Measurement and determination of procalcitonin

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The Medical Services Advisory Committee (MSAC) is an independent committee, which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by Ms Sandra Younie and Ms Bridie Murphy from Deakin Health Technology Assessment Group (DHTAG), Deakin Health Economics, Deakin University and an Advisory Panel of experts. The report was commissioned by the Department of Health and Ageing on behalf of the Medical Services Advisory Committee (MSAC). It was edited by Dr Lisa Lines, of Elite Editing.

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Contents

Tables

Figures

Executive summary

Assessment of Measurement and Determination of Procalcitonin

Purpose of Application

An application requesting MBS listing of a commercial immunoluminometric assay (ILMA) used to determine the concentration of procalcitonin (PCT) in human serum and plasma for for diagnosing life threatening infections and sepsis in patients and monitoring the course and control of antibiotic therapy was received from B.R.A.H.M.S Pty Ltd by the Department of Health in April 2009.

Procalcitonin (PCT), a glycoprotein, is a peptide precursor of the hormone calcitonin. However the exact origin and mechanisms of PCT remain largely unknown.. In microbial infections and severe systemic inflammatory responses, the serum level of PCT markedly increases approximately three hours after a pro-inflammatory stimulus or bacterial induction, reaching maximum values after 6-8 hours. Serum levels have been shown to reach levels >0.1 ng/mL in localised infection (e.g., lower respiratory tract infections (LRTIs)) and between 10 and 100 ng/mL or greater in severe sepsis. The increase in serum PCT levels in response to bacterial infection has been shown to correlate with the severity of the infection and with mortality.

Measured serum and plasma PCT levels are interpreted based on the clinical setting, the site and extent of infection, and co-morbidities. Increased levels of PCT may not always be related to systemic bacterial infection; the level of PCT has also been shown to markedly increase in:

- neonates <48 hours of age (physiological elevation).
- patients undergoing treatment with OKT3 antibodies and other drugs stimulating the release of pro-inflammatory cytokines.
- patients with invasive fungal infections, acute attacks of plasmodium falciparum malaria
- patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer, medullary C-cell carcinoma of the thyroid.
- patients with severe systemic inflammatory conditions such as inhalational injury, pulmonary aspiration, severe burns , pancreatitis, heat stroke, mesenteric infarction), multi-trauma, extensive surgery, and infections such as pneumonitis.

The measurement of PCT is a two-site immunoassay used to determine the concentration of PCT in human serum and plasma. All assays are based on the formation of a "sandwich" antigen-antibody complex. The intended purpose of the measurement of PCT is to determine the concentration of PCT in human serum and plasma in patients suspected of bacterial infection and to guide microbial therapy.

Proposal for public funding

Although not directly specified in the application, the MBS listing implied by the application could be summarised as presented in Table 1A.

Table 1A: Proposed MBS item descriptor

Category 6–PATHOLOGY SERVICES
Qantitation in human serum or plasma by any method except reagent tablet or reagent strip (with or without reflectance meter) of procalcitonin-1 test
Fee: $60.00

An independent evaluator team, Deakin Health Economics (DHE), was engaged by the Department of Health and Ageing to conduct an assessment of the intervention for consideration by MSAC. In conducting its assessment of procalcitonin, the evaluation team received advice from an Advisory Panel with expertise in this therapeutic area.

On the basis of advice from the Advisory Panel, the objective of the assessment to be conducted by the evaluation team was broadened:

(i) The intervention of interest was defined as 'measurement of procalcitonin'—that is, the assessment was not to be limited to consideration of the B.R.A.H.M.S commercial products.

Current arrangements for public reimbursement

Currently, there are no MBS items listed for measurement of procalcitonin. However, other relevant items are listed that directly or indirectly indicate the presence of sepsis. These include blood cultures for pathogenic micro-organisms - identification of cultured pathogens and if necessary antibiotic sensitivity; microscopy and culture to detect pathogenic micro-organisms from specimens of sputum - pathogen identification and antibiotic sensitivity testing and leucocyte count and C-reactive protein (CRP) quantitation.

Consumer Impact Statement

It appears that a procalcitonin test would be of most value if it could be a stand-alone or highly indicative test that clinical treatment could be guided by – rather than one of a number of tests. The present evidence does not support this in the areas where the most work has been done, that is: in intensive care; or for patients who present to a general practitioner; or the emergency department with the signs and symptoms of pneumonia/lower respiratory tract infection.

Meningitis in children is an area of concern for parents as the signs and symptoms are often not clearly differentiated from influenza (for parents and the medical profession), and the consequences of not detecting bacterial meningitis quickly enough can be dire. However, good quality evidence of the efficacy of a PCT test in diagnosing bacterial meningitis was lacking but it is acknowledged that this is an area that would be very hard to study with randomised controlled trials.

Clinical need

Sepsis is a major cause of morbidity and mortality and the diagnosis of infection is essential to the success of antibiotic therapy and should be made before commencement of therapy. Early diagnosis and assessment of the systemic inflammatory response to infection is crucial. However, there are certain limitations to the microbiological culture technique, concerning low sensitivity and the time until reliable culture results are available. There is a need for a timely laboratory marker to discriminate systemic inflammatory response syndrome (SIRS) from a non-infectious cause and sepsis.

The Advisory Panel advised that the populations who have the greatest capacity to benefit from the measurement of PCT include:

1. patients in an intensive care unit who have the signs and symptoms of sepsis.

2. patients who present to a general practitioner (GP) or the emergency department (ED) with the signs and symptoms of LRTI.

The population in an intensive care unit who are at risk of sepsis is distinguished from patients who present to a GP or the ED with the signs and symptoms of LRTI because the clinical management of the former group of patients differs from that of the latter.

Typical management algorithms for both populations are presented in Figure 1A and Figure 2A. For each population, the clinical decision is a scenario where the measurement of PCT is not available (the current scenario) and the clinical decision is a scenario where the measurement of PCT is available (the proposed scenario) is presented.

Figure 1A: Clinical decision tree for patients suspected of, or with, sepsis in ICU

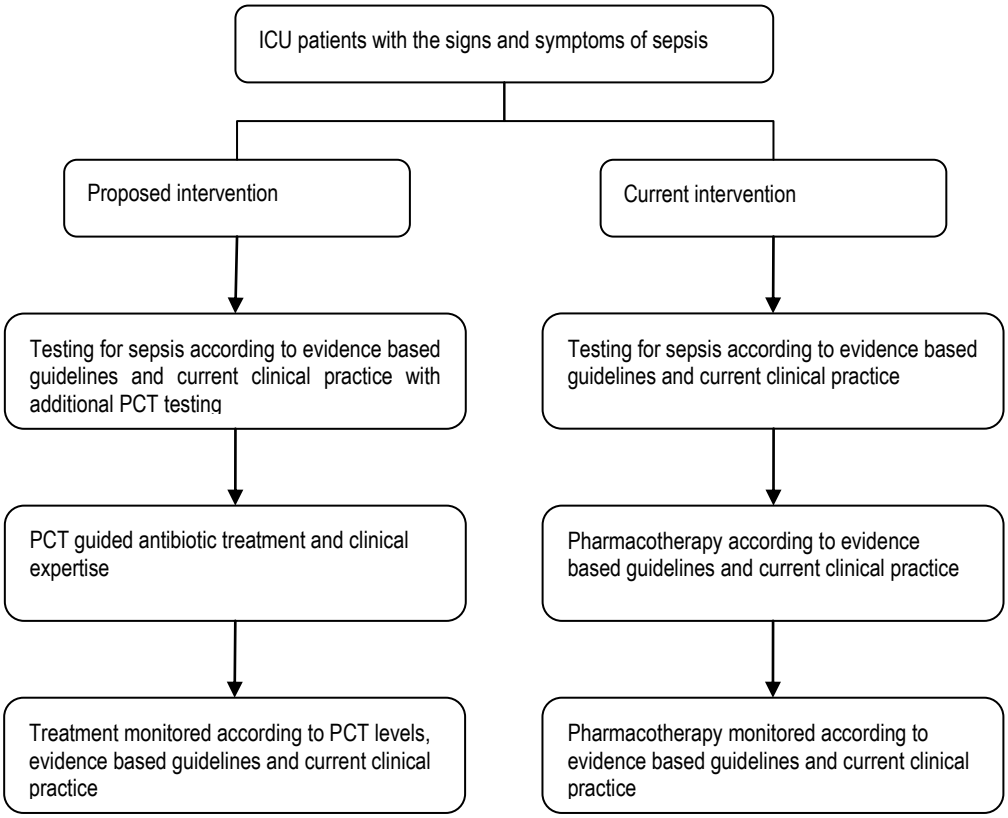
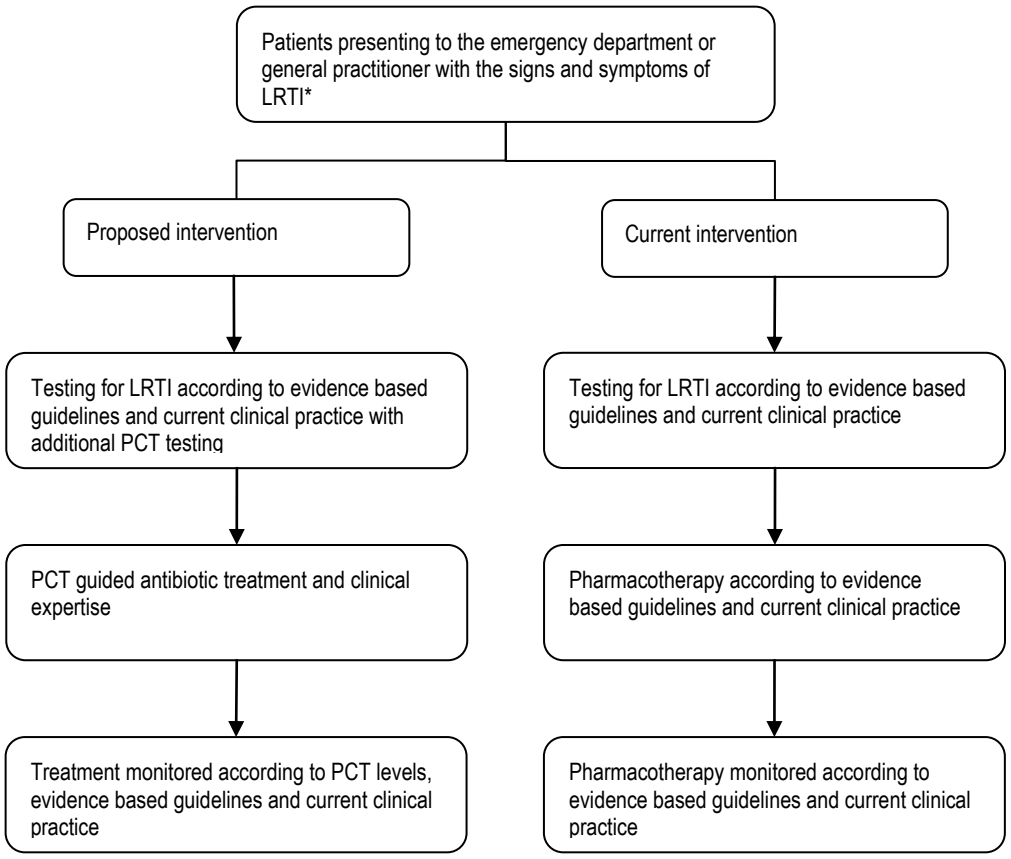


Figure 2A: Clinical decision tree for diagnosis of LRTI in a patient presenting to a general practitioner or emergency department



The MSAC assessment considers the following listing, summarised in Table 2A.

Table 2A: MBS descriptor implied by the application

Category 6–PATHOLOGY SERVICES
Qantitation in human serum or plasma by any method except reagent tablet or reagent strip (with or without reflectance meter) of: procalcitonin-1 test
Fee $60.00

The assessment will address the research question of whether management that involves the use of measurement of PCT to determine the presence of a bacterial infection and to guide antibiotic therapy compared with current management excluding this test, results in an improvement in quality-adjusted survival for:

1. patients who have the signs and symptoms of sepsis in an intensive care unit
2. patients who present to their GP or ED with a suspected LRTI.

Comparator

Comparator to the proposed intervention

For patients in an ICU who have the signs and symptoms of sepsis and patients who present to a GP or ED with the signs and symptoms of LRTI, the measurement of PCT is not likely to be used in isolation for decision making. It is recommended that PCT

should always be interpreted in the clinical context of the patient and the PCT results used in conjunction with other laboratory findings.

It was considered that the use of the measurement of PCT is unlikely to replace any of the currently used biological markers of infection to any substantial degree and would not be used in isolation for decision making.

The comparator assumed to be relevant to the assessment of the measurement of PCT is therefore current practice, or "no use of the measurement of PCT".

Scientific basis of comparison

A literature search located the following studies that directly addressed the question of whether the use of measurement of PCT was used to guide antibiotic use and the consequences of using PCT-guided antibiotic therapy

Table 3A: Included randomised controlled studies

Study and location	Level of evidence and quality assessment	Study design	Study population	Outcomes assessed
Intensive care studies				
Bouadma (2010) Germany & France	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Multi-centre, open-label RCT	N=630 ICU patients 5 ICUs participated	Primary outcomes - Death from any cause day 30 and day 60 (inferiority) - Number of days without antibiotics (superiority) Secondary outcomes - % of patients with relapse or super-infection - Number of days without MV - SOFA score (days 1, 7, 14, 21 and 28) - Length of stay ICU - Days of exposure to each antibiotic - Duration of antibiotic treatment per infection site - % of emerging multi-resistant bacteria isolated from specimens taken from routine microbiological assessments (days 1–28)
Jensen (2011)		Multi centre, Blinded RCT Blinded to outcomes, control group blinded to PCT levels	N=1,200 Mixed surgical/medical ICU patients	Primary outcome - 28-day survival Secondary outcomes - Duration of organ failure - Length of stay in ICU
Schroeder (2009) Germany	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	Open-blinded RCT	N=27 ICU patients	- Length of antibiotic treatment - Length of hospital and ICU stay
Nobre (2008) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Open-label RCT Single-centre	N=79 ICU patients	Primary outcome - Duration of antibiotic therapy - Antibiotic exposure days - Days alive without antibiotics Secondary outcome - 28-day mortality - In-hospital mortality - Length of stay in hospital and ICU - Clinical cure(resolution of baseline clinical signs) - Recurrence of initial infection - Nosocomial super-infection
Stolz (2009) Switzerland & USA	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	Multi-centre RCT Control group physician blinded to PCT level	N=101 ICU patients 7 ICUs participated	Primary outcome -Antibiotic free days after 28 days Secondary outcome - Number of MV free days - ICU free days alive - Length of hospital - Evolution of signs and symptoms linked to pulmonary infection - VAP related clinical deterioration rate - SOFA, ODIN, CPIS scores - Mortality at day 28
Svoboda (2007) Czech republic	Level of evidence II (RCT) Quality assessment	Single-centre RCT	N=72 ICU patients	- Mortality at day 28 - Sepsis-related complications - Duration of stay in ICU

	C1(direct comparison) Q3(poor quality information)			- Ventilator days
Hochreiter (2009) Germany	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Open-blinded RCT	N=110 surgical ICU patients	- Length of antibiotic treatment - Duration of intensive care stay
Emergency department/primary care studies				
Burkhardt (2010) Germany	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	RCT non-inferiority trial Physicians blinded	N=550 with symptoms of acute RTI	Primary outcome - Days with impairment during everyday life and/or leisure activities due to RTI within the first 14 days according to self-assessment (health impairment) Secondary outcome: - Frequency of prescription of antimicrobial treats - Days with antibiotic induced side effects - Symptoms of RTI on days 14 and 28 - Visit at Drs office with RTI within 28 days - Change of antibiotics within 28 days - Hospitalisation within 28 days - Mortality within 28 days
Briel (2008) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Randomised, open-label non-inferiority RCT multi-centre	N=458 primary care patients 53 primary care physicians participated	Primary outcome - Days with restrictions from ARTI Secondary outcome - Antibiotic prescription rate - Duration of antibiotic use - Days off work - Days with side effects - Relapse rate from ARTI within 28 days after randomisation
Kristoffersen (2009) Denmark	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	Multi-centre RCT Control group blinded	N=223 hospital admission for LRTI	Primary outcome - Days of antibiotic treatment during hospitalisation - Length of hospital stay Secondary outcome - Proportion of patients for whom physician disregarded treatment guidelines
Schuetz (2009) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Open-label non-inferiority RCT Multi-centre Outcomes assessed by unblinded study physicians	N=1,359 ED patients 6 EDs participated	Primary outcome (non-inferiority) - Overall composite adverse outcome (death from any cause, ICU admission for any reasons, disease specific complications and acute respiratory distress syndrome) Secondary outcome(superiority) - Antibiotic exposure - Adverse effects from antibiotics - Length of hospital stay
Stolz (2007) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) Q3(poor quality of information)	Single-centre RCT	N=266 ED patients	Primary outcome - Total antibiotic use at index exacerbation and up to 6 months Secondary outcome - Measures of clinical outcomes (success, self-reported functional status and symptom scores) - Steroid dose - Length of stay - Need for ICU - Death

Christ-Crain (2006) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	open-label RCT physicians blinded radiologist blinded	N=302 consecutive ED patients	Primary outcome - Total antibiotic use (prescription and duration) Secondary outcome - Laboratory outcome - Clinical outcomes (death, recurrence, relapse and radiologic signs of CAP)
Christ-Crain (2004) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	Prospective cluster-randomised controlled, single-blinded trial	N=243 ED patients	Primary outcome - Use of antibiotics (rate of prescriptions and antibiotic exposure) Secondary endpoints - Laboratory outcomes (including quality of life, temperature, leucocytes and CRP) - Frequency and length of admission - Need for ICU admission - Death in patients with LRTI - Rate of re-exacerbation and readmission of patients with acute exacerbations of COPD after 6 months

ED=emergency department, ICU=intensive care patients, MV=mechanical ventilation, nos=number

Comparative safety

A literature search found no reports that related to studies that specifically investigated the safety of measurement of serum PCT.

Key results

A literature search found no reports that related to studies that specifically investigated the safety of measurement of serum PCT. Given the nature of this intervention it is not anticipated that it will be associated with any safety issues.

Comparative effectiveness

A literature search identified two RCTs conducted in a general practice setting, five RCTs conducted in the ED setting and seven studies conducted in the ICU setting. The key results from these studies are shown in the tables below.

Key results

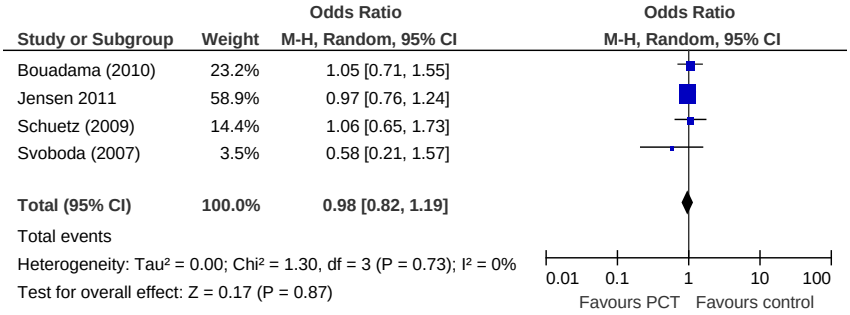
Four studies included as a primary endpoint, mortality. Table 4A below presents this data, and Figure 3A, summarises the odds ratios across the trials.

Table 4A: Studies with mortality as a primary endpoint

Study	variable	PCT	Control	Risk difference % (95% CI)	P value
Schuetz (2009)#	30 days	34/671 (5.1%)	33/688 (4.8%)	0.3 (-2.1to 2.5)	NS
Jensen (2011)(p)	28-day mortality	190/604 (31.5%)	191/596 (32.0%)	0.6 (-4.7 to 5.9)	NS
Bouadma (2010)	28-day mortality	65/307 (21.2%)	64/314 (20.4%)	0.8 (-4.6 to 6.2)	NS
Svoboda (2007)	28-day mortality	10/38 (26%)	13/34 (38%)	-0.12* (-0.33 to 0.10)	P=0.28

NR—not reported; NS—not significant
Primary endpoint composite, which included mortality; (p) Primary endpoint of the trial
*calculated based on information provided in the published journal article

Figure 3A: Pooled analysis of studies with mortality as primary endpoint



Analysis from the individual studies does not reveal any significant different in mortality between, the PCT-guided arm and the control arm. Pooling the mortality data from the four studies supports the conclusion that mortality was comparable between the two treatment groups. The study by Svoboda et al (2007) appears to show quite a strong trend towards fewer deaths in the PCT-guided arm, but the confidence intervals (CIs) are wide due to the small numbers in this study (information about whether the sample size was powered to detect a difference in mortality was not provided in the study report). The mortality endpoint reported by Schuetz et al. (2009) forms part of composite primary endpoint of adverse events.

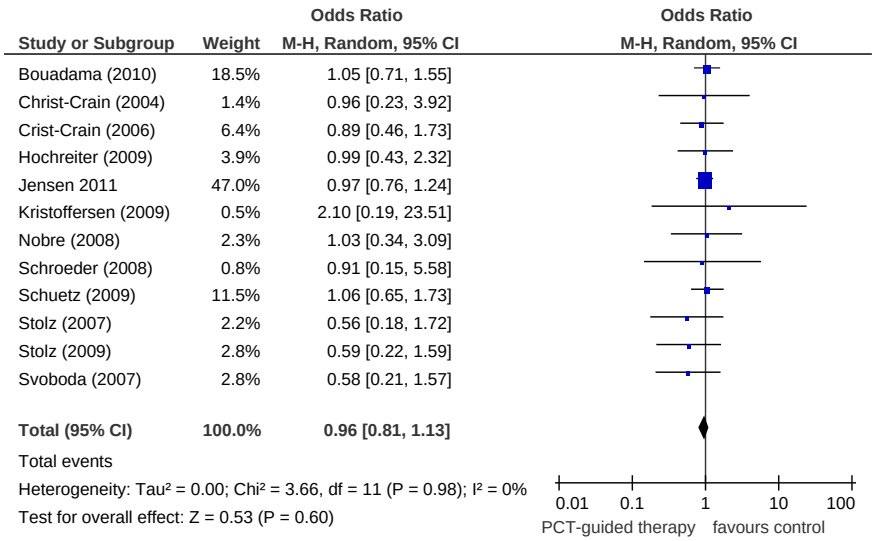
Table 5A presents the mortality data reported by all the included studies, primary and secondary endpoints. Figure 4A presents a summary of the odds ratio across the trials for the deaths.

Table 5A: Outcome—mortality

Study	Variable description	PCT	Control	Risk difference% (95% CI)	P value
Primary care					
Burkhardt (2010)**	Mortality up to day 28	0	0	NR	NR
Briel(2008)**		NR	NR	NR	NR
Emergency department					
Kristoffersen (2009)	Death during admission	2/103 (2%)	1/107 (1%)	0.01* (-02 to 0.04)	0.54
Christ-Crain (2004)**	Mean after 13 days	4/124 (3%)	4/119 (3%)	-0.00* (-0.05 to 0.04)	0.95
Christ-Crain (2006)**	6 weeks	18/275 (12%)	20/275 (13%)	-0.01* (-0.05 to 0.04)	0.73
Schuetz (2009)(p)#	30 days	34/671 (5.1%)	33/688 (4.8%)	0.3 (-2.1 to 2.5)	NS
Stolz (2007)	Death, any cause within 6 months	5/102 (4.9%)	9/106 (8.5%)	-0.04* (-0.10 to 0.03)	0.409
Intensive care					
Jensen (2011)(p)	28-day mortality	190/604 (31.5%)	191/596 (32.0%)	0.6 (-4.7 to 5.9)	NS
Svoboda (2007)(p)	28-day mortality	10/38 (26%)	13/34 (38%)	-0.12* (-0.33 to 0.10)	0.28
Bouadma (2010)(p)	28-day mortality 60-day mortality	65/307 (21.2%) 92/307 (30.0%)	64/314 (20.4%) 82/314 (26.1%)	0.8 (-4.6 to 6.2)* 3.8 (-2.1 to 9.7)*	NS
Nobre (2008)	28-day mortality	8/39 (20.5%)	8/40 (20%)	0.01* (-0.17 to 0.18)	0.82
Stolz (2009)	28-day mortality In-hospital mortality	8/51 (16%) 10/51 (20%)	12/50 (24%) 14/50 (28%)	-0.08* (-0.24 to 0.07)	0.327 0.322
Hochreiter (2009)	Not specified	15/57 (26.3%)	14/53 (26.4%)	-0.00* (-0.17 to 0.16)	NS
Schroeder (2009)	Not specified	3/14 (21.4%)	3/13 (23.1%)	-0.02* (-0.33 to 0.30)	NS

NR—not reported; NS—not significant; * calculated based on information provided in the published journal article
(p) Primary endpoint of the trial; # Primary endpoint composite, which included mortality; ** Secondary outcome

Figure 4A: Forrest plot of pooled odds ratios for mortality



Thirteen studies included the number of patients who were deceased during the course of the trial. The exception was the study by Briel (2008), conducted in a primary care setting. Burkhardt (2010) is not included in the analysis as no patients were recorded as having died during the trial period. Pooled analysis indicated that the use of PCT-guided antibiotic therapy did not appear to have a deleterious effect on patients, or a beneficial effect (Figure 4A).

Table 6A presents the data from the trials on the number of antibiotics prescribed in the trials. Figure 5A summarises the data across the trials.

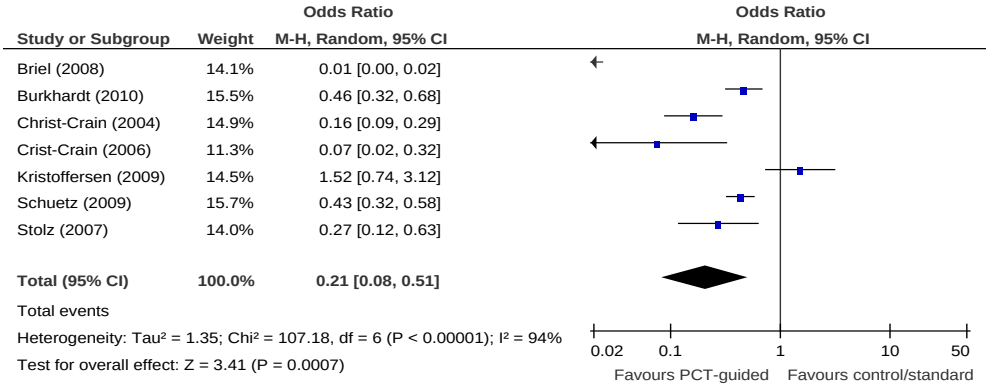
Table 6A: Outcome—antibiotics prescribed

Study	Variable description	PCT N=275	Control N=275	Risk difference % (95% CI)	P value
Primary care					
Burkhardt (2010)	Antibiotic at baseline and during follow-up	59[a]/274 (21.5%)#	101/272 (37.1%)**	NR	0.0005
Briel (2008)		58/232 (25%)	219/226 (97%)	-72 (-78 to -66)	
Pooled primary care		**117/506 (23%)**	**320/498 (64%)**	**-0.41 (-0.46 to -0.36)**	**<0.00001**
Emergency department					
Kristoffersen (2009)(p)		88/103 (85%)	85/107 (79%)	NR	0.25
Christ-Crain (2004)(p)		55/124 (44.4%)	99/119 (83%)	NR	<0.0001
Christ-Crain (2006)(p)		128/151 (85%)	149/151 (99%)	NR	<0.001
Schuetz (2009)(p)		506/671 (75.4%)§	603/688 (87.6%)§	-12.2 (-16.3 to -8.1)	
Stolz (2007)(p)	Index exacerbation ECOPD: number of courses of antibiotics within 6 months	(21/51) (40%) 46	36/50 (72%) 43	NR	<0.0001 0.290
Pooled ED		**798/1100(72.5%)**	**972/1115(87.2%)**	**-0.15 (-0.18 to -0.11)**	**<0.00001**

NR—not reported

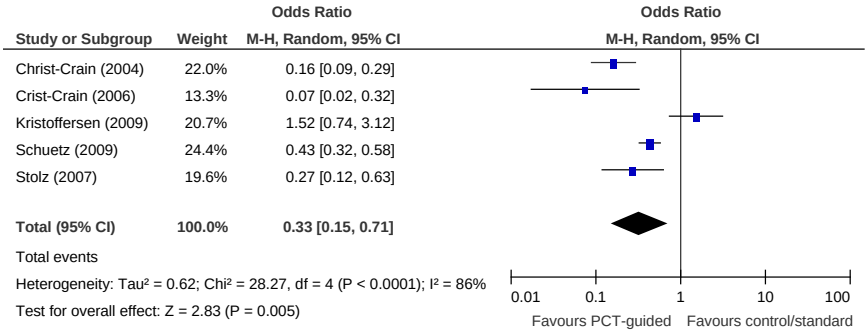
[a] In total, includes as advised by PCT=23, PCT overruled by Dr=36; # Lost to follow-up n=1; ** Lost-to-follow-up n=3; (p) Primary endpoint of the trial; § Includes both hospitalised plus outpatients

Figure 5A: Forrest plot of pooled odds ratios for antibiotics prescribed



Seven studies reported as an outcome, the number of antibiotics prescribed. All studies, with the exception of Kristoffersen (2009), reported significant reductions in antibiotic prescribing. The use of a PCT guided algorithm resulted in a significant decrease in antibiotic prescribing, across the studies, pooled OR 0.21 (95%CI 0.08, 0.51). However, there was significant heterogeneity in the results ((χ^2=107.18, I^2=94%). Across the studies, the rate of antibiotic prescribing in the control arm varied markedly, from a low of 37.1 to 99% reflecting differences in the trial populations and the trial settings. Both trials conducted in the primary setting had results that were very favourable towards PCT-guided therapy. Briel (2008), in particular, was very favourable. Figure 6A, presents data on the prescription of antibiotics outcome only for the studies conducted in the ED.

Figure 6A: Forrest plot of pooled odds ratios for prescription of antibiotics, emergency department



The rate of antibiotic prescription was 798/1100 (72%) in the PCT-guided group and 972/1115 (87%) in the control group. The use of a PCT guided algorithm resulted in a significant decrease in antibiotic prescribing pooled OR 0.33 (95% CI 0.15, 0.71)). However, significant heterogeneity remains across the trials ((χ^2=28.27, I^2=86%). The study by Kristoffersen (2009), has results that differ in direction from the other studies. This is likely because the investigators did not contact the participating departments or physicians to check whether they were actually adhering to the PCT guidelines. Additionally, in this study, the guidelines recommended a lower level of PCT (>0.5 ug/l) at which to initiate antibiotic therapy.

Table 7A presents data on the number of patients hospitalised in the trials.

Table 7A: Outcome—hospitalisations

Study	Variable description	PCT N=275	Control N=275	Risk difference % (95% CI)	P value
Primary care					
Burkhardt (2010)		0	1	NR	NR
Emergency department					
Christ-Crain (2004)		101/124 (81%)	88/119 (74%)	NR	0.16
Christ-Crain (2006)		146/151 (97%)	146/151 (97%)	NR	1.0
Schuetz (2009)	 Recurrence/ Rehospitalisation	628/671 (93.7%) 25 (3.7%)	629/688 (91.4%) 45 (6.5%)	NR -2.8 (-5.1 to -0.4)	NR
Stolz (2007)	Rate for ECOPD within 6 months	18 (17.7%)	22 (20.8%)	NR	0.507

NR—not reported;

Five studies reported on hospitalisation as an outcome measure. None of the studies reported a significant difference between PCT-guided patients or control/standard therapy in patients requiring hospitalisations.

Table 8A presents data on the length of hospital stay for patients in the trials.

Table 8A: Outcome—length of hospital stay in days

Study	Variable description	PCT	Control	Days difference [relative mean change] (95% CI)	P value
Emergency department					
Kristoffersen (2009)(p)	Mean (95% CI)	5.9 (5.1–6.9)	6.7 (5.9–7.7)	NR	0.22
Christ-Crain (2004)	Mean (SD)	10.7 (8.9)	11.2 (10.6)	NR	0.89
Christ-Crain (2006)	Mean (SD)	12.0 (9.1)	13.0 (9.0)	NR	0.35
Schuetz (2009)	Mean Patients with CAP	9.4 8 (5–13)	9.2 8 (4–12)	[1.8]* (-6.9 to 11.0)	NR
Stolz (2007)	Median (IQR)	9 (1–15)	10 (1–15)	NR	0.960
Intensive care studies	ICU unit stay				
Svoboda (2007)	Mean (SD)	16.1 (6.9)	19.4 (8.9)	NR	0.09
Jensen (2011)	Median (IQR) ICU admission length	6 (3–12)	5 (3–11)	NR	0.04
Bouadma (2010)	ICU stay mean (SD) Hospital stay mean (SD)	15.9 (16.1) 26.1 (19.3)	14.4 (14.1) 26.4 (18.3)	1.5 (-0.9 to 3.9) -0.3(-3.2 to 2.7)	P=0.23 P=0.87
Hochreiter (2009)	ICU stay mean (SD)	15.5±12.5	17.7±10.1	NR	0.046
Stolz (2009)	Median (IQR)	26 (7–21)	26 (16.8–22.3)	NR	0.153
Stolz (2009)	ICU free days alive Median (IQR)	10 (0–18)	8.5 (0–18)	NR	0.526
Schroeder (2009)		16.4±8.3	16.7±5.6	NR	NS
Nobre (2008)(ITT)	ICU length of stay median (range) Hospital length of stay median (range)	4 (1–21) 17 (3–96)	7 (1–91) 23.5 (5–44)	NR	0.02 0.85

NR—not reported; NS—not significant
(p) Primary endpoint of the trial, *relative mean change

All studies, conducted in the ED or ICU reported on length of hospital/ICU stay as a trial outcome. The studies by Hochreiter (2009) and Nobre (2008) reported a significant decrease in ICU stay for patients in the PCT-guided group, of 2 days and 3 days respectively. However, the study by Jensen et al. (2011) and Bouadma (2010) report increases in time spent in the ICU, of one day, for patients in the PCT-guided group. The other studies reported non-significant results.

Table 9A presents data on the need for admission to ICU for patients in the trials.

Table 9A: Outcome—need for admission to an intensive care unit

Study	PCT	Control	Risk difference% (95% CI)	P value
Emergency department				
Kristoffersen (2009)	7/103 (7%)	5/107 (5%)	0.02* (-0.04 to 0.08)	0.51
Christ-Crain (2004)	5/124 (4%)	6/119 (5%)	-0.01* (-0.06 to 0.04)	0.71
Christ-Crain (2006)	20/151 (13%)	21/151 (14%)	-0.01* (-0.08 to 0.07)	0.87
Schuetz (2009)(p)	43/671 (6.4%)	60/688 (8.7%)	-2.3 (-5.2 to 0.4)	NR
Pooled analysis	75/1049(	92/1065	-0.01* (-0.04 to 0.01)	0.21

NR—not reported; * calculated based on information provided in the published journal article
(p) Primary endpoint of the trial

Four of the studies undertaken in the ED reported on the need for admission to an ICU as a trial outcome. The use of PCT-guided therapy did not appear to result in an increase in the need for ICU admission.

Table 10A reports on the days with adverse events from antibiotic therapy.

Table 10A: Outcome—days with adverse events from antibiotics

Study	Variable description	PCT	Control	Days [risk]difference (95% CI)	P value
Primary care					
Burkhardt (2010)	With RTI symptoms day 28	5.6* (2.2)	6.1* (3.7)	NR	0.940
Briel (2008)	Within 14 days (SD) Rate difference	2.3 (4.6)	3.6 (6.1)	0.8 (0.4 to 1.2)	NR
Emergency department					
Schuetz (2009) #	Number (%)	133/671 (19.8%)	193/688 (28.1%)	[-8.2] (-12.7 to -3.7)	NR

NR—not reported;
* N=1 lost in PCT arm and N=3 lost to follow-up in control arm; # Part of composite primary outcome

The Schuetz et al. (2009) trial, conducted in an ED, reported that patients in the PCT-guided arm had a statistically significant reduction in adverse events, such as diarrhoea, rash, nausea, compared to patients in the standard therapy arm, reflecting the increased prescribing rate that was recorded in the control arm (Table 6A). Both of the studies conducted in a primary care setting reported on the median number of days patients suffered from adverse events from antibiotics. There was no statistical difference in the trials between those patients treated according to PCT-guided therapy and the control.

Table 11A presents data from the trials reporting on the disease specific complications.

Table 11A: Days with disease specific complications or organ support

Study	Variable description	PCT	Control	Risk difference (95% CI)
Intensive care				
Schuetz (2009)	Disease specific complications (%)	17 (2.5%)	14 (2.0%)	0.5 (-1.1 to 2.0)
	Death	34 (5.1%)	33 (4.8%)	0.3 (-2.1 to 2.5)
Jensen (2011)	Mechanical ventilation	3569 (65.5%)	2861 (60.7%)	-4.9 (-6.7 to -3.0)*
	ICU days spent with dialysis treatment	1214 (22.3%)	982 (20.8%)	-1.5 (-3.1 to 0.1)
	ICU days with vasopressors/inotropes	1564 (28.7%)	1393 (29.5%)	0.8 (-1.0 to 2.6)
	ICU days with severe sepsis/septic shock	1097 (20.1%)	924 (19.6%)	-0.6 (-2.1 to 1.0)
	Death	190/604 (31.5%)	191/596 (32.0%)	0.6 (-4.7 to 5.9)

The Schuetz et al. (2009) and Jensen et al. (2011) trials reported on disease specific complications and both studies expressed some concern about the outcomes for the PCT-guided arm. The results from Schuetz et al. (2009) show that the trend is towards increased disease-specific complications and death in the PCT guided arm of the trial, although results did not reach significance. The results from the Jensen et al. (2011) show that the need for organ support, such as mechanical ventilation, was significantly greater in the PCT-guided arm, but that the number of deaths did not differ between the two arms of the trial.

Diagnostic accuracy

The requested listing is for measurement of PCT to be included alongside, clinical assessment, other indirect biomarkers of infection (e.g. CRP) and other tests, and not as a stand-alone diagnostic test for bacterial infection. However, background information of the evidence about the accuracy of PCT in the diagnosis of sepsis and in particular threshold cut-offs used in the studies to diagnose infection is included in the body of the report. The studies included are not exhaustive and are only studies conducted within the populations of interest to this assessment. The assessment of the clinical effectiveness of PCT is not based on these studies.

Economic evaluation

Assessment of measurement of PCT will not substitute for any other direct or indirect measure of sepsis. A comparative cost analysis of measurement of PCT compared to no PCT is presented. Cost effectiveness analyses were undertaken based on the evidence of clinical effectiveness from the included studies in the primary care and ED settings but not in the ICU setting. This is because unequivocal evidence of clinical benefit of PCT-guided therapy in the ICU setting was lacking.

Costs associated with treatment of infection

A cost of $60.00 per measurement of PCT is assumed, based on information provided by the application. It is proposed that measurement of PCT will be an additional test alongside other laboratory tests and clinical judgement, incurring an additional cost to the treatment of infection.

Table 12A presents a list of other MBS items that are used to diagnose or indicate the presence of infection. The number of services and benefits for 2010 is also presented.

Table 12A: MBS items associated with inflammation and infection

Item	Description fee	MBS expenditure in 2010	MBS services in 2010	Average expenditure per service in 2010
58500	Chest lung fields by direct radiology Fee: $35.35	$330,606	10,586	$31.23
69354	Blood culture for pathogenic micro-organisms To a maximum of 3 sets of cultures–1 set of cultures Fee: $30.95	$3,606,891	148,605	$24.27
69357	2 sets of cultures described in item 69354	$949,338	20,072	$61.85
69360	3 sets of cultures described in item 69354	$432,803	6,090	$92.80
69333	Microscopy and culture to detect pathogenic micro-organisms from specimens of sputum Fee: $34.00	$3,733,632	132,213	$28.23
73802	Leucocyte count, erythrocyte sedimentation rate, examination of blood film (including differential leucocyte count), haemoglobin, haematocrit or erythrocyte count Fee: $4.60	$156,462	39,563	$3.95
66500	Quantitation in serum, plasma, urine or other body fluid (except amniotic fluid), by any method except reagent tablet or reagent strip (with or without reflectance meter) of: acid phosphatise, alanine aminotransferase, albumin, alkaline phosphatise, ammonia, amylase, aspartate aminotransferase, bicarbonate, bilirubin (total), bilirubin (any fractions), C-reactive protein, calcium (total or corrected for albumin), chloride, creatine kinase, creatinine, gamma glutamyl transferase, globuline, glucose, lactate, dehydrogenase, lipase, magnesium, phosphate, potassium, sodium total protein, total cholesterol, trigylcerides, urate or urea Fee: $9.75	5,801,711	702,529	$8.26

Cost effectiveness of the measurement of PCT in the primary care setting

Table 13A presents a cost effectiveness evaluation based on the two trials conducted in patients who visited their GP with the signs and symptoms of RTI.

Table 13A: Incremental cost of avoiding a course of antibiotic therapy in primary care

Trial	PCT		Standard		Increment
	N	Antibiotics Prescribed	N	Antibiotics prescribed	
Burkhardt (2010)	232	58	226	219	
Briel (2008)	272	59	272	191	
Pooled analysis	504	117	498	320	
		0.23		0.64	**0.41 (0.46, 0.36)**
Cost	**PCT test**	**Antibiotics**	**PCT test**	**Antibiotics**	
PCT test	60	29.5	60	29.5	
Proportion	100	0.23	0	0.64	
Total costs		66.79		18.96	47.83
Additional cost per course of antibiotics avoided					**$117 ($104, $324)**

Table 13A shows that to avoid a course of antibiotics through testing patients, who visit their GP with the signs and symptoms of RTI, for PCT levels , will incur an additional cost of $117 per patient for each course of antibiotics avoided. Only the costs of the PCT test and antibiotics are included within this economic evaluation because additional information about consequences that may (or may not) occur from not prescribing antibiotics were not available from the trials. To the extent that some patients may require admission to hospital and parental therapy, the cost of antibiotic therapy may be an underestimate. One patient in the control arm of the Burkhardt (2010) trial did require hospitalisation but this was not reported as being of significance.

Cost effectiveness of the measurement of PCT in the emergency department setting

Table 14A presents a cost effectiveness evaluation based on the trials conducted in patients who visited an ED with signs and symptoms of CAP or ECOPD.

Table 14A: Incremental cost of avoiding course of antibiotics in the emergency department

Trial	PCT		Standard		Increment‡
	N	Antibiotics prescribed	N	Antibiotics prescribed	
Pooled	1100	798	972	1115	
		0.725		0.872	**-0.146 (-0.18 to -0.11)**
Schuetz (2009)	671	506	688	603	
		0.754		0.876	**-0.122 (-0.163 to -0.081)**
Cost					
PCT test $60		5#		0	$300
Antibiotics Mild/mod $724.58 Severe $2,255.14		 0.69 0.06		 0.789 0.09	
Total antibiotic cost**		$644.49		$768.54	($124.05)
Length hospital stay		10 days		9.5	
Cost of hospital stay $1,077/day		$10,770		$10,231.50	$0*
Adverse events		0.213438735		0.255389718	
Cost of adverse events $85.00†		$18.17		$21.75	($3.57)
				Total incremental cost	**$172.38**
Additional cost per course of antibiotics avoided (benefit from Schuetz)					**$1,409 ($2,128, $1,058)**
Additional cost per course of antibiotics avoided (using pooled benefit)					**$1,178 ($1,567, $958)**

Table 14A shows that testing patients who present to an ED for their PCT levels, as part of PCT-guided antibiotic therapy, may incur an additional cost of approximately $1,409 for each course of antibiotics avoided. To estimate these costs, the study by Schuetz et al. (2009) was used as a basis because this study had been powered to detect a difference in the consequences of not prescribing antibiotics. The additional cost per course of antibiotics avoided, based on the pooled numbers from all trials in the ED setting, is included for comparison. Some costs could not be included. For example, the study reported that patients in the standard therapy arm had a greater likelihood of being admitted to an ICU, but the length of time patients were in an ICU was not reported in the trial. As the length of hospital stay was reported, it has been used as a proxy. This may favour the control arm. Another cost that was not included in the analysis above, is that for disease specific complications. The study reported that these complications occurred more frequently in the PCT group, but the type of complications was not made clear in the study. This may favour the PCT-guided arm.

Overall conclusion with respect to comparative cost-effectiveness

Longer-term analysis, for example of the likely benefit of reduced amount of antibiotic prescriptions concerning antibiotic resistance has not been done. This is primarily because it is difficult to separate out the role of the prescribing of antibiotics for non-bacterial RTI from other postulated causes of antibiotic resistance, such as the use of antibiotics in animal populations and patients not finishing their courses of antibiotics. In the event that it was

possible to separate out the effects of the role of prescribing of antibiotics on the emergence of resistance, expert advice is that the measurement of PCT effect size on the emergence of resistance is very small, whereas the confounders are very large in these specific populations.

Measurement of PCT is not cost saving from a health care perspective compared to no measurement of PCT. The additional cost per antibiotic prescription avoided may range from $117 to $1,409, depending on the setting in which patients are being tested and taking into consideration assumptions about likely benefits in terms of number of antibiotic prescriptions avoided. Longer-term benefits in the form of hospitalisations avoided or mortality reductions were not included in the economic evaluation, as these benefits were not demonstrated by the available evidence. These are not costs that are borne by the MBS.

Financial/budgetary impacts

To estimate the financial implications for the government of listing the measurement of PCT on the MBS, surrogate measures were used to try to estimate the number of tests that may be ordered. The focus was on general practice because expert clinical advice holds that this setting would likely use measurement of PCT most widely. However, estimates of the likely use of the test in the private hospital setting are also included.

To estimate the potential number of PCT tests that may be requested if measurement of PCT was listed on the MBS, an attempt was made to estimate the number of patients who may visit their GP with the signs and symptoms of a LRTI as well as those with a diagnosis of chronic obstructive airways disease (COAD).

The estimates of the number of patients seen with LRTI by GPs and the numbers and rates of pathology ordering by GPs for respiratory conditions are derived from data obtained from the Bettering the Evaluation and Care of Health (BEACH) program. The BEACH study does not record a diagnosis of LRTI, but does record specific diagnosis, (e.g. bronchitis). Rates of community acquired pneumonia (CAP) are recorded in a category of other respiratory infections, rather than separately, as the rates are too low.

Table 15A provides a breakdown of the type and rate of respiratory problems encountered by GPs from the BEACH study.

Table 15A: Management rates of respiratory problems, 1998–99 and 2007–08

	Rate per 100 encounters (95% CI)		Percentage of all problems (95% CI)		Percentage of respiratory problems		
	1998–99 (*n* = 96,901)	2007–08 (*n* = 95,898)	1998–99 (*n* = 140,824)	2007–08 (*n* = 145,078)	1998–99 (*n* = 23,554)	2007–08 (*n* = 18,641)	Change[a]
Respiratory—all (ICPC-2 rubric/group)	**24.3 (23.6–25.0)**	**19.4 (18.8–20.1)**	**16.7 (16.2–17.2)**	**12.9 (12.4–13.3)**	**100.0**	**100.0**	↓
Upper respiratory tract infection	6.8 (6.4–7.3)	6.2 (5.7–6.7)	4.7	4.1	28.1	31.9	—
Acute bronchitis/ bronchiolitis	3.3 (3.1–3.5)	2.4 (2.2–2.6)	2.3	1.6	13.5	12.4	↓
Asthma	3.2 (3.0–3.4)	2.2 (2.0–2.3)	2.2	1.4	13.1	11.2	↓
Preventive immun/ vacc/meds—respiratory	2.5 (2.1–2.9)	1.8 (1.5–2.1)	1.7	1.2	10.3	9.2	↓
Sinusitis acute/chronic	1.6 (1.4–1.7)	1.3 (1.2–1.4)	1.1	0.9	6.4	6.7	↓
Tonsillitis	1.5 (1.3–1.6)	1.0 (0.9–1.1)	1.0	0.6	6.0	5.0	↓
Chronic obstructive pulmonary disease	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.5	0.5	3.2	4.0	—
Allergic rhinitis	1.0 (0.9–1.1)	0.6 (0.5–0.7)	0.7	0.4	3.9	3.0	↓
Cough	0.6 (0.6–0.7)	0.5 (0.5–0.6)	0.4	0.4	2.6	2.7	↓
Influenza	0.5 (0.4–0.6)	0.4 (0.3–0.5)	0.3	0.3	1.9	2.1	—
Respiratory infection, other	0.5 (0.4–0.6)	0.4 (0.3–0.5)	0.3	0.3	2.0	1.9	—

(a) The direction and type of change is indicated for each variable: ↑/↓ indicates a statistically significant change, ↑/↓ indicates a marginal change, and — indicates there was no change.

Note: CI—confidence interval; immun—immunisation; vacc—vaccination; meds—medications.

Table 15A reports on the rates of respiratory problems encountered by GPs during the year 1998-99 compared to 2007-08. The change recorded in the final column of Table 15A indicates the change between the years 1998-99 and 2007-08 indicating a statistically significant decrease in respiratory problems encountered.

Table 16A estimates the number of respiratory problems seen by GPs, separated into the relevant individual respiratory conditions that fall within the definition or symptoms of LRTI or COPD.

Table 16A: Estimates of the number of problems seen by GPs and the number of problems that fall within the definition of LRTI 1998-99 and 2007-08

	1998-99		2007-08	
Respiratory problems	**Rate per encounters**	**Number of problems**	**Rate per encounters**	**Nos. of problems**
National	145.3	149,100,000	151.3	165,673,500
Respiratory	24.3	24,920,136	19.4	21,243,000
Acute bronchitis	3.3	3,384,216	2.4	2,628,000
COAD	0.8	820,416	0.8	876,000
cough	0.6	615,312	0.5	547,500
Other respiratory infections	0.5	512,760	0.4	438,000

Note: The number of general practice professional services claimed from Medicare Australia for the financial year 1998-99 was 102.6 million and for 2007-08 it was 109.5 million

Based on the figures for 2007-08 in Table 16A, Table 17A estimates the likely cost to the MBS of requests for PCT tests in the general practice setting.

Table 17A: Likely costs to the MBS based on the estimate of the number of problems seen by general practitioners that fall within the definition of LRTI 2007-08

Respiratory problems	Nos of problems	Cost of PCT test	If 100% of patients visiting GP referred for test $	If 20% of patients visiting GP referred for test $	If 3%* of patients visiting GP referred for test $
Acute bronchitis	2,628,000	$60	157,680,000	31,536,000	4,730,400
COAD	876,000	$60	52,560,000	10,512,000	1,576,800
cough	547,500	$60	32,850,000	6,570,000	985,500
Other respiratory infections	438,000	$60	26,280,000	5,256,000	788,400
Total #	**4,489,500**				**8,081,100**

#in the trials conducted in the general practice setting, all patients presenting with a respiratory tract infection were ordered a PCT test. Therefore, these figures may underestimate the likely number of tests,, if testing according to the trials, because patients presenting with URTI (the largest percentage of respiratory problems) would also need to be included, and these figures are not included in this table.
*Pathology ordering for respiratory problems accounted for 3.0% of total pathology tests in 2000–02 and 2.9% in 2006–08

Table 17A indicates that if measurement of PCT is listed on the MBS for use in the general practice setting for patients who present to their GP with the signs and symptoms of LRTI then the likely financial implications to the MBS may be approximately $8 million. An assumption that 3% of patients visiting their GP, have a pathology test for respiratory problems is used as the basis for this calculation.

In the event that measurement of PCT is listed on the MBS for patients with the signs and symptoms of sepsis, another setting for which there is likely to be a financial implications for the MBS is inpatients in a private hospital.

Expert advice is that PCT is most likely to mimic the CRP pathology test in terms of requests. MBS item 66500, includes CRP but also includes a suite of other measures. It is not possible to separate out the number of requests for CRP alone. Direct measures of infection for patients with sepsis are blood cultures, and for CAP, sputum cultures. Expert advice is that in the general practice setting, GPs are unlikely to order blood cultures or sputum cultures, for query LRTI (although they may order a chest x-ray) because these tests are deemed to be hospital-based tests and GPs usually diagnose and start antibiotics rather than run patients through a diagnostic regimen. Information about the frequency of requests for sputum or blood cultures could not be obtained from BEACH statistics reports of the most frequently requested pathology tests. Given the infrequency with which blood and sputum cultures appear to be requested by a GP, the Medicare statistics reporting the number of blood and sputum culture services are assumed to be for patients in a private hospital setting.

The PCT-guided algorithms, used in the clinical trials, recommend multiple measurements of PCT to indicate when to initiate antibiotic therapy, as a gauge of whether the antibiotic therapy is appropriate and as an indicator to cease antibiotic therapy. If the MBS listing and use of measurement of PCT is in accordance with these PCT-guided antibiotic algorithms then each patient suspected of sepsis may have multiple tests. Table 18A lists the number of services requested for blood and sputum cultures in 2010, using the information provided in Table 12A.

Table 18A: Estimates of the potential number of tests to measure PCT levels

MBS item	Description	Services 2010	Level at which PCT may be requested	Cost of PCT test	Likely cost if listed on MBS
69354	Blood cultures 1 set of cultures	148,605	148,605	$60	$8,916,300
69318	Sputum cultures 1 or more tests on 1 or more specimens	132,213	132,213	$60	$7,932,780

Using the number of services requested for blood and sputum cultures, Table 18A, estimates the likely number of tests that may be requested for measurement of PCT. In estimating these figures it is assumed that one set of blood cultures will equate to one request for measurement of PCT. Multiple blood cultures, up to a maximum of three, may be ordered for each episode of suspected bacteremia but they attract different MBS item numbers. If following the PCT-guided algorithms used in the trials, multiple tests for PCT measurement may be ordered for each episode of suspected sepsis, with some studies requiring daily PCT measurements. Therefore, the number of blood cultures is likely to be an underestimate of the number of PCT tests that may be requested. Trying to extrapolate from the number of sputum cultures to the likely number of PCT tests, has not been attempted, as it is not likely to be meaningful because the relevant MBS item may refer to one test, multiple tests or multiple specimens.

From these estimates, the likely financial implications for the government of the listing of measurement of PCT for patients presenting to their GP with the signs and symptoms of LRTI may be approximately $8 million dollars per year. If the listing also includes patients with the signs and symptoms of sepsis, the likely financial implications may be an additional $9 million per year. The likely number of tests may be 283,290 or greater at a potential cost to the MBS of $17 million per year. This may be an underestimate as it is possible that multiple tests of PCT may be done for each episode of sepsis or LRTI to guide antibiotic therapy.

Key uncertainties

Key uncertainties

There were no key uncertainties around the evidence and conclusions for safety.

Overall conclusion with respect to comparative safety

A literature search found no reports that that related to studies that specifically investigated the safety of measurement of serum PCT. Given the nature of this intervention it is not anticipated that it will be associated with any safety issues.

Key uncertainties

The following uncertainties were noted with respect to the evidence concerning the use of measurement of PCT to guide antibiotic therapy in patients with suspected sepsis.

- The majority of studies conducted in the ED setting were not powered to answer the question: Were there any consequences for patients in reducing antibiotic therapy? The only study, Schuetz et al. (2009), that was powered to answer this question showed a non-significant increase in deaths and disease specific complications.

- Neither study conducted in the primary care setting was powered to address the question of whether there were any consequences in the form of relapse, hospitalisation or death from the reduction in antibiotic treatment.

- The patient populations for the studies conducted within ICU differed, within, and between studies with some studies including mainly medical patients only (Bouadma 2010, 90% medical), a mixture of surgical and medical patients (Stolz 2009, Nobre 2008, Jensen 2011)or, only surgical/multiple trauma patients (Svoboda 2007, Hochreiter 2008, Schroeder 2009). This difference in the underlying populations, makes summarising outcomes across the studies not necessarily meaningful, as other factors such as, surgery or blood transfusions can also be reasons for increases in PCT levels.

- The underlying rationale for the PCT-guided algorithm does not seem to be based on analytical sensitivity of the tests. The algorithm used, was mostly consistent across the studies (i.e., it was recommended by the company) but lower levels of PCT were used to indicate the need for antibiotics in the study by Kristoffersen (2009).

- It is unclear whether following a PCT-guided algorithm for initiating or ceasing antibiotic therapy will have consequences for patients, in terms of increased risk of death, as the majority of the studies, in the ICU setting, were not powered to answer this question. The one study that was powered to detect 28-day mortality, Jensen et al. (2011), reported no difference in survival, but did report concern regarding the need for more intensive organ related support, and prolonged admission to ICU, of patients in the PCT-guided arm.

- The corresponding obligatory guidelines, used alongside the PCT measurements, affected the rate at which antibiotics were prescribed. Guidelines that initiated antibiotics at lower levels of PCT (Kristoffersen 2009) resulted in more prescriptions in the PCT arm and those studies that initiated PCT at higher levels of PCT resulted in fewer prescriptions.

- Analytical sensitivity of the assays used in the reported studies, has been evaluated for patients in the ICU setting, but interpretative risk assessment criteria has only be done for PCT levels below 0.5 ng/ml or for levels above 2.0 ng/ml.

- The frequency at which PCT levels were obtained from hospitalised patients varied. Some studies undertook PCT readings daily while others only at the time that antibiotic therapy was being reviewed.

- The meaningfulness of comparison across the studies is limited due to high levels of heterogeneity observed in the pooled analysis. This is particularly true of the outcomes measuring the levels of prescribing of antibiotics and duration of antibiotic therapy.

- The data examined in the assessment is only from the ED, general practice and ICU settings. This is because it was in these clinical areas that the majority of randomised controlled trials were situated. The report did not examine evidence from other settings, such as paediatrics. These clinical areas would have been

examined if it were found that the evidence from the ED, general practice or ICU settings was of a robustness to justify examining the use of PCT in other settings. If there is a role for PCT it may plausibly be in very defined clinical circumstances but these clinical settings could not be identified because the published trials were underpowered to show unequivocally that measurement of PCT is effective, as used in the trials.

Overall conclusion with respect to comparative clinical effectiveness

Routine measurement of PCT, with corresponding obligatory guidelines for antimicrobial therapy, for patients presenting to the ED with query LRTI or exacerbation of chronic obstructive pulmonary disease (ECOPD), alongside clinical assessment and other measures of sepsis, usually resulted in a reduction in the use of antibiotics. However, only one of the trials set in the ED was powered to address the question of whether this reduction in antibiotic therapy had any consequences for patients, and it reported non-significant increases in mortality and disease specific complications. The routine use of a PCT test for every person with a query LRTI, in the emergency department, would result in a large number being requested. The available evidence does not justify the routine measurement of PCT and use of a PCT-guided algorithm for antimicrobial therapy in the ED, as used in these trials.

The routine measurement of PCT, with corresponding obligatory guidelines for antimicrobial therapy, as an indicator of sepsis alongside clinical assessment for patients in an ICU setting may not result in a reduction in antibiotic therapy. It was unclear whether following a PCT-guided algorithm for initiating or ceasing antibiotic therapy would have consequences for patients, as the majority of the studies in the ICU setting were not powered to answer this question. The one study that was powered to detect 28-day mortality reported no difference in survival, but did report that patients in the PCT-guided arm suffered increased rates of organ-related harm and had prolonged admission to ICU. The routine use of a PCT test in the ICU setting, often recommended on a daily basis, would result in a large number being requested. The available evidence does not justify the routine measurement of procalcitonin, and use of a PCT-guided algorithm for antimicrobial therapy in the ICU setting.

The routine measurement of PCT, with corresponding obligatory guidelines for antimicrobial therapy, for patients presenting to their GP with symptoms of respiratory tract infection (RTI), alongside clinical assessment, resulted in a reduction in the use of antibiotics in the two studies evaluated. However, neither of the trials was powered to measure any consequences to patients that may result from a reduction in antibiotic therapy. The routine use of a PCT test for every person who presents to their GP with the symptoms of RTI would result in a large number being requested. The evidence does not justify the routine measurement of PCT and use of a PCT-guided algorithm for antimicrobial therapy in the general practice setting.

Consistent information regarding the accuracy of levels of PCT needed to reliably differentiate between infectious and non-infectious SIRS appears to be lacking.

Introduction

The Medical Services Advisory Committee (MSAC) evaluates new and existing health technologies and procedures, for which funding is sought under the Medicare Benefits Scheme (MBS), in terms of their safety, effectiveness and cost effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

An application was made to MSAC by B.R.A.H.M.S Pty Ltd requesting public subsidy, via the MBS, of a commercial immunoluminometric assay (ILMA) used to determine the concentration of procalcitonin (PCT) in human serum and plasma for diagnosing life threatening infections and sepsis in patients and monitoring the course and control of antibiotic therapy. Although not directly specified in the application, the MBS listing implied by the application could be summarised as presented in Table 1.

Table 1: MBS descriptor implied by the application

Category 6: PATHOLOGY SERVICES
Quantitation in human serum or plasma by any method except reagent tablet or reagent strip (with or without reflectance meter) of procalcitonin-1 test
Fee $60.00 For comparison, the MBS fee, at 1 May 2011, for item 66500—quantitation of C-reactive protein—is $9.75.

An independent review of the assessment of a commercial ILMA used to determine the concentration of PCT in human serum and plasma for diagnosing life threatening infections and sepsis in patients and monitoring the course and control of antibiotic therapy is presented in this report.

This technology involves a measurement of PCT by a two-site immunoassay used to determine the concentration of PCT in human serum and plasma.

Consistent with MSAC's standard approach, the assessment provided in this report does not consider the merits of a specific commercial product. Instead, the report provides an assessment of the 'generic' product. This is appropriate because any relevant MBS item descriptor would describe the service in a generic manner and would not specify a particular proprietary product. This is to ensure that if other equivalent technologies enter the market (with regulatory approval) they would not require a separate MSAC assessment.

MSAC's Terms of Reference and membership are listed in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for the measurement of PCT in patients with the signs and symptoms of sepsis. The report is to inform a decision as to whether such a technology should be subsidised under the MBS.

Background

Intervention name

Measurement of Procalcitonin (PCT).

The technology

PCT, a glycoprotein, is a peptide precursor of the hormone calcitonin. However, the exact origin and mechanisms of PCT remain largely unknown. In contrast to calcitonin, which is produced in response to hormonal stimuli in neuroendocrine cells, mainly the parafollicular cells (C-cells) of the thyroid, PCT is produced in response to inflammation or infection in multiple tissues and cell types throughout the body (Muller et al. 2001). The ubiquitous release of PCT is thought to be induced either directly via microbial toxins (e.g., endotoxins) or indirectly via a humoral (e.g., interleukin-1, interleukin-2, interleukin-6 and tumour necrosis factor-α) or cell-mediated host response (Muller et al. 2001).

The normal serum level of PCT in healthy individuals aged ≥3 days is <0.05 ng/mL (below detection limit), with normal levels for neonates aged 0–48 hours given in Table 2.

Table 2: PCT reference ranges for neonates of 0–48 hours of age

Age in hours	PCT (ng/mL)
at birth	0.094
at 24 hours	2.47 (1.97–3.09)
at 48 hours	0.83 (0.67–1.02)

Source: Assumma et al. (2000)

In microbial infections and severe systemic inflammatory responses, the serum level of PCT markedly increases approximately three hours after a pro-inflammatory stimulus or bacterial induction, reaching maximum values after 6–8 hours (Maruna, Nedelnikova & Gurlich 2000). Serum levels have been shown to reach levels >0.1 ng/mL in localised infection such as lower respiratory tract infections (LRTIs) and between 10 and 100 ng/mL or greater in severe sepsis (Zeni, Viallon & Assicot 1994). The increase in serum PCT level in response to bacterial infection has been shown to correlate with the severity of the infection (Assicot et al. 1993; Whang et al. 1998) and with mortality (Whang et al. 1998).

Measured serum and plasma PCT levels are interpreted based on the clinical setting, the site and extent of infection and co-morbidities. Increased levels of PCT may not always be related to systemic bacterial infection; the level of PCT has also been shown to increase markedly in:

- neonates <48 hours of age (physiological elevation) (Chiesa et al. 1998).
- patients undergoing treatment with OKT3 antibodies and other drugs stimulating the release of pro-inflammatory cytokines (Meisner 2000).
- patients with invasive fungal infections or acute attacks of plasmodium falciparum malaria (Hollenstein et al. 2000).

- patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer or medullary C-cell carcinoma of the thyroid (Meisner 2000).
- patients with severe systemic inflammatory conditions such as inhalational injury (Nylen et al. 1992), pulmonary aspiration (Nylen et al. 1996), severe burns (Carsin et al. 1997; O'Neill et al. 1992), pancreatitis (Rau, Schilling & Beger 2004), heat stroke (Nylen et al. 1997), mesenteric infarction (Merle et al. 2004), multi-trauma (Sauerland et al. 2003), extensive surgery (Hammer et al. 2004; Meisner at al. 1998) and infections such as pneumonitis (Hollenstein et al. 1998).

The level of serum and plasma PCT can also be an indication of the resolve of a systemic infection. With an in-vivo half-life of 20–24 hours (Meisner 2000), PCT levels may be used to monitor the course and prognosis of clinically relevant bacterial infections and sepsis and to control the use of therapeutic interventions.

What is the test?

The measurement of PCT is a two-site immunoassay used to determine the concentration of PCT in human serum and plasma. All assays are based on the formation of a 'sandwich' antigen-antibody complex.

Currently there are five different commercial immunoassays available for quantitative determination of PCT concentrations, with the choice of assay dependent on the intended clinical use.

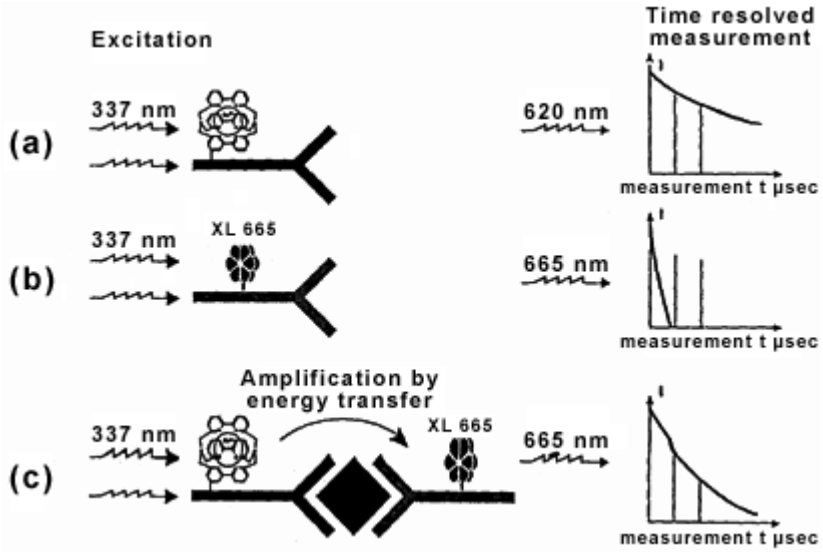
1) B.R.A.H.M.S PCT sensitive KRYPTOR
2) B.R.A.H.M.S PCT sensitive LIA
3) B.R.A.H.M.S PCT LIA
4) LIAISON® B.R.A.H.M.S PCT
5) B.R.A.H.M.S PCT-Q

In all assays, serum or plasma samples may be used. Sample size depends on the assay choice, ranging from 20 to 200 µL.

1) B.R.A.H.M.S PCT sensitive KRYPTOR

The B.R.A.H.M.S PCT sensitive KRYPTOR assay uses time-resolved-amplified-cryptate-emission technology, which is based on a non-radiative transfer of energy between two fluorescent tracers, a donor and an acceptor. The signal measured during the formation of the antigen-antibody 'sandwich' complex is accompanied by amplification and the intensity of the signal is proportional to the amount of PCT. As this assay is homogeneous, without the need for separation or washing, high concentration samples are detected in the first few seconds of incubation (the total incubation time is nineteen minutes). The measuring principle is shown in Figure 1.

Figure 1: Measuring principle of B.R.A.H.M.S PCT sensitive KRYPTOR



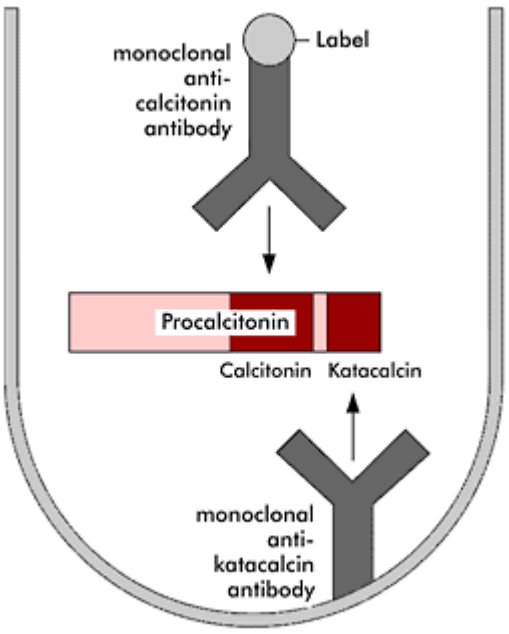
Source: B.R.A.H.M.S (2011)

This assay method does not require the construction of a standard curve. The normal serum and plasma PCT level in healthy individuals measured using this assay is 0.064 ng/mL (95% percentile).

2) B.R.A.H.M.S PCT sensitive LIA and 3) B.R.A.H.M.S PCT LIA

The B.R.A.H.M.S PCT sensitive LIA and B.R.A.H.M.S PCT LIA assays use a coated-tube technique to measure PCT. As depicted in Figure 2, two antigen-specific monoclonal antibodies that bind PCT at two different binding sites (the calcitonin and katacalcin segments) are added in excess. One antibody is fixed to the inner walls of the tube, and the other is labelled using a luminescent acridine derivative.

Figure 2: Measuring principle of B.R.A.H.M.S PCT sensitive LIA

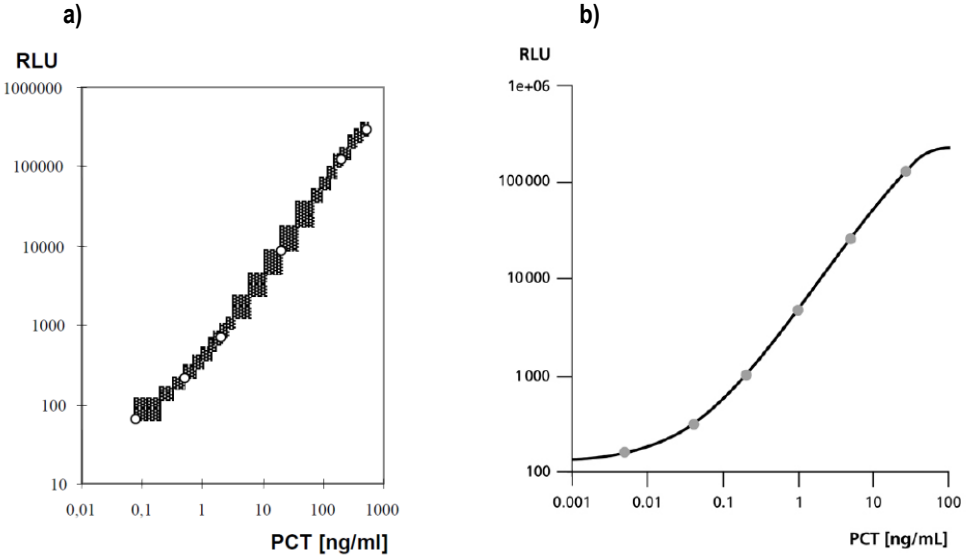


Source: B.R.A.H.M.S (2011)

Incubation time is two and a half hours for B.R.A.H.M.S PCT sensitive LIA and one hour for B.R.A.H.M.S PCT LIA. During the course of incubation, both antibodies react with PCT molecules to form 'sandwich' complexes. Consequently, the luminescence labelled antibody is bound to the inner surface of the tube. Once the reaction is complete, the excess tracer is completely removed from the tube by washing and is discarded.

The amount of residual tracer bound to the test tube wall is quantified by measuring the luminescence signal using a suitable luminometer. The intensity of the luminescence signal is directly proportional to the PCT concentration in the sample. After a standard curve has been established (see Figure 3), using standards with known antigen concentrations, calibrated against recombinant intact human PCT (B.R.A.H.M.S PCT sensitive LIA) or synthetic intact human PCT (B.R.A.H.M.S PCT LIA), the unknown PCT concentration in the patient sample can be quantitated by comparing the test value with the curve.

Figure 3: Example standard curves produced using a) B.R.A.H.M.S PCT LIA assay and b) B.R.A.H.M.S PCT sensitive LIA assay



Source: a) B.R.A.H.M.S (2004); b) B.R.A.H.M.S (2008a)

4) LIAISON® B·R·A·H·M·S PCT

LIAISON® B.R.A.H.M.S PCT is a two-site ILMA. Two different highly specific monoclonal antibodies are used for the coating of the solid phase (magnetic particles) and for the tracer. Incubation time is twenty minutes. The LIAISON® analyser automatically calculates the PCT concentration in each sample by means of a calibration curve, which is generated by a two-point calibration master-curve procedure. Recalibration is required every two weeks, after exchange of reagent integral or starter reagents or after servicing of the analyser.

5) B.R.A.H.M.S PCT-Q

B.R.A.H.M.S PCT-Q is a semi-quantitative immunochromatografic assay with results available after 30 minutes. The assay uses a monoclonal mouse anti-catacalcin antibody, conjugated with colloidal gold (tracer) and a polyclonal sheep anti-calcitonin antibody

(solid phase). The patient sample is applied to a test trip on which the tracer binds to the PCT in the sample and a marked antigen-antibody forms. This complex moves by means of capillarity through the test system and passes through the test band in which the marked antigen-antibody complex binds to the fixed anti-calcitonin antibodies and forms a 'sandwich' complex. A coloured band forms, with the colour intensity of the band directly proportional to the PCT concentration of the sample, given as a concentration range and read using a reference card.

Summary of assay characteristics

The assay characteristics and measurement ranges are summarised in Table 3.

Table 3: Measurement range of available PCT assays

Assay name	Assay characteristics	Measurement range	Use
B·R·A·H·M·S PCT sensitive KRYPTOR	High-sensitive, quantitative automated assay; B·R·A·H·M·S KRYP TOR system required; Incubation time: 19 min	0.06 (FAS), 50 ng/mL (direct measurement range) up to 1,000 ng/mL (extended measurement range)	Diagnosis and monitoring of clinically relevant bacterial infections and sepsis
B·R·A·H·M·S PCT sensitive LIA	High-sensitive, quantitative manual assay; Luminometer is required; Incubation time: 30 min + 2 h	0.05 (FAS), 20 ng/mL	
LIAISON® B·R·A·H·M·S PCT	Quantitative automated assay; LIAISON system required; Incubation time: 2 x 10 min	0.3 (FAS), 500 ng/mL	Diagnosis and monitoring of sepsis
B·R·A·H·M·S PCT LIA*	Quantitative manual assay; Luminometer is required; Incubation time: 1 h	0.3 (FAS), 500 ng/mL	
B·R·A·H·M·S PCT-Q	Semi-quantitative, rapid assay; No instrument required; Incubation time: 30 min	<0.5 ng/mL; 0.5-<2 ng/mL; 2-<10 ng/mL; ≥10 ng/mL	Rapid information for assessment of the probability of systemic infection (sepsis)

FAS— functional assay sensitivity; * Former product name: LUMItest®
Source: B.R.A.H.M.S (2008b)

Reference ranges and differential diagnosis

The following are reference ranges and clinical interpretations of measured PCT concentrations, adapted from the literature (Christ-Crain & Muller 2005), provided as a guide by B.R.A.H.M.S. The company notes this guidance is dependent on the clinical setting, the site and extent of infection, co-morbidities (e.g., immunosuppression) and the clinical implications drawn.

The clinical interpretation of measured PCT concentrations for the differential diagnosis of LRTIs is provided in Table 4.

Table 4: Differential diagnosis of LRTIs

PCT <0.1 ng/ml	Indicates absence of bacterial infection Use of antibiotics strongly discouraged, also in the presence of impaired pulmonary reserve in AECOPD
PCT >0.1 and <0.25 ng/ml	Bacterial infection unlikely The usage of antibiotics is discouraged
PCT >0.25 and <0.5 ng/ml	Bacterial infection is possible Advice to initiate antibiotic therapy
PCT >0.5 ng/ml	Suggestive of the presence of bacterial infection Antibiotic treatment strongly recommended

AECOPD— acute exacerbations of chronic obstructive pulmonary disease
Source: B.R.A.H.M.S (2011)

The clinical interpretation of measured PCT concentrations for the diagnosis of systemic bacterial infection/sepsis is provided in Table 5.

Table 5: Diagnosis of systemic bacterial infection and sepsis

PCT <0.5 ng/ml Local bacterial infection is possible Systemic infection (sepsis) is not likely	Caution: PCT levels below 0.5 ng/ml do not exclude an infection, because localised infections (without systemic signs) may be associated with such low levels If the PCT measurement is done very early after following bacterial challenge (usually <6 hours), these values may still be low In this case, PCT should be reassessed 6–24 hours later Low risk for progression to severe systemic infection (severe sepsis)
PCT >0.5 and <2 ng/ml Systemic infection (sepsis) is possible, but various conditions are known to induce PCT as well (see below)	Moderate risk for progression to severe systemic infection (severe sepsis) The patient should be closely monitored both clinically and by re-assessing PCT within 6–24 hours
PCT >2 and <10 ng/ml Systemic infection (sepsis) is likely, unless other causes are known	High risk for progression to severe systemic infection (severe sepsis)
PCT >10 ng/ml Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock	High likelihood of severe sepsis or septic shock

Source: B.R.A.H.M.S (2011)

A sensitive PCT assay that can precisely detect PCT concentrations at 0.1 ng/mL is required for the differential diagnosis of LRTI. B.R.A.H.M.S PCT-Q, LIA and LIAISON® are not suitable for this indication due to high functional sensitivity limits.

Analytical sensitivity

The United States Federal Drug Administration (FDA) has evaluated the safety and effectiveness of the B·R·A·H·M·S PCT sensitive KRYPTOR® and B·R·A·H·M·S PCT LIA assay (VIDAS® B.R.A.H.M.S PCT). These premarket reports are available in their 510K database (FDA 2010). The following information is from these reports.

B·R·A·H·M·S PCT sensitive KRYPTOR®

Based on Clinical and Laboratory Standards Institute (CLSI) testing, the analytic sensitivity of the B·R·A·H·M·S PCT sensitive KRYPTOR was determined to be 0.02 ng/ml and the functional assay sensitivity (FAS) was determined to be 0.06 ng/ml. In addition, the total precision ranges from 3.2 to 13.4% contingent variation (CV) and within run precision ranges from 1.0 to 13.6% CV(FDA 2010).

B.R.A.H.M.S PCT LIA

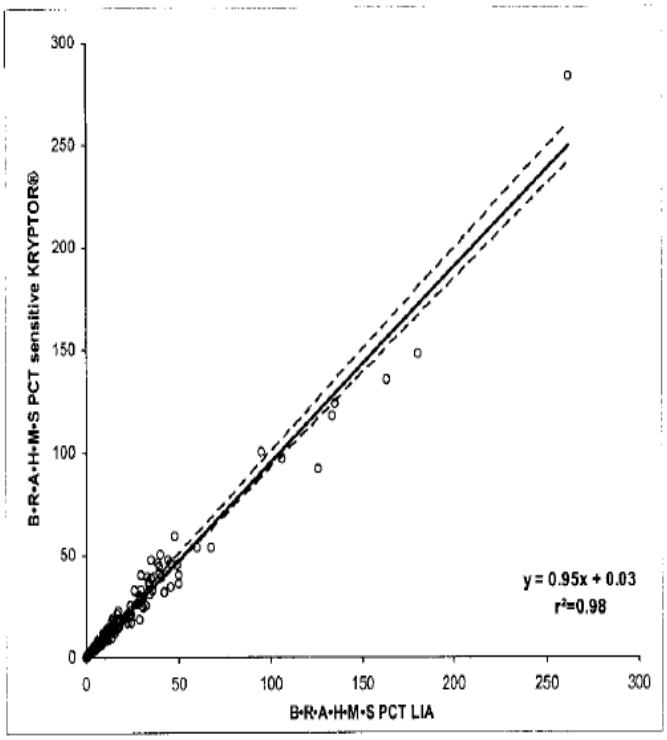
Based on NCCLS (now called CLSI) guidelines , the analytical sensitivity was determined to be 0.1 ng/ml and the functional assay sensitivity was determined to be 0.3 ng/ml. In addition, the total precision ranges from 5.3 to 16.6% CV and the within run precision ranges from 2.4 to 10% CV(FDA 2010).

Method comparison summary

The B·R·A·H·M·S PCT sensitive KRYPTOR® and B·R·A·H·M·S PCT LIA assay both detect PCT in human serum or plasma. A correlation study was performed, in accordance with NCCLS guidelines EP9-A 'Method comparison and Bias Estimation using Patient Samples (2002),' between the B·R·A·H·M·S PCT sensitive KRYPTOR® and B·R·A·H·M·S PCT LIA assay. There were 184 samples from three sites, all of which had B·R·A·H·M·S PCT LIA of 0.3 ng/ml (the FAS of B·R·A·H·M·S PCT LIA)

or higher and/or B·R·A·H·M·S PCT sensitive KRYPTOR® measurements of 0.06 ng/ml (the FAS of B·R·A·H·M·S PCT sensitive KRYPTOR®) or higher. Passing-Bablok analysis shows a nearly perfect correlation between the B·R·A·H·M·S PCT sensitive KRYPTOR® and B·R·A·H·M·S PCT LIA assay (see Figure 4).

Figure 4: Correlation graph for B·R·A·H·M·S PCT sensitive KRYPTOR® and B·R·A·H·M·S PCT LIA assay



Interference and cross reactivity

The FDA safety and effectiveness summaries (510K reports), based on CLSI testing, found the following substances not to affect the test performance of B·R·A·H·M·S PCT sensitive KRYPTOR® or B·R·A·H·M·S PCT LIA assay at concentrations reasonably and consistently found in clinical situations:

- Bilirubin
- Haemoglobin
- Triglycerides
- Albumin
- Substances that share amino acid sequences with PCT
- Drugs that are typically used for septic patients in intensive care units (ICUs)
- Drugs that may be commonly used in subjects at greater risk of developing community acquired pneumonia (CAP) than the general population, such as those with asthma and/or chronic obstructive pulmonary disease (COPD)

Interpretation of results

The B·R·A·H·M·S PCT sensitive KRYPTOR® is intended to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock. PCT should always be interpreted in the clinical context of the patient. Therefore, clinicians should use the PCT results in conjunction with other laboratory findings and clinical signs of the patients. Data support the following interpretative risk assessment criteria:

PCT levels **above 2.0 ng/ml** on the first day of ICU admission represent a high risk for progression to severe sepsis and/or septic shock.

PCT levels **below 0.5 ng/ml** on the first day of ICU admission represent a low risk for progression to severe sepsis and/or septic shock.

Note: PCT levels below 0.5 ng/ml do not exclude an infection, because localised infections (without systemic signs) may also be associated with such low levels. If the PCT measurement is done very early after the systemic infection process has started (usually <6 hours), these values may still be low.

As various non-infectious conditions are known to induce PCT as well, PCT levels between 0.5 ng/ml and 2.0 ng/ml should be reviewed carefully to take into account the specific clinical background and condition(s) of the individual patients.

In normal subjects, PCT concentrations are <0.1 ng/ml.

Intended purpose

The intended purpose of the measurement of PCT is to determine the concentration of PCT in human serum and plasma in patients suspected of bacterial infection.

Clinical need

Sepsis is a major cause of morbidity and mortality and the diagnosis of infection is essential to the success of antibiotic therapy and should be performed before commencement of therapy. Early diagnosis and assessment of the systemic inflammatory response to infection is crucial. However, there are certain limitations to the microbiological culture technique, concerning low sensitivity and the time until reliable culture results are available. There is a need for a timely laboratory marker to discriminate systemic inflammatory response syndrome (SIRS) from a non-infectious cause and sepsis.

Table 6 provides the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) definition for sepsis. These definitions includes four clinical entities SIRS, sepsis, severe sepsis and septic shock or multiple organ dysfunction syndrome. These currently used sepsis criteria are credited with improving the epidemiological data through the standardisation of the inclusion criteria in clinical studies (Herzum & Renz 2008).

Table 6: The ACCP/SCCM consensus conference definitions for sepsis

Sepsis degree	Criteria
SIRS Systemic inflammatory response syndrome	Systemic reaction to different agents, presenting two or more of the following symptoms: Body temperature >38° or <36°C Heart frequency >90/min Breath frequency >20/min or $PaCO_2$ <32 mm Hg White blood cell count >12,000/cu mm, <4,000/ cu mm, or >10% immature (band) forms
Sepsis	SIRS with proven infection or bacterial invasion of physiologically sterile tissue or body fluids
Severe sepsis	Sepsis with signs of organ failure, disturbed perfusion, metabolic acidosis, oliguria or neurological disorders
MOFs Multiple organ failure (septic shock)	Multiple organ failure with disseminated intravascular coagulation

The inflammatory cascade in response to an agent involves the expression and interaction of various humoral and cellular responses, complement, and cytokine cascades. Important mediators include platelet-activating factor, tumour necrosis factor-alpha and interleukins 1, 6, 8 and 10. The variable host reactivity, mirrored in the cytokine response, seems to play a major role in defining the prognosis of septic patients (Marty et al. 1994; Oberhoffer et al. 1999).

Micro-organisms initiate sepsis in different ways. Bacteria have a wide range of components that can injure the host and these components vary fundamentally. For instance, Gram-negative bacteria have endotoxins, or lipopolysaccharide, in their cell wall, which activates the hosts' complement and coagulation cascades and triggers inflammatory cytokine release. Gram-positive bacteria do not possess endotoxins but instead, many of them produce soluble exotoxins, which affect the host cell in various ways in order to facilitate bacterial spread (Cohen 2008). However, apart from ensuring the appropriate antibiotic is chosen, there is no difference in the way that a patient is treated. In the clinical picture, sepsis is a 'final common pathway' that results from activation of the host response to overwhelming infection; by the time it is recognised by the clinician it is no longer possible to differentiate the process that initiated it (Cohen 2008).

Sepsis, and its marked unbalancing of the immune system, in parallel to the subsequent activation of the host response, represents a major challenge to the intensive care therapy (Herzum & Renz 2008). While milder cases of sepsis often respond to simple treatments such as oxygen, a fluid bolus, and antibiotics, deterioration is unpredictable and mortality from severe sepsis remains high.

Epidemiology

Sepsis is a common condition associated with a high mortality rate and considerable healthcare resources. The epidemiology of sepsis and severe sepsis in Australia has been shown to be similar to that reported in North America and Europe (Sundararajan et al. 2005). A number of studies have estimated the incidence of sepsis in hospital and ICU admissions. These are detailed below.

- Between 1 July 1999 and 30 June 2003, Sundararajan et al. (2005) reported the incidence of sepsis in Victoria, Australia, using Victorian Admitted Episodes Dataset maintained by the Victorian State Department of Human Services, which compiles hospital data by individual private and public hospitals in the state of Victoria. The study identified 33,741 patients with sepsis within this period

(hospital incidence of 1.1%), 23.8% of whom received at least some of their care in an ICU. They reported that most patients with sepsis were originally admitted via an emergency department (ED). The overall hospital mortality for all sepsis (including severe) patients was 18.4%.

- Between 1 May 1999 and 31 July 1999, Finfer et al. (2004) investigated the incidence of severe sepsis in an adult population in 23 Australian and New Zealand ICUs and reported an incidence of 11.8 (95% CI 10.9–12.6) per 100 ICU admissions. The calculated annual incidence of severe sepsis in adult patients treated in Australian and New Zealand ICUs was 0.77 per 1,000 population. Of the study population (691 adults), 752 episodes of severe sepsis were diagnosed. The main sites of infection were pulmonary (50.3% of episodes), intra-abdominal (19.3%) and blood (10.1%). One hundred and eighty-three (26.5%) patients died in ICU, 224 (32.4%) died within 28 days and 259 (37.5%) died in hospital. The study reported that screened patients without sepsis had a median duration of ICU stay of 3 days and mortality of 15.8%; in patients with severe sepsis, the median duration of ICU stay increased to 6 days and mortality increased to 26.5%.

- Angus et al. (2001) estimated that in the United States, severe sepsis has a national incidence of 751,000 (3.0 cases per 1,000 population and 2.26 cases per 100 hospital discharges) of whom 383,000 (51.5%) received intensive care and an additional 130,000 (17.3%) were ventilated in an intermediate care unit or cared for in a coronary care unit. Mortality was reported to be 28.6%, increasing with age from 10% in children to 38.4% in those aged >85 years old. The average cost per case was reported to be $22,100 with an annual total cost of $16.7 billion nationally.

- Brun-Buisson et al. (1995) recorded 11,828 admissions to 170 ICUs during an eight-week study period in France. One thousand and sixty four episodes of clinically suspected severe sepsis were reported in 1052 patients (9% of admissions, 95% CI 8.5–9.5). A clinically identified source of infection with associated microbial documentation was found in 742 episodes (71%), resulting in an estimated incidence of documented severe sepsis of 6.3 (5% CI, 5.8–6.7) per 100 ICU admissions. Severe sepsis was community acquired in 48% (357) of episodes and hospital acquired (nonsocomial)in 52% (381) of episodes.

Mortality

Sepsis and related conditions are significant causes of morbidity and mortality, particularly in elderly, immunocompromised and critically ill patients (Angus et al. 2001). In the United States, severe sepsis is associated with as many deaths annually as those from acute myocardial infarction (Angus et al. 2001) and it was the tenth leading cause of death in 2005 (Kung et al. 2008).

Mortality is dependent on disease progression down the sepsis pathway and development of complications. Overall, hospital mortality has been shown to increase from 3% in patients with no SIRS, to 10–16% in patients with sepsis (Rangel-Frausto et al. 1995; Sundararajan et al. 2005), 20–37% in patients with severe sepsis (Angus et al. 2001; Finfer et al. 2004; Rangel-Frausto et al. 1995; Sundararajan et al. 2005) and 46% in patients with septic shock (Rangel-Frausto et al. 1995). ICU mortality has been reported to be 10% for patients with sepsis (Sundararajan et al. 2005), 26–34% in patients with severe sepsis (Angus et al. 2001; Finfer et al. 2004; Sundararajan et al. 2005; Vincent & Marshall 2008) and 54% in patients with septic shock (Vincent & Marshall 2008). Mortality rates for

patients with either severe sepsis or septic shock have been reported to be 36–59% (hospital mortality) and 27–56% (ICU mortality) (Brun-Buisson et al. 1995; Vincent & Marshall 2008). It should be noted that all figures represent overall mortality rate; the mortality rate directly attributable to the infections or systemic inflammatory responses is unknown (Rangel-Frausto et al. 1995).

Lower respiratory tract infection

LRTI is a term used mainly to describe CAP, but also includes acute bronchitis and lung abscess. CAP is pneumonia contracted in the community at large, as distinguished from that acquired nosocomially or in a nursing or long-term care facility. The signs and symptoms of CAP include fever >38ºC, raised respiratory rate, focal chest signs and shortness of breath, cough, chest pain (pleuritic), confusion and rigors or night sweats. Similar symptoms may be caused by acute bronchitis and a variety of non-infectious diseases. It is important to assess whether the symptoms are caused by an infection (bacterial or viral) or by another non-infectious disorder such as asthma, COPD, heart failure or lung infarction. The main reason for detecting microbiological causes of symptoms is firstly to select patients who could benefit from antibiotic treatment and secondly to enable therapy with narrow-spectrum antibiotics to contain bacterial resistance, side effects and costs (Woodhead et al. 2005). LRTI has a high burden of morbidity and mortality (File et al. 2004), particularly in the elderly and those associated with risk factors for resistant pathogens (Xu et al. 2010). A large proportion of patients with LRTI do not benefit from antimicrobial treatment. In Australia, primary care consultations for acute bronchitis are common (3.5 per 100 consultations), whereas primary care consultations for CAP are approximately two per 1,000 population per year.

Diagnosis of CAP is difficult based solely on clinically examination, as symptoms in most patients presenting to primary care physicians may be absent or less pronounced. A chest x-ray is usually required for definitive diagnosis. The most frequent cause of CAP is *streptococcus pneumonia* (Charles et al. 2008; Fang et al. 1990; Lim et al. 1989).

Antibiotic treatment is usually continued for 5–10 days. The Pneumonia Severity Index (PSI) has been developed to group patients with CAP into one of five classes to determine which patients require hospital admission and predict 30-day mortality. The classes range from 0.1% (risk class I) through to 27% (risk class V) (Fine et al. 1997). The PSI is recommended by the Australian Therapeutic Guidelines: Antibiotic (2003). Predictor variables include demographics, coexisting illnesses and physical examination, laboratory and radiologic findings. Treatment is based on the PSI class and therapeutic guidelines.

The Australian CAP study of 885 episodes of CAP presenting to EDs found that 34.0% of episodes were class IV, 19.5% class V, 18.2% class III, 15.8% class II and 12.4% class I (Xu et al. 2010). The 30-day mortality rate was 5.6%. The study found that 26.9% of episodes had COPD as co-morbidity and that mechanical ventilation or vasopressor support was required in 10.6% of episodes.

Mortality rate among outpatients is low, but for hospitalised patients it is between 10 and 25% (Bartlett & Mundy 1995). A meta-analysis of CAP prognosis and outcomes reported overall mortality to be 13.7% and highly dependent on the type of patients in the study cohort (Fine et al. 1996). Patient mortality was lowest in hospitalised and ambulatory patients (5.1%), increasing in hospitalised only (13.5%), elderly (17.6%), bacteremic (19.6%), nursing home (30.8%) and ICU patients (36.5%) (Fine et al. 1996). Poor prognostic factors in patients with CAP included congestive heart failure, alcohol abuse, diabetes mellitus, immunosuppression, neoplastic disease, coronary artery disease

and neurologic disease (Fine et al. 1997). Microbial etiology has also been shown to be associated with mortality, with mortality highest in cases of pneumonia due to Gram-negative enteric bacilli (Ruiz et al. 1999).

In 2008–09, Australia had 54,970 principal diagnoses of pneumonia—organism unspecified (J18), with overnight acute separations—in public and private hospitals (ICD-10-AM grouping). Of these, 45,768 were in public hospitals and 9,202 were in private hospitals (AIHW 2010). There were a total of 52,672 principal diagnoses of other COPDs (J44), 45,164 of which were in public hospitals, with the remaining 4,508 in private hospitals (AIHW 2010).

COPD is characterised by airflow limitation that is not fully reversible. The progressive and relentless loss of lung function is caused by emphysema, due to the destruction of lung parenchyma and by the narrowing of small airways as a result of chronic inflammation, fibrosis and loss of elastic recoil. This results in progressive airflow limitation, air trapping and progressive shortness of breath on exertion (Barnes 2007). Pneumonia is an important complication of COPD, often occurring after treatment for exacerbation of chronic obstructive pulmonary disease (ECOPD) (Calverley et al. 2011).

Patients suffering from acute bronchitis present with bronchial obstruction and inflammation. It is defined by an acute cough of less than fourteen days duration with at least one other respiratory tract symptom, when there is no other obvious cause (e.g., asthma, sinusitis, COPD).

Antibiotics are not recommended for acute bronchitis as it is predominately of viral origin (Christiansen 1996); most episodes are self-limiting, lasting between 1–3 weeks and only symptomatic or causal treatment is required (Woodhead et al. 2005). Despite this, acute bronchitis is often treated with antibiotics (Stocks et al. 2004). In 2002, it was reported that in Australian general practitioners (GPs), the rate of antibiotic prescribing for acute bronchitis was 75.7% (95% CI 71.8–79.6) (Stocks et al. 2004). Antibiotic treatment should only be considered in patients with LRTI with suspected or definite pneumonia, selected exacerbations of COPD, cardiac failure, insulin-dependent diabetes mellitus or a serious neurological disorder (i.e., stroke) or when they are aged >75 years and have a fever (Woodhead et al. 2005).

The Bettering the Evaluation and Care of Health (BEACH) study (FRMC 2011) is a national study of GP activity in primary care in Australia, in which a random sample of approximately 1,000 GPs provide details for 100 consecutive GP–patient encounters. Table 7Table 7 reports the number of individual acute bronchitis/bronchiolitis and COPD problems managed by 930 primary care physicians in Australia in 2006–07 (Britt et al. 2009). Of the 2,047 acute bronchitis/bronchiolitis episodes managed, 1,476 were newly managed problems. Overall, acute bronchitis/bronchiolitis was the twelfth most frequently managed problem in 2006–07, among the surveyed population. However, it should be noted that further data on COPD is not available as only the 30 most frequently managed problems are reported. COPD was the thirteenth most frequently managed chronic problem in 2006–07. Table 7Table 7 presents the findings from the BEACH study.

Table 7: Number of individual acute problems managed by primary care physicians, 2006–07

Problem managed	Number	Per cent of total problems (n=136,333)	Rate per 100 encounters (n=91,805)	95% LCL	95% UCL
Acute bronchitis/bronchiolitis	2,047	1.5	2.2	2.1	2.4
Chronic obstructive pulmonary disease	778	0.6	0.8	0.8	0.9

LCL—lower confidence limit; UCL—upper confidence limit
Source: Britt et al. (2009)

Antibiotic therapy

The inappropriate use of antibiotics is believed to be a primary cause of the spread of antibiotic resistant bacteria. *Streptococcus pneumoniae* is the most frequent cause of CAP and the emergence of resistance in the drugs used to treat infections caused by *S. pneumoniae* is of public health significance. Between 1 January 1990 and 31 July 2000, a study of 2,265 unique *S. pneumoniae* specimens in the South Western Sydney Area Health Service underwent susceptibility testing (1,312 from respiratory tract) and revealed that resistance (intermediate and high) to penicillin steadily increased, reaching 35% in 2000, for specimens from sites other than cerebrospinal fluid (CSF) and blood cultures (Gosbell & Neville 2000).

It is recommended that unnecessary exposure to antibiotics be minimised and that they only be prescribed when an infection is serious and likely to respond to treatment (Ferguson 2004). Efforts to decrease the excess use of antibiotics are an essential step in combating the increased incidence of antibiotic resistant micro-organisms (Guillemot & Courvalin 2001). It is proposed that use of PCT could improve the diagnosis of LRTI and sepsis, and be used to monitor both the progression and prognosis of the bacterial infections. Antibiotic treatment based on PCT values is proposed using empirical rules to guide antibiotic use and duration of treatment, potentially resulting in a decrease in the duration of antibiotic therapy (Tang et al. 2009).

Antibiotic use in the community

The number of prescriptions written for antibiotics in Australia has reportedly peaked, declining from 26.5 million in 1993–94 to just less than 24 million in 1998. Prior to 1994, the use of antibiotics in Australia was higher than in most developed counties (Donovan 2001). Between 1990 and 1995, there was little change in the level of antibiotics dispensed through Australian community pharmacies, with an estimated 24.7 defined daily doses (DDDs) per 1,000 population per day dispensed in 1990, and 24.8 DDDs per 1,000 population per day dispensed in 1995 (McManus et al. 1997).

Table 8 reports the prescription counts for anti-infectives for systemic use as reported by Australian Statistics on Medicines 2007 (Robertson & Vanna 2009). Figures in this table show that even as late as 2006, levels of antibiotic use were less than reported in 1993–94. The reported counts include prescriptions for antibacterials, antimycotics, antimycobacterials, antivirals and vaccines.

Table 8: Prescription counts for anti-infectives for systemic use

Source	2005	2006	2007
PBS/RPBS	12,823,542	12,631,052	12,882,652
Estimated non-subsidised (survey)	11,431,499	11,437,566	14,245,150
Total	24,255,041	24,068,618	27,127,802

PBS— Pharmaceutical Benefits Scheme; RPBS—Repatriation Pharmaceutical Benefits Scheme
Source: Robertson and Vanna (2009)

The BEACH study (FMRC 2011) reported that three of five of the most frequently prescribed medications in 2006–07 were antibiotics (Britt et al. 2009). Reported at the Coding Atlas of Pharmaceutical Substances generic level, they are listed in Table 9.

Table 9: Most frequently prescribed medications for CAPS generic level, 2006–07

Generic medication	Number	Per cent of prescriptions (%) (N=76,430)	Rate per 100 encounters (N=91,805)	95% LCL	95% UCL
Amoxycillin	3,041	4.0	3.3	3.0	3.6
Cephalexin	2,146	2.8	2.3	2.2	2.5
Amoxycillin-potassium clavulanate	1,558	2.0	1.7	1.5	1.9

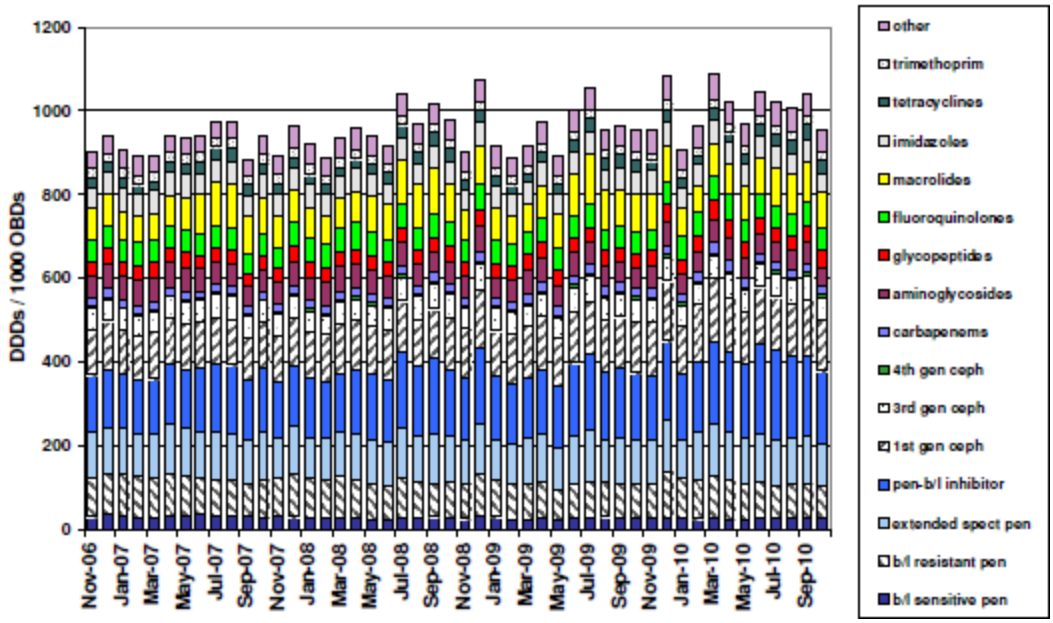
LCL—lower confidence limit; UCL—upper confidence limit
Source: Britt et al. (2009)

In 2006–07, the BEACH study (FMCR 2011) reported that 14,843 anti-infectives for systemic use were prescribed by 930 GPs, representing 19.4% of prescriptions and a rate of 16.2 per 100 encounters (95% LCL 15.6, 95% UCL 16.8).

Antibiotic use in hospitals

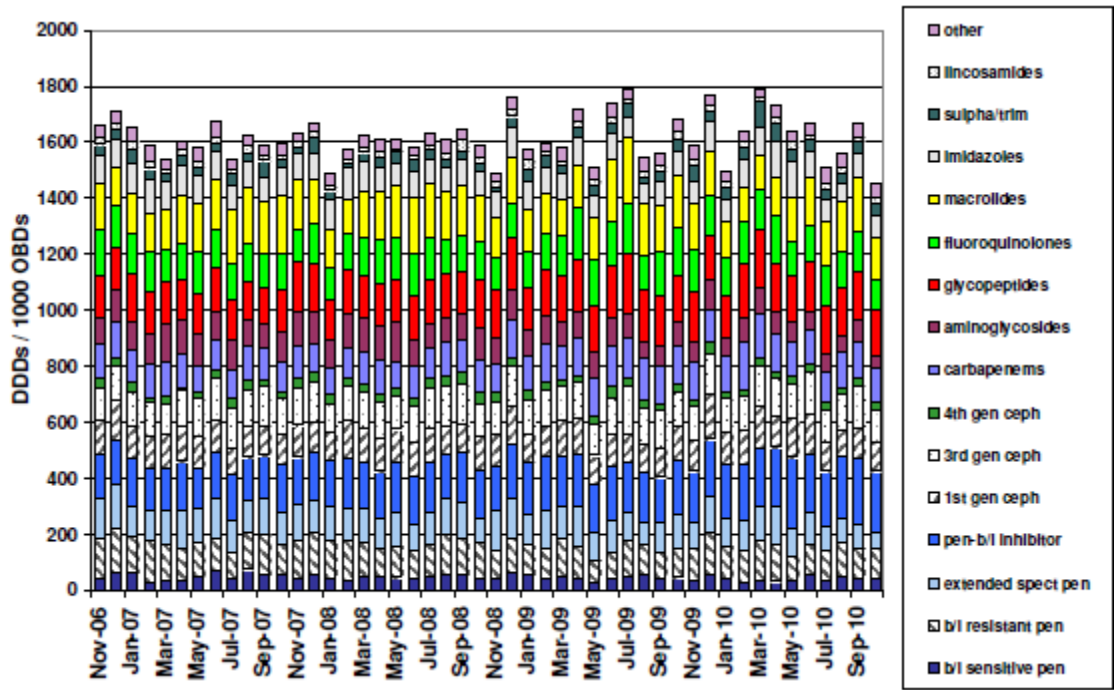
Since July 2004, the National Antimicrobial Utilisation Surveillance Program has collected ongoing data on antimicrobial utilisation in adults in Australian tertiary referral hospitals. Twenty-six public hospitals and one large private hospital contribute data. The antimicrobial utilisation rates are calculated using the number of DDDs of the antimicrobial agent or class consumed each month per 1,000 occupied bed days using the averaged data for all contributing hospitals. The total hospital antimicrobial use and total ICU antimicrobial use by class is shown in Figure 5 and Figure 6.

Figure 5: Total hospital antimicrobial use for all classes



Source: Copland & McNeil (2010)

Figure 6: Total ICU antimicrobial use by all contributors for all classes



Source: Copland & McNeil (2010)

In 1994, it was reported that hospitals accounted for only 7% of total retail sales of oral antibiotics in Australia (McManus et al. 1997).

Problems with the use of antibiotics

Adverse reactions

Adverse drug events (ADEs) associated with antibiotic use range from fever and nausea to major allergic reactions, including photodermatitis and anaphylaxis. ADEs are a significant cause of hospital admissions, responsible for an estimated 2.5% of ED visits for unintentional injuries in the US (2004–05), with 6.7% of those visits leading to hospitalisation. Antibiotics are commonly implicated in ADEs, it is estimated thatfor one in every eight ADEs treated in EDs antibiotics were implicated either alone or in combination with other drugs (Budnitz et al. 2006).

In Australia, 10.8% (249) of hospital admissions in 1992 across 28 hospitals in NSW and SA were associated with an ADE. Of these, 12.9% were associated with antibiotics (31.8% from an unknown drug type). Thirteen per cent of these cases were associated with permanent disability and 40% with high preventability. The most common reasons for drug-related injuries were errors in the method of use or dose, the drug being used inappropriately and inadequate monitoring of drug levels or other follow-up (Wilson et al. 1995).

Clinical need for monitoring antibiotic use

The effectiveness of many life-saving antibiotics is being undermined by the emergence of antibiotic resistance. Concern over this has translated into action by governments in many countries. In 2000, the Commonwealth Government response to the 1997 report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (DHA 2000) was an antimicrobial resistance risk-management program aimed at minimising the impact of antimicrobial resistance by:

- reducing the consumption of antibiotics in animals and humans in Australia;
- increasing the evidence base to enhance policy and interventions for the improper use of antibiotics, antimicrobial resistant infections and the transmission of resistant genes and bacteria;
- developing improvements to infection control and risk-management;
- improving awareness and education among professional groups and the community regarding antimicrobial resistance; and
- developing strategies for ongoing vigilance, early warnings and the national response to antimicrobial resistance.

Three major approaches are advocated to combat bacterial resistance: (1) develop new antibiotics to treat resistant organisms; (2) vaccinate to prevent infections; and (3) improve the use of antibiotics.

Improving the use of antibiotics means that antibiotics are only prescribed to patients with known or suspected bacterial infections (Scheld 2003) and that the antimicrobial agent chosen is the most narrow spectrum agent with optimal activity against the suspected pathogens at the dose and dosing frequency that maximises its effectiveness (Lieberman 2003).

Antibiotics are frequently used to treat acute respiratory infections, which are generally self-limiting infections.

A study of 51 Victorian hospitals (42 public and nine private) between 8 September and 14 September 1999, inclusive, reported on the use of ceftriaxone and cefotaxime (CEFX) and concordance with national antibiotic guidelines (Robertson et al. 2002). The

indication for use of CEFX was concordant with national guidelines in only 27% (174/653) of patients. A concordance of 29% (78/273) was found for patients with community acquired respiratory tract infection (RTI), dropping to only 10% (8/79) for patients treated for hospital-acquired RTI. The study reported that the proportion of patients treated in concordance with guideline recommendations differed significantly between hospitals, with concordance significantly lower in private hospitals.

There is widespread prescribing of antibiotics for RTIs, especially for those caused by viruses. From a sample of 33,203 GP–patient encounters, recorded in the August–September 1994 audit of the TREND project, in which 11.6% of encounters were for upper RTI/pharyngitis and 1.2% were for influenza (McManus et al. 1997), it was found that an antibiotic prescription was recorded in 57% of new urban cases of upper RTI/pharyngitis and in 73% of rural cases for the same condition. For influenza without pneumonia, antibiotics were prescribed in 30% of new urban cases and in 62% of rural patient encounters (McManus et al. 1997). The TREND project did not evaluate whether the prescription was only to be filled under certain conditions (e.g., if symptoms had not improved after a certain interval) so these figures may potentially be misleading as they do not reflect actual antibiotic use in these conditions.

Existing procedures/tests

Routine diagnostic investigations currently utilised for diagnosing severe bacterial infection and/or sepsis, directly and indirectly are summarised below.

Direct tests

- Blood culture
- Microscopy and culture (M&C) (e.g., urine, sputum and CSF)

Indirect tests

- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- White cell count (WCC) and differential
- Chest x-ray

Blood culture

Blood cultures are used to detect and identify the presence of bacteria or yeasts in the blood when a patient has the signs and/or symptoms of sepsis. Multiple samples of blood are taken from separate sites through venepuncture and immediately inoculated into appropriate media supplied by the laboratory. Organisms are identified by Gram stain, colony appearance after subculture to solid media and biochemical and/or antigen tests. Most pathogens grow within 1–2 days, with the Gram stain appearance guiding the initial choice of antibiotics, which may require modification after identification and antibiotic susceptibility testing. A preliminary report is usually available after one day, which will inform whether a positive result has been obtained, and if so, the results of the Gram stain. A second preliminary report may include a description of the bacteria growing on the subculture and the final report, which includes complete identification of any bacteria found and a list of the antibiotics to which the bacteria is sensitive, is usually reported after 5–7 days. Incubation is usually for 5–7 days before a negative result is reported.

Microscopy and culture

Sputum M&C is used to detect and identify the presence of respiratory bacteria or fungi in sputum. Gram staining and aerobic and mycobacterial cultures are performed on the sputum sample, expectorated, induced or taken via an endotracheal tube. Sputum M&C is used in the investigation of pneumonia, particularly when severe, appearing in an immunocompromised patient or causing exacerbations of respiratory symptoms in patients with cystic fibrosis or bronchiectasis.

Urine M&C is used to detect and identify bacteria and yeast in the urine and to detect the presence of red or white cells. In the context of this assessment, it is used in the investigation of renal involvement in systemic disease and unexplained fever. Any micro-organisms present in the urine sample will usually grow within 1–2 days, after which a negative result is reported. Gram staining is performed on any bacteria present.

CSF M&C is used in the diagnosis of bacterial or fungal meningitis and encephalitis. A CSF sample undergoes macroscopic inspection including microscopy of wet film and WCC, and as appropriate, Gram staining and bacterial cultures. The WCC is increased when there is inflammation of the central nervous system, with bacterial infections usually associated with the presence of neutrophils. Gram staining and bacterial cultures are used to detect and identify the presence of any micro-organisms.

C-reactive protein

CRP is produced by the liver during an inflammatory reaction and is therefore a serological marker of inflammation. CRP, in the context of this assessment is used for the assessment of acute phase reaction in inflammatory and infective disorders and in monitoring disease activity and developing infection. Blood levels start to rise approximately six hours after stimulation and peak at approximately 48 hours. CRP is a more sensitive early indicator of an acute phase response than ESR and returns towards normal values more rapidly with improvement of the disease.

Erythrocyte sedimentation rate

ESR is the rate at which red blood cells sediment in a period of one hour. This rate is increased in acute and chronic inflammatory disease. It is a non-specific indicator of inflammation and is affected by other conditions besides inflammation; it is therefore typically used in conjunction with other tests.

White cell count and differential

WCC and differential is the count of individual leucocytes (white blood cells) given as an absolute value x 10^9/L. It is performed by microscopic examination of stained blood film, recording the identity of 100 leucocytes, or by automated haematology analyser. Five types of white cells are normally found in the circulating blood: eosinophils, basophils, neutrophils, lymphocytes and monocytes. A high WCC can be an indicator of bacterial infection or inflammation. Specifically, raised neutrophils or monocytes may indicate bacterial infection.

Chest x-ray

Chest x-rays can be used to visualise any abnormalities of the lung, which may indicate infection, including nodules (discrete opacity in the lung) and cavities.

Marketing status of technology

The test for the measurement of PCT is listed, but not registered, with the Australian Therapeutic Goods Administration as 'B.R.A.H.M.S DYNOtest' or 'B.R.A.H.M.S LUMItest' kits (ARTG 26781). At the time of application, in-vitro diagnostic medical devices (IVDs) were exempt from pre-market regulatory scrutiny under the Therapeutic Goods Act 1989.

The new Medical Devices Amendment Regulations (DHA, 2010), which commenced on 1 July 2010, implemented a new regulatory framework that incorporates IVDs under chapter 4 of Therapeutic Goods Act 1989. A four-year transition period from the current to the new regulatory framework for IVDs has been provided. IVDs that are currently listed, registered or exempt must be included prior to the end of the transition period.

Current reimbursement arrangements

Relevant existing tests that are included on the MBS include blood cultures and CRP. Table 10 provides a list of relevant MBS items.

Table 10: MBS items of relevant diagnostic investigations

Item	Item description	Schedule fee	75% benefit	85% benefit
Blood tests				
66500	Quantitation in serum, plasma, urine or other body fluid (except amniotic fluid), by any method except reagent tablet or reagent strip (with or without reflectance meter) of: acid phosphatase, alanine aminotransferase, albumin, alkaline phosphatase, ammonia, amylase, aspartate aminotransferase, bicarbonate, bilirubin (total), bilirubin (any fractions), C-reactive protein, calcium (total or corrected for albumin), chloride, creatine kinase, creatinine, gamma glutamyl transferase, globulin, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, sodium, total protein, total cholesterol, triglycerides, urate or urea - 1 test	$9.75	$7.35	$8.30
65060	Haemoglobin, erythrocyte sedimentation rate, blood viscosity - 1 or more tests	$7.90	$25.50	$28.90
73802	Leucocyte count, erythrocyte sedimentation rate, examination of blood film (including differential leucocyte count), haemoglobin, haematocrit or erythrocyte count - 1 test	$4.60	$3.45	$3.95
Microscopy and culture				
69354	Blood culture for pathogenic micro-organisms (other than viruses), including sub-cultures and (if performed): a) identification of any cultured pathogen; and b) necessary antibiotic susceptibility testing, to a maximum of 3 sets of cultures - 1 set of cultures	$30.95	$23.25	$26.35
69357	2 sets of cultures described in 69354	$61.85	$46.40	$52.60
69360	3 sets of cultures described in 69354	$92.80	$69.60	$78.90
69318	Microscopy and culture to detect pathogenic micro-organisms from specimens of sputum (except when part of items 69324, 69327 and 69330), including (if performed): a) pathogen identification and antibiotic susceptibility testing; or b) a service described in items 69300, 69303, 69306 and 69312. 1 or more tests on 1 or more specimens	$34.00	$25.50	$28.90
69333	Urine examination (including serial examination) by any means other than simple culture by dip slide, including: a) cell count; b) culture; c) colony count; d) (if performed) stained preparations; e) (if performed) identification of cultured pathogens; f) (if performed) antibiotic susceptibility testing; and g) (if performed) examination for pH, specific gravity, blood, albumin, urobilinogen, sugar, acetone or bile salts	$20.70	$15.55	$17.60
69321	Microscopy and culture of postoperative wounds, aspirates of body cavities, synovial fluid, CSF or operative or biopsy specimens, for the presence of pathogenic micro-organisms involving aerobic and anaerobic cultures and the use of different culture media, and including (if performed): a) pathogen identification and antibiotic susceptibility testing; or b) a service described in item 69300, 69303, 69306, 69312 or 69318; specimens from 1 or more sites	$48.45	$36.35	$41.20
Chest x-ray				
58500	Chest (lung fields) by direct radiography (NR) Bulk bill incentive	$35.35	$26.55	$30.05
58503	Chest (lung fields) by direct radiography (R) Bulk bill incentive	$47.15	$35.40	$40.10

Source: DHA (2011)

Approach to assessment

Objective

To carry out a structured assessment of the following diagnostic test: measurement of PCT by ILMA to determine the concentration of PCT in human serum and plasma, based on a consideration of:

- the clinical need for the technology;
- the clinical effectiveness of the technology;
- the safety of the technology; and
- economic considerations.

Clinical decision pathway

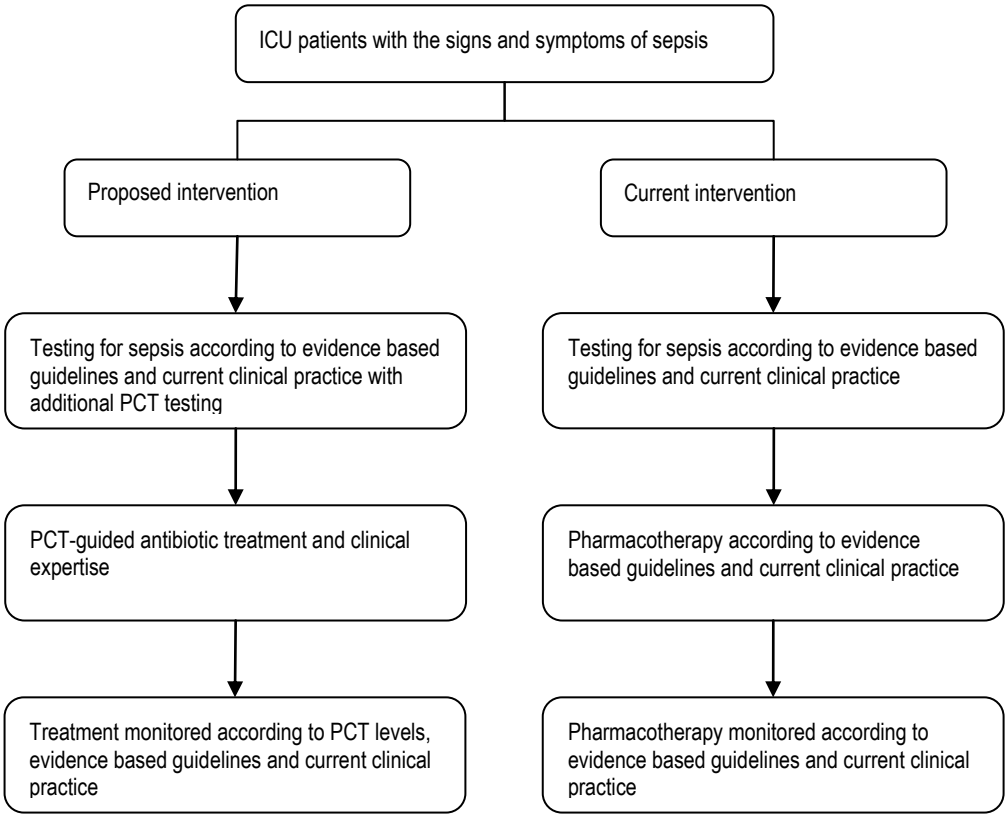
The Advisory Panel advised that the populations who have the greatest capacity to benefit from the measurement of PCT include:

1. patients in an ICU who have the signs and symptoms of sepsis; and
2. patients who present to a GP or ED with the signs and symptoms of LRTI.

The population in an ICU who are at risk of sepsis is distinguished from patients who present to a GP or ED with the signs and symptoms of LRTI because the clinical management of the former group of patients differs from that of the latter.

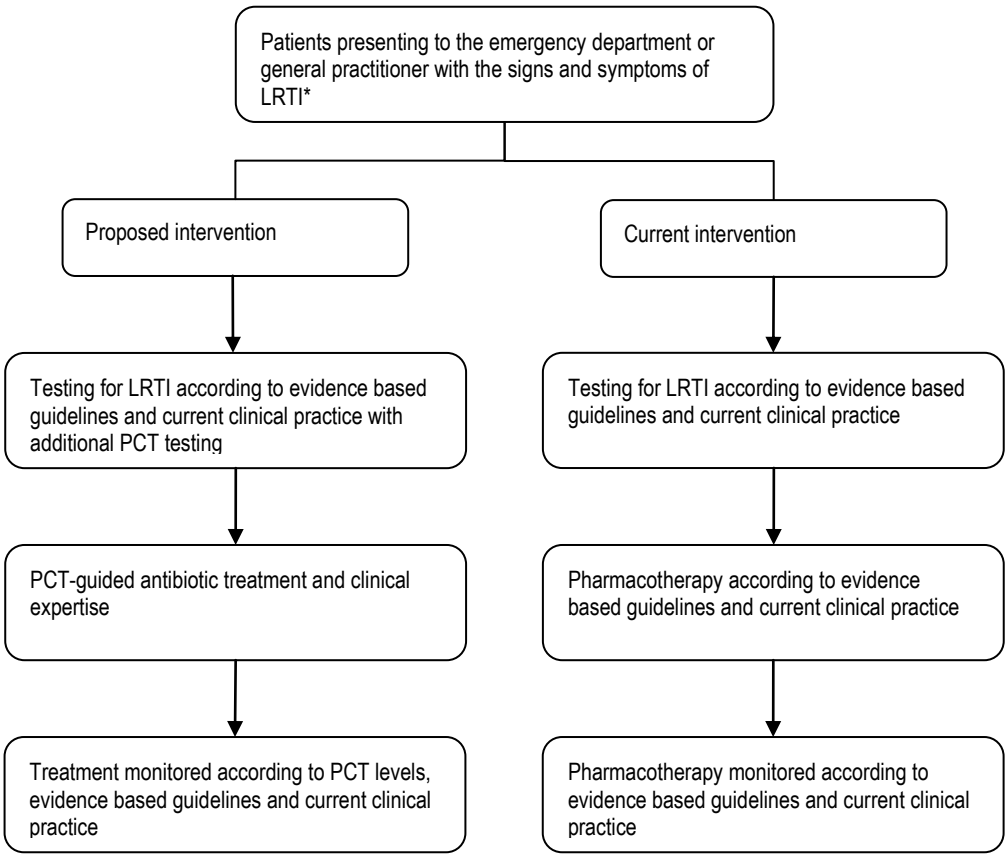
Typical management algorithms for both populations are presented in Figure 7 and Figure 8. For each population, the clinical decision is a scenario where the measurement of PCT is not available (the current scenario) and the clinical decision is a scenario where the measurement of PCT is available (the proposed scenario) is presented.

Figure 7: Clinical decision tree for patients suspected of, or with, sepsis in an ICU



NOTE: Guided antibiotic treatment may refer to initiation alone or initiation and cessation of antibiotic treatment.

Figure 8: Clinical decision tree for diagnosis of LRTI in a patient presenting to a general practitioner or emergency department



NOTE: Guided antibiotic treatment may refer to initiation alone or initiation and cessation of antibiotic treatment.

Comparator

The appropriate comparator for an assessment of a technology by MSAC is the test or procedure most likely to be replaced in practice if the technology under consideration were to be made available.

For patients in an ICU who have the signs and symptoms of sepsis, and patients who present to a GP or ED with the signs and symptoms of LRTI, the measurement of PCT is not likely to be used in isolation for decision making. It is recommended that PCT should always be interpreted in the clinical context of the patient and the PCT results used in conjunction with other laboratory findings.

It was considered that the use of the measurement of PCT is unlikely to replace any of the currently used biological markers of infection to any substantial degree and would not be used in isolation for decision making.

The comparator assumed to be relevant to the assessment of the measurement of PCT is therefore current practice, or 'no use of the measurement of PCT'.

The reference standard

The accuracy of a diagnostic technology is typically assessed by comparing the results generated by that technology with the results generated by an accepted reference standard.

It was considered important to present evidence of the diagnostic accuracy of the measurement of PCT because there may be significant cause of false positives (e.g., in patients with inflammatory conditions) or false negatives (e.g., in immunocompromised patients) that may need to be considered by clinicians.

Bacterial culture is considered to be the best method of diagnosis of infection. Therefore, blood culture positive for a pathogenic organism will be used in the report as the reference standard to determine the sensitivity of the test. In relation to the assessment of the diagnostic accuracy of the measurement of PCT in assessing the presence of a bacterial infection, positive blood cultures from a bacterially proven sepsis population will be used as the reference standard to determine the sensitivity of the test.

However, it is important to acknowledge that this standard may not represent a 'gold standard' due to the sensitivity of blood cultures in the presence of blood stream infection and the need for repeat cultures.

Research questions

The research question addressed by this assessment is:

Will the management that involves the use of measurement of PCT to determine the presence of a bacterial infection and to guide antibiotic therapy, compared with current management excluding this test, result in an improvement in quality-adjusted survival for:

1. patients who have the signs and symptoms of sepsis in an ICU; and
2. patients who present to their GP or ED with a suspected LRTI.

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews to inform the assessment of measurement of PCT as a means of determining bacterial infection and guiding antibiotic therapy.

Table 11Table 11 lists the electronic databases searched (and grey literature) and the period covered by the searches.

Table 11: Electronic databases searched

Database	Period covered
Medline	1950–24 September 2010 Additional search on May 20, 2011
Embase	<5 October 2010
EBM reviews:	<24 September 2010
- Cochrane Database of systematic Reviews	2005 to September 2010
- ACP Journal Club	1991–August 2010
- Database of Abstracts of Reviews of Effects	3rd Quarter 2010
- Cochrane Central Register of Controlled Trials	3rd Quarter 2010
- Cochrane Methodology Register	3rd Quarter 2010
- Health Technology Assessment	3rd Quarter 2010
- NHS Economic Evaluation Database	3rd Quarter 2010

EBM reviews—evidence based medicine reviews

The search terms used included: procalcitonin, PCT, sepsis, septic shock, severe sepsis, systemic inflammatory response syndrome, SIRS, septicaemia, blood stream infection, BSI, lower respiratory tract infection, LRTI, community acquired pneumonia, CAP, chronic obstructive airways disease, COAD, chronic obstructive pulmonary disease, COPD, fever, infection, bacterial infection, febrile, meningitis, critically ill, chronic airflow limitation, CAL, undifferentiated fever, pyrexia, pyrexia of unknown origin , PUO.

The aim of this search strategy was to generate a comprehensive list of potentially relevant studies. Therefore, it was not limited to specific patient outcomes.

Selection criteria

Table 12 summarises the selection criteria applied in the electronic searches. The search of the literature was not constrained by study design or patient outcomes to ensure that all studies that may have investigated the assessment of the determination of bacterial infection and monitoring of antibiotic therapy using the measurement of PCT were located.

Table 12: Selection criteria for included studies

Research question: Will the management that involves the use of measurement of PCT to determine the presence of a bacterial infection and to guide antibiotic therapy result in an improvement in quality-adjusted survival compared with current management excluding this test		
Selection criteria	**Inclusion**	**Exclusion**
Study design	All study design	Animal
Population	SIRS/sepsis	None
Prior tests	Not Specified	None
Intervention	Measurement of PCT	None
Reference standard	Not specified	None
Comparator	Not specified	Not specified
Outcomes	Not specified	None
Publication type	Not specified	None

Search results

The publications located by the electronic searches were then assessed to identify those reporting the results for studies that may have investigated the assessment of the determination of sepsis or the monitoring of antibiotic therapy using measurement of

PCT for the population of adults who visited their GP or ED with the signs and symptoms of LRTI or who had the signs and symptoms of sepsis in an ICU. Table 13 summarises the process used to identify all studies assessing the efficacy and safety of measurement of PCT in this population.

Search results

Table 13: Summary of the process used to identify studies assessing the efficacy or safety of measurement of PCT in determining bacterial infection or monitoring antibiotic therapy

Potentially relevant studies	Medline (n=166)	Embase (n=132)	EBM (n=97)	Grey literature (n=1)
Reasons for exclusion				
Not PCT study	40	9	27	
Wrong population	27	12	12	
Drug trial	18	9	20	
Review	10	15	0	
Comment/letter	2	4	0	
Case report	1	0	0	
Protocol/conference abstract/journal club discussion	3	3	0	
Cadavers/animals	0	1	0	
Duplicate	3	34	29	
Studies remaining for more detailed evaluation	**62**	**45**	**1**	**1**
Reasons for exclusion				
Neonates/children	7	14	1	
Non-LRTI ED (hospital inpatients)	1	3		
Neutropenia/steroids/HIV	4	3		
Renal		2		
Not mainly PCT (e.g., aPTT) or PCT combined	4	2		
Meta-analysis/survey	2	3		
Comparison of two PCT tests	0	2		
Meningitis	2	0		
Foreign language	7	3		
Trauma/surgery/neurotrauma/transplant	3	3		
Pancreatitis/abdominal sepsis	1	0		
Vaccine	1	0		
Sub-total	30	10	0	1
Sub-total	41			
Not randomised controlled trials	27			
Total	**14**			

Appendix D lists the studies included for evidence appraisal.

Appendix E lists the studies excluded from the evidence appraisal including studies that were in a foreign language.

Data extraction and analysis

Data were extracted using standardised extraction forms, which included key parameters: study population, intervention, analyses, setting and outcomes. Data extraction was performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion to gain consensus. Data were only reported when it was stated in the text, tables, graphs or figures of the article, or when it could be accurately extrapolated.

Appraisal of the evidence

Appraisal of the evidence was conducted at three stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review.

Stage 2: Appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (see Table 14) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 14: Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design*
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *p* value or, alternatively, the precision of the estimate of the effect. This reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

* see Table 15

Strength of the evidence

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The 'level of evidence' reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results.

The NHMRC evidence hierarchy provides a ranking of various study designs, or 'levels of evidence', by the type of research question being addressed (see Table 15).

Table 15: Designations of levels of evidence according to type of research question (including table notes) (NHMRC 2008)

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomised controlled trial
III-1	A pseudo randomised controlled trial (i.e., alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudo randomised controlled trial (i.e., alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm studies[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Table notes

[1] Definitions of these study designs are provided on pages 7–8. How to use the evidence: assessment and application of scientific evidence (NHMRC 1999).

[2] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of how the test affects patient management and health outcomes (MSAC 2005, Sackett & Haynes 2002).

[3] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (e.g., groups cannot be allocated to a potentially harmful exposure, such as nuclear radiation), then the 'etiology' hierarchy of evidence should be utilised.

[4] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of potentially poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than on whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome or result, as different studies (and study designs) might contribute to each different outcome.

[5] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al. 2003).

[6] Well-designed population based case-control studies (e.g., population based screening studies where test accuracy is assessed in all cases, with a random sample of controls) capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal or healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease or conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

[7] At study inception, the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

[8] All or none of the people with the risk factor(s) experiences the outcome and the data arises from an unselected or representative case series, which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[9] This also includes controlled before-and-after (pre-test/post-test) studies and adjusted indirect comparisons—that is, which utilise A v. B and B v. C, to determine A v. C with statistical adjustment for B.

[10] Comparing single arm studies (i.e., case series from two studies). This would also include unadjusted indirect comparisons—that is, which utilise A v. B and B v. C, to determine A v. C, but there is no statistical adjustment for B.

[11] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms or safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs. Harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question (e.g., level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence).

Source: Hierarchies adapted and modified from NHMRC (1999), Bandolier (1999), Lijmer et al. (1999) and Phillips et al. (2001).

Individual studies assessing diagnostic effectiveness were graded according to pre-specified quality and applicability criteria (MSAC 2005), as shown in Table 16.

Table 16: Grading system used to rank included studies

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed and to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Q1 high quality Q2 medium Q3 poor reference standard poor quality or insufficient information

Quality

The appraisal of intervention studies pertaining to treatment safety and effectiveness was undertaken using a checklist developed by the NHMRC (NHMRC 2000a). This checklist was used for trials and cohort studies. Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al. 2001). Studies of diagnostic accuracy were assessed using the QUADAS quality assessment tool (Whiting 2003).

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000b). Studies need to be appropriate to ensure that a real difference between groups will be detected in the statistical analysis.

Size of effect

For intervention studies of the measurement of PCT, it was important to assess whether statistically significant differences between the comparators were also clinically important. The size of the effect needed to be determined, as well as whether the 95% confidence interval included only clinically important effects.

Relevance of evidence

The outcomes being measured in this report should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000b).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2008). Five components are considered essential by the NHMRC when judging the body of evidence:

- The evidence base – which includes the number of studies sorted by their methodological quality and relevance to patients;
- The consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction (ie homogenous or heterogeneous findings);
- The potential clinical impact – appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;
- The generalisability of the evidence to the target population; and
- The applicability of the evidence – integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (see Table 17) (NHMRC 2008).

Table 17: Body of evidence assessment matrix

Body of evidence / Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population	population/s studied in the body of evidence are similar to the target population	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Adapted from (NHMRC 2008)

Expert advice

An Advisory Panel was established to provide guidance to the health technology assessors to ensure that the assessment is clinically relevant and takes into account consumer interests. Membership of the Advisory Panel is provided in Appendix B.

Results of assessment

Is it safe?

As discussed in the section titled 'Search Results', which summarises the results of the literature search, no reports relating to studies that specifically investigate the safety of measurement of PCT were found. Measurement of PCT requires patients to undergo a simple blood test. Therefore, it is anticipated that there will not be any safety concerns with this intervention, excepting the harm that may arise from a false positive or false negative result.

Summary of safety

No reports were located that related to studies that specifically investigated the safety of measurement of serum PCT.

Given the nature of this intervention, it is anticipated that it will not be associated with any safety issues.

Is it effective?

Table 18: Inclusion criteria for the identification of studies relevant to an assessment of the effectiveness of the intervention

Research Question Will management that involves the use of measurement of PCT to determine the presence of a bacterial infection and to guide antibiotic therapy result in an improvement in quality-adjusted survival, compared with current management excluding this test.	
Selection criteria	***Inclusion criteria***
Population	Adults with LRTI in a primary care or ED setting Adults with sepsis in an ICU setting
Intervention	Measurement of PCT
Comparator(s)	None specified
Outcomes	None specified
Search period	No limits were applied in the searches conducted
Study design	Randomised controlled studies
Language	Publications in any language will be included

Table 19 provides a list of the randomised controlled trials included in the review.

Table 19: Included randomised controlled studies

Study and location	Level of evidence and quality assessment	Study design	Study population	Outcomes assessed
Intensive care studies				
Bouadma (2010) Germany & France	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Multi-centre, open-label RCT	N=630 ICU patients 5 ICUs participated	Primary outcomes - Death from any cause day 30 and day 60 (inferiority) - Number of days without antibiotics (superiority) Secondary outcomes - % of patients with relapse or super-infection - Number of days without MV - SOFA score (days 1, 7, 14, 21 and 28) - Length of stay ICU - Days of exposure to each antibiotic - Duration of antibiotic treatment per infection site - % of emerging multi-resistant bacteria isolated from specimens taken from routine microbiological assessments (days 1–28)
Jensen (2011)		Multi centre, Blinded RCT Blinded to outcomes, control group blinded to PCT levels	N=1200 Mixed surgical/medical ICU patients	Primary outcome - 28-day survival Secondary outcomes - Duration of organ failure - Length of stay in ICU
Schroeder (2009) Germany	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	Open-blinded RCT	N=27 ICU patients	- Length of antibiotic treatment - Length of hospital and ICU stay
Nobre (2008) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Open-label RCT Single-centre	N=79 ICU patients	Primary outcomes - Duration of antibiotic therapy - Antibiotic exposure days - Days alive without antibiotics Secondary outcomes - 28-day mortality - In-hospital mortality - Length of stay in hospital and ICU - Clinical cure(resolution of baseline clinical signs) - Recurrence of initial infection - Nosocomial super-infection
Stolz (2009) Switzerland & USA	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	Multi-centre RCT Control group physician blinded to PCT level	N=101 ICU patients 7 ICUs participated	Primary outcome - Antibiotic free days after 28 days Secondary outcomes - Number of MV free days - ICU free days alive - Length of hospital - Evolution of signs and symptoms linked to pulmonary infection - VAP related clinical deterioration rate - SOFA, ODIN, CPIS scores - Mortality at day 28

Svoboda (2007) Czech republic	Level of evidence II (RCT) Quality assessment C1(direct comparison) Q3 (poor quality information)	Single-centre RCT	N=72 ICU patients	- 28-day mortality - Sepsis-related complications - Duration of stay in ICU and - Ventilator days
Hochreiter (2009) Germany	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Open-blinded RCT	N=110 surgical ICU patients	- Length of antibiotic treatment - Duration of intensive care stay
Emergency department/primary care studies				
Burkhardt (2010) Germany	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	RC T non-inferiority trial Physicians blinded	N=550 with symptoms of acute RTI	Primary outcomes - Days with impairment during everyday life and/or leisure activities due to RTI within the first 14 days according to self-assessment (health impairment) Secondary outcomes - Frequency of prescription of antimicrobial treats - Days with antibiotic induced side effects - Symptoms of RTI on days 14 and 28 - Visit at Drs office with RTI within 28 days - Change of antibiotics within 28 days - Hospitalisation within 28 days - Mortality within 28 days
Briel (2008) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Randomised, open-label non-inferiority RCT multicentre,	N=458 primary care patients 53 primary care physicians participated	Primary outcome - Days with restrictions from ARTI Secondary outcomes - Antibiotic prescription rate - Duration of antibiotic use - Days off work - Days with side effects - Relapse rate from ARTI within 28 days after randomisation
Kristoffersen (2009) Denmark	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	Multi-centre RCT Control group blinded	N=223 hospital admission for LRTI	Primary outcomes - Days of antibiotic treatment during hospitalisation - Length of hospital stay Secondary outcome - Proportion of patients for whom physician disregarded treatment guidelines
Schuetz (2009) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q2(potential for bias)	Open-label non-inferiority RCT Multi-centre Outcomes assessed by unblinded study physicians	N=1359 ED patients 6 EDs participated	Primary outcome (non-inferiority) - Overall composite adverse outcome (death from any cause, ICU admission for any reasons, disease specific complications and acute respiratory distress syndrome) Secondary outcomes (superiority) - Antibiotic exposure, - Adverse effects from antibiotics - Length of hospital stay
Stolz (2007) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) Q3(poor quality of information)	Single-centre RCT	N=266 ED patients	Primary outcome - Total antibiotic use at index exacerbation and up to 6 months Secondary outcomes - Measures of clinical outcomes (success, self-reported functional status, symptom scores) - Steroid dose - Length of stay - Need for ICU - Death

Christ-Crain (2006) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	Open-label RCT Physicians blinded Radiologist blinded	N=302 consecutive ED patients	Primary outcome - Total antibiotic use (prescription and duration) Secondary outcomes - Laboratory outcome - Clinical outcomes (death, recurrence, relapse and radiologic signs of CAP)
Christ-Crain (2004) Switzerland	Level of evidence II (RCT) Quality assessment C1(direct comparison) P1(population applicable) Q1(high quality)	Prospective cluster-randomised controlled, single-blinded trial	N=243 ED patients	Primary outcome - Use of antibiotics (rate of prescriptions, antibiotic exposure) Secondary outcomes - Laboratory outcomes (quality of life, temperature, leucocytes and CRP) - Frequency and length of admission - Need for ICU admission - Death in patients with LRTI - Rate of re-exacerbation and readmission of patients with acute exacerbations of COPD after 6 months

Table 20 provides information about the different assays used to measure PCT in the trials.

Table 20: Assays used in included studies

Study	Type	Functional assay sensitivity	Imprecision	Results
Bouadma (2010)	Kryptor PCT*	Detection concentration 0.06 μg/l Study laboratories# 0.25 μg/l 10 μg/l	=10% at 0.20 μg/l <6% at >0.30 μg/l 5.8%–8.8% 4.7%–40.8%	Transmitted to physicians within 2hours of blood drawing
Jensen (2011)	Kryptor PCT*	0.06 ng/mL		Collected between 3–6am, collected and arrived at central laboratory prior to 8am and cooled during transport. Results available before 11am
Schroeder (2009)	LIA PCT*			Upper normal reference range <0.5 ng/ml
Nobre (2008)	Kryptor PCT*	0.06 μg/l		Time to obtain plasma PCT levels about 1 hour. Results provided to clinical team of patients randomised to the PCT group within 3 hours of blood drawing, but kept in laboratory and not communicated to the treating physicians of control group
Stolz (2009)	Kryptor PCT*	0.06 μg/l		Assay time <20 minutes Results routinely available within 1 hour
Svoboda (2007)	PCT-Q*			12 samples tested against LUMI test* and correlation (r=0.93; p<0.001)
Hochreiter (2009)	LIA PCT*	0.5 ng/ml (0.5 μg /L)		
Burkhardt (2010)	Kryptor PCT	0.06	Precision cut-off (0.25 ng/ml)	Time to results is 19 minutes Time from blood collection to results <4 hours
Briel (2008)	Kryptor PCT	0.06 μg/l		Assay time 19 minutes with 20–50 μg/l of plasma or serum Results reported to study practice within 2–4 hours
Kristoffersen (2009)	Kryptor PCT*	0.06 μg/l		Test results available on following day (in 41 cases, the same in both groups), except for weekends when the sample could not be analysed within 24hours
Christ-Crain (2006)	Kryptor PCT	0.06 μg/l		Assay time <20 minutes Results routinely available within 1 hour
Christ-Crain (2004)	TRACE~ Kryptor PCT	0.06 μg/l		Assay time 19 minutes with 20–50 μg/l of plasma or serum Results can be obtained within 1 hour (although study does not say when results were reported)
Schuetz (2009)	Kryptor PCT*	0.06 μg/l		Assay time <20 minutes Results routinely available within 1 hour and communicated by web site to the treating physician
Stolz (2007)	Kryptor PCT*	0.06 μg/l		

Ug—micrograms; ng—nanogram

*Brahms Hennigsdorf, Germany; # data available from four of seven centres; ~TRACE: time-resolved-amplified-cryptate-emission technology assay (Brahms Hennigsdorf, Germany)

Kryptor PCT was used in the eight trials that included patients suspected of LRTI, and four of the trials conducted in the ICU setting. This assay is considered to be the most sensitive of the assays and applicable for detecting LRTI and sepsis. In two of the ICU setting trials, LIA PCT was used. This assay is considered to be applicable for diagnosing sepsis in patients. The trial by Svoboda et al. (2007) used the semi-quantitative PCT-Q test. This test is the least sensitive, recommended only if rapid information is required, and is considered by the maker only to be capable of providing information about the probability of sepsis, but not diagnosis (see Table 3).

Antibiotic therapy guidelines based on procalcitonin levels used in the studies

This section of the report includes a fuller description of the population in the included studies, and outlines the PCT algorithm used by each of the studies to start, continue or stop antibiotics based on measured PCT levels in the PCT arm of the trial. The treatment regimen in the control (standard therapy) arm is also discussed.

Intensive care studies

Jensen 2011

The population included in this study were adults, enrolled within 24 hours of admission to the ICU and expected to stay longer than 24 hours. Patients were excluded if their bilirubin or triglycerides levels were elevated. PCT samples were done immediately after inclusion in the study and everyday thereafter between 3 and 6 am. The samples were required to arrive for analysis before 8 am. The aim was to have the results entered into the database before 11am every day. Culture samples from blood, urine, airways and other suspected sites were performed on admission and subsequently, three times per week and whenever infection was suspected.

- PCT group: Use of antimicrobials was guided by the same clinical guidelines as in the standard-of-care group and was additionally, by daily PCT measurements, classified as 'alert procalcitonin' (PCT≥1.0 ng/mL and not decreasing by at least 10% from the previous day) or 'non-alert procalcitonin,' corresponding to an intervention algorithm. All sites were contacted everyday by telephone to assure that interventions were conducted according to the algorithm. An 'alert procalcitonin' indicated a need to increase the antimicrobial spectrum covered substantially and to intensify the diagnostic effort to find uncontrolled sources of infection. Antimicrobials were adjusted according to:

    1) Present and previous PCT values;
    2) Infectious state of the patient (clinical presentation, microbiology, radiology, etc.); and
    3) History of antimicrobial used.

PCT-guided antimicrobial escalation was mandatory, except when, firstly, there was a clear contraindication for administering it or, secondly, microbiology explained the source of the infection leading to specific therapy. All patients with septic shock were treated at the onset of hypotension (same as in the control group). Treatment was not to be delayed because the clinician was waiting for PCT results or low PCT levels.

- Control group: Antimicrobial treatment was guided according to current clinical guidelines (Dellinger et al. 2008; Russel 2006). PCT levels were not available to the treating clinician.

Bouadma 2010

The population included in this study were all patients with suspected bacterial infection on admission or during their stay in ICU. Seven ICUs participated: five medical and two surgical.

- PCT-guided group: PCT levels were used to guide physicians to start or discontinue antibiotics. The physicians were free to decide optimum duration and type of therapy (see Table 21 & 22). However, the study recommended broad spectrum antibiotics for initial empirical treatment, before responsible pathogens were known. It was encouraged that antibiotic treatment be commenced as soon as possible. PCT levels were assessed daily.
- Control group: Physicians were free to decide optimum duration of therapy and type of antibiotics, based on their own assessment of the infection's clinical course. However, the study recommended broad spectrum antibiotics for initial empirical treatment, before responsible pathogens were known. It was encouraged that antibiotic treatment be commenced as soon as possible (see Table 23).

Table 21: Guidelines for starting antibiotics (Bouadma 2010)

PCT levels	Recommendations	
Concentration <0.25 μg/L	Antibiotics strongly discouraged	Obtain 2nd PCT concentration 6–12 h later
Concentration ≥0.25 and <0.5 μg/L	Antibiotics discouraged	Obtain 2nd PCT concentration 6–12 h later
Concentration ≥ 0.5 and <1 μg/L	Antibiotics encouraged	
Concentration ≥1 μg/L	Antibiotics strongly encouraged	

Table 22: Guidelines for stopping antibiotics (Bouadma 2010)

PCT levels	Recommendations
Concentration <0.25 μg/L	Stopping antibiotics strongly encouraged
Decrease by ≥80% from peak concentration or concentration ≥0.25 and <0.5 μg/L	Stopping antibiotics encouraged
Decrease by <80% from peak concentration or concentration ≥ 0.5 μg/L	Continuing of antibiotics encouraged
Increase of concentration compared with peak concentration and concentration ≥0.5 μg/L	Changing of antibiotics strongly encouraged

Table 23: Guidelines for antibiotic treatment duration—control group (Bouadma 2010)

Infection site	Recommended duration of antibiotics (days)
Lower respiratory tract infections	
Community acquired pneumonia*	7–10
Ventilator associated pneumonia†	8–15
Abdominal infections‡	
Community acquired peritonitis	5–7
Nosocomial peritonitis	7–14
Non-complicated community acquired *S. aureus* bacteremia	14
Non-complicated catheter-related bacteremia	7–14
Bacterial meningitis	
Community acquired meningitis	
Streptococcus pneumoniae	10–14
Neisseria meningitidis	5–7
Listeria monocytogenes	21
Nosocomial meningitis	14
Urinary tract infections	
Complicated acute pyelonephritis	14
Acute prostatitis	28

*A longer duration (14 days) is recommended for pneumonia caused by Legionella pneumophila, Mycoplasma pneumoniae or Chlamydia pneumonia (Mandall et al. 2007; Woodhead et al. 2005);
†When the responsible pathogen is a non-fermenting Gram-negative bacillus in immunocompromised patients or when initial antimicrobial therapy was inappropriate, 15 days of treatment may be warranted (ATS 1996; Chastre et al. 2003);
‡Antibiotic therapy duration for patients with abdominal infection has not been evaluated by randomised trials

Schroeder (2009)

The population included in this study were patients diagnosed with severe sepsis and admitted to ICU, after abdominal surgery and start of antibiotic treatment. For either arm of the study, a calculated antibiotic regimen, according to the underlying infectious pathology, was applied. In the two groups, standard routine laboratory analysis was performed, including CRP and PCT in the PCT-guided group. The study does not provide information about when these tests were performed.

- PCT-guided group: Antibiotic therapy was discontinued if clinical signs and symptoms of sepsis improved and PCT values either decreased to 1 ng/ml or less or dropped to 25–35% of the initial PCT concentration over three consecutive days. The physician in charge was always free to decide to continue or change the antibiotic regimen based on clinical judgement.
- Control group: Antibiotic treatment was discontinued according to clinical signs and empiric rules. The physician in charge was always free to decide to continue or change the antibiotic regimen based upon clinical judgement.

Hochreiter (2009)

The population included in this study were surgical intensive care patients requiring antibiotic therapy based on confirmed or highly suspected bacterial infections and exhibiting at least two concomitant SIRS criteria. In the two groups, antibiotics were selected based on suspected micro-organisms and adjusted to the isolated organisms whenever possible. Laboratory tests were performed and PCT was determined daily for each group.

- PCT-guided group: Antibiotic therapy was discontinued if clinical signs and symptoms of sepsis improved and PCT values either decreased to 1 ng/ml or less

or dropped to 25–35% of the initial PCT concentration over three consecutive days.

- Control group: Antibiotic regimen was applied as a standard regimen over eight days.

Stolz (2009)

The population included in this study were ICU patients intubated for mechanical ventilation for at least 48 hours and clinically diagnosed with ventilator associated pneumonia (VAP)—new or persistent infiltrate on chest x-ray—plus at least two of the following: purulent tracheal secretions, temperature >38◦ or leukocyte count >11,000 μL or <3,000 μL. In both groups, antibiotics were commenced at day zero and the physicians were blinded to PCT levels. Daily PCT levels (blinded in control group) and leukocyte count at 10 days were done. The antibiotic regimen was at the discretion of physician.

- PCT-guided group: At 72 hours the physician was notified of the daily PCT level and advised to classify the patient into one of four groups (see Table 24) based on the probability of ongoing bacterial infection. After day two, PCT levels were taken daily and the results compared with the immediate previous value.
- Control group: At 72 hours, physicians were encouraged to treat according to the American Thoracic Society guidelines. They were recommended to stop antibiotics after 72 hours if the patient was improving and cultures were negative. If culture results were positive and the patient had improved, then antibiotics being administered were tailored to the culture results, including potential monotherapy.

Table 24: PCT guidelines for ongoing antibiotic therapy (Stolz 2009)

PCT levels	Recommendations
Concentration <0.25 μg/L	Suggests absence of VAP and discontinuation of antibiotics strongly suggested
Level between ≥0.25 and <0.5 μg/L or decrease by ≥80% from day 0	Bacterial infection unlikely and reduction or discontinuation of antibiotics encouraged
Level ≥0.5 μg/L or decrease by <80% compared with day 0	Considered to indicate unresolved bacterial infection and reduction or discontinuation of antibiotics discouraged
Levels >1 μg/L	Strongly suggests unresolved bacterial infection and antibiotic discontinuation strongly encouraged

Nobre (2008)

The population included in this study were patients with suspected severe sepsis and septic shock admitted to ICU and patients developing severe sepsis or septic shock during their ICU stay. On admission, blood cultures, urine cultures, bronchalveolar lavage (BAL) fluid and tracheal aspirates were done. Blood gases and imaging exams were performed as clinically indicated, and in both groups, PCT levels were measured (but physicians were blinded to the results in the control group). In both groups, the antibiotics were commenced by the treating physician based on local guidelines and susceptibility patterns. The physician was unaware of the initial PCT levels. Broad spectrum parenteral antibiotics were prescribed to patients with suspected severe sepsis or septic shock, depending on the suspected source of infection and microbiological cultures when available. A combination of macrolides plus ceftriaxone or amoxicillin/clavulanic acid was initially administered to patients with severe sepsis or shock due to CAP.

- PCT-guided group: Daily routine blood tests measured for seven days (PCT measured at 5-day intervals after this time). Patients received broad spectrum antibiotics for 72 hours and patients with positive blood cultures received at least five full days of parenteral antibiotic therapy. At day three, the patients were assessed and treated according to the algorithms in Table 25.
- Control group: Daily routine blood tests (including PCT measurement). Antibiotic spectrum narrowed, where possible, based on cultures obtained after patient's admission. Patients with positive blood cultures received at least five full days of parenteral antibiotic therapy. Investigators did not interfere with the duration of antibiotic therapy in these patients.

Table 25: PCT algorithm for continuing antibiotic therapy after day three

<table>
<tr><th colspan="4">Assessment day 3</th></tr>
<tr><td>PCT values on day 1&2:
<1.0 µg/L</td><td>PCT values of on day 3:
<1.0 µg/L</td><td>Bacterial infection highly unlikely
(Thorough clinical evaluation)</td><td>Stop antibiotic therapy</td></tr>
<tr><td rowspan="2">PCT values on day 1 or 2:
>1.0 µg/L</td><td rowspan="2">Continue antibiotic therapy for at least 2 days
On day 5: apply either of the following possible stop rules after careful clinical evaluation and overall assessment</td><td>Stop rule, option 1:
1) patient is stable; and
2) PCT has decreased to an absolute value <0.25 ug/l (antibiotic stop encouraged); or
3)PCT has decreased to an absolute value <0.1 ug/l (antibiotic stop strongly encouraged).</td><td rowspan="2">Stop antibiotic therapy</td></tr>
<tr><td>Stop rule, option 2:
1) Patient is stable; and
2) PCT has decreased by at least 90% from the baseline peak value.</td></tr>
</table>

Svoboda (2007)

The population included in this study were patients with severe sepsis after major abdominal surgery or surgery for multiple trauma. Standard supportive care, broad spectrum antibiotics and change of the intravascular catheters were provided to all septic patients based on evidence based guidelines. PCT was measured at the onset of the septic episode and subsequently, every day for the first week, then every third day until recovery or death.

- PCT-guided group: The more important role was given to the PCT level in the treatment decision. Severe sepsis with PCT >2ng/ml signalled bacteremia, and pushed the investigators to change antibiotics and intravascular catheters. Severe sepsis ≤2ng/mL prompted ultrasonography and/or computer tomography, followed by repeated surgery in patients with localised infection.
- Control group: Treatment was by standard evaluation of all parameters by a consultant surgeon.

Emergency department and primary care studies

Christ-Crain (2004)

The population in this study were patients presenting to the ED with cough and/or dyspnoea with suspected LRTI as the main diagnosis. The diagnostic procedures, therapeutic regimen and final decision to initiate antimicrobial treatment were left to the discretion of the treating doctor. Blood samples, for laboratory analysis, including for PCT levels, were taken at time of assessment. Re-evaluation 6–12 hours after admission

was possible in patients from whom antibiotics were withheld and included clinical and laboratory workup and re-measurement of PCT levels in the PCT group.

- PCT-guided group: Antibiotic therapy was guided by the algorithm in Table 26. Table 26 For patients on antimicrobial therapy at the time of admission, the study recommended discontinuation of antibiotics if PCT levels <0.25 μg/L.
- Control group: Patients were randomly assigned standard care. Re-evaluation was performed 6–12 hours after admission.

Table 26: PCT algorithm to guide antibiotic therapy (Christ-Crain 2004)

PCT levels	Recommendation	Monitoring
Concentration <0.1 μg/L	Absence of Infection. Antibiotics strongly discouraged*	Obtain 2nd PCT concentration 6–12 h later
Concentration 0.1–0.25 μg/L	Infection unlikely. Antibiotics discouraged	Obtain 2nd PCT concentration 6–12 h later
Concentration 0.25–0.5 μg/L	Possible bacterial infection. Antibiotics encouraged	
Concentration ≥0.5 μg/L	Suggests infection. Antibiotics strongly encouraged	

*This measure also used in the presence of impaired pulmonary reserve in acute exacerbations of COPD

Christ-Crain (2006)

The population in this study were adults with different severities of CAP admitted to the ED. Blood samples for laboratory analysis, including for PCT levels, were taken at time of assessment.

- PCT-guided group: Antibiotics were guided by serum PCT levels and physicians classified patients into four groups (see Table 27). The physician could override the PCT algorithm. A PSI was calculated. PCT levels were reassessed after 4 days, 6 days and 8 days and antibiotics were based on the PCT cut-offs in Table 27. If PCT >10 μg/L on admission, discontinuation of antibiotics was recommended if levels decreased to less than 10% of the initial value (e.g., <0.1 μg/l instead of <0.25 μg/l).
- Control group: Antibiotic therapy was based on usual practice guidelines and physicians were blinded to PCT levels. A PSI was calculated. The duration of antibiotic therapy was guided by clinical signs and standard guidelines.

Table 27: PCT algorithm to guide antibiotic therapy (Christ-Crain 2006)

PCT levels	Recommendation	Monitoring
Concentration <0.1 μg/L	Absence of Infection. Antibiotics strongly discouraged*	Obtain 2nd PCT concentration 6–12 h later
Concentration 0.1– 0.25 μg/L	Infection unlikely. Antibiotics discouraged	Obtain 2nd PCT concentration 6–12 h later
Concentration 0.25–0.5 μg/L	Possible bacterial infection. Antibiotics encouraged	
Concentration ≥0.5 μg/L	Suggests infection. Antibiotics strongly encouraged	

Kristoffersen (2009)

The population in this study were adults presenting to the ED and admitted with suspicion of CAP or with one or more clinical symptoms (cough, expectoration, dyspnoea or fever >38ºC. PCT results for patients in the PCT group were faxed to the respective departments and made available to the physicians making rounds or to the

physicians on call that day. In the control group, PCT was measured but physicians were not informed of tests results.

- PCT-guided group: Physicians were advised to follow a treatment algorithm based on serum PCT values (see Table 28). Physicians were not asked to wait for PCT results before initiating antimicrobial therapy. Therefore, PCT values were, in most cases, used to motivate either cessation or continuation of already initiated treatments. Physicians were not followed to assess whether they adhered to the PCT guidelines.
- Control group: Treatment was according to regional guidelines, which recommend benzylpenicillin as first-line treatment for suspected CAP, with a treatment duration of no less than 7 days and depending on clinical response. For severe infection, cefuroxime and/or clarithromycin was recommended. Clarithromycin was the recommended first-line treatment in cases of suspected atypical infection, with treatment duration of no less than 14 days.

Table 28: PCT algorithm to guide antibiotic therapy

PCT level	Recommendation
Serum PCT <0.25 μg/L*	Antibiotic treatment discouraged
Serum PCT 0.25–0.50 μg/L	Antibiotic treatment was encouraged
Serum PCT >0.50 μg/L	Antibiotic treatment was strongly encouraged

*If the patient had already received antibiotic treatment before determining PCT levels, it was still recommended to discontinue therapy if PCT levels fell below 0.25 μg/L. However, physicians were made aware of the possibility of infection with atypical agents, which can be associated with lower PCT values.

Schuetz (2009)

The population included in this study were adults with a primary diagnosis of LRTI treated in the ED of six participating hospitals. The antibiotic regimen (oral or IV) was at the discretion of the treating physician. Blood samples for laboratory tests were taken at assessment. All hospitalised patients were clinically reassessed for resolution of infection at three, five and seven days and at discharge.

- PCT-guided group: PCT levels, together with treatment recommendations for antibiotics based on PCT algorithm, were communicated in the PCT group via the web site (see Table 29). For patients with increased PCT values and receiving antibiotic therapy, PCT measures were repeated after days three, five and seven days.
- Control group: Antibiotic therapy was based on evidence based guidelines. Physicians were blinded to PCT levels. Antibiotics use was:
    - encouraged in CAP for 5–10 days in uncomplicated cases;
    - at least 14 days in L pneumophilia CAP;
    - at least 10 days in necrotising CAP, emphysema or lung abscess, where drainage was suggested;
    - for 5–10 days if severe COPD (GOLD IV) or purulent sputum plus one of the following:
        - ↑dyspnea and/or ↑sputum volume;
        - 3–5 days of purulent sputum plus an additional risk factor (>75 years old, fever, chronic heart failure, insulin-dependent diabetes or serious neurological disorder; and

- amoxicillin-clavulanate and/or clarithromycin prescribed for 7–21 days for bronchitis, depending on patient age, suspected pathogen, severity of illness and clinical characteristics respectively.

Table 29: PCT algorithm for antibiotic therapy (Schuetz 2009)

PCT levels	Recommendation	Monitoring
Concentration <0.1 µg/L	Absence of Infection. Antibiotics strongly discouraged	Obtain 2nd PCT concentration 6–12 h later Initial antibiotics can be considered in case of: - Respiratory or hemodynamic instability - Life threatening co-morbidity - Need for ICU admission - PCT <0.1 µg/L: CAP with PSI V or CURB65 >3 COPD with GOLD IV - PCT <0.25 µg/L: CAP with PSI ≥IV or CURB 65>2 COPD with GOLD>III - Localised infection (abscess or empyema) or *L. pneumophilia* - Compromised host defence (e.g., immune-suppression other than corticosteroids) - Concomitant infection in need of antibiotics
Concentration 0.1–0.25 µg/L	Infection unlikely. Antibiotics discouraged	
Concentration 0.25–0.5 µg/L	Possible bacterial infection. Antibiotics encouraged	Consider the course of PCT If antibiotics are initiated: - Repeated measurement of PCT on days 3, 5, 7 - Stop antibiotics using the same cut-offs above If initial PCT levels are >5–10 µg/L, then stop when 80–90% decrease of peak PCT - If initial PCT remains high, consider treatment failure (e.g., resistant strain, emphysema or ARDS) - Outpatients: duration of antibiotics according to the last PCT result: >0.25–0.5 µg/L: 3 days >0.5–1.0 µg/L: 5 days >1.0 µg/L: 7 days
Concentration ≥0.5 µg/L	Suggests infection. Antibiotics strongly encouraged	

Stolz (2007)

The population in this study were patients ≥40 years of age, admitted to the ED within the previous 48 hours, with an exacerbation of COPD and meeting post-bronchodilator therapy spirometric criteria. Except for the prescription of antibiotics at the index exacerbation, the prescription of all other medications was left entirely to the discretion of the treating physicians throughout the study period in both groups. Baseline assessment included routine blood tests, including PCT.

- PCT-guided group: Antibiotic use was based on the measurement of PCT levels at hospital admission based on the PCT algorithm (see Table 30).
- Control Group: Antibiotic therapy was started based on current guidelines, according to the decision of the attending physician, who was unaware of the patient's PCT levels.

Table 30: PCT algorithm for antibiotic therapy

PCT levels	Recommendation	Monitoring
Concentration <0.1 μg/L	Absence of Infection. Antibiotics strongly discouraged	Re-evaluation of circulating PCT levels and clinical status recommended after 6–24 hrs if antibiotic therapy withheld
Concentration 0.1– 0.25 μg/L	Possible infection. Antibiotics encouraged or discouraged, based on the stability of the patient's clinical condition	Re-evaluation of circulating PCT levels and clinical status recommended after 6–24 hrs if antibiotic therapy withheld
Concentration >0.25 μg/L	Suggest bacterial infection. Antibiotics encouraged	

Primary care

Briel (2008)

The population in this study were adults who the trial physicians consecutively screened with symptoms (first experienced within the previous 28 days) of acute respiratory tract infection (ARTI). The physician's intention to prescribe antibiotics was based on evidence based guidelines. Participating physicians received an interactive 2-hour seminar on updated evidence based guidelines for the treatment of ARTI. When a trial physician intended to give antibiotics to an eligible patient they called the study centre, and the patient was randomly allocated to either PCT-guided or standard therapy. Blood samples were collected from all patients for PCT measurement.

- PCT-guided group: PCT results were communicated to the study practice within 2–4 hours. Recommendation on initiation of treatment was based on the PCT algorithm in Table 31. The trial physicians then decided on the appropriate treatment and informed the patient by telephone. Patients to be given antibiotics were asked to fill a delayed prescription (a prescription issued under a reservation) or to pick up the antibiotic from the practice. The type of antibiotic prescribed was left to the discretion of the physicians.
- Control Group: Physicians were free to choose the type and duration of antibiotic therapy, but the use of evidence based guidelines was encouraged.

Table 31: PCT algorithm (Briel 2008)

<table>
<tr><th>PCT levels</th><th>Recommendation</th><th colspan="2">Monitoring</th></tr>
<tr><td>Concentration <0.1 μg/l</td><td>Absence of Infection. Antibiotics strongly discouraged*</td><td rowspan="2">Repeat levels 6–24 hrs later after re-evaluation of clinical status</td><td rowspan="2">Commence antibiotic if PCT >0.25 μg/l or if PCT level has increased by more than 50% from first measurement</td></tr>
<tr><td>Concentration 0.1–0.25 μg/l</td><td>Infection unlikely. Antibiotics discouraged</td></tr>
<tr><td>Concentration 0.25–0.5 μg/l</td><td>Possible bacterial infection. Antibiotics encouraged</td><td colspan="2" rowspan="2">Reassess after 3 days. Discontinue antibiotics if PCT level of ≤0.25 μg/l</td></tr>
<tr><td>Concentration ≥0.5 μg/l</td><td>Suggests infection. Antibiotics strongly encouraged</td></tr>
</table>

Burkhardt (2010)

The population included in this study were adults presenting with ARTI in a primary care setting. This study was in two stages. The first stage was a non-intervention observational study to document the antibiotic prescription rates, initial values for PCT and the outcome of 701 patients presenting with ARTI at 45 primary care physicians. The second part of the study was a randomised, controlled non-inferiority trial

comparing standard care with PCT-guided antimicrobial treatment in 550 patients in the same setting. PCT levels were determined at presentation.

- PCT-guided group: Antibiotics were recommended at a threshold of PCT 0.25 μg/L. The physician was encouraged to retain or change their diagnosis based on the recommendations of the PCT algorithm (see Table 32). In view of the recommendation, the physician made his final decision regarding the prescription of an antibiotic and informed the patient by telephone. The physician was allowed to overrule the recommendation but was asked to indicate the reasons behind this decision. Patients who required antimicrobial treatment according to clinical judgement received a prescription with the request to redeem the prescription only after they had been told to do so by phone. If the final decision was made against antibiotics, the patients were asked to return the prescription in a pre-paid envelope.
- Control group: The GP was recommended to retain their diagnosis and treat accordingly.

Table 32: Guidelines for starting antibiotics (Burkhardt 2010)

PCT levels	Recommendation	GP recommendation
Concentration <0.25 μg/L	Antibiotics NO	Recommendation to GP to retain the diagnosis
Concentration ≥0.25 μg/L	Antibiotics YES	
Concentration <0.25μg/L	Antibiotics YES	Recommendation to GP to change the diagnosis
Concentration ≥0.25 μg/L	Antibiotics NO	

Appendix D provides further details of the included studies, including the study design, population, inclusion and exclusion criteria, trial profile and randomisation and blinding.

Results

The following section presents the results from: the two RCT trials conducted in the primary care setting (Briel et al. 2008, Burkhardt 2010); the five trials conducted in the ED setting (Christ-Crain 2004 & 2006 at al., Stolz 2007, Kristoffersen 2009, Schuetz et al. 2009); and the seven trials conducted in the ICU setting (Jensen et al. 2011, Stolz 2009, Svoboda et al. 2007, Bouadma 2010, Nobre 2008, Hochreiter 2009, Schroeder 2009). None of these trials sought to determine the diagnostic accuracy of measurement of PCT. Rather they present the effect of the use of PCT-guided antibiotic therapy on antibiotic use and on patient relevant outcomes, such as death.

The main characteristics of the studies with intensive care patients are presented in Table 71and those for participants in the ED and primary care setting are shown in Table 72, Appendix D. Other relevant information included in the review, such as the inclusion/exclusion criteria for the trials and trial profiles are also included in Appendix D.

The populations of the two studies conducted in the primary care setting were similar in that participants were selected for the trial if they were adults exhibiting symptoms of an ARTI. The mean age of participants in the two primary care studies was similar, at 41–48 years of age, and females were approximately 60% of participants in both studies. Only Burkhardt (2010) recorded if participants were smokers (20%). A greater number of participants suffered from chronic lung disease/COPD in the Briel et al. (2008) trial. Approximately 15% of participants had this complaint compared to only 3.2% in the

Burkhardt (2010) trial. The next most common condition was insulin-dependent diabetes mellitus with similar proportions (approximately 5% with this condition) across both trials. The most common diagnosis in the Burkhardt (2010) trial was the common cold (57.8%), followed by acute bronchitis (33–34%) and tonsillitis/pharyngitis (14%). In the Briel et al. (2008) trial the most common diagnosis was acute bronchitis (25–31%) followed by acute rhinosinusitis (22%) and acute pharyngitis/tonsillitis (18–15%). Both trials were non-inferiority trials in which the analysis of secondary outcomes (which include outcomes of common interest with other trials) were done as per-protocol analyses.

The populations of the five trials conducted in the ED setting were similar but differed in the proportions suffering from particular conditions. In particular, the study by Stolz (2007) included patients with ECOPD, whereas the other studies included patients with suspected LRTI. However, in these other trials approximately 21–40% are recorded as either having COPD or an ECOPD. Compared to the primary care trial, participants were older, between 65 and 75 and had greater levels of co-morbidities, such as coronary heart disease, varying from 30–60%. The exception is Kristoffersen (2009), in which co-morbidities of the participants in the trial were not recorded. Slightly over 60% of participants included in the Christ-Crain at al. (2006) trial were male, but in the other trials participation was fairly equally distributedacross the sexes. The presenting conditions for seeking treatment at the ED varied slightly in severity across the trials. All participants in the Christ-Crain at al. (2006) trial had a diagnosis of CAP and all participants in the Stolz (2007) trial were recorded as having ECOPD. Conditions varied across the other three trials but the most common diagnosis was CAP, at 68% in the Schuetz et al. (2009) trial, 47% in Kristofferson (2009) and 38% in Christ-Crain (2004). This was followed by ECOPD, at 17%, 28% and 25% across the same three trials respectively. For, Christ-Crain et al. (2006) the primary and secondary outcomes were reported by the intention-to-treat (ITT) population and the sample was powered to 95% to detect a 30% reduction in antibiotic exposure (from ten to seven days). In Stolz (2007), the analyses were conducted on an ITT basis, and the sample size was powered to 85% to detect a 30% reduction in antibiotic use. The trial by Kristoffersen (2009) was powered to 90% to detect a 20% reduction in antibiotic use, but the analyses done on an ITT population (seven patients 'lost' in the PCT-guided arm and six 'lost' in the standard therapy arm). The trial by Schuetz et al. (2009) was a non-inferiority trial, with a composite overall adverse outcome (death from any cause, ICU admission for any reason and disease specific complications) occurring 30 days following ED admission as the primary end point. To define non-inferiority with regard to the endpoint, a 7.5% absolute difference (e.g., at worst, the risk of an overall adverse outcome in the PCT group was increased by <7.5%). Sample size was based on an overall adverse outcome rate of, at most, 20% and a power of 90%. Analysis was done on the ITT population. Christ-Crain (2004) had use of antibiotics as the primary endpoint and performed analysis on an ITT basis. Sample size gave the study 95% power to detect a 30% reduction in antibiotic exposure.

The populations of the seven trials in the ICU setting varied. Bouadma (2010) included mainly medical patients (90% medical); the studies of Jensen et al. (2011), Stolz (2009) and Nobre (2008) included a mixture of surgical and medical ICU patients as participants; and the studies of Svoboda et al. (2007), Hochreiter (2008) and Schroeder (2009) enrolled only surgical/multiple trauma ICU patients. Patients in these trials were slightly younger than the studies conducted in the ED, ranging from 43–69 years. The most common type of infection suffered by the participants in the trial was pulmonary infection at 100% of patients in the Stolz (2009) trial, 71–74% of those in the Bouadma

(2010) trial, 64–67% in the Nobre (2008) trial, 55.5% in the Jensen et al. (2011) trial, 42% in the Hochreiter (2008) trial and 28–30% in the Schroeder (2009) trial. The infection site was not recorded for participants in the Svoboda et al. (2007) trial. The next most common recorded infection was intra-abdominal at 69–71 % of those in the Schroeder (2009) trial and 51–57% in the Hochreiter (2008) trial. Approximately, 68% of patients were recorded to be in septic shock in the Jensen et al. (2011) trial, while septic shock presented in 43% of patients in the Bouadma (2010) trial, 44% in the Nobre (2008) trial, 68–71% in the Svoboda et al. (2007) trial and 24% in the Stolz (2009) trial. The study by Jensen et al. (2011) reported that at baseline, 591 patients (51.7% in PCT group v. 47% in control) had 'alert procalcitonin' (≥1.0 ng/mL, and not decreasing by at least 10% from the previous day), corresponding to a 59.3% sensitivity (591 of 996) in patients toward infection/host response. During follow-up, a total of 638 (53%) developed a first or recurrent 'alert procalcitonin'. The Schroeder (2009), Hochreiter (2008) and Svoboda et al. (2007) trials analysed the primary outcome by ITT analyses (no other information is provided by the articles about sample size). For the Stolz (2009) trial, sample size was based on the antibiotic use days in a prior study by Chastre et al. (2003) of antibiotic therapy for VAP, with 90% power to detect and α=0.05 using a two-tailed test. End points were analysed on an ITT basis. The Bouadma (2010) trial assessed the number of days alive without antibiotics; the sample size would provide 90% power at a two-side α=0.05 to detect a 3-day increase in the number of days without antibiotics. End points were analysed on an ITT basis. The Nobre (2008) study analysed the primary endpoint: duration of antibiotic treatment on an ITT basis. The trial was designed to obtain a power of 90% to detect a 33% (4-day) difference in the duration of antibiotic therapy between the two groups. The study by Jensen et al. (2011) analysed the primary endpoint on an ITT basis. The final (adjusted) sample size of 1,200 patients was based on an estimated mortality in the standard-of-care-only group of 31.0% and a proposed absolute risk reduction of 7.5%. These numbers were from a previous cohort study (Jensen et al. 2006). (Further information on the sample size is reported by the authors to be included in supplementary information, which is not yet publically available).

Outcomes

When possible, similar outcomes are reported in the same table to allow for comparison across trials. In addition, pooled analysis of outcomes, when there is sufficient information, is also presented. Statistical analyses were done using RevMan5. For dichotomous data, the Mantel-Haenszel method was used to combine results across studies to derive the forest plots of odds ratios, using a random effects model, with 95% CI. For continuous data, to pool all mean differences, the inverse-variance method was used to derive the forest plot using a random effects model with 95% CI.

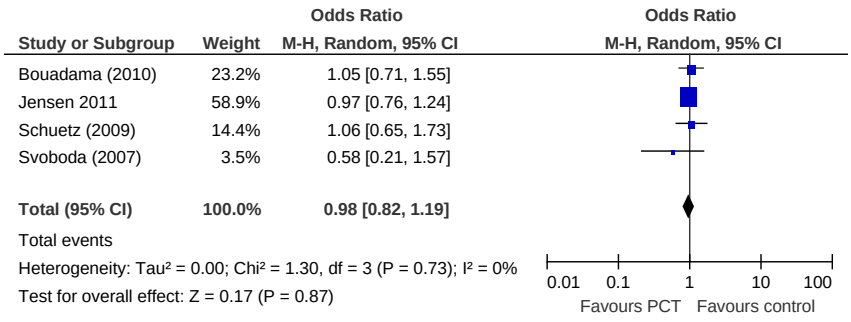
Four studies included as a primary endpoint, mortality. Table 33 below presents this data and Figure 9 is a forest plot presenting a summary of the odds ratios across the trials.

Table 33: Studies with mortality as a primary endpoint

Study	Variable	PCT	Control	Risk Difference (95% CI)	P value
Schuetz (2009)#	30 day mortality	34/671 (5.1%)	33/688 (4.8%)	0.3 (-2.1 to 2.5)	NS
Jensen (2011)(p)	28-day mortality	190/604 (31.5%)	191/596 (32.0%)	0.6 (-4.7 to 5.9)	NS
Bouadma (2010)	28-day mortality	65/307 (21.2%)	64/314 (20.4%)	0.8 (-4.6 to 6.2)	NS
Svoboda (2007)	28-day mortality	10/38 (26%)	13/34 (38%)	-0.12* (-0.33 to 0.10)	P=0.28

NR—not reported; NS—not significant; *calculated based on information provided in the published journal article
primary endpoint composite, which included mortality

Figure 9: Pooled analysis of studies with mortality as a primary endpoint



Four studies had mortality as a primary endpoint of the trial. Analysis from the individual studies does not reveal any significant difference in mortality between the PCT-guided arm and the control arm. Pooling the mortality data from the four studies supports the conclusion that mortality was comparable between the two treatment groups (see Figure 9). The study by Svoboda et al. (2007) appears to show quite a strong trend towards fewer deaths in the PCT-guided arm, but the CIs are wide due to the small numbers in this study (information about whether the sample size was powered to detect a difference in mortality was not provided in the study report). The mortality endpoint reported by Schuetz et al. (2009) forms part of a composite primary endpoint of adverse events.

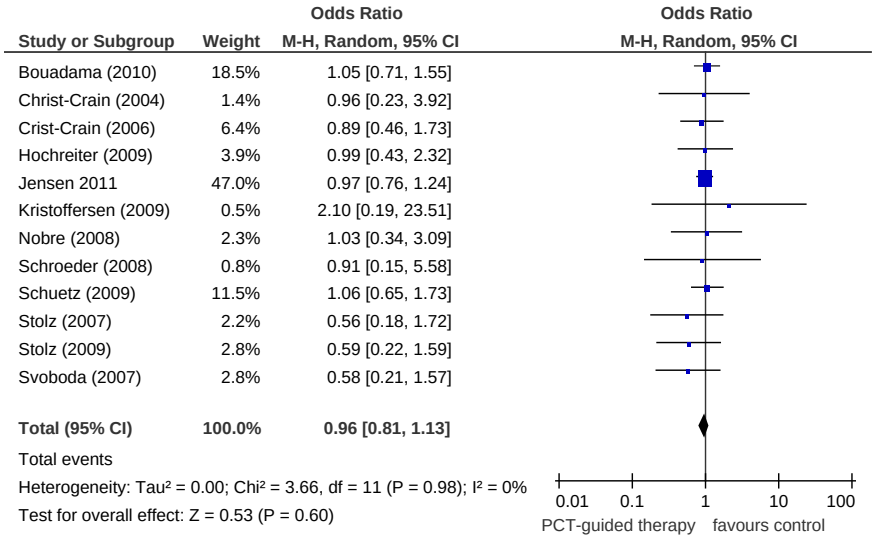
Table 34 and Figure 10 present mortality data from all the trials that reported this outcome.

Table 34: Outcome—mortality

Study	Variable description	PCT	Control	Risk difference% (95% CI)	P value
Primary care					
Burkhardt (2010)**	Mortality up to day 28	0	0	NR	NR
Briel(2008)**		NR	NR	NR	NR
Emergency department					
Kristoffersen (2009)	Death during admission	2/103 (2%)	1/107 (1%)	0.01* (-02 to 0.04)	0.54
Christ-Crain (2004)**	Mean after 13 days	4/124 (3%)	4/119 (3%)	-0.00* (-0.05 to 0.04)	0.95
Christ-Crain (2006)**	6 weeks	18/275 (12%)	20/275 (13%)	-0.01* (-0.05 to 0.04)	0.73
Schuetz (2009)(p)#	30 days	34/671 (5.1%)	33/688 (4.8%)	0.3 (-2.1 to 2.5)	NS
Stolz (2007)	Death any cause within 6 months	5/102 (4.9%)	9/106 (8.5%)	-0.04* (-0.10 to 0.03)	0.409
Intensive care					
Jensen (2011)(p)	28-day mortality	190/604 (31.5%)	191/596 (32.0%)	0.6 (-4.7 to 5.9)	NS
Svoboda (2007)(p)	28-day mortality	10/38 (26%)	13/34 (38%)	-0.12* (-0.33 to 0.10)	0.28
Bouadma (2010)(p)	28-day mortality 60-day mortality	65/307 (21.2%) 92/307 (30.0%)	64/314 (20.4%) 82/314 (26.1%)	0.8 (-4.6 to 6.2)* 3.8 (-2.1 to 9.7)*	NS
Nobre (2008)	28-day mortality	8/39 (20.5%)	8/40 (20%)	0.01* (-0.17 to 0.18)	0.82
Stolz (2009)	28-day mortality In-hospital mortality	8/51 (16%) 10/51 (20%)	12/50 (24%) 14/50 (28%)	-0.08* (-0.24 to 0.07)	0.327 0.322
Hochreiter (2009)	Not specified	15/57 (26.3%)	14/53 (26.4%)	-0.00* (-0.17 to 0.16)	NS
Schroeder (2009)	Not specified	3/14 (21.4%)	3/13 (23.1%)	-0.02* (-0.33 to 0.30)	NS

NR—not reported; NS—not significant; * calculated based on information provided in the published journal article;
(p) Primary endpoint of the trial; # Primary endpoint composite that included mortality; ** Secondary outcome; * not significant

Figure 10: Forest plot of pooled odds ratios for mortality



Thirteen studies included the number of patients who were deceased during the course of the trial (see Table 34). The exception was the study by Briel et al. (2008), conducted in a primary care setting. Burkhardt (2010) is not included in the analyses as no patients were recorded as having died during the trial period. Pooled analyses indicated that the use of PCT-guided therapy did not appear to have a deleterious or beneficial effect on patients (see Figure 10).

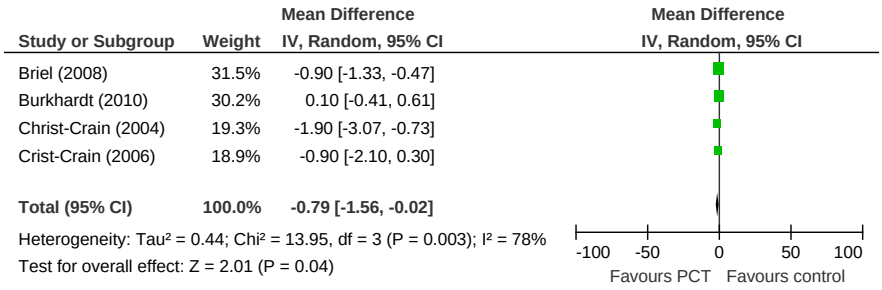
Table 35 and Figure 11 present data on the duration of antibiotic therapy from the included trials.

Table 35: Outcome—duration of antibiotic therapy (days on antibiotics)

Study	Variable description	PCT	Control	Rate difference % (95% CI)	P value
Primary care					
Burkhardt (2010)	Days on antibiotics-mean (SD)	7.8 (2.8)	7.7 (3.3)	NR	0.680
Briel (2008)**	Mean (SD)	6.2 (2.5)	7.1 (2.2)	-1.0 (-1.7 to -0.4)	NR
Emergency department					
Kristoffersen (2009)	Days mean (95%CI) (not included in pooled analysis)	5.1 (4.4–6.0)	6.8 (5.9–7.7)	NR	0.007
Christ-Crain (2004)(p)	Days on antibiotics-mean (SD)	10.9 (3.6)	12.8 (5.5)	NR	0.03
Christ-Crain (2006)(p)	Antibiotic duration (days) mean (SD) -with +ve blood cultures mean (SD)#	5.8 (5.3) 13.0 (8.9)	12.9 (6.5) 13.9 (4.9)	NR	<0.001 0.29
Schuetz (2009)(p)	Mean [IQR] not included in pooled analysis	5.7 (1–8)	8.7 (6–11)	-34.8 (-40.3 to -28.7)	NR
Pooled analysis (excluding Kristoffersen, Schuetz)	**Weighted mean difference (WMD)**	**905**	**892**	**-0.79 (-1.56,-0.02) I^2 =78%**	**0.003**
Intensive care	Mean (SD)				
Bouadma (2010)(p)	Nos of days *without* antibiotics	14.3 (9.1)	11.6 (8.2)	2.7 (1.4 to 4.1)	<0.0001
Bouadma (2010)**	Duration of 1st episode of antibiotic therapy Mean (SD)	6.1 (6.0)	9.9 (7.1)	-3.8 (-4.8 to -2.7)	NR
Jensen (2011)	Median [IQR] length of an antibiotic course	6 (3–11)	4 (3–10)	NR	NR
Hochreiter (2009)(p)	Mean (SD)	5.9 (1.7)	7.0(0.5)	NR	<0.001
Stolz (2009)(p)	Antibiotic free days Median (IQR) *Reduction* in duration of antibiotic therapy (days) median (IQR)	13 (2–21) 15 (10–23)	9.5 (1.5–7) 10 (6–16)	NR	0.038
Schroeder (2009)(p)	Mean (SD)	6.6±1.1	8.3±0.7	NR	<0.001
Nobre (2008)(p)	1st episode of infection, median (range)	6 (3–34)	9.5 (2–33)	NR	0.15
Overall Pooled analysis (excluding Kristoffersen, Schuetz, Bouadma, Jensen, Stolz, Nobre)		**1314**	**1309**	**-1.68 (-2.54,-0.82) I^2 =93%**	

§ The primary endpoint was antibiotic free days alive within 28 days of diagnosis of VAP–PCT group =13(2–21); Control group =9.5(1.5–17)
** Secondary endpoint (PP analysis); (p) primary endpoint of the trial; # Only these results included in pooled analysis

Figure 11: Forest plot pooled weighted mean difference for duration of antibiotic therapy



Ten studies reported the duration of antibiotic therapy (see Table 35). Studies that reported their results as mean and standard deviation were pooled. Overall, there was a significant reduction in the duration of antibiotic therapy in favour of the PCT-guided therapy group with a pooled weighted mean difference (WMD) of -1.68 (95% CI, -2.54 to -0.82). There was significant heterogeneity in the results (χ^2=219.71, $I^{2=}$93%), reflecting the incomparability of the results. Although all studies reported on the duration of antibiotic therapy, this outcome does not appear to be analogous across the studies. Duration of antibiotic therapy, for patients in ICU, may only be a record of the first episode of infection and may not reflect the length of time patients were on antibiotic therapy for the entirety of their time in ICU.

Figure 11 presents the pooled results from four of the studies conducted in patients presenting to a primary care physician or to the ED. Overall, there was a significant reduction in the duration of antibiotic therapy in favour of PCT-guided therapy with a pooled WMD of -0.79 (-1.56 to -0.02). The studies by Kristoffersen (2009) and Schuetz et al. (2009) have been excluded, (because they did not report their data as mean and standard deviation) but their exclusion is not likely to alter the conclusions, as both studies reported that the duration of antibiotic therapy in the PCT-guided arm was significantly reduced compared to control. Heterogeneity was lower in this comparison, but still significant. The mean days that patients were on antibiotic therapy differed between trials in the control arm. In the control group, across the trials, patients who presented to the ED could have a mean duration of antibiotic therapy that varied markedly between 6.8 to 12.9 days. This reflects the difference in trial population—that is, the proportion of patients diagnosed with CAP and/or ECOPD varied across the trials.

Table 36 and Figure 12 present data about number of antibiotics prescribed during the trials.

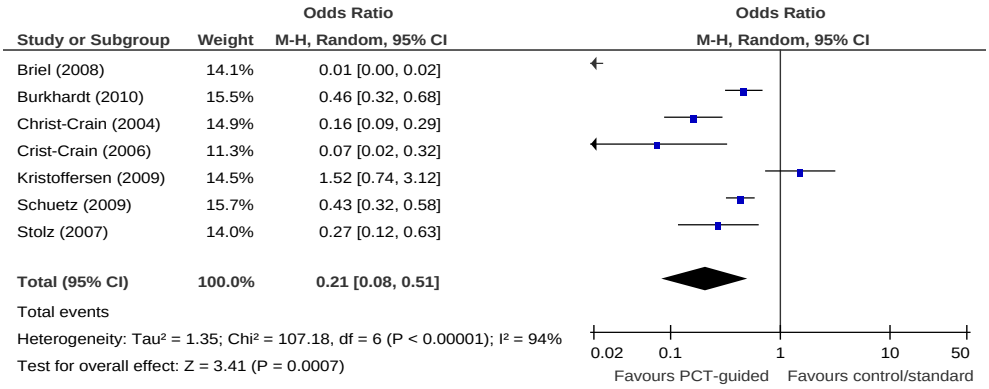
Table 36: Outcome—antibiotics prescribed

Study	Variable description	PCT N=275	Control N=275	Risk difference % (95% CI)	P value
Primary care					
Burkhardt (2010)	Antibiotics at baseline and during follow-up	59[a]/274 (21.5%)#	101/272 (37.1%)**	NR	0.0005
Briel (2008)		58/232 (25%)	219/226 (97%)	-72 (-78 to -66)	NR
Pooled primary care		**117/506 (23%)**	**320/498 (64%)**	**-0.41 (-0.46 to -0.36)**	**<0.00001**
Emergency department					
Kristoffersen (2009)(p)		88/103 (85%)	85/107 (79%)	NR	0.25
Christ-Crain (2004)(p)		55/124 (44.4%)	99/119 (83%)	NR	<0.0001
Christ-Crain (2006)(p)		128/151 (85%)	149/151 (99%)	NR	<0.001
Schuetz (2009)(p)		506/671 (75.4%)§	603/688 (87.6%)§	-12.2 (-16.3 to -8.1)	NR
Stolz (2007)(p)	Index exacerbation ECOPD: no of courses of antibiotics within 6 months	(21/51) (40%) 46	36/50 (72%) 43	NR	<0.0001 0.290
Pooled ED		**798/1100(72.5%)**	**972/1115(87.2%)**	**-0.15 (-0.18 to -0.11)**	**<0.00001**

NR—not recorded

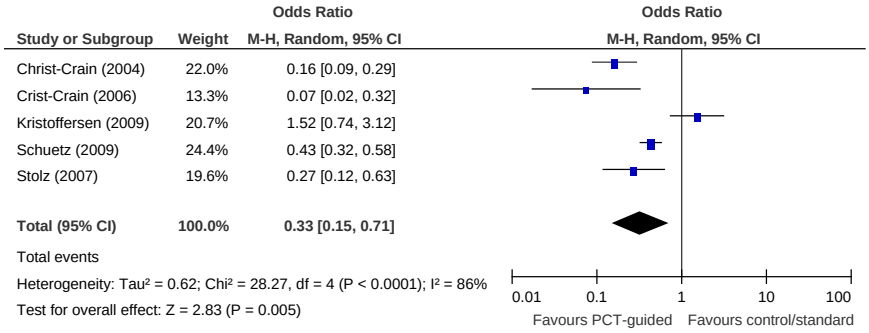
[a] In total, includes as advised by PCT=23, PCT overruled by Dr=36 ; (p) Primary endpoint of the trial; § Includes both hospitalised plus outpatients; ** Lost-to-follow-up, N=3; # Lost to follow-up, N=1

Figure 12: Forest plot of pooled odds ratios for antibiotics prescribed



Seven studies reported as an outcome, the number of antibiotics prescribed. All studies, with the exception of Kristoffersen (2009), reported significant reductions in antibiotic prescribing (see Table 36). The use of a PCT-guided algorithm resulted in a significant decrease in antibiotic prescribing across the studies, pooled OR 0.21 (95% CI 0.08–0.51). However, there was significant heterogeneity in the results (χ^2=107.18, $I^{2=}$94%). Across the studies, the rate of antibiotic prescribing in the control arm varied markedly, from a low of 37.1% to 99%, reflecting differences in the trial populations and the trial settings. Both trials conducted in the primary setting had results that were favourable towards PCT-guided therapy. Briel et al. (2008), in particular, was very favourable. Figure 13 presents data on the prescription of antibiotics outcome for only the studies conducted in the ED.

Figure 13: Forest plot of pooled odds ratios for prescription of antibiotics, emergency department



Five studies reported on the prescription of antibiotics in the ED (see Figure 13). The rate of antibiotic prescription was 798/1100 (72%) in the PCT-guided group and 972/1115 (87%) in the control group. The use of a PCT-guided algorithm resulted in a significant decrease in antibiotic prescribing, pooled OR 0.33 (95% CI 0.15–0.71). However, there is still significant heterogeneity in the results (χ^2=28.27, I^2=86%). The study by Kristoffersen (2009) has results that differ in direction from the other studies. This is likely due to the fact, that the investigators did not contact the participating departments or physicians to check whether they were adhering to the PCT guidelines. Additionally, in this study, the guidelines recommended a lower level of PCT (>0.5 ug/l) at which to initiate antibiotic therapy.

Table 37 presents data from the trial on the days of antibiotic exposure.

Table 37: Outcome—days of antibiotic exposure

Study	Variable description	PCT	Control	Absolute difference (95% CI)	P value
Intensive care					
Bouadma (2010)(p)	Per 1,000 days	653	812	-159 (-185 to -131)	p<0.0001
Stolz (2009)(p)	Antibiotic-agent days	1,077	1,341	NR	NS
Jensen (2011)	Spent with at least three antimicrobials	3570 (65.5)	2721 (57.7)	NR	0.002

NR—not reported; NS—not significant
(p) Primary endpoint of the trial

Three studies reported on the days of antibiotic exposure as an outcome of the trial. Jensen et al. (2011) reported on the number of ICU days spent with at least three antimicrobials and found significantly less days were spent by the standard-of-care-only group on at least three antibiotics compared to patients in the PCT-guided group. Bouadma (2010) reported a significant decrease in days of antibiotic exposure by patients in the PCT-guided group compared to those in the standard-of-care group, whereas Stolz (2009) reported no significant difference in the days of antibiotic exposure between the two arms of the trial (see Table 37). Stolz (2009) also reported on the rate of antibiotic discontinuation guided by the PCT algorithm, giving a hazard rate (95% CI) for PCT group v. control of 2.235 (1.077 to 4.64; P=0.031) and after adjustment for age, respiratory tract culture results and centre effect, for PCT v. control on day 28 of 1.66 (1.02 to 2.71).

Table 38 presents data on the number of patients hospitalised in the trials.

Table 38: Outcome—hospitalisations

Study	Variable description	PCT N=275	Control N=275	Risk difference (95% CI)	P value
Primary care					
Burkhardt (2010)		0	1	NR	NS
Emergency department					
Christ-Crain (2004)		101/124 (81%)	88/119 (74%)	NR	0.16
Christ-Crain (2006)		146/151 (97%)	146/151 (97%)	NR	1.0
Schuetz (2009)	 Recurrence/ rehospitalisation	628/671 (93.7%) 25 (3.7)	629/688 (91.4) 45 (6.5)	N/S -2.8 (-5.1 to -0.4)	NS
Stolz (2007)	Rate for ECOPD within 6 months	18 (17.7)	22 (20.8)	NR	0.507

NR—not reported; NS—not significant

Five studies reported on hospitalisation as an outcome measure. None of the studies reported a significant difference between PCT-guided patients or control/standard therapy in patients requiring hospitalisations (see Table 38).

Table 39 presents data on the length of hospital stay for patients in the trials.

Table 39: Outcome—length of hospital stay (days)

Study	Variable description	PCT	Control	Days difference (95% CI)	P value
Emergency department					
Kristoffersen (2009)(p)	Mean (95% CI)	5.9 (5.1–6.9)	6.7 (5.9–7.7)	NR	0.22
Christ-Crain (2004)	Mean (SD)	10.7 (8.9)	11.2 (10.6)	NR	0.89
Christ-Crain (2006)	Mean (SD)	12.0 (9.1)	13.0 (9.0)	NR	0.35
Schuetz (2009)	Mean Patients with CAP	9.4 8 (5–13)	9.2 8 (4–12)	1.8* (-6.9 to 11.0)	NR
Stolz (2007)	Median (IQR)	9 (1–15)	10 (1–15)	NR	0.960
Intensive care studies	ICU unit stay				
Svoboda (2007)	Mean (SD)	16.1 (6.9)	19.4 (8.9)	NR	0.09
Jensen (2011)	Median (IQR) ICU admission length	6 (3–12)	5 (3–11)	NR	0.04
Bouadma (2010)	ICU stay mean (SD) Hospital stay, mean (SD)	15.9 (16.1) 26.1 (19.3)	14.4 (14.1) 26.4 (18.3)	1.5 (-0.9 to 3.9) -0.3(-3.2 to 2.7)	P=0.23 P=0.87
Hochreiter (2009)	ICU stay, mean (SD)	15.5±12.5	17.7±10.1	NR	0.046
Stolz (2009)	Median (IQR)	26 (7–21)	26 (16.8–22.3)	NR	0.153
Stolz (2009)	ICU free days alive, median (IQR)	10 (0–18)	8.5 (0–18)	NR	0.526
Schroeder (2009)		16.4±8.3	16.7±5.6	NR	NS
Nobre (2008)(ITT)	ICU length of stay, median (range) Hospital length of stay, median (range)	4 (1–21) 17 (3–96)	7 (1–91) 23.5 (5–44)	NR	0.02 0.85

NR—not reported; NS—not significant; ITT—intention-to-treat; (p) primary endpoint of the trial; *relative mean change

All studies, conducted in the ED or ICU reported on length of hospital/ICU stay as a trial outcome (see Table 39). The studies by Hochreiter (2009) and Nobre (2008) reported a significant decrease in ICU stay for patients in the PCT-guided group, of two days and three days respectively. However, the studies by Jensen et al. (2011) and Bouadma (2010) report a one day increase in time spent in the ICU for patients in the PCT-guided group. The other studies reported non-significant results.

Table 40 presents data on the number of days on mechanical ventilation for patients in the ICU.

Table 40: Outcome—number of days on ventilator

Study	Variable description	PCT	Control	Absolute difference (95% CI)	P value
Intensive care					
Svoboda (2007)	Days on MV, mean (SD)	10.3 (7.8)	13.9 (9.4)	NR	0.08
Bouadma (2010)	Nos of days without mechanical ventilation, mean (SD)	16.2 (11.1)	16.9 (10.9)	-0.7 (-2.4 to 1.1)	NR
Stolz (2009)	Nos of day without mechanical ventilation, median (IQR)	21 (2–24)	19 (8.5–22.5)	NR	0.455
Jensen (2011)	Number of days with MV**	3569 (65.5%)	2861 (60.7%)	-4.9 (-6.7 to -3.0%)	NR

MV—mechanical ventilation; NR—not reported

**Estimates and statistics were made as a 'fraction of days followed in the intensive care unit' and percentages are calculated from the actual time in the ICU. Because the ICU length of stay was increased in the PCT group, statistics may underestimate the differences.

Four trials reported days on mechanical ventilation as a secondary trial outcome (see Table 40). The trial by Jensen et al. (2011) reports a statistically significant difference, in favour of the standard therapy group, in the number of days that patients required mechanical ventilation. There was no significant difference noted between patients in the PCT-guided group or standard therapy for days on mechanical ventilation for the other three trials.

Table 41Table 41 presents data on the need for admission to ICU for patients in the trials.

Table 41: Outcome—need for admission to an intensive care unit

Study	PCT	Control	Risk difference% (95% CI)	P value
Emergency department				
Kristoffersen (2009)	7/103 (7%)	5/107 (5%)	0.02* (-0.04 to 0.08)	0.51
Christ-Crain (2004)	5/124 (4%)	6/119 (5%)	-0.01* (-0.06 to 0.04)	0.71
Christ-Crain (2006)	20/151 (13%)	21/151 (14%)	-0.01* (-0.08 to 0.07)	0.87
Schuetz (2009)(p)	43/671 (6.4%)	60/688 (8.7%)	-2.3 (-5.2 to 0.4)	NR
Pooled analysis	75/1049(7.15%)	92/1065(8.64%)	-0.01* (-0.04 to 0.01)	0.21

NR—not reported; (p) primary endpoint of the trial; * calculated based on information provided in the published journal article;

Four of the studies undertaken in the ED reported on the need for admission to an ICU as a trial outcome (see Table 41). The use of PCT-guided therapy did not appear to result in an increase in the need for ICU admission.

Table 42 reports on the number of days of missed work due to illness for trial participants.

Table 42: Outcome—days of missed work

Study	Variable description	PCT	Control	P value
Burkhardt (2010)	Days incapable of working (SD)	4.3* (4.8)	3.9* (4.9)	0.066
Briel (2008)	Days of work missed within 14 days	4.9 (4.6)	4.8 (4.2)	NS

NS—not significant; * N=1 lost in PCT arm and N=3 lost to follow-up in control arm

Both studies conducted in a primary care setting reported on days of missed work as an outcome measure. Neither study reported any difference between the different trial groups for this outcome (see Table 42).

Table 43 reports on the patients with ongoing symptoms or relapsing infection at day 28.

Table 43: Outcome—patients with any ongoing symptoms of relapsing infection

Study	Variable description	PCT	Control	P value
Burkhardt (2010)	With RTI symptoms day 28	87/274* (27.6%)	76/272* (31.6%)	0.298
Briel (2008)	Ongoing or relapsing infection day 28	59 (30)	67 (30)	NS

NS—not significant; * N=1 lost in PCT arm and N=3 lost to follow-up in control arm

Both studies conducted in a primary care setting reported on patients presenting with ongoing symptoms of RTI after 28 days. Neither study reported any difference between those patients treated according to PCT-guided therapy and the control (see Table 43).

Table 44 reports on the days with adverse events from antibiotics.

Table 44: Outcome—days with adverse events from antibiotics

Study	Variable description	PCT	Control	Days [risk] difference (95% CI)	P value
Primary care					
Burkhardt (2010)	With RTI symptoms day 28	5.6* (2.2)	6.1* (3.7)	NR	0.940
Briel (2008)	Within 14 days (SD) Rate difference	2.3 (4.6)	3.6 (6.1)	0.8 (0.4 to 1.2)	NR
Emergency department					
Schuetz (2009) #	No.%	133/671 (19.8%)	193/688 (28.1%)	[-8.2] (-12.7 to -3.7)	NR

NR—not reported; * N=1 lost in PCT arm and N=3 lost to follow-up in control arm; # part of composite primary outcome

The Schuetz et al. (2009) trial, conducted in an ED, reported that patients in the PCT-guided arm had a statistically significant reduction in adverse events, such as diarrhoea, rash and nausea, when compared to patients in the standard therapy arm. This is reflective of the increased prescribing rate that was recorded in the control arm (see Table 36). Both of the studies conducted in a primary care setting reported on the median number of days patients suffered from adverse events from antibiotics. There was no statistical difference in the trials between those patients treated according to PCT-guided therapy and the control (see Table 44).

Table 45 presents data from the trials reporting on the disease specific complications.

Table 45: Days with disease specific complications or organ support

Study	Variable description	PCT	Control	Risk difference (95% CI)
Intensive Care				
Schuetz (2009)	Disease specific complications (%)	17 (2.5%)	14 (2.0%)	0.5 (-1.1 to 2.0)
	Death	34 (5.1%)	33 (4.8%)	0.3 (-2.1 to 2.5)
Jensen (2011)	Mechanical ventilation	3569 (65.5%)	2861 (60.7%)	-4.9 (-6.7 to -3.0)*
	ICU days spent with dialysis treatment	1214 (22.3%)	982 (20.8%)	-1.5 (-3.1% to 0.1)
	ICU days with vasopressors/inotropes	1564 (28.7%)	1393 (29.5%)	0.8 (-1.0% to 2.6)
	ICU days with severe sepsis/septic shock	1097 (20.1%)	924 (19.6%)	-0.6 (-2.1% to 1.0)
	Death	190/604 (31.5%)	191/596 (32.0%)	0.6 (-4.7 to 5.9)

The Schuetz et al. (2009) and Jensen et al. (2011) trials reported on disease specific complications and both studies expressed some concern about the outcomes for the PCT-guided arm (see Table 45). As mortality would also be a disease specific complication, these results have been included again in this table. The results from the Schuetz et al. (2009) trial show that the trend is towards increased disease specific complications and death in the PCT-guided arm of the trial, although results did not reach significance. The results from the Jensen et al. (2011) show that the need for organ support, such as mechanical ventilation, was significantly greater in the PCT-guided arm, significantly so, in the need for mechanical ventilation, but that the number of deaths did not differ between the two arms of the trial.

Emergency care studies

Five studies, of patients with the signs and symptoms of LRTI, were set within an ED (Christ-Crain 2004 & 2006 et al.; Kristoffersen 2009; Schuetz et al. 2009; Stolz 2007). The study by Schuetz et al. (2009) had as its primary outcome, an overall composite adverse outcome (death from any cause, ICU admission for any reason, disease specific complications and acute respiratory distress syndrome). Patients in the PCT-guided group did not have a higher risk of the combined adverse outcome compared to patients in the control group. However, there was a trend to poorer outcomes, in respect to the number of deaths and disease specific complications.

All studies reported as a study outcome, prescription of antibiotics. Three of the studies (Christ-Crain 2004 & 2006 et al.; Stolz 2007) reported a statistically significant reduction in prescriptions for antibiotics, and the pooled results indicate a significant reduction in the number of prescriptions for antibiotics (see Figure 12). The duration of antibiotic therapy was also statistically reduced in favour of the PCT-guided arm of the trial (see Figure 11). The potential consequences of a reduction in the prescription of antibiotics for LRTI, in the form of an increase in hospitalisation—Kristoffersen (2009) did not report this outcome as all patients were admitted— the length of hospital stay or an increase in mortality rates, were reported as secondary endpoints by most of the studies, with the exception of Schuetz et al. (2009). None of these studies reported an increase in the length of hospital stay or in the mortality rate resulting from adherence to the PCT-guided therapy (see Tables 34, 38 & 39). The study by Stolz (2007), which included only patients with ECOPD, reported that PCT-guided antibiotic therapy at the index

exacerbation allowed a significant sustained reduction in total antibiotic exposure for up to six months (RR, 0.76; 95% CI, 0.64 to 0.92; P=0.004) without any difference in either the mean time to the next exacerbation treated or the hospitalisation rate. Kristoffersen (2009) is the one study that did not demonstrate a reduction in antibiotic use, likely due to the lower levels of PCT at which antibiotic therapy was recommended.

It appears that measurement of PCT, and use of a PCT algorithm, alongside clinical assessment and other routine tests, results in a reduction in the use of antibiotics. However, consequences, in the form of an increase in disease specific complications or death, cannot be definitively dismissed. The majority of studies were not powered to answer this question, and the one study that was (Schuetz et al. 2009), showed a non-significant increase in deaths and disease specific complications.

Conclusions: primary care studies

The primary endpoint of the trial by Briel et al. (2008) was the restriction on activities that may result from a reduction in antibiotic use. The study did not find any difference in the restriction on activities for patients in the PCT-guided group compared to control (8.7 v. 8.6). For Burkhardt (2010) the primary endpoint was days with impairment due to RTI within the first fourteen days. Similarly, the study found that days with significant health impairment were similar (9.04 PCT v. 9.00 control). There was no difference found after adjusting for age, gender, BMI, symptom scores, co-morbidities, smoking, alcoholism and study site.

The two studies conducted in a general practice setting did not have mortality as an outcome. However they did explore whether use of PCT-guided therapy changed patient management. Both indicated that PCT-guided therapy resulted in significant reductions in prescriptions for antibiotic therapy (see Table 36) and both studies followed up participants to determine whether there were any ongoing consequences in terms of days of missed work, ongoing symptoms/infection or hospitalisation. No difference was found (see Tables 42, 43 & 44). In both these studies, the decision to treat with antibiotics was ultimately that of the GP who could accept or reject the advice from the PCT algorithm. Both studies had the same PCT threshold (0.25 ng/ml), under which it was considered unlikely that the participant would have an infection. This was the threshold for the prescription of antibiotics, alongside the initial decision of the treating physician. The use of PCT-guided therapy resulted in a change in management by clinicians resulting in a significant reduction in the use of antibiotics.

It appears, as demonstrated by Table 36, that measurement of PCT can be used to provide a reliable indication of the need for antibiotic treatment in RTI in the general practice setting and that routine use of measurement of PCT, alongside clinical assessment, results in a reduction in the use of antibiotics. However, neither study was powered to address the question of whether there were any consequences in the form of relapse, hospitalisation or death from the reduction in antibiotic treatment.

Intensive care studies

Seven studies reported on the use of PCT-guided therapy within an ICU setting. Three of these studies reported mortality as a primary endpoint of the trial for PCT-guided antibiotic therapy (Bouadma 2010; Jensen et al. 2011; Svoboda et al. 2007). None of these trials reported a statistically significant difference in mortality. The study by Svoboda et al. reports the most favourable results in favour of the PCT-guided therapy, but this study is small and the information published is not sufficient to determine if the trial was powered to detect difference between the arms of the trial in the number of

deaths. This study used high levels of PCT (≥2 mg/ml) to indicate the presence of bacteremia.

The trials reported the need for ongoing organ support of patients in the ICU, primarily in the form of the number of days that patients required mechanical ventilation. Jensen et al. (2011) also reported the difference in the need for ongoing dialysis and treatment with vasopressors and inotropes between the PCT-guided arm and standard therapy. The study by Jensen et al. (2011) reported a statistically significant difference, favouring standard therapy, for the days that patients required mechanical ventilation, whereas the other studies (Bouadma 2010; Stolz 2009; Svoboda et al. 2007) reported no statistically significant difference.

Five studies reported statistically significant reductions in the number of days that patients required antibiotic therapy, but the study by Jensen et al. (2011) reported that patients in the PCT-guided arm had an increase in the median duration of therapy. However, this outcome—duration of antibiotic therapy for patients in the ICU—is not equivalent across the trials. Some of the studies only reported the duration of the first therapy, while other studies report for the time in ICU, reducing the potential for meaningful comparison across the studies. Nevertheless, the reported reduction in antibiotic use did not appear to be accompanied by an increased risk in mortality for the PCT-guided group (see Table 34). The consequence of a reduction in antibiotic therapy—length of hospitalisation—was reported by two of the studies (Hochreiter 2008; Nobre 2008) conducted in the surgical ICUs. They noted that patients in the PCT-guided therapy had significantly shorter length of stay in the ICU. Conversely, the study by Jensen et al. (2011) reported a statistically significant increase in ICU stay of one day for patients in the PCT-guided arm. The other study in this population, Svoboda et al. (2007), was trending towards a significant decrease in ICU length of stay (P=0.09). The other studies were not significant for this outcome.

Jensen et al. (2011) reported a significant difference between the PCT-guided therapy arm compared to the control arm, in the administration of appropriate antimicrobials in blood stream infection, counting from the time of culture sampling (-0.1 days v. 0.8 days, PCT v. control, P=0.02).

The patient populations within the ICUs differed within the studies, and between studies, with some studies including mainly medical patients (Bouadma 2010, 90% medical), a mixture of surgical and medical patients (Jensen et al. 2011; Nobre 2008; Stolz 2009) or some surgical/multiple trauma patients (Hochreiter 2008; Schroeder 2009; Svoboda et al. 2007). The difference in the underlying populations makes any definitive summary of the studies and comparison across their outcomes difficult. It appears from the studies that measurement of PCT can be used alongside clinical assessment as an indicator of sepsis. However, it is not clear whether this will lead to a reduction in antibiotic therapy in the ICU setting. It is also unclear whether following a PCT-guided algorithm for initiating or ceasing antibiotic therapy will have negative consequences for patients in terms of increased risk of death, as the majority of the studies were not powered to answer this question. The one study that was powered to detect 28-day mortality (Jensen et al. 2011) reported no difference, but did report concern regarding the need for more intensive organ-related support of patients in the PCT-guided arm.

Other issues

Is it accurate?

In this section, evidence is presented about the diagnostic accuracy of the measure of PCT. The requested listing is for measurement of PCT to be included alongside clinical assessment, other indirect biomarkers of infection (e.g., CRP) and other tests, and not as a diagnostic test for bacterial infection. However, the expert Advisory Panel requested that evidence pertaining to the accuracy of PCT in the diagnosis of sepsis also be presented in the assessment and in particular threshold cut-offs used in the studies to diagnose infection. Therefore, this section of the report does not set out an exhaustive case for the diagnostic accuracy of the measure of PCT in diagnosing bacterial infection. Instead, it presents studies that have been conducted within the populations of interest to this assessment including patients with the signs and symptoms of LRTI in primary care or ED settings; or patients with the signs and symptoms of sepsis in an ICU setting, as well as published meta-analysis. The outcomes from these studies, when logical, are presented in the same table, to allow for comparison. Appendix D provides a full list of the included studies comprising inclusion and exclusion criteria, baseline characteristics of the included population and the assays used in the studies.

Table 46 presents a list of the studies included in the accuracy review.

Table 46: Included studies: measure of PCT compared to culture

Study	Quality	Country	Study design	Participants/setting	Outcome
Intensive care					
Luyt (2008)	II	France	Prospective cohort study PCT level Reference standard= clinically suspected VAP and BAL cultures	N=41 consecutive ICU patients with clinically suspected VAP after 48 hrs of MV 73 suspected episodes of VAP included in analysis	Diagnostic value of PCT measured the day VAP suspected (D1). Diagnostic value of PCT kinetics, using PCT values obtained within the 5 days preceding D1 also tested retrospectively. Sensitivity, specificity, PPV, NPV, NLR, PLR
Bell (2003)	II	Australia	Prospective cohort study Senior ICU registrars blinded to PCT results Reference standard= cultures of blood, BAL, sputum, urine	N=123 consecutive ICU patients fulfilling established criteria for SIRS included	Diagnostic accuracy of PCT in discrimination of infectious SIRS from non-infectious SIRS
Balci (2003)	II	Turkey	Prospective cohort study Treating clinicians blinded to PCT results and those performing PCT assays blinded to clinical status of patient Reference standard=blood cultures	N=33 consecutive ICU adults with SIRS, sepsis or septic shock	Determine PCT levels at early diagnosis and differentiation in patients with SIRS and sepsis (also a comparison with CRP, IL-2, IL-6 and IL-8)
Ruokonen (2002)	II	Switzerland	Prospective cohort study Reference standard=blood cultures	N=208 adult consecutive ICU patients over 12 months suspected of severe infection	Differentiation of sepsis and infection from systemic inflammation in critically ill patients
Du (2003)	III-1	China	Prospective cohort study Diagnosis done blind to lab results Reference standard=blood cultures, tracheal aspirate	N=51 ICU non-consecutive patients with a diagnosis of SIRS, sepsis or septic shock	Diagnostic accuracy of PCT to discriminate between sepsis and non-infectious SIRS

Cheval (2000)	III-3	France	Controlled study Reference standard=blood cultures	N=60, four groups of consecutively acutely ill patients Septic shock patients N=16; NSS (non-septic shock patients) N=18; Infected patients (infect group) N= 16; Control group without infection or shock N=10	Diagnostic accuracy of PCT to predict bacterial or fungal infection and severity of illness
Giamarellos-Bourboulis (2004)	II	Greece	Prospective cohort study Reference standard= blood cultures	N=105 consecutive ICU patients	Range of PCT conferring to specific diagnosis of sepsis, severe sepsis and septic shock Diagnostic accuracy
Brunkhorst 2000)	III-1	Germany	Prospective cohort study Reference standard=ACCP/SCCM	N=185 consecutive ICU patients	Diagnostic accuracy of PCT to differentiate SIRS, sepsis and severe sepsis
Ruiz-Alvarez (2009)	II	Spain	Prospective cohort study Reference standard=micro biological or x-ray (pneumonia)	N=103 consecutive ICU patients (N=22 surgical, N=81 medical) who had suspected sepsis/SIRS	Diagnostic accuracy Prognostic markers Comparison of PCT and CRP (not reported)
Castelli (2006)	II	Italy	Prospective cohort study Blinded to results of serum PCT levels Infection reference standard=ACCP/SCCM defined SIRS and definable infection (microbiology confirmed) and/or blood cultures	N=153 consecutive ICU patients Trauma patients admitted with trauma and studied in the acute phase SIRS patients with no defined source of infection No SIRS (or trauma) Sepsis/SS with SIRS and known source of infection and/or positive blood cultures Divided into septic shock, severe sepsis and sepsis	Variations of PCT in the diagnosis of sepsis, severity of disease and septic complications of trauma NOTE: Results reported as clinical events
Boussekey (2005)	II	France	Prospective cohort study Reference standard=BAL, endotracheal aspirate, blood or pleural fluid culture	N=110 consecutive patients admitted to ICU with severe CAP	ROC curves to assess the sensitivity and specificity to predict either a positive bacterial etiology or death Based on values of PCT upon admission to the ICU

Emergency department/primary care					
Lai (2010)	II	Taiwan	Prospective cohort study Infection specialists blinded to PCT levels Reference standard=blood cultures	N=262 consecutive adults ≥65 yrs with criteria for SIRS who visited ED	Diagnosis of bacteremia in patients with SIRS on admission Diagnostic sensitivity, specificity, PPV, NPV of very elderly patients with bacteremia
Muller (2010)	III-1	Switzerland	Prospective cohort study with predefined sub-study of ProHOSP RCT Reference standard=blood cultures	N=925 with radiologically confirmed CAP Adult patients admitted to hospital (via ED)	Secondary endpoint of ProHOSP RCT was prognostic accuracy of PCT for blood culture positive
Holm (2007)	II	Denmark	Prospective cohort study Radiologist blinded Reference standard=chest x-ray infiltrate, blood or sputum culture	N=364 consecutive adults with LRTI treated in primary care	Range of PCT values in primary care Accuracy of PCT to discriminate between bacterial and viral pneumonia Predict outcome
Jones (2007)	I*	USA	Systematic review of available studies Reference standard=blood cultures	Prospective investigation of adults and children with suspected infection in ED on admission N=2,008 subjects	Diagnostic accuracy of PCT test for diagnosis of bacteremia
Uzzan (2006)	I*	France	Systematic review of available literature	Adults in ICU or after surgery or trauma N=3,943	The accuracy of serum procalcitonin as a diagnostic test for sepsis, severe sepsis or septic shock

VAP—ventilator associated pneumonia; MV—mechanical ventilation, BAL—bronchalveolar lavage

*It is not possible to determine whether the systemic review was only of level II studies, as neither review includes a quality of assessment of the included studies.

Systematic reviews

Two systematic reviews and meta-analyses investigated the accuracy of PCT. The studies are Uzzan et al. (2003) and Jones et al. (2007). The review by Jones et al. (2007) includes studies of paediatric patients, which is a broader population than has been considered above.

1. Uzzan, B, Cohen, R, Nicolas, P, Cucherat, M & Perret, GY 2006, 'Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis', *Critical Care Medicine*, vol. 34, no. 7, pp. 1996–2003

This review used as its inclusion criteria, a PCT measure used as a diagnostic test in ICUs or after surgery or trauma. Only articles written in English and French were included. Medline via PUBMED was searched. The search identified 33 studies meeting the inclusion criteria (see Table 47). However, of these, eight studies were rejected, as no statistical calculation was possible. Results are presented in Table 48.

The included studies and results are included in Tables 47 & 48 below. The term sepsis used in the study is broader than that used in the ACCP/SCCM consensus conference criteria and includes sepsis, severe sepsis and septic shock. Non-septic SIRS refers to a systemic inflammatory response syndrome where no source of infection was found and non-infectious conditions (e.g., burns or pancreatitis) caused SIRS.

Table 47: Main characteristics of the studies eligible and assessed for meta-analysis

Study by first author	Type of patient	C	Blinded study	Eligible/assessed	N
Castelli (2004)	SIRS v. sepsis Polyvalent ICU	C	Yes	Assessed	150
Clec'h (2004)	Septic shock v. non-septic shock Polyvalent ICU	C	?	Assessed	75
Balci (2003)	SIRS v. sepsis Polyvalent ICU	C	Yes	Assessed (authors)	33
De Talance (2003)	SIRS v. sepsis medical ICU	?	Yes	Assessed	108
Du (2003)	SIRS v. sepsis Polyvalent ICU	C	Yes	Assessed	51
Geppart (2003)	Septic shock v. cardiogenic shock Cardiac ICU	?	?	Assessed (authors)	55
Luzzani (2003)	Polyvalent ICU	C	?	Assessed (authors)	70
Giamarellos-Bourboulis (2002)	SIRS v. sepsis Polyvalent ICU	?	?	Assessed	119
Ruokonen (2002)	SIRS v. sepsis Polyvalent ICU	C	?	Assessed (authors)	208
Tugrul (2002)	SIRS v. sepsis Polyvalent ICU	?	Yes	Assessed	85
Harbarth (2001)	SIRS v. sepsis Polyvalent ICU	C	Yes	Assessed	78
Yukioka (2001)	SIRS v. sepsis Medical ICU	C	Yes	Eligible	35
Brunkhorst (2000)	Medical ICU	C	Yes	Assessed	185
Cheval (2000)	Septic shock v. non-septic shock Polyvalent ICU	C	Yes	Assessed	60
Muller (2000)	Medical ICU	C	Yes	Assessed	101
Oberhoffer (2000)	SIRS v. sepsis Surgical ICU	C	?	Assessed (authors)	242
Selberg (2000)	SIRS v. sepsis Medical ICU	?	?	Assessed	33
Suprin (2000)	SIRS v. sepsis Medical ICU	C	Yes	Assessed	101
Ugarte (1999)	SIRS v. sepsis Medical ICU	C	?	Assessed	205
Whang (1998)	Polyvalent ICU	C	?	Eligible	29
De Werra (1997)	Septic v. cardiogenic shock Medical ICU	?	?	Eligible	29
Hensler (2003)	SIRS v. sepsis Trauma/surgical ICU	C	?	Assessed (authors)	137
Wanner (2000)	SIRS v. sepsis Trauma	C	No	Assessed	405
Benoist (1998)	SIRS v. sepsis Trauma/surgical ICU	C	?	Assessed	21
Dorge (2003)	Cardiac surgery + CPB/surgical ICU	C	?	Assessed	80
Kabir (2003)	SIRS v. sepsis Polyvalent ICU	C	?	Eligible	15
Meisner (2002)	SIRS v. sepsis CABG + prosthesis + CPB/surgical ICU	C	Yes	Assessed	208
Adamik (2000)	Cardiac surgery + CPB/surgical ICU	?	?	Eligible	83
Aouifi (2000)	Surgical ICU	?	Yes	Assessed	97
Baykut (2000)	SIRS v. sepsis Cardiac surgery + CPB/surgical ICU	C	?	Eligible	400
Boeken (2000)	SIRS v. sepsis Cardiac surgery + CPB/surgical ICU	No	?	Eligible	74
Reith (2000)	SIRS v. sepsis Surgical ICU	No	?	Eligible	312
Rothenburger (1999)	Cardiac surgery + CPB/surgical ICU	C	?	Assessed	59

C—the study included consecutive patients; SIRS—systemic inflammatory response syndrome; ICU—intensive care unit; CPB—cardiopulmonary bypass; CABG—coronary artery bypass graft; assessed study means a study where meta-analytic calculations could be performed for PCT; (authors) means that the study could be assessed thanks to additional data provided by authors

The mean age of the patients included in the review was 56 years, ranging from 29 years in patients in a trauma study to 66.5 years in patients in a polyvalent ICU. The 33 studies included 1,825 infected patients and 1,545 non-septic SIRS patients, the rest being non-septic non-SIRS controls. Global mortality rate was 29.3%. The pooled percentage of patients with positive blood cultures was 24.9%. It was reported that all studies but one had a prospective design (this study was included in the results). Twenty-three studies recruited their patients consecutively and observers were blinded to the results of PCT levels in thirteen studies. It was reported by the study that PCT was always obtained on admission or early in the course of sepsis and usually during the first week after admission, sepsis or surgery. For all studies included in the meta-analysis, PCT was measured using the same ILMA, with a functional detection limit of 0.3 ng/mL, with 20% interassay coefficient of variation (LUMItest PCT, Brahms Diagnostica GmbH, Berlin, Germany).

Results

To combine the data from the independent studies, this study used a three-step approach based on summary receiver operating characteristic (SROC) curves with an unweighted model using linear regression to combine the data. Firstly, for each study, sensitivity and specificity was calculated; secondly, the difference and sum for each study was calculated; and thirdly, a SROC curve using a simple linear regression model was constructed.

Table 48: Results of the individual studies (Uzzan 2006)

	Cut-off	Sensitivity %	Specificity %					
Study by first author	**PCT ng/ml**	**PCT**	**PCT**	**Non-septic SIRS No.**	**Septic shock No.**	**Total sepsis No.**	**Gender M/F**	**Death No. (%)**
Castelli (2004)	1.11	79	85	15	15	71	96/54	29/150 (19)
Clec'h (2004)	1	95	54	13	62	62	51/24	50/75 (67)
Balci (2003)	2.97	82	100	12	6	21	17/16	10/33 (30)
De Talance (2003)	2	91	89		27	90	76/32	31/108 (28.7)
Du (2003)	1.6	80	74	31	10	20	31/20	13/51 (25)
Geppart (2003)	2	87	75	40	15	15	41/14	36/55 (65.5)
Luzzani (2003)	2	76	84			38	?	14/70 (20)
Giamarellos-Bourboulis (2002)	1	94.5	64.5	29	10	38	84/35	43/119 (36)
Ruokonen (2002)	0.8	68	48	46	25	162	?	66/208 (31.4)
Tugrul (2002)	1.3	73	83	10	41	75	39/46	40/85 (47)
Harbarth (2001)	1.1	97	78	18	25	60	57/21	27/78 (34.6)
Yukioka (2001)				16	12	19	22/13	11/35 (31.4)
Brunkhorst (2000)	2	96	86	17	39	168	?	52/185 (28)
Cheval (2000)	5	88	67	28	16	32	34/26	21/60 (35)
Muller (2000)	1	89	94			58	55/46	23/101 (23)
Oberhoffer (2000)	1.35	84	83	117	45	70	152/90	
Selberg (2000)	3.3	86	54	11		22	20/13	16/33 (59)
Suprin (2000)	2	65	70	20	24	75	63/32	30/95 (31.6)
Ugarte (1999)	0.6	68	61	79		111	124/66	53/190 (27.9)
Whang (1998)	1.08	67	80					14/29 (50)
De Werra (1997)					15	22	18/11	()
Hensler (2003)	1.5	42	73	45		88	102/35	15/137 (11)
Wanner (2000)	1.5	75.5	77	161		45	301/104	93/405 (23)
Benoist (1998)	5	100	100	12		4	?	1/21 (5)
Dorge (2003)	5	63	62	53		27	55/25	17/80 (21.3)
Kabir (2003)				5		10	12/3	()
Meisner (2002)	2	87	78	193		15	?	()
Adamik (2000)				42	20	41	24/17	25/41 (61)
Aouifi (2000)	1	85	95	43	12	54	70/33	()
Baykut (2000)				364		27	269/131	()
Boeken (2000)				15		15	15/15	()
Reith (2000)	0.8			66		246	?	59/246 (24)
Rothenburger (1999)	4	86	98	44		7	?	()

NOTE: This table in the study by Uzzan et al. (2006) also included results for CRP but these have not been reported.

There appears to be a discrepancy with the results reported. The study reports that of the 33 studies identified as meeting the inclusion criteria, eight studies were rejected, as no statistical calculation was possible. This would leave 25 studies. However, the results in the table in this study include 27 studies with a PCT test and 26 studies reporting sensitivity and specificity results for PCT.

Uzzan et al. (2006) reports that of the 25 studies (or 26) using PCT (2,966 patients), sensitivities ranged from 42% to 100% and specificities ranged from 48% to 100%. The optimal cut-off values for PCT, determined from the receiver operating characteristics (ROC) curves, ranged from 0.6 to 5 ng/mL. When infection was compared with non-septic SIRS, PCT had a global diagnostic accuracy odds ratio of 15.7 (95% CI, 9.1–27.1, $p<.0001$). This means that the risk for a positive PCT test in infected patients was about 16-fold higher than in non-infected patients.

The study authors conclude that PCT represents a good biological diagnostic marker for sepsis, severe sepsis or septic shock and is superior to CRP.

2. Jones, AE, Fiechtl, JF, Brown, MD, Ballew, JJ & Kline, JA 2007, 'Procalcitonin test in the diagnosis of bacteremia: A meta-analysis', *Annals of Emergency Medicine*, vol. 50, no. 1, pp. 34–41.

This systematic review included seventeen studies that met the inclusion criteria of being an investigation involving an outpatient population studied either in the ED or at admission to the hospital, and a proportion of the subjects must have received both the PCT test and a test for blood culture. The included studies had 2,008 subjects. Quality of the reference standard was part of the inclusion criteria and a positive outcome was defined as a blood culture positive for a pathogenic organism (procedures for blood culture were not part of the inclusion criteria). Patients were both self-referred and physician referred. The methodological quality characteristics for studies included in the meta-analysis were the reference standard used, potential for differential reference standard bias and an appropriate patient spectrum. The meta-analysis used sensitivity analysis to assess for spectrum bias. They graded the patient's spectrum according to the following: Grade A included consecutive or random sampling of an outpatient population presenting with signs and symptoms of infection; grade B included selected subgroups(s) of outpatients with suspected infection; and grade C included case series or ambiguous inclusion criteria that could not be clarified by corresponding authors. All grade C studies were excluded from the analysis.

The primary data analysis was the PCT test performance assessed using SROC curve analysis, the diagnostic odds ratio and pooled sensitivity and specificity values. The SROC curve analysis was based on an unweighted least-squares regression model.

Results

Table 49 presents the results of the individual studies included in the Jones et al. (2007) systematic review.

Table 49: Summary of the included studies

Study by first author	N	Sensitivity %	Specificity %	Prevalence %	PCT cut-off ng/ml	Pop.	Patient Spect-rum	Patient Setting*	Patient† disposition
Han (1999)	105	66.7 (30.0–90.3)	97.0 (91.5–99.0)	5.7	0.5	Ped.	B	ED	Unclear
Fleischhack (2000)	110	56.3 (33.2–76.9)	87.2(79.0–92.5)	14.5	0.5	Ped.	A	ED	Admission
van Langeveide (2000)	381	81.8 (70.9–89.3)	51.4 (45.9–56.9)	17.3	0.5	Adult	A	Hospital	Admission
Lacour (2001)	91	100.0 (51.0–100.0)	60.9 (50.4–70.5)	4.4	0.9	Ped.	A	ED	Mixed
Guven (2002)	34	100.0 (77.2–100.0)	81.0 (60.0–92.3)	38.2	2.0	Adult	B	ED	Mixed
Chirouze (2002)	163	95.5 (78.2–99.2)	57.4 (49.2–65.3)	13.5	0.4	Adult	A	Hospital	Admission
Delevaux (2003)	168	81.0 (60.0–92.3)	81.0 (73.8–86.5)	12.5	0.5	Adult	A	Hospital	Admission
Han (2003)	90	87.1 (71.1–94.9)	49.2 (36.8–61.6)	34.4	0.5	Ped.	A	Hospital	Admission
Scott (2003)	24	100.0 (20.7–100.0)	69.6 (49.1–84.4)	4.2	0.5	Adult	B	ED	Mixed
Lacour (2003)	88	75.0 (30.1–95.4)	52.4 (41.8–62.7)	4.5	0.5	Ped.	B	ED	Mixed
Prat (2004)	65	100.0 (81.6–100.0)	83.3 (70.4–91.3)	26.2	2.0	Ped.	B	ED	Unclear
Ciaccio (2004)	54	89.7 (73.6–96.4)	16.0 (6.4–34.7)	53.7	0.5	Ped.	B	Hospital	Admission
Caterino (2004)	108	53.8 (29.1–76.8)	71.6 (61.8–79.7)	12.0	0.5	Adult	B	ED	Unclear
Giamarellou (2004)	158	48.1 (35.1–61.3)	65.1 (55.6–73.5)	32.9	1.0	Adult	B	Hospital	Admission
Bugden (2004)	183	88.9 (56.5–98.0)	89.1 (83.6–92.9)	4.9	0.5	Mixed	A	ED	Mixed
Persson (2004)	94	54.3 (38.2–69.5)	81.4 (69.6—89.3)	37.2	0.5	Adult	B	Hospital	Admission
Aslto (2004)	92	92.3 (66.7–98.6)	68.4 (57.5–77.6)	14.1	0.4	Adult	A	ED	Admission

ED—emergency department, Ped—Paediatric; Prevalence refers to the prevalence of bacteremia among outpatients
*Patient setting refers to the setting from which patients were identified (ED, ED Only and Hospital) at the time of admission to the hospital
†Patient disposition refers to the ultimate disposition of included patients (admitted, discharged, mixed, admitted and discharged patients or unclear)

The review reported that there was no evidence of a threshold effect among the seventeen studies with the slope of the regression line reported as near zero (β=0.018; 95% CI -0.44–0.48) and not statistically significant (P=0.93). There was, however, a substantial degree of inconsistency reported (I^2=64%). Consequently, the unweighted

SROC curve was considered to provide the best overall estimate of test performance, AUC=0.84 (95% CI 0.75–0.90). Most of the heterogeneity was explained by differences in the patient spectrum. When the SROC curve was limited to studies rated grade A for patient spectrum, only a small degree of inconsistency was found (I^2=31%). This did not affect the shape of the ROC and performance of the test did not change, AUC=0.86 (95% CI 0.78–0.90). The diagnostic odds ratio was reported as 9.86 (95% CI 5.72–17.02). The study reported that only including paediatric studies did not significantly change the shape of the SROC, AUC=0.85 (95% CI 0.63–0.95). A subgroup analysis included only the most common test threshold of 0.5 or 0.4 ng/mL, which revealed moderate inconsistency among results (I^2=46%). Independently pooled estimates for sensitivity and specificity were reported as 76% (95% CI 66–84%) and 70% (95% CI 60–79%) respectively.

One of the limitations of this review is that it does not report whether any of the studies were blinded. In addition, the review did not explore the characteristics of the test assays used in the individual studies.

The conclusion of the review by Jones et al. (2009) was that the diagnostic performance of the PCT for identifying bacteremia in ED patients was only moderate.

Individual intensive care studies of diagnostic accuracy

The study by Luyt et al. (2008) was a six-month prospective cohort study that included consecutive patients who were clinically suspected of having developed VAP after 48 hours of mechanical ventilation and who had a PCT measurement obtained 5 days preceding the first day. The 46 included patients were suspected of VAP 84 times during the study period. For eleven suspected episodes (five patients), a 'before' serum PCT measurement was not available and not included in the analysis. VAP was diagnosed when the following two criteria were met:

- Clinically suspected VAP was defined as a new pulmonary infiltrate or progression of an existing infiltrate on chest radiography and was associated with at least one of the following:
    - temperature of 38.3ºC or higher,
    - white blood cell count 10^9/l, and
    - purulent tracheal secretions.

    Note: in patients with acute respiratory distress syndrome, in whom the demonstration of radiological deterioration is difficult, at least one of the three preceding criteria sufficed.
- Significant growth ($\geq 10^4$ cu/ml) in quantitative cultures of distal BAL fluid samples was obtained by fiber-optic bronchoscopy.

None of the patients receiving antibiotics on day one had had their antibiotic regimen modified during the preceding three days.

The study by Bell et al. (2003) was a prospective cohort study in which consecutive adult patients who fulfilled established criteria for SIRS were included in the study. Senior ICU registrars, blinded to PCT results, completed a questionnaire on each patient on day one and day four to define clinical suspicion of bacterial sepsis. This questionnaire was then reviewed by the registrar involved in the study and patients were assigned to the clinical infection or non-infection groups. Patients were grouped as non-infectious SIRS if there was a low clinical suspicion of bacterial infection on both day one and day four, with all culture results negative. Mann-Whitney tests were used to assess the significance

of differences in maximum PCT and CRP between different subgroups of categorical variables. Spearman rank correlations were used to quantify the association between maximum PCT, CRP and other continuous variables. Logistic regression analysis was performed for blood culture status with results to maximum PCT and APACHE II.

Balci et al. (2003) conducted a six-month prospective study of consecutive patients staying more than 24 hours in the ICU. Patients who had chronic organ failure, thyroid cancer or pancreatitis, had received massive blood transfusions, or whose anticipated duration of stay was under 24 hours, were excluded from the study. Ten patients died on the second day following admission to the ICU, having undergone only two assessments. Thus, a total of 89 assessments ('conditions') of the patients clinical status were conducted, 48 of which indicated SIRS (53% of all patients), 35 sepsis (39% of all patients) and six septic shock (7% of all patients).

Ruokonen et al. (2002) did a twelve-month prospective study of consecutive heterogeneous patients admitted to an adult ICU suspected of having a severe infection. Patients were eligible for the study if they became febrile during their stay in the ICU and the clinician in charge decided to take samples for blood culture (suspected sepsis). The samples of patients with fever and consecutive septic shock, as defined by ATS/SCCP, were analysed as a subgroup. Blood samples for the analyses of PCT were taken from central intravenous catheters at the time of study inclusion, and thereafter every 8 hours over two days.

In the study by Cheval et al. (2000), four groups of consecutive acutely ill patients were included: a septic shock patients group, non-septic shock patients, infected patients and a control group without infection or shock. A total of 60 patients were included in the study. Septic shock was defined according to the ACCP/SCCM criteria. Non-septic shock was defined as a systolic blood pressure, <90 mm Hg, requiring more than 500 ml macromolecules or the use of vasopressive drugs, and as another cause of shock and non-ongoing infectious process. SIRS was defined as the presence of at least two of the following criteria: tachycardia more than 90 beats/min, tachypnoea more than twenty breaths/min, mechanical ventilation, temperature, abnormality (>38ºC or <36ºC) or white blood cell abnormality (>12000/mm^3 or <4000/mm^3). Infection was defined as SIRS with a proven site of bacterial infection without signs of severe sepsis. Control was defined as ICU admission for pathological processes unrelated to infection and without signs of organ hypoperfusion or shock. All patients with sepsis were treated by their own physicians using standard therapy for sepsis and septic shock and appropriate antimicrobials.

The study by Du et al. (2003) took place between October 2001 and March 2002, on all patients admitted to ICU with an expected ICU stay of more than 72 hours and who were screened for inclusion in the study. Within 24 hours of study inclusion, a routine septic workup including blood cultures was performed. The clinical investigation and classification were carried out without knowledge of the test results of PCT or IL-6, which were analysed as batch analyses at the end of the study.

The study by Ruiz-Alvarez et al. (2009) was a prospective observational study of consecutive patients admitted to an ICU, the majority of whom were classified as medical and suspected of SIRS/sepsis. Acute physiology and Chronic Health Evaluation II and SOFA scores were performed for each patient, based on their first 24 hours in ICU. Blood samples were collected within the first 24 hours of admission. Blood cultures were performed on the admission day and thereafter when a patient's temperature was >38ºC. The primary outcome was the infection status of the patients. The

ACCP/SCCM criteria were used to identify patients in the following categories: SIRS, sepsis, severe sepsis and septic shock.

Castelli et al. (2006) undertook a prospective observational study of consecutive adults patients admitted to ICU, with the exception of neurosurgical and elective surgical patients without complications. At the time of admission and every day thereafter, signs and symptoms and clinical and laboratory data were collected. Samples were collected from fluids, surgical wounds, catheters and drainage systems for culture, and blood cultures were collected if the patient's temperature >38º. The ACCP/SCCM criteria were used to identify patients with sepsis, severe sepsis, septic shock and SIRS. The grading of sepsis was assessed with sepsis score. Each clinical event (and results reported as clinical events) was recorded for a maximum of ten days and based on observations and laboratory results split into trauma, SIRS, no SIRS and sepsis/septic shock. Two hundred and fifty-five clinical events were reported in the study (150–152 patients appear to have been included).

Boussekey et al. (2005) enrolled consecutive patients within 48 hours of admission to ICU for severe CAP with collected PCT levels. Patients were compared based on identification of a causative agent. To test the prognostic value of PCT, patients were compared on the occurrence of bacteremia, septic shock, infection-related complications and mortality. PCT values were used to stratify the patients into three different classes, according to cut-offs recommended by the manufacturer of the test, PCT <0.5ng/ml (probable exclusion of any bacterial infection), ≥2 ng/ml (probable diagnosis of bacterial infection) and <2 ng/ml (no definitive conclusion).

Emergency department setting

The study by Lai et al. (2010) was a prospective observational study, which included consecutive adults aged ≥65, who attended the ED and fulfilled the criteria for SIRS. SIRS was defined as the presence of two or more of tachycardia, tachypnea or hypoxia, hyperthermia or hypothermia and leukocytosis, leukopenia or bandemia. Exclusion criteria from the study were missing data or loss of follow-up and pre-existing thyroid disease, because of its possible effect on PCT evaluation. Two hundred and sixty-two elderly patients with SIRS were recruited during the one-year study period.

Muller et al. (2010) did a sub-study of a subgroup of patients included in the ProHOSP RCT (Schuetz et al. 2009) of patients with LRTI, who were admitted from the community or nursing home to hospital and who had LRTI and radiologically confirmed CAP and two sets of pre-treatment blood cultures.

Primary care setting

Holm et al. (2007) undertook a prospective observation study of consecutive adults who presented to their primary care with LRTI; patients requiring hospitalisation were excluded. The study chose potentially clinically relevant cut-off points for PCT at the level of the functional sensitivity of the test (0.06 ng/ml) and at the two levels for suspected bacterial infection as stated by the manufacturer (0.25 and 0.50 ng/ml). Additionally, two cut-off points of 0.08 and 0.1 ng/ml between the functional sensitivity and the expected level for bacterial infection were also chosen.

Results

The mean age of patients who were included in the studies conducted in an intensive care setting, included in the accuracy review, differed widely from a low of 55 years in the Ruokonen et al. (2002) study through to 77 years in Ruiz-Alvarez et al. (2009). The proportion of males included in the trials varied from 51.5 to 76%. In respect to the type

of infection, most of the studies provide little information. Infection, when it was recorded, usually states bacterial and no site is recorded. Six of the studies record whether patients were suffering from SIRS, sepsis or septic shock at baseline. Boussekey et al. (2005) records that 38% of patients were suffering from septic shock, Brunkhorst et al. (2000) that 39% had septic shock, while 68% had sepsis/severe sepsis and 17% had SIRS. Du et al. (2003) reports 61% as suffering from SIRS and Balci (2003) recorded that 53% of patients had SIRS, 39% had sepsis and 7% had septic shock.

Two studies, Lai et al. (2010) and Muller et al. (2010), sought to determine the diagnostic accuracy of measurement of PCT in bacterial infection in the ED. The Holm et al. (2007) study sought to predict pneumonia in primary care and compared PCT to CRP. Only elderly patients were included in the Lai at al. (2010) study, at an average age of 77 years, which is similar to patients included in the study by Muller et al. (2010), at 73 years. Holm et al. (2007) does not record the age of included patients, just that they were adults.

Outcomes

The results of the individual studies in the intensive care setting are provided below in Table 50. The results for the studies set in the ED and primary care are shown in Table 54.

Table 50: Primary outcome from individual studies in intensive care patients

Study	Reference Standard	Sensitivity	Specificity	PPV	NPV	AUC	PLR	NLR
Luyt (2008) Day 1 PCT level	BAL cultures							
≥0.5 ng/ml		72 (57–84)	24 (14–38)	43 (31–55)	53 (34–71)		0.95	1.17
≥1 ng/ml		53 (37–68)	37 (24–51)	40 (27–53)	50 (34–66)		0.84	1.27
≥1.5 ng/ml		44 (29–59)	51 (37–65)	41 (27–56)	54 (40–68)		0.90	1.09
≥2 ng/ml		41 (26–56)	61 (47–74)	45 (29–61)	57 (43–70)		1.05	0.97
PCT increased 'before' D1[a]		41 (26–56)	85 (74–93)	68 (49–84)	65 (53–76)		2.73	0.69
=0 ng/ml		26 (14–41)	86 (74–93)	57 (35–77)	61 (49–72)		1.86	0.86
≥0.5 ng/ml		19 (10–34)	90 (81–96)	60 (35–81)	60 (49–71)		1.90	0.9
≥1 ng/ml								
						AUC	**Accuracy**	
Bell (2003)[b] Cut-off	BAL, blood and urine cultures							
≥3.03 ng/mL		83	48	50	83			
≥15.75 ng/mL		75	91	83	86			
Balci (2003) Reported best cut-off[c] 2.415 ng/mL	Blood cultures	85	91	89	95	0.969 ±0.016		
Ruokonen (2002) Patients with infection (95% CI)	Blood cultures					0.61 (0.52–0.70)		
Cut-off levels								
Day1 ≤0.8 ng/L		67.7	47.8				63.3	
Day2 ≤0.9/ng/L		60.9	63.0				61.2	
Cheval (2000) Discriminate SS from NSS	Blood cultures							
Threshold ≥5 ng/ml[e]		88±11%	67±16%			0.902 (0.73–0.98)		
Du (2003) Predict septic and non-infectious SIRS patients	Blood cultures and tracheal aspirate	80	52	52	80	0.817 ±0.064	63	
		Sensitivity	**Specificity**	**PPV**	**NPV**	**AUC**	**PLR**	**NLR**
Ruiz-Alvarez (2009) Diagnosis of sepsis	Blood cultures	83 (73.1–90.6)	62 (40.7–80.4)	88 (77.9–94.0)	54 (34.2–71.9)	0.8 (0.7–0.9)	2.2 (1.3–3.7)	0.3 (0.1–0.4)
Best cut-off value 0.32 ng/mL								
Castelli (2006) Diagnosis for sepsis/SS v. SIRS	Blood cultures or microbiology confirmed	83	81	80		0.88 (0.84–0.93)		
(excluding trauma patients) Best cut-off								

values 0.47 ng/mL Diagnosis of sepsis v. SIRS[i]						0.76 (0.67–0.85)		
Boussekey (2005)[i] Bacterial documentation[i] Survival[j]	BAL, tracheal aspirate or pleural fluid cultures and blood cultures					0.685 0.723		

PPV—positive predictive value; NPV—negative predictive value; PLR—positive likelihood ratio; NLR—negative likelihood ratio; VAP—ventilator associated pneumonia; MV—mechanical ventilation; BAL—bronchalveolar lavage; D1—day one; SS—septic shock; NSS—non-septic shock

[a] 'Before' to D1 differences were calculated with the following formula: PCT D1-'before'

[b] The positive group were all patients with positive blood cultures and those patients without a positive blood culture formed the negative group

[e] For predicting sepsis

[d] At a given specificity of 80%

[e] OR: 6.2, 95% CI:1.1–37, P=0.04)

[f] Prevalence of 38% for severe sepsis/septic shock

[g] PCT≤2.0

[h] Prevalence of 41% for septic shock ≤11.6 ng/ml

Not clear from study in trauma population (N=49) included or excluded.

[i] Study reports that could not identify a specific threshold to differentiate positive from negative CAP based on PCT values

[j] Unable to identify cut-off values that significantly related to mortality

The study by Luyt et al. (2008) reported that no best PCT cut-off values for VAP diagnosis could be established. Using a threshold of ≥0.5 ng/ml yielded 72% sensitivity but only 24% specificity, which is explained by day one PCT of 0.5 ng/ml or higher in 31 of the 41 refuted-VAP episodes. The predictive ability of the day one PCT concentration to diagnose VAP using four different thresholds in reported in Table 50 . Between 'before' and day one, PCT level increased in 41% of patients with VAP and 15% of patients without VAP. Thus, a PCT rise on day one, compared to its 'before' level, had 41% sensitivity and 85% specificity for diagnosing VAP, with respective positive predictive value (PPV) and negative predictive value (NPV) of 68% and 65%. The study concluded that crude values and PCT rise had a poor diagnostic value for VAP in this particular setting and that they should not be used to initiate antibiotics when VAP is clinically suspected.

The results from the study by Bell et al. (2003) indicate that, given the inherent trade-off between sensitivity and specificity, different cut-off values for the inflammatory markers can be chosen depending on whether it is to be used as a screening test to rule out sepsis (with a high sensitivity and NPV) or as a diagnostic test (with high specificity and PPV).

The study by Baci (2002) found that PCT exhibited the greatest sensitivity (85%) and specificity in differentiating patients with SIRS from those with sepsis, at a PCT cut-off value of 2.415 ng/mL. They conclude that as the NPV is high, this makes measurement of PCT a good screening test to rule out sepsis at this cut-off.

Ruokonen et al. (2002) found (in a large heterogeneous ICU patient population) that although PCT has a certain predictive value, it did not discriminate infection from inflammation with sufficient sensitivity and specificity to produce a substantial clinical benefit. In addition, PCT levels did not consistently increase in patients developing septic shock during the study. It was noted in this study that there was no difference in peak PCT levels between the patients with Gram-positive and Gram-negative infections. One hundred and sixty-two patients were infected in this study, with 59 diagnosed with LRTI, 32 with pneumonia, 32 with gastrointestinal tract infection, 20 with skin and soft

tissue infection and the other infections are not described. Twenty-two patients had positive blood cultures, but the determination of diagnostic accuracy is not limited to these patients but to 162 infected patients. It may be for this reason that the accuracy of the test in this study is only 63.3% in comparison to other studies, which compare only those patients with positive blood cultures to those without. Table 51 reports the peak PCT values of infected patients v. non-infected patients; infected patients with positive blood cultures v. those with negative blood cultures; and patients with shock v. patients without shock.

Table 51: Peak PCT values (Ruokonen 2002)

Total N=208	Non-infected N=46	Infected N=162	Bloodstream N=22	Shock N=25
Peak PCT ug/L, median [IQR]				
Day 1	1.1 [0.4–3.6]	1.9 [0.6–8.1]*	25.7 [2.0–68.8]***	18.4 [5.3–56.0]***
Day 2	0.7 [0.3–2.6]	1.4 [0.5–6.3]*	14.4 [4.4–43.8]**	16.9 [5.7–36.8]***

IQR—interquartile range
*P<0.05, **P<0.01, ***P<0.001

Du et al. (2003) found that the PCT results were elevated (>0.5 ug/L) in eighteen out of twenty (90%) septic patients and in 15 out of 31(48%) SIRS patients. The PCT concentrations of all septic patients were significantly higher than those of non-infectious SIRS patients. There was a statistically significant difference in the median (25%–75% percentiles) PCT levels reported—3.6(1.8–27.5) and 0.5 (0.2–1.8)—between septic and non-infectious SIRS patients respectively. The ability of PCT to predict septic and non-infectious patients, was reported as an AUC of 0.817, however the best predictor was reported to be IL-6 with an AUC of 0.871.

Ruiz-Alvarez et al. (2009) reported that the prognostic value of PCT levels showed no difference between survivors and non-survivors (P=0.23). This study reports that PCT (as well as SOFA scores) was independently associated with the diagnosis of infection in a multivariate logistic regression model (PCT, coefficient B 1.34, 95% CI, 1.24–11.82, P=0.02). The Hosmer-Lemeshow test was used to check the goodness of fit of the model.

The study by Castelli et al. (2006) reported that PCT levels correlated in trauma patients with SOFA (0.465, p<0.001; Pearson's correlation) and concentrations increased progressively with organ dysfunction. The correlation matrix and regression line of PCT and SOFA score was: trauma patients (PCT=-5+2.16SOFA), infected (PCT=-2.102+1.496SOFA) and non-infected (PCT=0.031+0.0663SOFA)

The study by Boussekey et al. (2005) used PCT values to stratify the patients into three different classes according to cut-offs recommended by the manufacturer; PCT <0.5ng/ml (probable exclusion of any bacterial infection), ≥2 ng/ml (probable diagnosis of bacterial infection) and <2 ng/ml (no definitive conclusion). The study found that even if the admission mean PCT value was far above the critical cut-off threshold of ≥2 ng/ml (24±80 ng/ml), 50% of the patients had values <2 ng/ml, with 20% at <0.5 ng/ml. It concluded that these results suggest that this marker is not an interesting tool to diagnose severe CAP. However, the study reported that PCT appears to be a better indicator to assess CAP severity; a high level is associated with a high incidence of bacteremia, severe sepsis, infection-related complications and finally, mortality (see Tables 52 &53). Forty-eight patients (43.7%) had the causative organism identified. Median initial PCT levels were higher when an etiologic agent was recovered—4.9 ng/ml

(1.2–20.8) v. 1.5 ng/ml (0.4–4.9); P=0.0009. A PCT level of ≥2 ng/ml was found in 81% of patients with pneumococcal CAP, in 43.8% of patients with CAP due to Gram-negative bacilli and in 72.7% of patients with CAP due to another agent (essentially *S. aureus*). In patients without any microbial documentation, a PCT level of ≥2 ng/ml was observed in 37.1% of cases.

Table 52: PCT levels according to bacterial diagnosis (Boussekey 2005)

Causative pathogen	PCT <0.5 ng/ml N=22	0.5≤PCT<2 ng/ml N=33	PCT ≥2 ng/ml N=55	Total	P value*
None (N=62) No. (%)	18 (29)	21 (33.9)	23 (37.1)	100%	0.003
Positive (N=48) No. (%)	4 (8.3)	21 (33.9)	32 (66.7)	100%	-
-Streptococcus pneumonia	2 (9.5)	12 (25)	17 (81)	100%	-
-Gram-negative bacilli	2 (12.5)	7 (43.7)	7 (43.8)	100%	-
-Other	0	3 (27.3)	8 (72.7)	100%	-

*Comparison between all groups

Table 53: Prognostic value of PCT and mortality (Boussekey 2005)

Patient outcome	PCT < 0.5 ng/ml N=22	0.5≤PCT ng/ml N=33	PCT ≥2 ng/ml N=55	Comparison between all groups P value
Deceased	3 (10)	4 (13.3)	23 (76.7)	0.003
Survivors	19 (23.7)	29 (36.3)	32(40)	

Individual studies undertaken in the emergency department/primary care

Table 54: ROC curves for prediction of bacteremia defined by positive blood cultures in the emergency department and in primary care

		AUC	AUC for group with bacteremia	Best cut-off value for PCT	Sensitivity	Specificity	PPV	NPV
Lai (2010)	65–74	0.554	0.639*	NR	NR	NR	NR	NR
	≥75 N=155	0.672	0.817*	0.383 ng/mL	96.0%	63.2%	33.8%	98.8%
Muller (2010)			0.82 (0.77–0.86)				LR+	LR-
	>0.1ng/ml				99	13	1.14	0.10
	>0.25ng/ml				96	40	1.59	0.11
	>0.5ng/ml				88	55	1.94	0.23
	>1.0 ng/ml				84	64	2.35	0.26
Holm (2007)	ng/ml						PPV	NPV
Pneumonia v. Non-Pneumonia	>0.06				0.70	0.66	0.24	0.94
	>0.08				0.49	0.83	0.30	0.91
	>0.10				0.36	0.92	0.41	0.91
	>0.25				0.23	0.99	0.73	0.89
	>0.50				0.17	1.00	1.00	0.89

NR—not reported
*P=0.02

The study by Lai et al. (2010) in Table 54, notes that bacterial infection was confirmed in 204 (77.9%) of elderly patients in the ED. The infection specialists who classified patients into the bacterial infection and non-bacterial infection groups were blinded to the PCT results. The majority of patients included in the study (76%) with bacterial infections were localised without bacteremia, and the PCT levels of patients with localised bacterial infections were significantly lower than those of patients with bacteremia. The study reports that PCT would be a useful tool in excluding bacteria in this group of elderly patients if a cut-off value of 0.38 ng/mL was established. The poor specificity and PPV of PCT in the study was reported to be due to slight but not significantly higher PCT levels in patients with local bacterial infection. It was concluded that the high sensitivity and NPV of the test could be used to rule out sepsis at the cut-off value of 0.383 ng/mL in those aged 75 years or over. The clinical characteristics of the patients in this study, stratified by infection status, is provided in Table 55.

Table 55: Comparison of clinical and laboratory features of elderly patient with SIRS and with or without bacteremia at emergency department admission (Lai 2010)

Variable	Patients without bacterial infection N=58**	Patients with bacterial infection N=204**	With bacteremia N=48	Without bacteremia N=156	P value
Age	76.3±7.6	77.4±8.3	75.4±8.1	78.1±8.2	0.47
Immunocompromised condition			28 (58.3)	87 (55.8)	<.001
Fever	33 (56.9)	138 (67.8)*	39 (81.3)	90 (57.7)	0.005
WBC, cells/ul, mean±SD	9,499±5,669	12,730±10,764	14,676±19,034	12,130±6,352	0.14
Procalcitonin, ng/mL, mean ±SD	0.89±2.45	7.3±26.7	17.0±45.0	4.3±16.7	0.004
CRP, mg/mL, mean ±SD	5.2±6.1	8.2±0.006	10.0±9.1	7.4±6.8	0.3

* The number reported in Table 2 of Lai et al. (2010) is 268, which is greater than the total number of patients enrolled in the study. This figure is calculated based on information provided in the journal article.
** The infection specialists who classified patients into the bacterial infection and non-bacterial infection groups were blinded to the PCT results.

Muller et al. (2010) concluded that in his study of patients with CAP admitted to hospital from the ED, PCT proved the most reliable predictor of blood culture positivity. Cut-offs at <0.25 ng/ml identified patients at very low risk for bacteremic episodes and helped avoid unnecessary blood culture sampling. Increased PCT levels of >0.5 ng/mL and especially >1 ng/mL identified patients who would benefit from early and aggressive diagnostic workup and antibiotic therapy. Muller et al. (2010) concluded that PCT correlates with the extent and severity of microbial infection and is a more useful biomarker than CRP and WCC.

The study by Holm et al. (2007) found that most adults diagnosed with LRTI in primary care had PCT levels below 0.06ng/ml (30% of pneumonia patients and 66% of patients with non-pneumonia LRTI). Elevated PCT was found to be significantly associated with pneumonia, bacterial infection of the lower respiratory tract, and the risk of hospitalisation within four weeks, but high PPVs were associated with unacceptably low sensitivities. The study concluded that there were not any findings to support the use of PCT in LRTI in primary care. A limitation of the study was that few patients had pneumonia and that an etiological agent was not found in a large proportion of the patients. However, both the proportion of patients found to have pneumonia and the proportion of patients with a final etiological diagnosis were noted to be similar to findings in other studies in primary care. The PCT levels of patients included in this study are shown in Table 56.

Table 56: PCT levels in the study population (Holm 2007)

PCT level	All patients N=364	Pneumonia N=48	Non-pneumonia N=316	P value
>0.06 ng/ml	139/357 (39%)	33/47 (70%)	106/310 (34%)	<0.001
>0.08 ng/ml	77/357 (22%)	23/47 (49%)	54/310 (17%)	<0.001
>0.10 ng/ml	41/357 (11%)	17/47 (36%)	24/310 (8%)	<0.001
>0.25 ng/ml	15/357 (4%)	11/47 (23%)	4/310 (1%)	<0.001
>0.50 ng/ml	8/357 (2%)	8/47 (17%)	0/0	<0.001
Below detection level <0.02 ng/ml	35/357 (10%)			
Below functional sensitivity <0.06 ng/ml	218/357 (61%)	14/47 (30%)	186/310 (60%)	
Median PCT ng/ml (IQR)	0.05 (0.04–0.08)			
Total range ng/ml	0.02–42.92			

In addition, the following three studies have recently been published

- Dallas et al. (2011) assessed the ability of PCT to diagnose nosocomial pneumonia among a cohort of 1,200 medical and surgical ICU patients who met predefined clinical and microbiologic criteria for definite nosocomial pneumonia. The report found that plasma PCT had minimal diagnostic value for nosocomial pneumonia.
- El-Solh et al. (2011) assessed the predictive accuracy of serum PCT to distinguish bacterial from aspiration pneumonia in 65 consecutive patients admitted to an ICU with pulmonary aspiration. Quantitative cultures from BAL were conducted. This study found that serum PCT levels had poor diagnostic value in separating bacterial aspiration pneumonia from aspiration pneumonia based on BAL culture. However, they reported that serial measurements of serum PCT might be helpful in predicting survival.
- Riedel et al. (2011) studied 295 patients admitted to the ED with symptoms of systemic infection, who had PCT levels obtained at the same time as blood cultures. PCT levels less than 0.1 ng/ml were considered negative, above this was considered positive for infection. This study calculated a threshold of 0.1475 ng/mL for PCT and the sensitivity and specificity of PCT assay were 75% and 79%. The PPV was 17% and the NPV was 98%. This study found PCT to be a useful marker to rule out sepsis and systemic inflammation in the ED.

Key uncertainties of the individual studies of diagnostic accuracy

The following uncertainties were noted with respect to the evidence concerning the accuracy of PCT in diagnosing sepsis:

- The inclusion and exclusion criteria of patients included in the studies are rarely discussed. This is important because patients can be excluded from the studies on the basis of factors that may affect PCT levels, for example:
    - Thyroid levels;
    - Recent Blood transfusions;
    - Pancreatitis; and
    - Chronic organ failure.

- In many studies, little information is provided about the site of the infection in patients.
- The underlying population of the patients that has been included—that is, only surgical patients, a mix of surgical and medical or medical patients only, is not always clear and this difference makes the summarising of results not necessarily meaningful.
- Reasons for admission to ICU are not always provided in the studies.
- How patients are categorised into sepsis or septic shock—that is, the criteria used, is not always reported.
- In some studies, PCT levels alone are used to categorise patients. In other studies, the PCT levels are included as part of a diagnostic criteria. The approach used in the studies is not always clear.
- Clear guidelines are not always provided about when blood cultures were taken, with some taken prior to admission to ICU, some on admission to ICU and others only when temperature >38°.
- It is not clear when antibiotic therapy was commenced in some patients.
- Length of time that patients have been in the ICU unit is not always reported.
- Consistent information about the accuracy of levels of PCT, needed to reliably differentiate between infectious and non-infectious SIRS, is lacking.

Key uncertainties of the individual studies of clinical effectiveness

The following uncertainties were noted with respect to the evidence concerning the use of measurement of PCT to guide antibiotic therapy in patients with suspected sepsis:

- The majority of studies conducted in the ED setting were not powered to answer the question: Were there any consequences for patients in reducing antibiotic therapy? The only study, Schuetz et al. (2009), that was powered to answer this question, showed a non-significant increase in deaths and disease specific complications.

- Neither study conducted in the primary care setting was powered to address the question of whether there were any consequences in the form of relapse, hospitalisation or death from the reduction in antibiotic treatment.

- The patient populations for the studies conducted within ICUs differed within and between studies, with some studies including mainly medical patients only (Bouadma 2010, 90% medical) a mixture of surgical and medical patients (Stolz 2009, Nobre 2008, Jensen et al. 2011) or only surgical/multiple trauma patients (Svoboda et al. 2007, Hochreiter 2008, Schroeder 2009). This difference in the underlying populations makes summarising outcomes across the studies not necessarily meaningful, as other factors such as surgery or blood transfusions can also be reasons for increases in PCT levels.

- The underlying rationale for the PCT-guided algorithm does not seem to be based on the analytical sensitivity of the tests. The algorithm used was mostly consistent across the studies (i.e., it was recommended by the company), but lower levels of PCT were used to indicate the need for antibiotics in the study by Kristoffersen (2009).

- It is unclear whether following a PCT-guided algorithm for initiating or ceasing antibiotic therapy will have consequences for patients in terms of increased risk of death, as the majority of the studies in the ICU setting were not powered to

answer this question. The one study that was powered to detect 28-day mortality, (Jensen et al. 2011), reported no difference in survival, but did report concern regarding the need for more intensive organ-related support and prolonged admission to ICU of patients in the PCT-guided arm.

- The corresponding obligatory guidelines, used alongside the PCT measurements, affected the rate at which antibiotics were prescribed. Guidelines that initiated antibiotics at lower levels of PCT (Kristoffersen 2009) resulted in more prescriptions in the PCT arm and those that initiated PCT at higher levels of PCT resulted in fewer prescriptions.
- Analytical sensitivity of the assays used in the reported studies, has been evaluated for patients in the ICU setting, but interpretative risk assessment criteria has only been done for PCT levels below 0.5 ng/ml or for levels above 2.0 ng/ml.
- The frequency at which PCT levels were obtained from hospitalised patients varied. Some studies undertook PCT readings daily, while others included measurements only at the time that antibiotic therapy was being reviewed.
- The meaningfulness of comparison across the studies is limited due to high levels of heterogeneity observed in the pooled analysis. This is particularly true of the outcomes measuring the levels of prescribing of antibiotics and duration of antibiotic therapy.
- The data examined in the assessment is only from the ED, general practice and ICU settings. This is because it was in these clinical areas that the majority of randomised controlled trials had been situated. The report did not examine evidence from other settings, such as paediatrics. These clinical areas would have been examined if it were felt the evidence from the ED, general practice or ICU settings was of sufficient robustness to justify examining the use of PCT in other settings. If there is a role for PCT it may plausibly be in very defined clinical circumstances, but these clinical settings were not able to be identified because the published trials were underpowered to show unequivocally that measurement of PCT is effective, as used in the trials.

Summary of effectiveness

Routine measurement of procalcitonin, with corresponding obligatory guidelines for antimicrobial therapy, for patients presenting to the emergency department with query lower respiratory tract infection or exacerbation of chronic obstructive pulmonary disease, alongside clinical assessment and other measures of sepsis, usually resulted in a reduction in the use of antibiotics. However, only one of the trials set in the emergency department was powered to address the question of whether this reduction in antibiotic therapy had any consequences for patients and it reported non-significant increases in mortality and disease specific complications. The routine use of a procalcitonin test for every person with a query lower respiratory tract infection , in the emergency department, would result in a large number being requested. The available evidence does not justify the routine measurement of procalcitonin, and use of a procalcitonin-guided algorithm for antimicrobial therapy, in the emergency department, as used in these trials.

The routine measurement of procalcitonin, with corresponding obligatory guidelines for antimicrobial therapy, as an indicator of sepsis, alongside clinical assessment, for patients in an intensive care unit setting, may not result in a reduction in antibiotic therapy. It was unclear whether following a procalcitonin-guided algorithm for initiating or ceasing antibiotic therapy would have consequences for patients, as the majority of the studies in the intensive care unit setting were not powered to answer this question. The one study that was powered to detect 28-day mortality reported no difference in survival, but did report that patients in the procalcitonin-guided arm suffered increased rates of organ-related harm and had prolonged admission to the intensive care unit. The routine use of a procalcitonin test, in the intensive care unit setting, often recommended on a daily basis, would result in a large number being requested. The available evidence does not justify the routine measurement of procalcitonin and use of a procalcitonin-guided algorithm for antimicrobial therapy in the intensive care setting.

The routine measurement of procalcitonin, with corresponding obligatory guidelines for antimicrobial therapy, for patients presenting to their general practitioner with symptoms of respiratory tract infection, alongside clinical assessment, resulted in a reduction in the use of antibiotics in the two studies evaluated. However, neither of the trials was powered to measure any consequences to patients that may result from a reduction in antibiotic therapy. The routine use of a procalcitonin test for every person who presents to their general practitioner with the symptoms of respiratory tract infection would result in a large number being requested. The evidence does not justify the routine measurement of procalcitonin and use of a procalcitonin-guided algorithm for antimicrobial therapy in the general practice setting.

Consistent data regarding the accuracy of levels of procalcitonin in reliably differentiating between infectious and non-infectious systemic-inflammatory response syndrome appears to be lacking.

What are the economic considerations?

Economic evaluation

Assessment of measurement of PCT will not substitute for any other direct or indirect measure of sepsis. A comparative cost analysis of measurement of PCT compared to no PCT is presented. Cost effectiveness analyses were undertaken based on the evidence of clinical effectiveness from the included studies in the primary care and ED settings but not in the ICU setting. This is because evidence of the clinical effectiveness of PCT-guided therapy in the ICU was lacking.

Costs associated with treatment of infection

A cost of $60.00 per measurement of PCT is assumed, based on information provided by the applicant. For comparison, another indirect measure of infection, quantitation of CRP, MBS Item 66500, attracts a schedule fee of $9.75 as at January 2011. Comparison can also be made with a direct measure of sepsis—MBS Item 69354—blood cultures for pathogenic micro-organisms, including sub-cultures and (if performed): (a) identification of any cultured pathogen; and (b) necessary antibiotic susceptibility testing, which attracts a schedule fee of $30.94, as at January 2011. Similarly, M&C to detect pathogenic micro-organisms from specimens of sputum including (if performed): (a) pathogen identification and antibiotic testing, attracts a schedule fee of $34.00. The cost of $60 for measurement of PCT is a higher cost than similar measures used to indicate the presence of sepsis (A 2006 UK study estimated the cost of a PCT test at £30, Bignardi et al. 2006).

It is proposed that measurement of PCT will be an additional test alongside other laboratory tests and clinical judgement, incurring an additional cost to the treatment of infection.

Table 57 presents a list of other MBS items that are used to diagnose or indicate the presence of infection. The number of services and benefits for 2010 is also presented.

Table 57: MBS items associated with inflammation and infection

Item	Description fee	MBS expenditure in 2010	MBS services in 2010	Average expenditure per service in 2010
58500	Chest lung fields by direct radiology Fee: $35.35	$330,606	10,586	$31.23
69354	Blood culture for pathogenic micro-organisms To a maximum of 3 sets of cultures–1 set of cultures Fee: $30.95	$3,606,891	148,605	$24.27
69357	2 sets of cultures described in item 69354	$949,338	20,072	$61.85
69360	3 sets of cultures described in item 69354	$432,803	6,090	$92.80
69318	Microscopy and culture to detect pathogenic micro-organisms from specimens of sputum Fee: $34.00	$3,733,632	132,213	$28.23
73802	Leucocyte count, erythrocyte sedimentation rate, examination of blood film, (including differential leucocyte count), haemoglobin, haematocrit or erythrocyte count Fee: $4.60	$156,462	39,563	$3.95
66500	Quantitation in serum, plasma, urine or other body fluid (except amniotic fluid), by any method except reagent tablet or reagent strip (with or without reflectance meter) of: acid phosphatise, alanine aminotransferase, albumin, alkaline phosphatise, ammonia, amylase, aspartate aminotransferase, bicarbonate, bilirubin (total), bilirubin (any fractions), C-reactive protein, calcium (total or corrected for albumin), chloride, creatine kinase, creatinine, gamma glutamyl transferase, globuline, glucose, lactate, dehydrogenase, lipase, magnesium, phosphate, potassium, sodium total protein, total cholesterol, trigylcerides, urate or urea Fee: $9.75	5,801,711	702,529	$8.26

Table 58 Table 58 presents a copy of the AR-DRG for patients admitted as an inpatient to a public or private hospital for treatment of respiratory infection.

Table 58: Costs associated with admission or readmission to hospital or increased length of stay

AR-DRG	Description	ALOS	Cost	Average cost per day
E62C	Admission to major urban teaching hospital for respiratory infection/inflammation-CC	3.11	$3415	$1,098
	Admission to private hospital	5.01	$2,966	
E62A	Admission to major urban teaching hospital for respiratory infection/inflammation+CCC	9.79	$10,549	$1,077
	Admission to private hospital	13.09	$8,751	

NOTE: Direct comparison of total patient costs cannot currently be made between private and public hospitals. Private hospital treatment may include medical, pharmacy and pathology costs that are not included in existing private hospital cost information. These costs are included in public cost information.

Table 59 provides information on the recommended duration for treating infections from the study by Bouadma (2010).

Table 59: Guidelines for antibiotic treatment duration—control group (Bouadma 2010)

Infection site	Recommended duration of antibiotics (days)
Lower respiratory tract infections Community acquired pneumonia* Ventilator associated pneumonia†	 7–10 8–15
Abdominal infections‡ Community acquired peritonitis Nosocomial peritonitis	 5–7 7–14
Non-complicated community acquired *S. aureus* bacteremia	14
Non-complicated catheter-related bacteremia	7–14
Bacterial meningitis Community acquired meningitis Streptococcus pneumoniae Neisseria meningitidis Listeria monocytogenes Nosocomial meningitis	 10–14 5–7 21 14
Urinary tract infections Complicated acute pyelonephritis Acute prostatitis	 14 28

*A longer duration (14 days) is recommended for pneumonia caused by Legionella pneumophila, Mycoplasma pneumoniae or Chlamydia pneumonia (Mandell et al. 2007; Woodhead et al. 2005);
†When the responsible pathogen is a non-fermenting Gram-negative bacillus in immunocompromised patients or when initial antimicrobial therapy was inappropriate, 15 days of treatment may be warranted (ATS 1996; Chastre et al. 2003);
‡Antibiotic therapy duration for patients with abdominal infection has not been evaluated by randomised trials

Recent advice from the National Prescribing Service (NPS) (2005) for treatment of CAP—oral empirical antibiotic therapy—is that:

- Dual therapy be given because it gives good coverage of causative organisms which are seen in CAP in Australia. The recommendation is:
    - amoxicillin 1 g 8-hourly for 7 days PLUS EITHER
        - doxycycline 200mg for the first dose, then 100mg daily for 5 more days, OR
        - roxithromycin 300mg daily for 7 days.
    - for patients with non-immediate penicillin hypersensitivity, cefuroxime 500mg 12-hourly for 7 days (in place of amoxicillin with doxycycline or roxithromycin, as above).
    - for patients with immediate penicillin hypersensitivity, gatifloxacin (not available on PBS but available on RPBS)or moxifloxacin (authority required PBS listing) 400mg daily for 7 days as monotherapy.

Based on the antibiotic therapeutic guidelines (2010) the following information is used to estimate the type and frequency of intravenous antibiotic therapy for use in treatment of CAP and to estimate the cost of antibiotic therapy.

- PSI class III or IV (ward-managed patients): it is recommended that benzypenicillin plus doxycycline be prescribed (7–10 days). Specifically benzylpenicillin 1.2 g IV, 6-hourly until significant improvement, followed by amoxicillin 1 g orally 8-hourly for a total of 7 days plus doxycycline 100mg 12-hourly for 7 days.
- PSI class V or ICU managed patients: it is recommended that benzylpenicillin 1.2 g IV, 4-hourly, plus gentamicin 4–6 mg/kg (for severe sepsis: 7mg/kg) IV, for one dose, for a maximum of either one or two further doses based on renal function be prescribed. For patients aged 30–60 years, it is recommended that the dose of gentamicin be 5 mg/kg up to 480 mg and for patients more than 60 years of age, 4 mg/kg up to 400 mg. For subsequent dosing, it will be assumed that gentamicin is given after 36 hours i.e. assumed that 2 doses are given.

Table 60Table 60 estimates the cost of antibiotic therapy to treat community-based pneumonia using the NPS recommendations.

Table 60: Costs associated with oral antibiotic therapy to treat CAP

Antibiotic	PBS item	DPMQ	Quantity	Frequency	Length of treatment	Tablets required	Cost
Amoxycillin 1g	8581P	10.57	14 tablets	8-hourly	7 days	7*3=21 tabs (2 packs)	$21.14
Doxycycline 100mg	2709N	8.36	7 tablets	daily	6 days	5 tabs	$8.36
Total cost of an oral course of antibiotics to treat CAP							**$29.50**
Intravenous therapy for mild to moderate hospitalised CAP							
Antibiotic	**PBS item**	**DPMQ**	**Quantity**	**Frequency**	**Length of treatment**	**Nos required**	**Cost**
Benzylpenicillin 600mg	1775K	42.92	2 amps	6-hourly	4	16 amps	$686.72
Amoxycillin 1gm	8581P	10.57	14 tablets	8-hourly	7 days	21 tablets (2 packs)	$21.14
Doxycycline 100mg	2709N	8.36	7 tablets	12-hourly	7 days	(2 packs)	$16.72
Total cost for intravenous antibiotics and oral antibiotics for mild to moderate CAP							**$724.58**
Intravenous therapy for severe hospitalised CAP							
Antibiotic	**PBS Item**	**DPMQ**	**Quantity**	**frequency**	**Length of treatment**	**Nos required**	**Cost**
Benzylpenicillin 600mg	1775K	42.92	2 amps	4-hourly	8 days	48	$2,060
Gentamicin 80mg	2824P	19.66	Weight (76.8kg) #**307.2mgs	0–36 hours	2 doses	8 amps	$157.28
Amoxycillin 1gm	8581P	10.57	14 tablets	8-hourly	7 days	21 tablets (2 packs)	$21.14
Doxycycline 100mg	2709N	8.36	7 tablets	12-hourly	7 days	(2 packs)	$16.72
Total cost for intravenous antibiotics and oral antibiotics for severe CAP, 8 day course							**$2,255.14**

* Time to step down to oral antibiotic treatment median 4 days (mean 4.3 days) (Charles et al. 2008)
# All calculation based on the study by RCT of Schuetz et al. (2009). The average age of patients was 72, therefore assume 4mg/kg up to 400 mg will be the dose and 55.2% were males
** The weight used to estimate the dose of gentamicin is from the Australian Bureau of Statistics (ABS) social trends (2007) (Average weight female 68 kg and the average weight male 84 kg). The average weight based on the gender mix in the trial was 76.8kgs

Cost of the measurement of procalcitonin in the primary care setting

Table 61Table 61 presents a cost effectiveness evaluation based on the two trials conducted in patients who visited their GP with the signs and symptoms of RTI.

Table 61: Incremental cost of avoiding a course of antibiotic therapy—primary care

Trial	PCT		Standard		Increment
	N	Antibiotics prescribed	N	Antibiotics prescribed	
Burkhardt (2010)	232	58	226	219	
Briel (2008)	272	59	272	191	
Pooled	504	117	498	320	
		0.23		0.64	**0.41 (0.46,0.36)**
Cost	**PCT test**	**Antibiotics**	**PCT test**	**Antibiotics**	
PCT test	60	29.5	60	29.5	
Proportion	100%	0.23	0	0.64	
Total costs		66.79		18.96	47.83
Additional cost per course of antibiotics avoided					**$117 ($104 , $324)**

Table 61Table 61 estimates that to avoid a course of antibiotics through testing patients, who visit their GP with the signs and symptoms of RTI, for PCT levels will incur an additional cost of $117 per patient for each course of antibiotics avoided. Only the costs of the PCT test and antibiotics are included within this economic evaluation because additional information about consequences that may (or may not) occur from not prescribing antibiotics were not available from the trials. To the extent that some patients may require admission to hospital and parental therapy, the cost of antibiotic therapy may be an underestimate. One patient in the control arm of the Burkhardt (2010) trial did require hospitalisation but this was not reported as being of significance.

Cost of the measurement of PCT in the emergency department setting

Table 62 presents a cost effectiveness evaluation based on the trials conducted on patients who presented to their ED with the signs and symptoms of CAP or ECOPD.

Table 62: Incremental cost of avoiding course of antibiotics—emergency department

Trial	PCT		Standard		Increment‡
	N	Antibiotics prescribed	N	Antibiotics prescribed	
Pooled	1100	798	972	1115	
		0.725		0.872	**-0.146 (-0.18 to -0.11)**
Schuetz (2009)	671	506	688	603	
		0.754		0.876	**-0.122 (-0.163 to -0.081)**
Cost					
PCT test $60		5#	60	0	$300
Antibiotics Mild/mod $724.58 Severe $2,255.14		 0.69 0.06		 0.789 0.09	
Total antibiotic cost**		$644.49		$768.54	($124.05)
Length hospital stay		10 days		9.5	
Cost of hospital stay $1,077/day		 $10,770		 $10,231.50	 $0*
Adverse events		0.213438735		0.255389718	
Cost of adverse events $85.00†		$18.17		$21.75	($3.57)
				Total incremental cost	**$172.38**
Additional cost per course of antibiotics avoided (benefit from Schuetz)					**$1,409 ($2,128.10, $1,057.52)**
Additional cost per course of antibiotics avoided (using pooled benefit)					**$1,178 ($1,567, $958)**

Study reported PCT measurements taken on admission, day 3, 5, 7 and at discharge;
* Assuming no difference in length of stay in hospital;
† Cost of adverse events due to antibiotic use from a study by Ambrose et al. (2005);
** To derive this cost the number of patients admitted to the ICU in each arm incurred the cost of treating severe CAP. The rest of the patients were assumed to have mild/moderate CAP;
‡ Risk difference

Table 62 shows that testing patients who present to an ED for their PCT levels will incur an additional cost of approximately $1,409 for each course of antibiotics avoided. To estimate these costs, the study by Schuetz et al. (2009) was used as a basis because this study had been powered to detect a difference in the consequences of not prescribing antibiotics. The additional cost per course of antibiotics avoided, based on the pooled numbers from all trials in the ED setting, is included for comparison. Some costs could not be included. For example, the study reported that patients in the standard therapy arm had a greater likelihood of being admitted to an ICU, but the length of time patients were in an ICU was not reported. As the length of hospital stay was reported, it has been used as a proxy. This may favour the control arm. Another cost that was not included in the analysis above, is that for disease specific complications. The study reported that these complications occurred more frequently in the PCT group, but the type of complications was not described in the study. This may favour the PCT-guided arm.

Overall conclusion with respect to cost effectiveness

Longer-term analysis, for example of the likely benefit of reduced amount of antibiotic prescriptions concerning antibiotic resistance has not been done. This is primarily because it is difficult to separate out the role of the prescribing of antibiotics for non-bacterial RTI from other postulated causes of antibiotic resistance, such as the use of antibiotics in animal populations and patients not finishing their courses of antibiotics. In the event it was possible to separate out the effects of the role of prescribing of antibiotics on the emergence of resistance, expert advice is that the measurement of PCT effect size on the emergence of resistance is very small whereas the confounders are very large in these specific populations.

Measurement of PCT is not cost saving from a health care perspective compared to no measurement of PCT. The additional cost, per antibiotic prescription avoided may range from $117 to $1,409, depending on the setting in which patients are being tested and taking into consideration assumptions about likely benefits in terms of number of antibiotic prescriptions avoided. Longer-term benefits in the form of hospitalisations avoided or mortality reductions were not included in the economic evaluation, as these benefits were not demonstrated by the available evidence.

Financial analysis

To estimate the financial implications for the government of listing the measurement of PCT on the MBS, surrogate measures were used to try to estimate the likely number of tests that may be ordered. The focus was on general practice because expert clinical advice holds that this setting would likely use measurement of PCT most widely. However, estimates of the likely use of the test in the private hospital setting are also included.

To estimate the potential number of PCT tests that may be requested if measurement of PCT was listed on the MBS, an attempt was made to estimate the number of patients who may visit their GP with the signs and symptoms of a LRTI, as well as those with a diagnosis of chronic obstructive airways disease (COAD).

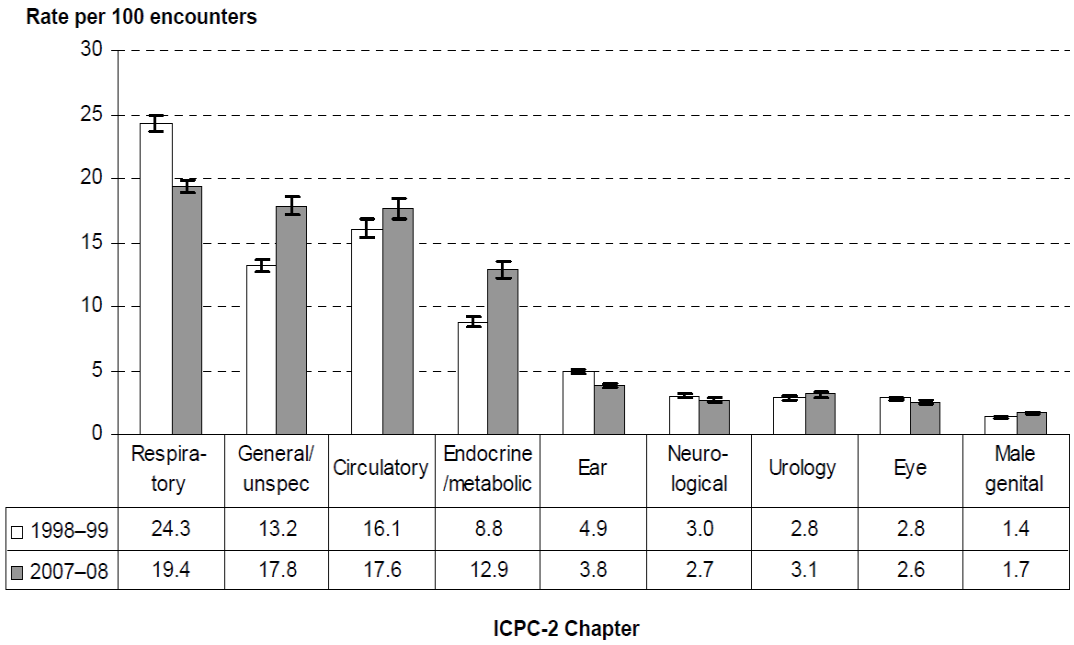
The estimates of the number of patients seen with LRTI by GPs and the numbers and rates of pathology ordering by GPs for respiratory conditions are derived from data obtained from the BEACH program (FMRC 2011). The BEACH program is a continuous national study of general practice activity in Australia. It has given rise to numerous publications. The information provided below is from a joint report between the Australian Institute of Health and Welfare and the University of Sydney, titled: 'General practice in Australia, health priorities and policies 1998 to 2008' (Britt & Miller 2009). LRTI is a term used mainly to describe CAP but it also includes acute bronchitis and lung abscess. The BEACH study does not record a diagnosis of LRTI, but does record specific diagnosis (e.g., bronchitis). Rates of CAP are recorded in a category of other respiratory infections, rather than separately, as the rates are too low.

During the decade between 1998–99 and 2007–08, the number of problems managed at encounters with GPs steadily increased from 145.3 (95% CI: 143.5–147.2) in 1998–99 to 151.3 (95% CI: 149.2–153.4) per 100 encounters in 2007–08. The majority of this increase occurred between 2005–06 and 2007–08. This suggests that nationally, in 1998–99 the general practice workforce dealt with 149.1 million problems at encounters with their patients, whereas in 2007–08 they dealt with 165.7 million problems—an increase of 16.6 million, or 11.1%[a]. Figure 14 shows the general types and rates of problems

[a] The national estimates are calculated by dividing the rate per 100 encounters of the selected event for 1998–99 by 100 and then multiplying by the total number of general practice services claimed through Medicare in that year (rounded to the nearest 100,000;

managed by GPs classified according to the International Classification of Primary Care-Version 2 (ICPC-2) (Britt & Miller 2009).

Figure 14: Significant changes in rates of problems managed by ICPC-2 chapter, 1998–99 and 2007–08 (95% CI)



	Respira-tory	General/ unspec	Circulatory	Endocrine /metabolic	Ear	Neuro-logical	Urology	Eye	Male genital
1998–99	24.3	13.2	16.1	8.8	4.9	3.0	2.8	2.8	1.4
2007–08	19.4	17.8	17.6	12.9	3.8	2.7	3.1	2.6	1.7

Source: Britt & Miller (2009, p.44 see Figure 4.6)

Table 63 provides a breakdown of the type and rate of respiratory problems encountered by GPs as reported in the BEACH study.

Table 2.1 p. 13) to give the estimated annual number of events in 1998–99. The process is then repeated for 2007–08. The difference between the two estimates (to the nearest 10,000) gives the estimated national change in the rate of encounters for that event over the period of interest. The number of general practice professional services claimed from Medicare Australia for the financial year 1998–99 was 102.6 million and for 2007–08, it was 109.5 million.

Table 63: Management rates of respiratory problems, 1998–99 and 2007–08

	Rate per 100 encounters (95% CI)		Percentage of all problems (95% CI)		Percentage of respiratory problems		
	1998–99 (*n* = 96,901)	2007–08 (*n* = 95,898)	1998–99 (*n* = 140,824)	2007–08 (*n* = 145,078)	1998–99 (*n* = 23,554)	2007–08 (*n* = 18,641)	Change[a]
Respiratory—all (ICPC-2 rubric/group)	**24.3 (23.6–25.0)**	**19.4 (18.8–20.1)**	**16.7 (16.2–17.2)**	**12.9 (12.4–13.3)**	**100.0**	**100.0**	↓
Upper respiratory tract infection	6.8 (6.4–7.3)	6.2 (5.7–6.7)	4.7	4.1	28.1	31.9	—
Acute bronchitis/ bronchiolitis	3.3 (3.1–3.5)	2.4 (2.2–2.6)	2.3	1.6	13.5	12.4	↓
Asthma	3.2 (3.0–3.4)	2.2 (2.0–2.3)	2.2	1.4	13.1	11.2	↓
Preventive immun/ vacc/meds—respiratory	2.5 (2.1–2.9)	1.8 (1.5–2.1)	1.7	1.2	10.3	9.2	↓
Sinusitis acute/chronic	1.6 (1.4–1.7)	1.3 (1.2–1.4)	1.1	0.9	6.4	6.7	↓
Tonsillitis	1.5 (1.3–1.6)	1.0 (0.9–1.1)	1.0	0.6	6.0	5.0	↓
Chronic obstructive pulmonary disease	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.5	0.5	3.2	4.0	—
Allergic rhinitis	1.0 (0.9–1.1)	0.6 (0.5–0.7)	0.7	0.4	3.9	3.0	↓
Cough	0.6 (0.6–0.7)	0.5 (0.5–0.6)	0.4	0.4	2.6	2.7	↓
Influenza	0.5 (0.4–0.6)	0.4 (0.3–0.5)	0.3	0.3	1.9	2.1	—
Respiratory infection, other	0.5 (0.4–0.6)	0.4 (0.3–0.5)	0.3	0.3	2.0	1.9	—

(a) The direction and type of change is indicated for each variable: ↑/↓ indicates a statistically significant change, ↑/↓ indicates a marginal change, and — indicates there was no change.

Note: CI—confidence interval; immun—immunisation; vacc—vaccination; meds—medications.

Source: Britt & Miller (2009, p.123 see Table 8.1)

Table 63 reports on the rates of respiratory problems encountered by GPs during the year 1998-99 compared to 2007-08. The change recorded in the final column of the table indicates the change between the years 1998-99 and 2007-08 indicating a statistically significant decrease in respiratory problems encountered.

Based on the information in Figure 14 and Table 63, Table 64 estimates the number of problems that would be seen by GPs and separates out the relevant individual respiratory conditions that fall within the definition or symptoms of LRTI or COPD.

Table 64: Estimates of the number of problems seen by general practitioners and the number of problems that fall within the definition of LRTI, 1998–99 and 2007–08

	1998–99		2007–08	
	Rate per Encounters	Nos. of problems	Rate per encounters	Nos. of problems
National	145.3	149,100,000	151.3	165,673,500
Respiratory	24.3	24,920,136	19.4	21,243,000
Acute bronchitis	3.3	3,384,216	2.4	2,628,000
COAD	0.8	820,416	0.8	876,000
Cough	0.6	615,312	0.5	547,500
Other respiratory infections	0.5	512,760	0.4	438,000

Note: Estimates derived as described in footnote a above. The number of general practice professional services claimed from Medicare Australia for the financial year 1998–99 was 102.6 million and for 2007–08, it was 109.5 million

Based on the figures for 2007–08, Table 65 estimates the likely cost to the MBS requests for PCT tests in the general practice setting.

Table 65: Likely costs to the MBS based on the estimate of the number of problems seen by general practitioners that fall within the definition of lower respiratory tract infection, 2007–08

	Nos of problems	Cost of PCT test	If 100% of patients visiting GP referred for test $	If 20% of patients visiting GP referred for test $	If 3%* of patients visiting GP referred for test $
Acute bronchitis	2,628,000	$60	157,680,000	31,536,000	4,730,400
COAD	876,000	$60	52,560,000	10,512,000	1,576,800
Cough	547,500	$60	32,850,000	6,570,000	985,500
Other respiratory infections	438,000	$60	26,280,000	5,256,000	788,400
Total #	**4,489,500**				**8,081,100**

#in the trials conducted in the general practice setting, all patients presenting with a respiratory tract infection were ordered a PCT test. Therefore, these figures may underestimate the likely number of tests,, if testing according to the trials, because patients presenting with URTI (the largest percentage of respiratory problems) would also need to be included, and these figures are not included in this table.
* Pathology ordering for respiratory problems accounted for 3.0% of total pathology tests in 2000–02 and 2.9% in 2006–08 (Britt & Miller 2009, p.73)

Table 65 indicates that if measurement of PCT is listed on the MBS for use in the general practice setting for patients who present to their GP with the signs and symptoms of LRTI then the likely financial implication to the MBS may be approximately $8 million.

In the event that measurement of PCT is listed on the MBS for patients with the signs and symptoms of sepsis, another setting for which there is likely to be financial implications for the MBS is in patients in a private hospital.

It is recommended that measurement of PCT should always be interpreted in the clinical context of the patient and clinicians should use the PCT results in conjunction with other laboratory findings and clinical signs of the patient. If measurement of PCT is listed on the MBS, use of the test is likely to track that of other currently available direct and indirect measures of sepsis in patients. Expert advice is that PCT is most likely to mimic CRP in terms of requests. As indicated in Table 10, MBS item 66500 includes CRP but also includes a suite of other measures. It is not possible to separate the number of requests for CRP alone. Direct measures of infection for patients with sepsis are blood

cultures, and for CAP, sputum cultures. Expert advice is that, in the general practice setting, GPs are unlikely to order blood cultures or sputum cultures for query LRTI (although they may order a chest x-ray) because these tests are deemed to be hospital-based tests and GPs usually diagnose and start antibiotics rather than run patients through a diagnostic regimen. The BEACH statistics from 2009–2010, which report the most common pathology tests, were examined to identify the number and types of pathology tests requested by GPs. Of the pathology tests ordered by GPs under the category of microbiology, sputum cultures are not recorded, as they are not a common enough test. Since the least common test reported for this category is a HIV test at 0.6 per cent of all pathology tests, requests for a sputum culture must account for less than 0.6 per cent of all pathology tests requested by GPs. A blood culture test does not have its own code and is included within a grouping—microbiology other—which includes 56 different tests. Even with 56 tests included in this category, it only accounts for 2.2 per cent of all pathology tests requested by GPs. Given the infrequency with which blood cultures or sputum cultures appeared to be requested by a GP, and expert advice, the Medicare statistics reporting the number of blood cultures and sputum cultures services are assumed to be for patients in a private hospital setting.

The PCT-guided algorithms used in the clinical trials recommend multiple measurements of PCT to indicate when to initiate antibiotic therapy, as a gauge of whether the antibiotic therapy is appropriate and as an indicator to cease antibiotic therapy. If the MBS listing and use of measurement of PCT is in accordance with these PCT-guided antibiotic algorithms then each patient suspected of sepsis may have multiple tests.

Table 66Table 66 lists the number of services requested for blood and sputum cultures in 2010, using the information provided in Table 57.

Table 66: Estimates of the potential number of tests to measure procalcitonin levels

MBS item		Services 2010	Level at which PCT may be requested	Cost of PCT test	Likely cost if listed on MBS
69354	Blood cultures 1 set of cultures	148,605	148,605	$60	$8,916,300
69318	Sputum cultures 1 or more tests on one or more specimens	132,213	132,213	$60	$7,932,780

Using the number of services requested for blood cultures and sputum cultures,

Table 66Table 66 estimates the likely number of tests that may be requested for measurement of PCT. In estimating these figures, it is assumed that one set of blood cultures will equate to one request for measurement of PCT. Multiple blood cultures, up to a maximum of three, may be ordered for each episode of suspected bacteremia, but they attract different MBS item numbers. If following the PCT-guided algorithms used in the trials, multiple tests for PCT measurement may be ordered for each episode of suspected sepsis, with some studies requiring daily PCT measurements. Therefore, the number of blood cultures is likely to be an underestimate of the number of PCT tests that may be requested. Trying to extrapolate from the number of sputum cultures to the likely number of PCT tests, has not been attempted in the report, as it is not likely to be meaningful because the relevant MBS item may refer to one test, multiple tests or multiple specimens.

From these estimates, the likely financial implications for the MBS of the listing of measurement of PCT for patients presenting to their GP with the signs and symptoms of

LRTI may be approximately $8 million dollars per year. If the listing also includes patients with the signs and symptoms of sepsis, the likely financial implications may be an additional $9 million per year. The likely number of tests may be 283,290 or greater at a potential cost to the MBS of $17 million per year. If multiple tests of PCT are done for each episode of sepsis or LRTI to guide antibiotic therapy, the actual cost may be even higher.

Conclusions

Safety

No reports were located that related to studies that specifically investigated the safety of measurement of serum PCT. Given the nature of this intervention, it is not anticipated that it will be associated with any safety issues.

Effectiveness

Routine measurement of PCT, with corresponding obligatory guidelines for antimicrobial therapy, for patients presenting to the ED with query LRTI or ECOPD, alongside clinical assessment and other measures of sepsis, usually resulted in a reduction in the use of antibiotics. However, only one of the trials in the ED was powered to address the question of whether this reduction in antibiotic therapy had any consequences for patients, and it reported non-significant increases in mortality and disease specific complications. The routine use of a PCT test for every person with a query LRTI, in the ED, would result in a large number being requested. The evidence does not justify the routine measurement of PCT and use of a procalcitonin-guided algorithm for antimicrobial therapy in the ED, as used in these trials.

The routine measurement of PCT, with corresponding obligatory guidelines for antimicrobial therapy, as an indicator of sepsis, alongside clinical assessment, for patients in an ICU setting, may not result in a reduction in antibiotic therapy. It is also unclear whether following a PCT-guided algorithm for initiating or ceasing antibiotic therapy will have consequences for patients, as the majority of the studies in the ICU setting were not powered to answer this question. The one study that was powered to detect 28-day mortality reported no difference in survival, but did report that patients in the PCT-guided arm required more intensive, organ-related support and had prolonged admission to ICU. The routine use of a PCT test in the ICU setting, often on a daily basis, would result in a large number being requested. The evidence does not justify the routine measurement of PCT and use of a PCT-guided algorithm for antimicrobial therapy in the ICU setting.

The routine measurement of PCT, with corresponding obligatory guidelines for antimicrobial therapy, for patients presenting to their GP with symptoms of RTI, alongside clinical assessment, resulted in a reduction in the use of antibiotics. However, neither of the trials in the general practice setting was powered to measure any consequences to patients that may result from a reduction in antibiotic therapy. The routine use of a PCT test for every person who presents to their GP with the symptoms of RTI would result in a large number of tests being requested. The evidence does not justify the routine measurement of PCT, and use of a PCT-guided algorithm for antimicrobial therapy in the general practice setting.

Consistent data regarding the accuracy of levels of procalcitonin in reliably differentiating between infectious and non-infectious systemic-inflammatory response syndrome are lacking.

Economic considerations

Measurement of PCT is not cost saving from a health care perspective compared to no measurement of PCT. The additional cost per antibiotic prescription avoided may range from $117 to $1,409, depending on the setting in which patients are being tested and taking into consideration assumptions about likely benefits in terms of number of

antibiotic prescriptions avoided. Longer-term benefits in the form of hospitalisations avoided or mortality reductions were not included in the economic evaluation, as these benefits were not demonstrated by the available evidence.

Financial costing

The expected uptake of measurement of PCT is estimated at approximately 283,290 tests annually but this is likely an underestimate.

The total cost to the government for the measurement of PCT is estimated to be $17 million annually, although this is likely an underestimate.

Appendix A MSAC terms of reference and membership

The Medical Services Advisory Committee (MSAC) is an independent scientific committee comprising individuals with expertise in clinical medicine, health economics and consumer matters. It advises the Minister for Health and Ageing on whether a new medical service should be publicly funded based on an assessment of its comparative safety, effectiveness, cost-effectiveness and total cost, using the best available evidence. In providing this advice, MSAC may also take other relevant factors into account. This process ensures that Australians have access to medical services that have been shown to be safe and clinically effective, as well as representing value for money for the Australian health care system.

MSAC is to:

- Advise the Minister for Health and Ageing on medical services including those that involve new or emerging technologies and procedures, and, where relevant, amendment to existing MBS items in relation to:
    - the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
    - whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
    - the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
    - the circumstances, in which there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
    - other matters related to the public funding of health services referred by the Minister.
- Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to undertake its role effectively. MSAC may delegate some of its functions to its executive sub-committee.

The membership of MSAC at the 54th meeting held November 2011 comprised a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers and health administration and planning:

Member	**Expertise or Affiliation**
Professor Robyn Ward (Chair)	Medical Oncology
Dr Frederick Khafagi (Deputy Chair)	Nuclear Medicine
Professor Jim Butler (Chair, Evaluation Sub-committee)	Health Economics
Associate Professor John Atherton	Cardiology
Associate Professor Michael Bilous	Anatomical Pathology
Professor Chris Baggoley	Interim Commonwealth Chief Medical (Officer) (*ex officio*)
Associate Professor Kirsty Douglas	General Practice/Research
Professor Kwun Fong	Thoracic Medicine
Professor Paul Glasziou	Evidence-based health care
Dr Scott Jansson	Pathology
Professor David Little	Orthopaedics
Mr Russell McGowan	Consumer Health Representative
Professor David Roder	Health medicine/Epidemiology
Associate Professor Bev Rowbotham	Haematology
Dr Graeme Suthers	Genetics/Pathology
Professor Ken Thomson	Radiology
Dr Christine Tippett	Obstetrics/Gynaecology
Dr Simon Towler	AHMAC Representative (*ex officio*)
Associate Professor David Winlaw	Paediatric Cardiothoracic Surgery
Dr Caroline Wright	Colorectal Cancer/Surgery

Appendix B Advisory panel and health technology assessors

Advisory Panel - Measurement and Determination of Procalcitonin (PCT) Application 1139

Member	Nomination / Expertise or Affiliation
Prof Peter Cameron (Chair)	Professor of Emergency Medicine, Member of MSAC (until 31 Dec 2010)
Dr Shiong Tan (Deputy Chair)	General Practitioner MSAC Member (until February 2010)
Dr Graeme Suthers (Deputy chair)	Member of MSAC; Genetics/Pathology (from February 2010)
Dr Graham Jones	Pathologist
Dr Daman Langguth	Royal College of Pathologists of Australasia
Prof Andrew Lloyd	Professor in Infectious Diseases
Belinda Miller	Respiratory Physician
Prof Bala Venkatesh	Professor in Intensive Care
Dr Janet Wale	Consumer Health Forum representative

Evaluation Sub-committee Input

Name	
Prof Jim Butler	Member of MSAC Evaluation Sub-Committee, Health Economics

Evaluators

Name	Organisation
Sandra Younie	Deakin Health Technology Assessment Group
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Appendix C Search strategies

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews to inform the assessment of measurement of PCT as a means of determining bacterial infection and guiding antibiotic therapy. Table 67 Table 11 lists the electronic databases searched and the period covered by the searches.

Table 67: Electronic databases searched

Database	Period covered
Medline	1950–24 September 2010 Additional search on May 20, 2011
Embase	<5 October 2010
EBM reviews	<24 September 2010
- Cochrane Database of Systematic Reviews	2005 to September 2010
- ACP Journal Club	1991–August 2010
- Database of Abstracts of Reviews of Effects	3rd Quarter 2010
- Cochrane Central Register of Controlled Trials	3rd Quarter 2010
- Cochrane Methodology Register	3rd Quarter 2010
- Health Technology Assessment	3rd Quarter 2010
- NHS Economic Evaluation Database	3rd Quarter 2010

EBM reviews—evidence based medicine reviews

The search terms used included: procalcitonin, PCT, sepsis, septic shock, severe sepsis, systemic inflammatory response syndrome, SIRS, septicaemia, blood stream infection, BSI, lower respiratory tract infection, LRTI, community acquired pneumonia, CAP, chronic obstructive airways disease, COAD, chronic obstructive pulmonary disease, COPD, fever, infection, bacterial infection, febrile, meningitis, critically ill, chronic airflow limitation, CAL, undifferentiated fever, pyrexia, pyrexia of unknown origin, PUO.

Appendix D Studies included in the review

Table 68: Study profiles of included studies on safety and effectiveness

Study and location	Level of evidence and quality assessment	Study design	Study population	Interv-ention	Inclusion/ exclusion criteria	Outcomes assessed	Duration of follow-up
Intensive care studies							
Bouadma (2010) Germany & France		Multi-centre, open-label RCT	N=630 ICU patients 5 ICUs participated			Mortality (non-inferiority analysis) Antibiotic use (superiority analysis)	
Jensen (2011) Denmark		Multi-centre, blinded RCT	N=1,200 9 mixed surgical/medical ICUs			Primary outcome: 28-day mortality Secondary outcome: duration of organ failure, ICU stay Subgroup analyses	5,447 of 5,700 days in ICU v. 4,717 of 5,194 days in control arm
Schroeder (2009) Germany		RCT	N=27 ICU patients			Length of antibiotic treatment	
Nobre (2008) Switzerland		Single-centre RCT	N=79 ICU patients			Reduction in duration of antibiotic therapy Adverse outcomes: septic shock, severe sepsis	
Stolz (2009) Switzerland & USA		Multi-centre RCT	N=101 ICU patients 7 ICUs participated			Antibiotic free days ICU free days alive Length of hospital	
Svoboda (2007) Czech republic		Single-centre RCT	N=72 ICU patients	ICU		28-day mortality Sepsis-related complications Duration of stay in ICU Ventilator days	
Hochreiter (2009) Germany		RCT	N=110 surgical ICU patients			Length of antibiotic treatment	

Emergency department studies and primary care							
Burkhardt (2010) Germany		RC non-inferiority trial	N=550 with symptoms of acute RTI	Primary care setting		Primary endpoint: days with impairment during everyday life and/or leisure activities due to RTI within the first 14 days according to self-assessment (health impairment) 2nd endpoint: frequency of prescription of antimicrobial treatments - days with antibiotic induced side effects - symptoms of RTI on days 14 and 28 - visit at Dr's office with RTI within 28 days - change of antibiotics within 28 days - hospitalisation within 28 days - mortality within 28 days	
Kristoffersen (2009) Denmark		Multi-centre RCT	N=223 hospital admission for LRTI	Hospital admission for LRTI		Reduction in antibiotic use and length of hospital stay	
Schuetz (2009) Switzerland		Multi-centre non-inferiority RCT	N=1,359 ED patients 6 EDs participated	6 EDs		Death ICU admission Disease specific complications, or recurrent infection requiring antibiotic treatment within 30 days Antibiotic exposure Adverse effects from antibiotics	
Briel (2008) Switzerland		Randomised, open multi-centre, non-inferiority trial	N=458 primary care patients 53 primary care physicians participated			Length of antibiotic use	
Stolz (2007) Switzerland		Single-centre RCT	N=266 ED patients	ED		Antibiotic prescription Antibiotic exposure	
Christ-Crain (2006) Switzerland		RCT open-intervention	N=302 consecutive ED patients	ED		Length of antibiotic treatment	
Christ-Crain (2004) Switzerland		Prospective cluster-randomised controlled, single-blinded trial	N=243 ED patients	ED		Number of antibiotic free days alive assessed 28 days after enrolment in the study (using algorithm) - Antibiotic therapy discontinuation related to death was a censored event. Secondary endpoints: - nos of mechanical ventilation-free days - nos of ICU free days alive - length of hospital stay	

Inclusion/exclusion criteria of included studies

Table 69: Inclusion criteria for intensive care studies

Inclusion criteria							
Intensive care unit studies	**Jensen (2011)**	**Bouadma (2010)**	**Hochreiter (2009)**	**Schroeder (2009)**	**Nobre (2008)**	**Stolz (2009)**	**Svoboda (2007)**
Enrolled within 24 hours of admission	√						
Not receiving antibiotics for <24 hrs (if intervals between admission and inclusion <12 hrs)		√					
Suspected bacterial infections at admission or during stay in intensive care		√					
Highly suspected or confirmed bacterial infections and at least two concomitant SIRS* criteria were eligible			√				
After abdominal surgery				√			
Started antibiotic treatment with diagnosis of severe sepsis**				√			
Severe sepsis or septic shock at admission or during stay					√		√
Intubated for mechanical ventilation ≥48h						√	
Diagnosed by VAP#						√	
Multiple trauma (ISS≥25)[β] and major intra-abdominal surgery (operation time >120 mins)							√

*SIRS (systemic inflammatory response syndrome) presents with two or more of the following symptoms:
- Body temperature >38°C or <36°C
- Heart frequency > 90/min
- Breath frequency >20/min order Pa Co_2 <32 mm Hg
- Leucocytes >12000/µl or <4000/ µl, or >10% left shift

** Defined according to ACCP/SSCM consensus conference criteria 1992 (see Table 6)

Defined by the ATS guidelines (new or persistent infiltrate on chest X-ray associated with at least two of the following:
- Purulent tracheal secretions
- Temperature >38°C
- leukocyte count >11,000 µL or <3,000 µL)

[β] ISS—The Injury Severity Score is an anatomical scoring system that provides an overall score for patients with multiple injuries

Table 70: Inclusion criteria for emergency department primary care studies

Inclusion Criteria							
Emergency Department Studies/primary care	**Briel 2008**	**Christ-Crain (2004)**	**Christ-Crain (2006)**	**Schuetz (2009)**	**Stolz (2007)**	**Kristoffersen (2009)**	**Burkhardt (2010)**
≥40 yrs					√		
Symptoms of ARTI	√						√
Symptoms 1st appeared ≤28days	√			√			
Consultation for: - Common cold or Rhinosinusitis - Pharyngitis or Tonsillitis - Tracheobrochitis or Otitis media - Influenza - Acute exacerbation of asthma - COPD - CAP (confirmed by chest x-ray)	 √ √ √ √ √ √ √						
Physician's intention to prescribe antibiotics based on evidence based guidelines	√						
Main symptoms/diagnosis of LRTI		√		√			
Presence of two or more acute signs and symptoms		√		√			
Main symptoms of CAP*			√	√			
COPD				√			
ECOPD[α] and meet post-bronchodilator therapy spirometric criteria					√		
Acute bronchitis defined as LRTI~				√			
Suspicion of pneumonia (cough, expectoration, dyspnoea or fever>38°) Chest x-ray signs of pneumonia not required						√	

CAP—community acquired pneumonia, defined as new infiltrate on chest X-ray; COPD=Chronic obstructive pulmonary disease, defined by post-bronchodilator spirometric criteria;
ECOPD—'a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations, which is acute in onset and necessitates a change in regular medication in a patients with underlying COPD';
** Cough, sputum production, dyspnea, core body temperature exceeding 38.0°C, auscultatory findings of abnormal breath sounds and rates and leukocyte count >$10x10^9$ or less than $4x10^9$ cells L^{-1};
~ In the absence of an underlying lung disease or focal chest signs and infiltrates on chest radiograph, respectively

Table 71: Exclusion criteria for intensive care studies

Exclusion Criteria							
Intensive Care Unit Studies	**Jensen (2011)**	**Bouadma (2010)**	**Hochreiter (2009)**	**Schroeder (2009)**	**Nobre (2008)**	**Stolz (2009)**	**Svoboda (2007)**
<18 yrs	√	√				√	√
Stay in ICU<3 days		√					
Bilirubin levels >40 mg/dL Triglycerides >1,000 mg/dL	√						
Bone marrow transplant or chemotherapy induced neutropenia (<500 neutrophils/mL) or severely immunocompromised		√			√	√	
Infections requiring long-term antibiotics (e.g., infective endocarditis, TB, brain abscess)		√			√		
Poor chance of survival (SAPS II>65) and do not resuscitate order		√			√		√
Microbiologically documented infection caused by: Pseudomonas eruginose, Acinetobacter baumannii, Listeria spp., Legionella pneumophila, Pneumocystis jiroveci, or Mycobacterium tuberculosis					√		
Severe infections due to viruses or parasites (e.g., malaria)					√		
Antibiotics started ≥48 before enrolment					√		
Chronic localised infections (e.g., chronic osteomyelitis)					√		
Absence of antibiotic treatment despite clinical suspicion of sepsis							
Pregnant						√	
Long-term corticosteroid therapy or immunosuppressants						√	
Coexisting extra-pulmonary infection diagnosed between day 1 and 3 and requiring antibiotic therapy >3 days						√	
Chemical or burn trauma							√
Increased risk from blood sampling	√						

SAPS—simplified acute physiology score

Table 72: Exclusion criteria for emergency department and primary care studies

Exclusion Criteria							
Emergency Department Studies	**Briel (2008)**	**Christ-Crain (2004)**	**Christ-Crain (2006)**	**Schuetz (2009)**	**Stolz (2007)**	**Kristoffersen (2009)**	**Burkhardt (2010)**
<18 yrs			√	√		√	√
Antibiotic use ≤28days	√						√
Psychiatric disorders or inability to give informed consent	√			√	√		√
Not available for follow-up	√						
Not fluent in German	√						
Severe immunosuppression	√	√	√	√	√		√
Cystic fibrosis, active TB	√	√	√		√		
Nosocomial pneumonia (pneumonia ≥48 hours after hospital admission or hospitalised within 14 days before presentation)		√	√	√			√
Need for hospitalisation	√			√			
Active intravenous drug use				√			
Life threatening co-morbidities leading to possible imminent death				√			
Chronic infection requiring antibiotic therapy				√			
Alternative explanation for the presenting signs and symptoms other than a worsening of the underlying COPD					√		
Presence of infiltrates on chest x-ray					√		
Autoimmune or systemic disorders, dialysis, medullary C-cell carcinomas, other inflammatory diseases							√
Chronic Liver disease							√
Major surgery that required hospitalisation <4 weeks							√

Baseline characteristics of participants in the included studies

Table 73: Baseline characteristics of participants in the intensive studies

Study	Bouadma (2010)		Schroeder (2009)		Nobre (2008)		Hochriter (2008)		Svoboda (2007)		Stolz (2009)		Jensen (2011)	
	PCT N=307	Control N=314	PCT N=14	Control N=13	PCT n=39	Control N=40	PCT N=57	Control N=53	PCT N=38	Control N=34	PCT N=51	Control N=50	PCT N=604	Control N=596
Age mean ± SD Median [IQR]	61.0 ±15.2	62.1 ± 15.0	69.3 ±10.6	68.4 ±13.7	64.0¥ ±12.3	66.9¥ ±13.8	67.3 ±14.4	66.6 ±15.5	43 (19–88)	49 (20–86)	53 (21–88)	59 (18–83)	67 (58–76)	67 (58–75)
Gender (M) (%)	207 (67)	204 (65)	8 (57)	7 (54)	21¥ (67.7)	25¥ (67.6)	29 (51)	29 (55)	23 (61)	23 (68)	38 (75)	37 (74)	330 (54.6)	333 (55.9)
Admission Category (%) - Medical - Emergency surgery - Elective surgery	 275 (90) 20 (7) 12 (4)	 280 (89) 25 (8) 9 (3)									 27 (53) 23 (45) 1 (2)	 26 (52) 20 (40) 3 (6)	 336 (56.3)	 377 (62.4)
Origin - ED - Medical/ surgical unit - Other ICU	 144 (47) 138 (45) 25 (8)	 168 (54) 119 (38) 27 (9)												
Severe co-morbidities: - NYHA III/IV heart failure (cardiac) - IDDM - Cirrhosis/hepatic - O_2 therapy at home - Chronic renal failure requiring dialysis - Metastatic cancer - Immunocompromised* - COPD - Substance abuse 1 chronic co-morbidity 2 chronic co-morbidity ≥3 chronic co-morbidity	 16 (5) 27 (9) 20 (7) 23 (7) 17 (6) 8 (3) 47 (15)	 13 (4) 22 (7) 13 (4) 18 (6) 11 (4) 5 (2) 51 (16)									 38 (74.5) 10 (20) 4 (8) 9 (18) 3 (6) 8 (16) 5 (10)	 39 (78.0) 13 (26) 3 (6) 7 (14) 5 (10) 11 (22) 8 (16)	 257(42.6) 171(28.3) 53(8.8)	 279(46.8) 173(29.0) 42(7.1)
SAPS II (±SD)	47.1 (17.9)	46.9 (17.2)	45.6 ±18.5	53.7 ±14.7										
SOFA score (±SD)	8.0 (4.7)	7.7 (4.6)	7.3 ±3.5	8.3 ±4.2										

Organ or system failure† - Respiratory - Cardiovascular - Renal - CNS - Hepatic - Coagulation - Acidosis - Shock - ARDS	 153 (50) 140 (46) 60 (20) 117 (38) 19 (6) 24 (8)	 131 (42) 141 (45) 49 (16) 111 (35) 16 (5) 25 (8)			 27 (69.2) 1 (2.5) 2 (5.1) 8 (20.5) 15 (38.5) 15 (38.5) 8 (20.5)	 31 (77.5) 8 (20) 2 (5) 5 (12.5) 21 (52.5) 21 (52.5) 6 (15)								
Reason for admission to ICU - Septic shock - Non-septic shock - Acute respiratory failure - Renal failure - Neurological failure - Multiorgan failure - Other‡ Circulatory failure Gastrointestinal disease Postoperative complications Trauma	 53 (17) 46 (15) 115 (37) 9 (3) 34 (11) 20 (7) 30 (10)	 55 (18) 46 (15) 127 (40) 6 (2) 36 (11) 20 (6) 24 (8)			 17 (43.6)	 17 (42.5)							 410 (67.9) 81 (13.6) 101 (16.7) 57 (9.4) 257 (42.6) 96 (15.9) 106 (17.6) 106 (17.6)	 422 (70.8) 103 (17.1) 78 (13.1) 68 (11.4) 263 (44.1) 128 (21.5) 123 (20.6) 113 (19.0)
At inclusion to study														
SAPS II	43.8 (16.1)	43.4 (15.4)			67.5 (11.2) 3 points	69.9 (12.6)	40.1 ±17.1	40.5 ±15.1						
SOFA score	7.5 (4.4)	7.2 (4.4)			5.9 (3.3) points	6.7 (2.9)								
APACHE II mean±SD Median (IQR)									15.7±7.9	17.3±9.3			18 (13–25)	18 (13–24)
CDIN											1.9±0.9	2.3±1.0		
Organ or system failure† Respiratory - Cardiovascular - Renal - CNS - Hepatic - Coagulation	 148 (48) 135 (44) 58 (19) 101 (33) 13 (4) 25 (8)	 137 (44) 127 (40) 48 (15) 100 (32) 13 (4) 21 (7)												
Mechanical ventilation	211 (69)	208 (66)									51 (100)	50 (100)	401 (66.4)	401 (67.3)
Types of infection - Community acquired - Hospital-acquired	 153 (50) 154 (50)	 173 (55) 141 (45)												
Septic Shock (%)	138 (45)	129 (41)							27 (71)	23 (68)	11 (22)	12 (24)	247 (40.9)	212 (35.6)

Serum lactate (>2 mmol/L)§	91 (37)	96 (38)												
Positive blood cultures (%)	55 (18)	53 (17)									14 (28)[π]	18 (36)[π]		
Positive bacterial cultures											71%	76%		
Procalcitonin (μg/L)# Mean ± SD Median (IQR)	12.0± 30.9; 1.6 (0.5–6.6)	12.0± 32.6; 1.5 (0.4–6.8)							>2ng/mL 21(55)	>2ng/mL 16(47)	0.66 (0.22–2.69)	0.73 (0.21–2.36)	312 (51.7)[┼]	279 (47.0) [┼]
CRP (mg/L) Mean ± SD Median (IQR) (%)	156 ± 109.2) 144.2 (63.0–229.0)	159.6 ± 114.2) 137.2 (61.0–244.0)							167±90	189±98			161 (56–271)	152 (54–266)
IL-6 (pg/mL)									467±194	532±201				
TNF (pg/mL)									139±61	154±73				
Leucocytesx10[6] median (IQR)													12.4 (8.0–18.1)	13.0 (8.8–18.1)
Infection site (%)	**	**												
- Pulmonary	183 (71)††	211 (74)‡‡	4 (28.5)	4	25 (64)	27 (67)	24 (42)	19 (36)			51 (100)	50 (100)		
- Urinary tract	24 (9) [β]	18 (6) [β]		(30.8)	7 (18)	5 (10)	2 (3.5)	3 (5.6)						
- Skin and soft tissue	5 (2)	6 (2)					2 (3.5)	1 (1.9)						
- Intra-abdominal	14 (5)	20 (7)	10			6 (15)	29 (51)	30 (57)						
- CNS	7 (3)	6 (2)	(71.4)	9	2 (5)									
- Catheter-related infection	5 (2) 9 (3)	3 (1) 11 (4)		(69.2)										
- Primary blood stream	11 (4) [##]	9 (3) [##]			5 (13)	2 (8)								
- Other														
Multiple traumas (%)														
- Head, spine cord, n									11 (28.9)	11 (32.4)				
- Thoracic, n									11 (28.9)	9 (26.5)				
- Abdominal, n									21 (55.3)	19 (55.9)				
- Other, n									19 (50.0)	15 (44.1)				
After abdominal surgery									11 (29)	12 (35)				
No Infection (%)													86 (14.2)	118 (19.8)

ICU—intensive care unit; NYHA—New York Heart Association Stage of disease; SAPS II—simplified acute physiology score; SOFA—sequential organ failure assessment

* Includes patients with acquired immunodeficiency syndrome, solid organ transplantation or haematological malignancy and those receiving chemotherapy or radiotherapy, immunosuppressive agents or long-term corticosteroid therapy; † Defined by SOFA score >2; ‡ Other defined for Bouadma [Trauma (n=5 patients in PCT group, n=4 in control group), need for continuous monitoring (n=12, n=10) and cardiac arrest (n=13, n=10)];

§ Data were obtained for 247 patients in the PCT group and 255 in the control group. Data were missing for remaining patients; # Data were obtained for 307 in PCT group and 192 in control group. Data were missing for remaining patients; ** Data obtained for 258 patients in the PCT group, and 284 in control group. Data missing remaining patients; ## Endocarditis (n=1 in PCT group), mediastinitis (n=1 in control group) and unknown (n=10 in PCT group; n=8 in control group. Cases of endocarditis and mediastinitis were diagnosed after inclusion so these patients were not excluded from the analysis); β if study reports urosepsis or urinary tract infection, results recorded against urinary tract and not against catheter-related infection. Only reported against catheter-related infection if stated explicitly)

π within 48 hours; ¥ Per-protocol population; ┼ Alert procalcitonin, no. (%): PCT level not decreasing by at least 10% from the previous day and >1.0 ng/mL. If only one measurement is available: absolute PCT level >1.0 ng/ml

Table 74: Baseline characteristics of participants in the emergency department studies

Study	Briel (2008)		Schuetz (2009)		Christ-Crain (2006)	
	PCT N=232	STG N=226	PCT N=671	STG N=688	PCT N=151	Control N=151
Age mean ±SD [IQR]	48± 18	48± 18	73 [59–82]	72 [59–82]	70±17	70±17
Gender M (%)	98 (42.2)	87 (38.5)	402 (59.9)	380 [55.2]	94 (62)	93 (62)
Days of RA median [IQR]	4.5 [3–7]	5 [3–7]				
Degree of discomfort from infection median [IQR]	6 [5–8]	7 [5–8]				
Presence of any co-morbidity (%) - Chronic lung disease/COPD - Diabetes mellitus - Heart failure - Coronary heart disease - Cerebrovascular disease - Renal dysfunction - Neoplastic disease - Peripheral vascular disease - Other co-morbidities (liver)	33 (14) 12 (5.2) 6 (2.6) 8 (3.4) 7 (3.0)	37 (16) 14 (6.2) 7 (3.1) 6 (2.6) 10 (4.4)	 265 (39.5) 118 (17.0) 146 (21.8) 54 (8.1) 156 (23.3) 69 (10.3)	 268 (39.0) 113 (16.4) 136 (19.8) 56 (8.1) 146 (21.2) 98 (14.2)	 44 (29) 32 (21) 7 (5) 91 (60.3) 8 (5) 36 (24) 25 (17) 11 (7) 12 (8)	 32 (21) 29 (19) 9 (6) 84 (55.6) 8 (5) 45 (30) 23 (15) 9 (6) 19 (13)
Use of diagnostic test other than PCT	190 (82)	176 (78)				
PCT median [IQR] mean (SD) µg/L	0.08 [0.06–0.1], 0.39 (2.7)	0.08 [0.06–0.1], 0.24 (1.3)	0.24 [0.12–1.18]	0.24 [0.11–1.60]	0.57 [0.2–2.5]	0.44 [0.2–1.9]
CRP median [IQR] mean (SD) mg/dL	28 [7–71] 51 (65)	34 [10–76], 51 (55)	115 (38–212)	114 (41–220)	111 [57–204]	152 [72–212]
Leukocyte count cells/µL Median [IQR] ±SD			11,600 [8,500–15,400]	11,200 [8,400–15,200]	13.7±6.7	13.4±6.6
Diagnosis - Common cold - Acute rhinosinusitis - Acute pharyngitis or tonsillitis - Acute laryngitis or tracheitis - Acute otitis media - Acute bronchitis - Influenza - Exacerbated COPD - Exacerbated asthma - CAP - Other diagnosis	 13 (5.6) 52 (22) 42 (18) 8 (3.5) 0 58 (25) 3 (1.3) 12 (5.2) 6 (2.6) 38 (16)	 18 (8.0) 52 (23) 33 (15) 4 (1.8) 5 (2.2) 70 (31) 1 (0.4) 9 (4.0) 3 (1.3) 31 (14)	 69 (10.3) 115 (17.1) 460 (68.6) 27 (4.0)	 82 (11.9) 113 (16.4) 465 (67.6) 28 (4.0)		
Antibiotics before presentation			187 (28.0)	175 (25.8)	27 (18)	34 (23)
Corticosteroids pre-treatment			76 (11.6)	75 (11.2)		
Risk assessment in patients with CAP PSI class No. (%) I II III IV V			N=460 76 (11.0) 138 (20.1) 147 (21.4) 243 (35.3) 84 (12.2)	N=465 63 (9.3) 124 (18.4) 152 (22.7) 252 (37.6) 80 (11.9)	 99.7±36.1* 54 (36)# 68 (45) 29 (19)	 99.2±34.5* 66 (44)# 62 (41) 23 (15)
Hospitalised patients No. (%) - Initial prescription of antibiotics			628 (93.7) 492 (78.3)	629 (91.4) 568 (90.3)		
Outpatients No. (%) - Initial prescription of antibiotics			43 (6.4) 14 (32.6)	59 (8.6) 35 (59.3)		

STG—standard therapy group; IQR—interquartile range; RA—restricted activity; CRP—C-reactive protein; PCT—procalcitonin; CAP—community acquired pneumonia; COPD—chronic obstructive pulmonary disease; PSI—pneumonia severity index;
* PSI points; # PSI class I, II, III

Baseline characteristics of participants in the emergency department studies (continued)

Study	Christ-Crain (2004)		Stolz (2007)		Kristoffersen (2009)	
	PCT N=124	Control N=119	PCT N=102	STG N=106	PCT N=103	Control N=107
Age mean ± SD [IQR]	62.8± 19.8	65.3± 17.3	69.5 (65–77)	69.5 (64.8–79)	67.2±17.6	67±15.6
Gender M (%)	67 (54)	61 (51)	50 (49)	44 (41.5)	54 (52)	58 (54)
Smoking history (packs/year)	41.4 (25)	40.0 (26)	43 (30–58.5)	50 (30–60)		
Current smokers	27 (22)	35 (29)	40 (39.2)	54 (50.9)	68 (66)	82 (77)
Duration of COPD			128±82	123±85		
Degree of discomfort from infection median [IQR]			()	()		
Presence of any co-morbidity (%) - Chronic lung disease/COPD - Diabetes mellitus - Heart failure - Coronary heart disease# - cerebrovascular disease - Renal dysfunction - Neoplastic disease - Peripheral vascular disease - Liver disease - Other co-morbidities (osteoporosis)	 15 (12) 11 (9) 27 (22) 4 (3) 22 (18) 10 (8) 6 (5)	 17 (14) 7 (6) 32 (27) 5 (4) 18 (15) 9 (8) 6 (5)	 12 (11.8) 42 (41.2) 23 (22.5) 5 (4.9) 12 (11.8)	 11 (10.4) 49 (46.2) 27 (25.5) 12 (11.3) 14 (13.2)		
Use of diagnostic test other than PCT - Positive Blood cultures - Positive Sputum cultures	 84 (68) 87 (70)	 79 (66) 73 (61)	 37 (36)	 40 (38)	 8/72 (11)	 4/79 (5)
PCT median [IQR] mean (SD) µg/L			()	()	0.14 0.05–42.13 2.18±7.6	0.13 [0.02–30.12] 0.95±3.3
CRP median [IQR] mean (SD) mg/dL			11.7±8.4	11.5 (4.6)	1091±1,080	971±1,000
Leukocyte count cells/µL Median [IQR] ±SD			()	()	13.2±7.5	12.1±5.9
Diagnosis - Common cold - Acute rhinosinusitis - Acute pharyngitis or tonsilitis - Acute laryngitis or tracheitis - Acute otitis media - Acute bronchitis - Influenza - Exacerbated COPD - Exacerbated asthma - CAP - Other diagnosis	 28 (23) 29 (23) 10 (8) 42 (34) 15 (12)	 31 (26) 31 (26) 3 (3) 45 (38) 9 (8)	 102 (100)	 106 (100)	 2 (2) 3 (3) 28 (27) 2 (2) 47 (46) 21 (20)	 2 (2) 5 (5) 32 (30) 3 (3) 50 (47) 15 (14)
Antibiotics before presentation Duration (days)	28 (23)	21 (18)	23 (22.5) 1.3±3.5	22 (20.8) 0.6±1.7	48 (47)	46 (43)

Baseline characteristics of participants in the emergency department studies (continued)

Corticosteroids pre-treatment			41 (40.2)	29(27.4)***		
Risk assessment in patients with CAP			()	()		
PSI class No. (%) mean (SD) I II III IV V	84.3 (41.3)	84.9 (28.9)			79.2±27.8 65 (63)* 35 (34) 3 (3)	75.8±24.3 78 (73) 27 (25) 2 (2)
Severity of COPD (Gold) Stage 1 (FEV ≥80% Stage II (FEV ≥50 to <80%) Stage III (FEV ≥30 to <50%) Stage IV (FEV ≤30%)			 6 (5.9) 15 (14.7) 47 (46.1) 34 (33.3	 5 (4.7) 25 (23.6) 51 (48.1) 25 (23.6)		
Hospitalised patients No. (%) - Initial prescription of antibiotics			()	()		
Outpatients No. (%) - Initial prescription of antibiotics			()	()		
Hospitalisation in previous year for ECOPD			1.1±1.4	0.98±1.3		

*** P=0.050; # Includes heart disease and hypertension; ECOPD—exacerbation of COPD; GOLD—global initiative for Chronic Obstructive Lung Disease

Baseline characteristics of participants in the emergency department studies (continued)

Study	Burkhardt (2010)	
	PCT N=275	Control N=275
Age mean ± SD [IQR]	41.4± 15.3	43.4± 15.5
Gender M (%)	111 (40.4)	114 (41.5)
Smoking history (packs/year)		
Current smokers	66 (24)	73 (26.5)
Duration of COPD		
Degree of discomfort from infection median [IQR]		
Presence of any co-morbidity (%) - Chronic lung disease/COPD - Diabetes mellitus - Heart failure - Coronary heart disease# - cerebrovascular disease - Renal dysfunction - Neoplastic disease - Peripheral vascular disease - Liver disease - Other co-morbidities (osteoporosis)	 9 (3.2) 15 (5.5) 5 (1.8)	 9 (3.2) 9 (3.2) 5 (1.8)
Use of diagnostic test other than PCT - Positive Blood cultures - Positive Sputum cultures		
PCT median [IQR] mean (SD) µg/L		
CRP median [IQR] mean (SD) mg/dL		
Leukocyte count cells/µL Median [IQR] ±SD		
Diagnosis - Common cold - Acute rhinosinusitis - Acute pharyngitis or tonsillitis - Acute laryngitis or tracheitis - Acute otitis media - Acute bronchitis - Influenza - Exacerbated COPD - Exacerbated asthma - CAP - Other diagnosis	 159 (57.8) 78 (28.4) 40 (14.5) 24 (8.7) 4 (1.6) 91 (33.1) 5 (1.8) 2 (0.7) 2 (0.7) 0	 159 (57.8) 63 (22.9) 39 (14.2) 19 (6.9) 9 (3.3) 95 (34.5) 3 (1.0) 4 (1.4) 1 (0.3) 3 (1.0)

Trial profile

Table 75: Trial profile of the intensive care studies

Study		N	No PCT testing	Died	Lost to follow-up	Withdrew consent	Total excluded from analysis	Included for analysis
Stolz (2009)	**PCT**	51						51
	Control	50						50
Svoboda (2007)	**PCT**	38		10				28
	Control	34		13				21
Hochreiter (2009)	**PCT**	57		15				42
	Control	53		14				39
Schroeder (2009)	**PCT**	14		3				11
	Control	13		3				10
Bouadma (2010)	**PCT**	311				4	4	307
	Control	319			1	4	5	314
Nobre (2008)	**PCT**	39		4*			0	39 (31#)
	Control	40		2*			0	40 (37#)
Jensen (2011)	**PCT**	604		1**			0	604
	Control	596		2**			0	596

* PCT group=4 excluded or transferred before day 5; control group=2 deceased or transferred before day 5; # Per-protocol analysis;
** Died prior to PCT level taken

Table 76: Randomisation and blinding in the intensive care studies

Study	Randomisation	Blinded PCT	Blinded to group assignment	Blinded to outcomes
Stolz (2009)	Arbitrary allocation based on sealed opaque envelopes, block size was twenty envelopes	Both groups initial antibiotics started without knowledge of PCT levels Control group physician blinded to PCT level throughout study	No	NS
Svoboda (2007)	Computer-generated random treatment list, in opaque sealed numbered enveloped and envelope with lowest number always used for consecutive patients	NS	NS	NS
Hochreiter (2009)	Not stated	Open-blinded study	No	NS
Schroeder (2009)	Not stated	Open-blinded study	No	NS
Bouadma (2010)	Centralised computer-generated randomisation sequence. Stratified by centre with random block sizes of 2, 4 or 6	Open-label design	No	Unaware of aggregate outcomes during the study
Nobre (2008)	Computer-generated random number generation using opaque sealed numbered envelopes	Open-label	No	NS
Jensen (2011)	Computerised algorithm with concealed block size, pre-stratified for site of recruitment, initial APACHE and age (entered in an encrypted screening form in a password protected web site)	Control group of physicians and investigators blinded to PCT levels in control group	Yes	Yes

NS—not stated; APACHE—Acute Physiology and Chronic Health Evaluation

Table 77: Trial profile of the emergency department and primary care studies

Study		N	No PCT testing	Died	Lost to follow-up	Withdrew consent	Total excluded from analysis	Included for analysis
Christ-Crain (2006)	**PCT**	151		18	2			151
	Control	151		20	0			151
Schuetz (2009)	**PCT**	687		34	1	16	16	671
	Control	694		33	0	6	6	688
Briel (2008)	**PCT**	232			1			232 (231#)
	Control	226		1	1			226 (223#)
Stolz (2007)	**PCT**	113		3			11*	102
	Control	113		2			7*	106
Kristoffersen (2009)	**PCT**	110	2			2	7	103
	Control	113	1			2	6	107
Christ-Crain (2004)	**PCT**	124		4	8		12	112
	Control	119		4	5		9	110
Burkhardt (2010)	**PCT**	275					21	275
	Control	275						275

* Excluded secondarily for absence of COPD according to GOLD

Table 78: Randomisation and blinding in the emergency department and primary care studies

Study	Randomisation	Blinded PCT	Blinded to group assignment	Outcomes
Christ-Crain (2006)	Sealed opaque envelopes	Open-label design	No Senior radiologist blinded to group assignment and lab findings	NS Senior radiologist reviewing chest X-rays blinded to lab findings
Schuetz (2009)	Concealed website	Open-label design	No	NS
Briel (2008)	Centralised randomised computer-generated listed. Randomisation was in fixed blocks of 4, and a separate randomisation list was kept for each physicians practice*.	Open-label design	No	No
Stolz (2007)	NS	NS	NS	NS
Kristoffersen (2009)	computer-generated randomisation scheme	PCT results not available to control group physicians	No	NS
Christ-Crain (2004)	Computer-generated week-wise randomisation scheme	Both groups initial antibiotics started without knowledge of PCT levels Control group physician blinded to PCT level throughout study	No	NS
Burkhardt (2010)	Web=based randomisation	Blinded	Yes	NS

NS—not stated; *Randomisation stratified by general practice.

Assays used in included studies

Table 79: Assays used in included studies

Study	Type	Functional assay sensitivity	Imprecision	Results
Bouadma (2010)	Kryptor PCT*	Detection concentration 0.06 µg/l Study laboratories# 0.25 µg/l 10 µg/l	=10% at 0.20 µg/l <6% at >0.30 µg/l 5.8%–8.8% 4.7%–40.8%	Transmitted to physicians with 2hr after blood drawn
Jensen (2011)	Kryptor PCT*	0.06 µg/l		
Briel (2008)	Kryptor PCT	0.06 µg/l		Assay time 19 mins with 20–50 µg/l of plasma or serum Results reported to study practice within 2–4 hours
Christ-Crain (2004)	TRACE~ Kryptor PCT	0.06 µg/l		Assay time 19 mins with 20–50 µg/l of plasma or serum Results can be obtained within 1 hour (although study doesn't report when results reported)
Christ-Crain (2006)	Kryptor PCT	0.06 µg/l		Assay time <20 minutes Results routinely available within 1 hour
Hochreiter (2009)	LIA PCT*	0.5ng/ml (0.5 µg /L)		
Schroeder (2009)	LIA PCT*			Upper normal reference range <0.5 ng/ml
Nobre (2008)	Kryptor PCT*	0.06 µg/l		Time to obtain plasma PCT levels about 1 hour Results provided to clinical team of patients randomised to the PCT group, within 3 hours after blood drawing but kept in laboratory and not communicated to the treating physicians of control group
Schuetz (2009)	Kryptor PCT*	0.06 µg/l		Assay time <20 minutes Results routinely available around the clock within 1 hour and communicated by Web site to treating physician
Stolz (2009)	Kryptor PCT*	0.06 µg/l		Assay time <20 minutes Results routinely available within 1 hour
Stolz (2007)	Kryptor PCT*	0.06 µg/l		
Svoboda (2007)	PCT-Q*			12 samples tested against LUMI test* and correlation (r=0.93; p<0.001)
Kristoffersen (2009)	Kryptor PCT*	0.06 µg/l		Test results available on following day, except for weekends (in 41 cases (the same in both groups)sample could not be analysed within 24h
Burkhardt (2010)	Kryptor PCT	0.06	Precision cut-off (0.25 ng/ml)	Time to results is 19 min Time from blood collection to results <4 hours

Ug—micrograms; ng—nanogram;

* Brahms Hennigsdorf Germany; # Data available from four of seven centres; ~ TRACE—time-resolved amplified cryptate emission technology assay (Brahms Hennigsdorf Germany)

Study profiles of included studies on accuracy

Table 80: Study profiles of included studies on accuracy

Study	Quality	Country	Study design	Participants/setting	Outcome
Intensive care					
Luyt (2008)	II	France	Prospective cohort study PCT level Reference standard: clinically suspected VAP and BAL cultures	N=41 consecutive ICU patients with clinically suspected VAP after 48 hrs of MV 73 suspected episodes of VAP included in analysis	Diagnostic value of PCT measured the day VAP suspected (D1). Diagnostic value of PCT kinetics, using PCT values obtained within the 5 days preceding D1 also tested retrospectively. Sensitivity, specificity, PPV, NPV, NLR, PLR
Bell (2003)	II	Australia	Prospective cohort study Senior ICU registrars blinded to PCT results Reference standard: cultures of blood, BAL, sputum, urine	N=123 consecutive ICU patients fulfilling established criteria for SIRS included	Diagnostic accuracy of PCT in discrimination of infectious SIRS from non-infectious SIRS
Balci (2003)	II	Turkey	Prospective cohort study Treating clinicians blinded to PCT results and those performing PCT assays blinded to clinical status of patient	N=33 consecutive ICU adults with SIRS, sepsis or septic shock	Determine PCT levels at early diagnosis and differentiation in patients with SIRS and sepsis (also a comparison with CRP, IL-2, IL-6 and IL-8)
Ruokonen (2002)	II	Switzerland	Prospective cohort study	N=208 adult consecutive ICU patients over 12 months suspected of severe infection	Differentiation of sepsis and infection from systemic inflammation in critically ill patients
Du(2003)	III-1	China	Prospective cohort study Diagnosis done blind to lab results References=blood cultures, tracheal aspirates	N=51 ICU non-consecutive patients with a diagnosis of SIRS, sepsis or septic shock	Diagnostic accuracy of PCT to discriminate between sepsis and non-infectious SIRS AUC
Cheval (2000)		France	Controlled study	N=60 Four groups of consecutively acutely ill patients septic shock patients N=16; Non-septic shock patients N=18; Infected patients N= 16; Control group without infection or shock N=10.	Diagnostic accuracy of PCT to predict bacterial or fungal infection and severity of illness
Ruiz-Alvarez	II	Spain	Prospective cohort study	N=103 consecutive ICU patients (n=22 surgical, n=81	Diagnostic accuracy

(2009)			Reference standard: microbiological or x-ray (pneumonia)	medical) who had suspected sepsis/SIRS	Prognostic markers Comparison of PCT and CRP (not reported)
Castelli (2006)	II	Italy	Prospective cohort study Blinded to results of serum PCT levels Infection reference standard: ACCP/SCCM defined SIRS and definable infection (microbiology confirmed) and/or blood cultures	N=153 consecutive ICU patients Trauma patients admitted with trauma and studied in the acute phase SIRS patients with no defined source of infection No SIRS (or trauma) Sepsis/SS with SIRS and known source of infection and/or positive blood cultures. Divided into septic shock, severe sepsis, and sepsis	Variations of PCT in the diagnosis of sepsis, severity of disease and septic complications of trauma NOTE: Results reported as clinical events
Boussekey (2005)	II	France	Prospective cohort study Referencestandard:= BAL, endotracheal aspirate, blood or pleural fluid culture	N=110 consecutive patients admitted to ICU with severe CAP	ROC curves to assess the sensitivity and specificity to predict either a positive bacterial etiology or death. Based on values of PCT upon admission to the ICU
Emergency department					
Lai (2010)	II	Taiwan	Prospective cohort study Infection specialists blinded to PCT levels Reference standard: blood cultures	N=262 consecutive adults ≥65 yrs with criteria for SIRS who visited ED	Diagnosis of bacteremia in patients with SIRS at admission Diagnostic sensitivity, specificity, PPV, NPV of very elderly patients with bacteremia
Muller (2010)	III-1	Switzerland	Prospective cohort study with predefined sub-study of ProHOSP RCT Reference standard: blood cultures	N=925 with radiologically confirmed CAP Adult patients admitted to hospital (via ED)	Secondary endpoint of ProHOSP RCT was prognostic accuracy of PCT for blood culture positive
Holm (2007)	II	Denmark	Prospective cohort study Radiologist blinded Reference standard: chest x-ray infiltrate, blood or sputum culture	N=364 consecutive adults with LRTI treated in primary care	Range of PCT values in primary care Accuracy of PCT to discriminate between bacterial and viral pneumonia Predict outcome
Jones (2007)	I*	USA	Systematic review of	Prospective investigation of adults and children with	Diagnostic accuracy of PCT test for diagnosis of bacteraemia

			available studies Reference standard=blood cultures	suspected infection in ED on admission N=2,008	
Uzzan (2006)	I*	France	Systemic review of available literature	Adults in ICU or after surgery or trauma	The accuracy of serum PCT as a diagnostic test for sepsis, severe sepsis, or septic shock

VAP—ventilator associated pneumonia; MV—mechanical ventilation, BAL—bronchalveolar lavage

*It is not possible to determine whether the systemic review was only of level II studies, as nether systemic review includes a quality assessment of the included studies

Inclusion/exclusion criteria of included studies in accuracy review

Table 81: Inclusion criteria for the intensive care studies

Intensive Care	Luyt (2008)	Bell (2003	Balci (2002)	Ruokonen (2002)	Cheval (2000)	Du (2003)
ICU	√	√	√	√	√	√
48 hrs MV	√					
>72 hrs ICU						√
Preceding PCT level <5 days	√					
Suspected VAP	√					
Meet criteria SIRS		√	√			√
>24 hours ICU			√			
Febrile				√		
Blood cultures				√*		√

* These are taken if a patient's body temperature is >38.3ºC, if they have signs of severe sepsis or if they need vasopressor therapy for suspected septic shock

Inclusion criteria for the intensive care studies (continued)

Intensive Care	Ruiz-Alvarez (2009)	Castelli (2006)	Boussekey (2005)
ICU	√	√	√
48 hrs MV			
>72 hrs ICU			
Preceding PCT level <5 days			
Suspected VAP			
Meet criteria SIRS	√		
>24 hours ICU			
Febrile			
Blood cultures			

Table 82: Exclusion criteria for intensive care studies

Intensive Care	Balci (2002)	Ruiz-Alvarez (2009)	Castelli (2006)
Chronic organ failure	√		
Thyroid cancer or pancreatitis	√		
Massive blood transfusion	√		
Received blood transfusion before stay in ICU		√	
Stay in ICU<24 hrs	√	√	
Primary fatal condition e.g., cerebral death			
Chronic organ failure		√	
Pregnant		√	
Neurosurgical patients			√
Elective surgical patients without complications			√

NOTE: only these studies described their exclusion criteria

Table 83: Inclusion criteria for the emergency department and primary care studies

Emergency Department	Lai (2010)	Muller (2010)	Holm (2007)
>65	√		
>18 yrs		√	√
Meet criteria SIRS with presence of two or more of: Tachycardia, tachypnea, hypoxia, hypothermia or hyperthermia, leukocytosis, leukopenia, bandemia	√		
Hospital admission from community or nursing home for LRTI[2]		√	
HIV and immunosuppression			
Clinical diagnosis of LRTI			√

[2] LRTI was defined by the presence of at least one respiratory symptom (cough with or without sputum production, dyspnea, tachypnea or pleuritic pain) plus one auscultatory finding or one sign of infection (core body temperature >38.0ºC, shivers or WCC count > 10g/L or < 4 g/L) independent of antibiotic pre-treatment. Diagnosis of CAP was made if, in addition to the LRTI criteria, an underlying infiltrate on chest radiograph was present

Table 84: Exclusion criteria for the emergency department and primary care studies

Emergency Department	Lai (2010)	Muller (2010)	Holm (2007)
Missing data or loss of follow-up	√		
Pre-existing thyroid disease	√		
Unable to give consent		√	
Active illegal IV drug use		√	
Previous hospitalisation for LRTI ≤14 days LRTI<7 days		√	 √
Severe immunosuppression		√	
Chronic infection or endocarditis Severe medical co-morbidities where death imminent		√	
Pregnancy			√
Requires hospitalisation			√

Baseline characteristics of included studies in accuracy review

Table 85: Baseline characteristics of intensive care studies

Characteristics	Luyt (2008) N=41	Bell (2003) N=123	Baci (2002) N=33	Ruokonen (2002) N=208	Cheval (2000) N=60	Du (2003) N=51	Brunkhorst (2000) N=185
Age, yrs, median, *mean* (IQR)±SD	60 (50–71)	61 (43–72)	58±16	55 (44–70)	61	64.7±16.3	63 (14–86)
Sex male (%)	29 (71)	81 (65.8)	17(51.5)	149 (71.6)	34 (57)	31 (60.7)	
McCabe and Jackson co-morbidity score ≥2 (%)	27 (66%)						
SAPS II median (IQR)	54 (44–69)				103±27[f]		
SOFA score median (IQR)	12 (7–15)						
APACHE score, median, *mean* [IQR]		22 [9.0–16.1]	NR			17.4±7.6	
Admission category (%) - Medical - Emergency surgery - Elective surgery	 20 (49) 19 (46)[a] 2 (5)[b]		 13 (39.4) 20 (60.6)[d]	 140 (67.3) 68 (32.6)[d]	 37 (74)		
Underlying condition (%) - Diabetes mellitus - Malignancy - Chronic kidney disease - Liver cirrhosis - Autoimmune disease	 24 (59)[C]						
Reason for MV (%) - Acute respiratory failure - Postoperative respiratory failure - Neurological - Shock - SIRS[g] - Pneumothoraxes - Other	 13 (32) 21 (51) 1 (2)				 1 (1.6) 2 (3.3) 18 (30) 16 (26.6) 6 (10) 1 (1.6)		130 (70.2)
Others (%)	6 (15)						
Solid organ transplantation (%)	3 (7)						
Corticosteroid use or (%)chemotherapy	14 (34)						
Total duration of MV, median [IQR]	22 (13–42)						
Hospital days, median [25–75%)		28.3 [32.5–50.1]					
ICU days, median [25–75%] ±SD		12.3 [9.0–16.1]	7.4±6.78	6 [3–13]			
ICU mortality (%)	17 (41)					13 (25)	
Bacterial infection				162			102 (55.1)
SIRS[g]			53%[e]		16 (26.6)	31 (60.7)	17
Sepsis/severe sepsis			39% [e]			10 (19.6)	61/68
Septic shock			7% [e]			10 (19.6)	39
Type of infection (%) - Pneumonia					 5 (0.8)	 8 (15.7)	 105 (56.8)

- Bacteremia					2 (3.3)	3 (5.8)	50 (27.0)
- UTI						1 (1.9)	7 (3.8)
- Intra-abdominal infection					6 (10)	5 (9.8)	4 (2.1)
- Skin & soft tissue infection							15 (8.1)
- Meningitis					1 (1.6)		13 (7.0)
- Catheter-related infection							
- Necrotising fasciitis					1 (1.6)	1 (1.9)	5 (2.7)
- Endocarditis					1 (1.6)		4 (2.2)
White blood cell count (cells/uL) median [IQR]		17.5 [12.5–26.1]					
CRP mg/mL, median [IQR]		142 [93–230]					
Blood cultures				22			
Hospital mortality (%)	22 (54)	38 (31)	10 (30.3)	66 (31.7)	21 (35)	13 (25)	52 (21)[g]
PCT, median [IQR]		3.45 [0.74–11.60]					

[a] All admitted to ICU after recent cardiac surgery
[b] Acute lung injury, ARDS, pneumonia or multiorgan failure complicating cardiac surgery
[C] Defined as serum creatinine>180 umol/l or need for renal replacement therapy
[d] Study doesn't state whether emergency or elective surgery
[e] Measured by assessment of patients' clinical condition not so numbers do not equate to study participant numbers
[f] Only infected group (n=32)
[g] Non-infectious SIRS
[g] Mortality was 23.5% in patients with SIRS, 13.1% in sepsis, 22.1% in severe sepsis and 65% in septic shock

Baseline demographics and clinical characteristics of the intensive care unit studies (continued)

Characteristics	Ruiz-Alvarez (2009) N=103					Castelli (2006)	Boussekey (2005)
	Overall N=103	Non-infected SIRS[b] (I) N=25	Sepsis[b] (II) N=20	Severe sepsis[b] (III) N=11	Septic shock[b] (IV) N=47	N=152[h]	N=110
Age, yrs, median, *mean* (IQR) ±SD	67 (17–84)	49 (17–77)[c]	61 (28–77)[c]	77 (26–83)[c]	70 (29–84)[c]	59.2 (15–89)	58.8±16.3
Sex male (%)	75 (72.8)	19 (25)	17 (23)	6 (8)	33 (44)	96 (64)	70 (64)
McCabe and Jackson co-morbidity score ≥2 (%)							
SAPS II, median (IQR)							43±21.2
OSF score							1.6±1
SOFA score, median (IQR)		4±2[f]	5±2[f]	8±5[f]	8±2[f]		
APACHE score, median, *mean* [IQR]		14±6[e]	15±4[e]	16±7[e]	21±6[e]		
Admission category (%) - Medical - Emergency surgery - Elective surgery	81 22[a]						110(100)
Underlying condition (%) - Diabetes mellitus - Malignancy - Chronic kidney disease - Liver cirrhosis - Autoimmune disease - Acute pancreatitis - Multiple trauma - Enterectomy - Pulmonary embolism - Other							
MV(%) reason - Acute respiratory failure/LRTI - Postoperative respiratory failure - Neurological - Shock - SIRS[g] - Pneumothoraxes - Other							74(67.2) 74(67.2)
Others (%)							
Solid organ transplantation (%)							
Corticosteroid use or (%) chemotherapy							
Total duration of MV, median [IQR]							
Hospital days, median [25–75%)							

ICU days, median [25–75%] ±SD		6 (2–45)	8 (1–72)	13 (6–34)	13 (1–120)		
ICU mortality (%)		2 (6)[g]	3 (9)[g]	4 (12.9)[g]	22 (71)[g]	29 (19)	
Bacterial infection							
SIRS[g]							
Sepsis							
Severe sepsis							
Septic shock							42 (38.2)
Type of infection (%) - Pneumonia/LRTI - Bacteremia - UTI - Intra-abdominal infection - Skin & soft tissue infection - Meningitis/CNS - Catheter-related infection - Necrotising facitis - Endocarditis - Other							110 (100)
White blood cell count (cells/uL) median [IQR]							
CRP mg/mL, median [IQR]							
Blood cultures							
Hospital mortality (%)		2 (6)[g]	3 (9)[g]	4 (12.9)[g]	22 (71)[g]		30 (27.3)
PCT, median [IQR] ng/mL,		0.3 (0.1–14.7)[d]	1.1 (0.1–183.9)[d]	1.9 (0.03–68.3)[d]	9.1 (0.1–358.5)[d]		2[i] (0.6–8.6)

OSF—organ system failure score

[a] Not specified if elective or emergency

[b] Classified into four diagnostic categories according to the ACCP/SCCM between May 2004 and January 2006 (case ascertainment was done retrospectively by two independent investigators and concordance (k=0.79, 95% CI, 0.71–0.88)

[c] P=0.002 (I-IV), (I-III), (II-III)

[d] P<0.001 (I-IV), (I-III), (II-IV)

[e] P<0.001 (I-IV), (II-IV), (I-III)

[f] P<0.001 (I-IV), (II-IV)

[g] P<0.003 (I-III), (I-IV), (II-IV)

[h] Article reports results according to clinical events and not patient numbers. Patient numbers derived from the number of the population that were male, n=96 and the accompanying proportion (64%) and the number of patients who died, n=29 and accompanying proportion (19%). From this, it appears that between 150 and 152 patients were included in the study.

[i] 50% has PCT level >2ng/ml, 30% had a level between 0.5 and 2 ng/ml and 20% had level <0.5ng/ml

Table 86: Baseline demographics and clinical characteristics of the emergency department studies

Characteristics	Lai (2010) N=262	Muller (2010) N=925	Holm (2007) N=364
Age, yrs, median [IQR]	77.2±8.1	73 (59–82)	
Sex: male (%)	60.3%	544 (59)	
Admission category (%) - Medical - Emergency surgery - Elective surgery			
Underlying condition (%) - Diabetes mellitus - Malignancy - Chronic kidney disease - Liver cirrhosis - Autoimmune disease - Congestive heart failure - Cerebrovascular disease - Chronic Lung Disease - Coronary Heart Disease	 66 (32.4) 45 (22.1) 23 (11.3) 16 (7.8) 1 (0.5)	 162 (18) 118 (13) 206 (22) 22 (2) 159 (17) 82 (9) 282 (30 159 (17)	
Corticosteroid use or (%)chemotherapy	14 (6.9)		
Bacterial infection	204 (77.9%)		48 (13)
Type of infection (%) - Pneumonia - Bacteremia - UTI - Intra-abdominal infection - Skin & soft tissue infection - Meningitis - Catheter-related infection	 82 (40.2) 48 (23.5) 48 (23.5) 33 (16.2) 29 (14.2) 1 (0.5) 1 (0.5)		48 (13)
White blood cell count (cells/uL)	12,014	12.1 (9.0–16.4)[d]	
CRP mg/mL	7.4		
Hospital mortality (%)		50 (5.4)	
PCT			
Antibiotic pre-treatment (%)		236 (26)	
Active-smokers (%)		233 (26)	

[a] All admitted to ICU after recent cardiac surgery
[b] Acute lung injury, ARDS, pneumonia or multiorgan failure complicating cardiac surgery
[C] Defined as serum creatinine>180 umol/l or need for renal replacement therapy
[d] WCC count, x 10^9/L

Table 87: Assays used in the included studies

Study	Type	Functional assay sensitivity	Imprecision	Results
Luyt (2008)	Time-resolved amplified cryptate emission technology on a Kryptor analyser*			
Lai (2010)	Time-resolved amplified cryptate emission technology on a Kryptor analyser*	0.06 ng/mL		Blood samples collected within 2 hours of admission
Bell (2003)	LUMItest, Brahms			
Baci (2002)	LUMItest, Brahms			
Oberhoffer (1999)	LUMItest, Brahms	<0.5ng/mL	2±0.12ng/ml	
Ruokonen (2002)	LUMItest, Brahms	0.3ug/L		
Muller (2010)	Time-resolved amplified cryptate emission technology on a Kryptor analyser*	0.06 ug/L		
Cheval (2000)	LUMItest PCT*			
Du (2003)	LUMItest PCT*			
Giamarello-Bourboulis (2002)	Immunochemiluminometric assay in ng/ml*	0.08 ng/ml		Concentration <0.5ng/ml considered normal
Giamarello-Bourboulis (2004)	Immunoluminometric assay*	0.08 ng/mL		
Brunkhorst (2000)	Immunoluminometric assay*	Inter-assay and intra-assay variation at high and low concentrations is <0.08 and 0.07 respectively		Needs 2–3 hours and 20 uL of serum or plasma Upper normal limit is 0.5 ng/ml
Ruiz-Alvarez (2009)	Kryptor automated immunofluorescent assay*	0.5 ng/mL	Coefficient of variation 3%	
Castelli (2006)	Immunoluminometric assay, LUMItest PCT ILMA-kit;* Liamat instruments#			Stored at -20° for <2 weeks
Boussekey (2005)	Immunoluminometric assay, LUMItest PCT	0.5 ng/ml		
Holm (2007)	Kryptor PCT assay*	0.06 ng/ml	Inter-assay coefficient of variation 20%	Detection limit reported by manufacturer at 0.02 ng/ml

* Brahms AG, Germany; # BYK Gulden, Italy

Appendix E Excluded studies

Table 88: List of excluded studies

Study	Count	Study	Participants/ setting	Outcome
Andermahr (2002)	Germany	Single-centre prospective cohort study	N=266 ER and ICU	Predictive value of PCT and other parameters for development of posttraumatic pneumonia
Oberhoffer (1999)	Germany	Single-centre prospective cohort study	N=242 ICU	AUC of ROC
Muller (2006)	Switzerland	Pre-planned post-hoc analysis of two controlled intervention trials	N=545 ER	Diagnostic accuracy of PCT to diagnose bacteremia and severity of CAP
Lavrentieva (2007)	Greece	Single-centre prospective cohort study	N=43 ICU (burns)	Diagnostic value of PCT (and other markers of sepsis) as marker of sepsis
Rammaert (2009)	France	Prospective cohort study	N=116 ICU	Clinical and biological predictors of mortality
Liaudat (2001)	Switzerland	Prospective case-control study	N=200 N=50 consecutive patients who had blood cultures Hospital admission	Diagnostic accuracy in patients who undergo blood cultures
Bin (2003)	China	Prospective cohort study	N=51	Sensitivity and specificity of PCT (and other parameters) to diagnose bacteremia
Huang (2008)	USA	Multi-centre prospective cohort study	N=1651 28 ED	30-day mortality Adverse outcomes
Indino (2008)	Canada	Prospective cohort study	N=173 ED	Diagnostic accuracy of PCT to diagnose bacteremia
Giamarellos-Bourboulis (2002)	Greece	Prospective cohort study	N=119 ICU	Diagnostic accuracy of PCT to diagnose bacteremia
Giamarellos-Bourboulis (2004)	Greece	Prospective cohort study	N=105 consecutive patients ICU	To find the diagnostic threshold Range of concentrations conferring to a specific diagnosis
Brunkhorst (2000)	Germany	Prospective cohort study	N=185 ICU	The value of PCT as an early marker for diagnosis and differentiation of SIRS, sepsis, severe sepsis and septic shock
Jongwutiwes (2009)	Thailand and USA	Single-centre prospective cohort study	N=56 Hospital patients	Diagnostic accuracy Correlation of PCT levels to severity of sepsis

				Prognostic value Correlation among different assays
Jebali (2007)	France	Single-centre prospective cohort study	N=100 Cardiac surgery with CPB	Diagnostic accuracy of PCT to diagnose bacteremia
Claessens (2009)	France	Multi-centre prospective cohort study blinded evaluation	N=549 12 ED	Diagnostic accuracy of PCT to determine hospital admission Threshold levels

RCT—randomised controlled trial; ED—emergency department; ICU—intensive care unit; CPB—cardiopulmonary bypass; AUC—area under the curve; ROC—receiver operating characteristic

Not in English, and not of a higher level of evidence than the English language literature

Table 89: Potential studies not in English

Authors	Journal and Abstract
Marc, E, Menager, C, Moulin, F, Stos, B, Chalumeau, M, Guerin, S, Lebon, P, Brunet, F, Raymond, J & Gendrel, D (2002)	'Procalcitonin measurement for reducing antibiotic treatments during outbreak of viral meningitis in children' *Archives de Pediatrie*, vol. 9, no. 4, pp. 358–364. Objective. Viral meningitis is often treated with antibiotics in emergency because routine analysis of CSF is not always efficient for distinguishing between viral and bacterial infection. The aim of the study was to evaluate the usefulness of procalcitonin (PCT) to reduce antibiotic treatments. Methods and results. A blood PCT level <0.5 ng/mL was prospectively used for the diagnosis of viral origin of meningitis in 58 patients (two months—14 years), in which enterovirus was isolated by culture or PCR during an outbreak (May–June 2000). CSF cells range was 10 to 2800/mL (m: 244), PMN 5 to 2464/mL and CSF proteins range was 0.19 to 0.92 mg/dL (m: 0.37). Seventeen patients received antibiotic therapy in admission. In nine patients, PCT (dosage was routinely measured 3/week) result <0,5 ng/mL was obtained in 24 h and in 48 h in six: treatment was then stopped and children left hospital. In two patients, PCT was > 1 ng/mL because of bacterial coinfection. CSF and PCT values were similar to those of an already published control group. Conclusion. PCT dosage allowed to shorten hospitalisation of 4.47 (controls) to 2.06 (patients) days in patients receiving unnecessary antibiotic treatments. During this outbreak, PCT dosage allowed to reduce 40 days of hospitalisation.
Reina, PM, Alcantara, IR, Mico, SV, Lucea, JLL-P & Alapont, VMI (2010)	'Accuracy of the procalcitonin test in the diagnosis of occult bacteremia in paediatrics: A systematic review and meta-analysis', *Anales de Pediatria*, vol. 72, no. 6, pp. 403–12. Objective: To evaluate the diagnostic accuracy of serum procalcitonin (PCT) to detect severe bacterial infection (SBI) in ambulatory children attended in the emergency room (ER) for fever without source (FWS). Material and methods: A search was made in MEDLINE, OVID and EMBASE (to January 2010). We searched for papers that evaluated the diagnostic accuracy of serum PCT to detect SBI in children that, being previously well, were seen in the ER for FWS. We rated the methodological quality of each paper using objective validity criteria (QUADAS, CASPE) and included only those with the maximum quality in the analysis. The statistical meta-analysis was performed using the software, Meta-DiSc 1.1.1 for Windows. Results: The search identified 115 papers. Only six studies (prospective observational and analytic cohorts) fitted the inclusion criteria, with a sample size of 1139 patients. The prevalence of SBI was between 12.8% and 29% with a weighted mean of 18%. The overall sensitivity was 0.771 (95% CI=0.707–0.826), the overall specificity was 0.804 (95% CI=0.777–0.830), the overall positive likelihood ratio was 3.610 (95% CI=2.481–5.253) and the overall negative likelihood ratio was 0.218 (95% CI=0.106–0.446). The diagnostic OR was 18.922 (95% CI=10.076–35.534), the area under the SROC curve was 0.8801 (95% CI=0.821–0.939), and the optimal diagnostic cut-off value was Q*=0.8106 (95% CI=0.7512–0.8699). Conclusions: Based on our analysis, in children with FWS seen in the ER, the serum PCT test accurately identifies those that have a SBI. We cannot extrapolate these results to other types of patients.
Biernacka, J, Wosko, J, Dabrowski, W & Nestorowicz, A (2004)	'Procalcitonin PCT-Q strip test', *Anestezjologia Intensywna Terapia*, vol. 36, no. 4, pp. 252–4. Objective. It has recently been suggested that procalcitonin (PCT) is of significant value in the diagnosis of sepsis, but its quantitative immunoluminometric assay is difficult to perform and time consuming. For emergencies, a rapid, semi-quantitative PCT-Q test was introduced. The purpose of the study was to compare the usefulness of both tests in septic patients. Methods. 31 adult septic patients, both sexes, were enrolled in the study. Both tests were always performed at the same time. The sensitivity of the PCT-Q test was assessed by comparison with the quantitative assay. Results. 105 assays were performed. The overall sensitivity of the PCT-Q test was 91%, with eleven results of the quantitative assays being outside the range indicated in the rapid test. Discussion and conclusion. The PCT-Q test is a useful screening method for detecting sepsis, but its use for therapy monitoring in severe cases is somehow controversial. The highest range indicated by the test is above 10 ng ml(-1), t.m. it will be positive with procalcitonin concentrations of, e.g., 12 and 70 ng ml(-1). Therefore, if procalcitonin concentration is to be regarded as an indicator of sepsis severity, it has to be assayed by the quantitative method.
Mironov, PI & Lykov, AV (2010)	'Diagnostics and treatment of sepsis in the acute phase of severe heat injury', (Russian) *Khirurgiia*, vol. 1, pp. 22–4. Objective: A prospective non-randomised, single-centred controlled study aimed the optimisation of treatment and diagnostic algorithm of the early burn sepsis. 47 patients were included. Conclusions: The combination of bacterial wound colonisation and procalcitonin blood level >or =2 ng\ml was the reliable marker of the early burn sepsis and indicates the necessity of de-escalation antibiotic therapy.
Long, W, Deng, XQ, Tang, JG, Xie, J, Zhang, YC, Zhang, Y, Gao, YY	'The value of serum procalcitonin in treatment of community acquired pneumonia in outpatient', (Chinese) *Chung-Hua Nei Ko Tsa Chih Chinese Journal of Internal Medicine*, vol. 48, no. 3, pp. 216–9. Objective: To evaluate the value of serum procalcitonin (PCT) on antibiotic use in treatment of community

& Lu, G (2009)	acquired pneumonia (CAP) in outpatient. Methods: From November 2006 to February 2008, a total of 127 outpatients with CAP were randomly assigned into two groups: PCT group (n = 63) and control group (n = 64). PCT levels of all patients were measured after study admission. Based on normal treatment, the control group received antibiotics according to the attending physicians and the PCT group were treated with antibiotics according to serum PCT levels. Antibiotic treatment was applied with PCT level > or = 0.25 microg/L and was discouraged with PCT level Results: Clinical efficacy of the PCT group was similar with the control group (92.1% v. 87.5%, P > 0.05); rate and costs of antibiotics use was lower and antibiotic duration of the PCT group was shorter than that of the control group. Conclusion: PCT could be used in treatment of CAP for antibiotic use in outpatient and may reduce antibiotic use, shorten antibiotic duration and lower costs of antibiotic.
Hochreiter, M, Kohler, T, Schweiger, AM, Keck, FS, Bein, B, von Spiegel, T & Schroder, S (2008)	'Antibiotic treatment of surgical intensive care patients: procalcitonin to guide duration of therapy', (German) *Anaesthetist*., vol. 57, no. 6, pp. 571–7. The development of resistance by infective bacterial species is an incentive to reconsider the indications and administration of available antibiotics. Correct recognition of the indications and duration of therapy are particularly important for the use of highly potent substances in the intensive care situation. There has as yet been no clinical chemical parameter that is capable of specifically distinguishing a bacterial infection from a viral or non-infectious inflammatory reaction, but it now appears that procalcitonin (PCT) offers this possibility. The present study was intended to clarify whether PCT can be used to guide antibiotic therapy in surgical intensive care patients. A total of 110 patients in a surgical intensive care ward receiving antibiotic therapy after confirmed infection or a high grade suspicion of infection were enrolled in this study. In 57 of these patients, a new decision was reached each day as to whether the antibiotic therapy should be continued after daily PCT determination and clinical assessment. The control group consisted of 53 patients with a standardised duration of antibiotic therapy over 8 days. Demographic and clinical data were comparable in both groups. However, in the PCT group the duration of antibiotic therapy was significantly shorter compared to controls (5.9+/-1.7 v.. 7.9+/-0.5 days).
Hryckiewicz, K, Juszczyk, J, Samet, A, Arlukowicz, E, Sledzinska, A, & Bolewska, B (2006)	'Procalcitonin as a diagnostic marker in systemic inflammatory response syndrome (SIRS) and sepsis', (Polish) *Przeglad Epidemiologiczny*, vol. 60, no. 1, pp. 7–15. Objective: Evaluation the value of procalcitonin as a diagnostic and prognostic marker in septic patients and patients with systemic inflammatory response syndrome (SIRS). Materials and methods: 126 patients were included into the study. The patients were divided into four groups: 1) septic patients with positive blood cultures, 2) septic patients with negative blood cultures, 3) patients with SIRS, 4) patients without sepsis and SIRS. PCT level was measured by immunoluminometric assay (LUMItest) and immunochromatographic assay (PCT-Q). Results: PCT level is higher in patients with sepsis than in patients with SIRS. PCT level is only slightly elevated in patients without sepsis and SIRS. The highest PCT level is found in patients with septic shock. In patients with the clinical improvement, the frequency of PCT level increase is approximately twice lower than in patients who died. Conclusions: Measurement of PCT level on the first, second and third day of hospitalisation has no prognostic value. There is no significant difference in PCT level in sepsis caused by Gram-positive and Gram-negative bacteria. PCT is a useful marker in diagnosis of sepsis but its role in monitoring the severity of sepsis requires further investigation.
Shimetani, N, Ohba, Y, Shimetani, K, Mashiko, T, Matsuyama, N, Ohtani H & Morii, M (2001)	'Assay for determination of the serum procalcitonin level: biochemical and clinical evaluation', (Japanese) *Rinsho Byori Japanese Journal of Clinical Pathology*, vol. 49, no. 1, pp. 56–60. Objective: In patients with inflammatory conditions such as infection, cytokines induce the production of C-reactive protein (CRP) and serum amyloid A protein (SAA) in hepatic cells. It has been reported that upon viral infection, the serum SAA level increases by a greater degree than the serum CRP level. Procalcitonin (PCT), the precursor of calcitonin, is a new type of inflammatory marker that is specifically induced by bacterial infection, sepsis and lethal multiple organ failure, but not by viral infection, autoimmune diseases, tumours or surgical stress. To evaluate the immunoluminometric assay (LUMI test PCT; Brahms Diagnostics, Berlin, Germany) procedure for determining the PCT level and to study the clinical significance of the serum PCT level, we determined the serum levels of PCT, CRP and SAA in patients with various inflammatory diseases and normal subjects. Results: The serum PCT level in the normal subjects was 20000 micrograms/dl, the PCT level was elevated only in those patients with severe bacterial infection. Conclusions: These results suggest that determining the PCT level may be useful in the differential diagnosis of severe bacterial infection.
Endo, S, Kasai, T & Inada, K (1999)	'Evaluation of procalcitonin levels in patients with systemic inflammatory response syndrome as the diagnosis of infection and the severity of illness', (Japanese) *Kansenshogaku Zasshi Journal of the Japanese Association for Infectious Diseases*, vol. 73, no. 3, pp. 197–204. Objective: To understand the presence or absence of bacterial infection in patients with systemic inflammatory response syndrome (SIRS), the level of procalcitonin (PCT), a precursor of calcitonin, was determined. Subjects consisted of 14 SIRS patients without complication by bacterial infection, 14 SIRS patients complicated by sepsis and 14 SIRS patients complicated by severe sepsis and septic shock. PCT levels in SIRS patients with sepsis (2.9 +/- 2.3 ng/ml) were significantly higher than in those without complication by infection (0.7 +/- 1.1 ng/ml). Results: However, there were no significant differences in the

	levels of C-reactive protein (CRP), interleukin 6 (I-6) or tumour necrosis factor-alpha (TNF-alpha) between the two groups. PCT levels in SIRS patients with severe sepsis and septic shock (172.2 +/- 276.3 ng/ml) were significantly higher than those in SIRS patients with sepsis. Levels of CRP, IL-6 and TNF-alpha were also significantly higher in the patients with sepsis compared to those in patients with local infection. Significant correlations were observed between the levels of PCT and those of CRP, IL-6 and TNF-alpha in SIRS patients. Conclusions: It was suggested that to measure the levels of procalcitonin in patients with SIRS is useful to diagnose the infection and severity of illness.

Glossary and abbreviations

ACCP	American College of Chest Physicians
ADE	Adverse drug events
ARTI	Acute respiratory tract infection
BAL	Bronchalveolar lavage
BEACH	Bettering the Evaluation and Care of Health (report)
CAP	Community acquired pneumonia
CEFX	Cefotaxime
CI	Confidence intervals
CLSI	Clinical and Laboratory Standards Institute
COAD	Chronic obstructive airways disease
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CV	Contingent variation
DDD	Defined daily dose
ECOPD	Exacerbation of chronic obstructive pulmonary disease
ED	Emergency department
ESR	Erythrocyte sedimentation rate
FAS	Functional assay sensitivity
FDA	The United States Federal Drug Administration
GP	General practitioner
ICU	Intensive care unit
ILMA	Immunoluminometric assay
ITT	Intention-to-treat
IVD	In-vitro diagnostic medical devices
LRTI	Lower respiratory tract infection
M & C	Microscopy and culture
MSAC	Medical Services Advisory Committee
MBS	Medicare Benefits Scheme
NHMRC	National Health and Medical Research Council
NPS	National Prescribing Service
NPV	Negative predictive value
PCT	Procalcitonin
PPV	Positive predictive value

PSI	Pneumonia severity index
RTI	Respiratory tract infection
SCCM	The Society of Critical Care Medicine
SIRS	Systematic inflammatory response syndrome
SROC	Summary receiver operating characteristic
VAP	Ventilator associated pneumonia
WCC	White cell count
WMD	Weighted mean difference

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ABS – see Australian Bureau of Statistics.

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ATS – see The American Thoracic Society.

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CLSI –Clinical and Laboratory Standards Institute formerly the National Committee for Clinical Laboratory Standards (see NCCLS).

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