic therapy in outpatient management of ARTIs in adults	To estimate the cost-effectiveness of PCT protocols in CAP.
Source of effectiveness information	Published literature.	Published literature.
Comparators	PCT-guided treatment vs. no PCT-guided treatment.	PCT-guided treatment vs. no PCT-guided treatment.

	Michaelidis 2013[74, 75]	Smith 2013[76]
Unit costs	antibiotic, PCT test and physician time costs.	antibiotic, PCT test and hospital stay costs.
Main measure of benefit	antibiotic prescriptions safely avoided and QALY.	QALYs
Study type	Cost-effectiveness study (based on evidence synthesis).	Cost-effectiveness study (based on evidence synthesis).
Assumptions	It was assumed that patients with an elevated PCT were prescribed antibiotic. No differences in clinical outcomes between the strategies were assumed, since neither trial revealed significant differences in symptom duration, hospitalisation or death between usual care and PCT testing. For the cost per QALY analysis: it was assumed that 15 % of patients given antibiotic developed antibiotic-associated side effects (duration of 4 days). The utility values of the acute respiratory tract infection and antibiotic-associated side effect health states were assumed to be 1.0, 0.7, and 0.7 respectively.	No differences in-hospital length of stay, hospitalisation costs, or quality of life between PCT and no PCT were assumed.
Perspective	Health care	Third-party payer.
Discount rate	Not mentioned.	Not mentioned.
Uncertainty around cost-effectiveness ratio expressed	Yes, cost-effectiveness acceptability curves.	Yes, cost-effectiveness acceptability curves.
Sensitivity analysis	Yes, all parameter values are varied using one-way sensitivity analysis and threshold analyses were performed.	Yes, all parameter values are varied using one-way sensitivity analysis.
Monetary outcomes	US$	US$
Outcomes per comparator	PCT versus no PCT (*analysis 1*): antibiotic prescriptions: 0.25 vs. 0.97 QALYs lost: 0.00746 vs. 0.00765 Costs: $51 vs. $29 PCT versus no PCT (*analysis 2*): antibiotic prescriptions: 0.14 vs. 0.37 QALYs lost: 0.00743 vs. 0.00749 Costs: $49 vs. $15	PCT versus no PCT: QALYs: values not mentioned Costs: values not mentioned
Summary of incremental analysis	Analysis 1: PCT resulted into 0.72 less antibiotic prescriptions and additional costs of $22 per patient, resulting in an ICER of $31 per antibiotic prescription safely avoided. Moreover, PCT remained more	Estimated QALYs were not reported. Moreover, PCT-guided treatment was considered more costly ($22 for low-risk patients using PCT for initiating antibiotic, $10 for low-risk patients using PCT for antibiotic initiation and

	Michaelidis 2013[74, 75]	Smith 2013[76]
	expensive in all sensitivity analyses except when the antibiotic cost >$61 or the PCT testing cost <$17 (in which PCT became dominant). Moreover, PCT resulted in 0.00019 QALYs gained leading into an ICER of $118,828 per QALY gained. Analysis 2: PCT resulted into 0.23 less antibiotic prescriptions and additional costs of $34 per patient, resulting in an ICER of $149 per antibiotic prescription safely avoided. Moreover, PCT remained more expensive in all sensitivity analyses except when the antibiotic cost >$61 or the PCT testing cost <$17 (in which PCT became dominant). Moreover, PCT resulted in 0.00006 QALYs gained leading into an ICER of $575,249 per QALY gained.	monitoring and $54 for high-risk patients using PCT for antibiotic initiation and monitoring). ICERs (calculated based on the probabilistic sensitivity analyses) showed that PCT-guided antibiotic therapy is likely to be cost-effective for willingness to pay values above $90,000 per QALY for low-risk patients using PCT for initiating antibiotic only, $40,000 per QALY when PCT is also used for monitoring antibiotic use for low-risk patients and for high-risk patients this is $170,000 per QALY (using PCT for both initiating antibiotic and monitoring antibiotic use). Results were most sensitive to variations in: antibiotic cost, the likelihood that antibiotic therapy was initiated less frequently or over shorter durations, and the likelihood that physicians were non-adherent to PCT protocols.

Abbreviations: PCT, procalcitonin; ARTI, acute respiratory tract infections; QALY, quality adjusted life-years; CAP, community-acquired pneumonia

Table 9: Study quality checklist for included full papers

	Michaelidis 2013[74, 75]	Smith 2013[76]
Study design		
The research question is stated	√	√
The economic importance of the research question is stated	√	√
The viewpoint(s) of the analysis are clearly stated and justified	×	×
The rationale for choosing alternative programmes or interventions compared is stated	√	√
The alternatives being compared are clearly described	√	√
The form of economic evaluation used is stated	√	√
The choice of form of economic evaluation is justified in relation to the questions addressed	√	√
Data collection		
The source(s) of effectiveness estimates used are stated	√	√
Details of the design and results of effectiveness study are given (if based on a single study)	√	√
Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	NA	NA
The primary outcome measure(s) for the economic evaluation are clearly stated	√	√
Methods to value benefits are stated	×	×
Details of the subjects from whom valuations were obtained were	×	×

	Michaelidis 2013[74, 75]	Smith 2013[76]
given		
Productivity changes (if included) are reported separately	NA	NA
The relevance of productivity changes to the study question is discussed	×	×
Quantities of resource use are reported separately from their unit costs	×	√
Methods for the estimation of quantities and unit costs are described	√	√
Currency and price data are recorded	√	√
Details of currency of price adjustments for inflation or currency conversion are given	NA	NA
Details of any model used are given	√	√
The choice of model used and the key parameters on which it is based are justified	×	×
Analysis and interpretation of results		
Time horizon of costs and benefits is stated	√	√
The discount rate(s) is stated	NA	NA
The choice of discount rate(s) is justified	NA	NA
An explanation is given if costs and benefits are not discounted	×	×
Details of statistical tests and confidence intervals are given for stochastic data	√	√
The approach to sensitivity analysis is given	√	√
The choice of variables for sensitivity analysis is justified	√	√
The ranges over which the variables are varied are justified	×	√
Relevant alternatives are compared	√	√
Incremental analysis is reported	√	√
Major outcomes are presented in a disaggregated as well as aggregated form	×	×
The answer to the study question is given	√	√
Conclusions follow from the data reported	√	√
Conclusions are accompanied by the appropriate caveats	×	√

Abbreviations: NA, not applicable

4.1.6 Overview of potentially relevant excluded studies

In addition to the included studies described above, seven potentially relevant studies that compared PCT testing with no PCT testing were excluded as they were either cost-minimisation studies[47, 81-85] or a cost-effectiveness analysis[86] using other outcomes than survival or QALYs. For completeness, an overview of these studies is provided in Table 10.

As was the case for the two cost-effectiveness analyses included in the review, the studies described in Table 10 were focused on short-term costs (and benefits). The comparison was PCT-guided treatment versus non PCT-guided treatment in all studies and considered (adult) sepsis patients on the ICU,[81, 83, 84] hospitalised children with pneumonia,[82] adult patients admitted to the hospital with LRTI,[86] adult patients with suspected CAP admitted to the ED[47] and patients with suspected ARTI in

three different settings.[85] In contrast to the two full economic evaluations included in the review, the cost-minimisation studies in the more severe populations (sepsis, ARTI and pneumonia) reported cost-savings when using PCT-guided treatment.[81-85] Whereas the two studies that focused on adult patients admitted to the hospital with LRTI[86] and adult patients with suspected CAP presenting to the ED[47] report additional costs when using PCT-guided treatment. The cost-effectiveness analysis by Cleves et al[86] reported an ICER for LRTI patients of £51 per additional percentage of correctly treated patients with antibiotics.

Table 10: Summary of excluded potentially relevant papers

	Deliberato 2013[81]	Dies-Padrisa 2012[82]	Wilke 2011[83]	Heyland 2011[84]
Population	Adult patients with microbiologically confirmed infections with sepsis, severe sepsis or septic shock.	Hospitalised children with clinical severe pneumonia.	Sepsis patients	Critically ill adult patients with infection.
Setting	ICU	In-hospital	ICU	ICU
Time horizon	From two days before sepsis diagnosis until 14 days after or after ICU discharge.	Diagnosis only	Not mentioned.	Not mentioned.
Objective	To assess whether a decrease in PCT levels could be used to reduce the duration of antibiotic therapy in intensive care unit patients with a proven infection without risking a worse outcome.	To evaluate the benefits of using PCT and CRP as pre-screening tools to predict blood culture positivity among Mozambican children with clinical severe pneumonia.	To determine possible savings in medication costs and costs for ICU-treatment using DRG data and favourable effects of a PCT-based treatment algorithm in sepsis patients.	To evaluate the effect of a PCT guided antibiotic strategy on clinical and economic outcomes.
Source of effectiveness information	Prospective randomised trial conducted in the ICU of a tertiary care, private hospital in São Paulo, Brazil.	Clinical trial.	German national minimal basic datasets and published literature.	Published literature.
Comparators	PCT-guided treatment vs. no PCT-guided treatment.	PCT-guided treatment vs. no PCT-guided treatment.	PCT-guided treatment vs. no PCT-guided treatment.	PCT-guided treatment vs. no PCT-guided treatment.
Unit costs	Antibiotic treatment and PCT costs.	Blood cultures measurement and PCT costs.	ICU costs, treatment on the regular ward, Main treatment related costs (e.g. surgery or cardiologic interventions). All costs were based on diagnoses related groups (DRGs).	antibiotic treatment, intravenous administration and PCT test costs. PCT costs ($49.42 per test) include assay material, reagents, technician time, purchase, maintenance of a bench top analyser, and overhead.
Main measure of	Duration of antibiotic therapy; ICU length of stay, hospital	No outcomes besides diagnostic accuracy.	No benefits are considered.	Duration of antibiotic utilisation, hospital mortality, 28 day

	Deliberato 2013[81]	Dies-Padrisa 2012[82]	Wilke 2011[83]	Heyland 2011[84]
benefit	length of stay.			mortality, ICU length of stay, hospital length of stay, recurrent or relapsing infections.
Study type	Cost-minimisation study (trial-based using the per-protocol analysis patient group (N=51)).	Cost-minimisation study (trial-based)	Cost-minimisation study (based on evidence synthesis).	Cost-minimisation study (based on evidence synthesis).
Assumptions	NA	NA	NA	NA
Perspective	Not mentioned.	Not mentioned.	Not mentioned.	Hospital perspective
Discount rate	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.
Uncertainty around cost-effectiveness ratio expressed	NA	NA	NA	NA
Sensitivity analysis	No	Yes, different costs for PCT testing	No	Yes, assuming different antibiotic costs.
Monetary outcomes	US$	US$	€	CAN$
Outcomes per comparator	PCT versus no PCT: Duration of antibiotic therapy: 9.0 vs. 13.0 days ICU length of stay: 3.5 vs. 4.0 days hospital length of stay: 10.5 vs. 14.0 days Costs: $977.40 vs. $1,367.65	PCT versus no PCT: Costs: $60-$67 vs. $72.5 (PCT test cost = $30) Costs: $40-$47 vs. $72.5 (PCT test cost = $10)	PCT versus no PCT: ICU costs: €17,940 vs. €18,826 Non-ICU costs: €6084 vs. €6220	PCT versus no PCT: Mean differences for duration of antibiotic utilisation, ICU length of stay, hospital length of stay are: -2.14[b], -1.50 and -1.86 respectively. Relative risks for hospital mortality, 28 day mortality and recurrent or relapsing infections are 1.06, 0.98 and 1.26 respectively. Costs: $2,597.94 vs $3,068.56
Summary of incremental	PCT resulted into savings of $388.25 per patient.	PCT lowered overall diagnosis costs by $5.5-$12.5 (PCT test	PCT resulted into savings of €886 (ICU) and €136 (non-ICU) per	PCT resulted in savings of $470.62 per patient. This was

	Deliberato 2013[81]	Dies-Padrisa 2012[82]	Wilke 2011[83]	Heyland 2011[84]
analysis	No incremental cost-effectiveness analyses are presented.	cost = $30) and $25.5-$32.5 (PCT test cost = $10) per patient. No incremental cost-effectiveness analyses are presented.	patient. No incremental cost-effectiveness analyses are presented.	$1,134.86 if more expensive antibiotic would be used while cheaper antibiotic would result in PCT becoming $193.64 more expensive than no PCT. No incremental cost-effectiveness analyses are presented.[a]

Abbreviations: ICU, intensive care unit; PCT, procalcitonin; NA, not applicable; vs, versus; MD: mean difference; HR: hazard ratio, CRP, C-reactive protein; LRTI, lower respiratory tract infections; ARTI, acute respiratory tract infection; CAP, community-acquired pneumonia

[a] Because the results of the meta-analysis demonstrate no difference in mortality, length of stay, or recurrent infections, a cost-minimisation analysis that considers only the acquisition costs of antibiotics, administration costs of intravenous antibiotics, and costs of the PCT test was considered appropriate.

[B] Statistically significant

Table 10 (contd): Summary of excluded potentially relevant papers

Study details	Cleves 2010[86]	Christ-Crain 2006[47]	Schuetz[85] (Bagshaw J, Clinical Strategic Marketing Manager bioMérieux UK Ltd, [personal communication] 02/10/2014)
Population	Adult patients admitted to the hospital with LRTI.	Adult patients with suspected CAP.	Patients with suspected ARTI.
Setting	In-hospital	Emergency department	Inpatient hospital setting (not in the ICU); ICU; outpatient clinic or emergency department.
Time horizon	Not mentioned (probably in-hospital period)	Up to 6 weeks.	Based on the clinical studies included in the meta-analytic data, the costs and outcomes of each ARTI episode is assessed over a 30-day period. Total costs and events are annualised based on the incidence of each condition and likelihood of treatment success and intensity.
Objective	To analyse the cost-effectiveness of PCT to identify bacterial infection in LRTI.	To assess PCT guidance for the initiation and duration of antibiotic therapy in CAP.	To assess the economic impact of adopting

Study details	Cleves 2010[86]	Christ-Crain 2006[47]	Schuetz[85] (Bagshaw J, Clinical Strategic Marketing Manager bioMérieux UK Ltd, [personal communication] 02/10/2014)
			PCT testing among patients with suspected ARTI
Source of effectiveness information	Published literature.	Randomised, controlled, open intervention trial.	Patient-level meta-analysis data of randomised trials.
Comparators	PCT-guided treatment vs. no PCT-guided treatment.	PCT-guided treatment (n=151) vs. no PCT-guided treatment (n=151).	PCT-guided treatment vs. no PCT-guided treatment.
Unit costs	Antibiotic and PCT test costs.	Antibiotic treatment and PCT costs (including assay material, reagents, technicians' time for processing specimens, and purchase and maintenance of durable laboratory equipment).	Antibiotic treatment, PCT costs and costs attributable to antibiotic resistance.
Main measure of benefit	Correctly treated cases (with antibiotic).	Antibiotic use, measures of laboratory and clinical outcome recorded on Days 4, 6, and 8 and at follow-up after 6 weeks.	No benefits are considered.
Study type	Cost-effectiveness study (based on evidence synthesis).	Cost-minimisation study (trial-based)	Cost-minimisation study (based on evidence synthesis).
Assumptions	To use a single value (76%) for both sensitivity and specificity. Moreover, it is assumed that doctors prescribe antibiotic based on the PCT test alone.	NA	It was assumed that the mean baseline number of antibiotic days corresponds to the average length of stay for a typical hospitalisation. Physician time associated with interpreting the PCT test was not included in the model because the associated costs have been found to be negligible.
Perspective	Not mentioned.	Not mentioned.	US payer perspective.
Discount rate	Not mentioned.	Not mentioned.	Not mentioned.
Uncertainty around cost-	No	NA	NA

Study details	Cleves 2010[86]	Christ-Crain 2006[47]	Schuetz[85] (Bagshaw J, Clinical Strategic Marketing Manager bioMérieux UK Ltd, [personal communication] 02/10/2014)
effectiveness ratio expressed			
Sensitivity analysis	Yes, different sensitivity and specificity values, LRTI prevalence and antibiotic costs.	Yes, Yes, assuming different antibiotic and PCT costs and assuming less than 3.5 PCT measures (base case value) per patient.	Yes, one-way sensitivity analyses (+/- 20% for key parameters) and lowering the antibiotic initiation rate.
Monetary outcomes	£	US$ (converted from CHF)	US$
Outcomes per comparator	PCT versus no PCT: Correctly treated: 76% vs. 34% Costs: £35.72 vs. £14.30	PCT versus no PCT: antibiotic was withheld on admission for 15% vs 1%. The antibiotic discontinuation was higher in the PCT group (HR: 3.2[b]). antibiotic duration: 5 vs. 12 days. Costs: $290 vs. $190.	PCT versus no PCT: Costs: Inpatient hospital setting: $416 vs. $555 ICU: $616 vs. $755 Outpatient clinic and emergency department: $105 vs. $204 Weighted average: $977 vs. $1,368 per patient (all calculated based on Table 5 retrieved from this paper).
Summary of incremental analysis	PCT resulted into additional costs of £21.42 per patient (despite lower antibiotic costs) and yielded 42% extra patients that are correctly treated with antibiotic. This resulted in an ICER of £51 per additional % of correctly treated patients. This varied between £45-£120 in the sensitivity analyses.	PCT resulted into additional costs of $100 per patient (despite lower antibiotic costs). PCT would be cost-saving if the PCT costs are below $25. No incremental cost-effectiveness analyses are presented.	PCT resulted into savings of $103 per patient (weighted average calculated based on Table 5 retrieved from this paper). PCT remained cost saving in the sensitivity analyses (it was most sensitive to antibiotic costs). No incremental cost-effectiveness analyses are presented.

Abbreviations: ICU, intensive care unit; PCT, procalcitonin; NA, not applicable; vs, versus; MD: mean difference; HR: hazard ratio, CRP, C-reactive protein; LRTI, lower respiratory tract infections; ARTI, acute respiratory tract infection; CAP, community-acquired pneumonia

[a] Because the results of the meta-analysis demonstrate no difference in mortality, length of stay, or recurrent infections, a cost-minimisation analysis that considers only the acquisition costs of antibiotics, administration costs of intravenous antibiotics, and costs of the PCT test was considered appropriate.

[B] Statistically significant

4.2 Review of health-related quality of life studies

4.2.1 Search strategy

Searches were undertaken to locate relevant utility value studies on adults and children presenting to or being treated at emergency departments and intensive care units with sepsis or bacterial infection.

Utility values

The following databases were searched for relevant studies from database inception date to September 2014:

- MEDLINE (OvidSP): 1946 - August Week 3 2014
- MEDLINE In-Process Citations and Daily Update (OvidSP): up to 2 September 2014
- Embase (OvidSP): 1974 to 2 September 2014
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to Issue 8 of 12, August 2014
- Health Technology Assessment (HTA) Database (Wiley): up to Issue 3 of 4, July 2014
- PubMed (http://www.ncbi.nlm.nih.gov/pubmed): up to 3 September 2014
- PROQOLID (Internet) (http://www.proqolid.org/): up to 3 September 2014

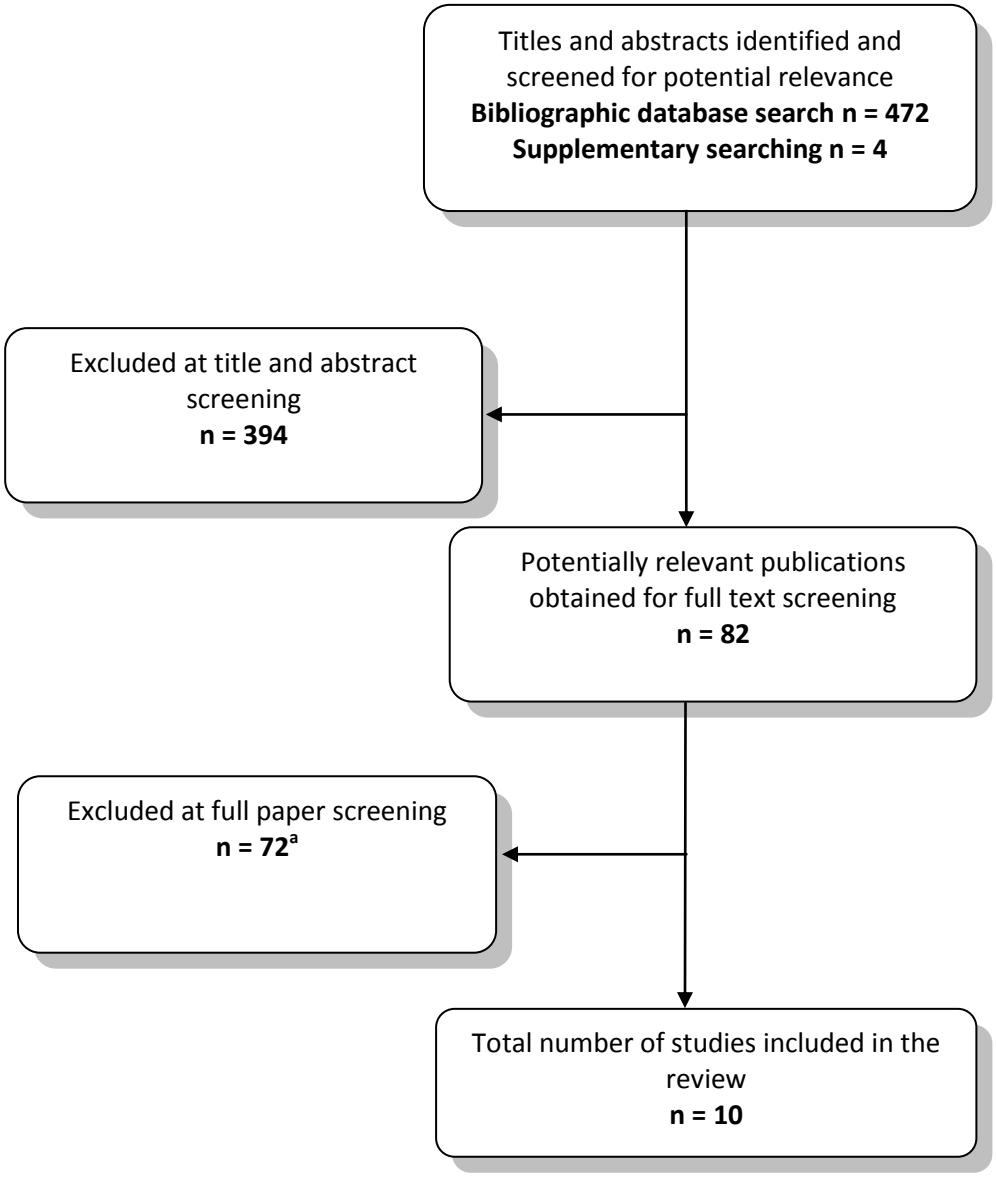
4.2.2 Inclusion criteria

Studies reporting on health-related quality of life (HRQoL), in terms of utility scores, for patients with confirmed/highly suspected sepsis in intensive care settings or patients presenting to the ED with suspected bacterial infection were eligible for inclusion.

4.2.3 Results

The literature search identified 476 records (472 through database searches and four through supplementary searching). After title and abstract screening, 82 potentially relevant records were identified and after full text screening nine studies (10 papers) were considered eligible for inclusion (Figure 22). This included one study conducted for paediatric patients at the ED,[87] one study conducted in a paediatric ICU[88] and six studies conducted in adult patients at the ICUs.[89-95] Moreover, for one study[96] (abstract only) the specific setting (other than in-hospital) was not stated but the study was likely to have been conducted in an ICU setting, as it included patients with severe sepsis of presumed infectious origin; we have therefore assumed that this study was conducted in an ICU setting. The HRQoL studies are described in more detail below and summarised in Appendix 6.

Figure 22: Flowchart (review of HRQoL studies)



[a] Reasons for exclusion: duplicate (n=1), protocol (n=1), no original/relevant utility data reported (n=63), wrong setting/population (n=7)

Adult intensive care unit[89-96]

All seven studies that considered adult patients with sepsis, who were being treated in the ICU, used the EQ5D to elicit utility scores. Only one[96] of these studies (abstract only) reported short-term utility scores for a sepsis patient group (n=93) that stayed in hospital (56% of the patients were in the hospital at day 30). This study reported utility values for 30, 60, 90 and 180 days after admission of 0.53, 0.62, 0.68 and 0.69 respectively. Long-term follow-up utility values found in the literature were 0.84[92] and 0.67[95] at six months, 0.75[93] at 1.4 years, 0.72[94] at two years, 0.64[91] at 3.5 years and 0.68[91] at five years. One study reported a utility value of 0.68[89, 90] for patients one year or later after

discharge. The long-term utility values varied substantially between studies. These differences between the studies may be caused by context related factors (e.g. patient mix, countries and valuation functions). Studies with longitudinal data, tended to show an increasing utility score over time (i.e. positive correlation between utility score and time since ICU admission). The Scottish study by Cuthbertson et al[91] probably provides the most representative long-term utilities for the UK population (0.64 at 3.5 years and 0.68 at five years).

With regard to the long-term impact of sepsis ICU admission on HRQoL, the Finnish study by Karlsson et al[93] concluded (based on the intention-to-treat population) that there is a long-term utility decrement due to sepsis ICU admission, as the utility value at 17 months was lower than utility values measured before sepsis. It should be noted, however, that in most cases the first questionnaire (at the ICU considering HRQOL before acute critical illness) was filled out by a next of kin.

Paediatric intensive care unit[88]

A Dutch study measured long-term HRQoL (median follow-up interval: 10 years) using the Health Utilities Index Mark (HUI) in patients who experienced meningococcal septic shock and were admitted to the paediatric ICU (median age at admission: three years). The utility values reported by the respondents (n=120) were 0.82 (HUI3) and 0.88 (HUI2) and were considered to be lower compared with a representative sample of 1,435 Dutch school children aged between 5 and 13 years (HUI2: 0.93 and HUI3: 0.94).

Paediatric emergency department[87]

In a study conducted in the United States, a total of 94 parents who presented at the paediatric ED with their children (aged between 3 and 36 months) were asked to elicit utility values to eight health state descriptions for their children using the standard gamble method. These health states and their valuations were: death (0.02), meningitis with severe brain damage (0.39), meningitis with minor brain damage (0.74), meningitis with deafness (0.86), meningitis with recovery (0.98); hospitalisation for antibiotic (0.99); local infection (0.99) and blood drawn (1.00). It was concluded that extremely high utility values were found for health states without permanent sequelae (blood drawn, local infection, hospitalisation for antibiotic and meningitis with recovery).

4.3 Model structure and methodology

4.3.1 Model structure

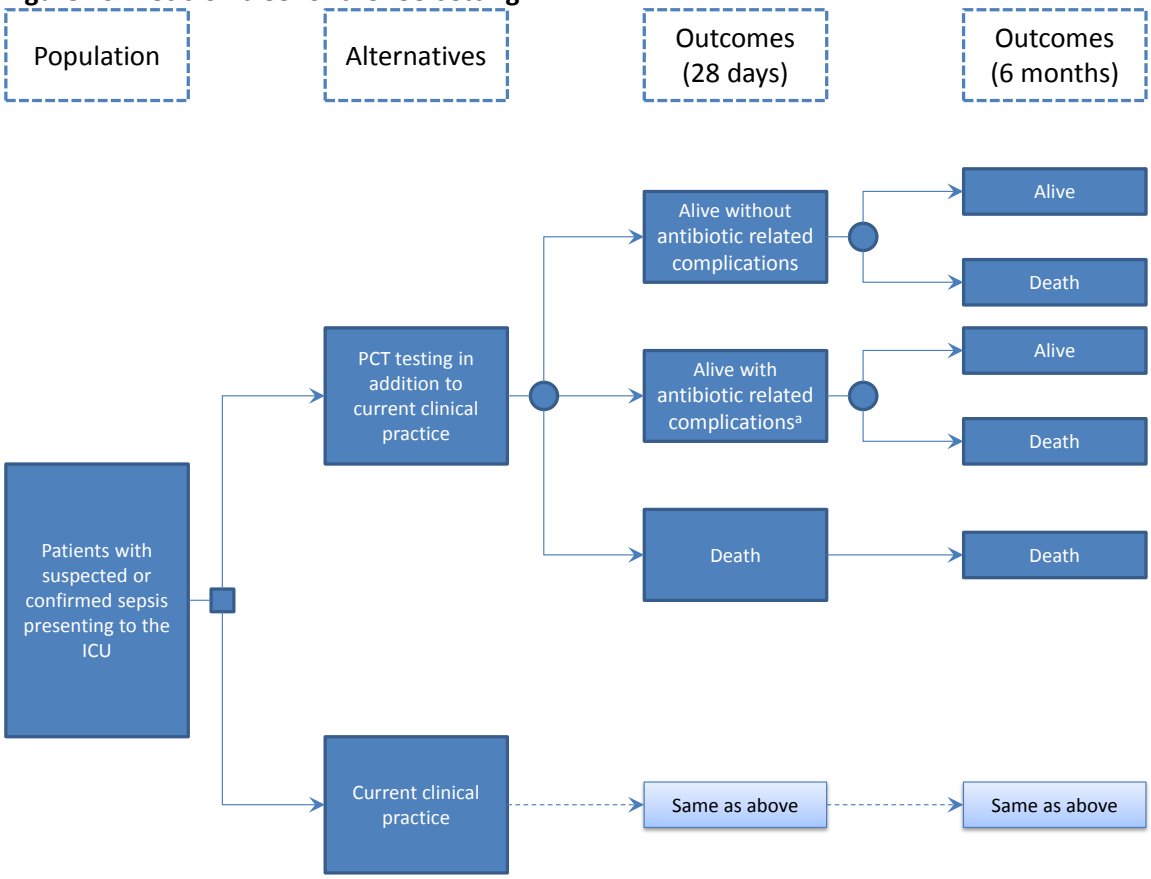
In a de novo health economic analysis (in Microsoft Excel), in accordance with the published protocol for this assessment (PROSPERO registration number CRD42014010822), PCT testing in

addition to current clinical practice was compared with current clinical practice without PCT testing for: (i) adults with confirmed or highly suspected sepsis in an ICU setting (ii) adults with suspected bacterial infection presenting to the ED; (iii) children with suspected bacterial infection presenting to the ED. Children with confirmed or highly suspected sepsis in an ICU setting were not considered due to the lack of data.

As shown in figures 23 and 24, the structure of the decision tree starts with one decision node that denotes the use of PCT or current clinical practice without PCT. The key endpoints are: (i) alive with antibiotic related complications, (ii) alive without antibiotic related complications and (iii) death. It is important to notice that treatment initiation was only explicitly incorporated in the ED setting (Figure 24). This is because PCT testing is mainly expected to be used to discontinue antibiotic therapy in the ICU setting (all patients with sepsis in the ICU are treated with antibiotics) whereas, in the ED setting, it is expected to be used to initiate antibiotics. This is reflected in the trials included in section 3. What this means for parameter estimation is that, for the ED setting only, parameters are required to estimate both the probability of initiation and the duration of antibiotic use *conditional* on initiation. For the ICU setting, parameters for duration of antibiotic use only are required (See resource use and costs in Section 4.3.2).

The time horizon is six months (183 days), divided into an initial short-term (28 days) phase and a subsequent phase lasting 155 days (see Figures 23 and 24). The six months' time horizon and the initial phase of 28 days were adopted to be consistent with the outcomes reported in the studies identified in section 3 of this report. The mean expected costs, life years (LYs), duration of antibiotic treatment and QALYs are calculated separately for both strategies.

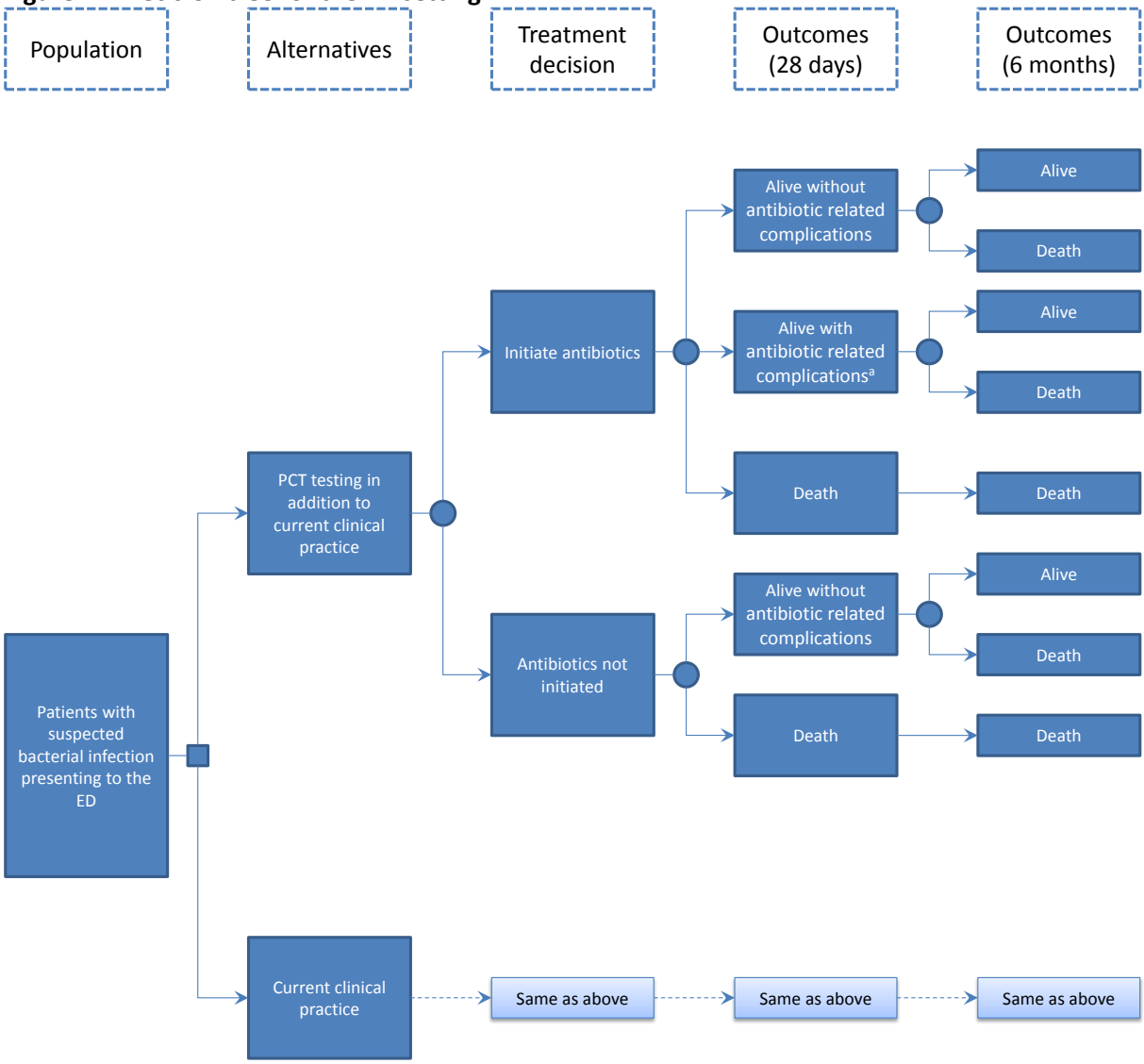
Figure 23: Decision tree for the ICU setting



Abbreviations: ICU, intensive care unit

[a] Antibiotic related complications are included in the model through a disutility for the duration of antibiotic treatment

Figure 24: Decision tree for the ED setting



Abbreviations: ED, emergency department;
[a] Antibiotic related complications are included through a disutility for the duration of antibiotic treatment

4.3.2 Model parameters

Estimates for the input parameters were mainly retrieved through systematic literature searches and meta-analyses that are described in this assessment (see Section 3.2 for mortality and resource use parameters and Section 4.2 for utility values).

Given the variation within the patient groups of interest (described in Section 3.2.3 *study details* and Section 3.2.4 *study details*), a 'lower clinical extreme' and a 'higher clinical extreme' is specified for each population and setting (i.e. children in ED, adults in ED and adults in ICU). For these 'clinical extremes' different baseline values (based on selected studies) are used for mortality, duration of antibiotic therapy, probability of initiation of antibiotic treatment (ED setting only), length of

hospital stay and/or length of ICU stay while applying the same relative risk or mean difference estimates for both clinical extremes (derived from the meta-analyses in Section 3.2).

All-cause mortality

The assessment of clinical effectiveness (Section 3.2 of this report) was the primary input for the baseline probabilities and relative risks used for the economic evaluation. Whenever a meta-analysis over the results of the identified studies was not possible, the most plausible source was chosen. This was based on two criteria: (i) compatibility with the population in the given scenario (low risk vs. high risk); (ii) availability of data for relevant outcomes.

Table 11 gives an overview of the selected sources used for the baseline mortality probabilities for each of the populations and the justifications for each of the choices. Table 12 gives an overview of the baseline mortality probabilities and mortality relative risks used.

Table 11: Summary of studies selected for the baseline mortality probabilities

Population	Clinical Extremes	Study selected	Main population	Justification
Children ED population	Lower	National mortality rates [97]	Children with LRTI	Mortality rates were not available from the identified studies. Personal communication with experts has indicated that mortality rates for children ED are close to zero (ref 5/11/2014) and therefore National background mortality rates assumed. The average age was considered equal to that of control group in Baer (2013) [44] (i.e. 3 years old children)
Children ED population	Higher	National mortality rates [97]	Children with CAP	Mortality rates were not available from the identified studies. Personal communication with experts (ref. 5/11/2014) has indicated that indeed mortality rates for children ED are close to zero and therefore national background mortality rates assumed. The average age was considered equal to that of control group in Esposito (2011) [53] (i.e. 5 years old children)
Adults ED population	Lower	Christ-Crain (2004) [49] for 28 day probability and Roh (2013) [59] for baseline 6 months probability.	Adults with suspected LRTI	Christ-Crain (2004) [49] was selected among the least severe end of the range given the availability of data on all parameters. Roh (2013) [59] was selected based on the fact that the data extend to

Population	Clinical Extremes	Study selected	Main population	Justification
				6 months and other 6-months follow-up studies like Stolz (2007))[3] seem inconsistent (i.e. too low 6 months probabilities) compared with the 28 day probabilities from Christ-Crain (2004)[49]
Adults ED population	Higher	Christ-Crain (2006) [47] for 28 day probability and Roh (2013) [59] for baseline 6 months probability	Adults with CAP	Christ-Crain (2006) [47] was selected among the most severe end of the range given the availability of data on all parameters Roh (2013)[59] was selected on the fact that the data extend to 6 months and other 6-months follow-up studies like Stolz (2007)[3] seem inconsistent (i.e. too low 6 months probabilities) compared with the 28 day probabilities from Christ-Crain (2006) [47].
Adults ICU population	Lower	Bouadma (2010) [46] for 28 days; 6m conditional probability (after 28 days) assumed equal to ED probability	Adults with suspected bacterial infection	Bouadma (2010) [46] was the only study available for 28 days follow up. The 6 months conditional (after being alive at 28 days) probability was assumed equal to the 6 months probability for ED conditional on being alive at 28 days.
Adults ICU population	Higher	Qu (2012) [57]; 6m conditional probability (after 28 days) assumed equal to ED probability	Adults with suspected bacterial infection and no clear source of infection	Qu (2012) [57] was chosen as it has a follow-up of 28 days and refers to patients with sepsis or septic shock and has the highest mortality probabilities. The 6 months conditional (after being alive at 28 days) probability was assumed equal to the 6 months probability for ED conditional on being alive at 28 days.

Table 12: All-cause mortality

Parameter	Period	Estimate	Se / (95%CI)	Distribution	Source
Baseline probability for all-cause mortality					
Children in ED Lower clinical extreme	28 days	<0.001	-	Fixed	Office for National Statistics (2014) [97]
Children in ED Lower clinical extreme	6 months	<0.001	-	Fixed	
Children in ED Higher clinical extreme	28 days	<0.001	-	Fixed	
Children in ED Higher clinical extreme	6 months	<0.001	-	Fixed	
Adults in ED Lower clinical extreme	28 days	0.062	0.015	Beta	Christ-Crain (2004)[49]
Adults in ED Lower clinical extreme	6 months	0.121	0.034	Beta	Roh (2013)[59]
Adults in ED Higher clinical extreme	28 days	0.072	0.543	Beta	Christ-Crain (2006)[47]
Adults in ED Higher clinical extreme	6 months	0.121	0.034	Beta	Roh (2013)[59]
Adults in ICU Lower clinical extreme	28 days	0.169	0.019	Beta	Bouadma (2010)[46]
Adults in ICU Lower clinical extreme[a]	6 months	0.222	0.043	Beta	Bouadma (2010)[46] Christ-Crain (2004)[49] Roh (2013)[59]
Adults in ICU Higher clinical extreme	28 days	0.182	0.384	Beta	Qu (2012)[57]
Adults in ICU Higher clinical extreme [a]	6 months	0.225	0.064	Beta	Christ-Crain (2006)[47] Qu (2012)[57] Roh (2013)[59]
Relative risk for all-cause mortality					
Children in ED	28 days	0.950	(0.710-1.270)	Log Normal	meta-analysis
Children in ED	6 months	0.950	(0.710-1.270)	Log Normal	meta-analysis
Adults in ED	28 days	0.980	(0.710-1.360)	Log Normal	meta-analysis
Adults in ED	6 months	0.850	(0.450-1.590)	Log Normal	meta-analysis
Adults in ICU	28 days	0.980	(0.760-1.270)	Log Normal	meta-analysis
Adults in ICU	6 months	0.980	(0.760-1.270)	Log Normal	meta-analysis

Abbreviation: se, standard error; 95%CI, 95% confidence interval;

[a] Probability calculated based on 6 months mortality probability conditional on being alive at 28 days for adults at the ED

Adverse events

Antibiotic related adverse events were incorporated through the time on antibiotic treatment (using a disutility for being on antibiotic treatment) as antibiotic related adverse events were mostly reported as a compound endpoint instead of the individual adverse events. No differences in disease specific complications were found between the intervention and comparator groups for any adverse clinical outcome assessed (see Section 3.2.3). Moreover, disease specific complications were also reported as a compound endpoint, making it difficult to incorporate these complications using complication specific disutilities. Therefore, the disease specific complications were not included and thus assumed to be equal for the comparators.

Health state utilities

The systematic review of HRQoL studies (Section 4.2) was used as input for utility values for the economic evaluation (Table 13). For adults being treated in the ICU, a utility of score of 0.53 was used for the decision tree period, while a utility of 0.68 was used for the period thereafter (both retrieved from Drabinksi et al[96] the only study with short-term utility values). In a scenario analysis the utility value of 0.68 was replaced with the 3.5 year utility value of 0.64 from Cuthbertson et al[91] which was judged to provide the most representative long-term utilities for the UK population.

No utility values for adults presenting to the ED with suspected infection were identified in the systematic review of HRQoL studies. Therefore, this utility value was retrieved from Oppong et al[79] which estimated a utility value (EQ-5D) for adults presenting to their primary care clinician with LRTI. The baseline and four week utility values reported in this study were used to calculate a weighted average (based on the number of patients per utility estimation) for England and Wales for the initial 28 days decision tree period (0.70) and thereafter (0.86).

For children presenting to the ED, a constant base utility of 0.99 was assumed (utility for local infection) from Bennett et al[87] (only study available).

To incorporate antibiotic related adverse events in adults being treated in the ICU, a disutility of 0.046 for being on antibiotic treatment was taken from Oppong et al[79] (weighted average for England and Wales). Although this disutility might be higher for people being treated in the ICU, due to the intravenous route of administration, it was conservatively assumed that this disutility is equal for all settings and populations. Moreover, it was conservatively assumed that there is no disutility for staying in hospital.

Table 13: Health state utility values

	Estimate	Se	Distribution	Source
Base utility up to 28 days				
Adults in the ICU	0.53	0.01[a]	Beta	Drabinski (2001)[96]
Adults in the ED (Wales)	*0.68*	*0.02*	*Beta*	Oppong (2013)[79]
Adults in the ED (England)	*0.74*	*0.02*	*Beta*	Oppong (2013)[79]
Adults in the ED (weighted)	0.70	[b]		
Children on the ED	0.99	0.00	Beta	Bennett (2000)[87]
Base utility up to 6 months				
Adults in the ICU	0.68	0.01[a]	Beta	Drabinski (2001)[96]
Adults in the ICU (sensitivity analysis)	0.64	0.04	Beta	Cuthbertson (2013)[91]
Adults in the ED (Wales)	*0.83*	*0.02*	*Beta*	Oppong (2013)[79]
Adults in the ED (England)	*0.89*	*0.02*	*Beta*	Oppong (2013)[79]
Adults in the ED (weighted)	0.86	[b]		
Children in the ED	0.99	0.01[a]	Beta	Bennett (2000)[87]
Disutility				
Disutility for antibiotic related adverse events	0.05	0.00[a]	Normal	Oppong (2013)[79]

Abbreviation: se, standard error;

[a] If the standard error was not reported/could not be derived, it was assumed that the standard deviation

[b] Based on the input parameters (and their Beta distributions) used to calculate this weighted average.

Resource use and costs

Resource use consisted of duration of hospital stay (days), ICU stay (days) and antibiotic treatment duration (days). The estimates were retrieved from studies identified in the systematic review. The same criteria, as described above for the probabilities and relative risks, are used to choose a study for a specific input parameter.

For the ED, antibiotic duration was calculated based on the probability of initiation of antibiotic treatment and the duration of antibiotic treatment conditional on that antibiotic treatment having been initiated i.e. the mean from the studies excluding those patients with zero use. For the ICU, it was assumed that antibiotics were initiated for all patients and thus the antibiotic treatment duration mean for the whole sample from the studies was used.

The studies chosen for baseline resource use and the accompanying justification are given in Table 14 below. The resource use parameters are given in Table 15 below.

Table 14: Main sources and justification for baseline resource use (hospital/ICU days, antibiotic initiation and antibiotic duration)

Population	Clinical Extremes	Study selected	Main population	Justification
Children ED population	Lower	Baer (2013)[44] except for length of ICU stay	Children with LRTI	Non-CAP LRTI subgroup from Baer (2013)[44] selected as the low risk. Length of ICU stay taken from Stolz (2007)[3] as it is the only study reporting this.
Children ED population	Higher	Esposito (2011)[53] except for antibiotic duration and length of ICU stay	Children with CAP	Esposito (2011)[53] selected as a study representing the high risk population. The CAP subgroup from Baer (2013)[44] was selected for antibiotic duration and antibiotic treatment initiation (not provided in Esposito 2011). Length of ICU stay taken from Stolz (2007)[3] as it is the only study reporting this.
Adults ED population	Lower	Christ-Crain (2004)[49] except for length of ICU stay	Adults with suspected LRTI	Christ-Crain (2004)[49] was selected among the least severe end of the range given the availability of data on all parameters. Stolz (2007)[3] was chosen length of ICU stay as it is the only study available.
Adults ED population	Higher	Christ-Crain (2006)[47] except for length of ICU stay	Adults with CAP	Christ-Crain (2006)[47] was selected among the most severe end of the range given the availability of data on all parameters. Stolz (2007)[3] was chosen for length of ICU stay as it is the only study available.
Adults ICU population	Lower	Bouadma (2010)[46]	Adults with suspected bacterial infection	Bouadma (2010)[46] was the only study available for 28 days follow up.
Adults ICU population	Higher	Qu (2012)[57] and Annane (2013)[98]	Adults with suspected bacterial infection and no clear source of infection	Qu (2013)[57] was chosen as the study reporting the highest duration of antibiotic therapy. Annane (2013)[98] was chosen based on availability of parameters and inclusion of people with apparent septic shock.

Table 15: Resource use

Parameter	Estimate	SE / (95%CI)	Distribution	Source
Baseline duration of antibiotic therapy				
Children in ED Lower clinical extreme (conditional on initiation of antibiotic therapy)	9.600	35.588	Gamma	Baer (2013)[44]
Children in ED Higher clinical extreme (conditional on initiation of antibiotic therapy)	11.512	59.962	Gamma	Baer (2013)[44]
Adults in ED Lower clinical extreme (conditional on initiation of antibiotic therapy)	15.386	55.634	Gamma	Christ-Crain (2004)[49]
Adults in ED Higher clinical extreme (conditional on initiation of antibiotic therapy)	13.073	54.478	Gamma	Christ-Crain (2006)[47]
Adults in ICU Lower clinical extreme	9.900	7.100	Gamma	Bouadma (2010)[46]
Adults in ICU Higher clinical extreme	16.060	0.413	Gamma	Qu (2012)[57]
Mean difference in duration of antibiotic therapy				
Children in ED (conditional on initiation of antibiotic therapy)	-3.908	123.397	Normal	Baer (2013)[44a]
Adults in ED (conditional on initiation of antibiotic therapy)	1.476	7.710	Normal	meta-analysis
Adults in ICU	3.190	1.145	Normal	meta-analysis
Baseline probability for antibiotic initiation				
Children in ED Lower clinical extreme	0.167	0.048	Beta	Baer (2013)[44]
Children in ED Higher clinical	0.790	0.040	Beta	Baer (2013)[44]
Adults in ED Lower clinical extreme	0.832	0.034	Beta	Christ-Crain (2004)[49]
Adults in ED Higher clinical extreme	0.987	0.009	Beta	Christ-Crain (2006)[47]
Relative risks for antibiotic initiation				
Children in ED	0.970	(0.670-1.400)	Log Normal	meta-analysis
Adults in ED	0.770	(0.680-0.870)	Log Normal	meta-analysis
Length of hospital stay				
Children in ED Lower clinical extreme; total	2.300	3.704	Gamma	Baer (2013)[44]
Children in ED Lower clinical extreme; % in ICU	[redacted]	[redacted]	[redacted]	Carrol E., Professor in Paediatric Infection, University of Liverpool ,

Parameter	Estimate	SE / (95%CI)	Distribution	Source
				[Personal communication] 05/11/2014
Children in ED Higher clinical extreme; total	5.010	0.330	Gamma	Esposito (2011)[53]
Children in ED Higher clinical extreme; % in ICU	[redacted]	[redacted]	[redacted]	Carrol E., Professor in Paediatric Infection, University of Liverpool , [Personal communication] 05/11/2014
Adults in ED Lower clinical extreme; total	11.200	10.600	Gamma	Christ-Crain (2004)[49]
Adults in ED Lower clinical extreme; ICU	3.700	2.100	Gamma	Stolz (2007)[3]
Adults in ED Higher clinical extreme; total	13.000	9.000	Gamma	Christ-Crain (2006)[47]
Adults in ED Higher clinical extreme; ICU	3.700	2.100	Gamma	Stolz (2007)[3]
Adults in ICU Lower clinical extreme; total	26.400	18.300	Normal	Bouadma (2010)[46]
Adults in ICU Lower clinical extreme; ICU	14.400	14.100	Normal	Bouadma (2010)[46]
Adults in ICU Higher clinical extreme; total	33.000	42.963	Gamma	SIGN (2008)[98]
Adults in ICU Higher clinical extreme; ICU	23.000	37.037	Gamma	SIGN (2008)[98]
Mean difference in length of hospital stay				
Children in ED; total	-0.620	0.283	Normal	meta-analysis
Adults in ED; total	-0.800	0.804	Normal	meta-analysis
Adults in ED; ICU	-0.400	0.337	Normal	Stolz (2007)[3]
Adults in ICU; total	-4.200	1.865	Normal	meta-analysis
Adults in ICU; ICU	-1.620	1.222	Normal	meta-analysis

Abbreviation: se, standard error; 95%CI, 95% confidence interval

[a] Based on the whole population from Baer et al.[44]

Data for the cost analyses were drawn from routine NHS sources (e.g. NHS reference costs and British National Formulary (BNF)) and discussions with manufacturers of the PCT tests. Table 16 gives an overview of the unit prices and their sources as used in the health economic analysis.

Table 16: Unit prices

Unit prices	Estimates/Unit price (£)	Distribution	Source
Antibiotic treatment ICU setting/day	£12.90	Fixed	British National; Formulary[99]
Antibiotic treatment ED setting/day (children)	£3.99	Fixed	
Antibiotic treatment ED setting/day (adults)	£2.20	Fixed	
Hospital stay/day (children)	£819.56	Fixed	Department of Health (2012) [100]
Hospital stay/day (adults)	£819.56	Fixed	
ICU stay/day (children)	£1,493.98	Fixed	
ICU stay/day (adults)	£1,168.45	Fixed	
ED stay/day (children)	£124.41	Fixed	
ED stay/day (adults)	£124.41	Fixed	

Antibiotic treatment costs were calculated using average unit prices per day. These average prices were calculated separately for the ED setting (children and adults) and for the ICU setting (adults). Antibiotic prices were retrieved from BNF.[99] The price per day for antibiotic treatment were calculated based on the dosage recommended in the treatment guidelines. LRTI treatment guidelines were used for the hospitalised non-ICU setting[101] and treatment guidelines for suspected or confirmed sepsis were used for the ICU settings.[102] The prices of different antibiotic treatment strategies (recommended by the guideline for a specific setting) were averaged. It was assumed that there was no wastage with regards to the antibiotic use (i.e., antibiotics were provided in perfectly dividable packages that correspond to the duration of the treatment as in the treatment strategy). This assumption would be plausible especially for the ICU setting given the 'return for re-issue' approach used for handling partially used packs in UK hospitals. On the other hand, given the low unit costs of antibiotics the effects of the drug wastage on total costs are expected to be very small for both settings. It should be noted that the costs of antibiotic related adverse events are conservatively not incorporated.

Costs of hospital stay, ED stay and ICU stay were retrieved from the UK's National Schedule of Reference Costs.[100] The costs were calculated as weighted averages of the specific services taking into account the national average unit cost and the total number of attendances for each of the cost categories. The reference codes were: XB01Z- XB09Z for paediatric ICU stay, XC01Z - XC07Z for adults

ICU stay, VB01Z - VB09Z for children/adults ED stay, and DZ22D - DZ22J for children/adults hospital stay for unspecified acute lower respiratory infection.

The unit price for the PCT test was calculated based on the information provided by assay manufacturers in response to the request for information made by NICE at the beginning if the assessment and forwarded by NICE (Nixon F., Health Technology Analyst, Diagnostics Assessment Programme, NICE [Personal communication] July 2014). The average price was based on the listed prices of the test (excluding the VAT) and with no discounts assumed (see the upper part of Table 17). Moreover, overhead costs including capital, service/maintenance, and calibration costs (see Table 17) were included. Overhead costs were calculated incorporating the initial capital costs (wherever these were provided by the Manufacturer(s)), the lifetime of the assay (assumed to be five years) and the average number of tests/day (an average of 272 tests/day). A similar estimation was performed taking into account the frequency of the maintenance and calibration costs whenever they were provided by the Manufacturers. The inclusion of capital costs and other costs was considered as a conservative approach and therefore used in the base case analysis. A separate scenario analysis considered the exclusion of overhead costs.

Table 17: Total cost per test

Name of test	Manufacturer	Listed price/test	Source
ELECSYS® BRAHMS PCT	Roche	£12.15	Manufacturers' response to request for information made by NICE (Nixon F., Health Technology Analyst, Diagnostics Assessment Programme, NICE [Personal communication] July 2014).
ADVIA Centaur BRAHMS PCT	Siemens	£16.81	
VIDAS BRAHMS PCT	bioMérieux	£12.80	
B.R.A.H.M.S PCT KRYPTOR	Thermo Fisher Scientific	£12.23*	
1. Average price/test		***£13.50***	
Overhead costs		Average costs (max or listed)	
Capital costs/test		£0.10	Manufacturers' response to request for information made by NICE
Service or maintenance costs /test		£0.07	
Calibration costs		£0.08	

Name of test	Manufacturer	Listed price/test	Source
			(Nixon F., Health Technology Analyst, Diagnostics Assessment Programme, NICE [Personal communication] July 2014).
2. Total other costs/test		***£0.26***	
3. Total average costs/test (1+2)		***£13.79****	

Note: * Prices were given in Euros and converted in British Pounds where 1 British Pound = 1.2521 Euros[103]; The total average cost per test with the discount varied from [redacted] to [redacted] depending on the extent of the discount described by the Manufacturers.

The number of PCT tests used was considered different for the ED and the ICU setting as in Table 18 below.

Table 18: Number of PCT tests used in different settings

	Estimate	Se	Distribution	Source
Number of PCT tests in ED	2.0	0.2	Gamma	Cleves (2010)[86]
Number of PCT tests in ICU	3.5	0.4	Gamma	Christ-Crain (2006)[47]

4.3.3 Overview of main assumptions

The first phase in the decision tree period is assumed 28 days in line with the 28 day mortality reported for most studies. The decision tree period extends to six months in the second phase. The main assumptions in the health economic analyses were:

- The number of hospitalisation days retrieved from the systematic review (section 3) also includes the hospitalisation days after (potential) infection relapse/recurrence.
- Relative risks for all-cause mortality for ED children are assumed to be equal to those for ED adults as no data were found in the literature.
- There is no disutility for the hospital stay.
- The baseline utility for children in the ED was constant over time.
- The disutility for being on antibiotic treatment was equal for all settings and populations.
- To estimate the number of PCT tests, it was assumed that PCT testing was used for initiation of antibiotics in the ED and discontinuation of antibiotics in the ICU.
- There are no costs associated with antibiotic related adverse events.

- No differences were considered between comparators in disease specific complications.
- No differences were considered between comparators in long-term costs and effects (including any effects on antibiotic resistance).

4.4 Model analyses

Expected costs, duration of antibiotic treatment, LYs and QALYs were estimated for both treatment strategies. No discounting was applied because the time horizon was less than one year. Incremental cost and QALYs were calculated, as well as the incremental cost-effectiveness ratio (ICER). Probabilistic sensitivity analyses (10,000 simulations) were performed, and cost-effectiveness acceptability curves (CEACs) were constructed.

4.4.1 Sensitivity and scenario analyses

One-way sensitivity analyses were performed for all stochastic input parameters between the 95% confidence intervals. Moreover, the following scenario analyses were performed to assess the impact of assumptions on the estimated outcomes:

- Assume no difference in mortality (i.e. a relative risk of 1)
- Assume an increased costs of £50 per test
- Assume no overhead costs for the tests
- Alternative utility value for adults on the ICU (based on Cuthbertson et al[91])
- Assume no disutility for being on antibiotic treatment
- Assume no difference in duration of antibiotic treatment
- Assume no difference in hospital stay (including ICU stay)
- Assume lower price for hospital and ICU stay: £886 per paediatric ICU day (Paediatric Critical Care, High Dependency), £619 per ICU day for adults (Adult Critical Care, 0 Organs Supported) and £212 per non-ICU hospital day (Unspecified Acute Lower Respiratory Infection with CC Score 11-14).[100]
- Assume that PCT testing in the ED was solely used to initiate antibiotic treatment (not to discontinue antibiotic treatment). Given that there were no studies that solely used PCT for the initiation of antibiotic treatment for children in the ED, this was only possible for adults in the ED. For this purpose, the probability of initiating antibiotic treatment from Stolz et al[3] was used while assuming no difference in the duration of antibiotic treatment. All other parameters were equal to the base case analysis.

All sensitivity and scenario analyses where whether PCT is cost effective or not changes compared with the base case analysis (based on a willingness to pay threshold of £30,000 per QALY) or with an ICER below £100,000 are presented in the results section.

4.5 Results of cost-effectiveness analyses

4.5.1 Base case analysis

The base case analysis compared two strategies, PCT-guided treatment and current clinical practice for each combination of setting and population for which clinical effectiveness data were available, i.e., children in ED, adults in ED, and adults in ICU. Moreover the results were calculated for both the lower and higher clinical extremes.

PCT testing resulted in a positive gain in terms of LYs in comparison with current clinical practice, for all settings and scenarios considered (Table 19). However, it should be noted that these gains were relatively small (less than 0.01 life years).

Table 19: Probabilistic results for base case analysis: life years

Population and setting	Scenario	Strategy	Life years	Incremental
Children ED	Low risk	Current clinical practice	0.496 (95% CI: 0.496 - 0.496)	
		PCT testing	0.496 (95% CI: 0.496 - 0.496)	<0.001
Children ED	High risk	Current clinical practice	0.496 (95% CI: 0.496 - 0.496)	
		PCT testing	0.496 (95% CI: 0.496 - 0.496)	<0.001
Adults ED	Low risk	Current clinical practice	0.439 (95% CI: 0.409 - 0.464)	
		PCT testing	0.445 (95% CI: 0.396 - 0.474)	0.006
Adults ED	High risk	Current clinical practice	0.439 (95% CI: 0.409 - 0.461)	
		PCT testing	0.444 (95% CI: 0.397 - 0.472)	0.006
Adults ICU	Low risk	Current clinical practice	0.390 (95% CI: 0.354 - 0.427)	
		PCT testing	0.391 (95% CI: 0.342 - 0.433)	0.002
Adults ICU	High risk	Current clinical practice	0.388 (95% CI: 0.324 - 0.444)	
		PCT testing	0.389 (95% CI: 0.316 - 0.447)	0.002

Abbreviation: 95%CI, 95% confidence interval

Table 20 shows the results for antibiotic duration (in days) for all settings and scenarios. The days on antibiotic treatment were reduced with the PCT strategy, for all combinations of setting and population except the lower clinical extreme scenario for children in the ED setting. For children in ED setting the differences between the PCT and the current clinical practice varied from 0.01 days (lower clinical extreme) to -0.12 days (higher clinical extreme). The differences between PCT and current clinical practice for the adults in ED setting varied from -1.94 days (lower clinical extreme) to -1.69 days (higher clinical extreme) while for the ICU setting these differences were -2.96 and -3.18 days respectively.

Table 20: Probabilistic results for base case analysis: Antibiotic duration (days)

Population and setting	Scenario	Strategy	Antibiotic duration (days)	Incremental
Children ED	Low risk	Current clinical practice	1.60 (95% CI: 1.56 - 1.64)	
		PCT testing	1.61 (95% CI: 0.00 - 6.35)	0.01
Children ED	High risk	Current clinical practice	9.08 (95% CI: 1.47 - 23.33)	
		PCT testing	8.96 (95% CI: 0.00 - 34.27)	-0.12
Adults ED	Low risk	Current clinical practice	12.83 (95% CI: 4.44 - 25.73)	
		PCT testing	10.88 (95% CI: 0.00 - 24.58)	-1.94
Adults ED	High risk	Current clinical practice	12.94 (95% CI: 3.47 - 28.24)	
		PCT testing	11.25 (95% CI: 0.00 - 27.15)	-1.69
Adults ICU	Low risk	Current clinical practice	9.84 (95% CI: 1.07 - 27.50)	
		PCT testing	6.88 (95% CI: 0.00 - 24.50)	-2.96
Adults ICU	High risk	Current clinical practice	16.05 (95% CI: 15.26 - 16.89)	
		PCT testing	12.87 (95% CI: 10.55 - 15.24)	-3.18

Abbreviation: 95%CI, 95% confidence interval

The base case analyses indicated that PCT dominates current clinical practice for all populations in that it was both cost saving and more effective (Table 21). The cost savings ranged from £368 for children with suspected bacterial infection presenting to the ED (lower clinical extreme) to £3,268 for adults with confirmed or highly suspected sepsis in an ICU setting (lower clinical extreme). PCT testing resulted in only a small QALY gain. For adults with suspected bacterial infection presenting to the ED this was 0.005 for the lower and higher clinical extremes and for adults with confirmed or highly suspected sepsis in the ICU setting it was 0.001 for both clinical extremes. For children with suspected bacterial infection presenting to the ED, the QALY gains were less than 0.001 for both clinical extremes.

Table 21: Probabilistic results for base case analysis: costs and QALYs

Population and setting	Scenario	Strategy	Costs (95% CI) (£)	QALYs (95% CI)	ΔCosts(£)	ΔQALYs	ΔCosts / ΔQALYs
Children ED	Low risk	Current clinical practice	2,312 (95% CI: 7 - 12,943)	0.492 (95% CI: 0.489 - 0.495)			
		PCT testing	1,943 (95% CI: 25 - 12,269)	0.492 (95% CI: 0.489 - 0.495)	-368	<0.001	Dominant
Children ED	High risk	Current clinical practice	4,987 (95% CI: 4,167 - 5,964)	0.491 (95% CI: 0.488 - 0.494)			
		PCT testing	4,406 (95% CI: 3,461 - 5,491)	0.491 (95% CI: 0.487 - 0.494)	-581	<0.001	Dominant
Adults ED	Low risk	Current clinical practice	11,004 (95% CI: 2,160 - 33,827)	0.364 (95% CI: 0.337 - 0.388)			
		PCT testing	10,342 (95% CI: 1,534 - 32,849)	0.369 (95% CI: 0.327 - 0.397)	-662	0.005	Dominant
Adults ED	High risk	Current clinical practice	12,270 (95% CI: 3,073 - 30,341)	0.364 (95% CI: 0.337 - 0.386)			
		PCT testing	11,556 (95% CI: 2,463 - 29,775)	0.369 (95% CI: 0.327 - 0.396)	-715	0.005	Dominant
Adults ICU	Low risk	Current clinical practice	29,890 (95% CI: 6,441 - 71,591)	0.254 (95% CI: 0.230 - 0.280)			
		PCT testing	26,622 (95% CI: 2,948 - 68,581)	0.256 (95% CI: 0.223 - 0.284)	-3,268	0.001	Dominant
Adults ICU	High risk	Current clinical practice	45,464 (95% CI: 1,233 - 174,178)	0.252 (95% CI: 0.210 - 0.290)			
		PCT testing	42,602 (95% CI: 210 - 170,189)	0.254 (95% CI: 0.206 - 0.292)	-2,862	0.001	Dominant

Cost-effectiveness acceptability curves (shown in Appendix 7) illustrate that, for any willingness to pay threshold ranging from £0 to £60,000 per QALY, PCT testing always has a higher probability of being cost-effective than current clinical practice. For a willingness to pay threshold of £20,000 the probability of PCT testing being cost effective over current clinical practice is: (i) 85% and 98% respectively for both the lower and higher clinical extremes for children with suspected bacterial infection presenting to the ED; (ii) 88% for adults with suspected bacterial infection presenting to the ED (both clinical extremes); (iii) 97% and 95% respectively for the lower and higher clinical extremes for adults with confirmed or highly suspected sepsis in the ICU setting. It should be noted that these probabilities vary within small limits (1-3 percentage points) for the other willingness to pay thresholds (see Appendix 7).

4.5.2 Sensitivity and scenario analyses

The one-way sensitivity analysis for the relative mortality risk for adults with suspected bacterial infection presenting to the ED, showed that when using the upper bound of the 95% confidence interval (1.590; base case value: 0.850) PCT-guided treatment was less costly (£772) and less effective (QALY loss: 0.025) compared with current clinical practice, leading to savings per QALY lost of £30,469 (lower clinical extreme) and £30,446 (higher clinical extreme). In this case, PCT-guided treatment can be considered cost-effective for all willingness-to-pay thresholds below this ICER, indicating that a QALY lost of 0.025 is accepted given the obtained savings of £772.

The scenario analyses that assumed no difference in hospital stay had a substantial impact on all analyses. For all analyses PCT-guided treatment became more costly (incremental costs varied between £7 for adults at the ICU and £25 for children at the ED) and remained more effective (QALY gain varied between <0.001 for children at the ED and 0.007 for adults at the ICU) compared with current clinical practice without PCT. For children presenting to the ED with suspected bacterial infection, this resulted in an ICER of £287,076 for the lower clinical extreme and £35,219 for the higher clinical extreme. For adults in both settings (and both clinical extremes), the ICER varied between £3,390 and £3,948.

Neither the remaining sensitivity analyses nor any of the remaining scenario analyses changed whether PCT is cost effective compared with the base case analysis or provided an ICER lower than £100,000 per QALY. Hence, PCT-guided treatment was cost-effective in all remaining one-way sensitivity analyses and scenarios analyses for all settings and populations.

5. DISCUSSION

5.1 Statement of principal findings

5.1.1 Clinical effectiveness

All studies included in the review were parallel group RCTs. Eight studies provided data on the effectiveness of adding PCT testing to the information used to guide antibiotic therapy for the treatment of confirmed or highly suspected sepsis in ICU settings [1, 2, 38, 42, 46, 54, 57, 63] and all of these studies included only adult participants. Ten studies provided data on the effectiveness of adding PCT testing to the information used to guide antibiotic therapy in people presenting to the ED with suspected bacterial infections, of which eight included only adults[3-5, 47, 49, 58-60] and two included only children.[44, 53] Additional searches for non-RCT paediatric studies, described in Section 3.1.1, did not identify any studies that met the inclusion criteria for this assessment.

The majority (12) of the included studies measured plasma/serum PCT levels using the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA). [2-5, 42, 44, 46, 47, 49, 53, 60, 63] Two studies measured plasma/serum PCT levels using the VIDAS BRAHMS PCT (bioMérieux, Marcy l'Etoile, France). The remaining four studies used quantitative PCT assays, but did not specify the assay manufacturer.[38, 57-59]

Only four of the eight studies conducted in ICU settings fully matched the participant inclusion criteria for this review (adults with confirmed or highly suspected sepsis, in whom antibiotic therapy is indicated, who are being treated in ICUs).[1, 2, 38, 42] One study included a mixed population, comprising adults who were being treated in an ICU for suspected bacterial infection and those who developed sepsis during their ICU stay.[46] The inclusion criteria specified in our protocol, for the ICU population, were extended to include studies of people suspected bacterial infections that did not specify sepsis as the target condition. Two additional studies included as a result of this change were conducted in populations considered to be at increased risk of developing sepsis;[104-106] one study included adults with acute pancreatitis[57] and the other included adults with VAP.[63] The final ICU study included adults who were being treated for suspected bacterial infections.[54] This was the only study, conducted in an ICU setting, to assess the effectiveness of adding PCT testing to the information used to guide the initiation of antibiotic treatment, reflecting the lower level of symptom severity in the included population.[54] All of the other studies conducted in ICU settings assessed the effectiveness of adding PCT testing to the information used to decide when to discontinue antibiotic treatment.[1, 2, 38, 42, 46, 57, 63] The details of the PCT algorithm varied between studies, however, all discontinuation algorithms included a component which strongly encouraged/encouraged discontinuation of antibiotics when the PCT level was <0.25 ng/mL,[2, 38, 42, 46,

[63] and/or encouraged discontinuation of antibiotics when the PCT level was <0.5 ng/mL.[1, 42, 46, 54, 57, 63] The results of meta-analysis, including all available data, indicated that addition of a PCT algorithm to the information used to decide when to discontinue antibiotic treatment was associated with a reduction in the duration of antibiotic therapy (WMD -3.19 days (95% CI: -5.44 to -0.95), I^2 95.2%, four studies) and uncertainty around this effect was reduced when the analysis was restricted to studies conducted in populations with suspected or confirmed sepsis (WMD -1.20 days (95% CI: -1.33 to -1.07), two studies). Data on resource use were consistent with the observed reduction in duration of antibiotic treatment, i.e. the results of meta-analysis, including all available data, indicated that addition of a PCT algorithm to the information used to decide when to discontinue antibiotic treatment was associated with a reduction in the duration of hospital stay (WMD -3.85 days (95% CI: -6.78 to -0.92), I^2 75.2%, four studies) and a trend towards reduction in the duration of ICU stay (WMD -2.03 days (95% CI: -4.19 to 0.13), I^2 81.0%, four studies). Again, uncertainty around these effect estimates was reduced when the analysis was restricted to studies conducted in populations with suspected or confirmed sepsis (duration of hospital stay WMD -4.32 days (95% CI: -6.50 to -2.14), two studies, and duration of ICU stay WMD -2.31 days (95% CI: -3.97 to -0.65), two studies). For antibiotic treatment and resource use outcome measures, studies that reported duration as median and IQR only failed to find any difference between the group in which a PCT algorithm was included in decision making and the group in which the decision to discontinue antibiotic treatment was made without information on PCT levels.[1, 42] Studies conducted in ICU settings reported a variety of general and disease-specific adverse clinical outcomes including mortality at various time points, infection relapse/recurrence, mechanical ventilation, MODS and SOFA score. No study reported a statistically significant difference between the intervention and comparator groups for any adverse clinical outcome assessed. No study reported data on antibiotic-related adverse events.

In summary, the available data indicate that addition of a PCT algorithm to the information used to decide when to discontinue antibiotic treatment in people being treated for suspected or confirmed sepsis, in ICU settings, may result in reduced antibiotic exposure and resource use (hospital and ICU stay) without any adverse consequences for clinical outcome. There was no evidence of variation in these effects between the two PCT assays (BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA) VIDAS BRAHMS PCT assay (bioMérieux, Marcy l'Etoile, France)) used.

The clinical presentation of participants varied between ED studies, however, with the exception of one study conducted in adults with UTI,[5] all were conducted in people with respiratory

presentations and possible bacterial infection. Where specified, all studies conducted in ED settings used the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA) assay. All but one of the studies conducted in emergency department settings assessed the effectiveness of adding PCT testing to the information used to guide the initiation of antibiotic treatment,[3, 4, 44, 47, 49, 53, 58-60] and six of these studies also assessed the effectiveness of adding PCT testing to the information used to guide the discontinuation of antibiotic treatment.[44, 47, 53, 58-60] The details of the PCT intervention varied between studies, however, all studies (both initiation and discontinuation) discouraged antibiotic use where the PCT level was <0.25 ng/mL. All studies conducted in adults indicated that the addition of PCT to the information used to decide whether or not to initiate antibiotic treatment was associated with a reduction in the proportion of people receiving antibiotics; the summary RR was 0.77 (95% CI: 0.68 to 0.87), seven studies. Data for children were sparse, however, meta-analysis restricted to children presenting with CAP also indicated that the addition of PCT to the information used to decide whether or not to initiate antibiotic treatment was associated with a reduction in antibiotic use (summary RR 0.86 (95% CI: 0.80 to 0.93), two studies). The summary effect estimate, derived from the two studies, conducted in adults that reported duration of antibiotic therapy as mean and s.d., indicated that inclusion of PCT in the clinical decision making process was associated with reduction in the duration of antibiotic therapy, which did not reach statistical significance, WMD -4.49 days (95% CI: -9.59 to 0.61); four further studies reporting data in a form that could not be included in the meta-analysis, consistently found that that inclusion of PCT in the clinical decision making process was associated with reduction in the duration of antibiotic therapy. Only one study conducted in children reported data on duration of antibiotic therapy; as with initiation of antibiotic therapy, subgroup data from this study indicated that the use of PCT was only associated with a reduction in antibiotic exposure for children with CAP (mean difference -3.4 days (95% CI: -4.9 to -1.7)).[44] It should be noted that data on duration of antibiotic use included participants with a zero value (i.e. participants who did not receive antibiotic treatment) and hence are not strictly applicable to assessing the effectiveness of using PCT algorithms to inform the decision on when to discontinue antibiotics. A meta-analysis, which included only data for those patients in the two adult ED studies who received antibiotic treatment, resulted in a WMD of 1.48 days (95% CI: -13.64 to 16.59), indicating no clear effect of PCT testing on duration of treatment; indeed data from one of these studies indicated that, in adults presenting to the ED who receive antibiotic treatment PCT testing may be associated with an increased duration of treatment.[47] Data on resource use outcomes were inconsistent for studies conducted in ED settings. Although meta-analysis of the two studies, conducted in adults, that reported data as mean and s.d., indicated that inclusion of PCT in the clinical decision making

process was associated with a trend towards reduction in the duration of hospital stay (WMD -0.80 days (95% CI: -2.37 to 0.78)), the effect of PCT on duration of hospital stay was inconsistent across the six adult studies reporting this outcome. As with antibiotic exposure outcomes, data for children were sparse, however meta-analysis of data from two studies indicated that including a PCT algorithm in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment was associated with a small reduction in the duration of hospital stay (WMD -0.74 days (95% CI: -1.17 to -0.31)). No study reported a statistically significant difference between the intervention and comparator groups for duration of ICU stay, hospital re-admission, or secondary ED visits. Studies conducted in ED settings reported a variety of general and disease-specific adverse clinical outcomes including mortality at various time points, infection relapse/recurrence, composite measures of adverse outcomes, mechanical ventilation, need for steroids, and complications of pneumonia. One study reported data indicating that inclusion of a PCT algorithm in both the information used to guide initiation and discontinuation of antibiotics was associated with a statistically significant reduction in infection relapse/recurrence rates (RR 0.57 (95% CI: 0.36 to 0.92)),[60] No other study reported a statistically significant difference between the intervention and comparator groups for any adverse clinical outcome assessed. Antibiotic-related adverse events were rarely reported, however, available data from one study in adults and two in children indicated that including a PCT algorithm in both the decision on whether or not to initiate antibiotic treatment and the decision on when to discontinue antibiotic treatment was associated with a reduction in antibiotic-related adverse events.

In summary, the available data indicate that addition of PCT information to the information used to guide antibiotic therapy in adults presenting to the ED with respiratory symptoms and suspected bacterial infection may result in reduced antibiotic exposure, primarily with respect to a reduction in the numbers of people receiving antibiotic treatment, without any adverse consequences for clinical outcome. However, there appears to be no consistent effect on resource use outcomes. Very limited data suggest that similar effects may apply for children with CAP. The draft NICE guideline on the diagnosis and management of community- and hospital-acquired pneumonia in adults reports that systematic review evidence showed that using PCT testing to inform antibiotic prescribing decisions in people presenting with acute respiratory tract infections, in any setting, may reduce initiation of antibiotic treatment with no evidence of any difference in mortality or other clinical adverse outcomes.[14] However, the guideline does not currently include any recommendations on the use of PCT testing.

5.1.2 Cost-effectiveness

The review of economic analyses of PCT testing identified two relevant studies in three publications.[74-76] These studies used a short-term decision tree to examine the cost-effectiveness of PCT-guided antibiotic treatment compared to usual care for adult patients with ARTI (outpatient setting)[74, 75] and CAP (in-hospital setting),[76] respectively. The results of both studies indicated that PCT-guided treatment was more expensive and more effective (in terms of QALYs). Michaelidis et al[74, 75] performed two analyses for two slightly different population: (i) adults presenting to an outpatient clinic with an ARTI and judged by their physicians to require an antibiotic prescription; and (ii) all adults presenting to an outpatient clinic with an ARTI prior to any decision to initiate antibiotic therapy. Their analyses resulted in ICERs of $118,828 and $575,249 per QALY gained for the first and second analyses respectively. Smith et al[76] assumed no differences in length of hospital stay between the treatment strategies and analysed the cost-effectiveness of PT-guided antibiotic therapy for: (i) low-risk CAP patients using PCT for initiating antibiotic only; (ii) low-risk CAP patients using PCT also for monitoring antibiotic use for low-risk patients and; (iii) using PCT for both initiating antibiotic and monitoring antibiotic use for high-risk patients. These analyses resulted in ICERs of $90,000, $40,000 and $170,000 per QALY gained respectively. Additionally, an overview of potentially relevant excluded studies (mainly cost-minimisation studies focussed on the short-term) indicated that PCT-guided treatment could result in cost-savings for adult patients with sepsis, ARTI and pneumonia,[81-85] while additional costs for PCT-guided treatment were found for adults with LRTI[86] and suspected CAP.[47]

In a de novo health economic analysis, the cost-effectiveness of PCT testing in addition to current clinical practice was compared with current clinical practice for: (i) adults with confirmed or highly suspected sepsis in an ICU setting (ii) adults with suspected bacterial infection presenting to the ED; (iii) children with suspected bacterial infection presenting to the ED. As specified in the protocol for this assessment, lack of evidence meant that the cost-effectiveness of PCT testing in addition to current clinical practice was not considered for children with confirmed or highly suspected sepsis being treated in an ICU setting. Also, as indicated by the design of trials in the clinical effectiveness review, antibiotic duration in the ICU was modelled assuming that PCT was used to decide when to stop treatment whereas in the ED it was modelled assuming that PCT was used to decide whether to initiate treatment. To examine the impact of variability in the study populations on the economic outcomes, a lower and higher clinical extreme was defined for each setting and population, using baseline risks and baseline resource use parameters while assuming an equal relative risk for mortality and mean difference for resource use parameters. The base case analyses indicated that PCT testing was cost-saving for all settings and populations considered, ranging from £368 for

children with suspected bacterial infection presenting to the ED (lower clinical extreme) to £3,268 for adults with confirmed or highly suspected sepsis in an ICU setting (lower clinical extreme). This could mainly be explained by the reduction in antibiotic treatment and a reduction in hospital stay (both ICU and non-ICU days) for PCT-guided treatment. For children presenting to the ED and adults in both the ED and ICU settings, PCT-guided treatment resulted in a small QALY gain (<0.001, 0.005 and 0.001, respectively) and thus dominated treatment without PCT-guidance. This QALY gain could be attributed to a reduction in mortality and less days on antibiotic treatment (leading to a smaller QALY loss due to antibiotic related adverse events) for PCT-guided treatment. The differences between the lower and higher clinical extremes were small for all settings and populations. Cost-effectiveness acceptability curves showed that PCT-guided treatment has a probability of 84% or higher of being cost-effective for all settings and populations considered (at willingness to pay thresholds of £20,000 and £30,000 per QALY).

It was difficult to compare the total costs estimated in our analyses with those from cost(-effectiveness) studies found in the literature as most studies did not incorporate hospital stay costs[47, 74, 75, 81, 82, 84-86] or assumed this to be equal for both comparators.[76] However, the cost-minimisation by Wilke et al[83] did incorporate ICU costs and consistent with our analyses estimated cost savings for PCT-guided treatment for septic patients. The QALY gain of 0.005 estimated in our analysis for adults presenting to the ED was larger compared with the only other incremental QALY estimate of 0.00019 found in the literature reported by Michaelidis et al[74, 75] for adult patients with ARTI. Differences between these incremental QALY estimates can possibly be explained by the longer time horizon used in our analyses (six months versus duration of ARTI treatment episode) and the inclusion of mortality in our analyses.

The one-way sensitivity and scenario analyses indicated that the base case outcomes were robust. In particular, even if there was no effect on mortality (relative risk of 1), PCT would remain cost effective. Only one sensitivity analyses showed a relevant change in the incremental outcomes. This was the one-way sensitivity analysis for the relative mortality risk for adults with suspected bacterial infection presenting to the ED. This analysis showed that when using the upper bound of the 95% confidence interval PCT-guided treatment was less costly and less effective compared with current clinical practice, leading to savings of £30,469 (lower clinical extreme) and £30,446 (higher clinical extreme) per QALY lost. This indicates that PCT-guided treatment is cost-effective based on a threshold of £30,000, i.e. that a QALY lost is accepted given the obtained savings for PCT-guided treatment. The scenario analyses that assumed no difference in hospital stay had a substantial impact on all analyses. For all analyses PCT-guided treatment became more costly and remained

more effective (instead of dominating current clinical practice). For the children presenting to the ED, this resulted in an ICER of £287,076 for the lower clinical extreme and £35,219 for the higher clinical extreme. For adults in both settings and both clinical extremes the ICER varied between £3,390 and £3,948.

In summary, the available evidence suggests that the addition of PCT testing to current clinical practice leads to cost savings and a very small QALY gain and thus dominates current practice. Hence PCT testing potentially represents a cost-effective use of NHS resources for adults with confirmed or highly suspected sepsis in an ICU setting, adults with suspected bacterial infection presenting to the ED and children with suspected bacterial infection presenting to the ED.

5.2 Strengths and limitations of assessment

5.2.1 Clinical effectiveness

Our assessment included only those study designs with the potential to provide information on the 'added value' of including PCT in clinical decision making processes on whether to initiate antibiotic treatment and when to discontinue treatment. We believe this approach to be most appropriate since, in practice, PCT would not be used in isolation to determine the presence or absence of bacterial infection and hence appropriate management. A recent systematic review showed that the diagnostic performance of PCT alone is insufficient to distinguish people with sepsis form those with SIRS (sensitivity 77% (95% CI: 72 to 81), specificity 79% (95% CI: 74 to 84).[26]

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. We used a two stage approach for searching bibliographic databases, which included the use of sensitive search filter to identify RCTs, followed by unrestricted searches for non-RCT studies in children when no RCTs conducted in paediatric intensive care unit (PICU) settings were identified. Despite this, we were unable to identify any studies, conducted in PICU settings, that met the inclusion criteria for this assessment, and available data for children were generally very sparse.

The possibility of publication bias cannot be ruled out. Due to the small number of included studies (maximum seven included in any one meta-analysis) we were unable to undertake a formal assessment of publication bias. However, our search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts.

Clear inclusion criteria were specified in the registered protocol for this review (PROSPERO registration number CRD42014010822). The eligibility of studies for inclusion is therefore

transparent. In addition, we have provided specific reasons for exclusion for all of the studies which were considered potentially relevant at initial citation screening and were subsequently excluded on assessment of the full publication (Appendix 5). The review process followed recommended methods to minimise the potential for error and/or bias;[33] studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were done by one reviewer and checked by a second (MW and PW). Any disagreements were resolved by consensus.

Studies included in this review were assessed for risk of bias using the Cochrane risk of bias tool.[39] The results of the risk of bias assessment are reported, in full, for all included studies in Appendix 4 and are summarised in Section 3.2.2. Studies were generally of unclear quality due to limitation in reporting. Three[1-3] of the 18 studies were judged to be at high risk of bias. Loss to follow-up was the reason for the high risk of bias rating in two studies.[1, 2] Both studies reported per. protocol analyses in addition to the main ITT analyses used in Section 3.2.3 of this report; in one case 14% of study participants were not included in the per. protocol analysis,[2] and in the other 33% of study participants were not included in the per. protocol analysis.[1] In both studies the per. protocol analyses showed a statistically significant reduction in the duration of antibiotic therapy, associated with the PCT intervention (mean difference -3.2 days (95% CI: -5.1 to -1.1),[2] and median (IQR) 9 (5 to 24) in the PCT group and 13 (3 to 45) in the control group[1]), which was not apparent from the ITT analyses. In addition there are some methodological issues which are inherent to the nature of the research question. Because studies are assessing the effects of providing additional information (PCT) to treating clinicians, it is not possible to blind study personnel to intervention group. Similarly, outcomes which relate to the extent of antibiotic exposure (i.e. treatment decisions) cannot be assessed blind to intervention group.

Our findings are in line with those of previously published systematic reviews, conducted in ICU[107-112] and mixed[113-116] settings, which have consistently found that the inclusion of PCT levels/algorithms in the information used to guide antibiotic treatment reduced antibiotic exposure without any adverse effects on clinical outcome.

We believe that our assessment provides information of direct relevance to UK clinical practice as we focus on two distinct secondary care settings, ED and ICU, in which PCT testing might routinely be applied as part of the decision making process on antibiotic treatment. These settings are considered separately, as people presenting to the ED are likely to have a different range and severity of conditions to those being treated in ICU settings. Where information was available, we have also considered adults and children separately. We have further structured our report to

provide information on the potential benefits of including PCT in clinical decision making processes, balanced against any possible adverse clinical effects.

The majority (12/18) of the included studies measured plasma/serum PCT levels using the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA). [2-5, 42, 44, 46, 47, 49, 53, 60, 63] Two studies measured plasma/serum PCT levels using the VIDAS BRAHMS PCT (bioMérieux, Marcy l'Etoile, France).[1, 54] We found no data on the clinical effectiveness of PCT algorithms/levels measured using the Elecsys BRAHMS PCT assay (Roche Diagnostics GmbH, Mannheim, Germany), the ADVIA Centaur BRAHMS PCT assay (Siemens Healthcare Diagnostics Ltd., Camberley, UK), or the LIAISON BRAHMS PCT assay (DiaSorin S.p.A., Saluggia, Italy).

It should also be noted that none of the studies included in the systematic review component of this assessment were conducted in the UK. Our review considers the effectiveness of adding PCT testing to the information used by clinicians to inform decisions on antibiotic treatment and, as such, differences in the behaviour/routine practice of clinicians in different countries and health care settings may influence the effectiveness of the PCT intervention. It is therefore unclear whether the data included in this assessment are generalisible to UK settings.

5.2.2 Cost-effectiveness

Our analyses is the most comprehensive full economic evaluation to date to examine cost per QALY of the addition of PCT testing to current clinical practice for adults with confirmed or highly suspected sepsis in an ICU setting, adults with suspected bacterial infection presenting to the ED and children with suspected bacterial infection presenting to the ED. In an effort to incorporate all relevant evidence, systematic searches were performed for all stochastic input parameters included in the economic analysis.

As in any economic model, a number of major and minor assumptions had to be made. It is important to understand the impact of these assumptions in order to correctly interpret the results of the economic analysis. The main uncertainty regarding the assessment of cost-effectiveness lies in the inability to explore long-term costs and effects (beyond six months), i.e. assuming long-term costs and effects do not impact the incremental outcomes. This includes (i) the potential costs and effects arising from reduced antibiotic resistance as a result of a decreased antibiotic treatment duration and; (ii) the long-term impact of short-term survival differences. Although, the long-term costs and effects of antibiotic resistance (due to decreased antibiotic treatment duration) are difficult to quantify, it is likely that inclusion of these costs and effects would make the cost-effectiveness ratio more favourable for PCT-guided treatment. Inclusion of the long-term

consequences that originate from short-term survival differences are also likely to favour PCT-guided treatment. However, for children presenting to the ED, these differences were so small that the long-term consequences are likely to be negligible. It was assumed that staying in the hospital would not have any additional impact on the utility (e.g. through adding a disutility). This can be regarded as a conservative assumption given that the hospital stay (both ICU and non-ICU) was shorter for PCT-guided treatment. Hence adding a disutility for hospital stay would make the results more favourable for PCT-guided treatment. Furthermore, the disutility for being on antibiotic treatment (reflecting antibiotic related adverse events) was conservatively assumed to be constant for all populations and settings. Although this disutility might be higher for the ICU due to the intravenous administration, incorporating a higher disutility would also favour PCT-guided treatment. Finally, uncertainty may arise since not all consequences are incorporated in the economic analysis, this includes adverse events other than antibiotic related adverse events. However, these adverse events probably do not differ between the comparators (see assessment of clinical effectiveness) and hence are unlikely to impact the incremental outcomes.

It should be emphasised that the uncertainty resulting from the above mentioned assumptions was not parameterised and is therefore not reflected in the probabilistic sensitivity analyses nor in the cost-effectiveness acceptability curves.

5.3 Uncertainties

5.3.1 Clinical effectiveness

There was a lack of data on the clinical effectiveness of including PCT levels/algorithms in the information used to guide antibiotic treatment decisions in children. We were only able to identify two RCTs, both conducted in children presenting to the ED with respiratory symptoms,[44, 53] and widening searches to include other study designs failed to yield any further relevant studies. In addition, all but one of the adult studies conducted in ED settings were in people presenting with respiratory symptoms. It is therefore unclear, whether our findings for the ED setting would be generalisable to adults or children with suspected bacterial infections in other sites. We are aware of one RCT, conducted in young children (aged 1 to 36 months) presenting to the ED with fever of unknown origin. This study did not meet our inclusion criteria because it used a qualitative PCT assay, but found that whether or not PCT test results were available to treating clinicians had no effect on antibiotic exposure or hospitalisation rates.[25]

There is less uncertainty around which patient groups, in the ICU setting, may benefit from treatment management guided by PCT. Studies in our systematic review, with a variety of infection-related inclusion criteria (suspected or confirmed sepsis,[2, 38] suspected bacterial infection or

development of sepsis whilst in the ICU,[46] severe acute pancreatitis,[57] and VAP[63]) found that the addition of a PCT algorithm to the information used to determine when to discontinue antibiotic treatment was associated with a reduction in the duration of antibiotic treatment. The use of PCT levels to monitor patients who are being treated in ICU settings, regardless of whether or not sepsis or bacterial infection are suspected, was outside the scope of this assessment. However, one excluded study identified by our searches, which randomised people with an expected ICU stay ≥24 hours (no infection criteria specified) to receive antibiotic treatment according to current clinical guidelines or according to current clinical guidelines supplemented by a drug escalation algorithm and intensified diagnostics based on daily PCT measurements.[117] This study found that the escalation strategy had no effect on 28 day all-cause mortality (absolute risk reduction 0.6% (95% CI: -4.7% to 5.9%), but was associated with small increases in the proportion of ICU days on mechanical ventilation (4.9% (95% CI: 3.0% to 6.7%)) and the risk of impaired renal function defined by a glomerular filtration rate of <60 mL/min/1.73 m^2 (RR 1.21 (95% CI:1.15 to 1.27)).[117] The results of this study support the idea that PCT measurements to be used only in selected populations (where bacterial infection/sepsis is suspected) and in conjunction with clinical judgement.

One further possible consideration is the extent to which the apparent effects on antibiotic exposure, seen in our assessment and other systematic review, of providing PCT information to treating clinicians may be mediated by increased information/levels of awareness of antibiotic prescribing issues. Trials of PCT algorithms generally provide clinicians with information/education on the interpretation of PCT levels and frequently classify antibiotic prescribing decisions that are not in line with the algorithm as 'overrules', this is unlikely to reflect the way PCT levels are used in practice and it is possible that additional 'message re-inforcement' may exaggerate the effects of PCT. It is also possible that information provision in itself, regardless of the nature of the information, may result in increased awareness of the issues around over prescribing of antibiotics and hence reduced prescription rates. Conversely, it could be argued that any effects of increased awareness may be expected to be present in both trial arms, simply as a result of participating in a research study. Only one of the studies included in our systematic review clearly reported that the information provided to clinicians in the control arm and clinical component of information provided to clinicians in the intervention arm were the same (approved reminder, including condition-specific recommendation for the duration of antibiotic treatment);[46] this study found a reduction in antibiotic exposure associated with the PCT intervention, arguing against increased awareness as a mediator of effect.

Despite the apparent reduction in antibiotic exposure associated with adding PCT levels/algorithms to the information used to guide antibiotic treatment decisions observed in this assessment and in other published systematic reviews, it remains uncertain whether similar effects could be achieved by other means (e.g. other biomarkers such as C-reactive protein (CRP)). It may be argued that CRP levels are part of current standard practice and, as such, any studies that included CRP in both arms, i.e. that compared PCT + standard clinical practice (including CRP) to standard clinical practice (including CRP), would meet the inclusion criteria for this assessment. Studies of this type could provide information on whether the addition of another biomarker (PCT) is beneficial. The studies included in our systematic review do not provide a detailed breakdown of which investigations were included in standard clinical practice. Eight of the RCTs included in our review reported baseline CRP levels in both study arms, indicating that CRP was part of standard practice.[1, 4, 42, 44, 46, 47, 49, 60] Six of these studies reported results indicating that the PCT intervention arm was associated with a reduction in antibiotic exposure outcomes,[4, 44, 46, 47, 49, 60] i.e. adding PCT to the information available to treating clinicians reduced participant antibiotic exposure in situations where CRP levels were also available. However, as discussed above, the availability of a biomarker assay result is unlikely to be equivalent to implementation of an algorithm which includes specific treatment advice linked to a range of decision thresholds. Comparison of PCT algorithms + standard practice to algorithms based on other biomarkers (e.g. CRP) + standard practice was outside the scope of this assessment, however, our searches identified one RCT of this type.[118] This study was conducted in ICU settings and included adults with severe sepsis or septic shock. It compared the use of a PCT-based algorithm to a CRP-based algorithm to inform when to discontinue antibiotic treatment. For both study arms the discontinuation algorithm was applied once there were no active signs of infection and the SOFA score was decreasing and in both arms the final discontinuation decision was at the discretion of the treating clinician. The PCT algorithm specified that where initial levels were <1 ng/mL PCT should be re-assessed on day four and where initial levels were ≥1 ng/mL PCT should be re-assessed on day five; if PCT was then <0.1 ng/mL or had decreased by ≥90% discontinuation was advised, if these criteria were not met PCT levels were repeated daily until discontinuation criteria were met or until seven days of antibiotic treatment. The CRP algorithm followed a similar structure and specified that where initial levels were <100 mg/L CRP should be re-assessed on day four and where initial levels were ≥100 mg/L PCT should be re-assessed on day five; if CRP was then <25 mg/L or had decreased by ≥50% discontinuation was advised, if these criteria were not met CRP levels were repeated daily until discontinuation criteria were met or until seven days of antibiotic treatment. This study found no difference in the duration of antibiotic therapy according to which algorithm was used, (median (IQR) 7.0 (6.0 to 8.5) days in the PCT group and 6.0 (5.0 to 7.0) days in the CRP group, hazard ratio

1.21 (95% CI: 0.77 to 1.30)) and no differences in resource use outcomes or adverse clinical outcomes.[118] This study may indicate that implementation of a CRP-based algorithm may have similar effects to a PCT-based algorithm, however, it should be noted that only a single study of this type was identified and this study did not include a control (standard care only) arm.

There is a lack of direct data to support the clinical effectiveness of PCT testing using some of the PCT assays currently available to NHS laboratories (Elecsys BRAHMS PCT assay, Roche Diagnostics GmbH, Mannheim, Germany; ADVIA Centaur BRAHMS PCT assay, Siemens Healthcare Diagnostics Ltd., Camberley, UK; LIAISON BRAHMS PCT assay, DiaSorin S.p.A., Saluggia, Italy). Where assay type was specified, most of the studies included in our systematic review used the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific Inc., Waltham, MA, USA), see Section 5.2.1, above. However, where another assay was used (VIDAS BRAHMS PCT (bioMérieux, Marcy l'Etoile, France)), there was no evidence to suggest a difference in effect between assays (see Section 3.2.3). In addition, all of the commercially available PCT assays use the same monoclonal anti-PCT antibody, under licence from Thermo Fisher Scientific Inc., Waltham, MA, USA; the main difference between assays being the method of detection (see Section 2.2). All commercial assays have been standardised using the BRAHMS PCT LIA. This was the original manual PCT assay and is not included in this assessment as it is no longer being marketed. However two studies using the LIA were identified by our searches; one assessed the addition of PCT levels to the information used to decide whether or not to initiate antibiotic treatment in patients post cardiac surgery and found that use of PCT was associated with a reduction in antibiotic exposure (RR 0.40 (95% CI: 0.25 to 0.63),[119] and the other assessed the addition of a PCT algorithm to the information used to decide when to discontinue antibiotics in people with severe sepsis who were being treated in an ICU and found that the PCT algorithm was associated with a reduction in the duration of antibiotic treatment (mean difference -1.70 days (95% CI: -2.39 to -1.01)).[120] Neither study found a statistically significant difference in any adverse clinical outcome between the intervention and control groups.[119, 120] The results of these two studies further support the view that there is no evidence to suggest that the effects of including PCT information in decisions about antibiotic treatment differ according to which PCT assay is used. With regards to the technical performance characteristics of different PCT assays, a study submitted in the information provided by Siemens Healthcare Diagnostics Ltd shows good agreement in the PCT levels measured in clinical samples between the Roche Elecsys PCT assay and the BRAHMS PCT Sensitive Kryptor assay (r = 0.987) and between the Siemens ADVIA Centaur PCT assay and the BRAHMS PCT Sensitive Kryptor assay (r= 0.977).[21] Given the lack of evidence to suggest any differences in clinical effects between different PCT assays, and the availability of data indicating good measurement consistency,

it may be reasonable to assume that the clinical effects of including PCT information in decisions about antibiotic treatment are likely to be consistent across different PCT assays.

It has been suggested that, if the use of PCT testing is associated with a reduction in antibiotic prescribing and in particular the use of broad spectrum antibiotic use in ICU settings, this may have healthcare system benefits in terms of a reduction in antibiotic resistance/healthcare associated infections. Evaluation of any possible long-term, healthcare system benefits was outside the scope of this assessment; further research in this area may be warranted if PCT testing is recommended.

5.3.2 Cost-effectiveness

The uncertainty regarding the generalisability of the results from the ED setting to other populations than patients with respiratory symptoms, as discussed in the clinical effectiveness section above, is also applicable to the cost-effectiveness estimates. Additionally, although most clinical studies were based in Europe (whenever reported), none of the studies were based in the UK. Hence the generalisability of the results to the UK settings is uncertain. This is particularly true for the resource use parameters (hospital stay) and the exact application of PCT (potentially affects antibiotic treatment duration and the number of tests) which might be setting dependent. As hospital stay was one of the main influential parameters, the economic outcomes may well differ for the UK. However, the scenario analyses showing that even when assuming no differences in hospital stay between the comparators, are reassuring that PCT might potentially be cost-effective in the UK for adults at the ICU and ED.

In short, PCT testing may be cost-effective in the UK. However, although the economic analysis indicates that there is little decision uncertainty, not all uncertainties can be captured in the parameters and thus be reflected in the outcomes of the economic assessment. This ‘scenario uncertainty’ includes the generalisability of the results to the UK setting. Consequently, the presented outcomes might provide a certain degree of pseudo-certainty. Therefore, it is important to note that the results of the economic assessment should be interpreted with caution. This applies in particular to the ED setting as another generalisability issue arises: the applicability of the presented outcomes to other patients than patients with respiratory symptoms. The paucity of evidence on long-term outcomes might further add to uncertainty.

6. CONCLUSIONS

6.1 Implications for service provision

The addition of a PCT algorithm to the information used to guide antibiotic treatment may reduce antibiotic exposure in adults being treated for suspected or confirmed sepsis in ICU settings and in adults presenting to the ED with respiratory symptoms and suspected bacterial infection, without any adverse consequences for clinical outcome. In ICU settings, the PCT algorithm was primarily used to inform decisions on when to discontinue antibiotic treatment, where as in ED settings the primary application was decisions on whether or not to initiate antibiotic treatment. The use of a PCT algorithm may also be associated with reductions hospital and ICU stay. Very limited data suggest that similar effects may apply for children presenting to the ED with respiratory symptoms and suspected bacterial infection, in particular the subgroup with CAP. No evidence was identified on the effectiveness using a PCT algorithm to guide antibiotic treatment for children with suspected or confirmed sepsis in the ICU.

Available evidence suggests that the addition of PCT testing to current clinical practice leads to cost savings and a very small QALY gain and thus dominates current practice. Hence PCT testing potentially represents a cost-effective use of NHS resources for adults with confirmed or highly suspected sepsis in an ICU setting, adults with suspected bacterial infection presenting to the ED and children with suspected bacterial infection presenting to the ED. However, although the economic analysis indicates that there is little decision uncertainty, not all uncertainties can be captured in the parameters and thus be reflected in the outcomes of the economic assessment. This 'scenario uncertainty' includes the generalisability of the results to the UK setting. Therefore, it is important to note that the results of the economic assessment should be interpreted with caution. This applies in particular to the ED setting as another generalisability issue arises: the applicability of the presented outcomes to other patients than patients with respiratory symptoms. The paucity of evidence on long-term outcomes might further add to uncertainty.

6.2 Suggested research priorities

Further studies are needed to assess the effectiveness of adding PCT algorithms to the information used to guide antibiotic treatment in children with suspected or confirmed sepsis in ICU settings. Additional research is needed to examine whether the outcomes presented in this report are fully generalisable to the UK setting and whether the outcomes found for the ED setting are also applicable for other patients than patients with respiratory symptoms. Finally, although it is only likely to add to the gain in effectiveness and/or cost savings for PCT-guided treatment, it would be of

relevance to examine long-term costs and effects of PCT-guided treatment, including its potential impact on antibiotic resistance.

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APPENDIX 1: LITERATURE SEARCH STRATEGIES

Clinical effectiveness search strategies

Rapid appraisal searches

The Cochrane Library
Searched: 07.04.14
Records found:

CDSR Issue 4 of 12, April 2014 = 14
DARE Issue 1 of 4, January 2014 = 13
HTA Issue 1 of 4, January 2014 = 0
NHS EED Issue 1 of 4, January 2014 = 5

#1 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees3265
#2 "systemic inflammatory response syndrome" or SIRS 1130
#3 sepsis* or septic* or sepses 6770
#4 bacill*emia* or bacter*emia* or endotox*emia* or pyoh*emia* or py*emia* 2020
#5 fusobacterium near/2 necrophorum 6
#6 Lemierre* near/2 (disease* or syndrome*) 1
#7 necrobacillosis or necrobacilloses or meningococc*emia or urosepsis or fung*emia or candid*emia 265
#8 Neisseria near/2 meningitidis near/2 bacter*emia 0
#9 staphylococc* near/2 bacter*emia 74
#10 (bacter*emic or bacterial or endotoxin* or toxi*) near/3 shock* 47
#11 toxic near/2 forward near/2 failure 0
#12 blood near/2 poison* 136
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 9831
#14 MeSH descriptor: [Protein Precursors] explode all trees 2483
#15 MeSH descriptor: [Calcitonin] this term only 553
#16 #14 and #15 141
#17 PCT 369
#18 procalcitonin or "pro-calcitonin" or "56645-65-9" or (calcitonin near/2 precursor*) 270
#19 brahms or KRYPTOR or "b r a h m s" 21
#20 #16 or #17 or #18 or #19 543
#21 #13 and #20 131
(CDSR = 14; DARE = 13; HTA = 0; NHS EED = 5)

PROSPERO
http://www.crd.york.ac.uk/prospero/ up to 2014/04/09
Searched: 07.04.14

SEARCH TERM (all fields)	RECORDS
sepsis or septic or blood poisoning	49
procalcitonin or pro-calcitonin or calcitonin or brahms or kryptor	5
Total before deduplication	54
Total after deduplication	52

National Institute for Health and Care Excellence (NICE) Guidance
http://www.nice.org.uk/ up to 2014/4/8
Searched: 08.04.14

Limited to information type "Guidance"

SEARCH TERM (all fields)	Records
brahms	2
kryptor	1
procalcitonin	3
pro-calcitonin	0
calcitonin	1
Sepsis	73
Septic	16
blood poisoning	10
Total	106

NIHR Health Technology Assessment (HTA) Programme
http://www.hta.ac.uk/ up to 2014/04/08
Searched: 08.04.14

SEARCH TERM (all fields)	Search website	Search Project Portfolio (hand-sifted for relevance)
brahms	0	0
kryptor	0	0
procalcitonin	0	3
pro-calcitonin	0	0
calcitonin	0	0
Sepsis	0	12
Septic	0	1
blood poisoning	0	0
Total	0	16
Total after deduplication	0	16

US Food & Drug Administration (FDA)
http://www.fda.gov/ up to 2014/04/08
Searched: 08.04.14

Searched whole site

SEARCH TERM (all fields)	Records
brahms	48
procalcitonin	48
kryptor	6
Total	103

Guidelines International Network (G-I-N)
http://www.g-i-n.net/ up to 2014/04/09
Searched: 09.04.14

SEARCH TERM	Search website	Search guidelines	Total
brahms	1	0	1
kryptor	0	0	0
procalcitonin	0	0	0
pro-calcitonin	0	0	0
calcitonin	0	0	0
Sepsis	4	11	15
Septic	1	2	3
blood poisoning	0	0	0
Total	6	13	19
Total after deduplication	5	10	15

National Guidelines Clearinghouse (NGCH)
http://www.guideline.gov/index.aspx up to 2014/04/09
Searched: 09.04.14

SEARCH TERM (all fields)	Records
brahms	0
kryptor	0
procalcitonin OR pro-calcitonin	11
calcitonin	34
Sepsis or septic	173
"blood poisoning"	0
Total	218

Medicines and Healthcare Products Regulatory Agency (MHRA)
http://www.mhra.gov.uk/index.htm up to 2014/04/09
Searched: 09.04.14

SEARCH TERM (all fields)	Records
brahms or kryptor	10
procalcitonin or pro-calcitonin	2
"blood poisoning"	10
Total	22

The Medion Database
http://www.mediondatabase.nl/ up to 2014/4/9
Searched: 23.9.14

SEARCH TERM (Topic field)	RECORDS
brahms	0

kryptor	0
procalcitonin	0
pro-calcitonin	0
calcitonin	0
Sepsis	0
Septic	0
blood poisoning	0
Total	0

RCT searches

Embase (OvidSP)

1974 to 2014 June 27
Date searched: 30.6.14
Records found: 1210

1 exp systemic inflammatory response syndrome/ (172787)
2 exp bacterial infection/ (745043)
3 (systemic inflammatory response syndrome$ or SIRS).ti,ab,ot,hw. (10736)
4 (sepsis$ or septic$ or sepses).ti,ab,ot,hw. (191638)
5 (bacill?emia$ or bacter?emia$ or endotox?emia$ or pyoh?emia$ or py?emia$).ti,ab,ot,hw. (48133)
6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (1164)
7 (Lemierre$ adj2 (disease$ or syndrome$)).ti,ab,ot,hw. (798)
8 (necrobacillosis or necrobacilloses or meningococc?emia or urosepsis).ti,ab,ot,hw. (3762)
9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (19)
10 tetanus.ti,ab,ot,hw. (34768)
11 ((bacter?emic or bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,ot,hw. (11163)
12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
13 (blood adj2 poison$).ti,ab,ot,hw. (257)
14 infect$.ti,ab,ot. (1461612)
15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection or disease$)).ti,ab,ot,hw. (60674)
16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter$ or legionnaire$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc$ or Streptococc$ or "e coli").ti,ab,ot,hw. (475125)
17 or/1-16 (2327414)
18 Procalcitonin/ (4820)
19 PCT.ti,ab,ot. (6593)
20 (procalcitonin or pro-calcitonin or 56645-65-9 or (calcitonin adj2 precursor$)).ti,ab,ot,hw,rn,tn. (5087)
21 brahms.af. (915)
22 KRYPTOR.af. (221)
23 b r a h m s.af. (11)
24 or/18-23 (10280)
25 17 and 24 (4786)
26 Random$.tw. or clinical trial$.mp. or exp health care quality/ (3261790)
27 25 and 26 (1231)
28 animal/ (1569119)
29 animal experiment/ (1782343)

30 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5658580)
31 or/28-30 (5658580)
32 exp human/ (14900947)
33 human experiment/ (326401)
34 or/32-33 (14902376)
35 31 not (31 and 34) (4528206)
36 27 not 35 (1218)
37 limit 36 to yr="1995 -Current" (1210)

Based on Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in Embase. Journal of the Medical Library Association 2006;94(1):41-7.

MEDLINE (OvidSP)

1946 to June Week 3 2014
Date searched: 30.6.14
Records found: 739

1 exp Systemic Inflammatory Response Syndrome/ (94981)
2 exp bacterial infections/ (719780)
3 (systemic inflammatory response syndrome$ or SIRS).ti,ab,ot,hw. (6774)
4 (sepsis$ or septic$ or sepses).ti,ab,ot,hw. (123216)
5 (bacill?emia$ or bacter?emia$ or endotox?emia$ or pyoh?emia$ or py?emia$).ti,ab,ot,hw. (36734)
6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (896)
7 (Lemierre$ adj2 (disease$ or syndrome$)).ti,ab,ot,hw. (483)
8 (necrobacillosis or necrobacilloses or meningococc?emia or urosepsis).ti,ab,ot,hw. (1520)
9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (17)
10 tetanus.ti,ab,ot,hw. (24082)
11 ((bacter?emic or bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,ot,hw. (8473)
12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
13 (blood adj2 poison$).ti,ab,ot,hw. (139)
14 infect$.ti,ab,ot. (1157024)
15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection$ or disease$)).ti,ab,ot,hw. (46704)
16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter$ or legionnaire$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc$ or Streptococc$ or "e coli").ti,ab,ot,hw. (367834)
17 or/1-16 (1896545)
18 exp Protein Precursors/ and Calcitonin/ (2200)
19 PCT.ti,ab,ot. (3921)
20 (procalcitonin or pro-calcitonin or 56645-65-9 or (calcitonin adj2 precursor$)).ti,ab,ot,hw,rn. (2468)
21 brahms.af. (318)
22 KRYPTOR.af. (68)
23 b r a h m s.af. (18)

24 or/18-23 (5718)
25 17 and 24 (2279)
26 randomized controlled trial.pt. (376175)
27 controlled clinical trial.pt. (88531)
28 randomized.ab. (274544)
29 placebo.ab. (146796)
30 drug therapy.fs. (1708719)
31 randomly.ab. (194627)
32 trial.ab. (284610)
33 groups.ab. (1250317)
34 or/26-33 (3208598)
35 exp animals/ not (exp animals/ and humans/) (3954108)
36 34 not 35 (2730725)
37 25 and 36 (752)
38 limit 37 to yr="1995 -Current" (739)

Trials filter:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update (OvidSP)

June 27, 2014
Date searched: 30.6.14
Records found: 67

1 exp Systemic Inflammatory Response Syndrome/ (100)
2 exp bacterial infections/ (628)
3 (systemic inflammatory response syndrome$ or SIRS).ti,ab,ot,hw. (361)
4 (sepsis$ or septic$ or sepses).ti,ab,ot,hw. (6694)
5 (bacill?emia$ or bacter?emia$ or endotox?emia$ or pyoh?emia$ or py?emia$).ti,ab,ot,hw. (1503)
6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (52)
7 (Lemierre$ adj2 (disease$ or syndrome$)).ti,ab,ot,hw. (49)
8 (necrobacillosis or necrobacilloses or meningococc?emia or urosepsis).ti,ab,ot,hw. (121)
9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (2)
10 tetanus.ti,ab,ot,hw. (793)
11 ((bacter?emic or bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,ot,hw. (229)
12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
13 (blood adj2 poison$).ti,ab,ot,hw. (15)
14 infect$.ti,ab,ot. (77602)
15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection$ or disease$)).ti,ab,ot,hw. (1024)
16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter$ or legionnaire$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc$ or Streptococc$ or "e coli").ti,ab,ot,hw. (15810)
17 or/1-16 (93626)

18 exp Protein Precursors/ and Calcitonin/ (4)
19 PCT.ti,ab,ot. (358)
20 (procalcitonin or pro-calcitonin or 56645-65-9 or (calcitonin adj2 precursor$)).ti,ab,ot,hw,rn. (291)
21 brahms.af. (26)
22 KRYPTOR.af. (7)
23 b r a h m s.af. (0)
24 or/18-23 (525)
25 17 and 24 (255)
26 randomized controlled trial.pt. (957)
27 controlled clinical trial.pt. (84)
28 randomized.ab. (23138)
29 placebo.ab. (8510)
30 drug therapy.fs. (1798)
31 randomly.ab. (20509)
32 trial.ab. (24490)
33 groups.ab. (117569)
34 or/26-33 (157619)
35 exp animals/ not (exp animals/ and humans/) (2712)
36 34 not 35 (157125)
37 25 and 36 (67)
38 limit 37 to yr="1995 -Current" (67)

Trials filter:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

PubMed http://www.ncbi.nlm.nih.gov/pubmed/

1995 to 14.7.14
Date searched: 14.7.14
Records found: 86

- This strategy aims to identify records that are on PubMed, but not included in MEDLINE or MEDLINE In-Process (OvidSP). Line #7 limits the search results in this way.
- The sepsis/bacterial infection facet was excluded to keep search as broad as possible

#10,"Search ((((((((((protein precursors[MeSH Terms]) AND calcitonin[MeSH Terms])) OR PCT[Title/Abstract]) OR (((procalcitonin[Title/Abstract]) OR ""pro-calcitonin""[Title/Abstract]) OR ""calcitonin precursor*""[Title/Abstract])) OR (((brahms) OR kryptor) OR ""b r a h m s""))) AND (((((""randomized controlled trial""[Publication Type]) OR ""controlled clinical trial""[Publication Type])) OR (((((randomized[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract])) OR ""drug therapy""[MeSH Subheading])) AND ((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]))))) NOT (animals [mh] NOT humans [mh])",86
#9,"Search animals [mh] NOT humans [mh]",3904987

#8,"Search (((((((protein precursors[MeSH Terms]) AND calcitonin[MeSH Terms])) OR PCT[Title/Abstract]) OR (((procalcitonin[Title/Abstract]) OR ""pro-calcitonin""[Title/Abstract]) OR ""calcitonin precursor*""[Title/Abstract])) OR (((brahms) OR kryptor) OR ""b r a h m s""))) AND (((((""randomized controlled trial""[Publication Type]) OR ""controlled clinical trial""[Publication Type])) OR (((((randomized[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract])) OR ""drug therapy""[MeSH Subheading])) AND ((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]))",86
#7,"Search (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])",1792621
#6,"Search ((((""randomized controlled trial""[Publication Type]) OR ""controlled clinical trial""[Publication Type])) OR (((((randomized[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract])) OR ""drug therapy""[MeSH Subheading]",3394868
#5,"Search (((((protein precursors[MeSH Terms]) AND calcitonin[MeSH Terms])) OR PCT[Title/Abstract]) OR (((procalcitonin[Title/Abstract]) OR ""pro-calcitonin""[Title/Abstract]) OR ""calcitonin precursor*""[Title/Abstract])) OR (((brahms) OR kryptor) OR ""b r a h m s"")",6314
#4,"Search ((brahms) OR kryptor) OR ""b r a h m s""",394
#3,"Search ((procalcitonin[Title/Abstract]) OR ""pro-calcitonin""[Title/Abstract]) OR ""calcitonin precursor*""[Title/Abstract]",2617
#2,"Search PCT[Title/Abstract]",4327
#1,"Search (protein precursors[MeSH Terms]) AND calcitonin[MeSH Terms]",2189

Trials filter:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

CINAHL (EBSCO)

1995 – 25.6.14
Date searched: 30.6.14
Records found: 205

S1 (MH "Systemic Inflammatory Response Syndrome+") (6,393)
S2 (MH "Bacterial Infections+") (50,338)
S3 "systemic inflammatory response syndrome" or SIRS (965)
S4 sepsis* or septic* or sepses (11,696)
S5 bacill#emia* or bacter#emia* or endotox#emia* or pyoh#emia* or py#emia* (14,336)
S6 fusobacterium N2 necrophorum (26)
S7 Lemierre* N2 (disease* or syndrome*) (93)
S8 necrobacillosis or necrobacilloses or meningococc#emia or urosepsis (116)
S9 Neisseria N2 meningitidis N2 bacter#emia (1)
S10 tetanus (1,899)
S11 (bacter#emic or bacterial or endotoxin* or toxi*) N3 shock* (368)
S12 toxic N2 forward N2 failure (0)
S13 blood N2 poison* (133)
S14 infect* (159,239)

S15 bacterial N2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection* or disease*) (4,245)
S16 bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc* or "e coli" (18,464)
S17 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 (193,148)
S18 (MH "Protein Precursors+") (2,085)
S19 (MH "Calcitonin") (816)
S20 S18 AND S19 (199)
S21 PCT (725)
S22 procalcitonin or "pro-calcitonin" or "56645-65-9" or (calcitonin N2 precursor*) (376)
S23 brahms or KRYPTOR or "b r a h m s" (12)
S24 S20 OR S21 OR S22 OR S23 (1,011)
S25 S17 AND S24 (393)
S26 (MH "Prognosis+") (146,028)
S27 (MH "Study Design+") (521,326)
S28 random* (144,824)
S29 S26 OR S27 OR S28 (629,916)
S30 S25 AND S29 (205)
S31 (ZR "1995") or (ZR "1996") or (ZR "1997") or (ZR "1998") or (ZR "1999") or (ZR "2000") or (ZR "2001") or (ZR "2002") or (ZR "2003") or (ZR "2004") or (ZR "2005") or (ZR "2006") or (ZR "2007") or (ZR "2008") or (ZR "2009") or (ZR "2010") or (ZR "2011") or (ZR "2012") or (ZR "2013") or (ZR "2014") (2,807,096)
S32 S30 AND S31 (205)

Trials Filter
Wong SS, Wilczynski NL, Haynes RB. Optimal CINAHL search strategies for identifying therapy studies and review articles. J Nurs Scholarsh 2006;38(2):194-199.

Cochrane Central Register of Controlled Trials (The Cochrane Library - Wiley)

Issue 5 of 12, May 2014
Date searched: 30.06.14
Records found: 203

#1 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 3289
#2 [mh "bacterial infections"] 14301
#3 "systemic inflammatory response syndrome" or SIRS 1164
#4 sepsis* or septic* or sepses 6903
#5 bacill*emia* or bacter*emia* or endotox*emia* or pyoh*emia* or py*emia* 2052
#6 fusobacterium near/2 necrophorum 6
#7 Lemierre* near/2 (disease* or syndrome*) 1
#8 necrobacillosis or necrobacilloses or meningococc*emia or urosepsis 82
#9 Neisseria near/2 meningitidis near/2 bacter*emia 0
#10 tetanus 1529
#11 (bacter*emic or bacterial or endotoxin* or toxi*) near/3 shock* 47
#12 toxic near/2 forward near/2 failure 0
#13 blood near/2 poison* 136
#14 infect* 69614

#15 bacterial near/2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection* or disease*) 1954
#16 bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc* or "e coli" 8400
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 79707
#18 MeSH descriptor: [Protein Precursors] explode all trees 2487
#19 MeSH descriptor: [Calcitonin] this term only 557
#20 #18 and #19 142
#21 PCT 374
#22 procalcitonin or "pro-calcitonin" or "56645-65-9" or (calcitonin near/2 precursor*) 288
#23 brahms or KRYPTOR or "b r a h m s" 22
#24 #20 or #21 or #22 or #23 561
#25 #17 and #24 Publication Year from 1995 to 2014, in Trials 203

Science Citation Index (Web of Science)

1995 – 27.6.14
Date searched: 30.06.14
Records found: 1292

 # 27 1,292 #25 not #26
26 1,748,209 TOPIC: (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)
25 1,341 #24 AND #20
24 4,218,379 #23 OR #22 OR #21
23 779,600 TOPIC: ((study OR studies) SAME design)
22 3,726,032 TOPIC: ((clinic* SAME trial*) OR (placebo* OR random* OR control* OR prospectiv*))
21 173,285 TOPIC: ((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
20 3,010 #19 AND #15
19 9,574 #18 OR #17 OR #16
18 363 TOPIC: (brahms or KRYPTOR or "b r a h m s")
17 3,384 TOPIC: (procalcitonin or "pro-calcitonin" or "56645-65-9" or (calcitonin near/2 precursor*))
16 7,037 TOPIC: (PCT)
15 1,203,220 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
14 239,288 TOPIC: (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc* or "e coli")
13 17,350 TOPIC: (bacterial near/2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection* or disease*))
12 973,337 TOPIC: (infect*)
11 108 TOPIC: (blood near/2 poison*)
10 0 TOPIC: (toxic near/2 forward near/2 failure)
9 6,314 TOPIC: ((bacter$emic or bacterial or endotoxin* or toxi*) near/3 shock*)
8 9,233 TOPIC: (tetanus)

7 7 TOPIC: (Neisseria near/2 meningitidis near/2 bacter$emia)
6 1,124 TOPIC: (necrobacillosis or necrobacilloses or meningococc$emia or urosepsis)
5 488 TOPIC: (Lemierre* near/2 (disease* or syndrome*))
4 525 TOPIC: (fusobacterium near/2 necrophorum)
3 4,297 TOPIC: (bacill$emia* or bacter$emia* or endotox$emia* or pyoh$emia* or py$emia*)
2 87,338 TOPIC: (sepsis* or septic* or sepses)
1 14,020 TOPIC: ("systemic inflammatory response syndrome" or SIRS)

LILACS (Latin American and Caribbean Health Sciences Literature)
http://regional.bvsalud.org/php/index.php?lang=en

1995 to date
Date searched: 01.07.14
Records found: 5

procalcitonin OR pct OR brahms OR kryptor AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials")

NIHR Health Technology Assessment Programme
http://www.nets.nihr.ac.uk/programmes/hta

1995 to date
Date searched: 01.07.14
Records found: 0

procalcitonin OR pct OR brahms OR kryptor

ClinicalTrials.gov http://clinicaltrials.gov/

Date searched: 14.7.14
Records found: 136

procalcitonin OR "pro-calcitonin" OR "calcitonin precursor"

Current Controlled Trials http://www.controlled-trials.com

Date searched: 14.7.14
Records found: 59

Procalcitonin* OR pro-calcitonin OR calcitonin precursor*

WHO International Clinical Trials Registry Platform (ICTRP) http://www.who.int/ictrp/en/

Date searched: 14.7.14
Records found: 118

Procalcitonin* OR "pro-calcitonin" OR "calcitonin precursor*"

Royal College of Paediatrics and Child health (RCPCH) meetings
http://adc.bmj.com/content/supplemental
Date searched: 16.9.14
Records found: 0
Limits: 2009 – 2014
Title field only

	PCT	procalcitonin	pro-calcitonin	calcitonin precursor	brahms	KRYPTOR	TOTAL
2009	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0
2011	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0
2013	0	0	0	0	0	0	0
2014	0	0	0	0	0	0	0
TOTAL							0

ECCMID (European Congress of Clinical Microbiology and Infectious Diseases)
https://www.escmid.org/research_projects/eccmid/past_eccmids/
Date searched: 16.9.14
Records found: 31
Limits: 2009 – 2014
Title field only

	PCT	procalcitonin	pro-calcitonin	calcitonin precursor	brahms	KRYPTOR	TOTAL
2009	0 – oral 0 - Posters	0 – oral 5 - posters	0 – oral 0 - posters	0 – oral 0 - posters	0 – oral 0 - posters	0 – oral 0 - posters	0 – oral 5 - posters
2010	1 – oral 2 - posters	2 – oral 2 - posters	0 – oral 0 - posters	0 – oral 0 - posters	0 – oral 0 – oral	0 – oral 0 - posters	3 – oral 4 - posters
2011	0 – oral Posters - NA	1 – oral Posters - NA	0 –oral Posters - NA	0 – oral Posters - NA	0 – oral Posters - NA	0 – oral Posters- NA	1 oral Posters - NA
2012	0	5	0	0	0	0	5
2013	1	3 (plus 1 dupe)	0	0	0	0	4
2014	0	9	0	0	0	0	9
TOTAL							**31**

International Symposium on Intensive Care and Emergency Medicine
http://ccforum.com/supplements/
Date searched: 16.9.2014

Records found: 25
Limits: 2009 – 2014
Title field only

	PCT	procalcitonin	pro-calcitonin	calcitonin precursor	brahms	KRYPTOR	TOTAL
2009	0	5	0	0	0	0	5
2010	0	5	0	0	0	0	5
2011	0	3	0	0	0	0	3
2012	0	5	0	0	0	0	5
2013	0	4	0	0	0	0	4
2014	0	3	0	0	0	0	3
TOTAL	0	25	0	0	0	0	25

Paediatric searches

Embase (Ovid SP)

1974 to 2014 August 29
Date searched: 2.9.14
Records found: 297

1 exp systemic inflammatory response syndrome/ (175423)
2 exp bacterial infection/ (750468)
3 (systemic inflammatory response syndrome$ or SIRS).ti,ab,ot,hw. (10939)
4 (sepsis$ or septic$ or sepses).ti,ab,ot,hw. (194269)
5 (bacill?emia$ or bacter?emia$ or endotox?emia$ or pyoh?emia$ or py?emia$).ti,ab,ot,hw. (48625)
6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (1168)
7 (Lemierre$ adj2 (disease$ or syndrome$)).ti,ab,ot,hw. (804)
8 (necrobacillosis or necrobacilloses or meningococc?emia or urosepsis).ti,ab,ot,hw. (3815)
9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (19)
10 tetanus.ti,ab,ot,hw. (34954)
11 ((bacter?emic or bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,ot,hw. (11223)
12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
13 (blood adj2 poison$).ti,ab,ot,hw. (259)
14 infect$.ti,ab,ot. (1477857)
15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection$ or disease$)).ti,ab,ot,hw. (61241)
16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter$ or legionnaire$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc$ or Streptococc$ or "e coli").ti,ab,ot,hw. (478890)
17 or/1-16 (2349530)
18 Procalcitonin/ (5000)
19 PCT.ti,ab,ot. (6741)
20 (procalcitonin or pro-calcitonin or 56645-65-9 or (calcitonin adj2 precursor$)).ti,ab,ot,hw,rn,tn. (5268)
21 brahms.af. (929)
22 KRYPTOR.af. (225)
23 b r a h m s.af. (11)

24 or/18-23 (10524)
25 Emergency Treatment/ (14191)
26 Evidence Based Emergency Medicine/ (197)
27 Pediatric Advanced Life Support/ (421)
28 exp Emergency Care/ (22685)
29 Emergency/ (37050)
30 Emergency Medicine/ (27958)
31 Emergency Health Service/ (67376)
32 Emergency Patient/ (1522)
33 Emergency Ward/ (64201)
34 Intensive Care/ (88402)
35 Intensive Care Unit/ (86833)
36 (intensive care or high dependency unit$ or intensive therapy unit$).ti,ab,ot,hw. (213198)
37 (ICU or ICUs or PICU or PICUs or HDU or HDUs or CCU or CCUs or ITU or ITUs or ER or ERs or ED or EDs or AAU or AAUs).ti,ab,ot. (224054)
38 ((accident adj2 emergency) or "A&E" or "A & E").ti,ab,ot,hw. (31162)
39 ((emergency or emergencies) adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room or rooms or ward$ or care or medic$ or interven$ or therap$ or hospital$ or service$ or patient$ or unit$ or centre$ or center$ or facility or facilities)).ti,ab,ot,hw. (235516)
40 ((acute or critical) adj3 (admit$ or admission$ or care or medic$ or service$ or patient$)).ti,ab,ot,hw. (227520)
41 acute assessment unit$.ti,ab,ot,hw. (33)
42 (casualty adj2 (department$ or admit$ or admission$ or patient$)).ti,ab,ot,hw. (906)
43 or/25-42 (795109)
44 child/ or boy/ or girl/ or hospitalized child/ or preschool child/ or school child/ or toddler/ (1576924)
45 exp adolescent/ (1228544)
46 exp puberty/ (31712)
47 pediatrics/ or child urology/ (60377)
48 (paediatr$ or pediatr$).ti,ab,ot. (327061)
49 (Child$ or preschool$ or pre-school$ or toddler$ or juvenile$ or kid or kids).ti,ab,ot. (1300129)
50 (teen or teens or teenage$ or teen-age$ or adolescen$ or postpubescen$ or pubescen$ or minors or youth$ or puberty).ti,ab,ot. (358040)
51 or/44-50 (2777254)
52 17 and 24 and 43 and 51 (299)
53 animal/ (1574790)
54 animal experiment/ (1795561)
55 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5695924)
56 or/53-55 (5695924)
57 exp human/ (15058258)
58 human experiment/ (328401)
59 or/57-58 (15059687)
60 56 not (56 and 59) (4553031)
61 52 not 60 (299)
62 limit 61 to yr="1995 -Current" (297)

MEDLINE(OvidSP)

1946 to August Week 3 2014
Date searched: 2.9.14
Records found: 202

1 exp Systemic Inflammatory Response Syndrome/ (96440)
2 exp bacterial infections/ (728567)
3 (systemic inflammatory response syndrome$ or SIRS).ti,ab,ot,hw. (6898)
4 (sepsis$ or septic$ or sepses).ti,ab,ot,hw. (125025)
5 (bacill?emia$ or bacter?emia$ or endotox?emia$ or pyoh?emia$ or py?emia$).ti,ab,ot,hw. (37237)
6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (902)
7 (Lemierre$ adj2 (disease$ or syndrome$)).ti,ab,ot,hw. (488)
8 (necrobacillosis or necrobacilloses or meningococc?emia or urosepsis).ti,ab,ot,hw. (1539)
9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (17)
10 tetanus.ti,ab,ot,hw. (24411)
11 ((bacter?emic or bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,ot,hw. (8538)
12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
13 (blood adj2 poison$).ti,ab,ot,hw. (140)
14 infect$.ti,ab,ot. (1174805)
15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection$ or disease$)).ti,ab,ot,hw. (47254)
16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter$ or legionnaire$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc$ or Streptococc$ or "e coli").ti,ab,ot,hw. (371949)
17 or/1-16 (1922388)
18 exp Protein Precursors/ and Calcitonin/ (2245)
19 PCT.ti,ab,ot. (4007)
20 (procalcitonin or pro-calcitonin or 56645-65-9 or (calcitonin adj2 precursor$)).ti,ab,ot,hw,rn. (2522)
21 brahms.af. (323)
22 KRYPTOR.af. (73)
23 b r a h m s.af. (18)
24 or/18-23 (5836)
25 Emergency Treatment/ (8299)
26 Evidence-Based Emergency Medicine/ (216)
27 Life Support Care/ (7323)
28 emergency medical services/ or emergency service, hospital/ (74803)
29 Emergencies/ (34784)
30 Emergency Medicine/ (9931)
31 intensive care units/ or intensive care units, pediatric/ or respiratory care units/ (41628)
32 critical care/ or intensive care/ (40217)
33 (intensive care or high dependency unit$ or intensive therapy unit$).ti,ab,ot,hw. (111650)
34 (ICU or ICUs or PICU or PICUs or HDU or HDUs or CCU or CCUs or ITU or ITUs or ER or ERs or ED or EDs or AAU or AAUs).ti,ab,ot. (138941)
35 ((accident adj2 emergency) or "A&E" or "A & E").ti,ab,ot,hw. (18920)
36 ((emergency or emergencies) adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room or rooms or ward$ or care or medic$ or interven$ or therap$ or hospital$ or service$ or patient$ or unit$ or centre$ or center$ or facility or facilities)).ti,ab,ot,hw. (148389)

37 ((acute or critical) adj3 (admit$ or admission$ or care or medic$ or service$ or patient$)).ti,ab,ot,hw. (171915)
38 acute assessment unit$.ti,ab,ot,hw. (14)
39 (casualty adj2 (department$ or admit$ or admission$ or patient$)).ti,ab,ot,hw. (688)
40 or/25-39 (534145)
41 adolescent/ or exp child/ (2449325)
42 Minors/ (2323)
43 Puberty/ (11355)
44 Pediatrics/ (40916)
45 (paediatr$ or pediatr$).ti,ab,ot. (213041)
46 (Child$ or preschool$ or pre-school$ or toddler$ or juvenile$ or kid or kids).ti,ab,ot. (1007516)
47 (teen or teens or teenage$ or teen-age$ or adolescen$ or postpubescen$ or pubescen$ or minors or youth$ or puberty).ti,ab,ot. (271680)
48 or/41-47 (2772896)
49 17 and 24 and 40 and 48 (204)
50 exp animals/ not (exp animals/ and humans/) (3998545)
51 49 not 50 (204)
52 limit 51 to yr="1995 -Current" (202)

MEDLINE In-Process & Other Non-Indexed Citations (OvidSP)

August 29, 2014
Date searched: 2.9.14
Records found: 12

1 exp Systemic Inflammatory Response Syndrome/ (60)
2 exp bacterial infections/ (328)
3 (systemic inflammatory response syndrome$ or SIRS).ti,ab,ot,hw. (399)
4 (sepsis$ or septic$ or sepses).ti,ab,ot,hw. (7204)
5 (bacill?emia$ or bacter?emia$ or endotox?emia$ or pyoh?emia$ or py?emia$).ti,ab,ot,hw. (1555)
6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (53)
7 (Lemierre$ adj2 (disease$ or syndrome$)).ti,ab,ot,hw. (49)
8 (necrobacillosis or necrobacilloses or meningococc?emia or urosepsis).ti,ab,ot,hw. (123)
9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (2)
10 tetanus.ti,ab,ot,hw. (794)
11 ((bacter?emic or bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,ot,hw. (251)
12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
13 (blood adj2 poison$).ti,ab,ot,hw. (17)
14 infect$.ti,ab,ot. (80478)
15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection$ or disease$)).ti,ab,ot,hw. (1052)
16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter$ or legionnaire$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc$ or Streptococc$ or "e coli").ti,ab,ot,hw. (16515)
17 or/1-16 (97168)
18 exp Protein Precursors/ and Calcitonin/ (5)
19 PCT.ti,ab,ot. (412)
20 (procalcitonin or pro-calcitonin or 56645-65-9 or (calcitonin adj2 precursor$)).ti,ab,ot,hw,rn. (355)

21 brahms.af. (27)
22 KRYPTOR.af. (5)
23 b r a h m s.af. (0)
24 or/18-23 (602)
25 Emergency Treatment/ (7)
26 Evidence-Based Emergency Medicine/ (7)
27 Life Support Care/ (2)
28 emergency medical services/ or emergency service, hospital/ (84)
29 Emergencies/ (7)
30 Emergency Medicine/ (12)
31 intensive care units/ or intensive care units, pediatric/ or respiratory care units/ (34)
32 critical care/ or intensive care/ (28)
33 (intensive care or high dependency unit$ or intensive therapy unit$).ti,ab,ot,hw. (7281)
34 (ICU or ICUs or PICU or PICUs or HDU or HDUs or CCU or CCUs or ITU or ITUs or ER or ERs or ED or EDs or AAU or AAUs).ti,ab,ot. (14791)
35 ((accident adj2 emergency) or "A&E" or "A & E").ti,ab,ot,hw. (1794)
36 ((emergency or emergencies) adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room or rooms or ward$ or care or medic$ or interven$ or therap$ or hospital$ or service$ or patient$ or unit$ or centre$ or center$ or facility or facilities)).ti,ab,ot,hw. (10372)
37 ((acute or critical) adj3 (admit$ or admission$ or care or medic$ or service$ or patient$)).ti,ab,ot,hw. (11272)
38 acute assessment unit$.ti,ab,ot,hw. (3)
39 (casualty adj2 (department$ or admit$ or admission$ or patient$)).ti,ab,ot,hw. (34)
40 or/25-39 (38271)
41 adolescent/ or exp child/ (1534)
42 Minors/ (1)
43 Puberty/ (3)
44 Pediatrics/ (38)
45 (paediatr$ or pediatr$).ti,ab,ot. (18203)
46 (Child$ or preschool$ or pre-school$ or toddler$ or juvenile$ or kid or kids).ti,ab,ot. (65057)
47 (teen or teens or teenage$ or teen-age$ or adolescen$ or postpubescen$ or pubescen$ or minors or youth$ or puberty).ti,ab,ot. (23132)
48 or/41-47 (84088)
49 17 and 24 and 40 and 48 (12)
50 exp animals/ not (exp animals/ and humans/) (2110)
51 49 not 50 (12)
52 limit 51 to yr="1995 -Current" (12)

PubMed http://www.ncbi.nlm.nih.gov/pubmed/

1995 to 2.9.14
Date searched: 2.9.14
Records found: 26

- This strategy aims to identify records that are on PubMed, but not included in MEDLINE or MEDLINE In-Process (OvidSP). Line #9 limits the search results in this way.

#10 Search ((((((((((protein precursors[MeSH Terms]) AND calcitonin[MeSH Terms])) OR PCT[Title/Abstract]) OR (procalcitonin[Title/Abstract] OR "pro-calcitonin"[Title/Abstract] OR

"calcitonin precursor*"[Title/Abstract])) OR (brahms OR kryptor OR "b r a h m s"))) AND (emergency OR emergencies OR intensive OR acute OR critical OR casualty)) AND (child OR children OR adolescence OR adolescents OR paediatric OR pediatric))) AND (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) 26

#9 Search pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb] 1816157

#8 Search (((((((protein precursors[MeSH Terms]) AND calcitonin[MeSH Terms])) OR PCT[Title/Abstract]) OR (procalcitonin[Title/Abstract] OR "pro-calcitonin"[Title/Abstract] OR "calcitonin precursor*"[Title/Abstract])) OR (brahms OR kryptor OR "b r a h m s"))) AND (emergency OR emergencies OR intensive OR acute OR critical OR casualty)) AND (child OR children OR adolescence OR adolescents OR paediatric OR pediatric) 480

#7 Search child OR children OR adolescence OR adolescents OR paediatric OR pediatric 2952782

#6 Search emergency OR emergencies OR intensive OR acute OR critical OR casualty 1788387

#5 Search (((((protein precursors[MeSH Terms]) AND calcitonin[MeSH Terms])) OR PCT[Title/Abstract]) OR (procalcitonin[Title/Abstract] OR "pro-calcitonin"[Title/Abstract] OR "calcitonin precursor*"[Title/Abstract])) OR (brahms OR kryptor OR "b r a h m s") 6404

#4 Search brahms OR kryptor OR "b r a h m s" 398

#3 Search procalcitonin[Title/Abstract] OR "pro-calcitonin"[Title/Abstract] OR "calcitonin precursor*"[Title/Abstract] 2673

#2 Search PCT[Title/Abstract] 4389

#1 Search (protein precursors[MeSH Terms]) AND calcitonin[MeSH Terms] 2205

CINAHL (EBSCO)

1995-27 August 2014
Date searched: 2.9.14
Records found: 54

S1 (MH "Systemic Inflammatory Response Syndrome+") (6,506)

S2 (MH "Bacterial Infections+") (50,875)

S3 "systemic inflammatory response syndrome" or SIRS (986)

S4 sepsis* or septic* or sepses (11,903)

S5 bacill#emia* or bacter#emia* or endotox#emia* or pyoh#emia* or py#emia* (14,497)

S6 fusobacterium N2 necrophorum (26)

S7 Lemierre* N2 (disease* or syndrome*) (94)

S8 necrobacillosis or necrobacilloses or meningococc#emia or urosepsis (117)

S9 Neisseria N2 meningitidis N2 bacter#emia (1)

S10 tetanus (1,913)

S11 (bacter#emic or bacterial or endotoxin* or toxi*) N3 shock* (368)

S12 toxic N2 forward N2 failure (0)

S13 blood N2 poison* (134)

S14 infect* (161,096)

S15 bacterial N2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection* or disease*) (4,286)

S16 bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc* or "e coli" (18,644)

S17 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 (195,446)
S18 (MH "Protein Precursors+") (2,113)
S19 (MH "Calcitonin") (826)
S20 S18 AND S19 (202)
S21 PCT (731)
S22 procalcitonin or "pro-calcitonin" or "56645-65-9" or (calcitonin N2 precursor*) (385)
S23 brahms or KRYPTOR or "b r a h m s" (12)
S24 S20 OR S21 OR S22 OR S23 (1,022)
S25 (MH "Life Support Care") (1,562)
S26 (MH "Emergency Medical Services") (15,255)
S27 (MH "Emergency Service") (25,160)
S28 (MH "Emergencies") (4,480)
S29 (MH "Emergency Medicine") (5,115)
S30 (MH "Intensive Care Units") OR (MH "Intensive Care Units, Pediatric") (18,279)
S31 (MH "Respiratory Care Units") (72)
S32 (MH "Critical Care") OR (MH "Pediatric Critical Care Nursing") (11,195)
S33 "intensive care" or "high dependency unit*" or "intensive therapy unit*" (38,473)
S34 "ICU" or "ICUs" or "PICU" or "PICUs" or "HDU" or "HDUs" or "CCU" or "CCUs" or "ITU" or "ITUs" or "ER" or "ERs" or "ED" or "EDs" or "AAU" or "AAUs" (28,451)
S35 (accident N2 emergency) or "A&E" or "A & E" (3,163)
S36 (emergency or emergencies) N3 (treat* or admit* or admission* or episode* or case* or patient* or department* or room or rooms or ward* or care or medic* or interven* or therap* or hospital* or service* or patient* or unit* or centre* or center* or facility or facilities) (76,990)
S37 (acute or critical) N3 (admit* or admission* or care or medic* or service* or patient*) (62,718)
S38 "acute assessment unit*" (6)
S39 casualty N2 (department* or admit* or admission* or patient*) (79)
S40 S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 (172,300)
S41 (MH "Child+") (298,779)
S42 (MH "Adolescence+") (205,802)
S43 (MH "Minors (Legal)") (381)
S44 (MH "Puberty") (1,088)
S45 (MH "Adolescent Health Services") OR (MH "Adolescent Medicine") OR (MH "Adolescent Health") (5,725)
S46 (MH "Pediatrics") (6,891)
S47 paediatr* or pediatr* (71,880)
S48 child* or preschool* or "pre-school*" or toddler* or juvenile* or kid or kids (344,011)
S49 teen or teens or teenage* or "teen-age*" or adolescen* or postpubescen* or pubescen* or minors or youth* or puberty (218,322)
S50 S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 (498,421)
S51 S17 AND S24 AND S40 AND S50 (54)
S52 (ZR "1995") or (ZR "1996") or (ZR "1997") or (ZR "1998") or (ZR "1999") or (ZR "2000") or (ZR "2001") or (ZR "2002") or (ZR "2003") or (ZR "2004") or (ZR "2005") or (ZR "2006") or (ZR "2007") or (ZR "2008") or (ZR "2009") or (ZR "2010") or (ZR "2011") or (ZR "2012") or (ZR "2013") or (ZR "2014") or (ZR "2015") (2,839,540)
S53 S51 AND S52 (54)

Science Citation Index (Web of Science)

1995 - 29 August 2014
Date searched: 2.9.14
Records found: 230

 # 34 230 #32 not #33 Timespan=1995-2014
33 1,768,529 TOPIC: (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)
32 235 #31 AND #27 AND #19 AND #15
31 1,105,829 #30 OR #29 OR #28
30 363,206 TOPIC: (teen or teens or teenage* or "teen-age*" or adolescen* or postpubescen* or pubescen* or minors or youth* or puberty)
29 780,508 TOPIC: (child* or preschool* or "pre-school*" or toddler* or juvenile* or kid or kids)
28 198,580 TOPIC: (paediatr* or pediatr*)
27 415,622 #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20
26 287 TOPIC: (casualty near/2 (department* or admit* or admission* or patient*))
25 13 TOPIC: ("acute assessment unit*")
24 134,942 TOPIC: ((acute or critical) near/3 (admit* or admission* or care or medic* or service* or patient*))
23 83,387 TOPIC: ((emergency or emergencies) near/3 (treat* or admit* or admission* or episode* or case* or patient* or department* or room or rooms or ward* or care or medic* or interven* or therap* or hospital* or service* or patient* or unit* or centre* or center* or facility or facilities))
22 2,441 TOPIC: ((accident near/2 emergency))
21 176,728 TOPIC: ("ICU" or "ICUs" or "PICU" or "PICUs" or "HDU" or "HDUs" or "CCU" or "CCUs" or "ITU" or "ITUs" or "ER" or "ERs" or "ED" or "EDs" or "AAU" or "AAUs")
20 80,431 TOPIC: ("intensive care" or "high dependency unit*" or "intensive therapy unit*")
19 9,790 #18 OR #17 OR #16
18 364 TOPIC: (brahms or KRYPTOR or "b r a h m s")
17 3,479 TOPIC: (procalcitonin or "pro-calcitonin" or "56645-65-9" or (calcitonin near/2 precursor*))
16 7,200 TOPIC: (PCT)
15 1,222,200 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
14 242,871 TOPIC: (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc* or "e coli")
13 17,607 TOPIC: (bacterial near/2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection* or disease*))
12 989,171 TOPIC: (infect*)
11 112 TOPIC: (blood near/2 poison*)
10 0 TOPIC: (toxic near/2 forward near/2 failure)
9 6,377 TOPIC: ((bacter$emic or bacterial or endotoxin* or toxi*) near/3 shock*)
8 9,325 TOPIC: (tetanus)
7 7 TOPIC: (Neisseria near/2 meningitidis near/2 bacter$emia)
6 1,140 TOPIC: (necrobacillosis or necrobacilloses or meningococc$emia or urosepsis)
5 495 TOPIC: (Lemierre* near/2 (disease* or syndrome*))
4 532 TOPIC: (fusobacterium near/2 necrophorum)
3 4,355 TOPIC: (bacill$emia* or bacter$emia* or endotox$emia* or pyoh$emia* or py$emia*)

2 88,778 TOPIC: (sepsis* or septic* or sepses)
1 14,231 TOPIC: ("systemic inflammatory response syndrome" or SIRS)

LILACS (Internet) http://regional.bvsalud.org/php/index.php?lang=en

1995 to date
Date run: 2.9.14
Records found: 7

procalcitonin OR pct OR brahms OR kryptor [Words] and emergency OR emergencies OR intensive OR acute OR critical OR casualty [Words] and child OR children OR adolescence OR adolescents OR paediatric OR pediatric [Words]

Cost-effectiveness searches

Economic evaluations

NHS Economic Evaluation Database (NHS EED) (Wiley)

Issue 3 of 4, July 2014
Date searched: 20/08/14
Records found: 122

#1 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees3302
#2 [mh "bacterial infections"] 14341
#3 "systemic inflammatory response syndrome" or SIRS 1169
#4 sepsis* or septic* or sepses 6946
#5 bacill*emia* or bacter*emia* or endotox*emia* or pyoh*emia* or py*emia* 2063
#6 fusobacterium near/2 necrophorum 6
#7 Lemierre* near/2 (disease* or syndrome*) 1
#8 necrobacillosis or necrobacilloses or meningococc*emia or urosepsis 83
#9 Neisseria near/2 meningitidis near/2 bacter*emia 0
#10 tetanus 1532
#11 (bacter*emic or bacterial or endotoxin* or toxi*) near/3 shock* 47
#12 toxic near/2 forward near/2 failure 0
#13 blood near/2 poison* 136
#14 bacterial near/2 infect* 5074
#15 bacterial near/2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection* or disease*) 1967
#16 bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc* or "e coli" 8436
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 29349
#18 [mh ^"Emergency Treatment"] 248
#19 [mh ^"Evidence-Based Emergency Medicine"] 4
#20 [mh ^"Life Support Care"] 82
#21 [mh ^"Emergency Medical Services"] 878
#22 [mh ^"Emergency Service, Hospital"] 1633
#23 [mh ^Emergencies] 645

#24 [mh ^"Emergency Medicine"] 214
#25 [mh "Critical Care"] 1849
#26 [mh "Intensive Care Units"] 2619
#27 "intensive care" or ICU or ICUs or PICU or PICUs or NICU or NICUs or "high dependency unit*" or HDU or HDUs or "special care baby unit*" or SCBU or SCBUs or CCU or CCUs or "intensive therapy unit*" or ITU or ITUs or ER or ERs or ED or EDs or AAU or AAUs or "acute assessment unit*" 34978
#28 (accident near/2 emergency) or "A&E" or "A & E" 1069
#29 (emergency or emergencies) near/3 (treat* or admit* or admission* or episode* or case* or patient* or department* or room or rooms or ward* or care or medic* or interven* or therap* or hospital* or service* or patient* or unit* or center* or centre* or facility or facilities) 11157
#30 (acute or critical) near/3 (admit* or admission* or care or medic* or service* or patient*) 27057
#31 casualty near/2 (department* or admit* or admission* or patient*) 54
#32 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 64823
#33 #17 and #32 Publication Year from 2005 to 2014, in Economic Evaluations 122

Health Economic Evaluation Database (HEED) (Wiley):

2005 – 20.8.14
Date searched: 20.8.14
Records found: 98

ALL DATA: sepsis or sepses or septic or 'systemic inflammatory response syndrome' or SIRS or bacter* or tetanus

AND

ALL DATA: 'intensive care' or ICU* or PICU* or NICU* or 'high dependency unit' or 'special care baby unit' or 'high dependency units' or 'special care baby units' or SCBU* or 'acute care' or 'critical care' or emergency or emergencies or casualty

IDEAS via Research Papers in Economics (REPEC)
http://repec.org/

2005 – 20.8.14
Date searched: 20.8.14
Records found: 4

(sepsis | sepses | septic | "systemic inflammatory response syndrome" | SIRS | bacteria | bacterial | tetanus) + ("intensive care" | ICU | ICUs | PICU | PICUs | NICU |NICUs | "high dependency unit" | "special care baby unit" | "high dependency units" | "special care baby units" | SCBU | SCBUs | "acute care" | "critical care" | emergency | emergencies | casualty)

EconLit (EBSCO)

2005 – 1.7.14

Date searched: 20.8.14
Records found: 4 (5 before hand-sifting to exclude irrelevant hits)

S1 "systemic inflammatory response syndrome" or SIRS (1,144)
S2 sepsis* or septic* or sepses (21)
S3 bacill#emia* or bacter#emia* or endotox#emia* or pyoh#emia* or py#emia* (1,776)
S4 fusobacterium N2 necrophorum (0)
S5 Lemierre* N2 (disease* or syndrome*) (0)
S6 necrobacillosis or necrobacilloses or meningococc#emia or urosepsis (0)
S7 Neisseria N2 meningitidis N2 bacter#emia (0)
S8 tetanus (25)
S9 (bacter#emic or bacterial or endotoxin* or toxi*) N3 shock* (1)
S10 toxic N2 forward N2 failure (0)
S11 blood N2 poison* (0)
S12 bacterial N2 infect* (6)
S13 bacterial N2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection* or disease*) (7)
S14 bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc* or "e coli" (68)
S15 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 (3,035)
S16 "intensive care" or "high dependency unit*" or "special care baby unit*" or "intensive therapy unit*" or "acute assessment unit*" (91)
S17 (accident N2 emergency) (9)
S18 (emergency or emergencies) N3 (treat* or admit* or admission* or episode* or case* or patient* or department* or room or rooms or ward* or care or medic* or interven* or therap* or hospital* or service* or patient* or unit* or center* or centre* or facility or facilities) (465)
S19 (acute or critical) N3 (admit* or admission* or care or medic* or service* or patient*) (442)
S20 casualty N2 (department* or admit* or admission* or patient*) (1)
S21 S16 OR S17 OR S18 OR S19 OR S20 (971)
S22 S15 AND S21 (7)
S23 (ZR "2005") or (ZR "2006") or (ZR "2007") or (ZR "2008") or (ZR "2009") or (ZR "2010") or (ZR "2011") or (ZR "2012") or (ZR "2013") or (ZR "2014") or (ZR "2015") (538,841)
S24 S22 AND S23 (5)

Utility values

HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: http://www.nicedsu.org.uk

MEDLINE (Ovid)

1946 to August Week 3 2014
Date searched: 1.9.14
Records found: 178

1 exp Systemic Inflammatory Response Syndrome/ (96440)
2 exp bacterial infections/ (728567)
3 (systemic inflammatory response syndrome$ or SIRS).ti,ab,ot,hw. (6898)
4 (sepsis$ or septic$ or sepses).ti,ab,ot,hw. (125025)
5 (bacill?emia$ or bacter?emia$ or endotox?emia$ or pyoh?emia$ or py?emia$).ti,ab,ot,hw. (37237)
6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (902)
7 (Lemierre$ adj2 (disease$ or syndrome$)).ti,ab,ot,hw. (488)
8 (necrobacillosis or necrobacilloses or meningococc?emia or urosepsis).ti,ab,ot,hw. (1539)
9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (17)
10 tetanus.ti,ab,ot,hw. (24411)
11 ((bacter?emic or bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,ot,hw. (8538)
12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
13 (blood adj2 poison$).ti,ab,ot,hw. (140)
14 (bacterial adj2 infect$).ti,ab,ot. (27855)
15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection$ or disease$)).ti,ab,ot,hw. (47254)
16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter$ or legionnaire$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc$ or Streptococc$ or "e coli").ti,ab,ot,hw. (371949)
17 or/1-16 (1080823)
18 Emergency Treatment/ (8299)
19 Evidence-Based Emergency Medicine/ (216)
20 Life Support Care/ (7323)
21 emergency medical services/ or emergency service, hospital/ (74803)
22 Emergencies/ (34784)
23 Emergency Medicine/ (9931)
24 exp Critical Care/ (44541)
25 exp Intensive Care Units/ (57480)
26 (intensive care or high dependency unit$ or special care baby unit$ or intensive therapy unit$).ti,ab,ot,hw. (111839)
27 (ICU or ICUs or PICU or PICUs or NICU or NICUs or HDU or HDUs or SCBU or SCBUs or CCU or CCUs or ITU or ITUs or ER or ERs or ED or EDs or AAU or AAUs).ti,ab,ot. (144084)
28 ((accident adj2 emergency) or "A&E" or "A & E").ti,ab,ot,hw. (18920)
29 ((emergency or emergencies) adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room or rooms or ward$ or care or medic$ or interven$ or therap$ or hospital$ or service$ or patient$ or unit$ or centre$ or center$ or facility or facilities)).ti,ab,ot,hw. (148389)
30 ((acute or critical) adj3 (admit$ or admission$ or care or medic$ or service$ or patient$)).ti,ab,ot,hw. (171915)
31 acute assessment unit$.ti,ab,ot,hw. (14)
32 (casualty adj2 (department$ or admit$ or admission$ or patient$)).ti,ab,ot,hw. (688)
33 or/18-32 (539004)
34 quality-adjusted life years/ or quality of life/ (127222)
35 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (15523)
36 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (998)
37 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (2664)

38 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D of sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (421)
39 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (333)
40 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (251)
41 "health related quality of life".ti,ab,ot. (21008)
42 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (6111)
43 "assessment of quality of life".ti,ab,ot. (1137)
44 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (3881)
45 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (9828)
46 (hye or hyes).ti,ab,ot. (54)
47 health$ year$ equivalent$.ti,ab,ot. (39)
48 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (875)
49 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (608)
50 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (1666)
51 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (6810)
52 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (3629)
53 15d.ti,ab,ot. (1121)
54 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (240)
55 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (6655)
56 (utilities or disutili$).ti,ab,ot. (3927)
57 or/34-56 (150668)
58 animals/ not (animals/ and humans/) (3906728)
59 57 not 58 (149111)
60 letter.pt. (824027)
61 editorial.pt. (345769)
62 historical article.pt. (305884)
63 or/60-62 (1460723)
64 59 not 63 (142260)
65 17 and 33 and 64 (178)

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update (Ovid)

September 02, 2014
Date searched: 3.9.14
Records found: 10

1 exp Systemic Inflammatory Response Syndrome/ (78)
2 exp bacterial infections/ (448)
3 (systemic inflammatory response syndrome$ or SIRS).ti,ab,ot,hw. (400)
4 (sepsis$ or septic$ or sepses).ti,ab,ot,hw. (7244)
5 (bacill?emia$ or bacter?emia$ or endotox?emia$ or pyoh?emia$ or py?emia$).ti,ab,ot,hw. (1567)

6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (53)
7 (Lemierre$ adj2 (disease$ or syndrome$)).ti,ab,ot,hw. (49)
8 (necrobacillosis or necrobacilloses or meningococc?emia or urosepsis).ti,ab,ot,hw. (123)
9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (2)
10 tetanus.ti,ab,ot,hw. (799)
11 ((bacter?emic or bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,ot,hw. (252)
12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
13 (blood adj2 poison$).ti,ab,ot,hw. (17)
14 (bacterial adj2 infect$).ti,ab,ot. (2191)
15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection$ or disease$)).ti,ab,ot,hw. (1060)
16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter$ or legionnaire$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc$ or Streptococc$ or "e coli").ti,ab,ot,hw. (16657)
17 or/1-16 (27612)
18 Emergency Treatment/ (8)
19 Evidence-Based Emergency Medicine/ (7)
20 Life Support Care/ (2)
21 emergency medical services/ or emergency service, hospital/ (100)
22 Emergencies/ (14)
23 Emergency Medicine/ (14)
24 exp Critical Care/ (31)
25 exp Intensive Care Units/ (52)
26 (intensive care or high dependency unit$ or special care baby unit$ or intensive therapy unit$).ti,ab,ot,hw. (7364)
27 (ICU or ICUs or PICU or PICUs or NICU or NICUs or HDU or HDUs or SCBU or SCBUs or CCU or CCUs or ITU or ITUs or ER or ERs or ED or EDs or AAU or AAUs).ti,ab,ot. (15549)
28 ((accident adj2 emergency) or "A&E" or "A & E").ti,ab,ot,hw. (1814)
29 ((emergency or emergencies) adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room or rooms or ward$ or care or medic$ or interven$ or therap$ or hospital$ or service$ or patient$ or unit$ or centre$ or center$ or facility or facilities)).ti,ab,ot,hw. (10483)
30 ((acute or critical) adj3 (admit$ or admission$ or care or medic$ or service$ or patient$)).ti,ab,ot,hw. (11372)
31 acute assessment unit$.ti,ab,ot,hw. (3)
32 (casualty adj2 (department$ or admit$ or admission$ or patient$)).ti,ab,ot,hw. (34)
33 or/18-32 (38891)
34 quality-adjusted life years/ or quality of life/ (230)
35 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (1496)
36 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (397)
37 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (346)
38 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (51)
39 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (15)
40 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (27)

41 "health related quality of life".ti,ab,ot. (2605)
42 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (672)
43 "assessment of quality of life".ti,ab,ot. (102)
44 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (610)
45 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (1208)
46 (hye or hyes).ti,ab,ot. (1)
47 health$ year$ equivalent$.ti,ab,ot. (1)
48 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (102)
49 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (38)
50 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (223)
51 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (794)
52 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (406)
53 15d.ti,ab,ot. (107)
54 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (22)
55 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (677)
56 (utilities or disutili$ or Rosser).ti,ab,ot. (456)
57 or/34-56 (6892)
58 animals/ not (animals/ and humans/) (2580)
59 57 not 58 (6890)
60 letter.pt. (30900)
61 editorial.pt. (19188)
62 historical article.pt. (135)
63 or/60-62 (50199)
64 59 not 63 (6846)
65 17 and 33 and 64 (10)

Embase (Ovid)

1974 to 2014 September 02
Date searched: 3.9.14
Records found: 219

1 exp systemic inflammatory response syndrome/ (175736)
2 exp bacterial infection/ (751201)
3 (systemic inflammatory response syndrome$ or SIRS).ti,ab,ot,hw. (10962)
4 (sepsis$ or septic$ or sepses).ti,ab,ot,hw. (194582)
5 (bacill?emia$ or bacter?emia$ or endotox?emia$ or pyoh?emia$ or py?emia$).ti,ab,ot,hw. (48690)
6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (1168)
7 (Lemierre$ adj2 (disease$ or syndrome$)).ti,ab,ot,hw. (804)
8 (necrobacillosis or necrobacilloses or meningococc?emia or urosepsis).ti,ab,ot,hw. (3820)
9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (19)
10 tetanus.ti,ab,ot,hw. (34982)
11 ((bacter?emic or bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,ot,hw. (11234)

12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
13 (blood adj2 poison$).ti,ab,ot,hw. (259)
14 (bacterial adj2 infect$).ti,ab,ot. (37846)
15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection$ or disease$)).ti,ab,ot,hw. (61310)
16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter$ or legionnaire$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc$ or Streptococc$ or "e coli").ti,ab,ot,hw. (479436)
17 or/1-16 (1266381)
18 Emergency Treatment/ (14199)
19 Evidence Based Emergency Medicine/ (199)
20 Pediatric Advanced Life Support/ (421)
21 exp Emergency Care/ (22751)
22 Emergency/ (37166)
23 Emergency Medicine/ (28599)
24 Emergency Health Service/ (67637)
25 Emergency Patient/ (1529)
26 Emergency Ward/ (64723)
27 Intensive Care/ (88509)
28 Intensive Care Unit/ (87041)
29 (intensive care or high dependency unit$ or special care baby unit$ or intensive therapy unit$).ti,ab,ot,hw. (213813)
30 (ICU or ICUs or PICU or PICUs or NICU or NICUs or HDU or HDUs or SCBU or SCBUs or CCU or CCUs or ITU or ITUs or ER or ERs or ED or EDs or AAU or AAUs).ti,ab,ot. (233355)
31 ((accident adj2 emergency) or "A&E" or "A & E").ti,ab,ot,hw. (31213)
32 ((emergency or emergencies) adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room or rooms or ward$ or care or medic$ or interven$ or therap$ or hospital$ or service$ or patient$ or unit$ or centre$ or center$ or facility or facilities)).ti,ab,ot,hw. (236552)
33 ((acute or critical) adj3 (admit$ or admission$ or care or medic$ or service$ or patient$)).ti,ab,ot,hw. (227971)
34 acute assessment unit$.ti,ab,ot,hw. (33)
35 (casualty adj2 (department$ or admit$ or admission$ or patient$)).ti,ab,ot,hw. (906)
36 or/18-35 (799301)
37 quality adjusted life year/ or quality of life index/ (14180)
38 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (14361)
39 "International Classification of Functioning, Disability and Health"/ or "ferrans and powers quality of life index"/ (1336)
40 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (23787)
41 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1530)
42 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (4418)
43 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (731)
44 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (341)
45 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (445)

46 "health related quality of life".ti,ab,ot. (30295)
47 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (8975)
48 "assessment of quality of life".ti,ab,ot. (1742)
49 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (7306)
50 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (15522)
51 (hye or hyes).ti,ab,ot. (95)
52 health$ year$ equivalent$.ti,ab,ot. (38)
53 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (2151)
54 (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab,ot,hw. (797)
55 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (2131)
56 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (11417)
57 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (5436)
58 15d.ti,ab,ot. (1635)
59 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (305)
60 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (10123)
61 (utilities or disutili$ or Rosser).ti,ab,ot. (6550)
62 or/37-61 (96124)
63 animal/ or animal experiment/ (3358705)
64 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5700949)
65 or/63-64 (5700949)
66 exp human/ or human experiment/ (15080879)
67 65 not (65 and 66) (4556337)
68 62 not 67 (94364)
69 letter.pt. (855048)
70 editorial.pt. (455483)
71 note.pt. (567527)
72 or/69-71 (1878058)
73 68 not 72 (91336)
74 17 and 36 and 73 (261)

Cochrane Central Register of Controlled Trials (Wiley)

Issue 8 of 12, August 2014
Date Searched: 3.9.14
Records found: 83

#1 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 3307
#2 [mh "bacterial infections"] 14352
#3 "systemic inflammatory response syndrome" or SIRS 1178
#4 sepsis* or septic* or sepses 6978
#5 bacill*emia* or bacter*emia* or endotox*emia* or pyoh*emia* or py*emia* 2069

#6 fusobacterium near/2 necrophorum 6
#7 Lemierre* near/2 (disease* or syndrome*) 1
#8 necrobacillosis or necrobacilloses or meningococc*emia or urosepsis 85
#9 Neisseria near/2 meningitidis near/2 bacter*emia 0
#10 tetanus 1539
#11 (bacter*emic or bacterial or endotoxin* or toxi*) near/3 shock* 47
#12 toxic near/2 forward near/2 failure 0
#13 blood near/2 poison* 136
#14 bacterial near/2 infect* 5079
#15 bacterial near/2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection* or disease*) 1973
#16 bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc* or "e coli" 8460
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 29430
#18 [mh ^"Emergency Treatment"] 249
#19 [mh ^"Evidence-Based Emergency Medicine"] 4
#20 [mh ^"Life Support Care"] 83
#21 [mh ^"Emergency Medical Services"] 880
#22 [mh ^"Emergency Service, Hospital"] 1633
#23 [mh ^Emergencies] 645
#24 [mh ^"Emergency Medicine"] 214
#25 [mh "Critical Care"] 1851
#26 [mh "Intensive Care Units"] 2622
#27 "intensive care" or ICU or ICUs or PICU or PICUs or NICU or NICUs or "high dependency unit*" or HDU or HDUs or "special care baby unit*" or SCBU or SCBUs or CCU or CCUs or "intensive therapy unit*" or ITU or ITUs or ER or ERs or ED or EDs or AAU or AAUs or "acute assessment unit*" 35114
#28 (accident near/2 emergency) or "A&E" or "A & E" 1072
#29 (emergency or emergencies) near/3 (treat* or admit* or admission* or episode* or case* or patient* or department* or room or rooms or ward* or care or medic* or interven* or therap* or hospital* or service* or patient* or unit* or center* or centre* or facility or facilities) 11217
#30 (acute or critical) near/3 (admit* or admission* or care or medic* or service* or patient*) 27155
#31 casualty near/2 (department* or admit* or admission* or patient*) 55
#32 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 65072
#33 MeSH descriptor: [Quality-Adjusted Life Years] this term only 3652
#34 MeSH descriptor: [Quality of Life] this term only 14884
#35 sf36 or "sf 36" or "sf-36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six" 5057
#36 sf6 or "sf 6" or "sf-6" or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six" 120
#37 sf12 or "sf 12" or "sf-12" or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve" 766
#38 sf6D or "sf 6D" or "sf-6D" or "short form 6D" or "shortform 6D" or "sf six D" or sfsixD or "shortform six D" or "short form six D" 152
#39 sf20 or "sf 20" or "sf-20" or "short form 20" or "shortform 20" or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty" 69

#40 sf8 or "sf 8" or "sf-8" or "short form 8" or "shortform 8" or "sf eight" or sfeight or "shortform eight" or "short form eight" 42
#41 "health related quality of life" 5804
#42 "Quality adjusted life" or "Quality-adjusted-life" 5972
#43 "assessment of quality of life" 281
#44 euroqol or "euro qol" or eq5d or "eq 5d" 2180
#45 hql or hrql or hqol or "h qol" or hrqol or "hr qol" 2026
#46 hye or hyes 46
#47 "health* year* equivalent*" 5
#48 hui or hui1 or hui2 or hui3 or hui4 or "hui-4" or "hui-1" or "hui-2" or "hui-3" 1135
#49 quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being" 33313
#50 "Disability adjusted life" or "Disability-adjusted life" or "health adjusted life" or "health-adjusted life" or "years of healthy life" or "healthy years equivalent" or "years of potential life lost" or "years of health life lost" 325
#51 QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL* 4801
#52 timetradeoff or "time tradeoff" or "time trade-off" or "time trade off" or TTO or "Standard gamble*" or "willingness to pay" 1783
#53 15d 99
#54 HSUV* or "health state* value*" or "health state* preference*" or HSPV* 77
#55 utilit* near/3 ("quality of life" or valu* or scor* or measur* or health or life or estimat* or elicit* or disease*) 4400
#56 utilities or disutili* or rosser 10729
#57 #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 55551
#58 #17 and #32 and #57 1434
#59 #17 and #32 and #57 in Trials 83

Health Technology Assessment (HTA) Database (Wiley)

Issue 3 of 4, July 2014
Date Searched: 3.9.14
Records found: 5

#1 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees3307
#2 [mh "bacterial infections"] 14352
#3 "systemic inflammatory response syndrome" or SIRS 1178
#4 sepsis* or septic* or sepses 6978
#5 bacill*emia* or bacter*emia* or endotox*emia* or pyoh*emia* or py*emia* 2069
#6 fusobacterium near/2 necrophorum 6
#7 Lemierre* near/2 (disease* or syndrome*) 1
#8 necrobacillosis or necrobacilloses or meningococc*emia or urosepsis 85
#9 Neisseria near/2 meningitidis near/2 bacter*emia 0
#10 tetanus 1539
#11 (bacter*emic or bacterial or endotoxin* or toxi*) near/3 shock* 47
#12 toxic near/2 forward near/2 failure 0
#13 blood near/2 poison* 136
#14 bacterial near/2 infect* 5079

#15 bacterial near/2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection* or disease*) 1973
#16 bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc* or "e coli" 8460
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 29430
#18 [mh ^"Emergency Treatment"] 249
#19 [mh ^"Evidence-Based Emergency Medicine"] 4
#20 [mh ^"Life Support Care"] 83
#21 [mh ^"Emergency Medical Services"] 880
#22 [mh ^"Emergency Service, Hospital"] 1633
#23 [mh ^Emergencies] 645
#24 [mh ^"Emergency Medicine"] 214
#25 [mh "Critical Care"] 1851
#26 [mh "Intensive Care Units"] 2622
#27 "intensive care" or ICU or ICUs or PICU or PICUs or NICU or NICUs or "high dependency unit*" or HDU or HDUs or "special care baby unit*" or SCBU or SCBUs or CCU or CCUs or "intensive therapy unit*" or ITU or ITUs or ER or ERs or ED or EDs or AAU or AAUs or "acute assessment unit*" 35114
#28 (accident near/2 emergency) or "A&E" or "A & E" 1072
#29 (emergency or emergencies) near/3 (treat* or admit* or admission* or episode* or case* or patient* or department* or room or rooms or ward* or care or medic* or interven* or therap* or hospital* or service* or patient* or unit* or center* or centre* or facility or facilities) 11217
#30 (acute or critical) near/3 (admit* or admission* or care or medic* or service* or patient*) 27155
#31 casualty near/2 (department* or admit* or admission* or patient*) 55
#32 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 65072
#33 MeSH descriptor: [Quality-Adjusted Life Years] this term only 3652
#34 MeSH descriptor: [Quality of Life] this term only 14884
#35 sf36 or "sf 36" or "sf-36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six" 5057
#36 sf6 or "sf 6" or "sf-6" or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six" 120
#37 sf12 or "sf 12" or "sf-12" or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve" 766
#38 sf6D or "sf 6D" or "sf-6D" or "short form 6D" or "shortform 6D" or "sf six D" or sfsixD or "shortform six D" or "short form six D" 152
#39 sf20 or "sf 20" or "sf-20" or "short form 20" or "shortform 20" or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty" 69
#40 sf8 or "sf 8" or "sf-8" or "short form 8" or "shortform 8" or "sf eight" or sfeight or "shortform eight" or "short form eight" 42
#41 "health related quality of life" 5804
#42 "Quality adjusted life" or "Quality-adjusted-life" 5972
#43 "assessment of quality of life" 281
#44 euroqol or "euro qol" or eq5d or "eq 5d" 2180
#45 hql or hrql or hqol or "h qol" or hrqol or "hr qol" 2026
#46 hye or hyes 46
#47 "health* year* equivalent*" 5

#48 hui or hui1 or hui2 or hui3 or hui4 or "hui-4" or "hui-1" or "hui-2" or "hui-3" 1135
#49 quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being" 33313
#50 "Disability adjusted life" or "Disability-adjusted life" or "health adjusted life" or "health-adjusted life" or "years of healthy life" or "healthy years equivalent" or "years of potential life lost" or "years of health life lost" 325
#51 QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL* 4801
#52 timetradeoff or "time tradeoff" or "time trade-off" or "time trade off" or TTO or "Standard gamble*" or "willingness to pay" 1783
#53 15d 99
#54 HSUV* or "health state* value*" or "health state* preference*" or HSPV* 77
#55 utilit* near/3 ("quality of life" or valu* or scor* or measur* or health or life or estimat* or elicit* or disease*) 4400
#56 utilities or disutili* or rosser 10729
#57 #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 55551
#58 #17 and #32 and #57 1434
#59 #17 and #32 and #57 in Technology Assessment 5

PubMed http://www.ncbi.nlm.nih.gov/pubmed/

Date searched: 3.9.14
Records found: 76

- This strategy aims to identify records that are on PubMed, but not included in MEDLINE or MEDLINE In-Process (OvidSP). Line #25 limits the search results in this way.

#26,"Search ((((((((((Systemic Inflammatory Response Syndrome[MeSH Terms]) OR bacterial infections[MeSH Terms]) OR (sepsis* or septic* or sepses)) OR "bacterial infect*") OR (tetanus or "blood poison*")) OR ("bacterial meningitis" or "bacterial pneumonia" or "bacterial peritonitis" or "bacterial endocarditis" or "bacterial superinfection*" or "bacterial disease")) OR (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or "legionnaire* disease" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc*))) AND (emergency OR emergencies OR intensive OR acute OR critical OR casualty)) AND ((((((((((((("quality of life") OR "quality adjusted life years") OR ("sf36" or "sf-36" or "sf6" or "sf-6" or "sf12" or "sf-12" or "sf6d" or "sf-6d" or "sf20" or "sf-20" or "sf8" or "sf-8")) OR (euroqol or "euro qol" or "eq5d" or "eq 5d")) OR (hql or hrql or hqol or "h qol" or hrqol or "hr qol")) OR ("health* year* equivalent*" or hye or hyes)) OR ("quality of well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being")) OR ("Disability adjusted life" or "Disability-adjusted life")) OR ("health adjusted life" or "health-adjusted life" or "years of healthy life" or "healthy years equivalent" or "years of potential life lost" or "years of health life lost")) OR (QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL*)) OR ("time tradeoff" or "time trade-off")) OR ("Standard gamble*" or "willingness to pay")) OR ("health state* value*" or "health state* preference*")) OR (utilities or disutilities))) AND (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) 76
#25,"Search pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]",1815126
#24,"Search ((((((Systemic Inflammatory Response Syndrome[MeSH Terms]) OR bacterial infections[MeSH Terms]) OR (sepsis* or septic* or sepses)) OR ""bacterial infect*"") OR (tetanus or ""blood poison*"")) OR (""bacterial meningitis"" or ""bacterial pneumonia"" or ""bacterial

peritonitis"" or ""bacterial endocarditis"" or ""bacterial superinfection*"" or ""bacterial disease"")) OR (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or ""legionnaire* disease"" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc*)",1122718
#23,"Search bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter* or ""legionnaire* disease"" or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc* or Streptococc*",309305
#22,"Search ""bacterial meningitis"" or ""bacterial pneumonia"" or ""bacterial peritonitis"" or ""bacterial endocarditis"" or ""bacterial superinfection*"" or ""bacterial disease""",40777
#21,"Search tetanus or ""blood poison*""",40459
#20,"Search ""bacterial infect*""",367249
#19,"Search sepsis* or septic* or sepses",132167
#18,"Search bacterial infections[MeSH Terms]",726384
#17,"Search Systemic Inflammatory Response Syndrome[MeSH Terms]",94444
#16,"Search ((((((((((((""quality of life"") OR ""quality adjusted life years"") OR (""sf36"" or ""sf-36"" or ""sf6"" or ""sf-6"" or ""sf12"" or ""sf-12"" or ""sf6d"" or ""sf-6d"" or ""sf20"" or ""sf-20"" or ""sf8"" or ""sf-8"")) OR (euroqol or ""euro qol"" or ""eq5d"" or ""eq 5d"")) OR (hql or hrql or hqol or ""h qol"" or hrqol or ""hr qol"")) OR (""health* year* equivalent*"" or hye or hyes)) OR (""quality of well being"" or ""quality of wellbeing"" or ""index of wellbeing"" or ""index of well being"")) OR (""Disability adjusted life"" or ""Disability-adjusted life"")) OR (""health adjusted life"" or ""health-adjusted life"" or ""years of healthy life"" or ""healthy years equivalent"" or ""years of potential life lost"" or ""years of health life lost"")) OR (QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL*)) OR (""time tradeoff"" or ""time trade-off"")) OR (""Standard gamble*"" or ""willingness to pay"")) OR (""health state* value*"" or ""health state* preference*"")) OR (utilities or disutilities)",443537
#15,"Search utilities or disutilities",4299,10:01:10
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#10,"Search ""health adjusted life"" or ""health-adjusted life"" or ""years of healthy life"" or ""healthy years equivalent"" or ""years of potential life lost"" or ""years of health life lost""",19286
#9,"Search ""Disability adjusted life"" or ""Disability-adjusted life""",1379
#8,"Search ""quality of well being"" or ""quality of wellbeing"" or ""index of wellbeing"" or ""index of well being""",232441
#7,"Search ""health* year* equivalent*"" or hye or hyes",6527
#6,"Search hql or hrql or hqol or ""h qol"" or hrqol or ""hr qol""",11057
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#4,"Search ""sf36"" or ""sf-36"" or ""sf6"" or ""sf-6"" or ""sf12"" or ""sf-12"" or ""sf6d"" or ""sf-6d"" or ""sf20"" or ""sf-20"" or ""sf8"" or ""sf-8""",18526
#3,"Search ""quality adjusted life years""",8630
#2,"Search ""quality of life""",195317
#1,"Search emergency OR emergencies OR intensive OR acute OR critical OR casualty",1788774

PROQOLID - Patient-Reported Outcome and Quality Of Life Instruments Database
http://www.proqolid.org/

Date searched: 3.9.14
Records found: 0

Systemic Inflammatory Response Syndrome - 0 records found
Sepsis or septic or sepses - 0 records found
Bacterial - 0 relevant records
tetanus - 0 records found

APPENDIX 2: ONGOING TRIALS AND COMPETED TRIALS WITH NO PUBLISHED DATA

Contact investigator(s)	e-mail	Trial title	Population	Setting	Register ID	End date	Actions
Completed trials with published protocols, but no published results							
Evelien Assink-de Jong Albertus Beishuizen	beishuizen@vumc.nl	Stop Antibiotics on guidance of Procalcitonin Study (SAPS): a randomised prospective multicentre investigator-initiated trial to analyse whether daily measurements of procalcitonin versus a standard-of-care approach can safely shorten antibiotic duration in intensive care unit patients - calculated sample size: 1816 patients	Adults	ICU	NCT01139489[121, 122]	August 2014	Contacted 30/09/2014 No reply received
Completed trials with no publication							
Chien-Chang Lee, MD, MSc Yi-Min Zhu, BSc	cclee100@gmail.com csvzhuyimin@163.com	PROcalcitonin to SHORTen Antibiotics Duration in PEDiatricICU Patients (ProShort-Ped) Trial	Children	ICU	NCT01652404[123]	December 2012	Contacted 30/09/2014 No reply received
Chien-Chang Lee, MD, MSc	cclee100@gmail.com	Procalcitonin to Shorten Antibiotics Duration in ICU Patients (ProShort)	Adults	ICU	NCT01379547[124]		
Hendrikus J van Leeuwen	hjvanleeuwen@alysis.nl	Procalcitonin Guided Versus Conventional Antibiotic Therapy in Patients With Sepsis in the ICU	Adults	ICU	NCT00987818[125]	NR	Contacted 30/09/2014 Replied 30/09/2014 – no data yet

Contact investigator(s)	e-mail	Trial title	Population	Setting	Register ID	End date	Actions
							available
Steven Reynolds, MD	sreynolds.md@gmail.com	PCT and Clinical Algorithm for Determination of Duration of Antibiotics	Adults	ICU	NCT01572831[126]	May 2013	Contacted 30/09/2014
Laurence E Lacroix Children's Hospital, Geneva University Hospital	laurence.lacroix@hcuge.ch	Impact of the Lab-score on Antibiotic Prescription Rate in Children With Fever Without Source	Children	ED	NCT02179398[127]	July 2013	Contacted 24/09/2014 No reply received
Ongoing trials							
Hans Ibsen, M.D., D.M.Sc		Procalcitonin as a Marker of Antibiotic Therapy in Patients With Lower Respiratory Tract Infections	Adults	Unclear "hospitalised"	NCT02171338[128]	September 2014	None
Karla F Finotti, MD Vandack A Nobre A Nobre, PhD	karlafinotti@yahoo.com.br vandack@gmail.com	Procalcitonin Versus C-reactive Protein to Guide Therapy in Community Acquired Pneumonia (CAPMarker)	Adults	ICU?	NCT01018199[129]	January 2015	None
Emmanuel Montassier, PH	emmanuel.montassier@chu-nantes.fr	Clinical Reassessment Versus Procalcitonin in Order to Shorten Antibiotic Duration in Community acquired Pneumonia (CLINPCT)	Adults	Unclear "hospitalised"	NCT01723644[130]	April 2015	None
Ruud Duijkers, MSc, MD	R.Duijkers@mca.nl	Reduction of Antibiotic Therapy by Biomakers in Patients With CAP Episodes (REDUCE	Adults	Unclear "hospitalised"	NCT01964495[131]	October 2017	None

Contact investigator(s)	e-mail	Trial title	Population	Setting	Register ID	End date	Actions
		Study)					
Tammy L Eaton	eatontl@upmc.edu	Procalcitonin Antibiotic Consensus Trial (ProACT)	Adults	ED	NCT02130986[132]	June 2018	None

APPENDIX 3: DATA EXTRACTION TABLES

a. Baseline study details

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Annane(2013)[42, 43, 71] NCT01025180 **Country:** France **Funding:** Industry - assay manufacturer **Recruitment:** December 2006 - December 2009 **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 62	**Setting:** ICU **Population:** Adults **Presentation:** Apparent septic shock and no clear source of infection **Testing application**: Initiation and discontinuation **Inclusion criteria:** Adults admitted to participating ICUs; following symptoms in preceding 48 hours: SIRS, acute dysfunction of at least one organ, absence of indisputable clinical infection; negative microbial cultures **Exclusion criteria:** Pregnancy; burns over 15% or more of body surface area; trauma; outpatient or inpatient cardiac arrest; post-orthopaedic surgery status; drug-related neutropenia; withdrawal of or decision to withhold life-support therapies; indisputable clinical infection or antibiotic exposure for ≥48 hours before ICU admission	**Number randomised** **Age (Median, IQR):** **Male (%):** **SAPS (Median, IQR):** **SOFA (Median, IQR):** **PCT (ng/mL) (Median, IQR):** **CRP (mg/L) (Median, IQR):** **Diagnosis (%):** **Comorbidities (%):**	31 59 (40, 67) 80 32.5 (27, 47) 9.5 (8.5, 11) 1 (0.3, 5) 87 (52,142) NR NR	31 54 (46, 73) 67.9 43 (32, 52) 10 (8, 11) 0.7 (0.4, 2.4) 141 (77, 220) NR NR	**PCT:** 1 withdrew informed consent **Control:** 3 withdrew informed consent

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Baer(2013)[44, 45, 65] ProPAED (ISRCTN17057980) **Country:** Switzerland **Funding:** Mixed - assay manufacturer provided kits and platform **Recruitment:** January 2009 - February 2010 **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 339	**Setting:** ED **Population:** Children **Presentation:** LRTI **Testing application**: Initiation and discontinuation **Inclusion criteria:** Children (age 1 month to 18 years); presenting with LRTI to the EDs of two paediatric hospitals, regardless of antibiotic treatment history. Acute LRTI was defined as <14 days duration, presence of fever (≥38◦ C), at least one symptom (cough, sputum production, pleuritic pain, poor feeding), at least one sign (tachypnea, dyspnoea, wheezing, late inspiratory crackles, bronchial breathing, pleural rub) **Exclusion criteria:** Participant or care-giver unwilling; severe immunosuppression or immunosuppressive treatment; neutropenia; cystic fibrosis; acute croup; hospital stay within 14 days; other severe infection	**Number randomised** **Age (Median, IQR):** **Male (%):** **SAPS (Median, IQR):** **SOFA (Median, IQR):** **PCT (ng/mL) (Median, IQR):** **CRP (mg/L) (Median, IQR):** **Diagnosis (%):** **Comorbidities (%):**	168 20.7 (10.1, 50.2) 58 NR NR 0.26 (0.14, 16) 23 (8, 88) Non-CAP LRTI 36; CAP 64 NR	169 20.9 (10.2, 50.7) 58 NR NR 0.21 (0.12, 20.24) 20 (7, 55) Non-CAP LRTI 37; CAP 63 NR	**PCT**: 1 delayed or incomplete 14 day interview **Control**: 2 withdrew consent; 1 lost to follow-up; 4 delayed or incomplete 14 day interview

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Bouadma(2010)[46, 66] PRORATA NCT00472667 **Country:** France **Funding:** Industry - assay manufacturer (assay materials and Kryptor machines (if not already available on site) **Recruitment:** June 2007 - May 2008 **Multicentre study** **Design:** Non-inferiority parallel group RCT **Number randomised:** 630	**Setting:** ICU **Population:** Adults **Presentation:** Suspected bacterial infection **Testing application**: Initiation and discontinuation **Inclusion criteria:** Adults (≥18 years) with suspected bacterial infection at admission or during their stay in ICU, or who developed sepsis during their stay in ICU; not receiving antibiotics before inclusion, or received antibiotics for <24 hours and the interval between admission and inclusion was <12 hours. **Exclusion criteria:** Known pregnancy; expected ICU stay <3 days; bone-marrow transplant or chemotherapy-induced neutropenia; infections for which long-term antibiotic treatment is strongly recommended (e.g. infective endocarditis, osteoarticular infections, anterior mediastinitis after cardiac surgery, hepatic or cerebral abscess; chronic prostatitis; infection with Mycobacterium tuberculosis, Pneumocystis jirovecii, or Toxoplasma gondii; poor chance of survival (SAPS II >65); do-not-resuscitate order.	**Number randomised** **Age (Mean, SD):** **Male (%):** **SAPS (Mean, SD):** **SOFA (Mean, SD):** **PCT (ng/mL) (Median, IQR):** **CRP (mg/L) (Median, IQR):** **Diagnosis (%):** **Comorbidities (%):**	311 61 (15.2) 67 47.1 (17.9) 8 (4.7) 1.6 (0.5, 6.6) 144.2 (63, 229) *Reason for admission to ICU:* septic shock 17; non-septic shock 15; acute respiratory failure 37; renal failure 3; neurological failure 11; multiorgan failure 7; other 10. *Infection site:* Pulmonary 71; urinary tract 9; intra-abdominal 5; skin and soft tissue 2; CNS 3; catheter related 2; primary blood stream 3; other 4. Heart failure 5 ; insulin-dependent diabetes mellitus 9 ; cirrhosis 7; oxygen therapy at home 7; chronic renal failure requiring dialysis 6; metastatic cancer 3; immunocompromised 15	319 62.1 (15) 65 46.9 (17.2) 7.7 (4.6) 1.5 (0.4, 6.8) 137.2 (61, 244) *Reason for admission to ICU:* septic shock 18; non-septic shock 15; acute respiratory failure 40; renal failure 2; neurological failure 11; multiorgan failure 6; other 8. *Infection site:* Pulmonary 74; urinary tract 6; intra-abdominal 7; skin and soft tissue 2; CNS 2; catheter related 1; primary blood stream 4; other 3. Heart failure 4 ; insulin-dependent diabetes mellitus 7; cirrhosis 4; oxygen therapy at home 6; chronic renal failure requiring dialysis 4; metastatic cancer 2; immunocompromised 16	**PCT**: 4 withdrew consent; 1 lost to follow-up at day 15 **Control**: 4 withdrew consent; 1 randomised twice; 1 lost to follow-up at day 22

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Christ-Crain(2006)[47, 48] ProCAP-Study; ISRCTN04176397). **Country:** Switzerland **Funding:** Industry - drug manufacturer **Recruitment:** November 2003 - February 2005 **Design:** Parallel group RCT **Number randomised:** 302	**Setting:** ED **Population:** Adults **Presentation:** CAP **Testing application**: Initiation and discontinuation **Inclusion criteria:** Adults (>18 years) with principal diagnosis of CAP admitted to the ED; defined by a new infiltrate on chest radiograph and presence of ≥1 of the following: cough, sputum production, dyspnea, core body temperature >38 C, auscultatory findings of abnormal breath sounds and rales, and leukocyte count >10 x 10^9 or<than 4x10^9 cells/L. **Exclusion criteria:** Cystic fibrosis; active pulmonary tuberculosis; hospital-acquired pneumonia; severely immunocompromised patients.	**Number randomised** **Age (Mean, SD):** **Male (%):** **SAPS):** **SOFA:** **PCT (ng/mL) (Mean, CI):** **CRP (mg/L) (Mean, SD, CI):** **Diagnosis (%):** **Comorbidities (%):**	151 70 (17) 62 NR NR 0.5 (0.2, 2.5) 111 (57, 204) Pneumonia Severity Index class II (36); IV (45)l; V (19) CAD (33); hypertensive heart disease (28); congestive heart failure (5); peripheral vascular disease (7); cerebrovascular disease (5); renal dysfunction (24); liver disease (8), dibaetes (21); COPD (29); neoplastic disease (17).	151 70 (17) 62 NR NR 0.4 (0.2, 1.9) 152 (72, 212) Pneumonia Severity Index class II (44); IV (41); V (15) CAD (32); hypertensive heart disease (24); congestive heart failure (6); peripheral vascular disease (6); cerebrovascular disease (5); renal dysfunction (30); liver disease (13); dibaetes (19); COPD (21); neoplastic disease (15).	**PCT:** 18 died; 2 lost to follow-up **Control:** 20 died

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Christ-Crain(2004)[49, 67] NCT00099840 **Country:** Switzerland **Funding:** Mixed **Recruitment:** December 2002 - April 2003 **Design:** Parallel group RCT **Number randomised:** 243	**Setting:** ED **Population:** Adults **Presentation:** Suspected LRTI **Testing application**: Initiation **Inclusion criteria:** Suspected lower respiratory tract infection as the main diagnosis **Exclusion criteria:** Immunocompromised patients (with HIV and a CD4 count <200 cells/ml), neutropenic patients, stem cell transplant recipients, people with cystic fibrosis, active tuberculosis or nosocomial pneumonia	**Number randomised** **Age (Mean, SD):** **Male (%):** **SAPS:** **SOFA:** **PCT (ng/mL) (Mean, SD):** **CRP (mg/L) (Mean, SD):** **Diagnosis (%):** **Comorbidities (%):**	124 62.8 (19.8) 54 NR NR 1.6 (7.7) 82.8 (93.9) Community acquired pneumonia (34); acute exacerbation of COPD (23); acute bronchitis (23); acute exacerbation of asthma (8); others (12) CAD (22); congestive heart failure (9); peripheral vascular disease (8); cerebrovascular disease (3); renal dysfunction (18); liver dysfunction (5); diabetes mellitus (12)	119 65.3 (17.3) 51 NR NR 1.6 (4.2) 97.8 (106.1) Community acquired pneumonia (38); acute exacerbation of COPD (26); acute bronchitis (26); acute exacerbation of asthma (3); others (8) CAD (27); congestive heart failure (6); peripheral vascular disease (8); cerebrovascular disease (4); renal dysfunction (15); liver dysfunction (5); diabetes mellitus (14)	**PCT:** 4 died; 8 lost to follow-up **Control:** 4 died; 5 lost to follow-up

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Deliberato(2013)[1, 50] NCT01494675 **Country:** Brazil **Funding:** Not stated **Recruitment:** March 2008 - February 2010 **Only available as conference abstract:** False **Multicentre study:** False **Design:** Parallel group RCT **Number randomised:** 81	**Setting:** ICU **Population:** Adults **Presentation:** Suspected or confirmed sepsis **Testing application**: Discontinuation **Inclusion criteria:** Adults (at least 18 years) with microbiologically confirmed infections (blood, urine, tracheal aspirate, bronchoalveolar lavage fluid cultures), and suspected sepsis, severe sepsis or spetic shock. **Exclusion criteria:** Onset of antibiotic therapy >48 horus before cultures were performed; known pregnancy; infrections requiring prolonged antibiotic therapy (e.g. bacterial endocarditis, hepatic or brain abscess, mediastinitis, osteomyelitis); severe infection caused by viruses, parasites, fungi, or mycobacteria; chronic localised infections (e.g. chronic osteomyelitis or prostatitis).	**Number randomised** **Age (Mean, SD):** **Male (%):** **SAPS (Mean, SD):** **SOFA (Mean, SD):** **PCT (ng/mL) (Median, range):** **CRP (mg/L) (Mean, SD):** **Diagnosis (%):** **Comorbidities (%):**	42 68 (21) 57.2 56.9 (11.7) 6.3 (2.9) 5.6 (0, 187.5) 162 (106.3) Pulmonary sepsis 19; urinary sepsis 66.7; abdominal sepsis 9.5; other sepsis 4.8 COPD 4.8; cardiopathy 16.7; immunosupression 7.1; Diabetes mellitus 19; chronic renal failure 4.8; chronic liver disease 7.1; non-haematologic neoplasia 11.9; haematological malignancy 4.8	39 62 (19) 53.8 53.8 (12.3) 5.4 (3.3) 9.9 (0, 370.6) 207 (123.5) Pulmonary sepsis 17.9; urinary sepsis 48.7; abdominal sepsis 10.3; other sepsis 23.1 COPD 2.6; cardiopathy 18; immunosupression 12.8; Diabetes mellitus 23.1; chronic renal failure 18; chronic liver disease 10.3 ; non-haematologic neoplasia 5.1; haematological malignancy 2.6	**PCT**: refused consent after randomisation 12; complicated infection 5; tunneled catheter not removed 2; discharged from hospital with antibiotics 2; died 1 **Control**: discharged from hospital with antibiotics 3; complicated infection 1; died 4

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Drozdov(2014)[5, 51, 52] triple p in UTI (ISRCTN13663741) **Country:** Switzerland **Funding:** Public **Recruitment:** April 2012 - March 2014 **Design:** Parallel group RCT **Number randomised:** 129	**Setting:** ED **Population:** Adults **Presentation:** Community-acquired UTI **Testing application**: Discontinuation **Inclusion criteria:** Consecutive immunocompetent adults (≥18 years), presenting to the ED of a tertiary care hospital, with community-acquired, non-catheter-related, acute (<28 days) UTI as the main diagnosis (at least one clinical symptom: core body temperature ≥38 ◦C, urinary urgency, polyuria, dysuria, suprapubic pain, flank pain, costovertebral angle tenderness, nausea and vomiting, and one urinary criterion: pyuria >20 leukocytes/ µL and/or nitrites). **Exclusion criteria:** Other infections that required antibiotic therapy; pre-treatment with antibiotics <48 hours; pregnancy; prostatitis; implated foreign bodies in the urinary tract; urinary catheter; endovascular prostheses or foreign bodies; non-endovascular prostheses or foreign bodies within 6 months after implantation; forseable non-compliance or follow-up issues (e.g. current drug abuse); severe immunodeficiency; severe medical co-morbidity with iminent death	**Number randomised** **Age (Median, IQR):** **Male (%):** **SAPS:** **SOFA:** **PCT:** **CRP:** **Diagnosis (%):** **Comorbidities (%):**	63 73 (19, 96) NR NR NR NR NR NR NR	66 NR NR NR NR NR NR NR	**Total:** 4 withdrew consent immediately after randomisation; 5 died; 3 lost to follow-up

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Esposito(2011)[53] NR **Country:** Italy **Funding:** Public **Recruitment:** October 2008 - September 2010 **Design:** Parallel group RCT **Number randomised:** 319	**Setting:** ED **Population:** Children **Presentation:** CAP **Testing application**: Initiation and discontinuation **Inclusion criteria:** Children **(**age 1 month - 14 years); diagnosis of CAP made based on clinical signs and symptoms (history of fever or cough, tachypnea, dyspnea or respiratory distress, and breathing with grunting or wheezing sounds with rales) and confirmed by chest radiography (i.e. the presence of pulmonary infiltration or segmental or lobar consolidation); no demonstrable complications (i.e. pleural effusion, empyema, lung necrosis, pneumatocele). **Exclusion criteria:** Antibiotics < 10 days preceding admission; underlying chronic disease; severe malnutrition or other concurrent infections.	**Number randomised** **Age (Mean, SD, CI):** **Male (%):** **SAPS:** **SOFA:** **PCT:** **CRP:** **Diagnosis (%):** **Comorbidities (%):**	160 40.3 (3.8) 55 NR NR NR NR NR NR	159 40.7 (4) 57 NR NR NR NR NR NR	**PCT:** 5 withdrew consent **Control:** 4 withdrew conent

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Layios(2012)[54, 55] NR **Country:** Belgium **Funding:** Not stated **Recruitment:** April 2008 - December 2008 **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 509	**Setting:** ICU **Population:** Adults **Presentation:** Suspected infection **Testing application**: Initiation **Inclusion criteria:** Adults (>18 years), hospitalised for >2 days in one of 5 ICUs **Exclusion criteria:** NR	**Number randomised** **Age (Median, IQR):** **Male (%):** **SAPS (Median, IQR):** **SOFA:** **PCT:** **CRP:** **Diagnosis (%):** **Comorbidities (%):**	258 66 (55, 76) 59.7 39.3 (16.3) NR NR NR Underlying disease: non-fatal 62; ultimately fatal 28.7; rapidly fatal 9.3 Coronary disease 11.2; chronic heart failure 14; cerebrovascular disease 4.7; renal dysfunction 11.6; liver disease 7.8; diabetes 17.4; COPD or asthma 27.9; solid cancer 16.3; haematological cancer 6.6; transplant 3.1	251 65 (53, 75) 61 39 (16.7) NR NR NR Underlying disease: non-fatal 61.4 ; ultimately fatal 27.1 ; rapidly fatal 11.6 Coronary disease 8.4; chronic heart failure 13.6; cerebrovascular disease 6.4; renal dysfunction 14.3; liver disease 6.4; diabetes 15.1; COPD or asthma 26.3; solid cancer 17.5; haematological cancer 6; transplant 3.2	None reported

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Liu(2013)[38] NR **Country:** China **Funding:** Public **Recruitment:** January 2012 - June 2013 **Design:** Parallel group RCT **Number randomised:** 82	**Setting:** ICU **Population:** Adults **Presentation:** Sepsis **Testing application**: Discontinuation **Inclusion criteria:** Age >18 years; suspected bacterial sepsis **Exclusion criteria:** Patients with positive culture result for Psuedomanas aeruginosa, acinetobacter baumannii, mycobacterium tuberculosis, fungi; suspected virus or parasite infection; chronic local infection; >48 hours of antibmicrobial treament before randomisation; immunodeficiency (e.g. HIV or leikemia); malignant tumour	**Number randomised** **Age (Mean, SD, CI):** **Male (%):** **SAPS:** **SOFA:** **PCT:** **CRP:** **Diagnosis (%):** **Comorbidities (%):**	42 54.9 (13.8) 47.6 NR NR NR NR NR Cardiodysfunction (6); kidney dysfunction (10); respiratory failure (18); haemodialysis (11)	40 53.4 (12.2) 45 NR NR NR NR NR Cardiodysfunction (5); kidney dysfunction (8); respiratory failure (15); haemodialysis (9)	None reported

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Nobre(2005)[2, 56, 64] NCT00250666 **Country:** Switzerland **Funding:** Industry - assay manufacturer **Recruitment:** February 2006 - April 2007 **Design:** Parallel group RCT **Number randomised:** 79	**Setting:** ICU **Population:** Adults **Presentation:** Severe sepsis and septic shock **Testing application**: Discontinuation **Inclusion criteria:** Patients admitted to a mixed medical/surgical ICU with suspected severe sepsis or septic shock, or who developed severe sepsis or septic shock during their stay **Exclusion criteria:** Microbiologically documented infections caused by Pseudomonas aeruginosa, Acinetobacter baumanni, Listeria spp., Legionella pneumophila, Pneumocystis jiroveci, or Mycobacterium tuberculosis, for which a prolonged duration of antibiotic therapy is standard care; severe viral or parasitic infections; chronic infectious conditions requiring prolonged antibiotic therapy; antibiotic therapy started ≥48 enrollment; chronic, localised infections (e.g. chronic osteomyelitis); severely immunocompromised or on immunosuppressive therapy after solid organ transplant; neutropenia; withholding of life support; absence of antimicrobial treatment despite clinical suspicion of sepsis	**Number randomised** **Age (Mean, SD, CI):** **Male (%):** **SAPS 3 (Mean, SD, CI):** **SOFA (Mean, SD, CI):** **PCT (ng/mL) (Median, range):** **CRP:** **Diagnosis (%):** **Comorbidities (%):**	39 64.3 (13.6) 67.5 67.5 (11.2) 5.9 (3.3) 8.4 (0.1, 93) NR Sepsis type: pulmonary 64; abdominal 5; urinary 18; other 13, septic shock 43.6 Organ failure: acidosis 45.2; ARDS 22.6; coma 16.1; dialysis 16.1; heart failure 6.5; respiratory failure 74.2; shock 45.2; renal failure 3.2 Neoplasia 12.8; immunosuppression 2.6; cardiopathy 33.3; COPD 30.8; IDDM 0; NIDDM 10.3; chronic renal failure 5.1; peripheral vascular disease 5.1; chronic hepatopathy 12.8	40 65.8 (15) 69.2 69.9 (12.6) 6.7 (2.9) 5.9 (0.1, 497) NR Sepsis type: pulmonary 67; abdominal 15; urinary 10; other 8; septic shock 42.5 Organ failure: acidosis 54.1; ARDS 16.2; coma 10.8; dialysis 10.8; heart failure 5.4; respiratory failure 75.7; shock 54.1; renal failure 13.5 Neoplasia 12.5; immunosuppression 2.5; cardiopathy 42.5; COPD 17.5; IDDM 5; NIDDM 15; chronic renal failure 15; peripheral vascular disease 2.5; chronic hepatopathy 12.5	**PCT:** 4 died or transferred before day five; 4 complicated infections (pleural empyema, acute mastoiditis, pelvic abscess) **Control:** 2 died or transferred before day five; 1 pleural empyema

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Qu(2012)[57] NR **Country:** China **Funding:** Public **Recruitment:** March 2009 - September 2011 **Design:** Parallel group RCT **Number randomised:** 71	**Setting:** ICU **Population:** Adults **Presentation:** Severe acute pancreatitis **Testing application**: Initiation and discontinuation **Inclusion criteria:** onset of severe acute pancreatitis < 24 hours; age >18 years. **Exclusion criteria:** time interval between diagnosis and study inclusion >24 hours; thyroid disease ; shock; need for surgical interventions.	**Number randomised** **Age (Mean, SD, CI):** **Male (%):** **SAPS:** **SOFA (Mean, SD, CI):** **PCT:** **CRP:** **Diagnosis (%):** **Comorbidities (%):**	35 43.2 (39.4, 47) (11.1) 71 NR 2.5 (2.3, 2.7) (0.5) NR NR NR NR	36 43.7 (40, 47.4) (11) 72 NR 2.4 (2.2, 2.6) (0.5) NR NR NR NR	No withdrawals.

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Roh(2010)[58] NR **Country:** NR **Funding:** Not stated **Recruitment:** NR **Only available as conference abstract:** **Design:** Parallel group RCT **Number randomised:** 122	**Setting:** ED **Population:** Adults **Presentation:** CAP **Testing application**: Initiation and discontinuation **Inclusion criteria:** Adults with CAP **Exclusion criteria:** NR	**Number randomised** **Age (range):** **Male (%):** **SAPS:** **SOFA:** **PCT:** **CRP:** **Diagnosis (%):** **Comorbidities (%):**	60 24-82 NR NR NR NR NR NR NR	62 NR NR NR NR NR NR NR	No information

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Roh(2013)[59] NR **Country:** NR **Funding:** Not stated **Recruitment:** NR **Only available as conference abstract** **Design:** Parallel group RCT **Number randomised:** 164	**Setting:** ED **Population:** Adults **Presentation:** Elderly patients with CAP **Testing application**: Initiation and discontinuation **Inclusion criteria:** Elderly patients (age >70 years) requiring hospitalisation with CAP **Exclusion criteria:** NR	**Number randomised** **Age (Median, range):** **Male (%):** **SAPS:** **SOFA:** **PCT:** **CRP:** **Diagnosis (%):** **Comorbidities (%):**	80 NR NR NR NR NR NR NR NR	84 NR NR NR NR NR NR NR NR	No information

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Schuetz(2009)[60-62, 68-70] ProHOSP NCT00350987 (ISRCTN95122877) **Country:** Switzerland **Funding:** Mixed **Recruitment:** October 2006 - March 2008 **Multicentre study** **Design:** Non-inferiority parallel group RCT **Number randomised:** 1381	**Setting:** ED **Population:** Adults **Presentation:** Primary diagnosis of LRTI **Testing application**: Initiation and discontinuation **Inclusion criteria:** Adults (≥18 years); admitted from the community or a nursing home, via the ED; diagnosis of acute (<28 days duration) LRTI (presence of at least one rspiratory symptom (cough, sputum production, dyspnea, tachypnea, pleuritic pain), plus at least one finding during auscultation (rales, crepitation), or one sign of infection (core body temperature >38 ^{O}C, shivering, leukocyte count >10000/microlitre or <4000/microlitre independent of antibiotic pre-treatment. **Exclusion criteria:** Active intravenous drug use; severe immunosupression other than corticosteroid use; life-threatening medical co-morbidities, leading to possible iminent death; dospital acquired pneumonia at least 48 hours after admisssion or hospitalised 14 days before presentation; chronic infection requiring antibiotic treatment.	**Number randomised** **Age (Median, IQR):** **Male (%):** **SAPS:** **SOFA :** **PCT (ng/mL) (Median, IQR):** **CRP (mg/L) (Median, IQR):** **Diagnosis (%):** **Comorbidities (%):**	687 73 (59, 82) 59.9 NR NR 0.2 (0.1, 1.2) 115 (38, 212) Final diagnosis: CAP 68.6; Exacerbation of COPD 17.1; acute bronchitis 10.3; other 4 . CHD 21.8; cerebrovascular disease 8.1; renal dysfunction 23.3; COPD 39.5; neoplastic disease 10.3; diabetes 17	694 72 (59, 82) 55.2 NR NR 0.2 (0.1, 1.6) 114 (4, 220) Final diagnosis: CAP 67.6; Exacerbation of COPD 16.4; acute bronchitis 11.9; other 4 . CHD 19.8; cerebrovascular disease 8.1; renal dysfunction 21.2; COPD 39; neoplastic disease 14.2; diabetes 16.4 .	**PCT**: withdrew consent 16; lost to follow-up 1; died 34 **Control**: withdrew consent 6; died 33

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Stolz(2007)[72] **Country:** Switzerland **Funding:** Mixed **Recruitment:** November 2003 – March 2005 **Design:** Parallel group RCT **Number randomised:** 226	**Setting:** ED **Population:** Adults **Presentation:** Exacerbations of COPD **Testing application**: initiation **Inclusion criteria:** Age >=40 years; COPD exacerbation (ECOPD); met post-bronchodilator therapy spirometric criteria, according to the Global Initiative for Chronic Obstructive Lung Disease guidelines,<48 h of ED admission. An ECOPD was defined as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD." **Exclusion criteria:** Alternative explanation for the presenting signs and symptoms other than a worsening of the underlying COPD; psychiatric comorbidities; immunosuppression; asthma; cystic fibrosis; presence of infiltrates on chest radiographs on hospital admission.	**Number randomised** **Age (Median IQR):** **Male (%):** **COPD severity (%):** **Comorbidities (%):**	113 70 (65, 77) 49 GOLD I (5.9); GOLD II (14.7): GOLD III (46.1); GOLD IV (33.3) Cardiopathy (41%); arterial hypertension (23%); osteoporosis (17%); malignancy (12%); diabetes (12%); renal insufficiency (5%)	113 70 (65, 79) 42 GOLD I (4.7); GOLD II (23.6); GOLD III (48.1); GOLD IV (23.6) Cardiopathy (46%); arterial hypertension (26%); osteoporosis (9%); malignancy (13%); diabetes (10%); renal insufficiency (11%)	**PCT**: 11 excluded after randomisation (did not meet COPD criteria); 3 died within 14 days; 2 died within 6 months **Control**: 7excluded after randomisation (did not meet COPD criteria); 2 died within 14 days; 7died within 6 months

Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Stolz(2009)[63] ProVAP study (ISRCTN61015974) **Country:** Switzerland **Funding:** Mixed **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 101	**Setting:** ICU **Population:** Adults **Presentation:** VAP **Testing application**: Discontinuation **Inclusion criteria:** ICU patients intubated for mechanical ventilation for ≥48 h; >18 yrs; clinically diagnosed VAP as defined by the ATS guidelines (new or persistent infiltrate on chest radiography,≥2 of the following: purulent tracheal secretions, temperature >38^{o}C,leukocyte count >11,000 uL or <3,000 uL). **Exclusion criteria:** Pregnant; received immunosuppressants or long-term corticosteroid therapy; severely immunosuppressed, including AIDS; coexisting extrapulmonary infection diagnosed between day 1 and 3 requiring antibiotic therapy for >3 days.	**Number randomised** **Age (Median, IQR):** **Male (%):** **SAPS (Mean, SD, CI):** **SOFA (Mean, SD, CI):** **PCT (ng/mL) (Median, IQR):** **CRP:** **Diagnosis (%):** **Comorbidities (%):**	51 53 (21, 88) 75 42 (13) 7.3 (3.4) 0.6 (0.2, 2.6) NR Medical (53); emergency surgery (45); elective surgery (2) Coronary artery disease (18); hypertensive heart disease (16); congestive heart failure (41); renal dysfunction (18); liver disease (8); diabetes (20); COPD (16); neoplastic disease (6); substance abuse (10)	50 59 (18, 83) 74 45 (14) 8.2 (3.4) 0.7 (0.2, 2.3) NR Medical (52); emergency surgery (40); elective surgery (6) Coronary artery disease (8); hypertensive heart disease (16); congestive heart failure (54); renal dysfunction (14); liver disease (6); diabetes (26); COPD (22); neoplastic disease (10); substance abuse (16)	None

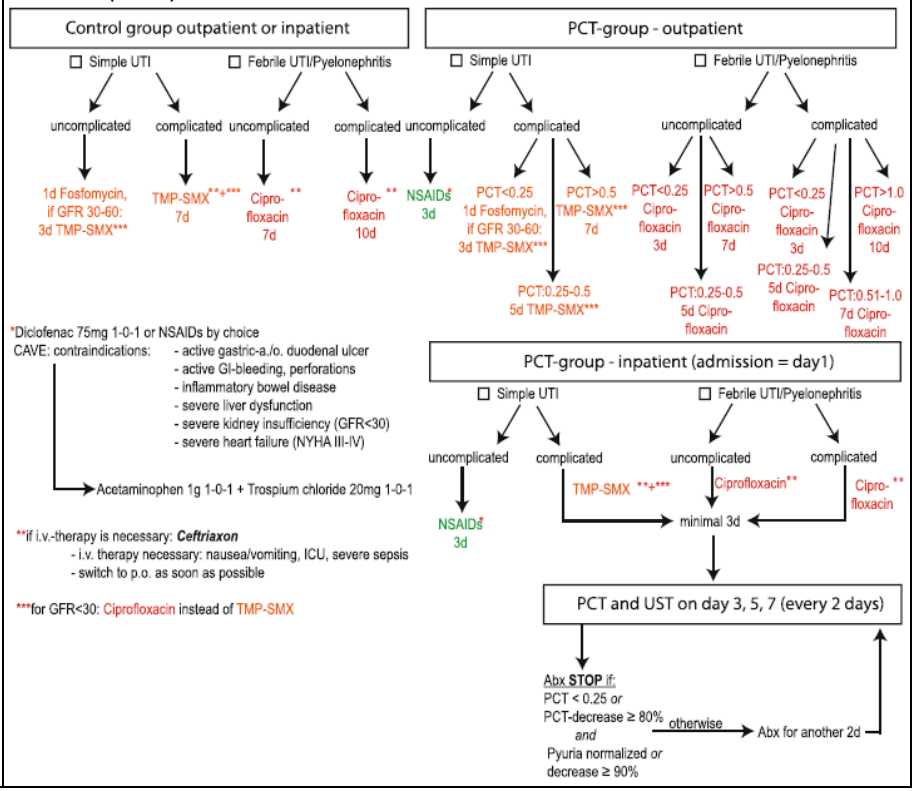
Study Details	Selection criteria	Participant characteristics	PCT based algorithm	Clinical judgement	Withdrawals
Tang(2013)[4] ICTRP ChiCTR-TRC-12002534 **Country:** china **Funding:** Public **Recruitment:** February 2005 - July 2010 **Design:** Parallel group RCT **Number randomised:** 265	**Setting:** ED **Population:** Adults **Presentation:** Suspected acute exacerbation of asthma **Testing application**: Initiation **Inclusion criteria:** Adults (≥18 years), with at least one of the following clinical features: dyspnea; wheeze; acute cough; increased effort of breathing; increased requirement for beta-2-agonist; oxygen saturation <95 ; peak expiratory flow 80% or less of their best known value over the preceding 12 months or their predicted value **Exclusion criteria:** treatment with antibiotics in the two weeks before recruitment; bacterial infection other than in the respiratory system; pneumonia confirmed by chest x-ray; other chronic respiratory disease; severe organ dysfunction	**Number randomised** **Age (Mean, SD, CI):** **Male (%):** **SAPS:** **SOFA :** **PCT (ng/mL) (median IQR):** **CRP (mg/L) (median IQR):** **Diagnosis (%):** **Comorbidities (%):**	132 54 (14) 50 NR NR 0.137 (0.068, 0.252); 8.2 (4.5, 15.7) Severity of asthma: mild 36.7; moderate 42.2; severe 13.3; critical 7.8 NR	133 55 (15) 46.5 NR NR 0.119 (0.057, 0.267) 6.9 (5.1, 17.6) Severity of asthma: mild 39.4; moderate 40.9; severe 13.4; critical 6.3 NR	**PCT**: 1 died; 1 withdrew from study; 2 lost to follow-up **Control:** 2 died; 1 withdrew from study; 3 lost to follow-up

b. Intervention and comparator details

Study details	PCT based algorithm					Comparator
	PCT Assay	Timing of PCT measurement	Initiation Algorithm	Discontinuation Algorithm	Clinical component	
Annane(2013)[42]	BRAHMS PCT-sensitive KRYPTOR - Thermo Fisher	6 hours; days 3 and 5	PCT <0.25 ng/mL: do not initiate antibiotics, discontinue antibiotics if already started PCT 0.25-0.49 ng/mL: antibiotics strongly discouraged PCT 0.5-4.99 ng/mL: antibiotics recommended PCT ≥5 ng/mL: antibiotics strongly recommended For participants enrolled ≤48 hours after surgery, the respective PCT cut-offs were <4 ng/mL, 4-9 ng/mL, and ≥9 ng/mL		Investigators were strongly asked not to over-rule the algorithm every day up to study day 5	Doctor's discretion
Baer(2013)[44]	BRAHMS PCT-sensitive KRYPTOR - Thermo Fisher	Baseline; days 3 and 5	PCT <0.1 ng/mL: definitely not antibiotics. PCT 0.1-0.25 ng/mL: probably not antibiotics PCT 0.26 ng/mL -0.49 ng/mL: probably require antibiotics PCT ≥0.5 ng/mL: definitely require antibiotics	PCT <0.25 ng/mL: discontinuation encouraged upon clinical stabilisation Initial PCT >10 ng/mL: discontinuation encouraged when levels decreased below 90% of initial value. Continuation of treatment on day 5 was determined as follows: >1 ng/mL: 7 days 0.51-1 ng/mL: 5 days 0.26-0.5 ng/mL: 3 days ≤0.25 ng/mL: no antibiotic	The PCT algorithm could be overruled for patients with life threatening infections, defined as severe co-morbidity, emerging ICU need during initial follow-up, or hemodynamic or respiratory instability.	Doctor assessment and clinical guidelines for a duration of 7–10 days for uncomplicated CAP and 14 or more days for complicated CAP

Study details	PCT based algorithm					Comparator
	PCT Assay	Timing of PCT measurement	Initiation Algorithm	Discontinuation Algorithm	Clinical component	
Bouadma(2010)[46]	BRAHMS PCT-KRYPTOR - Thermo Fisher	Baseline, at each infectious episode until day 28, and every morning in participants receiving antibiotics. 6-12 hours after admission in patients where antibiotics were initially witheld.	PCT <0.25 ng/mL: antibiotics strongly discourcaged PCT 0.25-0.49 ng/mL: antibiotics discouraged PCT 0.5-0.99 ng/mL: antibiotics encouraged PCT ≥1 ng/mL: antibiotics strongly encouraged	PCT <0.25 ng/mL: discontinuation strongly encouraged PCT 0.25-0.49 ng/mL or ≤80% of peak concentration: discontinuation encouraged PCT ≥0.5 ng/mL or >80% of peak concentration: discontinuation strongly discouraged PCT ≥0.5 ng/mL rising: Change of antibiotics strongly encouraged	Before the start of the study, all investigators received an approved reminder including recommendations for duration of antibiotic treatment for most frequent infections. Final treatment decisions were at the discretion of doctors.	
Christ-Crain(2006)[47]	BRAHMS PCT-KRYPTOR - Thermo Fisher	Baseline; days 4, 6, and 8. 6-24 hours after admission in patients where antibiotics were initially witheld.	PCT <0.1 ng/mL: antibiotics strongly discouraged PCT 0.1-0.25 ng/mL: antibiotics discouraged PCT 0.25-0.5 ng/mL: antibiotics encouraged PCT >0.5 ng/mL: antibiotics strongly encouraged	PCT <0.1 ng/mL: discontinuation strongly encouraged PCT 0.1-0.25 ng/mL: discontinuation encouraged PCT 0.25-0.5 ng/mL: discontinuation discouraged PCT >0.5 ng/mL: discontinuation strongly discouraged In patients with very high PCT values on admission (e.g., >10 g/L), discontinuation of antibiotics was encouraged if levels decreased to <10% of the initial value.	NR	Usual practice guidelines

Study details	PCT based algorithm					Comparator
	PCT Assay	Timing of PCT measurement	Initiation Algorithm	Discontinuation Algorithm	Clinical component	
Christ-Crain(2004)[49]	BRAHMS PCT-sensitive KRYPTOR - Thermo Fisher	Baseline; 6-24 hours after admission in patients where antibiotics were initially witheld.	PCT <0.1 ng/mL: antibiotics strongly discourcaged PCT 0.1-0.25 ng/mL: antibiotics discourcaged PCT 0.25-0.5 ng/mL: antibiotics advised PCT >0.5 ng/mL: antibiotics strongly recommended	PCT <0.1 ng/mL: discontinuation strongly encouraged PCT 0.1-0.25 ng/mL: discontinuation encouraged PCT 0.25-0.5 ng/mL: discontinuation discouraged PCT >0.5 ng/mL: discontinuation strongly discouraged For patients on antibiotics on admission, PCT < 0.25 ng/mL: discontinuation ecommended	Diagnostic procedures, therapeutic and antibiotic regimens were at the doctor's discretion.	
Deliberato(2013)[1]	VIDAS BRAHMS PCT - bioMérieux	Baseline; day 5 or 7 (blood culture positive) and every 48 hours until hospital discharge, death, or discontinuation of antibiotic thearpy.		Dicontinuation encouraged when PCT fell by >90% from the peak level or the absolute value of PCT was <0.5 ng/mL.	Continuation of antibiotic therapy against this guidance was clasified as "antibiotic discontinuation overruling."	No details reported

Study details	PCT based algorithm					Comparator
	PCT Assay	Timing of PCT measurement	Initiation Algorithm	Discontinuation Algorithm	Clinical component	
Drozdov(2014)[5]	BRAHMS PCT KRYPTOR - Thermo Fisher			Drovdov (2014):[5] 		

Study details	PCT based algorithm					Comparator
	PCT Assay	Timing of PCT measurement	Initiation Algorithm	Discontinuation Algorithm	Clinical component	
Esposito(2011)[53]	BRAHMS PCT-KRYPTOR - Thermo Fisher	Baseline; every two days until discharge, and during the two follow-up visits.	<0.25 ng/mL: antibiotics not administered ≥0.25 ng/mL: antibiotics given immediately	Antibiotics given until levels returned to <0.25 ng/mL, and resumed antibiotics only if their PCT levels subsequently increased to more than this value.	Untreated children showing no reduction in the clinical signs and symptoms of disease after three days or any severe deterioration could be treated with antibiotics regardless of their PCT levels or treatment could be modified.	SIP guidelines: antibiotic monotherapy chosen on the basis of age if mild; combined beta-lactam and macrolide therapy if severe. The duration of administration in the control group was that recommended by the SIP (i.e. 7-14 days depending on disease severity).
Layios(2012)[54]	VIDAS BRAHMS PCT - bioMérieux	As soon as patients were suspected of developing an infection	PCT <0.25 ng/mL: antibiotics more strongly discouraged PCT 0.25-0.5 ng/mL: antibiotics less strongly discouraged PCT 0.5-1 ng/mL: antibiotics less strongly recommended PCT >1 ng/mL: antibiotics strongly recommended The strategy was applied individually to each infectious episode during the ICU stay		NR	NR
Liu(2013)[38]	Quantitative; not specified	PCT value oberved every day.		PCT value decreased >90% or PCT <0.25 ug/L	Antibiotics could also be stopped when no active symptoms of infection were shown and APACHE Ⅱ scores declined	Treated according to principles of antibiotic usage

Study details	PCT based algorithm					Comparator
	PCT Assay	Timing of PCT measurement	Initiation Algorithm	Discontinuation Algorithm	Clinical component	
Nobre(2005)[2]	BRAHMS PCT-KRYPTOR - Thermo Fisher	Baseline (days 1 & 2) and daily until the 7th day of follow-up, and then at 5-day intervals or until antibiotics were stopped, death or hospital discharge.		Baseline PCT ≥1 ng/mL, re-evaluate at day 5: PCT levels dropped by >90% from baseline or peak value, discontinuation encouraged; PCT < 0.25 ng/mL, discontinuation encouraged. Baseline PCT <1 ng/mL, re-evaluate at day 3: PCT < 0.1 ng/mL, discontinuation encouraged.	The final decision on antibiotic therapy duration was at the discretion of the treating physician. Patients with positive blood cultures received at least 5 full days parenteral antibiotic thearpy.	Clinicians decided on the duration of antibiotic therapy, based on empirical rules. Patients with positive blood cultures received at least 5 full days parenteral antibiotic thearpy.
Qu(2012)[57]	Quantitative; not specified	Measured daily for a maximum of 28 days.	Antibiotic therapy was not applied until clinical signs and symptoms of infection appeared and the PCT value was >0.5ng/ml.	Antibiotic therapy discontinued if clinical signs and symptoms of infection improved and PCT <0.5 ng/ml over 3 days.	NR	Antibiotic therapy administrated for 14 days, or antibiotic therapy was continued because of confirmed infection until clinical signs and symptoms of infection disappeared over 3 days.
Roh(2010)[58]	Quantitative; not specified	NR	Appears that decision to start antibiotics also influenced by PCT level but this was not explicitly stated.	PCT <0.25 ug/L: dicontinue antiobiotics	NR	Usual practice guideline
Roh(2013)[59]	Quantitative; not specified	NR	PCT >0.25 ug/L: start antiobiotics	PCT <0.25 ug/L: dicontinue antiobiotics	NR	Usual practice guideline

Study details	PCT based algorithm					Comparator
	PCT Assay	Timing of PCT measurement	Initiation Algorithm	Discontinuation Algorithm	Clinical component	
Schuetz(2009)[60]	BRAHMS PCT-sensitive KRYPTOR - Thermo Fisher	Baseline, 3, 5 and 7 days after starting antibiotics, and at discharge. After 6-24hours where antibiotics where initially witheld.	PCT <0.1 ng/mL: antibiotics strongly discourcaged PCT 0.1-0.25: antibiotics discouraged PCT 0.25-0.5 ng/mL: antibiotics encouraged PCT >0.5 ng/mL: antibiotics strongly encouraged.	PCT <0.1 ng/mL: continuation strongly discourcaged PCT 0.1-0.25: continuation discouraged PCT 0.25-0.5 ng/mL: continuation encouraged PCT >0.5 ng/mL: continuation strongly encouraged.	The PCT algorithm could be overruled in patients with: immediate need for ICU admission; respiratory or haemodynamic instability; positive antigen test for Legionella pneumorphila; severe CAP. The PCT algorithm could also be overruled after consulting the study centre. Other routine laboratory tests were available. The choice of antibiotic regimen was at the discretion of the clinician.	Recommendations from up-to-date guidelines. Routine laboratory tests, other than PCT, were available. The choice of antibiotic regimen was at the discretion of the doctor.

Study details	PCT based algorithm					Comparator
	PCT Assay	Timing of PCT measurement	Initiation Algorithm	Discontinuation Algorithm	Clinical component	
Stolz(2009)[63]	BRAHMS PCT-KRYPTOR - Thermo Fisher	Baseline, after 72 h (day 2) daily PCT levels were measured.		PCT <0.25 ng/mL: discontinuation strongly encouraged PCT 0.25-0.5 ng/mL or a decrease ≥80%: reduction or discontinuation was encouraged PCT 0.5-1.0 ng/mL or decrease <80%: reduction or discontinuation discouraged PCT >1 ng/mL: antibiotic discontinuation was strongly discouraged.	NR	NR
Stolz(2007)[3]	BRAHMS PCT-KRYPTOR - Thermo Fisher	Baseline.	PCT< 0.1 ug/L: antibiotics discouraged. 0.1-0.25 ug/L: antibiotics discouraged or encouraged, based on the stability of the patient's clinical condition. PCT> 0.25: antibiotic treatment encouraged.		NR	Current guidelines, according to the decision of the attending doctor
Tang(2013)[4]	BRAHMS PCT-KRYPTOR - Thermo Fisher	Baseline; after 6-8 hours where antibiotics where initially witheld.	PCT <0.1 ng/mL: antibiotic treatment strongly discouraged PCT 0.1-0.25 ng/mL: antibiotic treatment discouraged PCT >0.25 ng/mL: antibiotic treatment encouraged.		NR	Antibiotic treatment was decided by the attending doctor

c. Study results (dichotomous outcomes)

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
Annane(2013)[42] **Population** ICU; Adults (Apparent septic shock and no clear source of infection)	Whole group **Analysis** ITT	All cause mortality **Timing:** 5 Days	3/31	3/31	1 (0.25, 4.04)	NR	
		ICU mortality	7/31	10/30	0.69 (0.31, 1.53)		
		In hospital mortality	7/31	10/30	0.69 (0.31, 1.53)		
	Whole group **Analysis** modified ITT	Antibiotic exposure (Number on antibiotics at day 5) **Timing:** 5 Days	18/30	22/28	0.77 (0.55, 1.08)		
Baer(2013)[44] **Population** ED; Children (LRTI) **Analysis** modified ITT	Whole group	Adverse Outcome (Any complication from pneumonia or other LRTI (e.g. parapneumonic infusions in need of puncture, e,pyema, lung abscess, necrotising pneumonitis, ARDS)) **Timing:** 14 Days	38/168	33/169	1.16 (0.77, 1.74)	NR	
	CAP		23/108	20/107	1.14 (0.67, 1.93)		
	Non-CAP LRTI		15/60	13/62	1.19 (0.63, 2.25)		
	Whole group	Antibiotic side effects **Timing:** 14 Days	56/168	57/169	0.99 (0.73, 1.33)		
	CAP		42/60	51/62	0.85 (0.7, 1.04)		
	Non-CAP LRTI		14/60	6/62	2.3 (0.98, 5.42)		
	Whole group	Hospitalisation **Timing:** 14 Days	104/168	100/169	1.05 (0.88, 1.24)		
	CAP		67/108	68/107	0.98 (0.8, 1.2)		
	Non-CAP LRTI		37/60	32/62	1.19 (0.87, 1.62)		
	Whole group	Initiation of antibiotic exposure **Timing:**	104/168	93/169	1.12 (0.94, 1.35)		
	CAP		77/108	83/107	0.92 (0.79, 1.08)		

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
	Non-CAP LRTI	Days	27/60	10/62	2.71 (1.46, 5.01)		
Bouadma(2010)[46] **Population** ICU; Adults (Suspected bacterial infection) **Analysis** modified ITT	Whole group	All cause mortality **Timing:** 28 Days	65/307	64/314	1.04 (0.76, 1.41)	OR: 0.8 (-4.6, 6.2)	Adjusted for age, sex, pre-exisiting comorbidities, location before and reason for admission, baseline SOFA score, infection type, blood culture results, septic shock and mechanical ventilation.
	Whole group	All cause mortality **Timing:** 60 Days	92/307	82/314	1.15 (0.89, 1.48)	OR: 1.09 (0.79, 1.51) HR 0.96 (95% CI 0.84 to 1.09)	
	Whole group	Infection (Isolation from the same or another site of one or more pathogens different from that identified during the first infectious episode, together with clinical signs or symptoms of infection) **Timing:** 28 Days	106/307	97/314	1.12 (0.89, 1.4)		
	Whole group **Analysis** modified ITT	Infection relapse/recurrence (Growth of one or more of the initial causative bacterial strains from a second sample taken from the same infection site at 48 h or more after stopping of antibiotics, combined with clinical	20/307	16/314	1.27 (0.68, 2.38)		

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
		signs or symptoms of infection) **Timing:** 28 Days					
	Whole group	Multidrug-resistant bacteria (One of the following: ticarcillin-resistant Pseudomonas aeruginosa, Acinetobacter baumannii, or Stenotrophomonas maltophilia; extended-spectrum β-lactam-producing Enterobacteriaceae; high-concentration cephalosporinase producing AmpC Enterobacteriaceae;) **Timing:** 28 Days	55/307	52/314	1.08 (0.77, 1.52)		
Christ-Crain(2004)[49] **Population** ED; Adults (Suspected LRTI) **Analysis** ITT	Whole group	Initiation of antibiotic exposure (Antibiotics prescribed) **Timing:** Days	55/124	99/119	0.54 (0.43, 0.66)	RR: 0.49 (0.44, 0.55)	Adjusted for clustering and potential confounding factors (age other NR)
	COPD acute admissions		11/29	27/31	0.45 (0.28, 0.71)	NR	
	Whole group	All cause mortality **Timing:** 14 Days	4/124	4/119	0.96 (0.27, 3.46)	NR	
	COPD acute admissions		1/29	1/31	1.07 (0.12, 9.7)		
	Whole group	Hospitalisation (Hospital admission)	101/124	88/119	1.1 (0.96, 1.26)		
	COPD acute exacerbations		27/29	25/31	1.15 (0.95, 1.4)		

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
	Whole group	ICU admission **Timing:** 14 Days	5/124	6/119	0.81 (0.27, 2.46)		
	COPD acute exacerbations		1/29	1/31	1.07 (0.12, 9.7)		
Christ-Crain(2006)[47] **Population** ED; Adults (CAP) **Analysis** ITT	Whole group	Initiation of antibiotic exposure	128/151	149/151	0.86 (0.8, 0.92)	NR	
		All cause mortality **Timing:** 6 Weeks	18/151	20/151	0.9 (0.5, 1.62)		
		Adverse Outcome ("Failed outcome" defined as death, recurrence, relapse, or persistence of clinical, laboratory, and radiologic signs of CAP, and patients lost to follow-up.) **Timing:** 6 Weeks	24/151	27/151	0.89 (0.54, 1.46)		
		ICU admission **Timing:** 6 Weeks	20/151	21/151	0.95 (0.54, 1.67)		
Deliberato(2013)[1] **Population** ICU; Adults (Suspected or confirmed sepsis) **Analysis** ITT	Whole group	ICU mortality **Timing:** NR	1/42	4/39	0.31 (0.05, 1.87)	NR	
		In hospital mortality **Timing:** NR	2/42	4/39	0.52 (0.12, 2.28)		
		Infection relapse/recurrence (Primary infection relapse) **Timing:** NR	2/42	1/39	1.55 (0.21, 11.19)		
Drozdov(2014)[5]	Whole group	Hospital re-admission **Timing:**	15/59	17/63	0.95 (0.53, 1.7)	NR	
	All hospitalised		13/45	15/45	0.81 (0.28, 1.59)		

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
Population ED; Adults (Community-acquired UTI) **Analysis** modified ITT	patients	90 Days					
	Complicated febrile UTI/ pyelonephritis		7/32	11/34	0.69 (0.32, 1.52)		
	Uncomplicated simple UTI		1/2	1/6	2.6 (0.46, 14.67)		
	Uncomplicated febrile UTI/ pyelonephritis		1/8	2/8	0.6 (0.1, 3.58)		
	Complicated simple UTI		6/16	2/11	1.81 (0.52, 6.32)		
	Whole group	Infection relapse/recurrence **Timing:** 90 Days	15/59	14/63	1.14 (0.61, 2.13)	NR	
	All hospitalised patients		13/45	11/45	1.1 (0.49, 2.30)		
	Complicated simple UTI		6/16	3/11	1.29 (0.45, 3.73)		
	Complicated febrile UTI/ pyelonephritis		6/32	8/34	0.81 (0.33, 2)		
	Uncomplicated febrile UTI/ pyelonephritis		2/8	1/8	1.67 (0.28, 9.95)		
	Uncomplicated simple UTI		1/2	1/6	2.6 (0.46, 14.67)		
Esposito(2011)[53] **Population** ED; Children (CAP)	Whole group	Initiation of antibiotic exposure	131/155	155/155	0.85 (0.79, 0.9)	NR	
	Severe CAP		76/79	76/76	0.96 (0.92, 1.01)		
	Mild CAP		52/76	79/79	0.69 (0.59, 0.8)		
	Whole group	Antibiotic side effects **Timing:**	6/155	39/155	0.16 (0.07, 0.37)		

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
Analysis modified ITT		28 Days					
	Whole group	Infection relapse/recurrence (CAP recurrence) **Timing:** 3 Weeks	1/155	6/155	0.23 (0.04, 1.34)		
	Whole group	Need for antibiotics at follow-up (New antibiotic prescriptions) **Timing:** 28 Days	1/155	4/155	0.33 (0.05, 2.09)		
Layios(2012)[54] **Population** ICU; Adults (Suspected infection) **Analysis** ITT	Whole group	Initiation of antibiotic exposure (Number withheld or withdrawn per episode)	71/353	51/314	1.24 (0.89, 1.71)	NR	
	Clinician confidence - possible infection		52/103	26/76	1.46 (1.02, 2.1)		
	Clinician confidence - uncertain infection		13/26	16/21	0.66 (0.43, 1.03)		
	Whole group	ICU mortality	56/258	53/251	1.03 (0.74, 1.43)		
Liu(2013)[38] **Population** ICU; Adults (Sepsis) **Analysis** ITT	Whole group	All cause mortality **Timing:** 28 Days	6/42	5/40	1.13 (0.39, 3.22)	NR	
		Clinical cure (not defined) **Timing:** 28 Days	33/42	34/40	0.93 (0.76, 1.13)		
		Adverse Outcome (Relapse) **Timing:** 28 Days	3/42	1/40	2.22 (0.34, 14.34)		
Nobre(2005)[2]	Whole group	All cause mortality	8/39	8/40	1.03 (0.44, 2.38)	NR	

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
Population ICU; Adults (Severe sepsis and septic shock)		**Timing:** 28 Days					
		Clinical cure (clinical signs and symptoms present at baseline that had resolved by the final assessment) **Timing:** NR	31/39	32/40	0.99 (0.8, 1.24)		
		In hospital mortality	9/39	9/40	1.03 (0.47, 2.25)		
		Infection relapse/recurrence **Timing:** NR	1/39	1/40	1.03 (0.11, 9.44)		
		Sepsis-related mortality **Timing:** NR	3/39	2/40	1.44 (0.3, 6.85)		
Qu(2012)[57] **Population** ICU; Adults (Severe acute pancreatitis) **Analysis** ITT	Whole group	All cause mortality **Timing:** 28 Days	7/35	8/36	0.91 (0.38, 2.16)	NR	
	Whole group	Adverse Outcome (Multi-organ dysfunction syndrome) **Timing:** NR	24/35	25/36	0.99 (0.73, 1.34)		
Roh(2013)[59] **Population** ED; Adults (Elderly patients with CAP) **Analysis** Not specified	Whole group	Initiation of antibiotic exposure	73/80	83/84	0.92 (0.86, 0.99)	NR	
		All cause mortality **Timing:** 6 Months	11/80	11/84	1.05 (0.49, 2.24)		
		Clinical cure (Not defined) **Timing:** 6 Weeks	65/80	70/84	0.98 (0.85, 1.12)		

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
Roh(2010)[58] **Population** ED; Adults (CAP) **Analysis** Not specified	Whole group	Initiation of antibiotic exposure	55/60	61/62	0.93 (0.86, 1.01)	NR	
		All cause mortality **Timing:** 6 Weeks	8/60	9/62	0.92 (0.39, 2.17)		
		Clinical cure (Not defined) **Timing:** 6 Weeks	50/60	53/62	0.98 (0.84, 1.13)		
Schuetz(2009)[60] **Population** ED; Adults (Primary diagnosis of LRTI) **Analysis** modified ITT	Whole group	Initiation of antibiotic exposure	506/671	603/688	0.86 (0.82, 0.91)		
	Exacerbation of COPD		56/115	79/113	0.7 (0.56, 0.87)		
	Community-acquired pneumonia		417/460	461/465	0.91 (0.89, 0.94)		
	Acute bronchitis		16/69	41/82	0.47 (0.29, 0.76)		
	Whole group	Adverse Outcome (Death, ICU admission, recurrence or re-hospitalisation, or disease-specific complication) **Timing:** 30 Days	103/671	130/688	0.81 (0.64, 1.03)		
	Acute bronchitis		6/69	8/82	0.91 (0.34, 2.39)		
	Community-acquired pneumonia		74/460	94/465	0.8 (0.61, 1.05)		
	Exacerbation of COPD		15/115	21/113	0.71 (0.39, 1.29)		
	Whole group	Adverse Outcome (Disease-specific complication) **Timing:** 30 Days	17/671	14/688	1.24 (0.62, 2.46)		
	Whole group		34/671	33/688	1.06 (0.66, 1.68)		
	Community-acquired pneumonia		24/460	26/465	0.93 (0.55, 1.59)		
	Exacerbation of COPD		4/115	5/113	0.8 (0.24, 2.72)		
	Acute bronchitis		1/69	0/82	3.56 (0.15,		

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
					86.04)		
	Whole group	Antibiotic side effects **Timing:** 30 Days	133/671	193/688	0.71 (0.58, 0.86)		
	Acute bronchitis		7/69	11/82	0.77 (0.33, 1.83)		
	Community-acquired pneumonia		108/460	154/465	0.71 (0.58, 0.87)		
	Exacerbation of COPD		14/115	18/113	0.77 (0.41, 1.46)		
	Whole group	ICU admission **Timing:** 30 Days	43/671	60/688	0.74 (0.51, 1.07)		
	Whole group	Infection relapse/recurrence or hospital re-admission **Timing:** 30 Days	25/671	45/688	0.57 (0.36, 0.92)		
Stolz(2007)[3] **Population** ED; Adults (COPD exacerbation) **Analysis** modified ITT	Whole group	Antibiotic exposure (Number of antibiotic courses) **Timing:** 6 Months	87/102	119/106	NA	NR	
		Antibiotic exposure (Number of antibiotic prescriptions) **Timing:** 21 Days	41/102	76/106	NA		
		All cause mortality **Timing:** 6 Months	5/102	9/106	0.6 (0.22, 1.66)		
		Clinical success (improvement of symptoms compared to exacerbation status)	84/102	89/106	0.98 (0.87, 1.11)		

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
		Timing: 21 Days					
		ICU admission **Timing:** 21 Days	8/102	11/106	0.77 (0.33, 1.79)		
		Need for steroids (Steroid use) **Timing:** 21 Days	89/102	93/106	0.99 (0.9, 1.1)		
		Secondary ED visits (Hospitalisation for ECOPD) **Timing:** 6 Months	18/102	22/106	0.85 (0.49, 1.48)		
Stolz(2009)[63] **Population** ICU; Adults (VAP)	Whole group	Antibiotic exposure (Antibiotic discontinuation) **Timing:** 10 Days	NR	NR	NR	HR: 1.66 (1.02, 2.71)	Cox regression Adjustment for age, respiratory tract culture results and centre effect
		Antibiotic exposure (Antibiotic therapy for >7 days) **Timing:** 28 Days	33/51	41/50	0.79 (0.62, 1)	NR	
		All cause mortality **Timing:** 28 Days	8/51	12/50	0.67 (0.31, 1.45)		
		In hospital mortality	10/51	14/50	0.71 (0.36, 1.42)		
		Adverse Outcome (VAP related clinical deterioration) **Timing:**	5/51	7/50	0.72 (0.26, 2.01)		

Study Details	Subgroup	Outcome	PCT based algorithm	Clinical judgment alone	Crude RR (95% CI)	Adjusted effect estimate (95% CI)	Analysis Details
			number of events/ number patients	number of events/ number patients			
		28 Days					
Tang(2013)[4] **Population** ED; Adults (Suspected acute exacerbation of asthma) **Analysis** Per-protocol	Whole group	Initiation of antibiotic exposure	59/128	95/127	0.62 (0.5, 0.76)	NR	
	Critical asthma		9/10	8/8	0.9 (0.74, 1.1)		
	Severe asthma		13/17	14/17	0.93 (0.67, 1.3)		
	Moderate asthma		21/54	36/52	0.57 (0.39, 0.83)		
	Mild asthma		16/47	37/50	0.47 (0.31, 0.71)		
	Whole group	Hospital re-admission **Timing:** 6 Weeks	5/128	8/127	0.64 (0.23, 1.82)		
		Mechanincal ventilation **Timing:** 6 Weeks	8/128	9/127	0.89 (0.36, 2.17)		
		Need for antibiotics at follow-up **Timing:** 6 Weeks	5/128	9/127	0.57 (0.21, 1.59)		
		Need for steroids (Repeated need for steroids or dosage increase) **Timing:** 6 Weeks	6/128	9/127	0.68 (0.26, 1.79)		
		Secondary ED visits (asthma exacerbation) **Timing:** 6 Weeks	8/128	13/127	0.62(0.27, 1.42)		

d. Study results (continuous outcomes)

Study Details	Outcome	Population	Baseline		Follow-up		MD at follow-up (95% CI) and p-value for difference:	Analysis Details
			Int	Comp	Int	Comp		
			Median IQR or Mean (sd) (CI) *(number of participants)*					
Annane(2013)[42] **Population:** ICU; Adults (Apparent septic shock and no clear source of infection) **Measure reported:** Median, IQR **Analysis:** modified ITT	Antibiotic exposure (Duration (days))	Whole group	NA		5 (2, 5) (*30*)	5 (3, 5) *(28)*	p-value=0.52	NR
	Antibiotic exposure (Antibiotic-free days)		NA		0 (0, 3) (*30*)	0 (0, 2) *(28)*	NR	
	Length of hospital stay (Days)		NA		27 (9, 49) (*30*)	33 (11, 69) *(28)*	p-value=0.22	
	Length of ICU stay (Days)		NA		22 (8, 42) (*30*)	23 (10, 60) *(28)*	p-value=0.58	
	Mechanical ventilation (Duration (Days))		NA		11 (5, 25) (*30*)	14 (8, 25) *(28)*	p-value=0.56	
	SOFA score (5 Days)		NR	NR	8 (5, 9) (*30*)	8 (7, 11) *(28)*	p-value=0.61	
Baer(2013)[44] **Population:** ED; Children (LRTI) **Measure reported:**	Antibiotic exposure (days)	Whole group	NA		4.5 (*168*)	6.3 *(169)*	-1.8 (-3.1, -0.5)	Wilcoxon rank sum test
		Non-CAP LRTI			2.4 (*60*)	1.6 *(62)*	0.8 (-0.5, 2)	
		CAP			5.7 (*108*)	9.1 *(107)*	-3.4 (-4.9, -1.7)	
	Length of hospital stay	Whole group	NA		2.6 (*168*)	2.7 *(169)*	-0.1 (-0.8, 0.5)	
		Non-CAP LRTI			2.5 (*60*)	2.3 *(62)*	0.3 (-0.8, 1.2)	

Study Details	Outcome	Population	Baseline		Follow-up		MD at follow-up (95% CI) and p-value for difference:	Analysis Details
			Int	Comp	Int	Comp		
			Median IQR or Mean (sd) (CI) *(number of participants)*					
Mean (95% CI) **Analysis:** modified ITT	(Days)	CAP			2.6 (*108)*	2.9 *(107)*	-0.3 (-1.1, 0.5)	
Bouadma(2010)[46] **Population:** ICU; Adults (Suspected bacterial infection) **Analysis:** modified ITT **Measure reported:** Mean, SD, CI	Antibiotic exposure (days)	Whole group	NA		6.1 (6) (*307)*	9.9 (7.1) *(314)*	-3.8 (-4.8, -2.7) p-value=<0.0001	t-test
		UTI:			7.4 (6.3) (*24)*	14.5 (9.3) *(18)*	-7.1 (-12.08, -2.12) p-value=0.0053	
		Community-acquired pneumonia:			5.5 (4) (*79)*	10.5 (6.4) *(101)*	-5 (-6.53, -3.47) p-value=<0.0001	
		Vantilator-associated pneumonia:			7.3 (5.3) (*75)*	9.4 (5.7) *(66)*	-2.1 (-3.92, -0.28) p-value=0.021	
		Infection with positive blood culture:			9.8 (7.7) (*55)*	12.8 (8.1) *(53)*	-3 (-5.98, -0.02) p-value=0.06	
		Intra-abdominal infection:			8.1 (7.7) (*14)*	10.8 (6.7)*(20)*	-2.7 (-7.69, 2.29) p-value=0.29	
	Antibiotic exposure (Antibiotic-free days)	Whole group:	NA		14.3 (9.1) (*307)*	11.6 (8.2)*(314)*	2.7 (1.4, 4.1) p-value=<0.0001	
	Antibiotic exposure (Total exposure days/1000 days (incidence rate ratio)		NA		653 (*307)*	812 *(314)*	-159 (-185, -131) p-value=<0.0001	
	Length of hospital stay (Days)		NA		26.1(19.3) (*307)*	26.4 (18.3) *(314)*	-0.3 (-3.2, 2.7) p-value=0.87	

Study Details	Outcome	Population	Baseline		Follow-up		MD at follow-up (95% CI) and p-value for difference:	Analysis Details
			Int	Comp	Int	Comp		
			Median IQR or Mean (sd) (CI) *(number of participants)*					
	Length of ICU stay (Days)		NA		15.9(16.1) (*307)*	14.4(14.1)*(314)*	1.5(-0.9, 3.9) p-value=0.23	
	Mechanical ventilation (Number of days without mechanical ventilation)		NA		16.2(11.1) (*307)*	16.9(10.9)*(314)*	-0.7(-2.4, 1.1) p-value=0.47	
	SOFA score (28 Days)		NR	NR	1.5(3) (*307)*	0.9(2.4)*(314)*	0.6(0, 1.1) p-value=0.037	
Christ-Crain(2004)[47] **Population:** ED; Adults (CAP) **Analysis:** ITT **Measure reported:** Median (IQR) or mean (sd)	Antibiotic exposure (Duration (days))	Whole group	NA		5.8(5.3) (*151)*	12.9(6.5)*(151)*	-7.10 (-8.44, -5.76) p-value=<0.001	Mann-Whitney/Wilcoxon test;
	Length of hospital stay (Days)		NA		12(9.1) (*151)*	13(9)*(151)*	-1.00 (-3.04, 1.04) p-value=0.35	
	Quality of life at 6 weeks		NR	NR	10(10) (*151)*	11(10)*(151)*	-1.00 (-3.26, 1.26) p-value=0.14	
	Antibiotic costs (Costs per patient (US $)) at 6 weeks		NA		100(33, 186) (*151)*	190(133, 337)*(151)*	NR	
	Costs (Antibiotics + PCT costs per patient) at 6 weeks		NA		290(212, 378) (*151)*	190(133, 337)*(151)*	p-value=<0.001	
Christ-Crain(2004)[49]	Antibiotic exposure	Whole group	NA		10.9(3.6) (*124)*	12.8(5.5)*(119)*	-1.90 (-3.07, -0.73) p-value=0.03	t-test

Study Details	Outcome	Population	Baseline		Follow-up		MD at follow-up (95% CI) and p-value for difference:	Analysis Details
			Int	Comp	Int	Comp		
			Median IQR or Mean (sd) (CI) *(number of participants)*					
Population: ED; Adults (Suspected LRTI) **Analysis:** ITT **Measure reported:** Mean, SD, CI	(Duration (days))	COPD acute exacerbations	NA		8.7(2.1) (*29*)	9.1(2.8)*(31)*	-0.40 (-1.65, -0.85) p-value=0.47	t-test
	Antibiotic exposure (Total exposure days/1000 days (incidence rate ratio))	Whole group	NA		332(433) (*124*)	661(398)*(119)*	-329.0 (-433.5, -224.5) p-value=<0.0001	t-test
		COPD acute exacerbations	NA		269(414) (*29*)	682(369)*(31)*	-413.0 (-611.9, -214.1) p-value=0.0001	Mann-Whitney/Wilcoxon test
	Length of hospital stay (Days)	Whole group			10.7(8.9) (*124*)	11.2(10.6)*(119)*	-0.50 (-2.97, 1.97) p-value=0.89	t-test
		COPD acute exacerbations			13.7(7.3) (*29*)	10.8(7)*(31)*	-1.00 (-4.75, 2.75) p-value=0.25	
	Antibiotic costs (Costs per patient (US $) at 14 Days	Whole group:	NA		96.3(172.8) (*124*)	202.5(250.6)*(119)*	-106.2 (-160..5, -51.9) p-value=<0.0001	Mann-Whitney/ Wilcoxon test
		COPD acute exacerbations			64.7(105.4) (*29*)	101.4(75.9)*(31)*	-36.7 (-83.5, 10.1) p-value=0.01	
	Quality of life (No details on questionnaire) at 14 days	Whole group	41.3(14.3) *(124)*	39.3(13.2) *(119)*	21.9(14.7) (*124*)	22.9(15.1)*(119)*	-1.00 (-4.75, 2.75) p-value=0.60	t-test
		COPD acute exacerbations	46.1(15.2) *(29)*	45.3(11.4) *(31)*	27.9(15.7) (*29*)	25.8(13.7)*(31)*	2.10 (-5.38, 9.58) p-value=0.85	
Deliberato(2013)[1] **Population:** ICU; Adults (Suspected or confirmed sepsis) **Analysis:** ITT;	Antibiotic exposure (Duration (days))	Whole group	NA		10(3, 39) (*20*)	11(2, 45)*(31)*	p-value=0.44	Mann-Whitney U test
	Length of hospital stay (Days)	Whole group	NA		11(3, 547) (*20*)	11(2, 228)*(31)*	p-value=0.70	

Study Details	Outcome	Population	Baseline		Follow-up		MD at follow-up (95% CI) and p-value for difference:	Analysis Details
			Int	Comp	Int	Comp		
			Median IQR or Mean (sd) (CI) *(number of participants)*					
Measure reported: Median, range**:**	Length of ICU stay (Days)	Whole group	NA		3.5(1, 57) (*20)*	3(1, 28)*(31)*	p-value=0.60	
Drozdov(2014)[5] **Population:** ED; Adults (Community-acquired UTI) **Analysis:** modified ITT **Measure reported:** Median, IQR	Antibiotic exposure (Duration (days))	Whole group:	NA		6(4, 8) (*61)*	10(7, 11)*(64)*	p-value=<0.001	Mann-Whitney U test
		Uncomplicated simple UTI:			0.5(0, 1) (*2)*	1(1, 1)*(6)*	p-value=0.127	
		Complicated simple UTI:			4(2.5, 5.5) (*16)*	7(7, 9)*(12)*	p-value=0.005	
		Uncomplicated febrile UIT ?pyelonephritis:			4(4, 6) (*9)*	7(7, 7.5)*(8)*	p-value=0.009	
		Complicated febrile UIT ?pyelonephritis:			7(6, 9) (*33)*	10.5(10, 11)*(34)*	p-value=<0.001	
		All hospitalised patients:			7 (5, 9) *(45)*	10 (8, 11) *(45*)	p-value=<0.001	
Esposito(2011)[53] **Population:** ED; Children (CAP) **Analysis:** modified ITT **Measure reported:** Mean, SD, CI	Length of hospital stay (Days)	Mild CAP	NA		4.7(2.88) (*76)*	5.61(1.99)*(79)*	-0.91 (-1.69, -0.13)	NR
		Severe CAP			5.01(2.43) (*79)*	5.93(1.7)*(76)*	-0.92 (-1.58, -0.26)	
	Oxygen therapy (Duration (Days))	Severe CAP	NA		3.4(1.99) (*79)*	3.88(1.58)*(76)*	-0.48 (-1.04, 0.08)	
Layios(2012)[54] **Population:** ICU; Adults (Suspected	Antibiotic exposure (Daily dose per 100 ICU days)	Whole group	NA		147.3(206) (*258)*	141.1(136.9)*(251)*	6.20 (-24.11, 36.51) p-value=0.96	ANOVA

Study Details	Outcome	Population	Baseline		Follow-up		MD at follow-up (95% CI) and p-value for difference:	Analysis Details
			Int	Comp	Int	Comp		
			Median IQR or Mean (sd) (CI) *(number of participants)*					
infection) **Analysis:** ITT; **Measure reported:** Mean (SD) or Median (IQR)	Antibiotic exposure (Percentage of ICU days)		NA		62.6(34.4) (*258)*	57.7(34.4)*(251)*	4.90 (-1.08, 10.88) p-value=0.11	ANOVA
	Mechanical ventilation (Duration (Days))		NA		3(1, 11) (*258)*	3(0, 11)*(251)*	NA p-value=0.99	NR
	SOFA score (Maximum score during ICU stay)		NR	NR	9.3(4.9) (*258)*	9.1(5.4)*(251)*	0.20 (-0.70, 1.10) p-value=0.42	ANOVA
Liu(2013)[38] **Population:** ICU; Adults (Sepsis) **Analysis:** ITT **Measure reported:** Mean, SD, CI	Antibiotic exposure (Duration (days))	Whole group	NA		8.1(0.3) (*42)*	9.3(0.3)*(40)*	-1.20(-1.33, -1.07) p-value=0.013	log rank test
	Length of hospital stay (Days)		NA		27(4.9) (*42)*	32(5.4)*(40)*	-5.00(-7.24, -2.76) p-value=0.431	Mann-Whitney/Wilcoxon test
	Length of ICU stay (Days)		NA		12(2.9) (*42)*	2.7(NR)*(14)*	9.30 (NR) p-value=0.632	Mann-Whitney/Wilcoxon test

Study Details	Outcome	Population	Baseline		Follow-up		MD at follow-up (95% CI) and p-value for difference:	Analysis Details
			Int	Comp	Int	Comp		
			Median IQR or Mean (sd) (CI) *(number of participants)*					
Nobre(2005)[2] **Population:** ICU; Adults (Severe sepsis and septic shock) **Analysis:** ITT **Measure reported:** Median, range	Antibiotic exposure (Duration (days))	Whole group	NA		6(2, 33) (*39)*	9.5(3, 34)*(40)*	-2.6(-5.5, 0.3) p-value=0.15	NR
	Antibiotic exposure (Total exposure days/1000 days (incidence rate ratio))		NA		541 (*39)*	644*(40)*	NR	
	Length of hospital stay (Days)				17(3, 96) (*39)*	23.5(5, 44)*(40)*	-2.5(-6.5, 1.5) p-value=0.85	
	Length of ICU stay (Days)		NA		4(1, 21) (*39)*	7(1, 91)*(40)*	-4.6(-8.2, 1) p-value=0.02	
Qu(2012)[57] **Population:** ICU; Adults (Severe acute pancreatitis) **Analysis:** ITT **Measure reported:** Mean, SD, CI	Antibiotic exposure (Duration (days))	Whole group	NA		10.89(2.85) (9.91, 11.9) (*35)*	16.06(2.48) (15.2, 16.9)*(36)*	-5.17 (-6.41, -3.93) p-value=<0.001	t-test
	Costs (Total cost of hospitalisation) at 28 days		NA		24401(2631) (*35)*	27813(2529.37)*(36)*	-3412 (-4613, -2210) p-value=<0.001	
	Length of hospital stay (Days)		NA		16.66(4.02)(15 .3, 18) (*35)*	23.81(7.56)(21. 3, 26.4)*(36)*	-7.15 (-9.96, -4.34) p-value=NR	
	Length of ICU stay (Days)		NA		11.11(2.94)(10 .1, 12.1) (*35)*	14.83(2.49)(14, 15.7)*(36)*	-3.72 (-4.99, -2.45) p-value=<0.001	

Study Details	Outcome	Population	Baseline		Follow-up		MD at follow-up (95% CI) and p-value for difference:	Analysis Details
			Int	Comp	Int	Comp		
			Median IQR or Mean (sd) (CI) *(number of participants)*					
Roh(2013)[59] **Population:** ED; Adults (Elderly patients with CAP) **Analysis:** Not specified **Measure reported:** Mean, SD, CI	Antibiotic exposure (Duration (days))	Whole group	NA		11.2 (*80)*	14.6*(84)*	p-value=<0.05	NR
	Length of hospital stay (Days)		NA		14.6 (*80)*	16*(84)*	p-value=>0.05	
Roh(2010)[58] **Population:** ED; Adults (CAP) **Analysis:** Not specified **Measure reported:** Mean, SD, CI	Antibiotic exposure (Duration (days))	Whole group	NA		9.2 (*60)*	14.6*(62)*	p-value=<0.001	**NR**
Schuetz(2009)[60] **Population:** ED; Adults (Primary diagnosis of LRTI) **Analysis:** modified ITT; **Measure**	Antibiotic exposure (Duration (days))	Whole group	NA		5(1, 8) (*671)*	9(6, 11)*(688)*	**Relative mean change**: -34.8(-40.3, -28.7)	Bootstrap percentile method
		Exacerbations of COPD			0(0, 4) (*115)*	6(0, 8)*(113)*	**Relative mean change**: -50.4(-64, -34)	
		Acute bronchitis			0(0, 0) (*69)*	1(0, 5)*(82)*	**Relative mean change**: -65(-84.7, -37.5)	
		CAP			7(4, 10) (*460)*	10(8, 12)*(465)*	**Relative mean change**: -32.4(-37.6, -26.9)	
	Length of hospital stay	Whole group	NA		8(4, 12) (*671)*	8(4, 12)*(688)*	**Relative mean change**: 1.8(-6.9, 11)	

Study Details	Outcome	Population	Baseline		Follow-up		MD at follow-up (95% CI) and p-value for difference:	Analysis Details
			Int	Comp	Int	Comp		
			Median IQR or Mean (sd) (CI) *(number of participants)*					
reported: Median, IQR	(Days)	CAP			8(5, 13) (*460)*	8(4, 12)*(465)*	**Relative mean change**: 5.3(-5.1, 16.8)	
		Exacerbation COPD			8(5, 11) (*115)*	8(5, 13)*(113)*	**Relative mean change**: -4.4(-19.1, 12.9)	
		Acute bronchitis:			4(1, 7) (*69)*	4(0, 9)*(82)*	**Relative mean change**: -10.3(-37.1, 27)	
Stolz(2007)[3] **Population:** ED; Adults (COPD exacerbation) **Analysis:** ITT **Measure reported:** Median (IQR) or mean (sd)	Length of hospital stay (Days)	Whole group:	NA		9(1, 15) (*102)*	10(1, 15)*(106)*	p-value=0.960	Mann-Whitney/ Wilcoxon test
	Length of ICU stay (Days)		NA		3.3(2.7) (*102)*	3.7(2.1)*(106)*	-0.40 (-1.06, 0.26) p-value=0.351	t-test
Stolz(2009)[63] **Population:** ICU; Adults (VAP) **Analysis:** ITT **Measure reported:** Median, IQR	Antibiotic exposure (Antibiotic free days alive)	Whole group:	NA		13(2, 21) (*51)*	9.5(1.5, 17)*(50)*	p-value=0.049	Mann-Whitney/ Wilcoxon test
	Antibiotic exposure (Duration (days))		NA		10 (6, 16) *(50)*	15 (10, 23) (*51)*	p-value=0.038	
	Length of hospital stay (Days)		NA		26(7, 21) (*51)*	26(16.8, 22.3)*(50)*	p-value=0.153	
	Length of ICU stay (ICU free days alive)		NA		10(0, 18) (*51)*	8.5(0, 18)*(50)*	p-value=0.526	

APPENDIX 4: RISK OF BIAS ASSESSMENTS

Study	Domain	Support for judgement	Risk of bias
Annane(2013)[42]	Random sequence generation	"Patients were randomised in a 1:1 ratio according to a computer-generated list. Randomisation was centralised through a secured website and performed by an independent statistician, and was stratified by the centre and according to whether or not patients underwent surgery in the past 48 h, using permutation blocks, the size of which remained unknown to the investigators."	**Low**
	Allocation concealment	No information	**Unclear**
	Participant/ Personnel blinding	"Masking of antibiotic therapy was not feasible in this study. In the control arm, patients, physicians, nurses, investigators, study coordinators, the statistician and the sponsor remained blinded to PCT levels throughout the study."	**Low**
	Outcome assessor blinding	See above	**Low**
	Incomplete outcome data	Modified ITT analyses (4 patients who withdrew consent, 1 from the PCT group and 3 from the standard care group, were excluded). There were no other exclusions.	**Low**
	Selective outcome reporting	Results were reporetd for all listed outcomes	**Low**

Study	Domain	Support for judgement	Risk of bias
Baer(2013)[44]	Random sequence generation	"Eligible patients were randomly assigned ... by a pre-specified computer-generated scheme (1:1 ratio). We used variable block randomization with stratification for the participating clinic and the type of LRTI"	**Low**
	Allocation concealment	"Patient allocated was concealed by use of web-based online patient registration."	**Low**
	Participant/ Personnel blinding	Unclear whether participants were blinded and the nature of the intervention prevented blinding of study personnel	**Unclear**
	Outcome assessor blinding	Outcomes were self-report (parient or care-giver diary)	**Unclear**
	Incomplete outcome data	modified ITT (2 patients, both in the standard care group, who withdrew consent after randomisation were excluded)	**Low**
	Selective outcome reporting	Results were reported for all outcomes kisted in the trial registry entry ISRCTN17057980	**Low**

Study	Domain	Support for judgement	Risk of bias
Bouadma(2010)[46]	Random sequence generation	Independent, centralised, computer-generated randomisation sequence	**Low**
	Allocation concealment	Investigators were masked to assignment before, but not after randomisation. This system was password protected and accessed by the principal investigator or study coordinator after the patient or surrogate gave consent and had met inclusion criteria. The patient's initials and date of birth were entered and then the patient's allocation was assigned.	**Low**
	Participant/ Personnel blinding	Unclear whether participants were blinded and the nature of the intervention prevented blinding of study personnel	**Unclear**
	Outcome assessor blinding	All investigators were unaware of aggregate outcomes during the study, and primary endpoints were strictly defined and not patient-reported.	**Unclear**
	Incomplete outcome data	Modified ITT (9 patients, 4/311 from the procalcitonin group and 5/319 from the standard care group, who withdrew consent after randomisation were excluded) analyses were reported	**Low**
	Selective outcome reporting	Results were reported for all listed outcomes	**Low**
Christ-Crain(2004)[49]	Random sequence generation	Patients were randomly assigned using a computer-generated weekwise randomisation scheme.	**Low**
	Allocation concealment	No information	**Unclear**
	Participant/ Personnel blinding	Says single-blind but it was unclear who was blinded	**Unclear**
	Outcome assessor blinding	Says single-blind but it was unclear who was blinded	**Unclear**
	Incomplete outcome data	Analysis was ITT, loss to follow-up was low (8/124 PCT and 5/119 standard group)	**Low**
	Selective outcome reporting	All outcomes appear to have been reported	**Low**

Study	Domain	Support for judgement	Risk of bias
Christ-Crain(2006)[47]	Random sequence generation	No details on generation of randomisation sequence	**Unclear**
	Allocation concealment	"On admission, patients were randomly assigned to one of the two groups by sealed, opaque envelopes."	**Low**
	Participant/ Personnel blinding	No details on participant blinding	**Unclear**
	Outcome assessor blinding	"A senior radiologist, blinded to group assignment and laboratory findings, reviewed all chest radiographs." No further details on outcome assessor blinding.	**Unclear**
	Incomplete outcome data	All patients included in ITT analysis. 18 died in PCT group and 2 lost to follow-up (total 151); 20/151 died in control group	**Low**
	Selective outcome reporting	Data reported for all outcomes pre-specified in methods; no protocol or trial registry entry available.	**Low**
Deliberato(2013)[1]	Random sequence generation	No information	**Unclear**
	Allocation concealment	No information	**Unclear**
	Participant/ Personnel blinding	Unclear whether participants were blinded and the nature of the intervention prevented blinding of study personnel	**Unclear**
	Outcome assessor blinding	The intervention was being used to guide the primary oucome (duration of antibiotic therapy) and blinding was therefore not possible. Mortality and re-infection outcomes are objective.	**Low**
	Incomplete outcome data	ITT and per protocol analyses were reported (ITT data extracted). However, 22/42 patients from the PCT group and 8/39 patients from the standard care group were excluded from the per protocol analysis and some results varied widely according to analysis method.	**High**
	Selective outcome reporting	Results were reporetd for all listed outcomes	**Low**

Study	Domain	Support for judgement	Risk of bias
Drozdov(2014)[5, 51]	Random sequence generation	pre-specified computer-generated	**Low**
	Allocation concealment	concealed using a centralised, password secured website	**Low**
	Participant/ Personnel blinding	No information	**Unclear**
	Outcome assessor blinding	No information	**Unclear**
	Incomplete outcome data	Modified ITT analyses (2/63 patients from the PCT/pyuria group and 2/66 patients form the standard care group were excluded because they withdrew consent). Per protocol analyses excluded 19/63 patients from the PCT/pyuria group and 14/66 patients from the standard care group, but results were similar to the ITT analysis.	**Low**
	Selective outcome reporting	Results reported for all listed outcomes	**Low**
Esposito(2011)[53]	Random sequence generation	"The patients were randomised to the PCT or control group using a previously prepared computer-generated randomisation list and sealed envelope."	**Low**
	Allocation concealment	"The patients were randomised to the PCT or control group using a previously prepared computer-generated randomisation list and sealed envelope."	**Low**
	Participant/ Personnel blinding	No information	**Unclear**
	Outcome assessor blinding	"At these follow-up visits, they were evaluated by a blinded researcher (CT) who defined the outcome."	**Low**
	Incomplete outcome data	5/160 patients in PCT and 4/159 in control group withdrew consent following randomisation; these were not included in the ITT analysis.	**Low**
	Selective outcome reporting	Outcomes were not clearly pre-specified in the methods section but data appear to have been report for all outcomes with no over emphasis on outcomes based on statisticaly significance.	**Low**

Study	Domain	Support for judgement	Risk of bias
Layios(2012)[54]	Random sequence generation	No information	**Unclear**
	Allocation concealment	No information	**Unclear**
	Participant/ Personnel blinding	Unclear whether participants were blinded and the nature of the intervention prevented blinding of study personnel	**Unclear**
	Outcome assessor blinding	No information	**Unclear**
	Incomplete outcome data	Analyses were ITT. PCT level was not obtained for 16/258 patients allocated to the PCT group. No other missing data were reported	**Low**
	Selective outcome reporting	Results were reported for all listed outcomes	**Low**
Liu(2013)[38]	Random sequence generation	Randomisation was based on a random number table	**Low**
	Allocation concealment	No information	**Unclear**
	Participant/ Personnel blinding	No information	**Unclear**
	Outcome assessor blinding	No information	**Unclear**
	Incomplete outcome data	No withdrawals	**Low**
	Selective outcome reporting	Results reported for all outcomes specified in the methods	**Low**

Study	Domain	Support for judgement	Risk of bias
Nobre(2005)[2]	Random sequence generation	"Randomization was performed using a computer-based random number generation."	**Low**
	Allocation concealment	"Allocation was issued using opaque, sealed, numbered envelopes."	**Low**
	Participant/ Personnel blinding	Unclear whether participants were blinded and the nature of the intervention prevented blinding of study personnel	**Unclear**
	Outcome assessor blinding	No information	**Unclear**
	Incomplete outcome data	ITT and per protocol analyses were reported (ITT data extracted). However, 8/39 patients from the PCT group and 3/40 patients from the standard care group were excluded from the per protocol analysis and some results varied widely according to analysis method.	**High**
	Selective outcome reporting	Results were reported for all outcomes listed in the trial registry entry NCT00250666	**Low**
Qu(2012)[57]	Random sequence generation	"Patients were randomly assigned to either a procalcitonin-guided (study group) or a antibiotic (control group) therapy."	**Unclear**
	Allocation concealment	See above	**Unclear**
	Participant/ Personnel blinding	No details on participant blinding	**Unclear**
	Outcome assessor blinding	No details on outcome assessor blinding	**Unclear**
	Incomplete outcome data	All randomised patients included in the analysis	**Unclear**
	Selective outcome reporting	All outcomes pre-specified in methods reported in results; no protocol or trial registry entry available.	**Low**

Study	Domain	Support for judgement	Risk of bias
Roh(2013)[59]	Random sequence generation	No information	**Unclear**
	Allocation concealment	No information	**Unclear**
	Participant/ Personnel blinding	No information	**Unclear**
	Outcome assessor blinding	No information	**Unclear**
	Incomplete outcome data	No information	**Unclear**
	Selective outcome reporting	Data were reported for outcomes specified as primary and secondary outcomes	**Low**
Roh(2010)[58]	Random sequence generation	No information	**Unclear**
	Allocation concealment	No information	**Unclear**
	Participant/ Personnel blinding	No information	**Unclear**
	Outcome assessor blinding	No information	**Unclear**
	Incomplete outcome data	No information	**Unclear**
	Selective outcome reporting	Data were reported for outcomes specified as primary and secondary outcomes	**Low**

Study	Domain	Support for judgement	Risk of bias
Schuetz(2009)[60]	Random sequence generation	"Randomization of patients to PCT guidance or guideline enforced antibiotic therapy is based on a pre-specified computer generated randomization list and concealed by using a centralized password-secured website."	**Low**
	Allocation concealment	See above	**Low**
	Participant/ Personnel blinding	No information	**Unclear**
	Outcome assessor blinding	Outcomes were independently asessed by medical students, blind to treatment allocation	**Low**
	Incomplete outcome data	Modified ITT analysis reported. Patients who withdrew consent after randomisation were excluded (16/687 from the intervention group and 6/694 from the control group).	**Low**
	Selective outcome reporting	Results were reported for all specifed outcomes.	**Low**

Study	Domain	Support for judgement	Risk of bias
Stolz(2007)[3]	Random sequence generation	No details on how randomisation sequence was generated: "Patients satisfying the entry criteria were randomly assigned to one of two groups at the time of admission to the emergency department"	**Unclear**
	Allocation concealment	No information	**Unclear**
	Participant/ Personnel blinding	No information	**Unclear**
	Outcome assessor blinding	"At the short-term follow-up visit (14 to 21 days), which was performed by a physician and a nurse on the study team, who were blinded to the group assignment, patients were evaluated based on clinical, laboratory, and lung functional criteria." "The long-term follow-up visit (at 6 months), which was performed by a physician and a nurse on the study team, who were blinded to the group assignment, comprised a clinical, laboratory, and lung function assessment."	**Low**
	Incomplete outcome data	Modified ITT analysis performed for all those who received allocated intervention; 18/226 (11 from PCT and 7 from standard care) randomised participants who did not meet COPD criteria were excluded.	**Low**
	Selective outcome reporting	Data were reported for all outcomes measures pre-specified in the results. However, single outcomes were reported in multiple different formats which could have resulted in confusion and a suggestion of a greater beneficial effect than was actually found.	**High**

Study	Domain	Support for judgement	Risk of bias
Stolz(2009)[63]	Random sequence generation	"Randomisation was through arbitrary allocation to one of the two treatment assignments based on sealed, opaque envelopes. Block size was 20 envelopes. Treating physicians were not aware of envelope contents before randomisation."	**Unclear**
	Allocation concealment	"Randomisation was through arbitrary allocation to one of the two treatment assignments based on sealed, opaque envelopes. Block size was 20 envelopes. Treating physicians were not aware of envelope contents before randomisation."	**Low**
	Participant/ Personnel blinding	No information	**Unclear**
	Outcome assessor blinding	No information	**Unclear**
	Incomplete outcome data	No patients lost to follow-up; all randomised patients included in analysis	**Low**
	Selective outcome reporting	All outcomes pre-specified in methods reported in results; no protocol or trial registry entry available.	**Low**

Study	Domain	Support for judgement	Risk of bias
Tang(2013)[4]	Random sequence generation	"Allocation to either intervention was conducted according to computer-generated random numbers produced by an independent statistician."	**Low**
	Allocation concealment	"After randomization, an opaque, sealed and sequentially numbered envelope containing the PCT or control protocol was prepared for each subject."	**Low**
	Participant/ Personnel blinding	"All patients, laboratory technicians, investigators and research designers were blinded to patient assignments until the data analysis was completed."	**Low**
	Outcome assessor blinding	"We appointed an independent investigator team blinded to the group assignment to monitor the adherence o the protocol, the safety and efficacy of the intervention, as well as primary and secondary outcomes during the six-week follow-up period"	**Low**
	Incomplete outcome data	Analyses included only those participants who completed six week follow-up. However, only 4/132 were missing from the intervention group and 6/133 from the control group	**Low**
	Selective outcome reporting	Results were reported for all listed outcomes	**Low**

APPENDIX 5: TABLE OF EXCLUDED STUDIES WITH RATIONALE

To be included in the review studies had to fulfil the following criteria:

Population:

1. Adults and children with confirmed or highly suspected sepsis, in whom antibiotic therapy is indicated, who are being treated in intensive care units.
2. Adults and children presenting to the emergency department with suspected bacterial infection.

Setting: ICU or ED

Intervention: Treatment decisions based on laboratory-based PCT testing, using any of the tests currently available to the UK NHS, as described in section 2.2, in addition to standard practice.

Comparator: Treatment decisions based on standard practice (as reported in individual studies), without PCT testing.

Outcome: Antibiotic exposure (initiation/duration of antibiotic therapy), resource use (number of hospital admissions, length of hospital/ICU stay, costs), adverse clinical outcomes (e.g. SOFA scores, in-hospital mortality, condition-specific outcomes), antibiotic-related adverse events.

Study Design: RCTs, or CCTs where no RCTs were available. Where no controlled trials were available for a specified population, studies assessing the change in diagnostic accuracy associated with the addition of PCT testing to standard diagnostic work-up were sought; such studies were required to use adjudication of infection by independent panel as the reference standard; microbiological testing alone was not considered adequate.

The table below summarises studies which were screened for inclusion based on full text publication, but did not fulfil one or more of the above criteria. The table shows which of the criteria each study fulfilled (“Yes”) and on which item it failed (“No” or “Other”). The comments column provides further details of the reasons for exclusion.

Study details	Design	Setting	Population	Intervention	Comparator	Comments
Anon (2013)[133]	Other					Duplicate report
ACTRN12612000601831(2012)[134]						Duplicate report
Agarwal (2014)[135]	Unclear	ED	Children	Yes	No	Not an RCT
Andreola (2007)[136]	Other	ED	Children	Yes	No	Fever without source; multivariable prediction model.
Beni (2011)[137]	RCT	Other	Adults	Yes	Yes	Abstract only, non-ICU (hospital acquired pneumonia)
Bogner (2010)[138]	Other					Not a primary study - summary of existing report
Bollu (2009)[139]	Other					Letter
Brahms (NR)[140]	RCT	ICU	Adults	Yes	Yes	Trial registry, terminated due to futility (very slow patient enrolment)
Brahms (2012)[141]	RCT	ICU	Adults	Yes	Yes	Trial registry only; trial terminated
Cals (2010)[142]	Other					Letter
Changi General Hospital (2007)[143]	RCT	Other	Adults	Yes	Yes	Trial registry entry for terminated study, no results or publications. Fever of unknown origin.
Charite University Berlin Germany(NR)[144]	RCT	Other	Adults	Yes	Yes	Trial registry entry, no results posted and no related publications. Stroke.
Charles (2008)[145]	Other	ICU	Other	No	No	Accuracy of PCT for secondary sepsis
Chen (2013)[146]	Prediction study	ED	Children		No	Predicting APN in children with febrile UTI. Only clinical features in model are age, gender, and fever.
ChiCTR-TRC-14004726 (2014)[147]		Other				Respiratory medicine and critical care medicine, Chinese trial registry
Chromik (2006)[148]	RCT	Other	Other	No	No	Comparison of pre-emptive antibiotics with standard treatment in patients with elevated PCT

Study details	Design	Setting	Population	Intervention	Comparator	Comments
Danish Procalcitonin Study (2010)[149]	RCT	ICU	Adults	Yes	Yes	Trial registry entry for other excluded studies[117, 150]
Danish Procalcitonin Study, (2013)[151]	RCT	Other	Adults	Yes	Yes	Pulmonary medicine department, trial registry only, no results posted or related publications
De Angelis (2011)[152]	Other	ICU	Other	No	No	SR only, review of antibiotic management measures
De (2013)[153]	Other	ED	Children	No	No	Accuracy of the traffic light system
Diaz-Flores (2012)[154]	Other					Letter
Ding (2013)[155]	RCT	Other	Adults	Yes	Yes	Respiratory department admissions for acute exacerbations of idiopathic pulmonary fibrosis
Dubos (2006)[156]	Other	Unclear	Children	No	No	PCT alone or with other lab tests not combined with clinical judgement. Reference standard acute onset of meningitis ("meningitis" in hospital notes) and documented bacterial infection in the CSF. Not "adjudication of infection by independent panel".
EUCTR2007-004333-42-DE (2008)[157]	RCT	ICU	Adults	No	No	trial registry
Federal University of Minas (2012)[158]	RCT	ICU	Other	Yes	Yes	Trial registry entry for excluded study[159] Index test: CRP & PCT
Gibot (2010)[160]	Other					Letter on the PRORATA trial
Gomez (2012)[161]	Other	ED	Children	Yes	No	"IBI was defined as the isolation of a bacterial pathogen in blood or cerebrospinal fluid culture."
Graber (2011)[162]	Other					Not a primary study
Herd (2007)[163]	Other					Not a primary study

Study details	Design	Setting	Population	Intervention	Comparator	Comments
Hochreiter (2009)[164]	RCT	ICU	Adults	Yes	Yes	related publication[165] Index test: LIA test
Hochreiter (2009)[165]	RCT	ICU	Other	Yes	Yes	Abstract relating to excluded study[164] Index test: LIA test
Hochreiter (2010)[166]	RCT	ICU	Adults	Yes	Yes	Commentary on an abstract[164]
Hospital Chang Gung Memorial Hospital Keelung (NR)[167]	RCT	Other	Adults	Yes	Yes	Trial registry entry, full paper identified and filed (Huang 2014). secondary peritonitis after surgery
ISRCTN10288268 (2009)[168]	RCT	ICU	Adults	Yes	Yes	Trial registry, results page refernces does not exist Index test: LIA test
ISRCTN61015974 (2006)[169]						trial registry entry for excluded study[170]
ISRCTN77261143 (2005)[171]						trial registry entry for excluded study[3]
Iwashyna (2010)[172]						Long term outcomes following sepsis
Jaimes (2013)[173]	Other	ED	Other	No	No	Exanple of latent class ROC analysis
Jaimes (2010)[174]	Other	Other	Other	No	No	Example of latent class analysis
Jensen (2011)[117]	RCT	ICU	Adults	Yes	Yes	Protocol[150] Trial registry[149] No sepsis or infection inclusion criteria, seems to be about early initiation of antibiotics
Jensen (2008)[150]	RCT	ICU	Adults	Yes	Yes	Protocol only Trial registry[149] Additional publication[117]
Jensen (2007)[175]	Other					Comment on a meta-analysis
Jensen (2012)[176]	Other					Letter

Study details	Design	Setting	Population	Intervention	Comparator	Comments
Kollef (2010)[177]	Other					letter on the PRORATA trial
Kompetenznetz Sepsis (NR)[178]	RCT	ICU	Adults	No	No	PCT used to guide therapy other than antibiotic
Kristoffersen (2009)[179]	RCT	Other	Adults	No	Yes	Medical admissions, intervention = single PCT measurement on admission
Kulik (2013)[180]	Other		Children	No	No	SR of prediction rules for bacterial meningitis (none included PCT)
Landman (2010)[181]	Other					Letter
Lee (2013)[182]	Other	Other	Adults	No	No	SR, accuracy of PCT for bacterial infection in the elderly
Leroy (2013)[183]	Other	ED	Children	No	No	Predicting APN; not the same as detecting bacterial infection so exclude? Model only included laboartoy values not clinical diagnosis so not additive value.
Leroy (2013)[184]	Other	ED	Children	Yes	No	Abstract only; algorithm only include PCT, CRP & dipstick. No details on reference standard. Insufficient data in abstract to be of use.
Levin (2012)[185]	Other	ICU	Other	No	No	Observational study on the 'accuracy' of clinical decisions to initiate antibiotics (no PCT)
Mahajan (2014)[186]	Other	ED	Children	Yes	No	"SBI by blood, urine, and/or cerebral spinal "uid (CSF) cultures were included."
Manzano (2010)[25]	RCT	ED	Children	Yes	Yes	Wrong PCT test (not quantitative)
Maravic-Stojkovic (2011)[119]	RCT	ICU	Adults	Yes	Yes	Quantitative PCT assay (un-listed version of BRAHMS) Index test: LIA test
Mintegi (2012)[187]	Other	ED	Children	Yes	No	Abstract only; reference standard not reported.
Mokart (2010)[188]	Other					Letter on the PRORATA trial

Study details	Design	Setting	Population	Intervention	Comparator	Comments
NCT00099840 (2004)[189]	RCT	Other	Adults	Yes	No	primary care, trial registry
NCT00250666 (2005)[190]						Duplicate trial registry entry
NCT00271752 (2006)[191]						Duplicate trial registry entry
NCT00350987 (2006)[192]						Duplicate trial registry entry
NCT00398775 (2006)[193]						Duplicate trial registry entry
NCT00472667 (2007)[194]						Duplicate trial registry entry
NCT00934011 (2009)[195]						Duplicate trial registry entry
NCT00987818 (2009)[196]						Duplicate trial registry entry
NCT01018199 (2009)[197]						Duplicate trial registry entry
NCT01025180 (2009)[198]						Duplicate trial registry entry
NCT01139489 (2010)[199]						Duplicate trial registry entry
NCT01264549 (2010)[200]						Duplicate trial registry entry
NCT01379547 (2011)[201]						Duplicate trial registry entry
NCT01494675 (2011)[202]						Duplicate trial registry entry
NCT01572831 (2012)[203]						Duplicate trial registry entry
NCT01652404 (2011)[204]						Duplicate trial registry entry
NCT01950936 (2012)[205]						Duplicate trial registry entry
NCT02130986 (2014)[206]						Duplicate trial registry entry
NCT02171338 (2014)[207]						Duplicate trial registry entry
NCT02173613(2013)[208]						Duplicate trial registry entry
Niewoehner (2007)[209]	Other					Not a primary study (ACP journal club)
Nijman(2014)[210]	Other					Not an RCT

Study details	Design	Setting	Population	Intervention	Comparator	Comments
Nijman(2013)[211]	Other					Not an RCT
Ning (2011)[212]	Other	Other	Other	Yes	Yes	SR, abstract ony
Oliveira (2011)[213]	RCT	ICU	Other	Yes	Yes	Index test: CRP & PCT
Oliveira (2013)[118]	RCT	ICU	Adults	Yes	No	Index test: CRP & PCT
Oliveira (2012)[159]	RCT	ICU	Other	Yes	Yes	Index test: CRP & PCT
Oostenbrink (2013)[214]	Other					Not an RCT
Prkno (2013)[215]	Other	Other	Adults	Yes	Yes	SR, abstract only
Ray (2007)[216]	Other	ED	Adults	No	No	Accuracy of CSF PCT to differentiate bacterial from viral meningitis
Reinhart (2007)[217]	Other					Comment on a meta-analysis
Saeed (2011)[218]	Other	Other	Adults	Yes	No	ICU + medical admissions, no comparator
Sanders (2008)[219]	Other	Other	Children	No	No	SR of accuracy of CRP in non-hospitalised children
Schroeder (2009)[120]	RCT	ICU	Adults	Yes	Yes	Index test: LIA test
Schuetz (2010)[220]	Other					Survey on guideline adherence
Schuetz (2012)[116]	Other	ED or ICU	Adults	Yes	Yes	SR, IPD analysis; studies do not match studies included in our review
Schuetz (2010)[221]	Other					Guideline, not original research
Schuetz (2013)[222]	Other					Abstract of SR
Sheu (2011)[223]	Other	ED	Children	Yes		UTI and prediction of APN and renal scarring; not detection of bacterial infection.
Soni (2012)[224]	Other					AHRQ evidence summary for clinicians
Sridharan (2013)[225]	Other	ICU	Adults	Yes	Yes	SR, abstract only
St. Justine's Hospital (NR)[226]	RCT	ED	Children	Yes	Yes	Qualitative PCT test

Study details	Design	Setting	Population	Intervention	Comparator	Comments
Stannard (2014)[227]	Other					Summary of Cochrane review
Tang (2007)[228]	Other					Letter
Tarnow-Mordi (2010)[229]	Other					Letter on the PRORATA trial
Thompson (2012)[230]	Other					SR of prediction rules for infection in children (development and accuracy studies)
Ulm (2013)[231]	RCT	Other	Adults	Yes	Yes	Stroke patients, unspecified setting, protocol only
University Hospital Basel Switzerland (NR)[232]	RCT	Other	Adults	Yes	Yes	Primary care
University Hospital, Grenoble (2014)[233]	RCT	Other	Adults	Yes	Yes	Hospitalised elderly, trial registry
University of Rochester (2014)[234]	RCT	Other	Adults	Yes	Yes	hospitalised for RTI, trial registry with no results or publications
Uusitalo-Seppala (2011)[235]	Other	ED	Adults	Yes	No	Not RCT
Van Den Bruel (2011)[236]	Other					SR of prediction rules for infection in children (development and accuracy studies)
Yu (2013)[237]	Other	Other	Other	No	No	SR, accuracy of PCT for acute appendicitis
Zhang (2012)[238]	Other	Other	Adults	Yes	Yes	SR, abstract only

APPENDIX 6: CHARACTERISTICS AND RESULTS OF INCLUDED HRQOL STUDIES

Reference / year	Buysse 2008[88]
Location	Netherlands
Setting	Paediatric intensive care unit
Population for which health effects were measured	Patients with septic shock and purpura who required intensive care. Median age at admission: 3.1 years (range: 3.7-17.4 years); median age at measurement: 14.5 years (range: 5.3-31.1 years).
Sample size sepsis group	120 (reference group: N=1435)
Method of elicitation and valuation	Health Utilities Index Mark (HUI) 2 and 3; valuation function based on Canadian respondents
Time point when measurements were made	Median follow-up interval: 9.8 years (range: 3.7-17.4 years)
Results	Utility for patients who had meningococcal septic shock: HUI3: 0.82 (sd: 0.25) HUI2: 0.88 (sd: 0.16)
Conclusion	In patients who survived meningococcal septic shock in childhood, reported poorer general health compared with a representative sample of 1435 Dutch school children aged 5 to 13 years.
Appropriateness for current cost-effectiveness analysis	Appropriate. Although it does not adhere to the NICE reference case (e.g. no EQ5D), it is the only source available in this population and setting.

Reference / year	Bennett 2000[87]
Location	United States
Setting	Paediatric emergency department
Population for which health effects were measured	Parents that presented at the paediatric ED with children aged between 3 and 36 months were asked to evaluate a description of the following health states for their children: death, meningitis with severe brain damage, meningitis with minor brain damage, meningitis with deafness, meningitis with recovery; hospitalisation; local infection and blood drawn.
Sample size sepsis group	94
Method of elicitation and valuation	Standard gamble

Time point when measurements were made	Presentation at ED
Results	Death: 0.0177 (sd: 0.07) Meningitis with severe brain damage: 0.3903 (sd: 0.37) Meningitis with minor brain damage: 0.7393 (sd: 0.29) Meningitis with deafness: 0.8611 (sd: 0.22) Meningitis with recovery: 0.9768 (sd: 0.08) Hospitalisation: 0.9921 (sd: 0.03) Local infection : 0.9941 (sd: 0.03) Blood drawn: 0.9971 (sd: 0.02)
Conclusion	Extremely high mean and median utility values were obtained for outcomes without permanent sequelae
Appropriateness for current cost-effectiveness analysis	Appropriate. Although it does not adhere to the NICE reference case (e.g. no EQ5D), it is the only source available in this population and setting.

Reference / year	Contrin 2013[89] and Lobo 2011 (abstract)[90]
Location	Brazil
Setting	Intensive care unit
Population for which health effects were measured	Patients discharged after being admitted to the ICU with severe sepsis
Sample size sepsis group	50 (control group consisting of critically ill patients admitted to the ICU without sepsis: N=50)
Method of elicitation and valuation	EQ5D; valuation function based on UK respondents.
Time point when measurements were made	More than 1 year after discharge
Results	Sepsis group: 0.678 (sd: 0.427); control group: 0.747 (sd: 0.327)
Conclusion	EQ5D QoL did not statistically significantly differ between sepsis patients and critically ill patients admitted to the ICU without sepsis. Moreover, older patients with sepsis had more moderate/severe problems in all QoL dimensions (EQ5D index score not presented; VAS scores are presented in Table 3).
Appropriateness for current cost-	Not appropriate. The exact time since discharge is unclear and

effectiveness analysis	the estimated utility values seem high compared with those estimated by Cuthbertson et al[91] which seems most representative for the UK.

Reference / year	Cuthbertson 2013[91]
Location	Scotland (26 hospitals)
Setting	ICU
Population for which health effects were measured	Patients were identified as having: a.) evidence of three of four systemic inflammatory response syndrome (SIRS) criteria within the previous 24 hours, b.) confirmed or clinically strongly suspected infection, c.) two or more sepsis induced organ failures of less than 24 hours duration, and d.) an Acute Physiology and Chronic Health Evaluation (APACHE II) score greater than or equal to 25 based within 24 hours.
Sample size sepsis group	439; 83 patients filled out the questionnaire at 3.5 years after discharge while this was 66 for 5 years
Method of elicitation and valuation	EQ5D; valuation function not specifically stated but expectedly based on UK respondents.
Time point when measurements were made	At 3.5 years (N=83) and 5 years (N=66) after discharge
Results	At 3.5 years: 0.64 (sd: 0.36), 5 years: 0.68 (sd: 0.32)
Conclusion	Based on a comparison with population (age and sex matched) norms using the SF-36, patients with severe sepsis have a significantly lower physical QOL but mental QOL scores were only slightly below population norms up to five years after severe sepsis.
Appropriateness for current cost-effectiveness analysis	Appropriate. This Scottish study probably provides the most representative long-term utility estimates for the UK.

Reference / year	Granja 2004[92]
Location	Portugal
Setting	ICU
Population for which health effects were measured	Patients in the sepsis group were those in whom severe sepsis and septic shock was the reason for admission to the ICU

Sample size sepsis group	104 (control group consisting of patients admitted to the ICU without sepsis: N=133)
Method of elicitation and valuation	EQ5D; valuation function based on UK respondents.
Time point when measurements were made	At 6 months after discharge
Results	Sepsis group median: 0.84 (IQR: 0.58-1.00); control group median: 0.76 (IQR: 0.56-0.91)
Conclusion	HR-QoL in sepsis survivors 6 months after ICU discharge is fair and is no worse than the HR-QoL of other critically ill patients admitted without sepsis.
Appropriateness for current cost-effectiveness analysis	Not appropriate. The estimated utility values seem high compared with those estimated by Cuthbertson et al.[91] which seems most representative for the UK.

Reference / year	Karlsson 2009[93]
Location	Finland (24 hospitals)
Setting	ICU
Population for which health effects were measured	Patients with severe sepsis
Sample size sepsis group	470; 252 and 156 patients filled out the first (Q1) and second (Q2) questionnaire while 98 patients filled out both questionnaires.
Method of elicitation and valuation	EQ5D (A majority of first questionnaires (156/252) were completed by next of kin); valuation function unclear.
Time point when measurements were made	At ICU concerning HRQOL before acute critical illness (Q1) and 17 months (range: 12–20 months; interquartile range: 16–18) after hospital discharge (Q2).
Results	Median Q1: 0.70 (IQR: 0.54-0.89); Median Q2: 0.75 (0.56-0.92). For patients (N=98) that filled out both questionnaires: median Q1: 0.81 (IQR: 0.62-0.90); Median Q2: 0.75 (0.56-0.94).
Conclusion	QOL was lower after severe sepsis than before critical illness as assessed by EQ5D. For both assessments QOL for sepsis patients was lower compared with reference values (age- and sex-

	adjusted) from the Finnish population. The mean calculated QALYs after severe sepsis was 10.9 (95% CI: 9.7–12.1).
Appropriateness for current cost-effectiveness analysis	Not appropriate. The estimated utility values seem high compared with those estimated by Cuthbertson et al[91] which seems most representative for the UK.

Reference / year	Korosec Jagodic 2006[94]
Location	Slovenia
Setting	ICU
Population for which health effects were measured	patients with severe sepsis and septic shock
Sample size sepsis group	66
Method of elicitation and valuation	EQ5D; valuation function based on US respondents.
Time point when measurements were made	2 years following ICU admission
Results	0.72 (sd: 0.24)
Conclusion	Quality of life was similar for patients with the two most frequent admission diagnoses admitted to the surgical ICU: sepsis and trauma.
Appropriateness for current cost-effectiveness analysis	Not appropriate. The estimated utility values seem high compared with those estimated by Cuthbertson et al[91] which seems most representative for the UK.

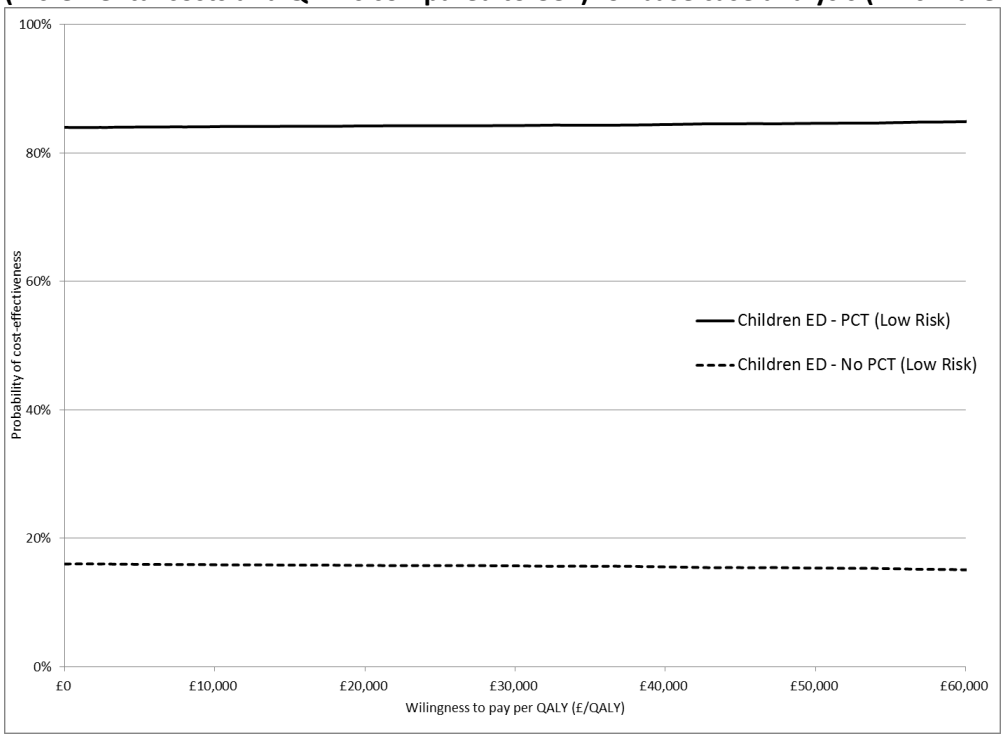
Reference / year	Orwelius 2013[95]
Location	Portugal
Setting	ICU
Population for which health effects were measured	Patients admitted to the hospital with community-acquired sepsis, severe sepsis or septic shock.
Sample size sepsis group	91 (control group consisting of patients admitted to the ICU without sepsis: N=222)
Method of elicitation and valuation	EQ5D; valuation function unclear.

Time point when measurements were made	6 months after ICU discharge
Results	Sepsis group median: 0.67 (IQR: 0.49-0.91), control group median: 0.67 (IQR: 0.45-0.86).
Conclusion	Patients admitted to ICU for CAS did not perceived different health-related quality of life compared with ICU patients admitted for other diagnoses.
Appropriateness for current cost-effectiveness analysis	Not appropriate. The estimated utility values seem high compared with those estimated by Cuthbertson et al[91] which seems most representative for the UK.

Reference / year	Drabinksi 2001 (abstract)[96]
Location	United States
Setting	In-hospital (not mentioned whether it is ICU)
Population for which health effects were measured	Patients with severe sepsis of presumed infectious origin
Sample size sepsis group	93
Method of elicitation and valuation	EQ5D; valuation function unclear.
Time point when measurements were made	30, 60, 90 and 180 days after admission (56% of the patients were in the hospital at day 30 and 7% thereafter)
Results	0.53 (day 30), 0.62 (day 60), 0.68 (day 90), 0.69 (day 180)
Conclusion	Sepsis survivors experienced a continual improvement towards population-based normal levels in their health utility scores over a 6-month period.
Appropriateness for current cost-effectiveness analysis	Appropriate. Although it is unclear whether patients were admitted to the ICU, this is likely the case for patients with severe sepsis. Moreover, this is the only study reporting utility values for sepsis patients before being discharged (56% of the patients were in the hospital at the 30-day measurement).

APPENDIX 7: COST-EFFECTIVENESS ACCEPTABILITY CURVES AND INCREMENTAL COST-EFFECTIVENESS PLANES FOR THE BASE-CASE ANALYSES

Figure 25: Cost-effectiveness acceptability curve and incremental cost-effectiveness plane (incremental costs and QALYs compared to CCP) for base case analysis (ED children – Low Risk)



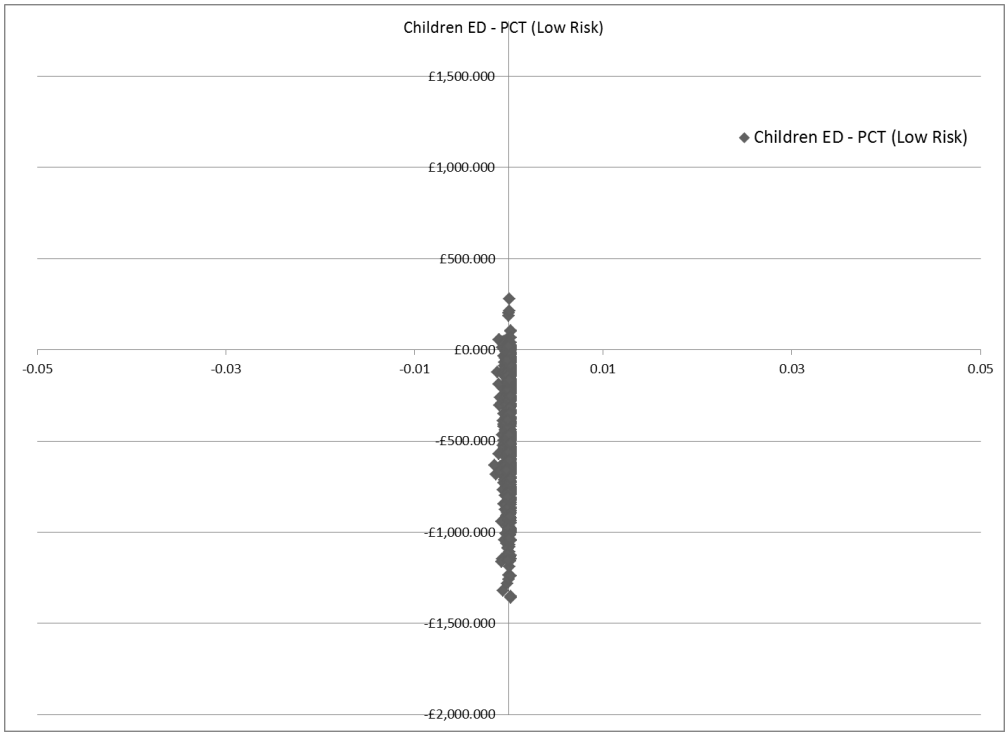
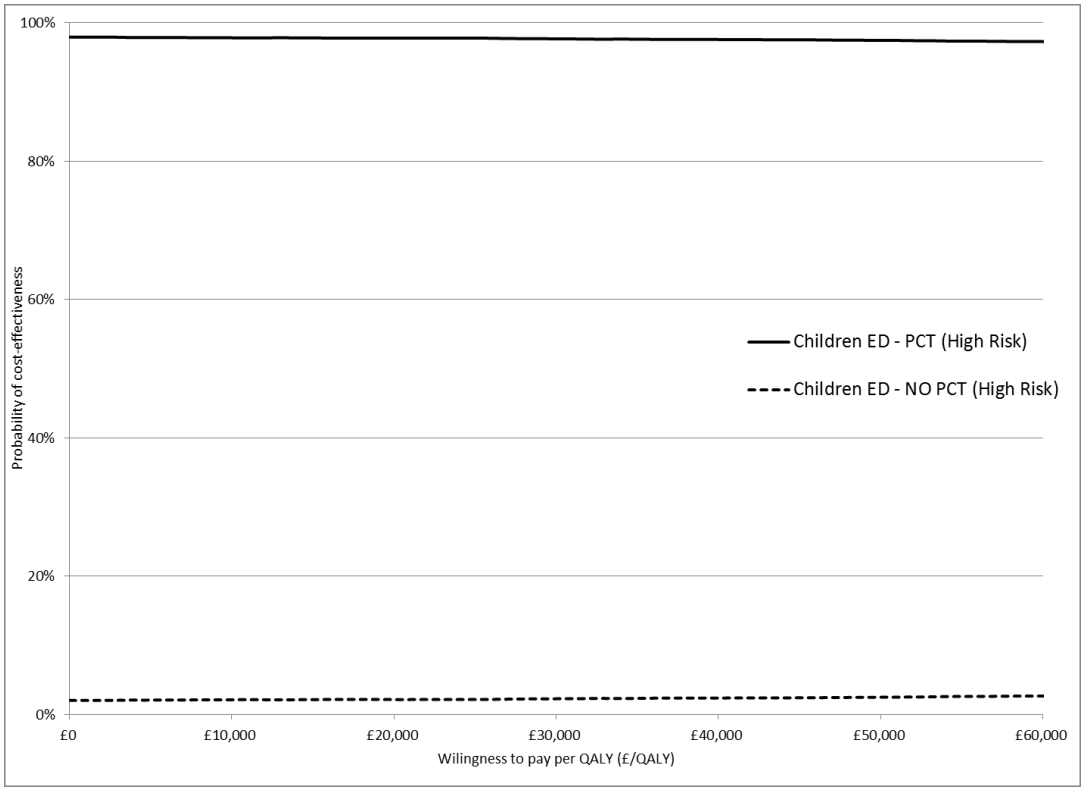


Figure 26: Cost-effectiveness acceptability curve and incremental cost-effectiveness plane (incremental costs and QALYs compared to CCP) for base case analysis (ED children – High Risk)



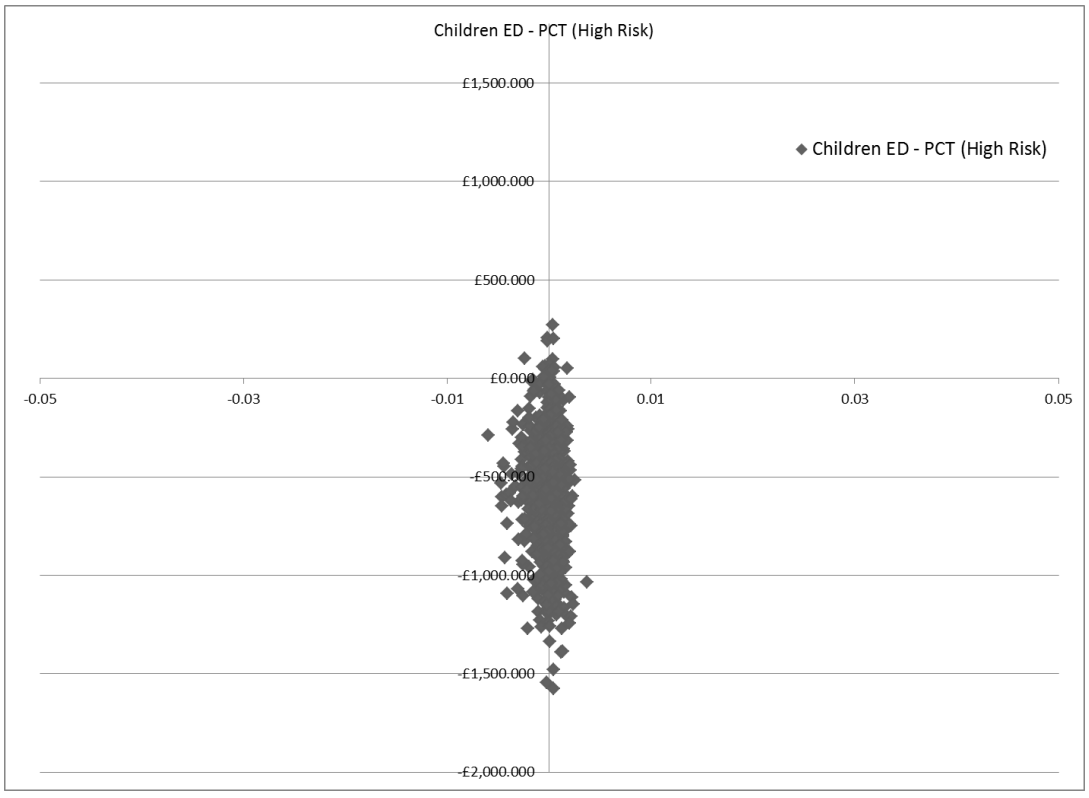
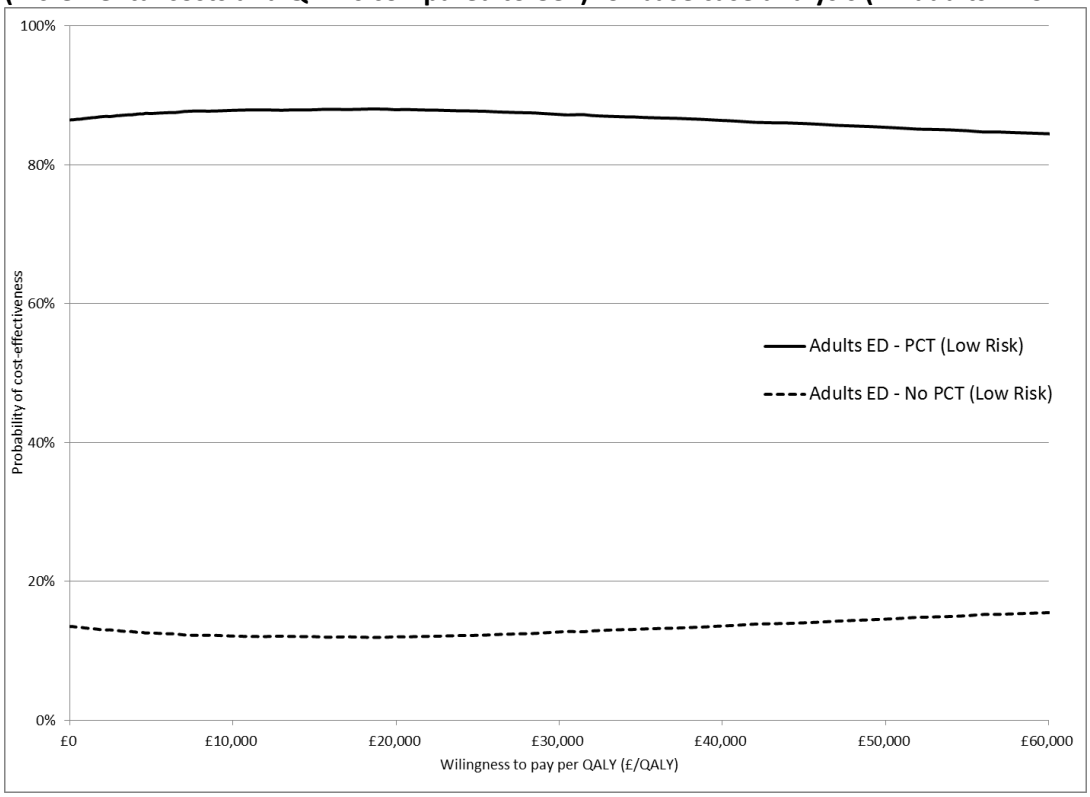


Figure 27: Cost-effectiveness acceptability curve and incremental cost-effectiveness plane (incremental costs and QALYs compared to CCP) for base case analysis (ED adults – Low Risk)



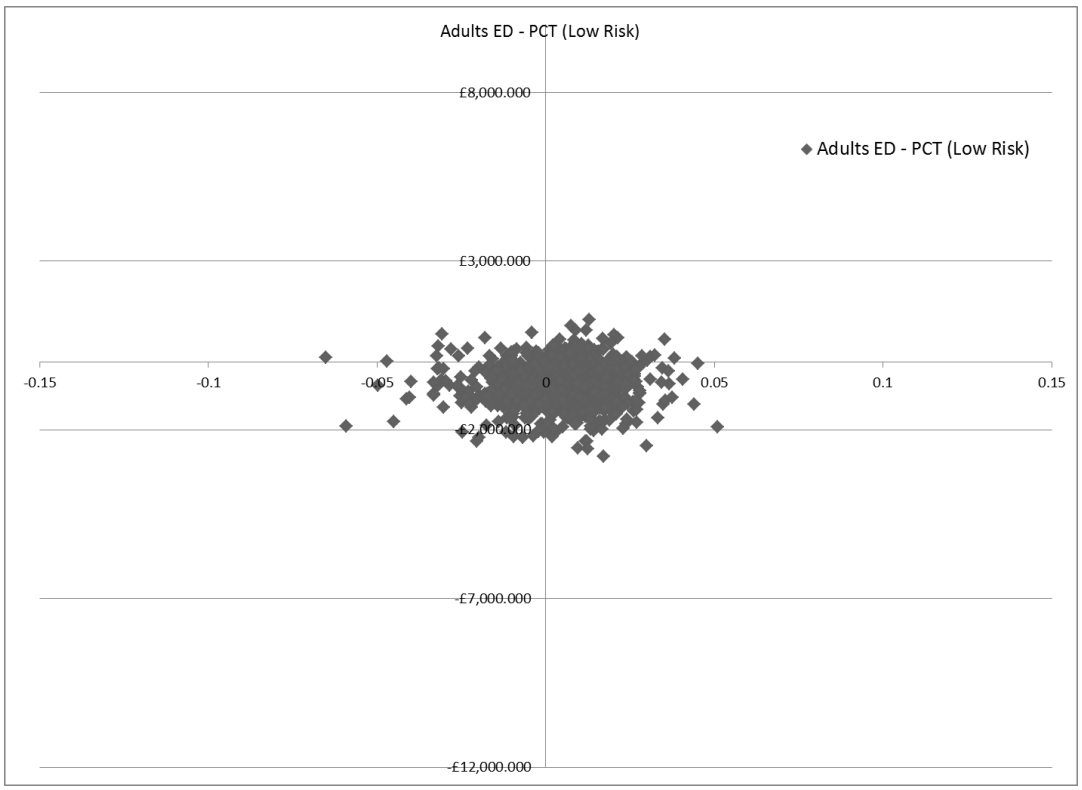
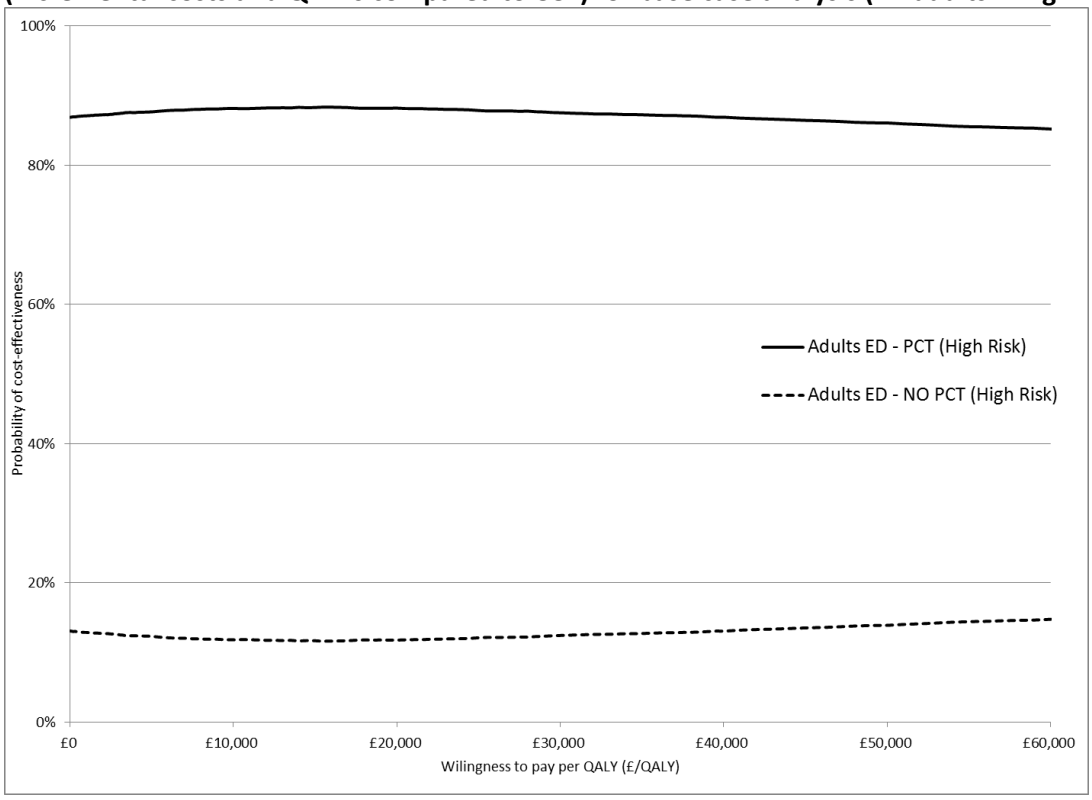


Figure 28: Cost-effectiveness acceptability curve and incremental cost-effectiveness plane (incremental costs and QALYs compared to CCP) for base case analysis (ED adults – High Risk)



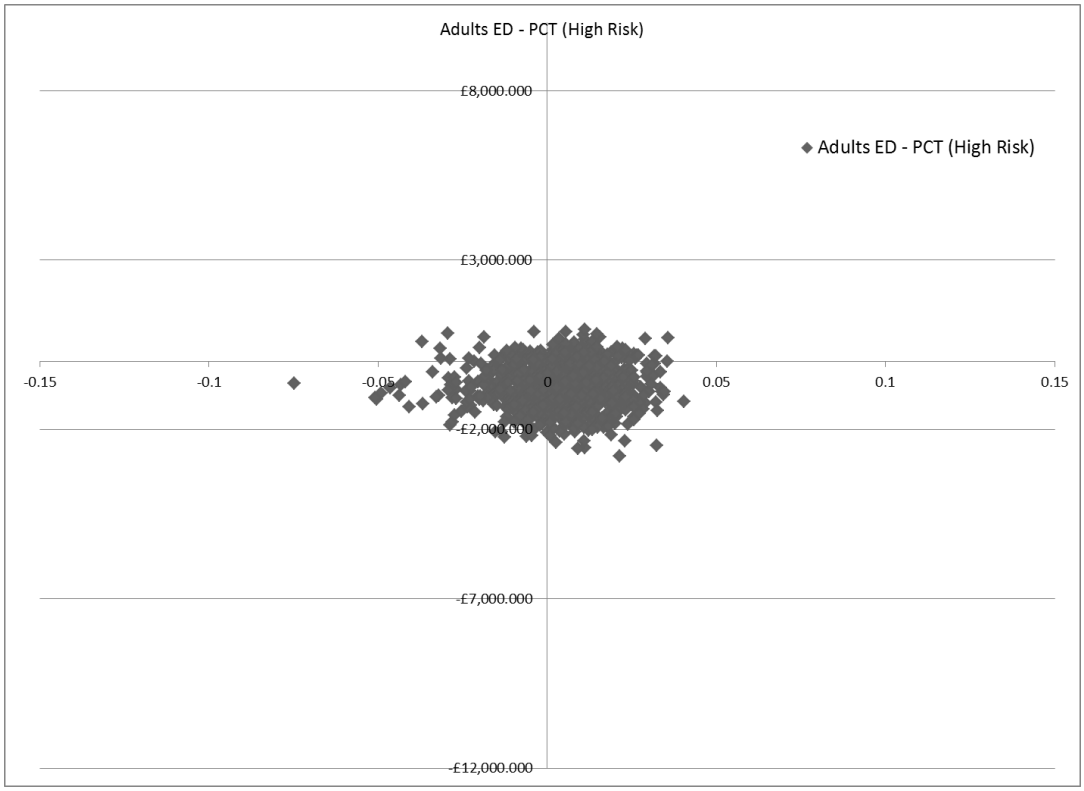
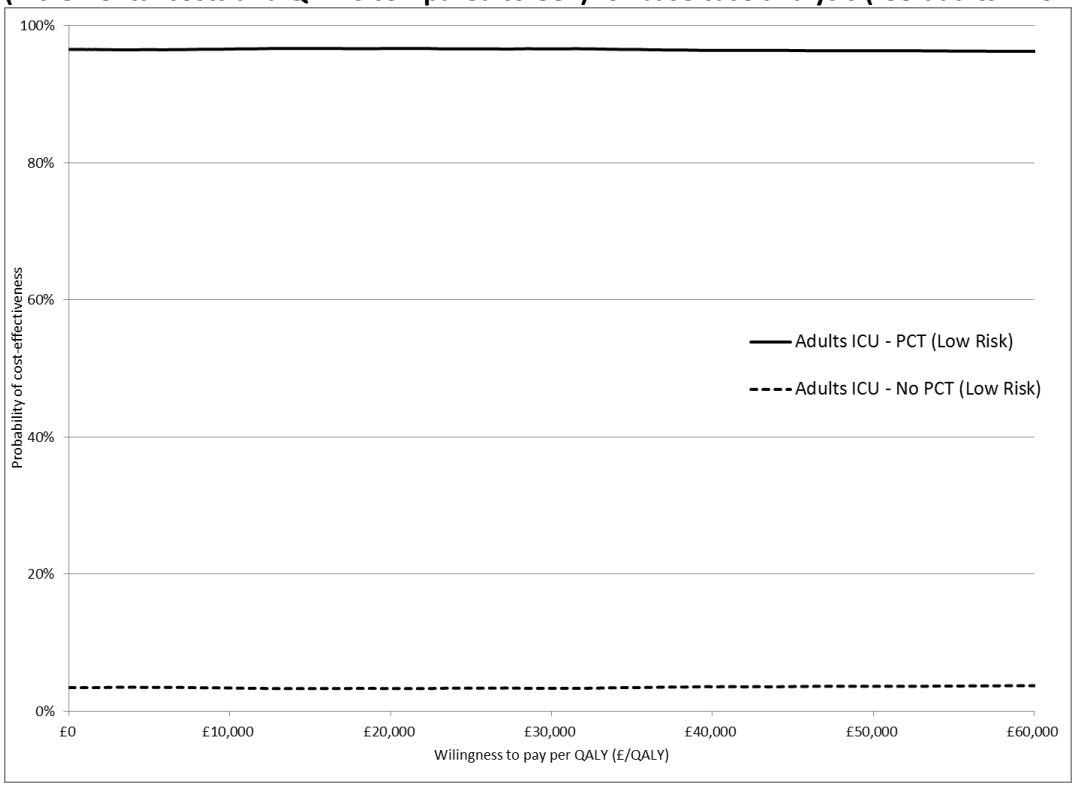


Figure 29: Cost-effectiveness acceptability curve and incremental cost-effectiveness plane (incremental costs and QALYs compared to CCP) for base case analysis (ICU adults – Low Risk)



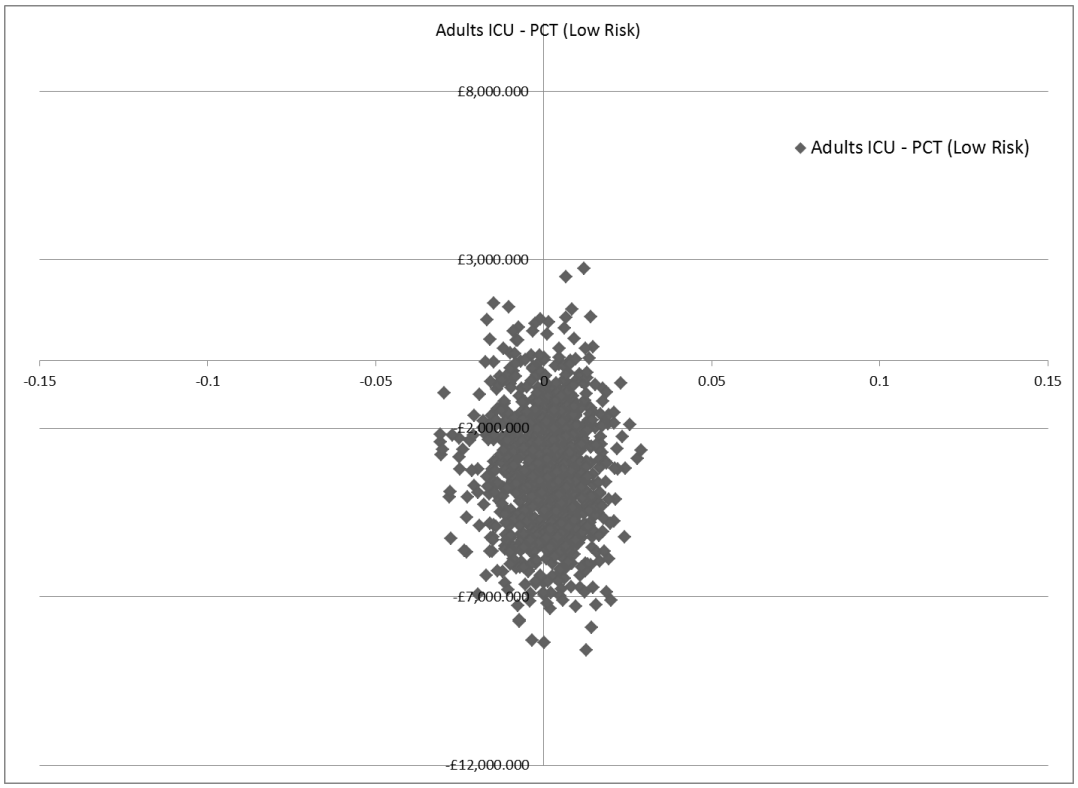
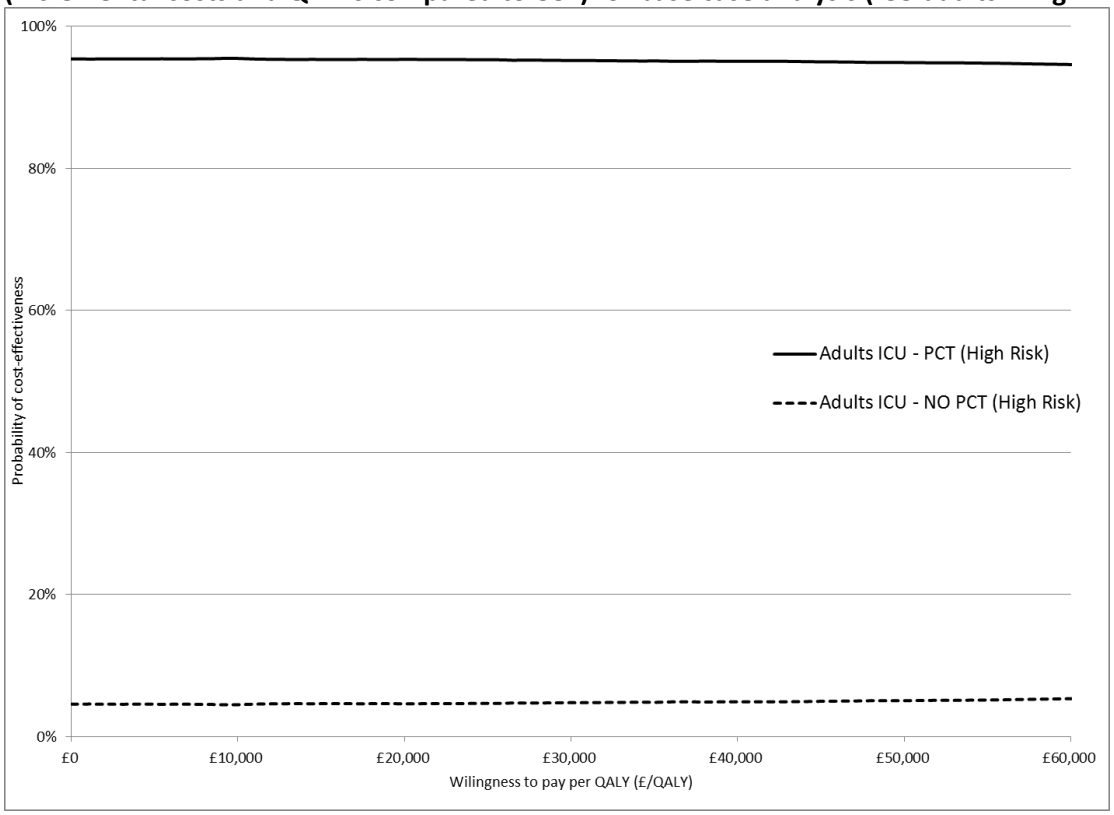
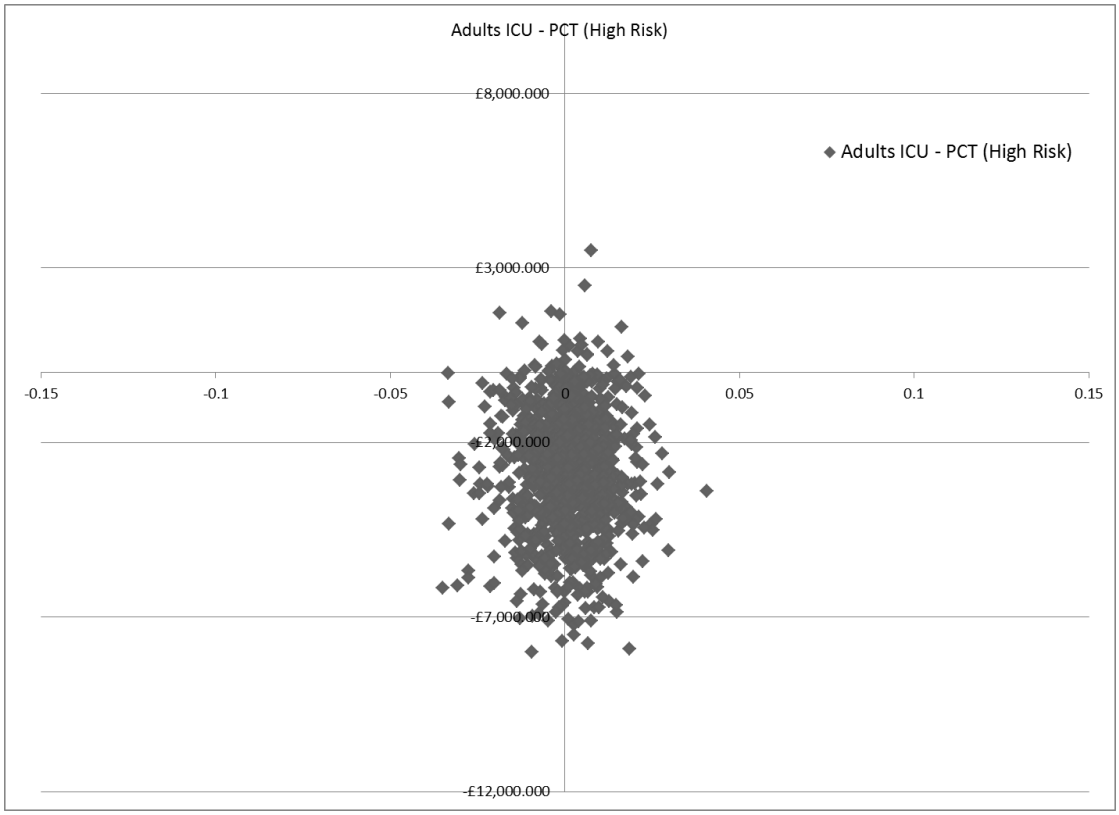


Figure 30: Cost-effectiveness acceptability curve and incremental cost-effectiveness plane (incremental costs and QALYs compared to CCP) for base case analysis (ICU adults – High Risk)





APPENDIX 8: ADDITIONAL ANALYSIS METHODS

In order to perform the meta-analysis of the conditional mean duration of antibiotic use (i.e. excluding patients with no antibiotic use), the following data was required from the published papers:

1) Number of patients with non-zero antibiotic use (N_nonzero)
2) Mean days antibiotic use of patients with non-zero antibiotic use (Mean_nonzero)
3) Standard deviation of days antibiotic use (SD_nonzero)

N_nonzero was reported in the papers. These are the methods of calculating these other two values for each arm of each trial:

2)

mean_nonzero = mean_all / p(intitiate)

Where p(intitiate) is the proportion who initiated antibiotics, which was reported in the papers.

3) Use:

var_all = sum(p(d_all) x (d-mean)^2)

= sum(p(initiate) x (d_nonzero-mean_all)^2) + sum(p(0) x (0-mean)^2)

= var_nonzero + (p(0) x mean_all^2)

So var_nonzero = var_all – (p(0) x mean_all^2)

So SD_nonzero = sqrt(var_all – mean_all^2)

where:

p(d_all) is the proportion of the sample where each day of antibiotic use was observed such that p(initiate) is the proportion where the days use were greater than zero and p(0) is the proportion where the number of days use was zero i.e. no initiation.

p(0) = 1-p(initiate)

var_all = SD_all^2 and SD_all is the standard deviation of days for the whole sample (including the nonzero patients), which is reported in the papers.

There was a problem with this method, which was that the standard deviation (SD_all) reported for the PCT arm of the Christ-Crane (2004) study was too low given the proportion of low proportion of those who initiated antibitics. This suggested that there was an error in the paper. Therefore, an alternative value for the PCT arm standard deviation was calculated based on the t test p value, which gives a corresponding t value, where, according to the Cochrane Handbook[239]:

t = meandiff / SE_meandiff

SE_meandiff = sqrt(var_c / N_c + var_i / N_i)

Where meandiff is the mean difference between the intervention (PCT) and control arms, SE_meandiff is the standard error of the mean difference and ‘i’ and ‘c’ refer to intervention and control respectively.

APPENDIX 9: NICE GUIDANCE RELEVANT TO THE MANAGEMENT OF SEPSIS OR SUSPECTED BACTERIAL INFECTION IN THE POPULATIONS SPECIFIED IN THIS ASSESSMENT

Published guidance

Pneumonia: Diagnosis and management of community- and hospital-acquired pneumonia in adults. NICE Clinical Guideline CG191 (December 2014). Available from: http://www.nice.org.uk/guidance/cg191 Date for review: December 2016. [accessed 09.12.14]

Intravenous fluid therapy in adults in hospital. NICE Clinical Guideline CG174 (December 2013) Available from: http://guidance.nice.org.uk/CG174 Date for review: TBC. [accessed 26.11.14]

Feverish illness in children: Assessment and initial management in children younger than 5 years. NICE Clinical Guideline CG160 (May 2013) Available from: http://guidance.nice.org.uk/CG160 Date for review: March 2015. [accessed 26.11.14]

The management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE Clinical Guideline CG102 (June 2010) Available from; http://guidance.nice.org.uk/CG102 Date for review: March 2015. [accessed 26.11.14]

Management of acute diarrhoea and vomiting due to gastroenteritis in children under 5. NICE Clinical Guideline CG84 (April 2009) Available from: http://guidance.nice.org.uk/CG84 Date for review: June 2012 – following consultation with stakeholders this guideline has now been placed on the static list. [accessed 26.11.14]

Prevention and treatment of surgical site infection. NICE Clinical Guideline CG74 (October 2008) Available from: http://guidance.nice.org.uk/CG74 Date for review: December 2016. [accessed 26.11.14]

Urinary tract infection: diagnosis, treatment and long-term management of urinary tract infection in children. NICE Clinical Guideline CG54 (August 2007) Available from: http://guidance.nice.org.uk/CG54 Date for review: October 2015. [accessed 26.11.14]

Related NICE guidance: under development

Intravenous fluids therapy in children. NICE Clinical Guideline. Expected publication: October 2015. http://www.nice.org.uk/guidance/indevelopment/GID-CGWAVE0655 [accessed 26.11.14]

Major trauma services: service delivery for major trauma. NICE Clinical Guideline. Expected publication: February 2016. http://www.nice.org.uk/guidance/indevelopment/GID-CGWAVE0641 [accessed 26.11.14]

Major trauma: assessment and management of airway, breathing and ventilation, circulation, haemorrhage and temperature control. NICE Clinical Guideline. Expected publication: February 2016. http://www.nice.org.uk/guidance/indevelopment/GID-CGWAVE0642 [accessed 26.11.14]

Sepsis: the recognition, diagnosis and management of severe sepsis NICE Clinical Guideline. Expected publication date: July 2016. http://www.nice.org.uk/guidance/indevelopment/GID-CGWAVE0686 [accessed 26.11.14]

NICE National Institute for Health and Care Excellence

Diagnosis and monitoring of sepsis: procalcitonin testing (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay)

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	Response
bioMérieux SA	1.	81 / 90-102 /		The reference [85] Schuetz P, Balk R, Briel M, et al., 2015 has been published in the meantime and is now publically available (**http://www.ncbi.nlm.nih.gov/pubmed/25581762**). The data in Table 10, pp 90-102 should therefore not be blackened anymore.	We will remove the AiC/CiC designation ahead of publication.
Roche diagnostics	2.	**17 & 123**	Summary & 5.1.1	This report presents a significant piece of work, highlighting the benefits of introducing procalcitonin testing guided algorithms in both, ICU & A&E pathways based on a robust evidence base of randomised interventional studies.	No response required.
Roche diagnostics	3.	**18 & 129**	Summary & 5.1.1	The presented de-novo economic model, using the findings from the clinical effectiveness analysis, presents to our knowledge the most relevant economic analysis for the use of procalcitonin tests in	No response required.

Diagnosis and monitoring of sepsis: procalcitonin testing (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay)

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	Response
				the NHS. It highlights that the benefits of introducing procalcitonin testing lead to substantial resource savings for the NHS.	
Roche diagnostics		**131, 133**	5.2 & 5.3	In our view, the limitations and uncertainties highlighted by the authors should acknowledge that, in spite of the issues associated with running randomised interventional studies in both environments (A&E and ICU), a significant number of studies (Section 3.2.1 and Appendix 3 of this report) met the inclusion criteria and were available to inform the analysis. Difficulties are exacerbated when conducting research with children, who also present a much smaller patient group. It is not surprising that the systematic review identified no RCT in a paediatric ICU setting. However, procalcitonin has demonstrated clinical utility in the A&E setting. In addition, diagnostic	No response required. The Wacker systematic review is cited in the discussion section of our report (Section 5.2.1). As noted, the accuracy of PCT testing reported in this article was poor. However, we do not believe that accuracy studies of the type included in the Wacker review are a useful way of assessing the clinical utility of PCT testing primarily because they assess the diagnostic performance of the test used

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	Response
				accuracy studies in the paediatric ICU settings are available and do not show a significant difference in diagnostic accuracy of procalcitonin compared to adult populations (Wacker et al. Lancet Infect Dis 2013; 13: 426–35). We feel it would reasonable to presume that the benefits of procalcitonin reported in adult ICU studies would also apply to the paediatric setting.	in isolation and hence are not representative of 'real world' clinical practice. The stakeholder suggests that the Wacker review found no difference in accuracy between studies conducted in adults and those in children and that this finding could provide a basis for assuming that our results for adults are transferable to children. In our view there are two main problems with this argument: 1. Similar accuracy for the test used in isolation, does not necessarily translate into similar 'real world' clinical performance as described above. 2. Even were we to assume that similar accuracy is an indication of similar clinical performance: The overall accuracy estimates (as indicated by Area Under the Curve), reported by Wacker et al., were indeed similar for adults and children. However, only three of the 30 included studies were conducted in PICU settings and two

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					of these used the obsolete PCT-LIA assay. The one PICU study that reported using "PCT-Kryptor" assay, reported a very low sensitivity (57%). The question of whether or not our findings in adults can be considered transferable to paediatric populations remains open and is an issue for discussion by the committee.
ThermoFisher Scientific		133	5.2.2	ThermoFisher Scientific fully appreciate the difficulty in modelling a long-term time horizon for the introduction of procalcitonin (PCT) and the acknowledgement that the inclusion of long-term outcomes would likely only make PCT more favourable compared to existing findings. However, we would like to comment purely from a utility perspective; the significance in terms of impact on the difference in benefit, if a longer time horizon had been used. This arises because the utility gains	We agree with the stakeholder's point that: "**if** PCT reduces either the number of patients who progress to sepsis or initiates accurate treatment more rapidly, resulting in better post-sepsis outcomes, the utility gains and cost effectiveness of PCT would be greater than that calculated by the authors" however, our systematic review did not find any evidence to suggest that PCT results in more rapid and appropriate treatment or better sepsis outcomes in the specified populations.

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				found – which are essentially driven by a reduction in adverse events from reduced antibiotic use – underestimate the potential utility gains from the identification and rapid appropriate treatment of potential sepsis cases that PCT can offer. ThermoFisher Scientific recently (October 2014) undertook a review of long-term utility values for post-sepsis survivors: For children, Buysse *et al.*(2008) looked at 120 sepsis survivors of meningococcal shock at a median of 9.8 years from the event. The mean utility value reported was 0.82 – this compares to the mean utility value for children in the current model arriving at ICU of 0.99. For adults, the utility values at least six years after an ICU event ranged from 0.71 to 0.63(Timmers *et al*. 2012). In addition, Karlsson *et al.* (2009) report a utility of 0.75 for post-sepsis survivors 17 months (median) after an ICU event. These compare to utility values of	

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				0.86 and 0.68 for adults up to six months after presentation in an emergency department or ICU, respectively, used in the current model. Whilst again acknowledging that the current modelling reveals PCT as being a cost effective, dominant strategy and that the authors state the analyses are conservative, we would state that if PCT reduces either the number of patients who progress to sepsis or initiates accurate treatment more rapidly, resulting in better post-sepsis outcomes, the utility gains and cost effectiveness of PCT would be greater than that calculated by the authors. **References:** Buysse, C. M.; Raat, H.; Hazelzet, J. A.; Hulst, J. M.; Cransberg, K.; Hop, W. C.; Vermunt, L. C.; Utens, E. M.; Maliepaard, M.; Joosten, K. F. Long-term health status in childhood survivors of meningococcal septic shock. *Archives of Prediatrics & Adolescent Medicine*; Nov 2008;162(11):1036-41 Timmers, T. K.; Verhofstad, M. H.; Moons, K. G.; Leenen, L. P. Patients' characteristics associated with	

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				readmission to a surgical intensive care unit. *American Journal of Critical Care*; Nov 2012;21(6):e120-8 Karlsson, S.; Ruokonen, E.; Varpula, T.; Ala-Kokko, T. I.; Pettila, V.; Finnsepsis Study, Group Long-term outcome and quality-adjusted life years after severe sepsis. *Critical Care Medicine*; Apr 2009;37(4):1268-74	
Royal College of Pathologists		N/A	N/A	The Royal College of Pathologists does not have any comments on this Diagnostic Assessment Report.	No response required.

Addendum from EAG

Corrections, clarifications and updates.

Errata;

1. There were errors in Table 17. Correct version

Table 17: Total cost per test

Name of test	Manufacturer	Listed price/test	Source
ELECSYS® BRAHMS PCT	Roche	£12.15	Manufacturers' response to request for information made by NICE (Nixon F., Health Technology Analyst, Diagnostics Assessment Programme, NICE [Personal communication] July 2014).
ADVIA Centaur BRAHMS PCT	Siemens	£16.81	
VIDAS BRAHMS PCT	bioMérieux	£12.80	
B.R.A.H.M.S PCT KRYPTOR	Thermo Fisher Scientific	£12.38*	
1. Average price/test		***£13.54***	
Overhead costs		Average costs (max or listed)	
Capital costs/test		£0.10	Manufacturers' response to request for information made by NICE (Nixon F., Health Technology Analyst, Diagnostics Assessment Programme, NICE [Personal communication] July 2014).
Service or maintenance costs /test		£0.07	
Calibration costs		£0.08	
2. Total other costs/test		***£0.26***	
3. Total average costs/test (1+2)		***£13.79****	

Note: * Prices were given in Euros and converted in British Pounds where 1 British Pound = 1.2521 Euros[103]; The total average cost per test with the discount varied from [redacted] to [redacted] depending on the extent of the discount described by the Manufacturers.

2. There were errors in reference 103. Correct version

[103] Bank of England. Daily spot exchange rates against Sterling [Internet]. London: Bank of England, 2014 [accessed 20.11.14]. Available from: http://www.bankofengland.co.uk/boeapps/iadb/Rates.asp?Travel=NIxRSx&into=GBP