SPONSOR BRIEFING DOCUMENT

VIDAS® B•R•A•H•M•S PCT™

MICROBIOLOGY DEVICES PANEL ADVISORY COMMITTEE

MEETING DATE: NOVEMBER 10, 2016

(*VERSION: OCTOBER 19, 2016*)

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

LIST OF ABBREVIATIONS

AECOPD	acute exacerbation of chronic obstructive pulmonary disease
ARI	acute respiratory infection
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CURB-65	Confusion - Urea - Respiratory rate - Blood pressure - aged >65 years
FDA	Food and Drug Administration
GOLD	Global initiative for chronic Obstructive Lung Disease
ICU	intensive care unit
IL-6	interleukin-6
IQR	interquartile range
LRTI	lower respiratory tract infection
MA	meta-analysis
OR	odds ratio
PCT	procalcitonin
PSI	Pneumonia Severity Index
RCT	randomized controlled trial
RR	risk ratio
SIRS	systemic inflammatory response syndrome
UN	United Nations
URTI	upper respiratory tract infection
VAP	ventilator acquired pneumonia
WHO	World Health Organization
WMD	weighted mean difference

1 SYNOPSIS

VIDAS® B•R•A•H•M•S PCT™ is an automated *in-vitro* diagnostic (IVD) test that determines the concentration of human procalcitonin (PCT), a prohormone released in response to proinflammatory stimulation, particularly bacterial infection, and certain other conditions such as trauma.

VIDAS B•R•A•H•M•S PCT is currently cleared by the U.S. Food and Drug Administration (FDA) as an aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock and in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock. bioMérieux is proposing two additional intended uses for VIDAS B•R•A•H•M•S PCT as an aid in decision making on antibiotic therapy when used in conjunction with other laboratory findings and clinical assessments. These new intended uses are: (1) for patients with suspected or confirmed lower respiratory tract infection (LRTI), defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD); and, (2) for patients with suspected or confirmed sepsis.

This briefing document was prepared in order to provide the Advisory Committee members with an overview of the state of the clinical evidence, including the results of meta-analyses conducted by bioMérieux, which evaluated the safety and effectiveness of using PCT for the additional proposed indications.

Public Health Need for Antibiotic Stewardship

LRTIs and sepsis account for substantial morbidity and mortality in the United States, and effective treatment of patients with LRTI or sepsis symptoms relies on prompt identification of the underlying disease (Macfarlane, 1993; Hall, 2011). However, laboratory documentation from microbiological work-up to support a differential diagnosis is often not available when physicians are presented with a treatment decision. As a result, many patients are prescribed antibiotics empirically without an understanding of whether the condition is of viral, bacterial, or non-infectious origin.

Inappropriate antibiotic use, due to either antibiotic initiation in the absence of a bacterial infection or prolonged treatment after elimination of an infection, is associated with significant risks. For individual patients, non-optimal antibiotic use exposes patients unnecessarily to antibiotic-related side effects, increases the risk of complicating infections, and delays administration of appropriate treatment. On a societal scale, inappropriate antibiotic use is directly contributing to the rise of antibiotic-resistant bacteria, one of the most serious and growing threats to global public health (World Health Organization [WHO], 2015). In the United States, the Centers for Disease Control and Prevention (CDC) estimates that drug-resistant bacteria cause approximately two million illnesses and 23,000 deaths each year (CDC, 2016).

The advancement of technologies and policies to combat the misuse and over-use of antibiotics in healthcare has been identified as a key initiative in the *National Action Plan for Combating Antibiotic-Resistant Bacteria* to ensure that "each patient receives *the right antibiotic at the right time at the right dose for the right duration* (White House, 2015) [emphasis in original]." Diagnostic tools that provide physicians with rapid results to aid in treatment decisions offer the potential to improve the care of patients with LRTIs and sepsis and to advance the public health need for greater antibiotic stewardship.

Utility of PCT as a Biomarker to Aid in Decision-Making for Antibiotic Treatment

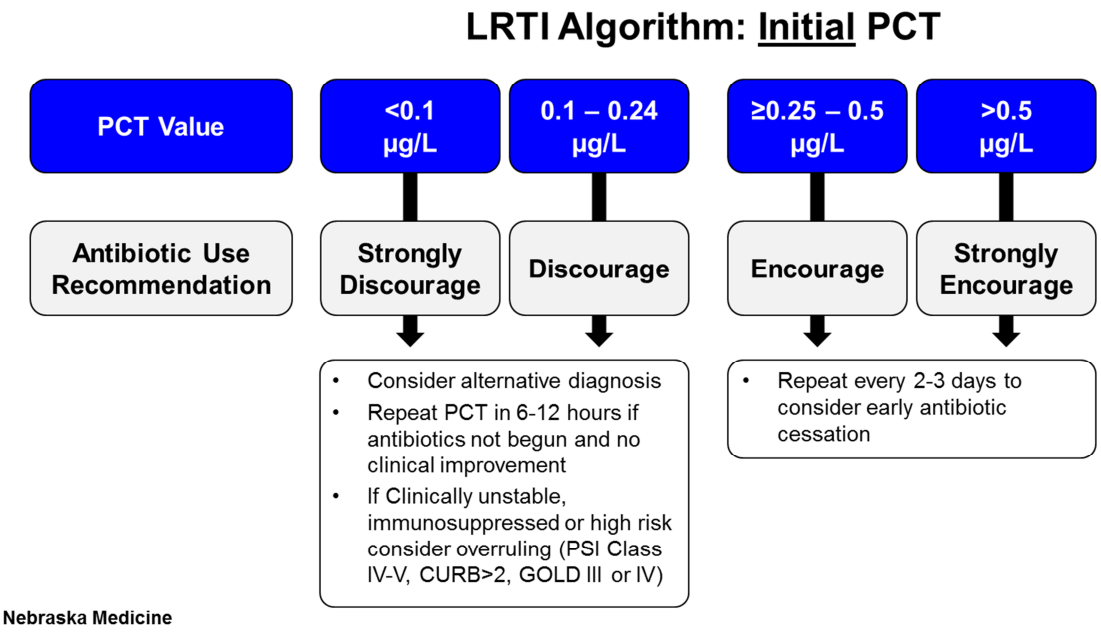
PCT is a marker protein of bacterial infection and sepsis. Over the last two decades, PCT has emerged as a useful biomarker in clinical practice that can be used to assist in making treatment decisions on antibiotic initiation and cessation. PCT concentrations change according to the presence and severity of an infection (Becker, 2010), and indicate the presence of a bacterially-induced systemic inflammatory reaction. PCT has been shown to be more specific and sensitive to infections of bacterial origin compared to other candidate biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP) (Cuquemelle, 2011; Rodriguez, 2016).

The normal range of PCT is considered less than 0.05 ng/mL (Morgenthaler, 2002). Reactions to a systemic bacterial insult induce elevations in PCT levels (>0.1 ng/mL). PCT levels greater than 0.5 ng/mL in the absence of other causes are strongly associated with the presence of sepsis. In severe cases, or among patients in septic shock, PCT levels often range between 2 and 10 ng/mL. Therefore, PCT concentrations can help differentiate the presence of a bacterial infection, for which antibiotics are warranted, from non-bacterial infections or self-limiting bacterial infections. In patients with LRTI or sepsis who have initiated antibiotic treatment, subsequent PCT measurements can indicate the presence of an infection and aid in the decision to discontinue antibiotic treatment.

The kinetics of PCT in bacterial infection and its characteristics as a discriminator for bacterial infection versus other conditions has led to many studies, including several randomized controlled trials (RCTs), on PCT-guided care. These incorporate evidence-based PCT-guided treatment algorithms to supplement clinical assessment for antibiotic initiation and cessation in patients with suspected or confirmed LRTI and cessation in confirmed or suspected sepsis.

Figure 1 shows a representative PCT-guided treatment algorithm for LRTI. Another representative example of PCT guidance for discontinuation of antibiotics in patients with sepsis is "… to stop the prescribed antibiotics if procalcitonin concentration decrease[s] by 80% or more of its peak value (relative stopping threshold), or when it reaches a value of 0.5 μg/L or lower (absolute stopping threshold)" (de Jong, 2016).

Figure 1: Example of PCT Algorithm Used to Guide Antibiotic Initiation and Discontinuation for LRTI



(Nebraska Medicine, 2016)

Rationale for the Use of Existing Data as a Basis of Approval for Proposed Intended Uses

Over the last two decades, several randomized controlled trials (RCTs) have evaluated the safety and effectiveness of PCT-guided algorithms for antibiotic therapy in respiratory tract infections and sepsis. These trials randomized patients into one of two groups: (1) a PCT group, which followed a PCT-guided algorithm for the initiation and/or duration of antibiotic therapy and (2) a "standard-of-care" control group, which used clinical judgment for antibiotic treatment decision making.

In an effort to be proactive in addressing the urgent public health need for enhanced antibiotic stewardship, bioMérieux and FDA agreed that a comprehensive evaluation of the published literature could provide the appropriate level of clinical evidence to support the proposed intended uses.

Methodology of Systematic Literature Review and Meta-Analyses

In consultation with the FDA, physicians with expertise in the development and use of PCT-guided algorithms, and independent statistical consultants, bioMérieux designed and conducted systematic literature reviews and meta-analyses of published RCTs of PCT-guided antibiotic therapy for LRTI and sepsis to evaluate the extent of reduction in inappropriate antibiotic use and the impact of PCT guidance on safety outcomes. One of the primary goals of the meta-analyses was to ensure that PCT-guided reductions in antibiotic therapy did not lead to safety

issues attributable to potential "false negatives" – either not initiating antibiotics when they should have been (in the case of LRTI) or prematurely discontinuing antibiotics (in the case of both LRTI and sepsis). The following outcome measures were prospectively defined and assessed following a systematic review of the literature:

- Antibiotic treatment initiation (LRTI only)
- Duration of antibiotic treatment in patients who were prescribed antibiotics
- Total exposure to antibiotics in all randomized patients
- Complications (e.g., death, re-hospitalization, recurrent or worsening infection)
- Length of hospitalization or ICU stay
- Mortality

(Note: The difference in the definitions of *duration* and *exposure* is that *exposure* evaluates the overall antibiotic burden in the population whereas *duration* reflects the burden only among those who initiated. For example, take five patients, two of whom did not initiate antibiotics and the three who did were on antibiotics for 4, 5, and 6 days, respectively. The duration of antibiotic therapy would be 5 days (i.e., the average of 4, 5, and 6) whereas the exposure would be 3 days (i.e., the average of 0, 0, 4, 5, and 6).)

Both study-level and patient-level meta-analyses were conducted for LRTI and sepsis. Study-level meta-analyses, which included RCTs whose results were published between 2004 and 2016, used descriptive study-level information to pool the overall estimates across studies (i.e., with summary statistics abstracted from papers rather than raw datasets). Patient-level meta-analyses, which included RCTs whose results were published from 2004 through 2011 (patient-level data was unavailable after that date), used patient-level data from the raw dataset of each of the RCTs, which allowed for additional subgroup and stratified analyses.

Results of LRTI Meta-Analysis

The study-level meta-analyses for LRTI included 11 RCTs with 4090 adult patients; the patient-level meta-analyses for LRTI included 13 RCTs with 3142 adult patients. A summary of results is shown in **Table 1**. The key findings from the meta-analyses include:

- Patients were significantly less likely to be initiated on antibiotics when treated with a PCT-guided algorithm as compared to standard of care in both study-level (odds ratio [OR] = 0.26) and patient-level (OR = 0.27) meta-analyses (both $p<0.001$)

- The mean duration of antibiotic treatment among patients who initiated antibiotics was estimated to be 1.3 and 2.9 days shorter using a PCT algorithm in the study-level (p=0.14)[1] and patient-level meta-analyses (p<0.001), respectively.
- The mean antibiotic exposure over all patients was reduced by 2.8 and 3.6 days in the study-level (p=0.003) and patient-level meta-analysis (p<0.001), respectively.
- Treatment under a PCT-guided algorithm did not adversely affect patient outcomes. Mortality rates and the average length of hospital stay were similar in the PCT and control groups in both the study-level and patient-level meta-analyses. In the patient-level meta-analysis:
    - The mortality rate was 6.7% in the PCT group and 7.4% in the control group (p=0.62).
    - The median length of hospital stay was 7 days (interquartile range [IQR], 0 to 12) in the PCT group and 6 days (IQR, 0 to 13) in the control group (p=0.61).
    - The rate of complications was lower in the PCT group than in the control group (18.0% vs. 21.1%, p=0.03).

Table 1: Summary Results of LRTI Meta-Analyses (Random-Effects Models)

Meta-Analysis	Antibiotic Initiation	Antibiotic Duration (days)	Antibiotic Exposure (days)	Hospital Length of Stay (days)	Mortality
	Odds Ratio (95% CI)	Mean Difference (95% CI)	Mean Difference (95% CI)	Mean Difference (95% CI)	Odds/Risk Ratio* (95% CI)
Study-Level† **N= 4,090** **11 Studies**	0.26 (0.13, 0.52) p<0.001	-2.2 (-3.3, -1.0) p<0.001	-2.8 (-4.6, -1.0) p=0.003	-0.2 (-0.6, 0.3) p=0.51	0.94 (0.69, 1.28) p=0.68
Patient-Level **N=3,142** **13 Studies**	0.27 (0.22, 0.33) p<0.001	-2.9 (-3.3, -2.5) p<0.001	-3.6 (-4.0, -3.2) p<0.001	-0.2 (-0.9, 0.5) p=0.61	0.95 (0.77, 1.16) p=0.62

* Odds ratio for patient-level meta-analysis and risk ratio for study-level meta-analysis; both calculated using the Control as the reference group.

† Results shown for the study-level meta-analyses are from the random-effects models. The number of trials included in the analysis for duration and exposure was 3 and 5, respectively.

[1] This result should be evaluated in the context of a low power to detect differences because of a small sample size (N=3 studies). The 95% confidence interval around the mean difference of -1.9 days was wide at-2.9, 0.4 (Table 2).

Results of Sepsis Meta-Analysis

The study-level meta-analysis for sepsis included 10 RCTs with 3489 adult patients; the patient-level meta-analysis for sepsis included 5 RCTs with 598 adult patients with suspected or confirmed sepsis due to an infection of the lung. Unlike uncomplicated LRTI, patients with suspected sepsis are initiated immediately on antibiotics as standard of care, so initiation of antibiotics was not a relevant parameter in the sepsis meta-analyses. A summary of results from the sepsis meta-analyses are shown in **Table 2**. The key findings include:

- The average duration of antibiotics was 1.5 days shorter in the PCT group than in the control group in the study-level meta-analysis ($p<0.001$).
- The average exposure to antibiotics among all patients was 3.2 days shorter in the PCT group than the control group in the patient-level meta-analysis ($p<0.001$). The median exposure to antibiotics was 8 days (IQR, 5 to 15) in the PCT group and 12 days (IQR, 8 to 18) in the control group.
- PCT-guided antibiotic treatment did not adversely affect outcomes for patients with sepsis. There were no significant differences noted in mortality rates or the average length of stay in the ICU or hospital in either patient- or study-level meta-analyses. In the patient-level meta-analysis:
    - The mortality rate was 19.9% in the PCT group and 23.8% in the control group.
    - The median length of ICU stay was 12 days (IQR, 6 to 23) in the PCT group and 12 days (IQR, 6 to 22) in the control group.
    - The median length of hospital stay was 21 days (IQR, 11 to 37) in the PCT group and 23 days (IQR, 13 to 38) in the control group.

Table 2: Summary Results of Sepsis Meta-Analyses

Meta-Analysis	Antibiotic Duration/ Exposure* (days)	ICU Length of Stay (days)	Mortality
	Mean Difference (95% CI)	**Mean Difference (95% CI)**	**Odds/Risk Ratio** (95% CI)**
Study-Level† N=3534 10 Studies of suspected or confirmed sepsis	-1.5 (-2.3, -0.7) *p*<0.001	-0.8 (-2.5, 0.8) *p*=0.33	0.90 (0.79, 1.03) *p*=0.11
Patient-Level N=598 5 Studies of suspected or confirmed sepsis caused by infection of the lung	-3.2 (-4.3, -2.1) *p*<0.001	1.1 (-1.3, 3.4) *p*=0.37	0.87 (0.64, 1.18) *p*=0.36

* Statistic for study-level meta-analysis based on antibiotic duration and patient-level meta-analysis based on antibiotic exposure

** Odds ratio for patient-level meta-analysis and risk ratio for study-level meta-analysis; both calculated using the Control as the reference group.

† Results shown for the study-level meta-analyses are from the random effects models

Conclusions

PCT is a specific biomarker for systemic bacterial infection that can help guide safe and effective treatment decisions when interpreted in conjunction with other laboratory findings and clinical assessments of a patient. In addition to reducing exposure of patients to unnecessary treatment, PCT-guided algorithms can play a role in the public health initiative for greater antibiotic stewardship.

The results of the LRTI meta-analyses demonstrated that the odds of initiating antibiotic therapy under PCT-guided treatment was reduced by approximately 75%, and the average duration of therapy was reduced by approximately 2-3 days. Similarly, among patients with sepsis, the average duration of antibiotic treatment was significantly reduced by approximately 1.5-3 days when PCT guidance was used to guide antibiotic cessation.

Importantly, the reductions in antibiotic exposure with PCT-guided therapy were not associated with any adverse effects on patient safety. Both patient-level and study-level meta-analyses on LRTI and sepsis estimated that the rates of mortality and lengths of stay in the hospital or ICU were similar in patients who were and were not treated under a PCT algorithm.

Overall, the totality of the scientific evidence from RCTs suggests that PCT-guided algorithms are safe and effective strategies for advancing antibiotic stewardship. Therefore, the VIDAS B•R•A•H•M•S PCT can be expected to provide relevant information that complements and enhances current clinical practice for the treatment of LRTI and sepsis.

2 NEED FOR ANTIBIOTIC STEWARDSHIP AND THE UTILITY OF PCT AS A BIOMARKER FOR BACTERIAL INFECTION

Summary

- Unnecessary or prolonged exposure to antibiotics can lead to drug toxicity, superinfection with antibiotic resist organisms, and collateral damage such as *Clostridium difficile* infections.
- Overuse and misuse of antibiotics contributes to the rise of antibiotic-resistant bacteria, a global issue calling for the need to improve antibiotic stewardship.
- LRTIs (including CAP, acute bronchitis, and COPD exacerbation) and sepsis are both associated with nonspecific clinical symptoms, and physicians lack diagnostic options to inform treatment decisions on the initiation and/or appropriate duration of antibiotic treatment.
- Bacterial infections, including those associated with LRTIs and sepsis, stimulate the production of procalcitonin (PCT).
- PCT levels can help inform treatment decisions for LRTIs and sepsis by providing results to aid with differentiating bacterial infections from other nonbacterial conditions.

2.1 Public Health Need for Antibiotic Stewardship

The rate of antibiotic resistance is rising faster than the development of new antibiotic products and is associated with substantial health and economic burdens. These consequences include longer hospitalization, increased mortality, less effective treatment of currently treatable infections, and increased risks associated with medical advancements (e.g., organ transplantation, chemotherapy, and surgeries) which require adjunctive antibiotic therapy (WHO, 2015). In the United States, drug-resistant bacteria cause an estimated two million illnesses and approximately 23,000 deaths each year (CDC, 2016). The growing threat of antibiotic resistance has risen as a global concern and has been recognized by the United Nations declaration in 2016, the World Health Organization, and the United States government (United Nations, 2016; WHO, 2016; White House, 2015).

Antibiotic stewardship is crucial to the de-escalation of this phenomenon and requires concerted efforts be made to optimize antibiotic use and reduce misuse. The CDC estimates that 20-50% of all antibiotics prescribed in the United States are either unnecessary or inappropriate (CDC, 2016), which unnecessarily exposes patients to the risks of antibiotic-associated adverse events, *Clostridium difficile* infection, and subsequent infections resulting from colonization by antibiotic-resistant microbes in the gut or skin. Reducing the unnecessary initiation and prolonged use of antibiotics in patients with LRTI and sepsis with improved diagnostics would

improve antibiotic stewardship and is in line with the *National Action Plan for Combating Antibiotic-Resistant Bacteria* (White House, 2015).

2.2 Background on LRTI and Sepsis

Lower respiratory tract infections are common across all age groups and account for 10% of the worldwide burden of morbidity and mortality (Macfarlane, 1993). Diagnosis and treatment decisions for LRTIs are generally based on non-specific clinical symptoms of cough, sputum production, fever, and dyspnea. The lack of rapid diagnostic tests in patient care settings and the overlapping clinical symptoms makes it difficult to differentiate bacterial LRTIs from other causes. Without a differential diagnosis, physicians lack crucial information needed to make appropriate treatment decisions.

While LRTIs are often treated with antibiotics and account for the majority of outpatient antibiotic prescriptions, a large proportion of suspected LRTI cases are of viral or non-infectious etiology and are unresponsive to antibiotic treatment (Fleming-Dutra, 2016). This is true for acute bronchitis, congestive obstructive pulmonary disease (COPD) exacerbation, and community acquired pneumonia (CAP) (Macfarlane, 2001; White, 2003; Jain, 2015). It is estimated that approximately 50% of antibiotics prescribed for acute respiratory issues in ambulatory care in the United States are unnecessary (Fleming-Dutra, 2016).

One million people in the United States develop sepsis each year; one quarter of these cases result in death (National Center for Health Statistics, 2011). Signs of sepsis, which include fever, tachypnea, tachycardia, and leukocytosis, are non-specific. While early empirical initiation of antibiotics is recommended when sepsis is suspected, it is important to differentiate between sepsis and systemic inflammatory response syndrome of non-infectious etiology in order to appropriately assign treatment. In cases where bacterial infections are not present, continuation of antibiotics leads to unnecessary risks of drug-related reactions, delays appropriate treatment, and leads to increased risk of mortality and prolonged hospitalization. The decision of how long to continue antibiotic treatment with sepsis is typically based on clinical observation with only limited information on the status of the individual's infection.

With both LRTIs and sepsis, the improper use of antibiotics exposes patients to the risk of drug-related reactions, antibiotic-associated infections such as *Clostridium difficile*, and highly resistant infections. Furthermore, it contributes to the public health issue of antibiotic resistance, a growing global concern, as highlighted by various national and international organizations. Solutions to aid the early diagnosis and successful management of bacterial infections for LRTIs and sepsis are needed to improve the judicious use of antibiotics and determine the optimal course of treatment for each patient.

2.3 Diagnostic Utility of PCT

Procalcitonin (PCT), a precursor of the hormone calcitonin, has emerged as a useful biomarker for bacterial infection (Becker, 2010). PCT is normally produced at low levels by neuroendocrine tissues in the human lungs, gut, and perhaps elsewhere (Snider 1997). PCT

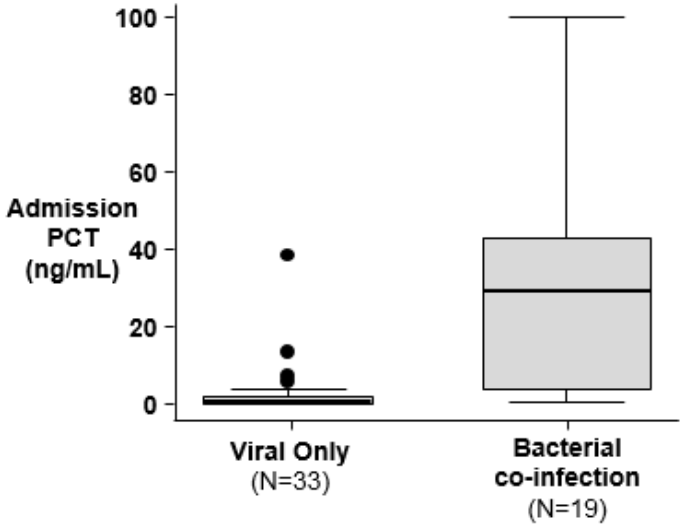
concentrations in healthy individuals are<0.05 ng/mL in greater than 98% of the population (Morgenthaler, 2002). PCT production outside of the neuroendocrine cells is stimulated locally by proinflammatory cytokines produced upon bacterial infection and under certain other conditions (e.g., surgery).

In humans, PCT levels substantially increase within 4 to 6 hours after bacterial induction, can peak at levels of up to 1,000-fold normal concentrations, and decrease by 50% daily as infection is eliminated (Becker, 2010; Dandona, 1994; Meisner, 2002). Levels of PCT stay elevated or heighten further if an infection remains present or worsens in severity (Harbarth 2001).

Kinetics are one factor that make PCT unique from other conventional inflammatory markers in providing timely information specific to systemic bacterial infection, with respect to its presence, course, and severity (Meisner, 1999). For example, cytokine and C-reactive protein (CRP) levels rise and fall much sooner or much later respectively after an insult. In addition, PCT is subject to stimulation by competing causes of inflammation to a lesser degree than these other markers (Meisner, 2002). Finally, PCT has been found to have superior discriminating power in both suspected LRTI and suspected sepsis (Müller, 2007; Horbath, 2001). Because of these factors, the levels of PCT are more relevant during the critical periods of clinical decision-making for suspected bacterial infections.

Significantly higher PCT levels are seen in patients with confirmed bacterial infections relative to those without documented bacterial infections (Rodriguez 2016). While PCT expression is stimulated by certain bacteria-induced cytokines, it is suppressed in the presence of viral-induced cytokines (e.g. interferon-gamma) (Christ-Crain 2005). For this reason, differences in PCT levels in viral vs bacterial infections can be marked (Cuquemelle, 2011) (**Figure 2**).

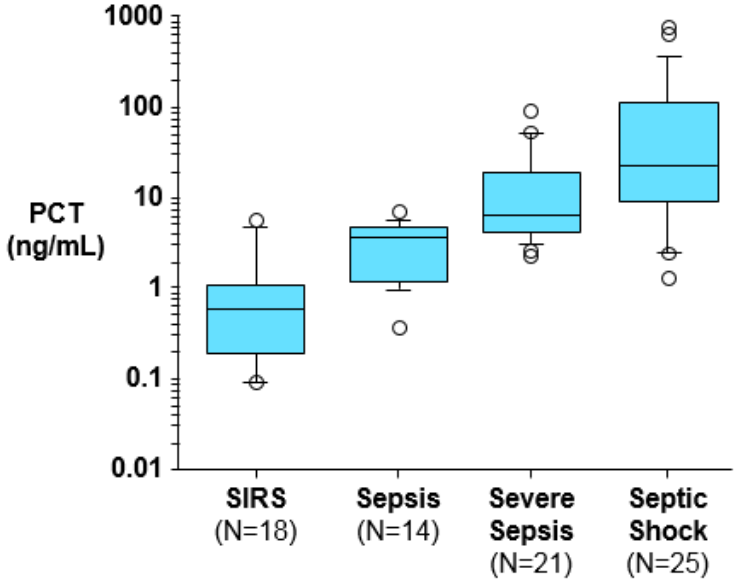
Figure 2: PCT Levels on ICU Admission in 52 Patients Having Isolated Influenza Alone or with Bacterial Co-Infection



(Cuquemelle, 2011)

Higher PCT levels correspond to more severe infections (Muller, 2010). The link between procalcitonin serum concentrations and the severity of a systemic bacterial infection is illustrated in **Figure 3**. Such observations and those showing PCT's ability to discriminate patients with severe sepsis and septic shock from others are central to the existing intended use of the VIDAS B.R.A.H.M.S PCT as an aid in the risk assessment of critically ill patients for progression to severe sepsis and septic shock. Specifically, PCT concentrations of <0.5 ng/mL are associated with lower risk of progression to severe sepsis and septic shock compared to levels >2.0 ng/mL. (VIDAS B.R.A.H.M.S PCT package insert).

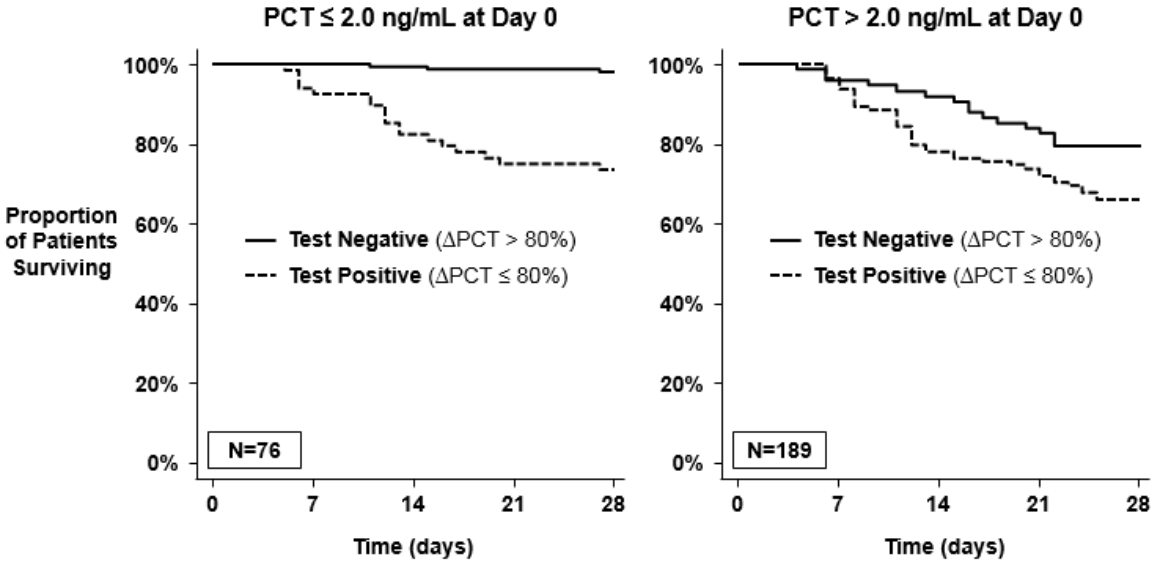
Figure 3: PCT Levels in Patients with Various Severities of Sepsis as Defined by ACCP/SCCM Criteria



Data are presented as box plots with median lines, 25- and 75-percentile boxes, and 10- and 90-percentile error bars, using a log scale for the Y-axis. The circles represent the outliers (Harbarth, 2001).

Absolute PCT serum levels as well as changes in levels have clinical significance. **Figure 4** shows data central to the existing intended use of the VIDAS B•R•A•H•M•S PCT as an aid in assessing the cumulative 28-day risk of mortality for patients diagnosed with severe sepsis or septic shock. In both patients with serum PCT levels lower than (left) or higher than (right) 2 ng/mL, the probability of survival at day 28 was significantly higher when PCT-levels decreased > 80% by Day 4.

Figure 4: Survival in Patients with Severe Sepsis or Septic Shock Based on Initial PCT Levels and Change in PCT at Day 4



(VIDAS B.R.A.H.M.S PCT package insert, 2016)

The clinical impact of these dynamics provide a biologic rationale for the proposed intended use for PCT as an aid in decision making on antibiotic discontinuation for patients with sepsis.

PCT monitoring can help inform treatment decisions by improving the accuracy of diagnosis when placed in the clinical context of each patient together with other pertinent clinical and laboratory data. For example, PCT plus clinical judgment has been shown to be superior to clinical judgment alone in discriminating severe sepsis and septic shock from Systemic Inflammatory Response Syndrome (SIRS) or sepsis (Harbarth, 2001).

PCT alone has a high negative predictive value (NPV) of over 0.9 for ruling out serious bacterial infection. Because NPV is the probability that a condition is absent when the test is negative, it is the most relevant of the operating characteristics considering whether to withhold antibiotic therapy. At a cut-off of 0.25 ng/ml, Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for discriminating between influenza patients with and without bacterial co-infection were .90, .31, .25, and .92, respectively (Rodriguez 2016). For discriminating between patients who did and did not require antibiotic therapy, these values were are .84, .98, .93, and .94, respectively (Stolz 2006). While these NPVs are excellent, no test is perfect and we again emphasize that PCT values are an aid to management that must be interpreted in the context of clinical status.

Many studies and meta-analyses, including ones by bodies such as the United Kingdom's National Institute for Health and Care Excellence (NICE) and the USA's Agency for Healthcare Research and Quality (AHRQ), have shown that PCT-guidance in conjunction with clinical assessment decreases antibiotic use in LRTI and sepsis without harmful effect.

PCT-guidance is starting to be reflected in well-respected guidelines. For example, the Surviving Sepsis Campaign's International Guidelines for Management of Severe Sepsis and Septic Shock, the German Sepsis Society Guidelines, and the European Treatment Guidelines for LRTI (Dellinger, 2016; Reinhart, 2010; Woodhead, 2012). An example in the US is the University of Nebraska Medicine, where PCT-based guidelines to aid antibiotic decision-making for patients with LRTI and Sepsis have been implemented (Nebraska Medicine, 2016).

The pathophysiology of PCT elevation, its kinetics, its discriminating power and high negative predictive value for bacterial infection have made PCT a widely used adjunct to clinical assessment in the management of suspected and confirmed bacterial infections, including LRTI and sepsis. It is estimated that in 2015, about 36 Million BRAHMS PCT-tests were conducted worldwide. In the United States, analysis of the Premier™ Healthcare Database shows that PCT is used in about half of all hospitals (Kadri, submitted).

In conclusion, PCT has the potential to be a safe and effective tool in antibiotic stewardship, improving patient outcomes by avoiding the potential deleterious effect of unnecessary antibiotics and helping to prevent the emergence of increasingly resistant organisms.

3 OVERVIEW OF VIDAS B•R•A•H•M•S PCT

Summary

- The VIDAS B•R•A•H•M•S PCT assay is an automated test for the determination of PCT in serum or plasma.
- The VIDAS B•R•A•H•M•S PCT reagents kit is used with the VIDAS family of instruments to perform all of the enzyme-linked fluorescent immunoassay steps in ~20 minutes.
- The VIDAS B•R•A•H•M•S PCT is currently approved to (1) aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock and (2) to aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or in the emergency department or other medical wards prior to ICU admission.
- The additional proposed indications are (1) to aid in decision making on antibiotic therapy for inpatients or outpatients with suspected or confirmed LRTI (defined as community-acquired pneumonia, acute bronchitis, and COPD exacerbation) and (2) to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.
- For LRTI patients, initiation of antibiotics is discouraged when initial PCT levels are ≤ 0.25 ng/mL, and antibiotic therapy may be discontinued when PCT levels drop to ≤ 0.25 ng/ml or have reduced by >80% from the peak concentration.
- For sepsis patients, antibiotic therapy may be discontinued when PCT levels are ≤ 0.50 ng/mL or have reduced by >80% from the peak concentration.

3.1 Description of VIDAS B•R•A•H•M•S PCT Assay

The VIDAS B•R•A•H•M•S PCT assay measures the concentration of procalcitonin in serum or plasma using the enzyme-linked fluorescent immunoassay (ELFA) technique. VIDAS B•R•A•H•M•S PCT reagents kit provides materials needed to perform the test, which takes approximately 20 minutes on any of the automated VIDAS instruments: VIDAS®, miniVIDAS®, or VIDAS® 3. The assay has a limit of detection of 0.03 ng/mL and a quantitative range of 0.05-200 ng/mL. The assay has been analytically validated for accuracy and precision at the diagnostic cut-offs. Specificity for PCT was validated against a panel of other compounds with no significant interference to PCT readings. The reagents kit and VIDAS instruments are shown in **Figure 5**.

Figure 5: VIDAS B•R•A•H•M•S PCT Assay Reagents Kit and VIDAS Family of Instruments

3.2 Current Intended Use

The VIDAS B•R•A•H•M•S PCT current intended use is as follows:

VIDAS® B•R•A•H•M•S PCT™ (PCT) is an automated test for use on the instruments of the VIDAS® family for the determination of human PCT in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique.

VIDAS® B•R•A•H•M•S PCT™ (PCT) is intended for use in conjunction with other laboratory findings and clinical assessments 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.

VIDAS® B•R•A•H•M•S PCT™ (PCT) is also intended for use to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality in conjunction with other laboratory findings and clinical assessments for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission.

3.3 Proposed New Intended Use

The proposed new intended use is as follows (with the new indications for LRTI and sepsis in **bold**):

VIDAS® B•R•A•H•M•S PCT™ (PCT) is an automated test for use on the instruments of the VIDAS® family for the determination of human PCT in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique.

Used in conjunction with other laboratory findings and clinical assessments, VIDAS® B•R•A•H•M•S PCT™ is intended for use as follows:

- 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,

- to aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, using a change in PCT level over time,
- **to aid in decision making on antibiotic therapy for inpatients or outpatients, with suspected or confirmed lower respiratory tract infections (LRTI) defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD),**
- **to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.**

Guidelines which will be provided in the labeling to aid decision-making on antibiotic therapy are shown in **Table 3** and **Table 4** and are consistent with the literature and current international clinical practice.

Table 3: Decision Making on Antibiotic Therapy for Patients with Suspected or Confirmed LRTI

Initiation				
PCT Result	**<0.10 ng/mL**	**0.10-0.25 ng/mL**	**0.26-0.50 ng/mL**	**>0.50 ng/mL**
Interpretation	Antibiotic therapy strongly discouraged. Indicates absence of bacterial infection.	Antibiotic therapy discouraged Bacterial infection unlikely.	Antibiotic therapy encouraged. Bacterial infection possible.	Antibiotic therapy strongly encouraged. Suggestive of presence of bacterial infection.
Follow-up	For inpatients, if antibiotics are withheld, repeat PCT measurement within 6-24 hours. For outpatients, reassess and/or repeat test if symptoms persist/worsen. In all cases, antibiotic therapy should be considered regardless of PCT result if the patient is clinically unstable, is at high risk for adverse outcome, has strong evidence of bacterial pathogen, or the clinical context indicates antibiotic therapy is warranted.		Follow up samples should be tested at regular intervals and antibiotic therapy may be adjusted using the discontinuation table below:	
Discontinuation				

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.25 ng/mL or if the ΔPCT > 80%.

- PCT_{Peak}: Highest observed PCT concentration.
- $PCT_{Current}$: Most recent PCT concentration.
- ΔPCT: Calculate by using the following equation:

$$\triangle PCT = \frac{PCT_{Peak} \square - PCT_{current} \square}{PCT_{Peak} \square} \times 100\%$$

Antibiotic therapy may be continued based upon other clinical findings, such as apparent progression on chest x-ray or ongoing/increasing toxicity.

If PCT remains high, consider treatment failure.

Table 4: Decision Making on Antibiotic Discontinuation for Patients with Suspected or Confirmed Sepsis

Discontinuation
After the initiation of antibiotic therapy for suspected or confirmed septic patients, follow up samples should be tested at regular intervals, such as every one to two days, to assess treatment success and to support a decision to discontinue antibiotic therapy. The frequency of follow up testing should be at physicians' discretion taking into account the patients' evolution and progress. Using the subsequent PCT results: **Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.50 ng/mL or if the ΔPCT > 80%.** • PCT_{Peak}: Highest observed PCT concentration. • $PCT_{Current}$: Most recent PCT concentration. • ΔPCT: Calculate by using the following equation: $\triangle PCT = \frac{PCT_{Peak} - PCT_{Current}}{PCT_{Peak}} \times 100\%$ Antibiotic therapy may be continued based upon other clinical findings, such as apparent progression on chest x-ray, failure to control a local infection, or ongoing physiologic instability. **If PCT remains high, consider treatment failure.**

4 OVERVIEW OF REGULATORY HISTORY AND CLINICAL STRATEGY

Summary

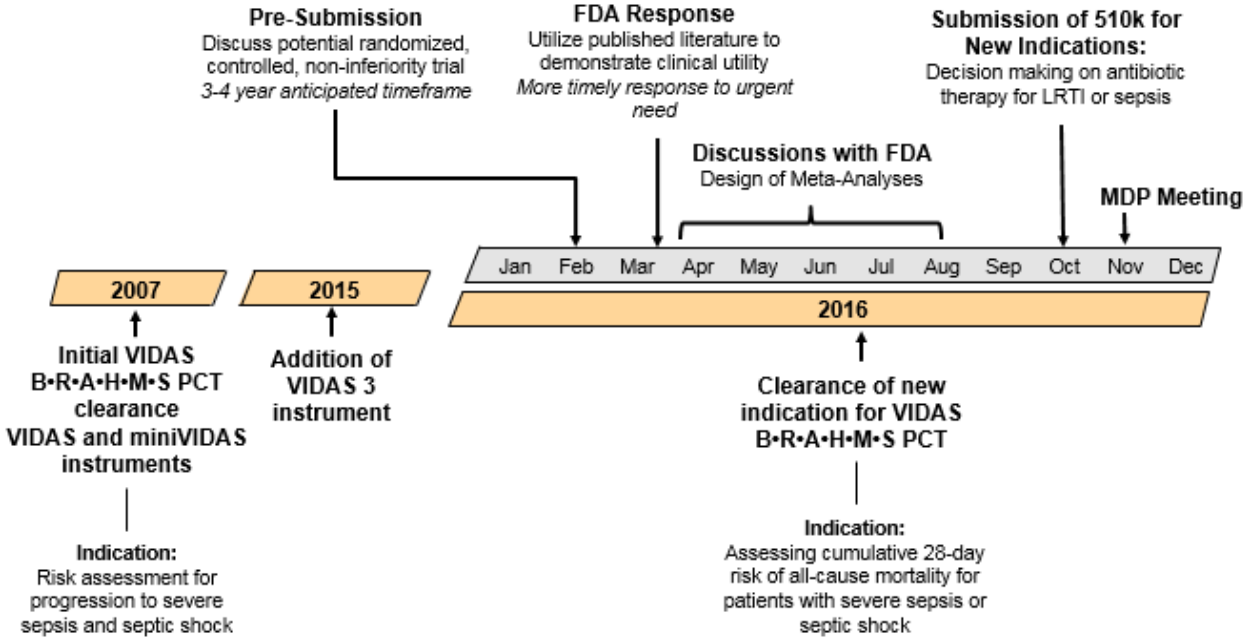
- The VIDAS B•R•A•H•M•S PCT received initial 510(k) clearance in October 2007.
- FDA and bioMérieux agreed that a comprehensive evaluation of the published literature could provide the appropriate level of clinical evidence to support the safety and effectiveness for the proposed intended uses.
- Rigorously conducted meta-analyses of randomized clinical trials are considered to be a reliable form of clinical evidence with high statistical power and is classified as the highest form of clinical evidence by the Cochrane Collaboration.
- bioMérieux designed the meta-analyses with input from FDA to evaluate the effect of PCT-guided decision-making on antibiotic use, mortality, and hospital/ICU length of stay.
- Two types of meta-analyses were conducted for both LRTI and sepsis: a study-level meta-analysis to aggregate study-level information, and a patient-level meta-analysis to aggregate individual-level information from raw datasets.

4.1 Key Regulatory Milestones

PCT diagnostic devices became widely available in 2007. In the United States, the VIDAS B•R•A•H•M•S PCT is used in over 1,000 sites and accounts for the majority of PCT tests conducted. In 2015, more than 35 million PCT tests, including non-VIDAS B•R•A•H•M•S PCT assays, were performed worldwide.

Figure 6 shows the regulatory milestones for the VIDAS B•R•A•H•M•S PCT as well as recent regulatory activities associated with the new proposed indications. The VIDAS B•R•A•H•M•S PCT received initial 510(k) clearance in the US as a Class II IVD in 2007. Subsequently, an additional VIDAS family instrument and a second indication for 28-day risk of all-cause mortality for patients with severe sepsis or septic shock were added to the cleared VIDAS B•R•A•H•M•S PCT. A 510(k) was submitted in October 2016 for the new indications detailed in this briefing document. Prior to this submission, bioMérieux had a series of discussions with FDA regarding the regulatory pathway and type of clinical evidence needed to support the proposed intended uses.

Figure 6: Regulatory Milestones of VIDAS B•R•A•H•M•S PCT



Initially a prospective RCT designed by the Antibacterial Resistance Leadership Group (ARLG), in collaboration with bioMérieux and the Division of Microbiology and Infectious Diseases (DMID), was proposed to support a regulatory filing for the new intended use in LRTI patients. However, the timeline of this study would significantly delay the availability of a new intended use that could potentially be of immediate value in guiding appropriate antibiotic use.

After exploring possible alternative pathways for approval, it was agreed that a comprehensive evaluation of the published RCT literature using a methodologically sound systematic review and meta-analyses could address the clinical validation required to support the new indications. This approach was consistent with current CDRH Regulatory Science Priority to leverage evidence from clinical experience and employ evidence synthesis to support regulatory decision making, and was a timelier solution to the urgent need to address appropriate antibiotic use in the United States (FDA, 2011). The final strategy using a meta-analytic approach was developed in collaboration with FDA and is outlined in **Section 4.3**.

4.2 Use of Meta-Analysis to Support New Indications

Meta-analyses are recognized in clinical research as powerful analytic tools. Meta-analysis is a useful approach to evaluate previous research and derive overall conclusions based on the pool of collective results (Haidich, 2010; Oxford Center for Evidence-Based Medicine[OCEBM], 2011). This approach differs from traditional clinical trials with regards to the following important considerations:

- The inclusion of different variables from multiple studies in a meta-analysis represents a cross-section of potential real world outcomes which may improve the external validity of the summary results
- Meta-analyses tend to have greater statistical power compared to a single study in establishing an effect size
- A meta-analysis may have greater power to detect patterns in outcomes associated with subgroup variables
- The quality of a meta-analysis is dependent on the quality and consistency of the contributing studies as well as the robustness of the literature identification process
- Unlike a prospective interventional study, a meta-analysis has limited control over selection of endpoints or consistency of study design, protocol implementation and data assessment across trials .

Given the number of prospective RCTs published on the use of PCT-guided algorithms for LRTI and sepsis, FDA and bioMérieux agreed that meta-analyses could viably provide valid clinical evidence on the proposed intended uses.

4.3 Overview of Clinical Strategy

The objective of the meta-analyses was to quantitatively summarize the existing data on PCT-guided antibiotic stewardship in LRTI and sepsis, and evaluate the effect of PCT-guided decision-making on antibiotic use, mortality, and hospital/ICU length of stay. Each meta-analysis was preceded by a systematic review of the literature for RCTs on PCT-guided antibiotic therapy to ensure that all relevant data were included in the meta-analyses. The systematic literature reviews were designed in accordance with best research practices (e.g., *Cochrane Handbook for Systematic Review of Interventions* [Higgins, 2011]) based on input from FDA, experts on PCT-guided algorithms, and independent statistical consultants, as well as principles from FDA guidance documents.

Two types of meta-analyses were conducted to support the new VIDAS B•R•A•H•M•S PCT indications. A study-level meta-analysis was used to aggregate study-level results across multiple RCTs. A patient-level meta-analysis was used to aggregate data from individual patients from multiple studies. Both types of meta-analyses provide valid overall estimates of effect, patient-level meta-analyses offer the additional opportunity and flexibility in evaluating the impact of patient characteristics (such as demographics and baseline attributes) on treatment effects.

Table 5 and **Table 6** summarizes both the publication timeframe and the outcomes evaluated for each meta-analysis. Study-level meta-analyses were conducted, one each for LRTI and sepsis, based on the results of separate literature searches for each indication. These included the results from RCTs published from 2004 to 2016. Patient-level meta-analyses were conducted, one each for LRTI and for sepsis caused by infection of the lung using the dataset from a 2012 published meta-analysis on PCT-guided antibiotic treatment in acute respiratory infections (ARIs)

(Schuetz, 2012). These included raw data sets from RCTs published through 2011, available at the time of the previous ARI meta-analysis.

Table 5: Meta-Analyses Conducted for LRTI

Meta-Analyses	Publication Timeframe	Effectiveness Outcomes	Safety Outcomes
Study-Level	January 2004 – May 2016	• Antibiotic initiation • Antibiotic duration • Antibiotic exposure	• Mortality • Hospital length of stay
Patient-Level*	January 2004 – May 2011	• Antibiotic initiation • Antibiotic duration • Antibiotic exposure	• Mortality • Complications** • Hospital length of stay

* Based on subset of data collected for 2012 published meta-analysis conducted for acute respiratory infections. All patients had suspected or confirmed LRTI, defined as CAP, AECOPD, or acute bronchitis.

** Complications defined as death, hospitalization/ICU admission/rehospitalization, LRTI-associated complications, recurrent/worsening infection, and patient report of LRTI symptoms

Table 6: Meta-Analyses Conducted for Sepsis

Analyses	Publication Timeframe	Effectiveness Outcomes	Safety Outcomes
Study-Level	January 2004 – May 2016	• Antibiotic duration	• Mortality • ICU length of stay
Patient - Level*	January 2004 – May 2011	• Antibiotic exposure	• Mortality • Hospital length of stay • ICU length of stay

* Based on subset of data collected for 2012 published meta-analysis conducted for acute respiratory infections. All patients had suspected or confirmed sepsis caused by infection of the lung

4.4 Supplemental Analysis.

To provide supplemental information on the effectiveness of PCT-guidance in real-world settings, a propensity-score weighted re-analysis of the ProREAL study (Albrich, 2012) was performed by bioMérieux. This was a pragmatic observational study of PCT-guided therapy in 1520 patients with LRTI, including 1155 patients at centers using the VIDAS B•R•A•H•M•S PCT assay. The study, which had very few entry criteria, was conducted in Switzerland, France, and the United States. The re-analysis showed that among patients with PCT levels <0.25 ng/mL at entry, antibiotic exposure was shorter among patients who were treated according to PCT guidance compared to those treated without regard to PCT guidance (1.8 days vs. 6.5 days; $p<0.0001$). In a subset of patients, those at centers which exclusively used the VIDAS B•R•A•H•M•S PCT assay, antibiotic treatment exposure was also shorter under PCT guidance (mean 2.5 days vs. 6.4 days; $p<0.0001$). There was a trend toward lower in-hospital complication

rates in both groups (all patients and VIDAS B•R•A•H•M•S PCT subset) and no differences in mortality. The results thus corroborated the findings of the meta-analyses of RCTs described in this briefing document.

4.5 Concordance

Additional studies have also been performed to evaluate the diagnostic concordance of the VIDAS B•R•A•H•M•S PCT compared to other commonly used PCT immunoassays. Results of one concordance study demonstrated diagnostic similarity of the VIDAS B•R•A•H•M•S PCT to the B•R•A•H•M•S PCT sensitive Kryptor and establishes the basis for generalizability of clinical results establishes among these assays. Overall agreement of 87%, 98%, 99%, and 98% was achieved at the 0.10, 0.25, 0.50, and 2.0 ng/mL cut-offs, respectively (Kappa coefficients 0.73-0.97).

Furthermore, VIDAS B•R•A•H•M•S PCT received 510k clearance based on substantial equivalence to the predicate B•R•A•H•M•S PCT LIA. Results of the concordance test demonstrated overall agreement between the assays of 97 and 94% at the 0.5 and 2 ng/mL cut-offs.

5 METHODOLOGY OF META-ANALYSES

Summary

- bioMérieux conducted two systematic literature searches for the LRTI and sepsis study-level meta-analyses. Relevant RTCs from 2004-2016 were identified following prospectively-defined procedures.
- All RCTs compared the use of PCT-guided antibiotic treatment algorithms to treatment under standard of care.
- For the study-level meta-analyses, descriptive data were extracted from publications.
- The patient-level meta-analyses for LRTI and sepsis used subsets of patient data from a previously published meta-analysis based on RCTs through 2011.
    - Patients with CAP, acute bronchitis, acute exacerbation of COPD were selected for the LRTI patient-level meta-analysis.
    - Patients with sepsis caused by an infection of the lung were selected for the sepsis patient-level meta-analysis.
- The LRTI study-level meta-analysis included 11 RCTs.
- The LRTI patient-level meta-analysis included a total of 1536 patients in the PCT group and 1606 patients in the control group with balanced representation of CAP, acute bronchitis, and COPD exacerbation

5.1 Methodology of Study-Level Meta-Analyses

5.1.1 Study-Level Literature Search Procedures

The study-level meta-analyses started with the identification of relevant published studies through formal literature searches. Separate systematic searches were conducted for LRTI and sepsis using both the PubMed database and Cochrane Database of Systematic Reviews. The search included publications from January, 2004, prior to commercialization of the first PCT immunoassay, to May, 2016, and was executed using prospectively identified search algorithms.

Search algorithm details are provided in **Appendix 1**. All articles were independently evaluated for inclusion by two reviewers with scientific or clinical expertise and/or the PCT literature; any disagreements between reviewers were handled according to a protocol. The final selection of articles for each meta-analysis was based upon the following inclusion criteria:

- RCTs with comparable and relevant treatment arms (PCT-guided antibiotic therapy vs. standard of care)
- Studies that examined PCT as aid in decision making on antibiotic therapy

- Targeted populations (adults with suspected or confirmed LRTI including AECOPD, acute bronchitis, and CAP[2]; adults with suspected or confirmed sepsis[3])
- Published in English[4]
- Full-text articles reporting original data

5.1.2 Study-Level Data Extraction

The final set of RCTs were then formally abstracted for data analysis. Data extraction was completed by two independent reviewers with expertise in meta-analysis and/or the PCT literature; discrepancies between the reviewers were resolved by consensus.

Details on study design, patient selection criteria, treatment arm interventions, PCT assessments, and outcomes were abstracted from each study. **Appendix 2** lists the specific information extracted for the study-level meta-analyses. Characteristics of the studies included in the study-level meta-analyses are summarized in **Section 5.1.4** for LRTI and **Section 5.1.5** for Sepsis.

5.1.3 Study-Level Endpoints and Statistical Analyses

For the study-level meta-analysis, the following effectiveness measures and their corresponding errors (e.g., standard error, standard deviation) were abstracted:

- Proportion of patients initiating antibiotics (Note: this was only for studies on LRTI, as nearly all patients with sepsis are empirically treated with antibiotics per standard of care.)
- Duration of antibiotic therapy (total days of therapy counting only patients who initiated antibiotics)
- Exposure to antibiotics (total days of therapy counting all randomized patients)

The important difference in the definitions of *duration* and *exposure* is that *exposure* evaluates the overall antibiotic burden in the population whereas *duration* reflects the burden only among those who initiated. For example, take five patients, two of whom did not initiate antibiotics and the three who did were on antibiotics for 4, 5, and 6 days, respectively. The duration of antibiotic

[2] Studies with inclusion criteria based on the suspicion of LRTI (including CAP, acute bronchitis and/or exacerbation of COPD)

[3] Studies with inclusion criteria based on the suspicion of sepsis

[4] Note that non-english studies were subsequently reviewed and translated as appropriate. Only one study each would have qualified for inclusion into the LRTI and sepsis; the results of these studies were consistent with those of the respective meta-analyses.

therapy would be 5 days (i.e., the average of 4, 5, and 6) whereas the exposure would be 3 days (i.e., the average of 0, 0, 4, 5, and 6).

In addition, the following safety measures were abstracted:

- Mortality
- Length of stay (days) in hospital only for LRTI)
- Length of stay (days) in ICU (only for sepsis)

Outcomes of interest were converted, when needed, to obtain compatible effect measures for the meta-analyses. Random-effects models were used to aggregate data across studies. Analyses were obtained for the overall population as well as several stratifications, which are reported in the meta-analysis results (**Section 6** and **Section 7**).

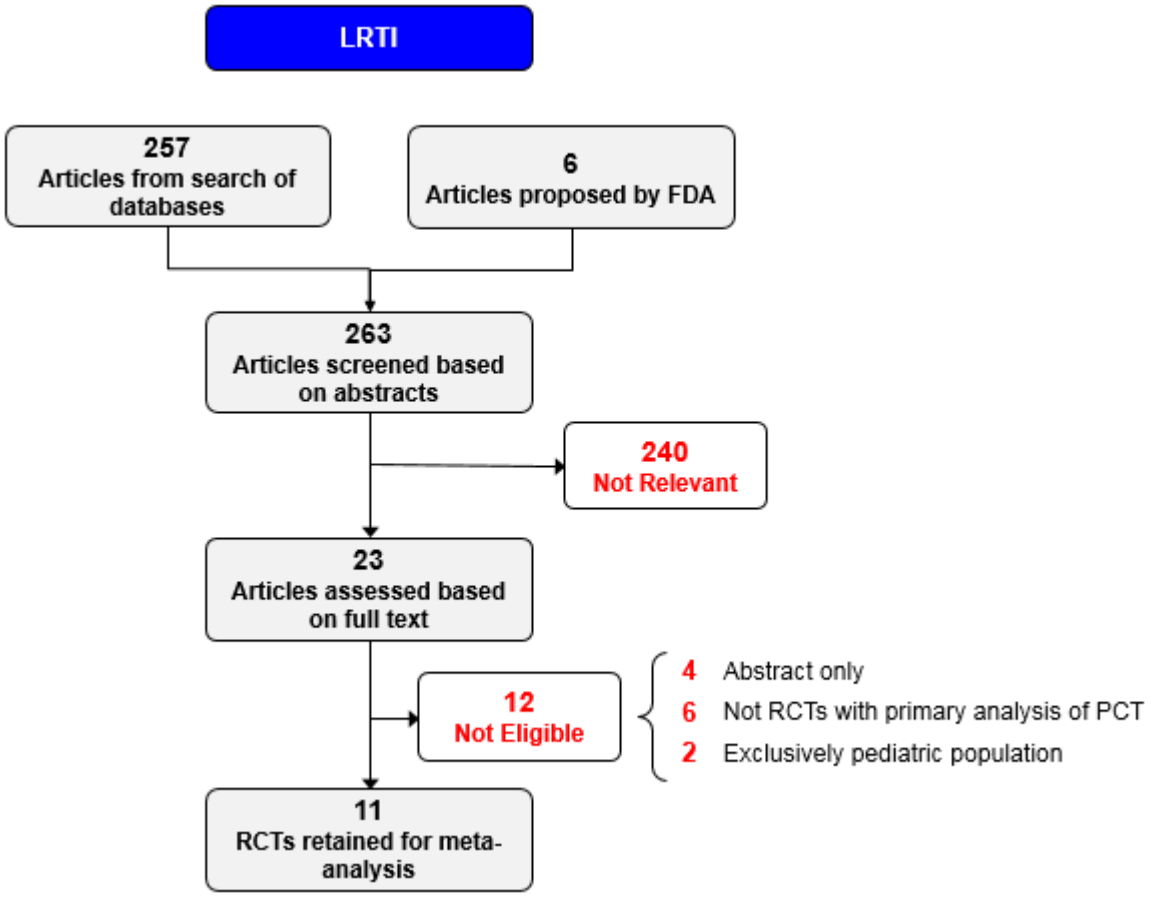
The Cochrane Risk of Bias Assessment Tool (Higgins, 2011) (**Appendix 3**) was used to assess the bias of individual studies and potential impact on overall results (for details, see **Appendix 4**).

5.1.4 Study-Level Literature Search Results (LRTI)

5.1.4.1 Articles Selected for Study-Level Meta-Analysis (LRTI)

Using the predefined search terms, 257 unique articles were found in the PubMed and Cochrane Database of Systematic Reviews. Search algorithms and results can be found in **Appendix 1**. During interactions with the FDA on the design and execution of the meta-analyses, FDA proposed an additional six unique articles for assessment. Of the 263 total articles, 23 articles contained relevant studies based on initial evaluation of the publication abstracts, and full-text articles as needed. After a complete review of the full-text articles against the selection criteria for the study-level meta-analysis, a subset of 11 articles were retained. **Figure 7** shows the selection process.

Figure 7: Retrieval and Selection of Articles for LRTI Study-Level Meta-Analysis



5.1.4.2 Study Characteristics – Study-Level Meta-Analysis (LRTI)

As shown in **Table 7**, the RCTs retained from the literature search represent a cross-section of research on the use of PCT to aid antibiotic decision-making with LRTI. These included multi-center and single-site studies, in both inpatient and outpatient settings, and ranged in size from 120 to over 1300 total patients. Studies were published between 2004 and 2016 in the United States, Switzerland, Germany, Denmark, China, and Italy. A total of 4090 patients were included in the 11 RCTs, with 2050 in the control groups and 2040 in the PCT groups.

Table 7: Study Characteristic of RCTs Selected for LRTI Study-Level Meta-Analysis

Publication	N PCT Group, Control Group	Country	Setting, Single- or Multi-center	Primary Study Population*	Primary Endpoint	Time to Endpoint	Follow-up†
Branche, 2015	151, 149	US	Hospital, Single-center	Nonpneumonic LRTI	Duration of AB therapy	30 days	83%
Briel, 2008	232, 226	Switzerland	Primary care, Multi-center	Acute respiratory tract infections (upper and lower)	Number of days patients' activities were restricted	28 days	99%
Burkhardt, 2010	275, 275	Germany	Primary care, Multi-center	Acute respiratory tract infections (upper and lower)	Number of days patients' activities were restricted	28 days	99%
Christ-Crain, 2004	124, 119	Switzerland	Emergency department, Single-center	Various, including CAP, AECOPD, bronchitis, asthma	Rate and duration of AB therapy	10-14 days; mortality at 6 weeks	95%
Christ-Crain, 2006	151, 151	Switzerland	Emergency department, Single-center	CAP	Rate and duration of AB therapy	6 weeks	99%
Corti, 2016	62, 58	Denmark	Hospital, Single-center	Acute exacerbation of COPD	Proportion of patients using antibiotics >5 days	28 days	Not reported
Kristoffersen, 2009	103, 107	Denmark	Hospital, Multi-center	Various (suspected LRTI)	Length of stay; Duration of AB therapy	Until hospital discharge	96%
Long, 2011	81, 81	China	Emergency department, Single-center	CAP	Rate and duration of AB therapy	28 days	91%
Schuetz, 2009	671, 688	Switzerland	Hospital, Multi-center	ECOPD, CAP, acute bronchitis	Composite adverse outcomes	30 days	98%
Stolz, 2007	102, 106	Switzerland	Hospital, Single-center	ECOPD	Rate and duration of AB therapy	14 days; Mortality at 6 months	92%
Verduri, 2015	88, 90	Italy	Hospital, Multi-center	ECOPD	Rate of subsequent ECOPD	6 months	97%

* Terminology for COPD in this table is as stated in the article. This includes "Acute exacerbation of COPD" and ECOPD (exacerbation of COPD)

† Follow-up accounts for patients reported as lost to follow-up or withdrew from study

AB=Antibiotic

In all studies, treatment using PCT-guided decision-making was compared to treatment under standard of care (i.e., control). Patient follow-up was high (83-99%) and the length of follow-up was most commonly 28 or 30 days (6 studies), but included 6 weeks (2 studies), 6 months (2 studies) or the duration of hospital stay (1 study).

Table 8 shows the studies that were pooled for a given meta-analysis outcome.

Table 8: Studies Contributing to Each LRTI Study-Level Meta-Analysis Endpoint

Publication	Effectiveness		Safety	
	Initiation of Antibiotics	Antibiotic Duration or Exposure	Mortality	Length of Hospitalization
Branche, 2015	X	X	X	Not reported
Briel, 2008	X	X	X	Not reported
Burkhardt, 2010	X	X	Excluded*	Not reported
Christ-Crain, 2004	X	X	X	X
Christ-Crain, 2006	X	X	X	X
Corti, 2016	X	X	X	X
Kristoffersen, 2009	X	X	X	X
Long, 2011	X	X	Excluded*	Not reported
Schuetz, 2009	X	X	X	X
Stolz, 2007	X	Not reported	X	X
Verduri, 2015	Excluded**	Not reported**	X	X

* Mortality rates were 0 in at least one treatment group

** Antibiotics were prescribed to all study patients and discontinued according to a schedule

5.1.4.3 PCT Treatment Algorithms – Study-Level Meta-Analysis (LRTI)

The VIDAS B•R•A•H•M•S PCT was used in two studies, while the B•R•A•H•M•S PCT sensitive Kryptor was used in the remaining studies (see **Section 4.3** for concordance between VIDAS B•R•A•H•M•S PCT and the other assays). Regardless of the PCT instrument used, the PCT-based treatment algorithms were identical or similar to the proposed indication. Ten of the 11 studies used PCT-guided algorithms for initiation of antibiotic therapy, eight of which also included recommendations for discontinuing treatment. One of the 11 studies did not use PCT as a guide for initiation, but only as a guide for early antibiotic cessation.

All studies used 0.25 ng/mL as a cut-off, below which initial antibiotic treatment was discouraged, and multiple studies supported the <0.1 and >0.5 ng/mL cut-offs corresponding respectively to strongly discouraged or strongly encouraged initial antibiotic use. In addition to these absolute cut-offs, discontinuation was also guided by relative reductions in subsequent PCT measurements. A PCT reduction of ≥80% and/or 90% from the initial or peak PCT measure was used in the algorithms of three studies. A comparison of the algorithms can be found in **Appendix 5**.

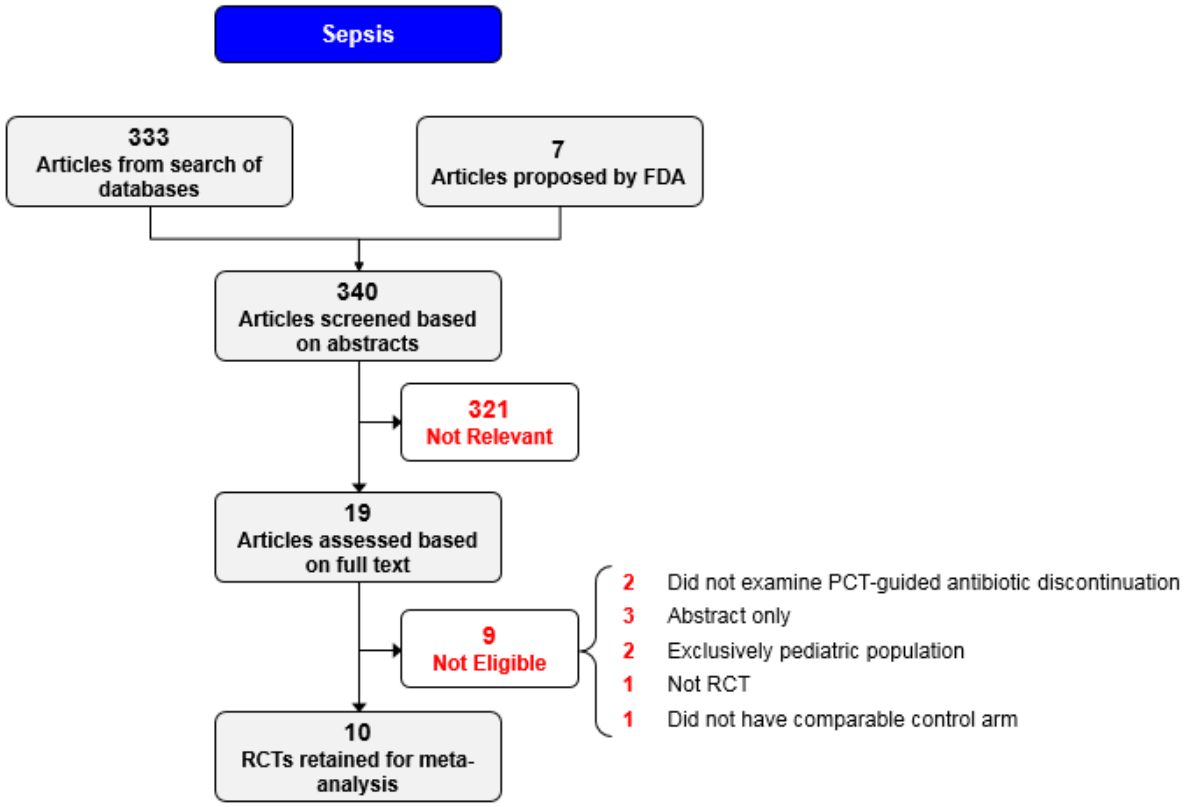
Adherence to the algorithms in treating patients in the PCT treatment group was reported in eight out of the 11 studies and ranged from 59% to 91%.

5.1.5 Study-Level Literature Search Results (Sepsis)

5.1.5.1 Articles selected for Study-Level Meta-Analysis (Sepsis)

Using the predefined search terms, 333 articles were found in PubMed and Cochrane Database of Systematic Reviews. An additional list of seven unique articles was proposed by FDA for assessment. Of the total 340 articles, 19 articles contained relevant studies based on initial evaluation of the publication abstracts, and full text articles as needed. After a complete review of the full-text articles against the selection criteria for the study-level meta-analysis, a subset of ten articles were retained which met the scope of the meta-analysis (**Figure 8**).

Figure 8: Retrieval and Selection of Articles for Sepsis Study-Level Meta-Analysis



5.1.5.2 Study Characteristics – Study-Level Meta-Analysis (Sepsis)

As shown in Table 9, the RCTs retained from the literature search represent a cross-section of research on the use of PCT to aid antibiotic decision-making with sepsis. These included multi-center and single-site studies in an ICU setting and ranged in size from 27 to over 1500 total patients. Studies were conducted in France, the Netherlands, Brazil, Germany, Belgium, Iran, Switzerland, and Australia and published between 2004 and 2016. A total of 3489 patients were included in the 10 RCTs, with 1754 in the control groups and 1735 in the PCT groups.

In all studies, treatment using PCT-guided decision making was compared to control, which was treatment under standard of care. Patient follow-up was 94% or higher for all but one study that reported patient disposition (**Table 9**). The duration of follow-up was 5 days in one study, 1 month in three studies, 2 months in one study, and not specified in the remaining studies.

Table 9: Study Characteristic of RCTs Selected for Sepsis Study-Level Meta-Analysis

Publication	N PCT Group, Control Group	Country	Setting, Single- or Multi-center	Primary Study Population	Primary Endpoint	Time to Endpoint	Follow-up†
Annane, 2013	31, 31	France	ICU, Multi-center	Suspected severe sepsis	Rate of AB therapy at Day 5	5 days	94%
Bouadma, 2010	307, 314	France	ICU, Multi-center	Suspected bacterial infections at ICU admission or during stay without prior AB (>24h)	Number of days without AB; Mortality	28 and 60 days	98%
de Jong, 2016	761, 785	Netherlands	ICU, Multi-center	ICU admission with recent AB initiation (<24h)	Rate and duration of AB therapy; Mortality	28 days	98%
Deliberato, 2013	42, 39	Brazil	ICU, Single-center	Confirmed sepsis, severe sepsis, septic shock	Duration of AB therapy	not specified	67%
Hochreiter, 2009	57, 53	Germany	ICU, Single-center	Suspected bacterial infections and >1 SIRS criteria	Duration of AB therapy	not specified	Not reported
Layios, 2012	258, 251	Belgium	ICU, Single-center	ICU stay >2 days	AB consumption and duration of AB therapy	not specified	Not reported
Najafi, 2015	30, 30	Iran	ICU, Single-center	>2 SIRS criteria*	Rate and duration of AB therapy	not specified	Not reported
Nobre, 2008	39, 40	Switzerland	ICU, Single-center	Suspected severe sepsis or septic shock	Duration of AB therapy	28 days	94%
Schroeder, 2009	14, 13	Germany	ICU, Single-center	Severe sepsis following abdominal surgery	Duration of AB therapy	not specified	Not reported
Shehabi, 2014	196, 198	Australia	ICU, Multi-center	Undifferentiated infection or suspected sepsis	Duration of AB therapy	28 days	99%

* body temperature above 38.0°C or below 36.0°C, tachycardia >90/min, tachypnea >20/min and leukocytosis >12x109/L or leucopenia <4x109/L were defined as SIRS

†Follow-up accounts for patients reported as lost to follow-up or withdrew from study

AB = Antibiotic

Table 10 shows the studies that were pooled for a given meta-analysis outcome.

Table 10: Studies Contributing to Each Sepsis Study-Level Meta-Analysis Endpoint

Publication	Effectiveness	Safety	
	Duration of Antibiotics	Mortality	Length of Stay in ICU
Annane, 2013	X	X	X
Bouadma, 2010	X	X	X
de Jong, 2016	X	X	X
Deliberato, 2013	X	X	X
Hochreiter, 2009	X	X	X
Layios, 2012	Excluded*	X	X
Najafi, 2015	Excluded*	X	X
Nobre, 2008	X	X	X
Schroeder, 2009	X	X	X
Shehabi, 2014	X	X	X

* Duration of treatment as reported in the study was an incompatible measurement

5.1.5.3 PCT Treatment Algorithms – Study-Level Meta-Analysis (Sepsis)

The VIDAS B•R•A•H•M•S PCT was used exclusively in one study and as one of multiple immunoassays in two studies. The B•R•A•H•M•S PCT sensitive Kryptor was used in five studies and the B•R•A•H•M•S PCT LIA was used in two studies (see **Section 4.3** for concordance between VIDAS B•R•A•H•M•S PCT and the other assays). While there were variations in the PCT algorithms used, they collectively support the proposed algorithm on antibiotic use for sepsis. As almost all sepsis patients were initiated on antibiotics, PCT was used to guide decisions on discontinuation based on absolute and relative PCT levels.

The absolute cut-off of 0.5 ng/mL was used most frequently. With respect to a relative cut-off, the proposed reduction of >80% was specified in two studies and bracketed by the relative reduction criteria in the other five studies that used a relative cut-off (>65% to >90%). A comparison of the algorithms can be found in **Appendix 5**.

Adherence to PCT-guided decisions was reported in 4 studies and ranged from 47% to 93%.

5.2 Methodology of Patient-Level Meta-Analyses

5.2.1 Patient-Level Literature Search Procedures

The patient-level meta-analyses for LRTI and sepsis were conducted based on the dataset of a previous meta-analysis in patients with acute respiratory infections (ARIs) (Schuetz, 2012). The original literature search corresponding to the previous meta-analysis is described below.

The objective of the literature search was to identify RCTs comparing the use of PCT-guided treatment to standard care in patients with upper or lower ARIs. This search was conducted

according to a prespecified protocol (Schuetz, 2008) using the Cochrane Controlled Trials Registry, Medline, and Embase, and encompassed all publications to May, 2011. Publications were selected for the original ARI meta-analysis based upon the following predefined criteria:

- RCTs with comparable and relevant treatment arms (PCT-guided antibody therapy vs. standard of care)
- Included targeted populations of adults with upper or lower acute respiratory infection

All articles were independently screened by two reviewers based on title, abstracts, full-text reports, or communication with investigators as needed. No exclusions were made based on language.

5.2.2 Patient-Level Data Extraction

From the original individual patient dataset used for the ARI meta-analysis, patients with CAP, acute bronchitis, or acute exacerbation of COPD were selected for the LRTI meta-analysis and patients hospitalized in the intensive care unit (ICU) with sepsis due to an infection of the lung were included in the sepsis meta-analysis. Characteristics of the studies included in the patient-level meta-analyses are summarized in **Section 5.2.4** for LRTI and **Section 5.2.5** for Sepsis. **Appendix 2** lists the specific information extracted for the patient-level meta-analyses.

5.2.3 Patient-Level Endpoints and Statistical Analyses

For the patient-level meta-analyses, the following effectiveness measures were analyzed to support the LRTI and sepsis indications:

- Proportion of patients initiating antibiotics (only for LRTI)
- Duration of antibiotic therapy (total days of therapy counting only patients who initiated antibiotics) (only for LRTI)
- Exposure to antibiotics (total days of therapy counting all randomized patients)

In addition, the following safety measures were evaluated:

- 30-day mortality
- Complications (defined as death, hospitalization/ICU admission/rehospitalization, ARI-specific complications [empyema, meningitis], recurrent or worsening infection, and patients reporting ongoing respiratory infection symptoms) (only for LRTI)
- Length of stay (days) in hospital
- Length of stay (days) in ICU (only for sepsis)

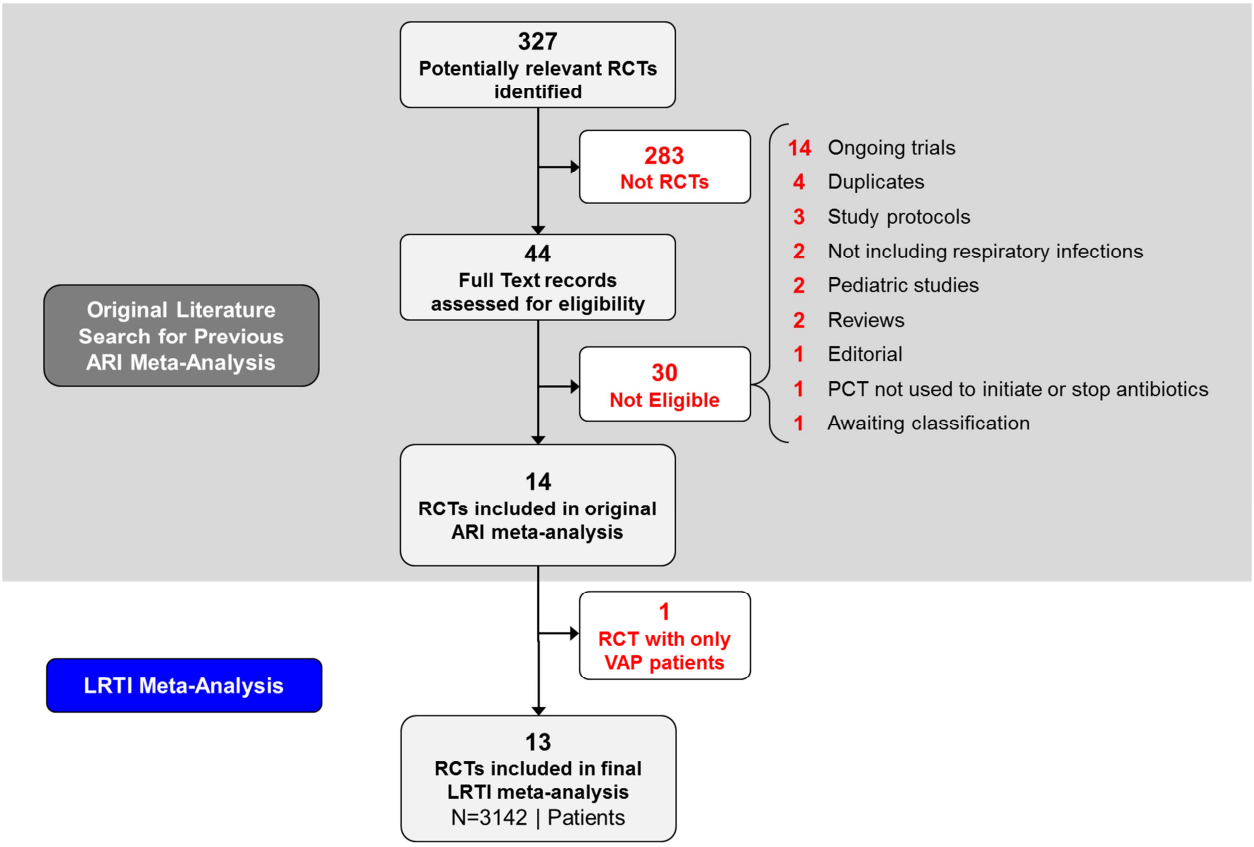
Effectiveness endpoints were evaluated using random-effects models adjusted for age; trial was treated as a random effect. Safety endpoints were evaluated using random-effects models adjusted for age and diagnosis; trial was treated as a random effect. For the safety analyses, patients lost to follow-up were assumed not to have experienced an event.

5.2.4 Patient-Level Literature Search Results (LRTI)

5.2.4.1 Articles Selected for Patient-Level Meta-Analysis (LRTI)

In the original literature review for ARI, 327 articles were found in the publication databases. Of these, 44 articles contained relevant studies. After review of the full text articles against the selection criteria, a subset of 14 were retained which met the scope of the original ARI search. For the current LRTI meta-analysis, one of these 14 RCTs, with a primary patient population of ventilator acquired pneumonia (VAP) patients, was excluded, leaving 13 studies with individual patient data. **Figure 9** shows the selection process used for the original ARI meta-analysis with the selection of studies for the current LRTI meta-analysis at the bottom.

Figure 9: Retrieval and Selection of Articles for LRTI Patient-Level Meta-Analysis



The number of patients extracted for use in the LRTI patient-level meta-analysis are shown in **Appendix 6 - 1**.

5.2.4.2 Study Characteristics – Patient-Level Meta-Analysis (LRTI)

As shown in **Table 11**, the 13 studies included multi-center as well as single-site studies in both an inpatient (including emergency department and ICU) and outpatient setting, and ranged in size from 27 to over 1300 total patients.

Table 11: Study Characteristic of RCTs Selected for LRTI Patient-Level Meta-Analysis

Publication	N PCT Group, Control Group	Country	Setting, Single- or Multi-center	Primary Study Population*	Primary Endpoint	Time to Endpoint	Follow-up†
Bouadma, 2010	311, 319	France	ICU, Multicenter	Suspected bacterial infections during ICU stay without prior AB (>24h)	All-cause mortality	2 months	98%
Briel, 2008	151, 149	Switzerland	Primary care, Multi-center	Acute respiratory tract infections (upper and lower)	Number of days patients' activities were restricted	28 days	99%
Burkhardt, 2010	275, 275	Germany	Primary care, Multi-center	Acute respiratory tract infections (upper and lower)	Number of days patients' activities were restricted	28 days	99%
Christ-Crain, 2004	124, 119	Switzerland	Emergency department, Single-center	Various, including CAP, AECOPD, bronchitis, asthma	Rate and duration of AB* therapy	10-14 days; mortality at 6 weeks	95%
Christ-Crain, 2006	151, 151	Switzerland	Emergency department, Single-center	CAP	Rate and duration of AB therapy	6 weeks	99%
Hochreiter, 2009	57, 53	Germany	Surgical ICU, Single center	Suspected bacterial infections and >1 SIRS criteria	AB use	Hospital stay	Not reported
Kristoffersen, 2009	110, 113	Denmark	Hospital, Multi-center	Various (suspected LRTI)	Length of stay; Duration of AB therapy	Until hospital discharge	96%
Long, 2011	86, 86	China	Emergency department, Single-center	CAP	Rate and duration of AB therapy	28 days	91%
Long, 2009	63, 64	China	ED, Outpatients, Single center	CAP with X-ray confirmation	AB use	1 month	100%
Nobre, 2008	39, 40	Switzerland	ICU, Single center	Suspected severe sepsis or septic shock	AB use	1 month	94%
Schroeder, 2009	14, 13	Germany	Surgical ICU, Single center	Severe sepsis following abdominal surgery	AB use	Hospital stay	Not reported
Schuetz, 2009	687, 694	Switzerland	Hospital, Multi-center	ECOPD, CAP, acute bronchitis	Composite adverse outcomes	30 days	98%
Stolz, 2007	113, 113	Switzerland	Hospital, Single-center	ECOPD	Rate and duration of AB therapy	14 days; Mortality at 6 months	92%

* Terminology for COPD in this table is as stated in the article. This includes "Acute exacerbation of COPD" and ECOPD (exacerbation of COPD)

† Follow-up accounts for patients reported as lost to follow-up or withdrew from study

AB=Antibiotic

There was considerable overlap between the articles selected in the patient-level search and the study-level search (eight studies), although five studies were unique to the patient-level retrieval due to different selection criteria (**Section 5.1.1** and **Section 5.2.1**). Of these five studies, four included critically ill patients in the ICU with a diagnosis of LRTI (specifically, CAP, COPD exacerbation, and acute bronchitis), and one was a non-English publication.

5.2.4.3 PCT Treatment Algorithms – Patient-Level Meta-Analysis (LRTI)

PCT measurements were made using the B•R•A•H•M•S PCT LIA in two studies and the B•R•A•H•M•S PCT sensitive Kryptor in ten studies; one study did not report the PCT instrument used (see **Section 4.3** for concordance between VIDAS B•R•A•H•M•S PCT and the other assays). Regardless of the PCT instrument used, the PCT-based treatment algorithms were similar and supportive of the LRTI proposed indication.

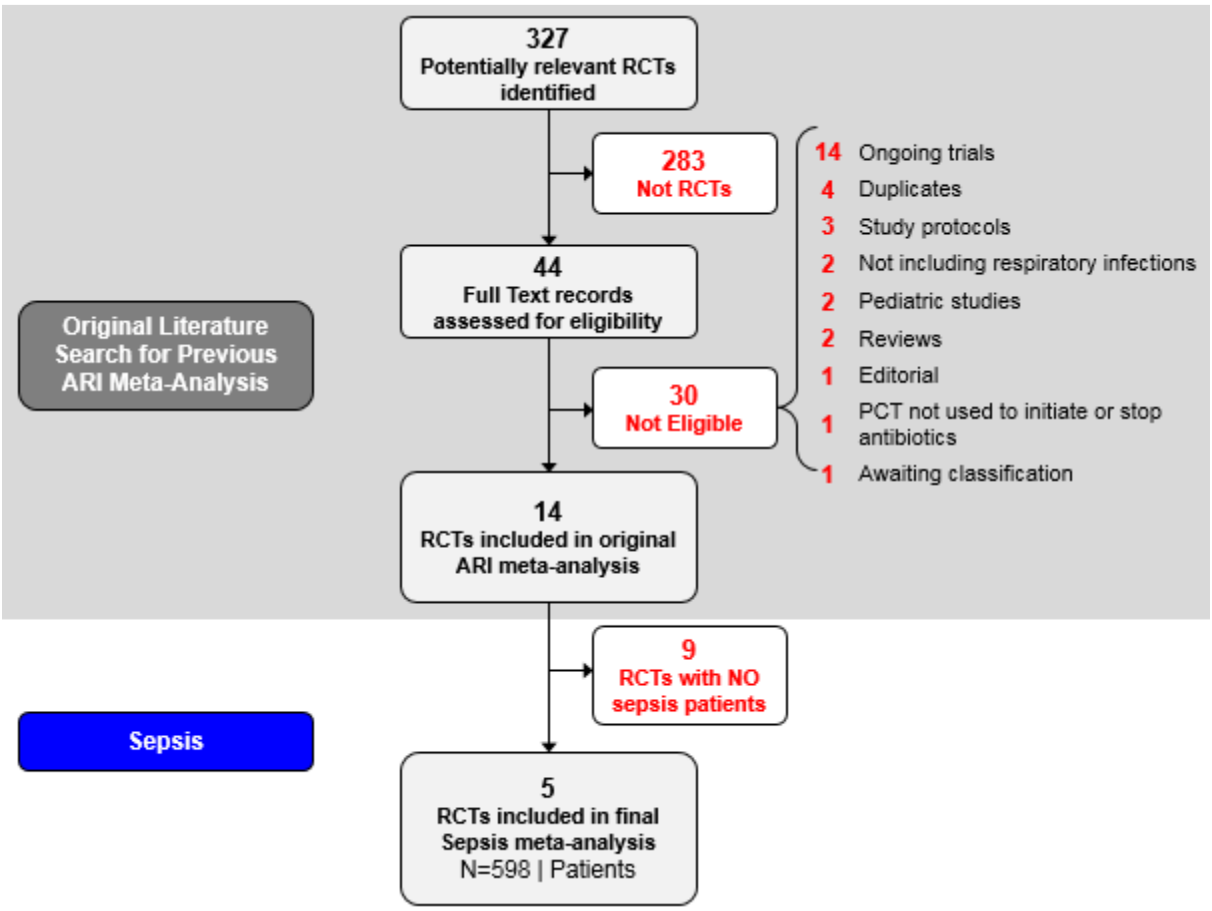
In the nine studies with LRTI patients outside of the ICU, a cut-off of <0.25 ng/mL was used to discourage initial antibiotic treatment. In addition to these absolute cut-offs, discontinuation was also guided by relative reductions in subsequent PCT measurements. A PCT reduction of ≥80% and/or 90% from the initial or peak PCT measure was used in the algorithms of four studies. A comparison of the algorithms can be found in **Appendix 5**.

5.2.5 Patient-Level Literature Search Results (Sepsis)

5.2.5.1 Articles Selected for Patient-Level Meta-Analysis (Sepsis)

The sepsis patient-level meta-analysis is based on the same publications selected for the previous ARI meta-analysis, detailed in Section 5.2.2. The only difference as shown in **Figure 10** is the selection of a subset of articles which included patients with sepsis to support the proposed sepsis intended use. Patients with sepsis due to their lung infection were identified in five of the 14 original articles for inclusion in the current sepsis meta-analysis. The number of patients extracted for use in the sepsis meta-analysis can be found in **Appendix 6 - 2**.

Figure 10: Retrieval and Selection of Articles for Sepsis Patient-Level Meta-Analysis



5.2.5.2 Study Characteristics – Patient-Level Meta-Analysis (Sepsis)

As shown in **Table 12**, the five studies included multi-center as well as single-site studies in both an ICU setting, and ranged in size from 27 to 630 total patients.

Table 12: Study Characteristic of RCTs Selected for LRTI and Sepsis Patient-Level Meta-Analysis

Publication	N PCT Group, Control Group	Country	Setting, Single- or Multi-center	Primary Study Population	Primary Endpoint	Time to Endpoint	Follow-up†
Bouadma, 2010	311, 319	France	ICU, Mult-center	Suspected bacterial infections during ICU stay without prior AB (>24h)	All-cause mortality	2 months	98%
Hochreiter, 2009	57, 53	Germany	Surgical ICU, Single center	Suspected bacterial infections and >1 SIRS criteria	AB use	Not specified	Not reported
Nobre, 2008	39, 40	Switzerland	ICU, Single center	Suspected severe sepsis or septic shock	AB use	1 month	94%
Schroeder, 2009	14, 13	Germany	Surgical ICU, Single center	Severe sepsis following abdominal surgery	AB use	Not specified	Not reported
Stolz, 2009	51, 50	France	ICU, Single center	Clinically diagnosed VAP	Days free of antibiotics	1 month	100%

† Follow-up accounts for patients reported as lost to follow-up or withdrew from study
AB=Antibiotic

There was considerable overlap between the articles selected in the patient-level search and the study-level search, although there was one study unique to the patient-level retrievals due to different selection criteria (**Section 5.1.1** and **Section 5.2.1**). For this study (Stolz, 2009) of ventilator acquired pneumonia (VAP) patients, access to the patient-level data, allowed for the determination that the patients were hospitalized in the intensive care unit (ICU) with sepsis due to an infection of the lung (VAP).

5.2.5.3 PCT Treatment Algorithms – Patient-Level Meta-Analysis (Sepsis)

The B•R•A•H•M•S PCT LIA was used in two studies, and the B•R•A•H•M•S PCT sensitive Kryptor was used in three studies (see **Section 4.3** for concordance between VIDAS B•R•A•H•M•S PCT and the other assays).

The PCT-based treatment algorithms were similar and supportive of the sepsis proposed indications. Studies used absolute PCT level cut-offs of around <0.5 ng/mL. In the five studies which focused on patients in an ICU setting, cut-offs of 0.5 ng/mL (2 studies), 1 ng/mL (2 studies), and 0.1-0.25 ng/mL (1 study) were used. In addition, a greater than 65-90% reduction in PCT levels also triggered antibiotic cessation in all five studies. A comparison of the algorithms can be found in **Appendix 5**.

6 LRTI META-ANALYSIS RESULTS

Summary

- Patients were significantly less likely to be initiated on antibiotics when treated with a PCT-guided algorithm as compared to standard of care in both study-level (odds ratio [OR] = 0.26) and patient-level (OR = 0.27) meta-analyses (both $p<0.001$)
- The average duration of antibiotic treatment among patients who initiated antibiotics was estimated to be 1.3 and 2.9 days shorter using a PCT algorithm in the study-level ($p=0.14$) and patient-level ($p<0.001$) meta-analyses, respectively.
- The average antibiotic exposure among all patients was estimated to be 2.8 and 3.6 days shorter using a PCT algorithm in the study-level ($p=0.003$) and patient-level ($p<0.001$) meta-analysis, respectively.
- Treatment under a PCT-guided algorithm did not adversely affect patient outcomes. There were no significant differences noted in the average length of hospital stay or mortality rates in either patient- or study-level meta-analyses.
- In the patient-level meta-analysis, with regard to safety:
  - The mortality rate was 6.7% in the PCT group and 7.4% in the control group ($p=0.62$).
  - The median length of hospital stay was 7 days (interquartile range [IQR], 0 to 12) in the PCT group and 6 days (IQR, 0 to 13) in the control group ($p=0.61$).
  - The rate of complications was lower in the PCT group than in the control group (18.0% vs. 21.1%, $p=0.03$).

For the remainder of the document, results from both the study- and patient-level meta-analyses will be presented together in order to evaluate the consistency of results across endpoints. Several detailed analyses are presented in appendices including:

- Results of the quality assessment are provided in **Appendix 4**.
- Forest plots summarizing the results of individual studies along with the overall study-level estimate for each effectiveness and safety endpoint are provided in **Appendix 6**. Stratification by algorithm adherence and risk of bias are also provided for each effectiveness and safety endpoint in this appendix.

6.1 Patient Populations

CAP, COPD, and acute bronchitis were well-represented in the study populations included in both the study-level and patient-level meta-analyses. Characteristics of the study-level populations are shown in **Table 13**.

Table 13: Patient Baseline Characteristics in LRTI Study-Level Meta-Analysis

Publication	N PCT Group, Control Group	Age (median or mean*)	Male (%)	Primary Study Population**
Branche, 2015	151, 149	63	44%	Nonpneumonic LRTI
Briel, 2008	232, 226	48	40%	Acute respiratory tract infections (upper and lower)
Burkhardt, 2010	275, 275	42	41%	Acute respiratory tract infections (upper and lower)
Christ-Crain, 2004	124, 119	64	53%	Various, including CAP, AECOPD, bronchitis, asthma
Christ-Crain, 2006	151, 151	70	62%	CAP
Corti, 2016	62, 58	72	39%	AECOPD
Kristoffersen, 2009	103, 107	67	53%	Various (suspected LRTI)
Long, 2011	81, 81	46	59%	CAP
Schuetz, 2009	671, 688	73	58%	ECOPD, CAP, acute bronchitis
Stolz, 2007	102, 106	70	45%	ECOPD
Verduri, 2015	88, 90	73	87%	ECOPD

* depending on what was reported in study
** Terminology for COPD in this table is as stated in the article. This includes "Acute exacerbation of COPD" and ECOPD (exacerbation of COPD)

The total N for the patient-level meta-analysis was 2181 (PCT group) and 2189 (control group), as shown in **Table 11**. Patients that did not classify as LRTI were removed prior to analysis (575 for PCT group and 653 for control group), leaving 1536 and 1606 patients in the PCT group and control group, respectively, as available for patient-level evaluation. Most patients in the LRTI meta-analysis had a diagnosis of CAP, with approximately 20% of patients diagnosed with the next most frequency diagnoses, COPD and acute bronchitis, respectively (**Table 14**). The overall PCT group and control group were balanced with respect to age, gender, type of LRTI, and baseline PCT levels.

Table 14: Patient Baseline Characteristics in LRTI Patient-Level Meta-Analysis

Characteristic	PCT Group (N=1536)	Control Group (N=1606)
Age, median (IQR)	66 (50, 79)	66 (49, 78)
Male, n (%)	865 (56%)	744 (54%)
Diagnosis, n (%)		
CAP	999 (65%)	1028 (64%)
Acute bronchitis	249 (16%)	282 (18%)
COPD exacerbation	288 (19%)	296 (18%)
PCT value at initiation (ng/mL), median (IQR)	0.23 (0.10, 0.96)	0.21 (0.09, 1.04)

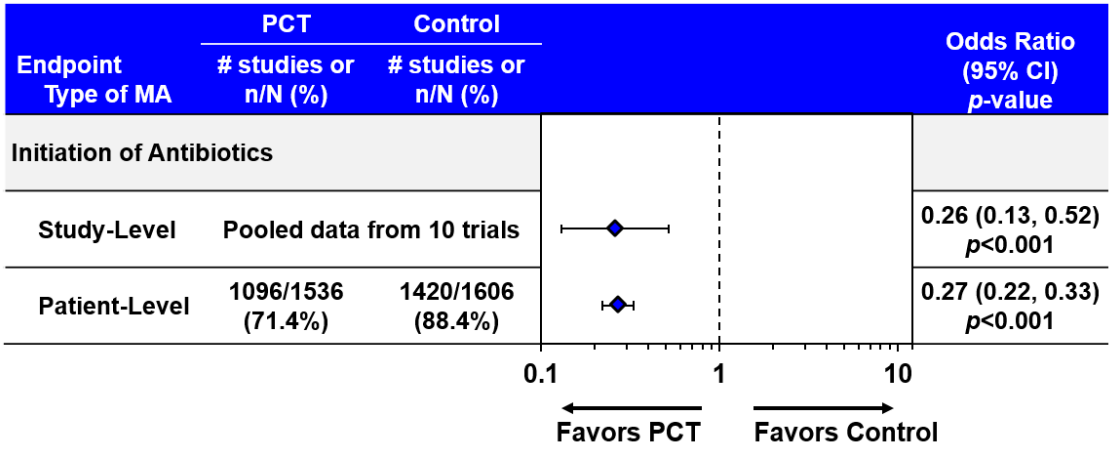
IQR – Interquartile range

6.2 Effectiveness Outcomes

6.2.1 Initiation of Antibiotics

As expected, PCT-guided antibiotic treatment was associated with reductions in antibiotic initiation in patients with LRTI. In the study-level meta-analysis, the pooled rates of antibiotic initiation yielded an odds ratio of 0.26 (95% CI: 0.13, 0.52), which represents a 74% reduction in the odds of antibiotic initiation in the PCT group relative to the control group. This reduction was mirrored in the patient-level meta-analysis with an odds ratio of 0.27 (95% CI: 0.22, 0.33). **Figure 11** illustrates the consistent effect size seen in both the study-level and patient level meta-analyses. Antibiotic initiation reported for individual studies is provided in **Appendix 6 - 3**.

Figure 11: Initiation of Antibiotics in Study-Level Meta-Analysis and Patient-Level Meta-Analysis – Overall LRTI Populations



The reduction in antibiotic initiation was robust and significant across the multiple LRTI diagnoses subgroups of CAP, acute bronchitis, and COPD exacerbation as well as in both the inpatient and outpatient setting, as demonstrated in the patient-level analysis (**Table 15**).

Table 15: Initiation of Antibiotics in Patient-Level Meta-Analysis – LRTI Subpopulations Based on Type of LRTI and Setting

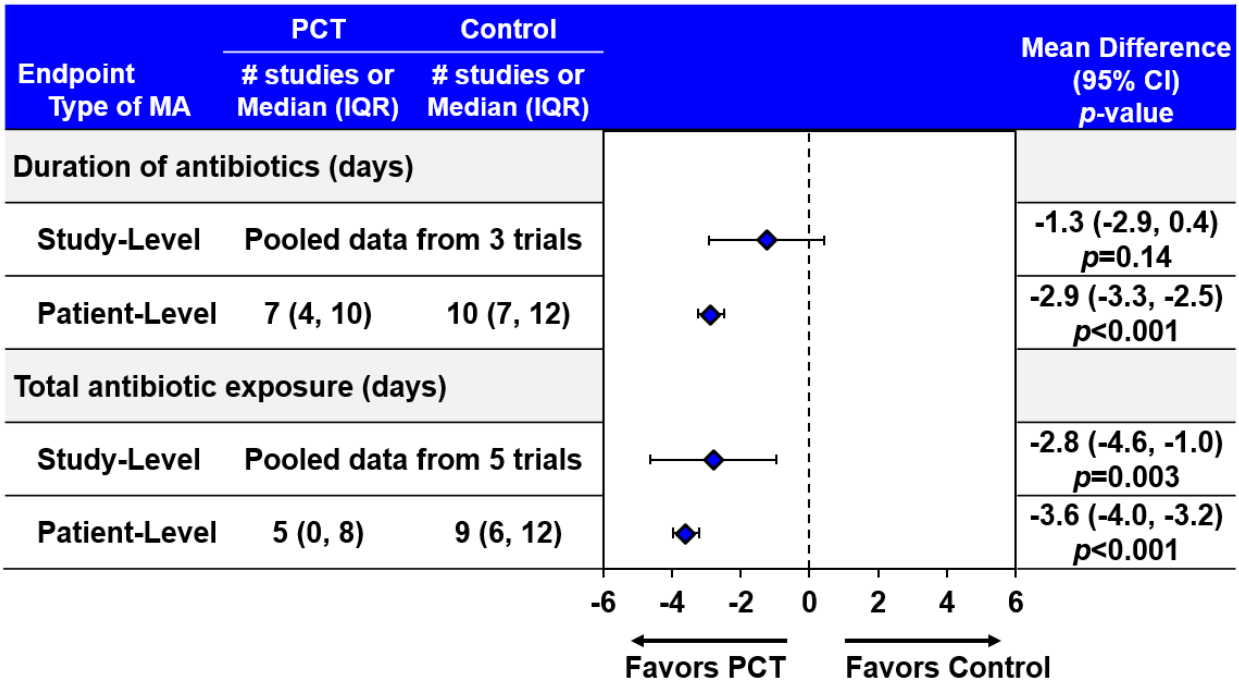
Subgroup		PCT Group Patients Initiating Antibiotics (%)	Control Group Patients Initiating Antibiotics (%)	Odds Ratio (95% CI) *p*-value
Type of LRTI	CAP	898 (90%)	1019 (99%)	0.07 (0.03, 0.14) $p<0.001$
	Acute bronchitis	61 (25%)	185 (66%)	0.15 (0.10, 0.23) $p<0.001$
	COPD exacerbation	137 (48%)	216 (73%)	0.32 (0.23, 0.46) $p<0.001$
Setting	Inpatient	881 (79.7%)	1039 (91.2%)	0.35 (0.27, 0.46) $p<0.001$
	Outpatient	215 (50.0%)	381 (81.6%)	0.13 (0.09, 0.19) $p<0.001$

6.2.2 Duration of Antibiotics

Duration of antibiotic therapy was significantly shorter with PCT-guided decision-making, as demonstrated in both study-level and patient-level meta-analyses (Figure 12). The mean reduction in duration of antibiotic therapy in the PCT group was 1.3 days in the study-level meta-analysis and 2.9 days in the patient-level meta-analysis. This result should be evaluated in the context of a low power to detect differences because of a small sample size (N=3 studies for this result).[5] Accordingly, the 95% confidence interval around the mean difference of -1.9 days was wide (i.e., -2.9 days to 0.4 days) (Table 2).

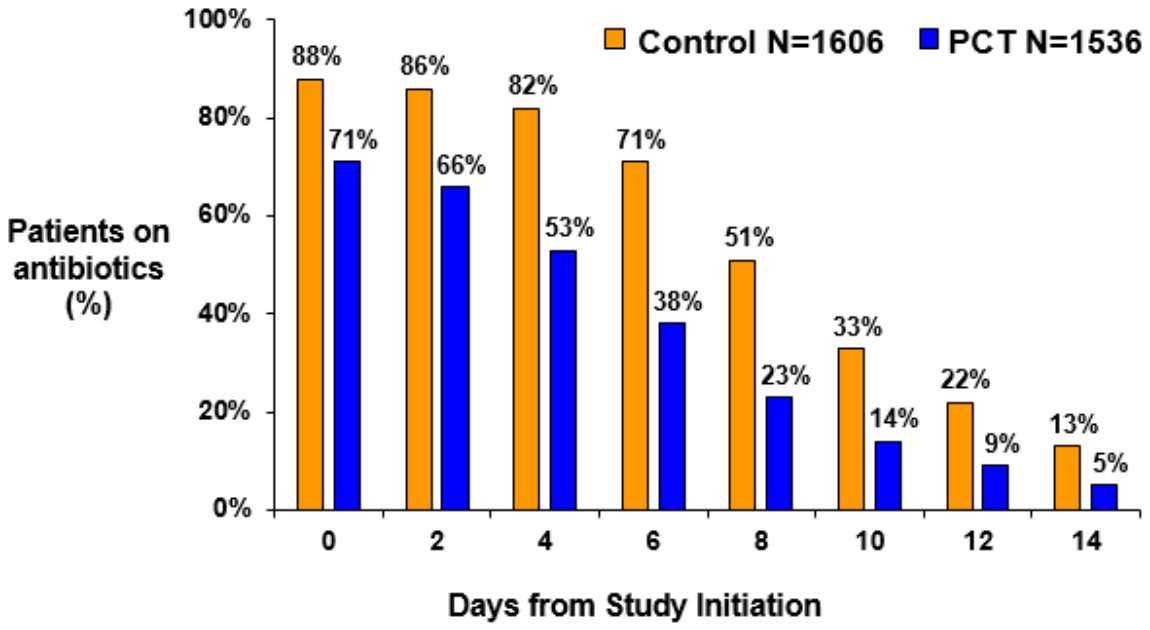
[5] Note: study-level data reported either antibiotic duration or exposure, but not both. More trials (n=5) reported exposure than duration (N=3) and reporting was indeterminate in 2

Figure 12: Duration of and Exposure to Antibiotics in Study-Level Meta-Analysis and Patient-Level Meta-Analysis – Overall LRTI Populations



The meta-analyses also evaluated total treatment exposure based on all patients randomized (**Figure 12**). When considering all patients (including those from whom antibiotics were withheld), the mean exposure was reduced by 2.8 days (95% CI: -4.6, -1.0) in the study-level meta-analysis and by 3.6 days (95% CI: -4.0, -3.2) in the patient-level meta-analysis from a median of 5 days in the PCT group to 9 days in the control group. **Figure 13** shows the difference in prevalence of antibiotics over 2 weeks following study initiation from the patient-level meta-analysis.

Figure 13: Antibiotic Use Over Time in Patient-Level Meta-Analysis – Overall LRTI Population



Significant reductions in exposure to antibiotics was consistent across the types of LRTI as well as patients in both inpatient and outpatient settings (**Table 16**).

Table 16: Exposure to Antibiotics in Patient-Level Meta-Analysis (in days) – LRTI Subpopulations Based on Type of LRTI and Setting

Subgroup		PCT Group Median (IQR)	Control Group Median (IQR)	Mean Difference (95% CI) *p*-value
Type of LRTI	CAP	6 (4, 10)	10 (8, 14)	-4.0 (-4.4, -3.5) *p*<0.001
	Acute bronchitis	0 (0, 0)	5 (0, 7)	-3.1 (-3.7, -2.4) *p*<0.001
	COPD exacerbation	0 (0, 6)	7 (0, 10)	-3.0 (-3.8, -2.3) *p*<0.001
Setting	Inpatient	6 (2, 9)	10 (7, 13)	-3.7 (-4.2, -3.3) *p*<0.001
	Outpatient	0.5 (0, 6)	7 (4, 9)	-3.5 (-4.0, -3.0) *p*<0.001

IQR – Interquartile Range

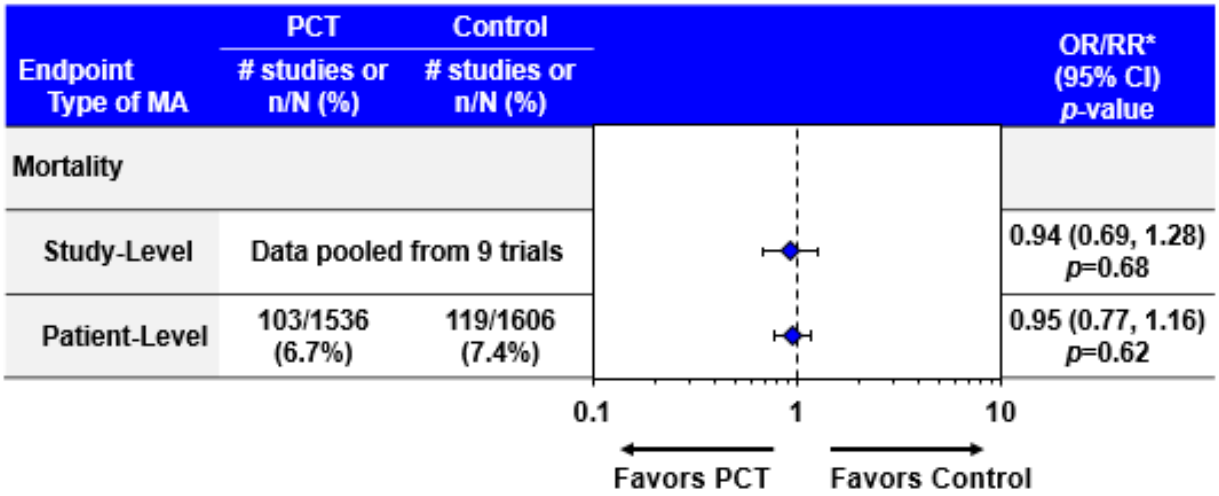
6.3 Safety Outcomes

6.3.1 Mortality

The reduction in antibiotic use associated with use of PCT-guided decision making did not adversely affect mortality rates. The study-level and patient-level summary mortality endpoint results are shown in **Figure 14**. In the study-level meta-analysis the risk ratio for mortality was 0.94 (95% CI: 0.69, 1.28) using a random effects model. (Note: risk ratios less than 1.0 indicate a lower risk of mortality in the PCT group.)

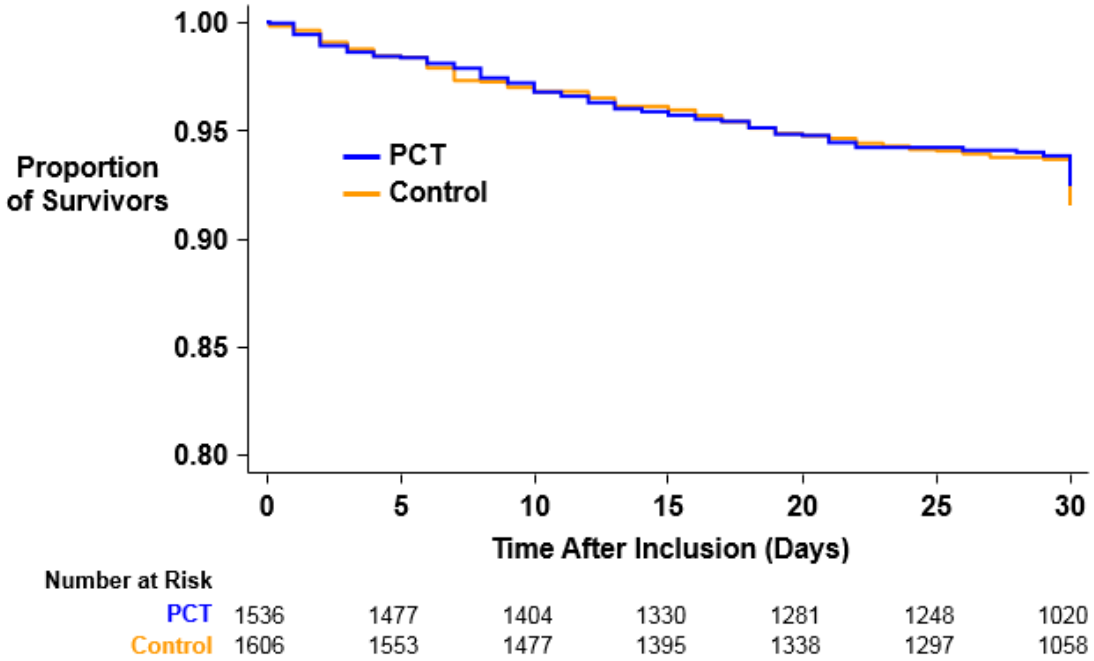
A similar trend was observed in the patient-level meta-analysis with an odds ratio of 0.95 (95% CI: 0.77, 1.16). The patient-level analysis allowed for Kaplan-Meier analysis (**Figure 15**). As can be seen in by the overlapping survival curves, the rate of survival over 30 days was not adversely affected when antibiotic use was guided by PCT algorithms.

Figure 14: Mortality in Study-Level Meta-Analysis and Patient-Level Meta-Analysis – Overall LRTI Populations



* OR for patient-level meta-analysis and RR for study-level meta-analysis

Figure 15: Survival in Patient-Level Meta-Analysis – Overall LRTI Population



Stratification by type of LRTI and setting in the patient-level meta-analysis also yielded similar mortality rates between the groups (**Table 17**). Kaplan-Meier survival curves for COPD exacerbation or CAP by group are provided in **Figure 16** and **Figure 17**, respectively.

Table 17: Mortality in Patient-Level Meta-Analysis – LRTI Subpopulations Based on Type of LRTI and Setting

Subgroup		PCT Group Mortality rate n/N (%)	Control Group Mortality rate n/N (%)	OR (95% CI) *p*-value
Type of LRTI	CAP	92/999 (9.2%)	111/1028 (10.8%)	0.92 (0.74, 1.15) *p*=0.47
	Acute bronchitis	2/249 (0.8%)	0/282 (0%)	NA*
	COPD exacerbation	9/288 (3.1%)	8/296 (2.7%)	1.15 (0.46, 2.89) *p*=0.76
Setting	Inpatient	101/1106 (9.1%)	116/1139 (10.2%)	0.95 (0.77, 1.17) *p*=0.63
	Outpatient	2/430 (0.5%)	3/467 (0.6%)	1.11 (0.28, 4.45) *p*=0.88

* Statistics could not be calculated due to the value of 0 in control group

Figure 16: Survival in Patient-Level Meta-Analysis –COPD Subpopulation

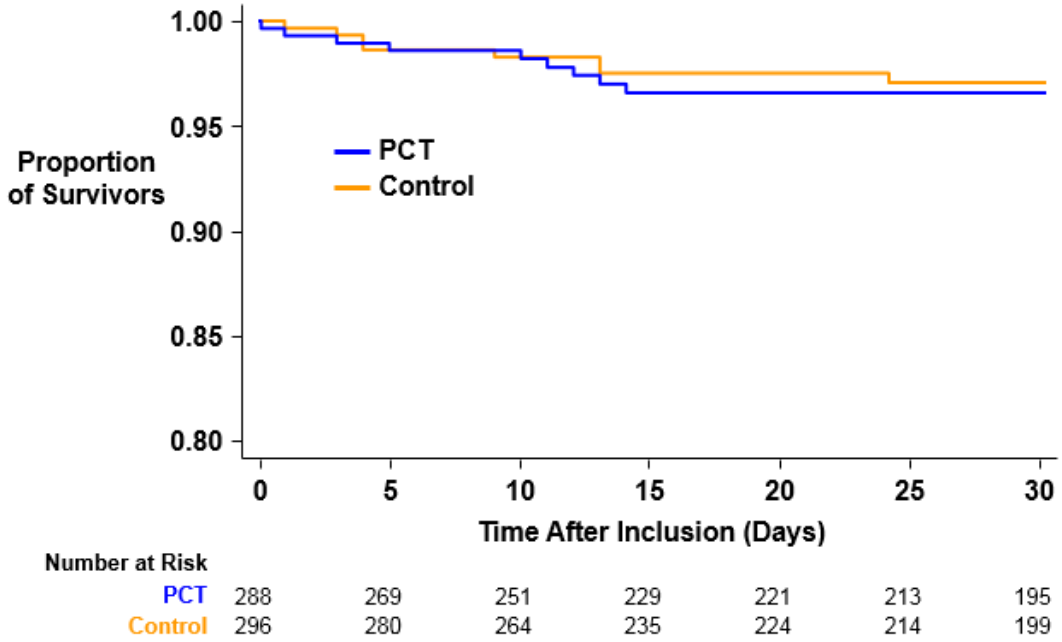
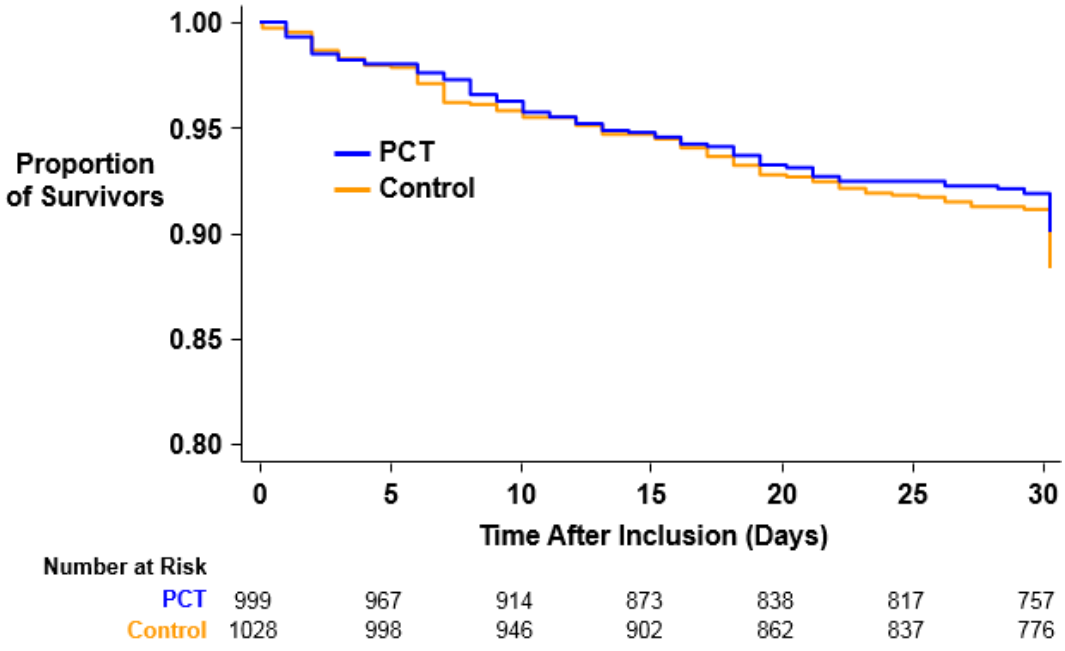


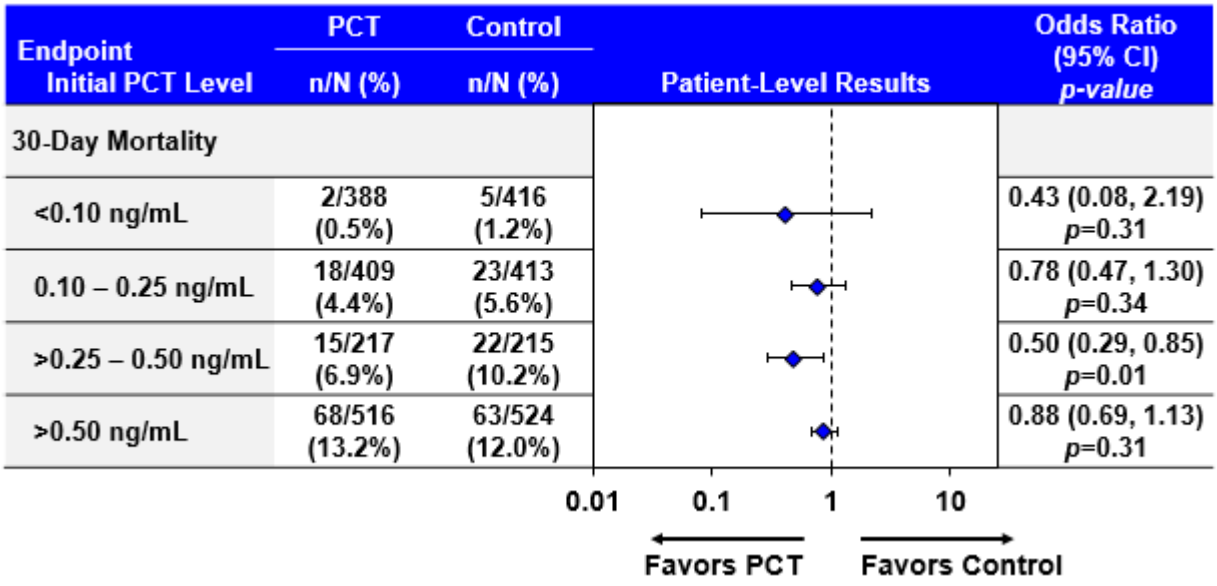
Figure 17: Survival in Patient-Level Meta-Analysis – CAP Subpopulation



Information on initial PCT concentrations were available in the patient-level meta-analysis, and stratification by initial PCT was performed to evaluate any associations with risk for mortality.

As shown in **Figure 18**, the mortality rates were similar between the PCT and control groups regardless of initial PCT levels.

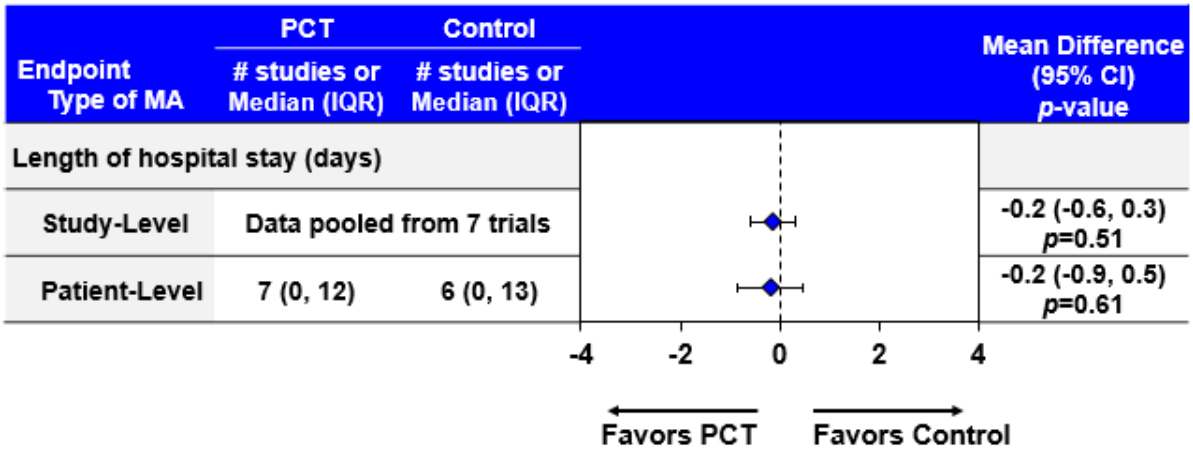
Figure 18: Mortality in Patient-Level Meta-Analysis – LRTI Subpopulations Based on Initial PCT Level



6.3.2 Length of Hospitalization

Length of hospital stay was not impacted by the implementation of PCT-guided antibiotic treatment (**Figure 19**). In the study-level meta-analysis, the overall length of hospitalization in the PCT and control arms was similar (mean difference: -0.2 days; 95% CI: -0.6, 0.3). Similarly, no effect on length of hospitalization was detected in the overall patient-level meta-analysis (median 7 vs. 6 days).

Figure 19: Length of Hospitalization (in days) in Study-Level Meta-Analysis and Patient-Level Meta-Analysis – Overall LRTI Populations



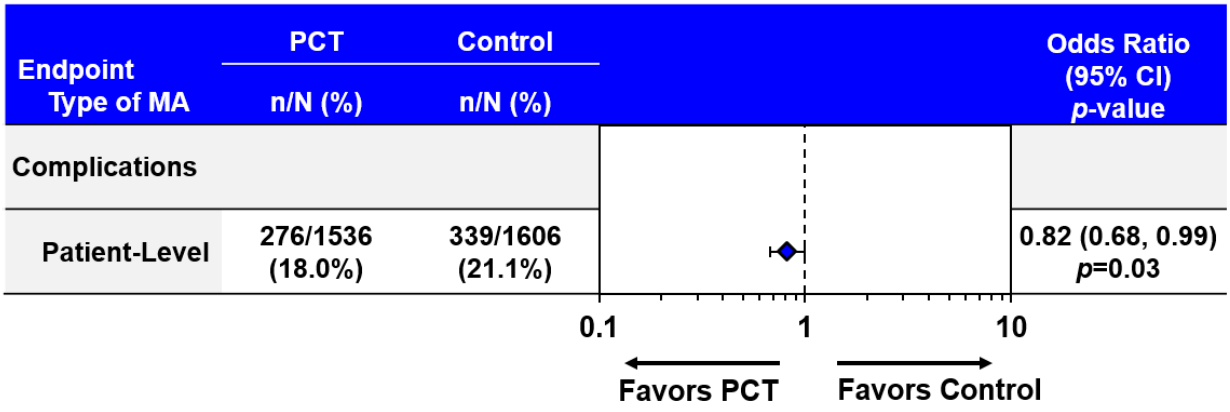
In the patient-level meta-analysis, no notable differences in safety profile were observed across all subgroups based on type of LRTI, setting, and level of initial PCT with regards to length of hospital stay. All point estimates for the mean difference in length of hospital stay were within ±1 day and all 95% CIs overlapped with 0.

6.3.3 Complications

Complications were evaluated in the patient-level meta-analyses and the results further corroborate the safety of PCT guidance in antibiotic decision-making.[6] A slightly lower risk of complications was observed with PCT-guided treatment (18.0%) relative to standard-of-care control (21.1%) in the overall LRTI population (OR: 0.82; 95% CI: 0.68, 0.98;

Figure 20), which was driven by a lower rate of ICU admissions in the PCT group. Subgroup analyses by type of LRTI, inpatient vs. outpatient setting, and initial PCT level at study entry were consistent with the overall result (i.e., slightly lower risk of complications in the PCT group) or had confidence intervals for the odds ratio overlapping with 1.0 (i.e., indicating no difference between groups).

Figure 20: Complications in Patient-Level Meta-Analysis – Overall LRTI Populations



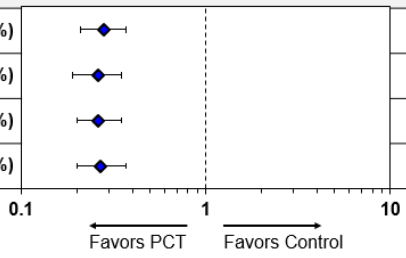
[6] Complications were defined as death, hospitalization/ICU admission/rehospitalization, ARI-specific complications [empyema, meningitis], recurrent or worsening infection, and patients reporting ongoing respiratory infection symptoms

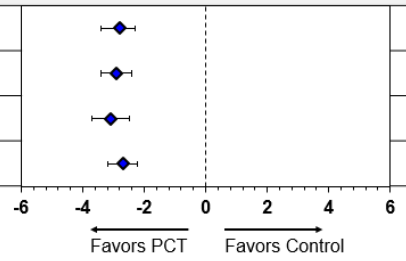
6.4 Subgroup Analyses by Age and Gender

Stratification based on age (<65 and ≥65 years) and gender in the patient-level analysis demonstrated that the overall reductions in antibiotic initiation, duration, and exposure associated with PCT-guided antibiotic use were independent of these two demographic variables as were the comparable risk of mortality, duration of hospitalization, and risk of complications (**Figure 21** and **Figure 22**).

Figure 21: Subgroup Analysis in Patient-Level Meta-Analysis – LRTI Subpopulations based on Age and Gender (Effectiveness Endpoints)

LRTI	PCT	Control	Odds Ratio or Difference (95% CI) *P-value*
Initiation of Antibiotics	n/N (%)	n/N (%)	
Female	455/671 (67.8%)	645/744 (86.7%)	0.28 (0.21, 0.37) *p*<0.001
Male	641/865 (74.1%)	775/862 (89.9%)	0.26 (0.19, 0.35) *p*<0.001
Age <65	476/717 (66.4%)	624/732 (85.3%)	0.26 (0.20, 0.35) *p*<0.001
Age ≥65	620/819 (75.7%)	796/874 (91.1%)	0.27 (0.20, 0.37) *p*<0.001
Duration of Antibiotics (days)	Median (IQR)	Median (IQR)	
Female	7 (4, 10)	10 (7, 12)	-2.8 (-3.4, -2.3) *p*<0.001
Male	7 (4, 10)	9 (7, 13)	-2.9 (-3.4, -2.4) *p*<0.001
Age <65	6 (4, 10)	9 (7, 12)	-3.1 (-3.7, -2.5) *p*<0.001
Age ≥65	7 (5, 10)	10 (7, 13)	-2.7 (-3.2, -2.2) *p*<0.001
Total Exposure of Antibiotics (days)	Median (IQR)	Median (IQR)	
Female	5 (0, 8)	8 (6, 12)	-3.6 (-4.1, -3.0) *p*<0.001
Male	5 (0, 8)	9 (6, 11)	-3.6 (-4.1, -3.1) *p*<0.001
Age <65	4 (0, 7)	7 (5, 11)	-3.8 (-4.3, -3.2) *p*<0.001
Age ≥65	5 (1, 9)	10 (7, 12)	-3.4 (-3.9, -2.9) *p*<0.001





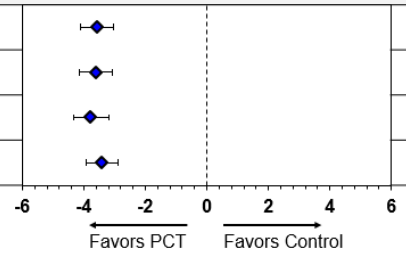


Figure 22: Subgroup Analysis in Patient-Level Meta-Analysis – LRTI Subpopulations based on Age and Gender (Safety Endpoints)

LRTI	PCT	Control	Odds Ratio or Difference (95% CI) *P-value*
30 Days Mortality	n/N (%)	n/N (%)	
Female	33/671 (4.9%)	43/744 (5.8%)	0.93 (0.67, 1.29) *p*=0.66
Male	70/865 (8.1%)	76/862 (8.8%)	0.96 (0.75, 1.24) *p*=0.77
Age <65	26/717 (3.6%)	32/732 (4.4%)	0.92 (0.62, 1.35) *p*=0.66
Age ≥65	77/819 (9.4%)	87/874 (10.0%)	0.97 (0.75, 1.25) *p*=0.80
		0.1 1 10	
		Favors PCT Favors Control	
Complications	n/N (%)	n/N (%)	
Female	119/671 (17.7%)	160/744 (21.5%)	0.80 (0.61, 1.06) *p*=0.12
Male	157/865 (18.2%)	179/862 (20.8%)	0.84 (0.66, 1.08) *p*=0.17
Age <65	118/717 (16.5%)	141/732 (19.3%)	0.79 (0.60, 1.05) *p*=0.11
Age ≥65	158/819 (19.3%)	198/874 (22.7%)	0.85 (0.65, 1.06) *p*=0.13
		0.1 1 10	
		Favors PCT Favors Control	
Hospital Length Of Stay (days)	Median (IQR)	Median (IQR)	
Female	5 (0, 11)	6 (0, 12)	-0.3 (-1.4, 0.9) *p*=0.64
Male	7 (1, 13)	7 (0, 13)	-0.1 (-0.9, 0.7) *p*=0.87
Age <65	0 (0, 7)	0 (0, 7)	-0.6 (-1.7, 0.5) *p*=0.27
Age ≥65	10 (5, 16)	9 (5, 15)	0.2 (-0.7, 1.0) *p*=0.71
		-6 -4 -2 0 2 4 6	
		Favors PCT Favors Control	

7 SEPSIS META-ANALYSIS RESULTS

Summary

- The average duration of antibiotics was 1.5 days shorter in the PCT group than in the control group in the study-level meta-analysis (p<0.001).
- The average exposure to antibiotics was 3.2 days shorter in the PCT group than the control group in the patient-level meta-analysis of patients with sepsis due to an infection of the lung (p<0.001). The median exposure to antibiotics was 8 days (IQR, 5 to 15) in the PCT group and 12 days (IQR, 8 to 18) in the control group.
- PCT-guided antibiotic treatment did not adversely affect safety outcomes for patients with sepsis.
  - Mortality: The RR for mortality in the study-level meta-analysis was 0.90 (95% CI: 0.79, 1.03). The OR for mortality in the patient-level meta-analysis was 0.87 (95% CI: 0.64, 1.18) and the observed mortality rates were 19.9% in the PCT group and 23.8% in the control group.
  - Length of hospital stay: The average difference in hospital stay was similar in both groups (mean difference: -1.4; 95% CI: -4.4, 1.7). The median length of hospital stay was 21 days in the PCT group and 23 days in the control group.
  - Length of ICU stay: The mean length of ICU stay was similar in the study-level (mean difference: -0.8; 95% CI: -2.5, 0.8) and patient-level (mean difference: 1.1; 95% CI: -1.3, 3.4) meta-analysis. The median length of stay was 12 days in the both groups in the patient-level meta-analysis.

7.1 Patient Populations

Studies selected for the sepsis meta-analyses were comprised of the targeted sepsis patient population: namely, adult patients with suspected or confirmed sepsis being admitted to the ICU or having developed an infection while in the ICU. The patient-level meta-analysis represents a subset of patients with sepsis due to an infection of the lung, as explained in **Section 5.2.5.1**, while the study-level meta-analysis includes study populations with suspected or confirmed sepsis due to any cause. **Table 18** shows study-level population characteristics.

Table 18: Sepsis Patient Baseline Characteristics in Study-Level Meta-Analysis

Publication	N PCT Group, Control Group	Age (median or mean*)	Male (%)
Annane, 2013	31, 31	57	74%
Bouadma, 2010	307, 314	62	66%
de Jong, 2016	761, 785	65	60%
Deliberato, 2013	42, 39	65	56%
Hochreiter, 2009	57, 53	67	53%
Layios, 2012	258, 251	66	60%
Najafi, 2015	30, 30	40	63%
Nobre, 2008	39, 40	65	68%
Schroeder, 2009	14, 13	69	56%
Shehabi, 2014	196, 198	64	54%

* depending on what was reported

The total N for the patient-level meta-analysis was 472 (PCT group) and 475 (control group), as shown in **Table** 12. Patients that did not classify as sepsis were removed prior to analysis (185 for PCT group and 164 for control group), leaving 287 and 311 patients in the PCT group and control group, respectively, as available for patient-level evaluation. Their baseline characteristics are summarized in **Table 19**.

Table 19: Sepsis Patient Baseline Characteristics in Patient-Level Meta-Analysis

Characteristic	PCT Group (N=287)	Control Group (N=311)
Age, median (IQR)	62 (50, 74)	65 (53, 75)
Male, n (%)	208 (72%)	216 (69%)
PCT value at initiation (ng/mL), median (IQR)	1.43 (0.39, 5.78)	1.20 (0.34, 4.74)

IQR – Interquartile range

Some of the exclusion criteria in the studies used in the study-level or the patient-level meta-analyses include patients with outpatient or inpatient cardiac arrest; conditions requiring long-term antibiotic therapy such as endocarditis; chronic localized infection such as osteomyelitis; trauma; severe immunosuppression; poor chance of survival or short expected ICU stay; withdrawal of life-supportive therapies or a decision to withhold them, neutropenia; various degrees of recent/prolonged antibiotic use; and women who were pregnant.

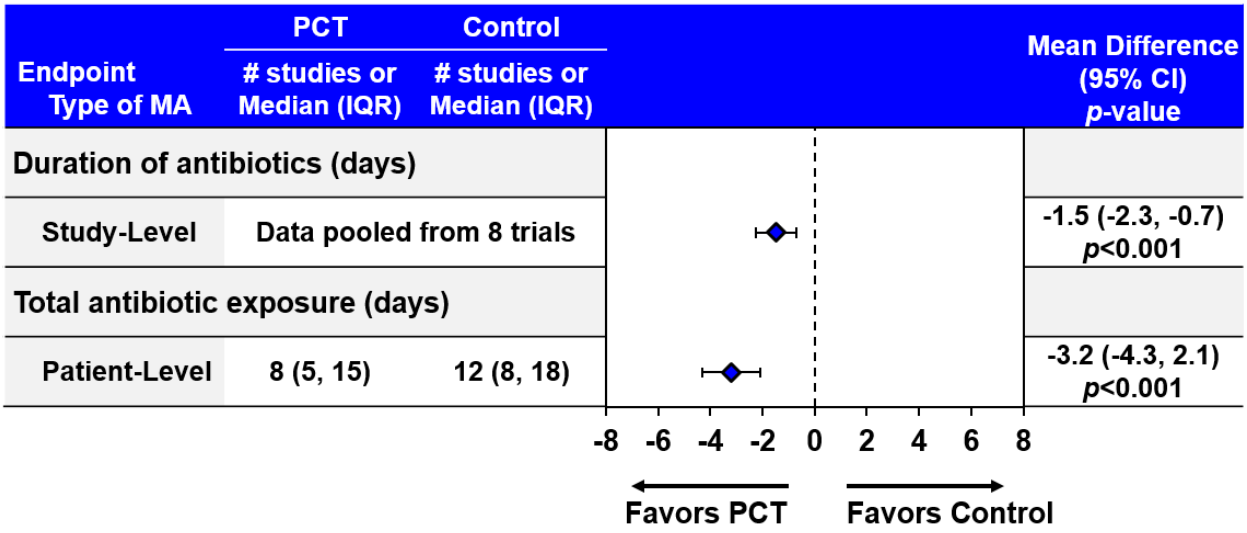
7.2 Effectiveness Outcomes – Antibiotics Duration

The goal of PCT algorithms in relation to sepsis is to reduce unnecessary prolonged use of antibiotics when bacterial infections are absent or have been adequately controlled. Both study-level and patient-level meta-analyses confirmed that discontinuation algorithms were effective in reducing duration and exposure to antibiotic in patients with sepsis, as shown in **Figure 23**.

As nearly all patients with suspected or confirmed sepsis are given antibiotic treatment under standard of care prior to study enrollment, the measures of antibiotic duration and antibiotic exposure are, in effect, the same. In the study-level meta-analysis, there was an estimated 1.5-day reduction (95% CI: -2.3, -0.7) in antibiotic use with PCT guidance.

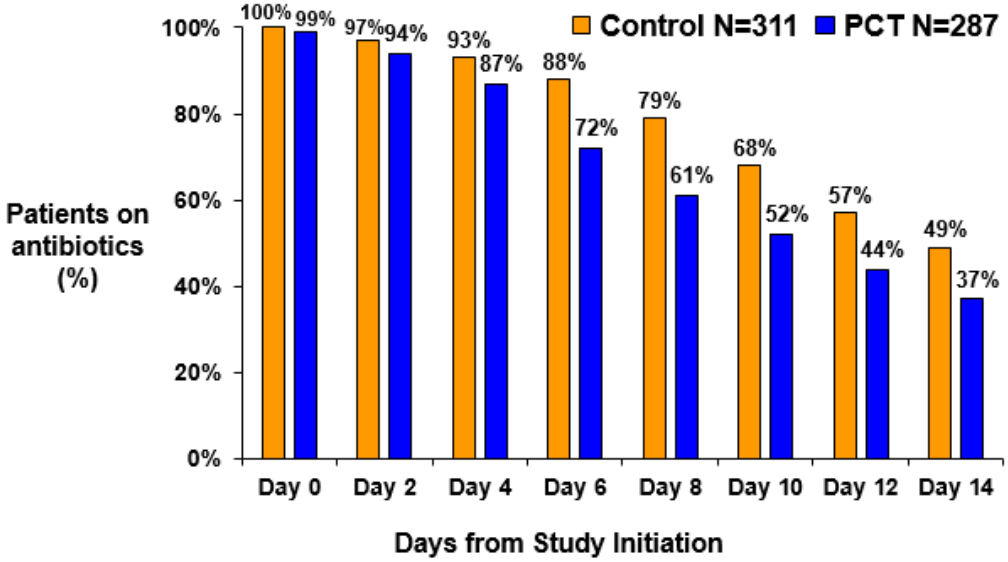
Total exposure to antibiotics in the patient-level meta-analysis was reduced an average of 3.2 days (95% CI: -4.3, -2.1) under PCT-guided treatment, with median exposures of 8 and 12 days among PCT and control patients, respectively. The overall patient-level results were also consistent among patients whose initial PCT levels were ≤0.5 ng/mL (mean reduction of 4.0 days) and >0.5 ng/mL (mean reduction of 3.8 days).

Figure 23: Duration of and Exposure to Antibiotics in Study-Level Meta-Analysis and Patient-Level Meta-Analysis – Overall Sepsis Populations



In the patient-level meta-analysis, more individuals discontinued antibiotics earlier under PCT-guided treatment as illustrated in **Figure 24** by the growing gap between the two groups starting at Day 2.

Figure 24: Antibiotic Use Over Time in Patient-Level Meta-Analysis – Overall Sepsis Population

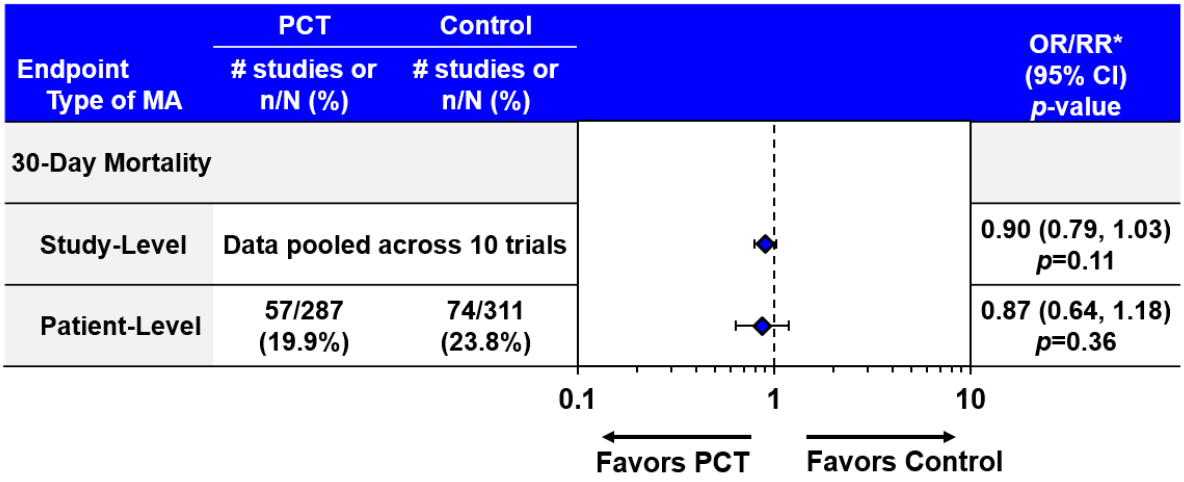


7.3 Safety Outcomes

7.3.1 Mortality

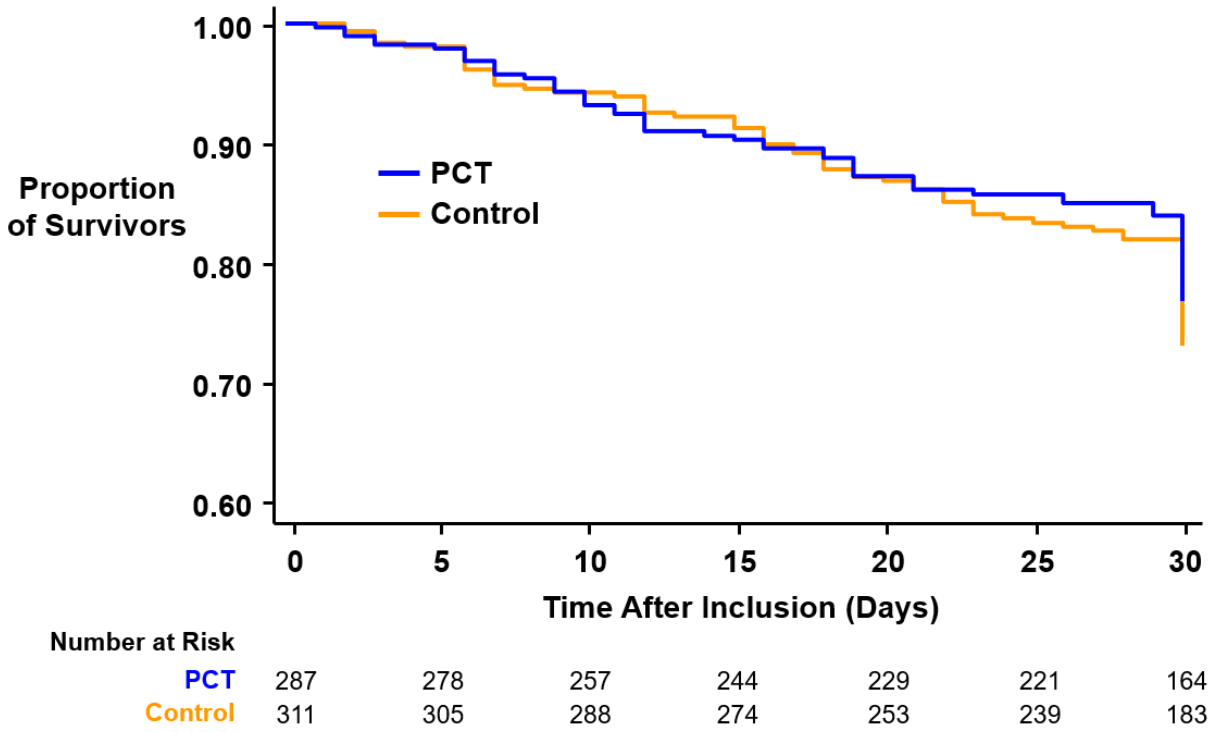
The reduction in antibiotic use associated with PCT-guided decision-making did not adversely affect patient safety as demonstrated by both study-level and patient-level meta-analyses (**Figure 25**). The estimated risk ratio (for the study-level meta-analysis) and odds ratio (for the patient-level meta-analysis) less than 1.0 do not indicate a safety signal associated with PCT guidance. Similar mortality rates for PCT and control groups are also evident from Kaplan-Meier analysis (**Figure 26**).

Figure 25: Mortality in Study-Level Meta-Analysis and Patient-Level Meta-Analysis – Overall Sepsis Populations



* OR for patient-level meta-analysis and RR for study-level meta-analysis

Figure 26: Survival in Patient-Level Meta-Analysis – Overall Sepsis Population



At the patient-level, stratification by initial PCT levels yielded similar ORs for mortality between PCT and control arms as the overall estimate. The OR for patients with an initial PCT level ≤0.5 ng/mL was 0.70 (95% CI: 0.41, 1.20) and the OR for patients with an initial PCT level >0.5

ng/mL was 0.81 (95% CI: 0.56, 1.17), indicating that the early cessation of antibiotics in each PCT category had no detrimental effect on patient survival.

7.3.2 Length of ICU or Hospital Stay

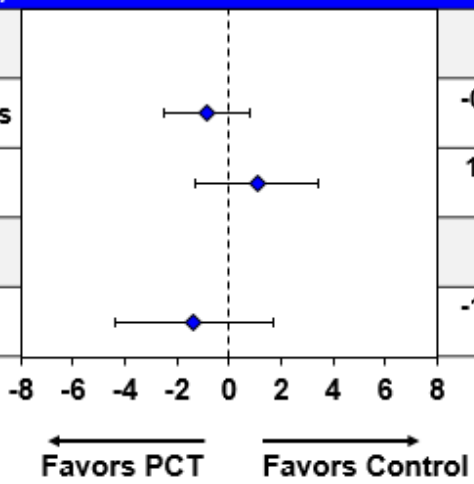
The overall length of stay in the ICU or hospital was unaffected by PCT-guided antibiotic discontinuation as compared to standard care (**Figure 27**). In the study-level meta-analysis using a random effects model, the average length of ICU stay was 0.8 days shorter (95% CI, -2.5, 0.8) in the PCT group. Similarly, in the patient-level meta-analysis, no significant difference was observed in the average ICU stay (mean difference: 1.1 days; 95% CI: -1.3 to 3.4), and the median length of stay was 12 days in both groups.

The patient-level meta-analysis also evaluated the total length of hospital stay. The median duration of hospital stay was 21 days in the PCT group and 23 days in the control group. The average difference between the groups was -1.4 days (95% CI: -4.4, 1.7).

No notable differences on either endpoint were noted on the basis of baseline PCT levels above or below 0.5 ng/mL.

Figure 27: Length of ICU or Hospital Stay in Study-Level Meta-Analysis and Patient-Level Meta-Analysis – Overall Sepsis Populations

Endpoint Type of MA	PCT # studies or Median (IQR)	Control # studies or Median (IQR)	Mean Difference (95% CI) *p*-value
Length of ICU stay (days)			
Study-Level	Data pooled across 10 trials		-0.8 (-2.5, 0.8) *p*=0.33
Patient-Level	12 (6, 23)	12 (6, 22)	1.1 (-1.3, 3.4) *p*=0.37
Hospital length of stay (days)			
Patient-Level	21 (11, 37)	23 (13, 38)	-1.4 (-4.4, 1.7) *p*=0.39



7.4 Subgroup Analyses by Age and Gender

Stratification based on age (<65 and ≥65 years) and gender in the patient-level meta-analysis demonstrated that the overall reduction in antibiotic exposure associated with PCT-guided antibiotic use were independent of these variables, as were the maintained risk of mortality and length of stay in the ICU and hospital (**Figure 28** and **Figure 29**).

Figure 28: Subgroup Analysis in Patient-Level Meta-Analysis – Sepsis Subpopulations based on Age and Gender (Effectiveness Endpoint)

Sepsis	PCT	Control	Odds Ratio or Difference (95% CI) *P-value*
Total Exposure of Antibiotics (days)	Median (IQR)	Median (IQR)	
Female	7 (5, 13)	11 (8, 19)	-4.8 (-6.9, -2.7) *p*<0.001
Male	9 (6, 16)	13 (8, 18)	-2.6 (-4.0, -1.3) *p*<0.001
Age <65	9 (5, 15)	14 (8, 20)	-3.5 (-5.0, -1.9) *p*<0.001
Age ≥65	8 (6, 14)	11 (8, 17)	-2.9 (-4.5, -1.4) *p*<0.001

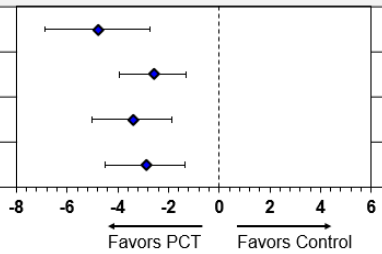


Figure 29: Subgroup Analysis in Patient-Level Meta-Analysis – Sepsis Subpopulations based on Age and Gender (Safety Endpoints)

Sepsis	PCT	Control	Odds Ratio or Difference (95% CI) *P-value*
30 Days Mortality	n/N (%)	n/N (%)	
Female	15/79 (19%)	26/95 (27%)	0.71 (0.41, 1.25) *p*=0.24
Male	42/208 (20.2%)	48/216 (22.2%)	0.95 (0.66, 1.37) *p*=0.78
Age <65	28/162 (17.3%)	31/152 (20.4%)	0.87 (0.55, 1.38) *p*=0.56
Age ≥65	29/125 (23.2%)	43/159 (27.0%)	0.86 (0.58, 1.30) *p*=0.48
		0.1 1 10 Favors PCT Favors Control	
Hospital Length Of Stay (days)	Median (IQR)	Median (IQR)	
Female	21 (12, 43)	25 (13, 38)	-1.6 (-8.0, 4.7) *p*=0.61
Male	21 (10, 36)	24 (13, 38)	-1.2 (-4.7, 2.2) *p*=0.48
Age <65	24 (11, 43)	25 (13, 43)	0.0 (-4.5, 4.4) *p*=0.98
Age ≥65	18 (11, 30)	21 (12, 36)	-3.2 (-7.5, 1.0) *p*=0.14
		-10 -5 0 5 10 Favors PCT Favors Control	
ICU Length Of Stay (days)	Median (IQR)	Median (IQR)	
Female	11 (5, 28)	10 (6, 22)	2.2 (-2.5, 6.9) *p*=0.37
Male	13 (6, 23)	13 (6, 22)	0.5 (-2.1, 3.2) *p*=0.70
Age <65	12 (6, 23)	14 (6, 24)	0.3 (-3.1, 3.6) *p*=0.87
Age ≥65	13 (6, 25)	11 (6, 21)	1.8 (-1.3, 5.0) *p*=0.26
		-10 -5 0 5 10 Favors PCT Favors Control	

8 SUMMARY OF RISKS AND BENEFITS ASSOCIATED WITH PCT-GUIDED ANTIBIOTIC TREATMENT OF LRTI AND SEPSIS

8.1 Benefits and Risks Associated with PCT Algorithms for LRTIs

Patient and Societal Benefits of PCT-Guided Treatment

In the meta-analyses, PCT-guided treatment algorithms reduced the odds of antibiotic initiation in patients with LRTIs by 75% and shortened the overall exposure to antibiotic treatment by 3-4 days without affecting patient outcomes compared to standard of care. Approximately 27 million patients receive antibiotics unnecessarily each year (Shapiro, 2014) and have the potential to benefit from more selective treatment. From an individual patient perspective, the benefits of reductions in initiation and duration of antibiotic treatment achieved through PCT guidance would reduce unnecessary exposure to the risks of antibiotics, including drug-related adverse events and *Clostridium difficile* infection as well as the risk of developing infection with antibiotic-resistant microbes. From a societal perspective, widespread implementation of PCT guidance for LRTIs has the potential to significantly curb antibiotic overuse and misuse and slow the growth and spread of antibiotic-resistant microbes in the United States.

Risks Associated with PCT-Guided Treatment

Results from the study- and patient-level meta-analyses confirmed that reductions in antibiotic use based on PCT guidance does not put patients at increased risk for an adverse outcome. Namely, PCT-guided treatment algorithms did not produce adverse safety signals for mortality or complications or prolong the length of hospital stay relative to treatment under standard of care.

Treatment with antibiotics is effective and necessary for patients with LRTIs when the symptoms stem from bacterial infections; withholding or stopping antibiotics if a patient really needed antibiotics would result in an inferior safety profile. However, the lack of a safety signal in the meta-analyses when interpreted in the context of other studies suggests that, in the context of clinical information, PCT is sensitive and specific enough, with a high enough negative predictive value, to differentiate patients who would benefit from antibiotics from those who would not. Thus, while allowing antibiotic treatment to be delivered to patients who need them, PCT results can safely support clinical decisions to withhold or stop antibiotics.

The utility of PCT in guiding safe antibiotic treatment is currently being incorporated into standard clinical practice. One instance is in the guidelines for management of LRTIs published by the Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases, which states: “Biomarkers, particularly PCT, may guide shorter treatment duration… Biomarkers can guide treatment duration by the application of predefined stopping rules for antibiotics [417–419]. It has been shown that such rules work even in most severe cases, including pneumonia with septic shock, and even if clinicians are allowed to overrule the predefined stopping rule [420,421]” (Woodhead, 2011).

8.2 Benefits and Risks Associated with PCT Algorithms for Sepsis

Patient and Societal Benefits of PCT-Guided Treatment

The meta-analyses for sepsis showed that PCT-guided discontinuation of antibiotics was safe and effective. Specifically, implementation of a PCT-guided treatment algorithm reduced the duration of antibiotic treatment by 1.5-3 days without adversely affecting patient outcomes. The unnecessary continuation of antibiotics in cases of suspected or confirmed sepsis contributes to the rise of antibiotic resistant bacteria while offering no clinical benefit to the patient. The reductions in unnecessary prolonged use of antibiotics in patients with sepsis can reduce the risks of drug-related reactions, *Clostridium difficile* infection, and subsequent infection with drug-resistant bacteria. Again, reductions in overuse of antibiotics would limit the emergence and spread of antibiotic-resistant bacteria in hospital and globally.

Risks Associated with PCT-Guided Treatment

Results from the study-level and patient-level meta-analyses confirmed that reductions in antibiotic use based on PCT guidance are not associated with increased patient risks. Patient outcomes including mortality and length of hospital and ICU stay were similar under PCT-guided antibiotic discontinuation and under standard care. Early treatment with antibiotics in patients with suspected sepsis is associated with decreased mortality and morbidity; early discontinuation of treatment has the potential to undermine benefits of current care. However, no safety signals were associated with PCT-guided antibiotic discontinuation, providing assurance that PCT-based algorithms have sufficient negative predictive values to select patients who would not benefit from continued antibiotic treatment.

The utility of PCT in antibiotic decision-making is recognized in the Surviving Sepsis Campaign guidelines, which are endorsed by the Infectious Diseases Society of America (IDSA). These guidelines recommend “Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C)” (Dellinger, 2013).

8.3 Complimentary Role of PCT in Clinical Evaluations

As with any diagnostic tool, the limitations of a single biomarker test must be understood and taken into account when reviewing the totality of clinical information. As such, the draft VIDAS B•R•A•H•M•S PCT package insert states:

> “VIDAS B•R•A•H•M•S PCT is not indicated to be used as a stand-alone diagnostic assay. PCT results should always be interpreted in the context of the clinical status of the patient and other laboratory results….
>
> Procalcitonin (PCT) can provide important information regarding the necessity, duration, and effectiveness of antibiotic therapy. This should always be seen in terms of risk evaluation or probability assessment under consideration of different influential factors, e.g. the clinical impression or state of the patient, imaging

studies and other laboratory or diagnostic tests, procedures, evaluation of the mortality risk, and the individual risk profile of the presumed infection. Decisions regarding antibiotic therapy should NOT be based solely on procalcitonin concentrations."

As iterated in the proposed PCT guidelines accompanying the indications (Section 3.3), clinical decisions on initiation and cessation of antibiotics must take into account other information including changes in clinical symptoms, clinical stability, severe comorbidities, ICU admission, risk for adverse outcome, or evidence of pathogens. Placed in the clinical context of a patient, the VIDAS B•R•A•H•M•S PCT provides important and actionable information that complements and enhances current clinical practice.

Curbing the societal burden of antibiotic resistance by limiting unnecessary antibiotic use is a call to action that has been emphasized by the CDC, WHO, United States government, and United Nations. Given that PCT-guided algorithms have the potential to reduce the adverse effects of antibiotic overuse for both society and patients without increasing safety risks in patients with LRTIs and sepsis, a net benefit is expected with the VIDAS B•R•A•H•M•S PCT. The body of evidence, as systematically evaluated in the meta-analyses, provide confidence that the VIDAS B•R•A•H•M•S PCT is safe and effective as an aid for physicians to make more informed decisions on antibiotic prescribing for LRTI and sepsis that result in less unnecessary antibiotic use and a high level of patient care.

9 REFERENCES

Albrich, W. C. *et al.* Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in 'real life': an international, multicenter poststudy survey (ProREAL). *Arch Intern Med* **172,** 715–722 (2012).

Annane, D. *et al.* Procalcitonin levels to guide antibiotic therapy in adults with non-microbiologically proven apparent severe sepsis: a randomised controlled trial. *BMJ Open* **3,** (2013).

Becker, K. L., Snider, R. & Nylen, E. S. Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and a therapeutic target. *Br J Pharmacol* **159,** 253–264 (2010).

Bouadma, L. *et al.* Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* **375,** 463–474 (2010).

Branche, A. R. *et al.* Serum Procalcitonin Measurement and Viral Testing to Guide Antibiotic Use for Respiratory Infections in Hospitalized Adults: A Randomized Controlled Trial. *J Infect Dis* **212,** 1692–1700 (2015).

Briel, M. *et al.* Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med* **168,** 2000-7-2008 (2008).

Burkhardt, O. *et al.* Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection. *Eur Respir J* **36,** 601–607 (2010).

CDC | Antibiotic / Antimicrobial Resistance. Available at: https://www.cdc.gov/drugresistance/. (Accessed: 6th October 2016)

Christ-Crain, M. *et al.* Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* **363,** 600–607 (2004).

Christ-Crain, M. *et al.* Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* **174,** 84–93 (2006).

Corti, C. *et al.* Point-of-care procalcitonin test to reduce antibiotic exposure in patients hospitalized with acute exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis* **11,** 1381–1389 (2016).

Cuquemelle, E. *et al.* Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicentre study. *Intensive Care Med* **37,** 796–800 (2011).

Dandona, P. *et al.* Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab* **79,** 1605–1608 (1994).

de Jong, E. *et al.* Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* **16,** 819–827 (2016).

Deliberato, R. O. *et al.* Clinical and economic impact of procalcitonin to shorten antimicrobial therapy in septic patients with proven bacterial infection in an intensive care setting. *Diagn Microbiol Infect Dis* **76,** 266–271 (2013).

Dellinger, R. P. *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* **39,** 165–228 (2013).

Fleming-Dutra, K. E. *et al.* Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. *JAMA* **315,** 1864–1873 (2016).

Food and Drug Administration (FDA). Advancing Regulatory Science at FDA: A Strategic Plan. (2011).

Haidich, A. B. Meta-analysis in medical research. *Hippokratia* **14,** 29–37 (2010).

Hall, M. J., Williams, S. N., DeFrances, C. J. & Golosinskiy, A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. National Center for Health Statistics (2011).

Harbarth, S. et al. Diagnostic Value of Procalcitonin, Interleukin-6, and Interleukin-8 in Critically Ill Patients Admitted with Suspected Sepsis. *Am J Respir Crit Care Med* **164,** 396–402 (2001).

Higgins, J. P. & Green, S. *Cochrane handbook for systematic reviews of interventions*. **Version 5.1.0 [updated March, 2011],** (The Cochrane Collaboration, 2011).

Hochreiter, M. *et al.* Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. *Crit Care* **13,** R83 (2009).

Jain, S. *et al.* Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med* **373,** 415–427 (2015).

Kristoffersen, K. B. *et al.* Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission--a randomized trial. *Clin Microbiol Infect* **15,** 481–487 (2009).

Layios, N. *et al.* Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. *Crit Care Med* **40,** 2304–2309 (2012).

Long, W. *et al.* [The value of serum procalcitonin in treatment of community acquired pneumonia in outpatient]. *Zhonghua Nei Ke Za Zhi* **48,** 216–219 (2009).

Long, W. *et al.* Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia. *Respirology* **16,** 819–824 (2011).

Macfarlane, J. *et al.* Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* **56,** 109–114 (2001).

Macfarlane, J. T., Colville, A., Guion, A., Macfarlane, R. M. & Rose, D. H. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet* **341,** 511–514 (1993).

Meisner, M. Procalcitonin: Erfahrungen mit einer neuen Me\s sgrö\s se für bakterielle Infektionen und systemische Inflammation. *LaboratoriumsMedizin/Journal of Laboratory Medicine* **23,** 263–272 (1999).

Meisner, M. Pathobiochemistry and clinical use of procalcitonin. *Clin Chim Acta* **323,** 17–29 (2002).

Morgenthaler, N. G. *et al.* Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA. *Clin Lab* **48,** 263–270 (2002).

Morgenthaler, N. G. *et al.* Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA. *Clin Lab* **48,** 263–270 (2002).

Najafi, A. *et al.* The Comparison of Procalcitonin Guidance Administer Antibiotics with Empiric Antibiotic Therapy in Critically Ill Patients Admitted in Intensive Care Unit. *Acta Med Iran* **53,** 562–567 (2015).

Nebraska Medicine | Omaha, NE. Procalcitonin Guidance - Antimicrobial Stewardship Program. Available at: http://www.nebraskamed.com/careers/education-programs/asp/procalcitonin-pct-guidance. (Accessed: 6th October 2016)

Nobre, V., Harbarth, S., Graf, J.-D., Rohner, P. & Pugin, J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med* **177,** 498–505 (2008).

OCEBM Levels of Evidence Working & others. *The Oxford 2011 levels of evidence*. (Oxford centre for evidence-based medicine Oxford, UK, 2011).

Petitjean, S., Mackensen, A., Engelhardt, R., Bohuon, C. & Assicot, M. Induction de la procalcitonine circulante apres administration intraveneuse d'endotoxine chez l'homme. *Act Pharm Biol Clin* **13,** 265–268 (1994).

Rodriguez, A. H. *et al.* Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis. *J Infect* **72,** 143–151 (2016).

Shapiro, D. J., Hicks, L. A., Pavia, A. T. & Hersh, A. L. Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09. *J. Antimicrob. Chemother* **69** (2013).

Schroeder, S. *et al.* Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. *Langenbecks Arch Surg* **394,** 221–226 (2009).

Schuetz, P. *et al.* Procalcitonin to initiate or withhold antibiotics in acute respiratory tract infections (Protocol). *Cochrane Database Syst Rev* **4,** (2008).

Schuetz, P. *et al.* Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* **302,** 1059–1066 (2009).

Schuetz, P. *et al.* Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* CD007498 (2012). doi:10.1002/14651858.CD007498.pub2

Shehabi, Y. *et al.* Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. *Am J Respir Crit Care Med* **190,** 1102–1110 (2014).

Snider, R. H. J., Nylen, E. S. & Becker, K. L. Procalcitonin and its component peptides in systemic inflammation: immunochemical characterization. *J Investig Med* **45,** 552–560 (1997).

Stolz, D. *et al.* Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Respir J* **34,** 1364–1375 (2009).

Stolz, D. *et al.* Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* **131,** 9–19 (2007).

Verduri, A. *et al.* Antibiotic treatment of severe exacerbations of chronic obstructive pulmonary disease with procalcitonin: a randomized noninferiority trial. *PLoS One* **10,** e0118241 (2015).

White, A. J., Gompertz, S. & Stockley, R. A. Chronic obstructive pulmonary disease . 6: The aetiology of exacerbations of chronic obstructive pulmonary disease. *Thorax* **58,** 73–80 (2003).

Woodhead, M. *et al.* Guidelines for the management of adult lower respiratory tract infections--full version. *Clin Microbiol Infect* **17 Suppl 6,** E1-59 (2011).

Zeni, F. *et al.* Procalcitonin serum concentrations and severity of sepsis. *Clin Intens Care* **5,** 89–98 (1994).

United Nations. PRESS RELEASE: High-Level Meeting on Antimicrobial Resistance. *General Assembly of the United Nations* (2016). Available at: http://www.un.org/pga/71/2016/09/21/press-release-hl-meeting-on-antimicrobial-resistance/. (Accessed: 5th October 2016)

WHO | Antibiotic resistance. *WHO* Available at: http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/. (2015) (Accessed: 5th October 2016)

WHO | Global action plan on antimicrobial resistance. *WHO* Available at: http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/. (2016) (Accessed: 5th October 2016)

APPENDIX 1

PubMed Database Search – Study-Level Meta-Analysis (LRTI)

Keywords and number of hits obtained from the PUBMED database for the literature search conducted on May 4th, 2016 (J. Hey and N. Picot). The final equation retrieved 204 publications for appraisal from the PUBMED database.

Search	Query	Items found
#1	Search **procalcitonin[Supplementary Concept]**	2405
#2	Search **(procalcitonin[Supplementary Concept]) AND "anti bacterial agents"[MeSH Terms]**	257
#3	Search **"Respiratory Tract Infections"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Bronchitis"[Mesh] OR "Pneumonia"[Mesh]**	355223
#4	Search **(((procalcitonin[Supplementary Concept]) AND "anti bacterial agents"[MeSH Terms])) AND ("Respiratory Tract Infections"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Bronchitis"[Mesh] OR "Pneumonia"[Mesh])**	112
#5	Search **(PROCALCITONIN OR PCT) AND (antibiotic OR antibiotics OR "antibacterial agent" OR "antibacterial agents" OR "anti bacterial agent" OR "anti bacterial agents" OR "antimicrobial agent" OR "antimicrobial agents" OR "anti microbial agent" OR "anti microbial agents") AND (LRTI OR "low respiratory tract infection" OR "low respiratory tract infections" OR pneumonia OR bronchitis OR copd OR "chronic obstructive pulmonary disease" OR "chronic obstructive pulmonary diseases")**	235
#6	Search **(PROCALCITONIN OR PCT) AND (antibiotic OR antibiotics OR "antibacterial agent" OR "antibacterial agents" OR "anti bacterial agent" OR "anti bacterial agents" OR "antimicrobial agent" OR "antimicrobial agents" OR "anti microbial agent" OR "anti microbial agents") AND (LRTI OR "low respiratory tract infection" OR "low respiratory tract infections" OR pneumonia OR bronchitis OR copd OR "chronic obstructive pulmonary disease" OR "chronic obstructive pulmonary diseases")** Field: **Title/Abstract**	192
#7	Search **((("procalcitonin" [Supplementary Concept] AND "Anti-Bacterial Agents"[Mesh]) AND ("Respiratory Tract Infections"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Bronchitis"[Mesh]**	253

	OR "Pneumonia"[Mesh]))) OR #6 Field: **Title/Abstract**	
#8	Search **(((("procalcitonin" [Supplementary Concept] AND "Anti-Bacterial Agents"[Mesh]) AND ("Respiratory Tract Infections"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Bronchitis"[Mesh] OR "Pneumonia"[Mesh]))) OR #6** Filters: **Publication date from 2004/01/01; Field: Title/Abstract**	244
#9	Search **(((("procalcitonin" [Supplementary Concept] AND "Anti-Bacterial Agents"[Mesh]) AND ("Respiratory Tract Infections"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Bronchitis"[Mesh] OR "Pneumonia"[Mesh]))) OR #6** Filters: **Publication date from 2004/01/01; English; Field: Title/Abstract**	204

Cochrane Database of Systematic Reviews Search – Study-Level Meta-Analysis (LRTI)

Keywords and number of hits with the Cochrane Database of Systematic Reviews for the literature search conducted on May 4th, 2016 (J.Hey and N. Picot): The final equation retrieved **104** publications for appraisal from the Cochrane database of Systematic Reviews.

Search Name: PCT LRTI FDA

Date Run: 04/05/16 15:54:58.653

Description:

ID	Search	Hits
#1	procalcitonin or pct	**750**
#2	antibiotic or antibiotics or "antibacterial agent" or "antibacterial agents" or "anti bacterial agent" or "anti bacterial agents" or "antimicrobial agent" or "antimicrobial agents"	**26928**
#3	LRTI or "low respiratory tract infection" or "low respiratory tract infections" or pneumonia or bronchitis or copd or "chronic obstructive pulmonary disease" or "chronic obstructive pulmonary diseases"	**22515**
#4	#1 and #2 and #3	**92**
#5	MeSH descriptor: [Respiratory Tract Infections] explode all trees	**10877**
#6	MeSH descriptor: [Pneumonia] explode all trees	**2800**
#7	MeSH descriptor: [Bronchitis] explode all trees	**1520**
#8	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees	**3093**
#9	MeSH descriptor: [Anti-Bacterial Agents] explode all trees	**10196**
#10	#1 and (#5 or #6 or #7 or #8) and #9	**41**
#11	#10 or #4	**104**

PubMed Database Search – Study-Level Meta-Analysis (Sepsis)

Find below the keywords and number of hits obtained with the Pubmed database for the literature search conducted on May 19th, 2016 (J. Hey and N. Picot). The final equation retrieved **275** publications from the Pubmed database.

Search	Query	Items found
#1	Search **(("Sepsis"[Mesh] OR "Shock, Septic"[Mesh] OR "Bacteremia"[Mesh]) OR ("Bacterial Infections"[Mesh] AND "Intensive Care Units"[Mesh])) AND "Anti-Bacterial Agents"[Mesh] AND "procalcitonin" [Supplementary Concept]**	97
#2	Search **sepsis OR septicemia OR septicemias OR bacteremia OR bacteremias OR bacteraemia OR bacteraemias OR "blood poisoning" OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections" OR "septic shock" OR "endotoxic shock" OR "toxic shock" OR (("intensive care unit" OR "intensive care units" OR ICU OR ICUs) AND ("bacterial infection" OR "bacterial infections"))**	174041
#3	Search **antibiotic OR antibiotics OR "antibacterial agent" OR "antibacterial agents" OR "anti bacterial agent" OR "anti bacterial agents" OR "antimicrobial agent" OR "antimicrobial agents" OR "anti microbial agent" OR "anti microbial agents"**	755523
#4	Search **procalcitonin OR PCT**	7651
#5	Search **(sepsis OR septicemia OR septicemias OR bacteremia OR bacteremias OR bacteraemia OR bacteraemias OR "blood poisoning" OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections" OR "septic shock" OR "endotoxic shock" OR "toxic shock" OR (("intensive care unit" OR "intensive care units" OR ICU OR ICUs) AND ("bacterial infection" OR "bacterial infections"))) AND (antibiotic OR antibiotics OR "antibacterial agent" OR "antibacterial agents" OR "anti bacterial agent" OR "anti bacterial agents" OR "antimicrobial agent" OR "antimicrobial agents" OR "anti microbial agent" OR "anti microbial agents") AND (procalcitonin OR PCT)**	405
#6	Search **(sepsis OR septicemia OR septicemias OR bacteremia OR bacteremias OR bacteraemia OR bacteraemias OR "blood poisoning" OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections" OR "septic shock" OR "endotoxic shock" OR "toxic shock" OR (("intensive care unit" OR "intensive care units" OR ICU OR ICUs) AND ("bacterial infection" OR "bacterial infections"))) AND (antibiotic OR**	315

Search	Query	Items found
	antibiotics OR "antibacterial agent" OR "antibacterial agents" OR "anti bacterial agent" OR "anti bacterial agents" OR "antimicrobial agent" OR "antimicrobial agents" OR "anti microbial agent" OR "anti microbial agents") AND (procalcitonin OR PCT) Field: **Title/Abstract**	
#7	Search **(#20) OR ((("Sepsis"[Mesh] OR "Shock, Septic"[Mesh] OR "Bacteremia"[Mesh]) OR ("Bacterial Infections"[Mesh] AND "Intensive Care Units"[Mesh])) AND "Anti-Bacterial Agents"[Mesh]) AND "procalcitonin" [Supplementary Concept])** Field: **Title/Abstract**	354
#8	Search **(#20) OR ((("Sepsis"[Mesh] OR "Shock, Septic"[Mesh] OR "Bacteremia"[Mesh]) OR ("Bacterial Infections"[Mesh] AND "Intensive Care Units"[Mesh])) AND "Anti-Bacterial Agents"[Mesh]) AND "procalcitonin" [Supplementary Concept])** Filters: **Publication date from 2004/01/01**	332
#9	Search **(#20) OR ((("Sepsis"[Mesh] OR "Shock, Septic"[Mesh] OR "Bacteremia"[Mesh]) OR ("Bacterial Infections"[Mesh] AND "Intensive Care Units"[Mesh])) AND "Anti-Bacterial Agents"[Mesh]) AND "procalcitonin" [Supplementary Concept])** Filters: **Publication date from 2004/01/01; English**	275

Cochrane Database of Systematic Reviews Search – Study-Level Meta-Analysis (Sepsis)

Find below the keywords and number of hits with the Cochrane Database of Systematic Reviews for the literature search conducted on May 19th, 2016 (J. Hey and N. Picot). The final equation retrieved **94** publications from the Cochrane database of Systematic Reviews.

Date Run: 19/05/16 09:05:10.429

Description:

ID	Search	Hits
#1	MeSH descriptor: [Sepsis] explode all trees	**3378**
#2	MeSH descriptor: [Bacteremia] explode all trees	**813**
#3	MeSH descriptor: [Bacterial Infections] explode all trees	**15234**
#4	MeSH descriptor: [Intensive Care Units] explode all trees	**3041**
#5	MeSH descriptor: [Shock, Septic] explode all trees	**497**
#6	#1 or #2 or (#3 and #4) or #5	**3528**
#7	MeSH descriptor: [Anti-Bacterial Agents] explode all trees	**10196**
#8	procalcitonin or PCT	**750**
#9	#6 and #7 and #8	**27**
#10	((sepsis or septicemia or septicemias or bacteremia or bacteremias or bacteraemia or bacteraemias or "blood poisoning" or "blood stream infection" or "blood stream infections" or "bloodstream infection" or "bloodstream infections" or "septic shock" or "endotoxic shock" or "toxic shock" or (("intensive care unit" or "intensive care units" or ICU or ICUs) and ("bacterial infection" or "bacterial infections"))) and (antibiotic or antibiotics or "antibacterial agent" or "antibacterial agents" or "anti bacterial agent" or "anti bacterial agents" or "antimicrobial agent" or "antimicrobial agents" or "anti microbial agent" or "anti microbial agents")) and (procalcitonin or PCT)	**89**
#11	#9 or #10	**94**

APPENDIX 2

Data Extracted from Studies Selected for the Study-Level Meta-Analyses

- Geographic location
- Setting
- Number of randomized patients
- Details on treatment and control arms
- Patient eligibility criteria
- Duration of follow-up
- Patient demographics and clinical characteristics
- PCT method of measurement
- PCT algorithm for antibiotic decision-making
- Level of adherence to PCT algorithm
- Outcomes as summarized in Section 5.1.3

Data Extracted from Studies Selected for the Patient-Level Meta-Analyses

- Geographic location
- Setting
- Number of randomized patients
- Details on treatment and control arms
- Patient eligibility criteria
- Duration of follow-up
- Patient demographics and clinical characteristics
- Details on PCT algorithm
- Level of adherence to algorithm
- Outcomes as summarized in Section 5.2.3

APPENDIX 3

Cochrane Risk of Bias Assessment Tool

RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.**	
Criteria for a judgment of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgment of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgment or some method of non-random categorization of participants, for example: • Allocation by judgment of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgment of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgment of 'Low risk' or 'High risk'.

ALLOCATION CONCEALMENT

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

Criteria for a judgment of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgment of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
Criteria for the judgment of 'Unclear risk' of bias.	Insufficient information to permit judgment of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

BLINDING OF PARTICIPANTS AND PERSONNEL

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.

Criteria for a judgment of 'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.

BLINDING OF OUTCOME ASSESSMENT **Detection bias due to knowledge of the allocated interventions by outcome assessors.**	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Attrition bias due to amount, nature or handling of incomplete outcome data.**	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.

Criteria for the judgment of 'High risk' of bias.	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgment of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.
SELECTIVE REPORTING **Reporting bias due to selective outcome reporting.**	
Criteria for a judgment of 'Low risk' of bias.	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgment of 'High risk' of bias.	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgment of 'Unclear risk' of bias.	Insufficient information to permit judgment of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
OTHER BIAS **Bias due to problems not covered elsewhere in the table.**	

Criteria for a judgment of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgment of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.
Criteria for the judgment of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.

APPENDIX 4

Quality Assessment Results for LRTI Based on Cochrane Risk of Bias Assessment Tool

Author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Branche, 2015	+	-	-	+	+	+
Briel, 2008	+	+	+	?	+	+
Burkhardt, 2010	+	+	+	+	+	+
Christ-Crain, 2004	+	?	-	?	+	+
Christ-Crain, 2006	?	+	-	-	-	+
Corti, 2016	+	+	-	-	+	+
Kristoffersen, 2009	+	+	-	-	+	+
Long, 2011	?	-	-	+	+	+
Schuetz, 2009	+	+	+	?	+	+
Stolz, 2007	?	?	+	+	+	+
Verduri, 2015	+	+	-	-	+	?

Quality assessment results for Sepsis based on Cochrane Risk of Bias Assessment Tool

First author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Annane, 2013	+	+	+	+	+	+
Bouadma, 2010	+	+	-	+	+	+
de Jong, 2016	+	?	-	-	-	+
Deliberato, 2013	+	+	-	-	-	+
Hochreiter, 2009	?	?	-	-	?	+
Layios, 2012	?	+	-	+	+	+
Najafi, 2015	+	?	?	?	+	-
Nobre, 2008	+	+	-	?	+	+
Schroeder, 2009	?	?	?	?	+	+
Shehabi, 2014	+	+	?	+	+	+

APPENDIX 5

PCT Algorithms Used in Meta-Analysis Studies – LRTI Antibiotic Initiation

Cut-offs (in ng/mL)

Study	Antibiotics strongly discouraged	Antibiotics discouraged	Antibiotics encouraged	Antibiotics strongly encouraged
Bouadma (2010) *(P)*	< 0.25	0.25 - 0.49	0.5 - 0.99	≥ 1
Branche (2015) *(S)*	≤ 0.1	0.11 - 0.24	0.25 - 0.49	≥ 0.5
Briel (2008) *(S)(P)*	< 0.1	0.10 - 0.25	> 0.25	-
Burkhardt (2010) *(S)(P)*	-	< 0.25	≥ 0.25	-
Christ-Crain (2004) *(S)(P)*	≤ 0.1	0.1 - 0.25	0.25 - 0.5	≥ 0.5
Christ-Crain (2006) *(S)(P)*	< 0.1	0.1 - 0.25	0.25 - 0.5	> 0.5
Corti (2016) *(S)*	≤ 0.15	0.15 - 0.25	> 0.25	-
Hochreiter (2009) *(P)*	-	-	-	-
Kristoffersen (2009) *(S)(P)*	-	< 0.25	0.25 - 0.5	> 0.5
Long (2009) *(P)*	-	< 0.25	≥ 0.25	-
Long (2011) *(S)(P)*	< 0.1	0.1 - 0.25	> 0.25	-
Nobre (2007) *(P)*	-	-	-	-
Schroeder (2009) *(P)*	-	-	-	-
Schuetz (2009) *(S)(P)*	< 0.1	0.1 - 0.25	0.26 - 0.5	> 0.5
Stolz (2007) *(S)(P)*	< 0.1	0.1 - 0.25	> 0.25	-
Verduri (2015) *(S)*	-	-	-	-
Applicant proposal	**< 0.10**	**0.10 - 0.25**	**0.26 - 0.50**	**> 0.50**

(S): In study-level meta-analysis; (P): In patient-level meta-analysis

PCT Algorithms Used in Meta-Analysis Studies – LRTI Antibiotic Discontinuation

Cut-offs (in ng/mL)

Study	Stop 1	Stop 2
Bouadma (2010) *(P)*	Refer to initiation cut-offs (≤ 0.49)	decrease by ≥ 80% of the initial PCT level
Branche (2015) *(S)*	Refer to initiation cut-offs (≤ 0.24)	-
Briel (2008) *(S)(P)*	≤ 0.25	-
Burkhardt (2010) *(S)(P)*	-	-
Christ-Crain (2004) *(S)(P)*	< 0.25	-
Christ-Crain (2006) *(S)(P)*	Refer to initiation cut-offs (≤ 0.25)	If PCT(on admission) > 10 ng/mL, use decrease by > 90% of the initial PCT
Corti (2016) *(S)*	Refer to initiation cut-offs (≤ 0.25)	If PCT(on admission) > 5 ng/mL, use decrease by > 80% of the peak PCT
Hochreiter (2009) *(P)*	< 1	≥ 65-75% change from initial PCT level AND current PCT level > 1 ng/mL
Kristoffersen (2009) *(S)(P)*	< 0.25	-
Long (2009) *(P)*	Refer to initiation cut-offs (< 0.25)	-
Long (2011) *(S)(P)*	Refer to initiation cut-offs (< 0.25)	-
Nobre (2007) *(P)*	< 0.25 ng/mL if initial PCT level ≥ 1, or <0.1 ng/mL if initial PCT level <1	> 90% change if initial PCT ≥ 1 ng/mL
Schroeder (2009) *(P)*	≤ 1	≥ 65-75% change from initial PCT level
Schuetz (2009) *(S)(P)*	Refer to initiation cut-offs (≤ 0.25)	If PCT(on admission) > 10 ng/mL, use decrease by ≥ 80% of the initial PCT
Stolz (2007) *(S)(P)*	-	-
Verduri (2015) *(S)*	< 0.1 ng/mL or < 0.25 ng/mL for patients without severe disease	-
Applicant proposal	**PCT level ≤ 0.25 ng/mL or decrease > 80%**	

(S): In study-level meta-analysis; (P): In patient-level meta-analysis

PCT Algorithms Used in Meta-Analysis Studies – Sepsis Antibiotic Cessation

Cut-offs (in ng/mL)

Study	Antibiotics stop (option 1)	Antibiotics stop (option 2)	Antibiotics stop (option 3)
Annane (2013) *(S)*	< 0.5	-	-
Bouadma (2010) *(S)(P)*	< 0.5	-	> 80% change from peak PCT level
De Jong (2016) *(S)*	≤ 0.5	-	≥ 80% change from peak PCT level
Deliberato (2013) *(S)*	< 0.5	-	> 90% change from peak PCT level
Hochreiter (2009) *(S)(P)*	< 1	-	≥ 65-75% change from initial PCT level AND current PCT level >1
Laiyos (2012) *(S)*	< 0.5	-	-
Najafi (2015) *(S)*	≤ 0.5	-	-
Nobre (2007) *(S)(P)*	< 0.25 if initial PCT level ≥ 1	< 0.1 if initial PCT level < 1	> 90% change if initial PCT ≥ 1
Schroeder (2008) *(S)(P)*	≤ 1	-	≥ 65-75% change from initial PCT level
Shehabi (2014) *(S)*	< 0.10	0.10-0.25 if infection unlikely	> 90% change from baseline PCT level
Stolz (2009) *(P)*	≤ 0.5	-	≥ 80% change from initial PCT level
Applicant proposal	**PCT level ≤ 0.5 ng/mL or decrease > 80%**		

(S): In study-level meta-analysis; (P): In patient-level meta-analysis

APPENDIX 6

Number of Patients Included in Patient-Level Meta-Analyses

Appendix 6 - 1: Number of Patients Contributing to LRTI Patient-Level Meta-Analysis

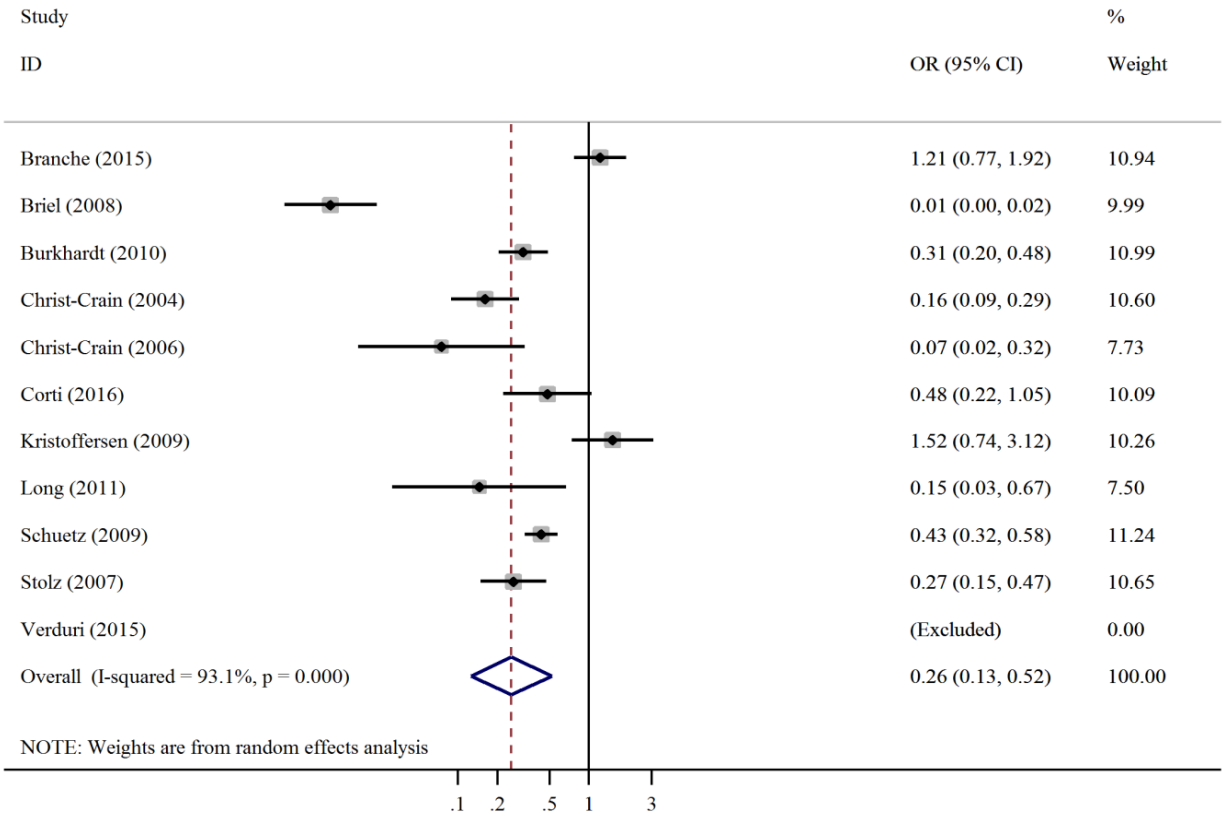
Publication	Total Number of Patients Included in Trial	Number of Patients Included in LRTI Analysis
Briel, 2008	458	218
Burkhardt, 2010	571	195
Christ-Crain, 2004	243	206
Christ-Crain, 2006	302	286
Stolz, 2007	226	208
Kristoffersen, 2009	223	165
Long, 2009	127	127
Schuetz, 2009	1381	1304
Long, 2011	172	156
Nobre, 2008	79	52
Schroeder, 2009	27	8
Hochreiter, 2009	110	43
Bouadma, 2010	630	174
Total	**4549**	**3142**

Appendix 6 - 2: Number of Patients Contributing to Patient-Level Meta-Analysis of Patients with Sepsis and Lung Infection

Publication	Total Number of Patients Included in Trial	Number of Patients Included in Sepsis Analysis
Nobre, 2008	79	52
Schroeder, 2009	27	8
Hochreiter, 2009	110	43
Stolz, 2009	101	101
Bouadma, 2010	630	394
Total	**947**	**598**

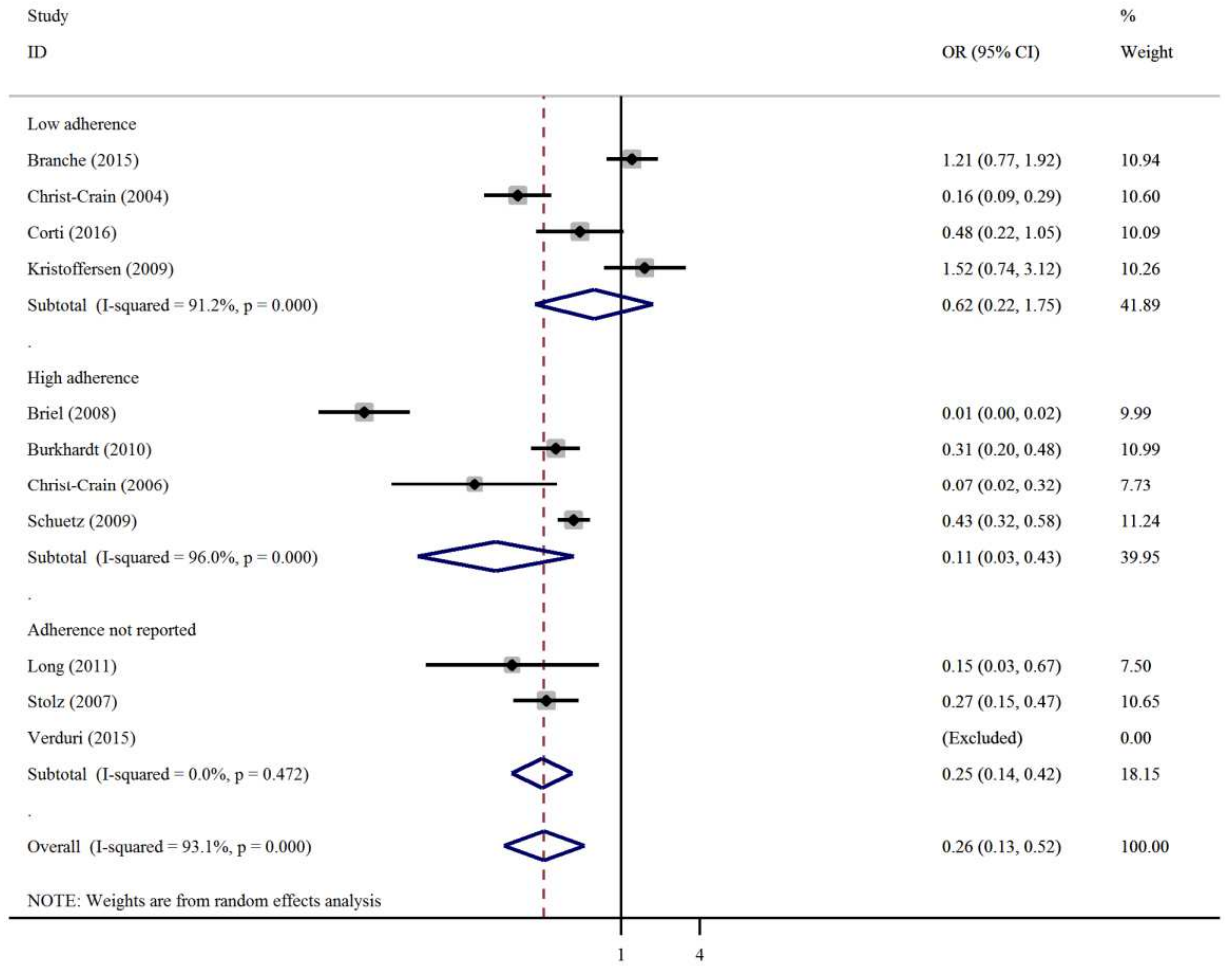
Initiation of Antibiotics – LRTI

Appendix 6 - 3: Antibiotic initiation (random effects model)



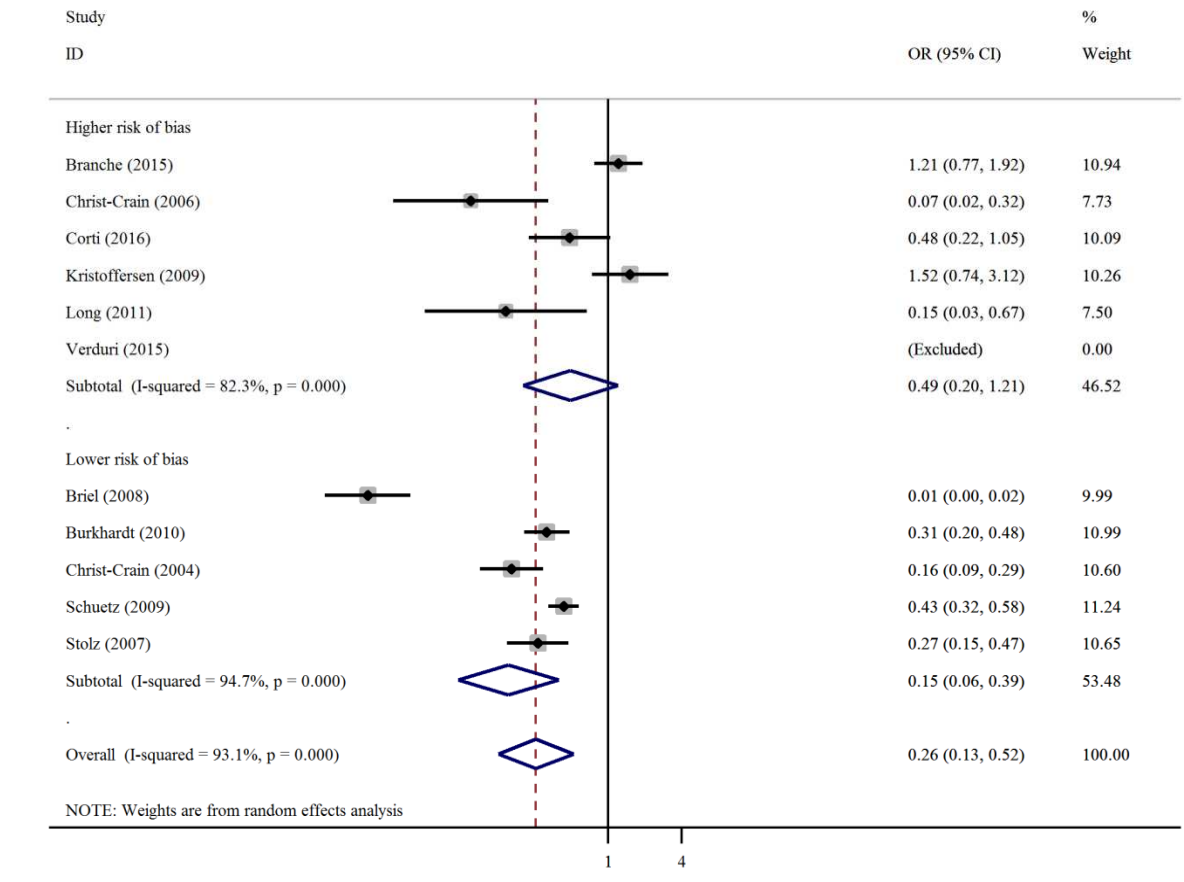
CI: confidence interval; OR: odds ratio

Appendix 6 - 4: Antibiotic initiation stratified by PCT adherence (random effects model)



CI: confidence interval; OR: odds ratio

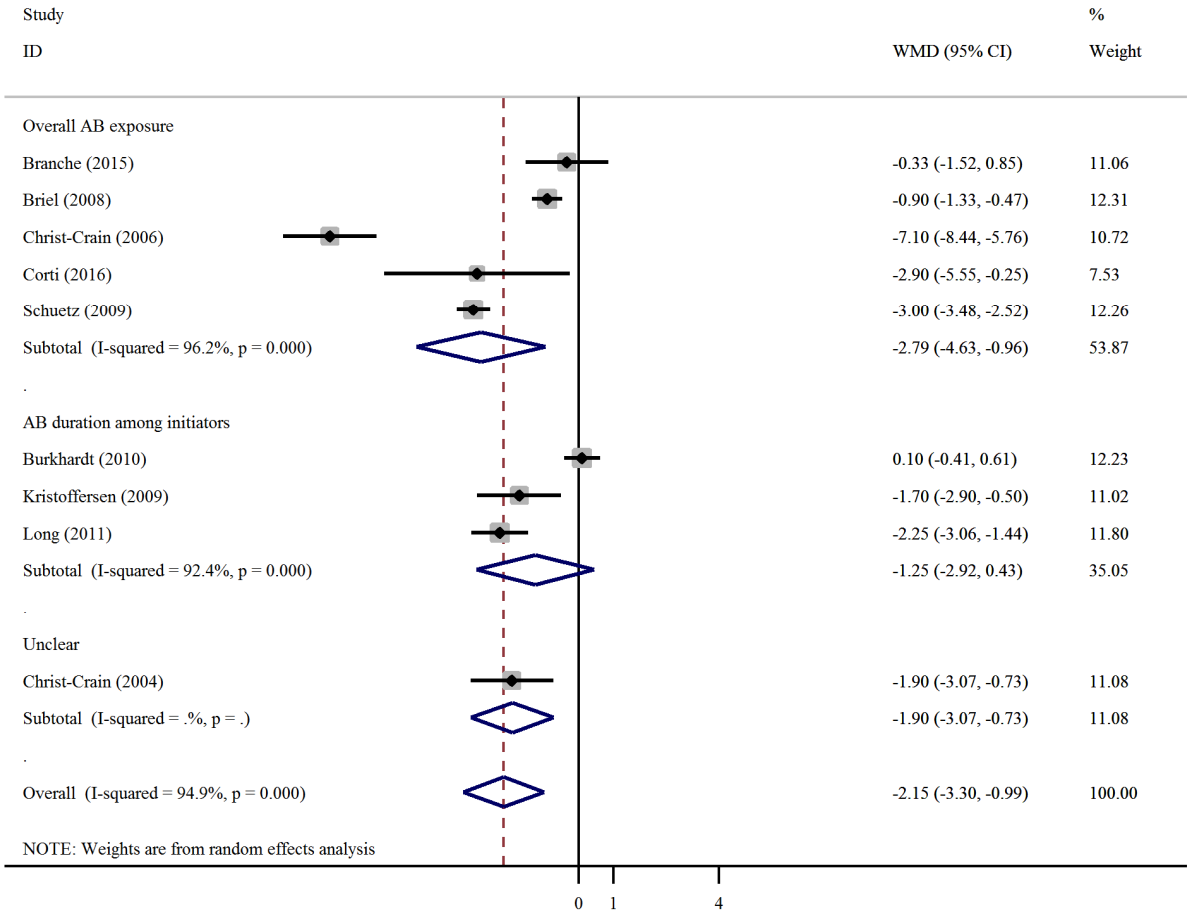
Appendix 6 - 5: Antibiotic initiation stratified by risk of bias (random effects model)



CI: confidence interval; OR: odds ratio

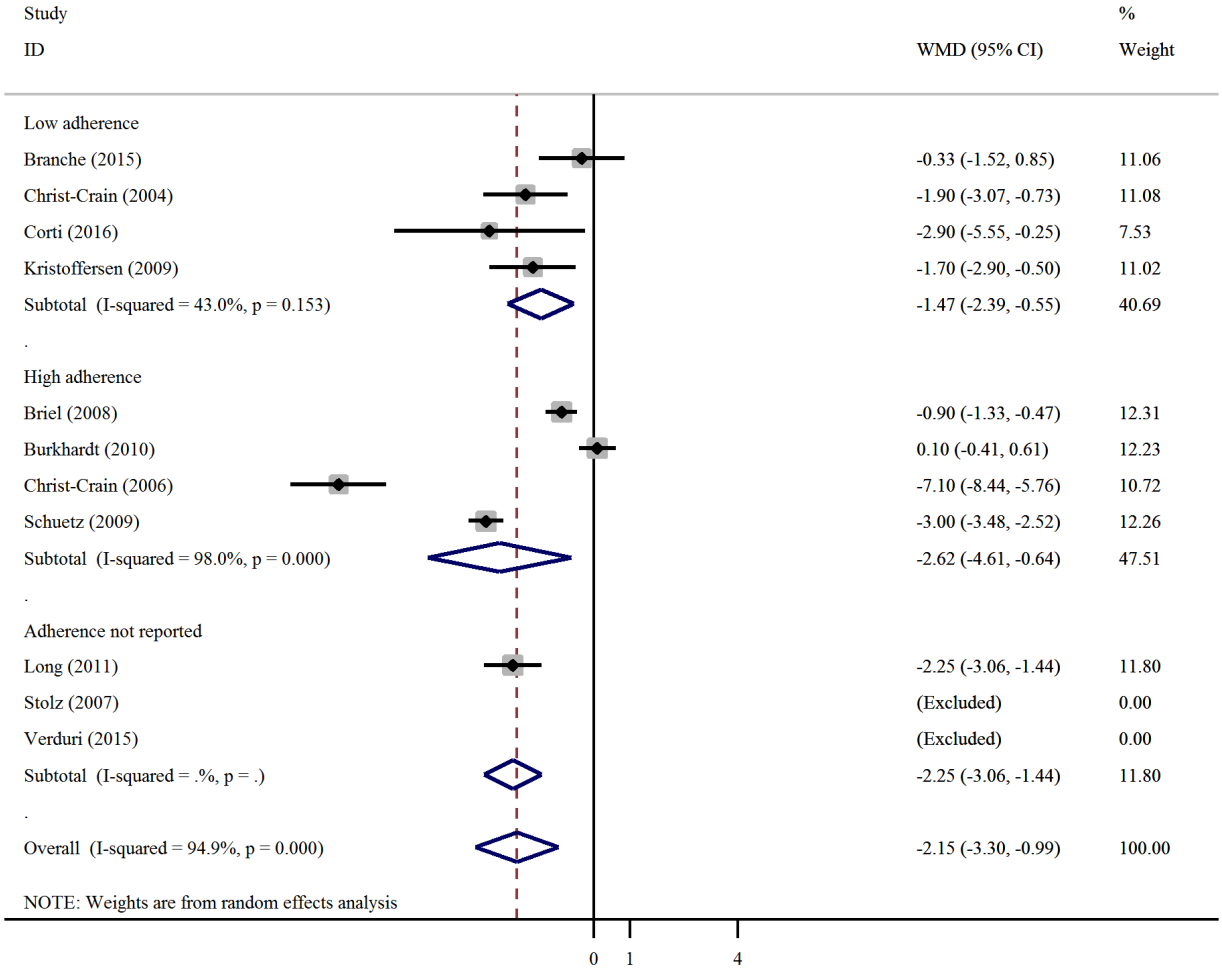
Duration of Antibiotics – LRTI

Appendix 6 - 6: Antibiotic duration stratified by the definition of antibiotic duration (random effects model)



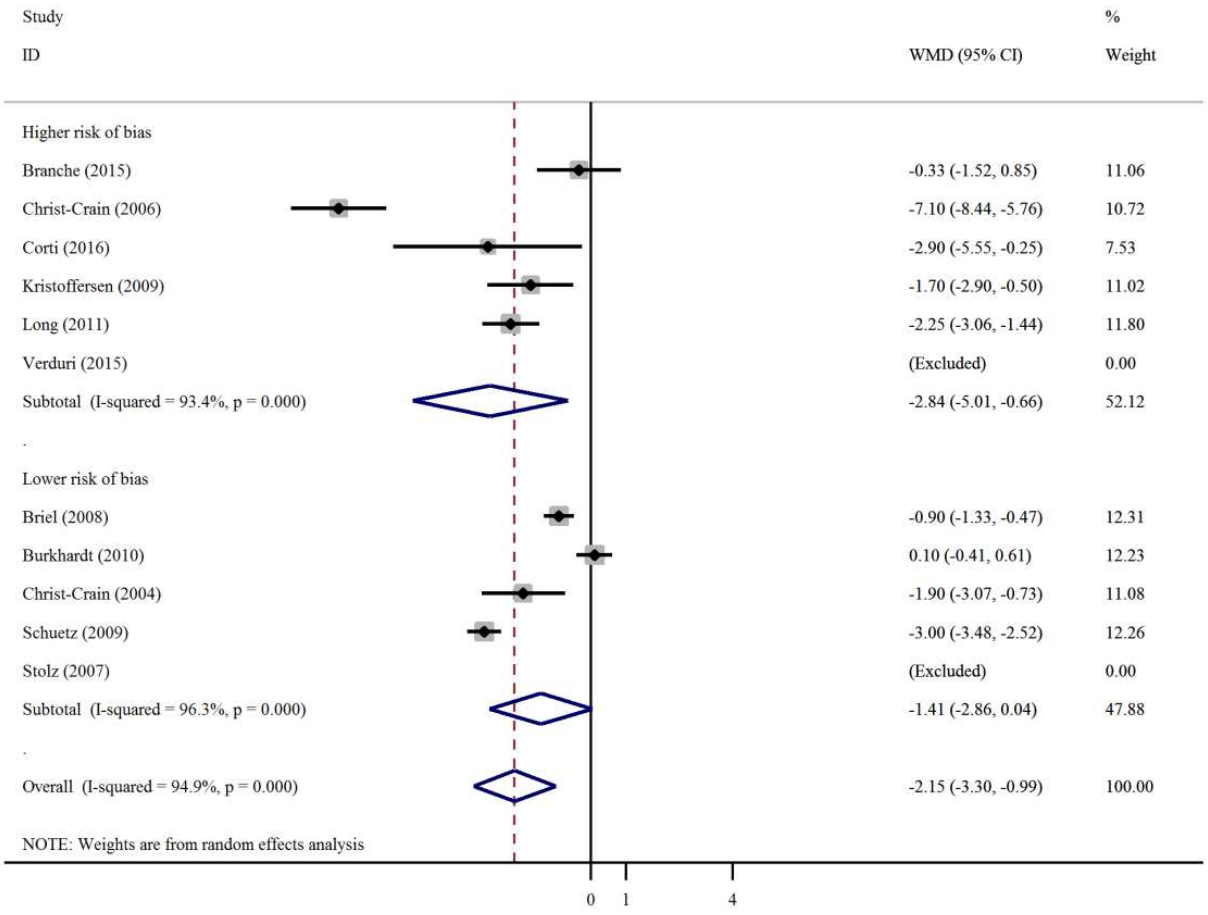
CI: confidence interval; WMD: weighted mean difference

Appendix 6 - 7: Antibiotic duration stratified by PCT adherence (random effects model)



CI: confidence interval; WMD: weighted mean difference

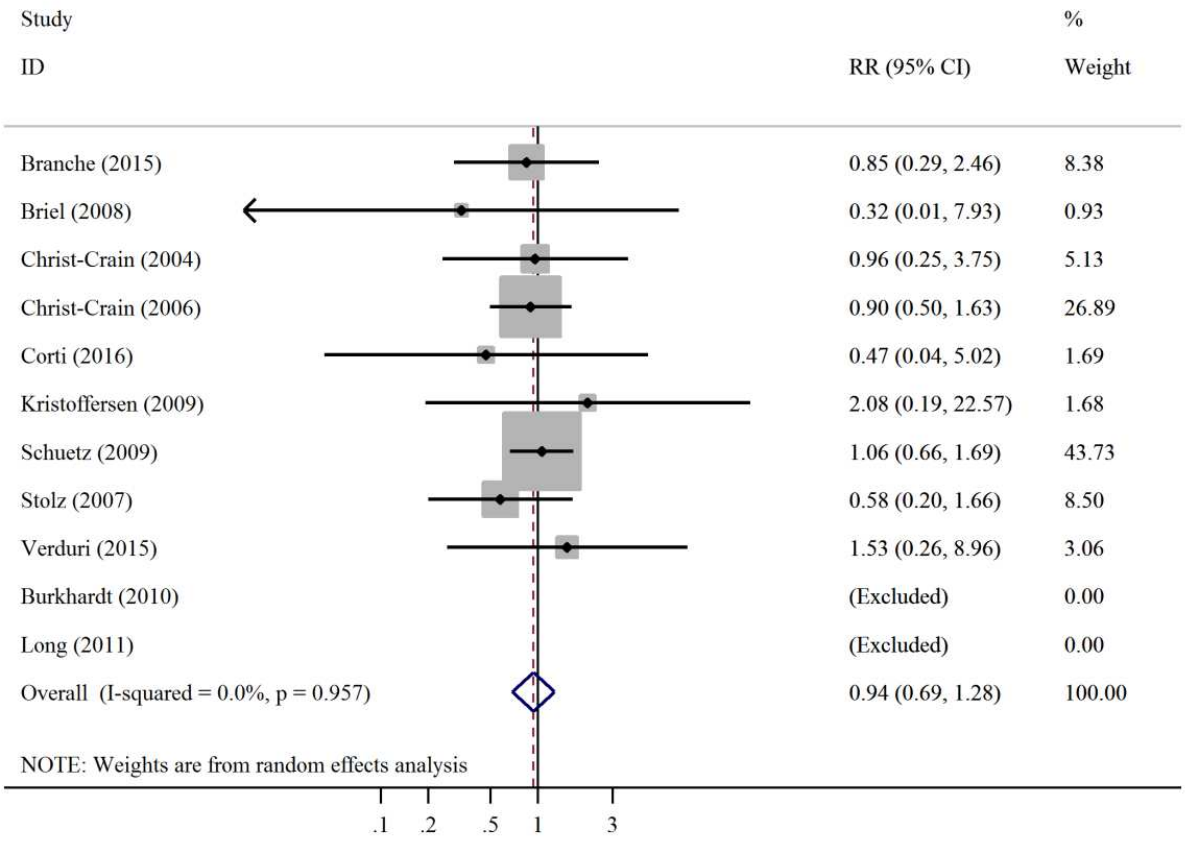
Appendix 6 - 8: Antibiotic duration stratified by risk of bias (random effects model)



CI: confidence interval; WMD: weighted mean difference

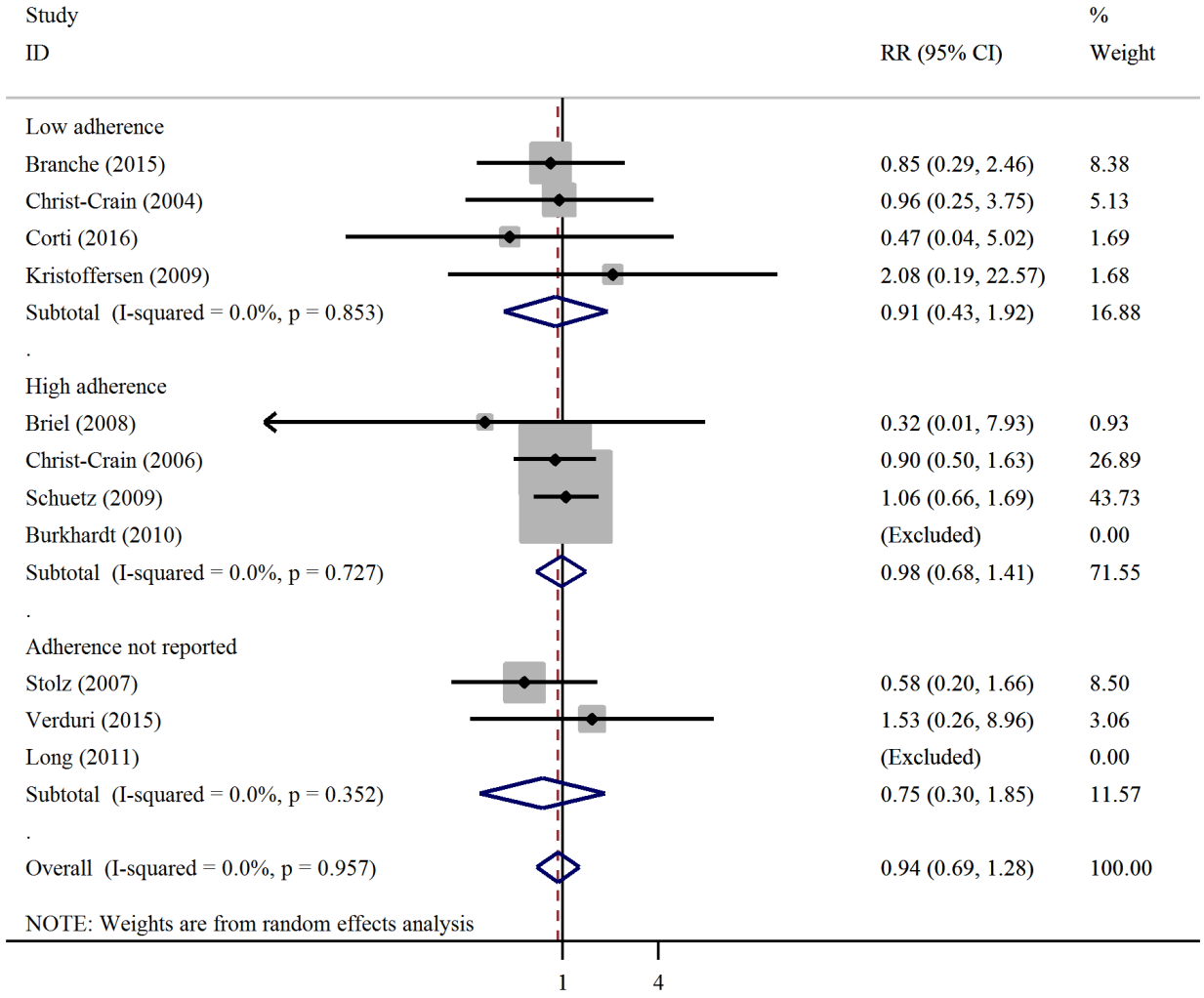
Mortality – LRTI

Appendix 6 - 9: Mortality (random effects model)



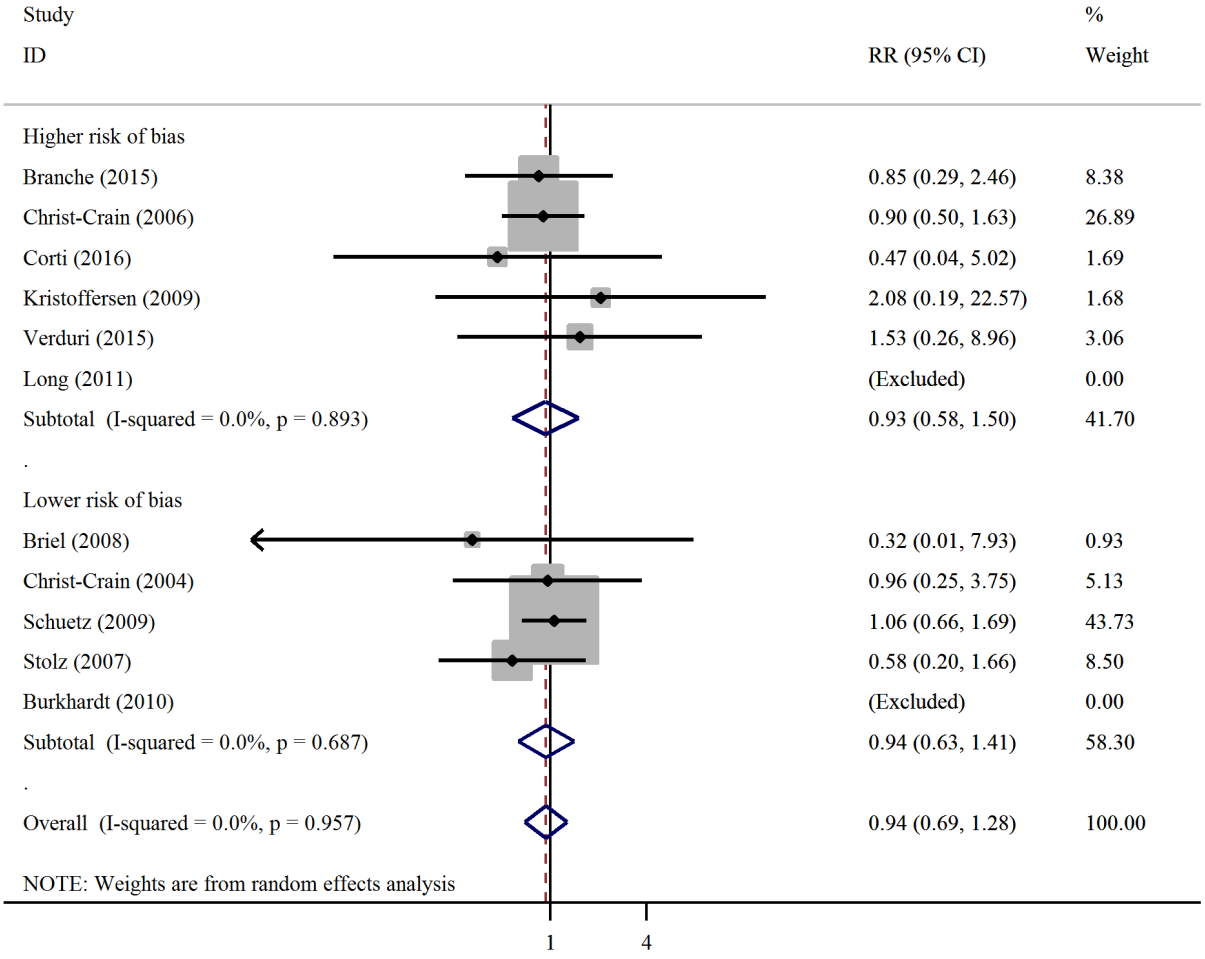
CI: confidence interval; RR: risk ratio

Appendix 6 - 10: Mortality stratified by PCT adherence (random effects model)



CI: confidence interval; RR: risk ratio

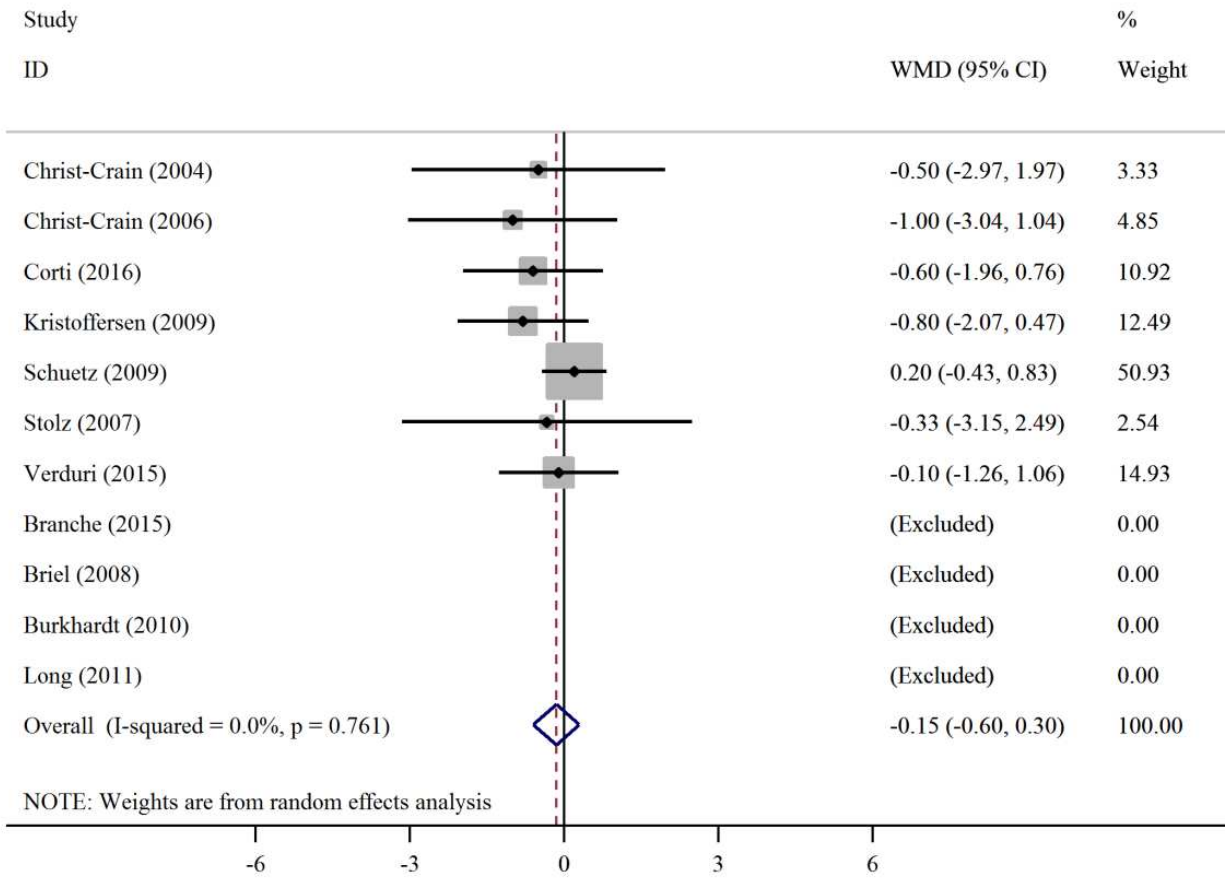
Appendix 6 - 11: Mortality stratified by risk of bias (random effects model)



CI: confidence interval; RR: risk ratio

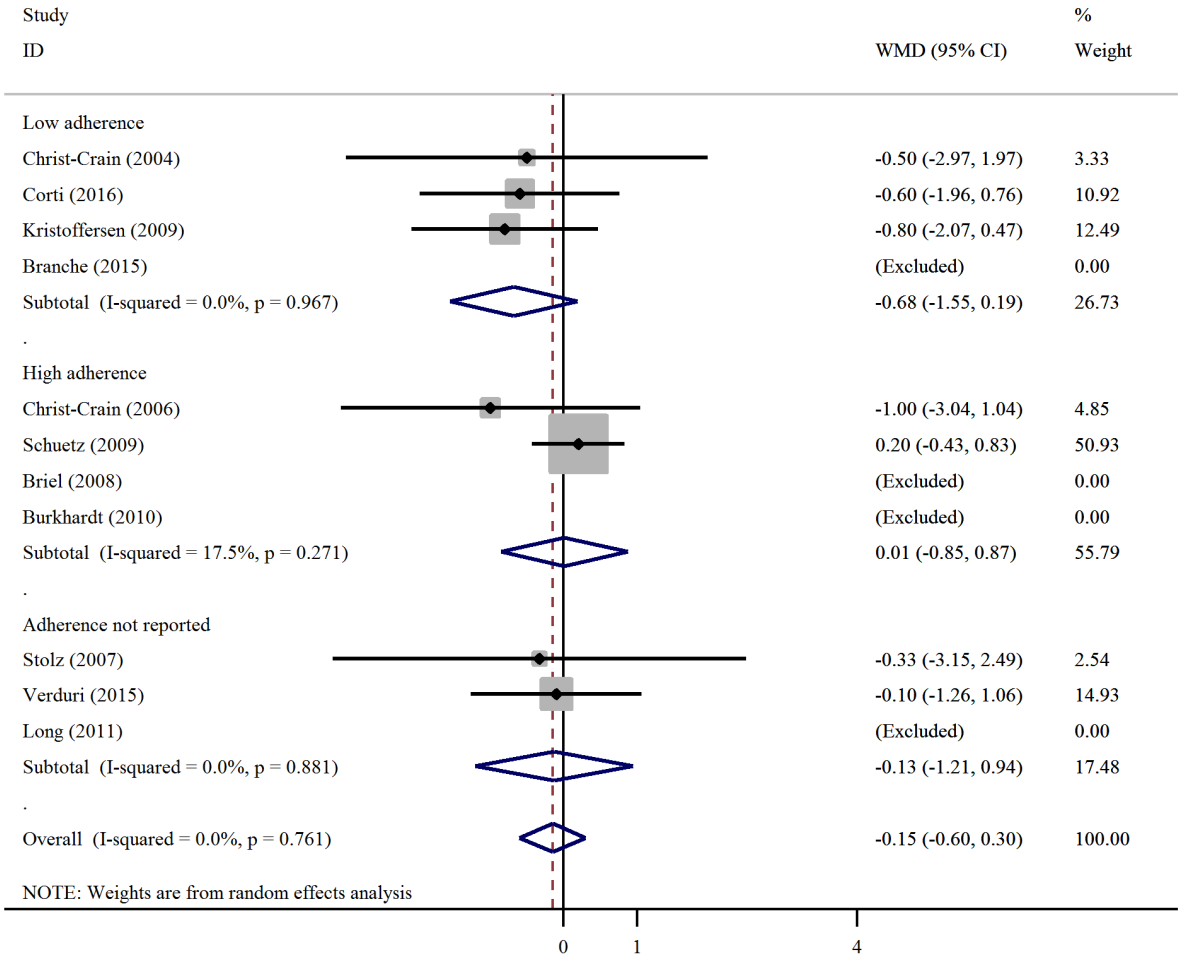
Length of Hospitalization – LRTI

Appendix 6 - 12: Length of hospital stay (random effects model)



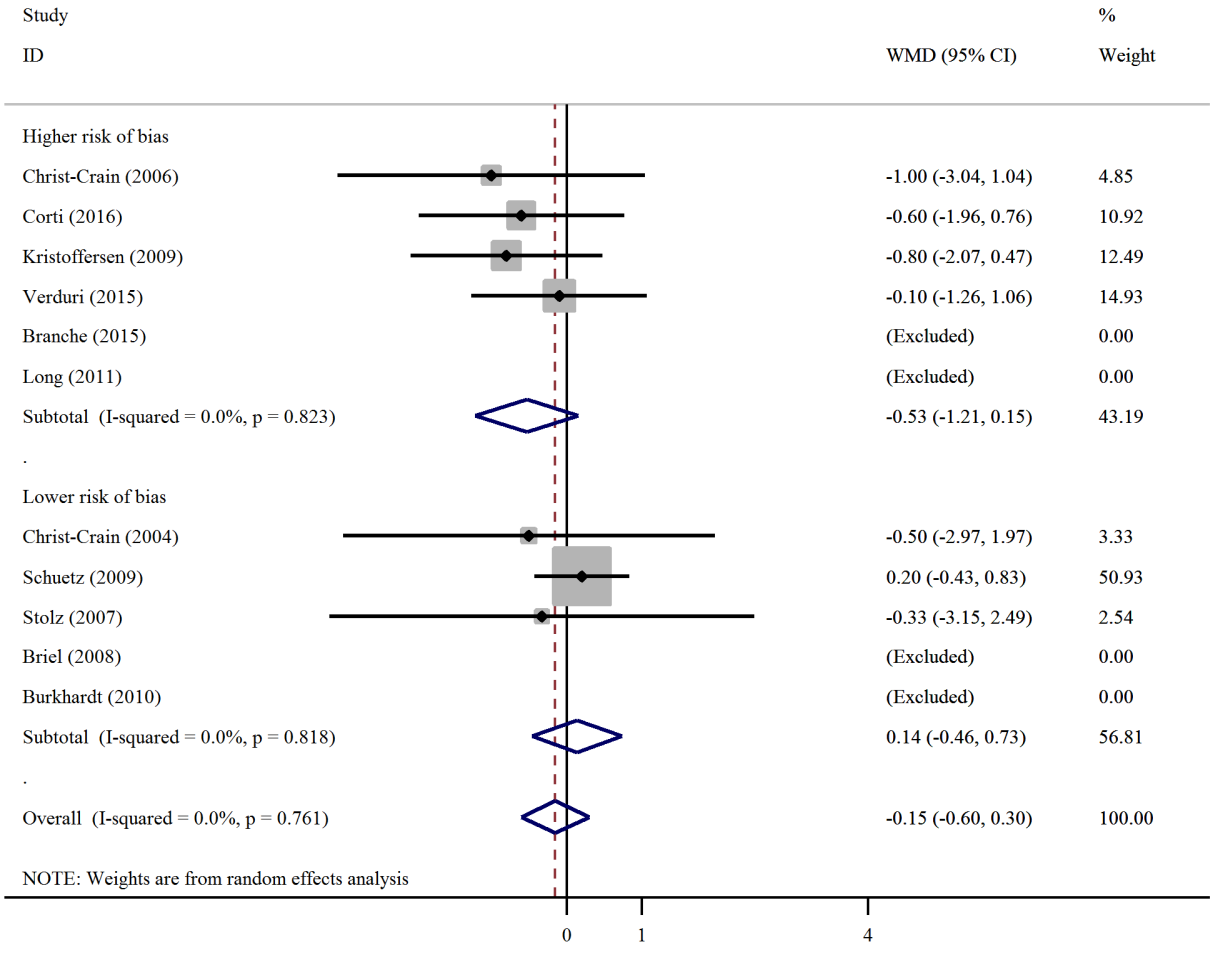
CI: confidence interval; WMD: weighted mean difference

Appendix 6 - 13: Length of hospital stay stratified by PCT adherence (random effects model)



CI: confidence interval; WMD: weighted mean difference

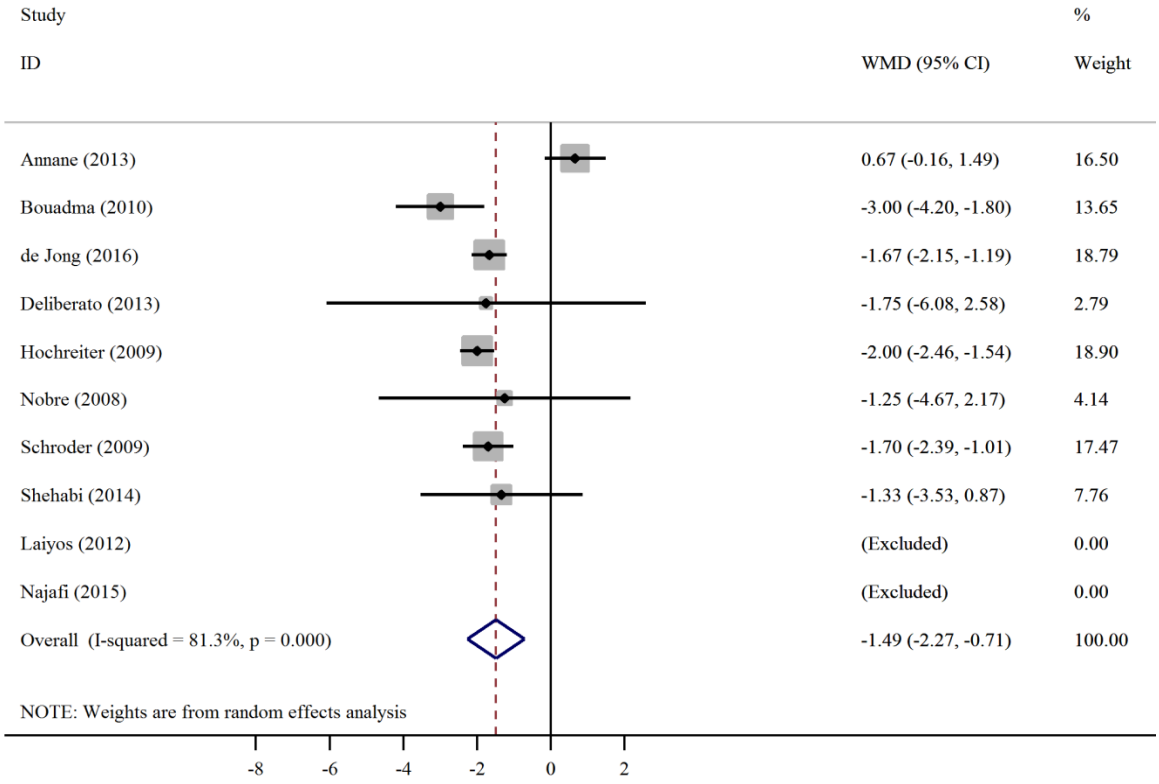
Appendix 6 - 14: Length of hospital stay stratified by risk of bias (random effects model)



CI: confidence interval; WMD: weighted mean difference

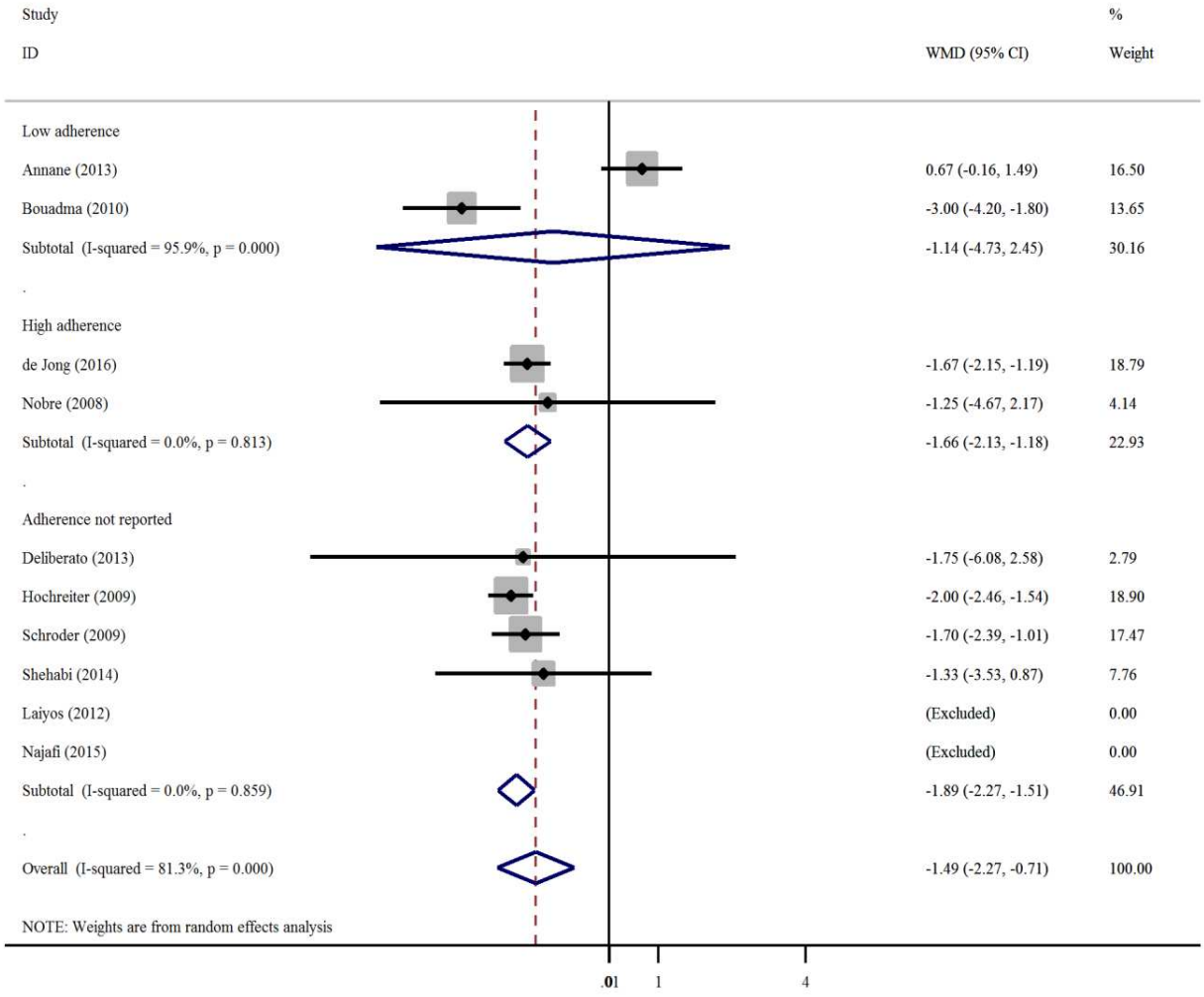
Duration of Antibiotics – Sepsis

Appendix 6 - 15: Length of antibiotic duration (random effects model)



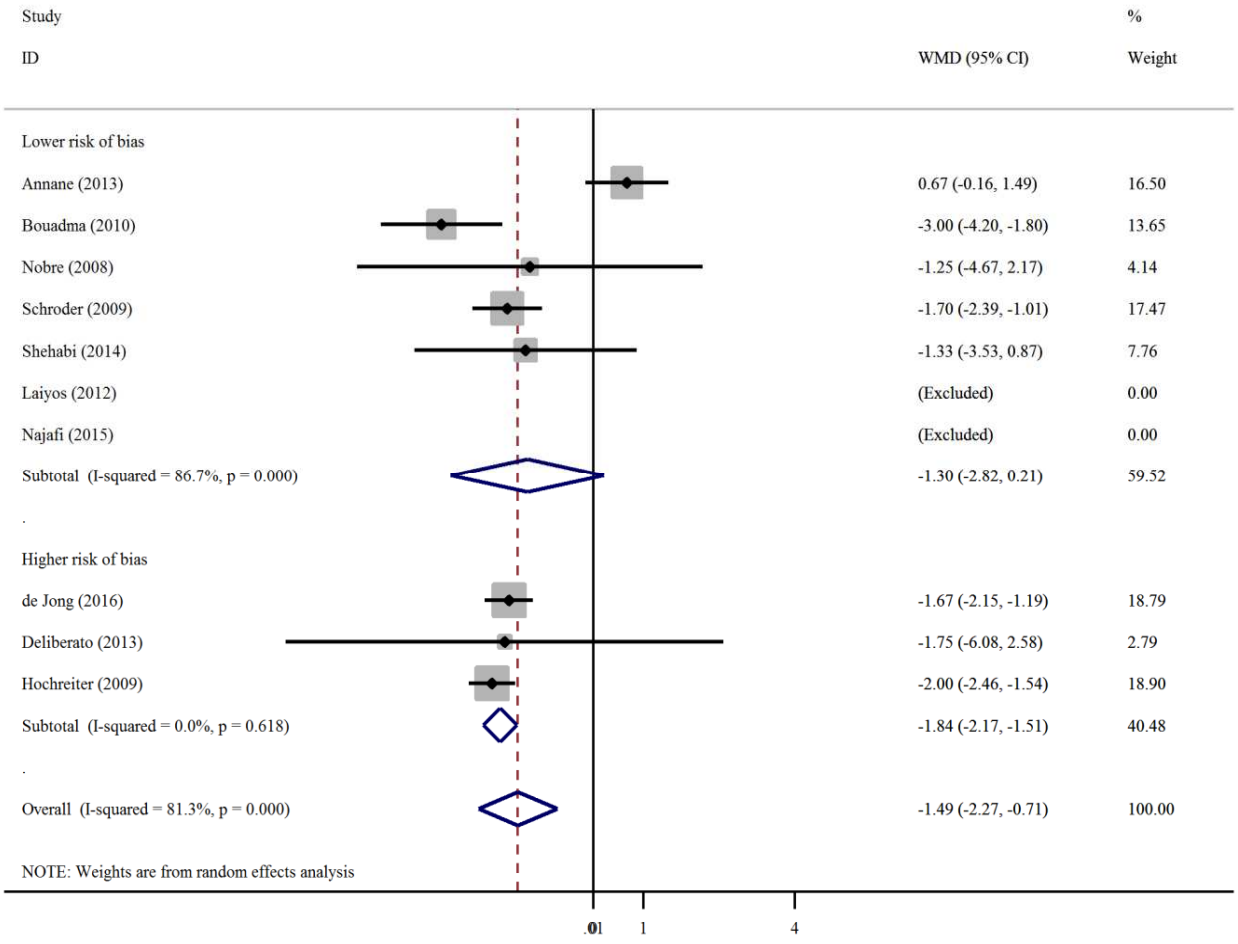
CI: confidence interval; WMD: weighted mean difference

Appendix 6 - 16: Antibiotic duration stratified by adherence (random effects model)



CI: confidence interval; WMD: weighted mean difference

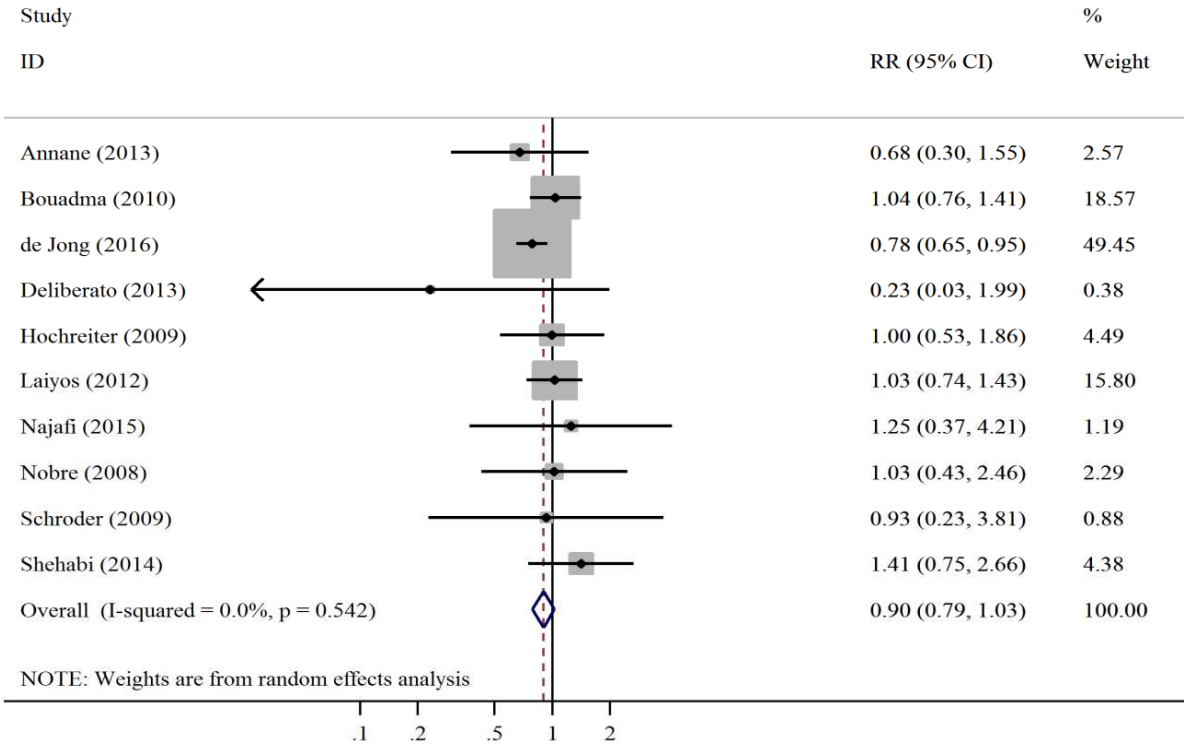
Appendix 6 - 17: Antibiotic duration stratified by risk of bias (random effects model)



CI: confidence interval; WMD: weighted mean difference

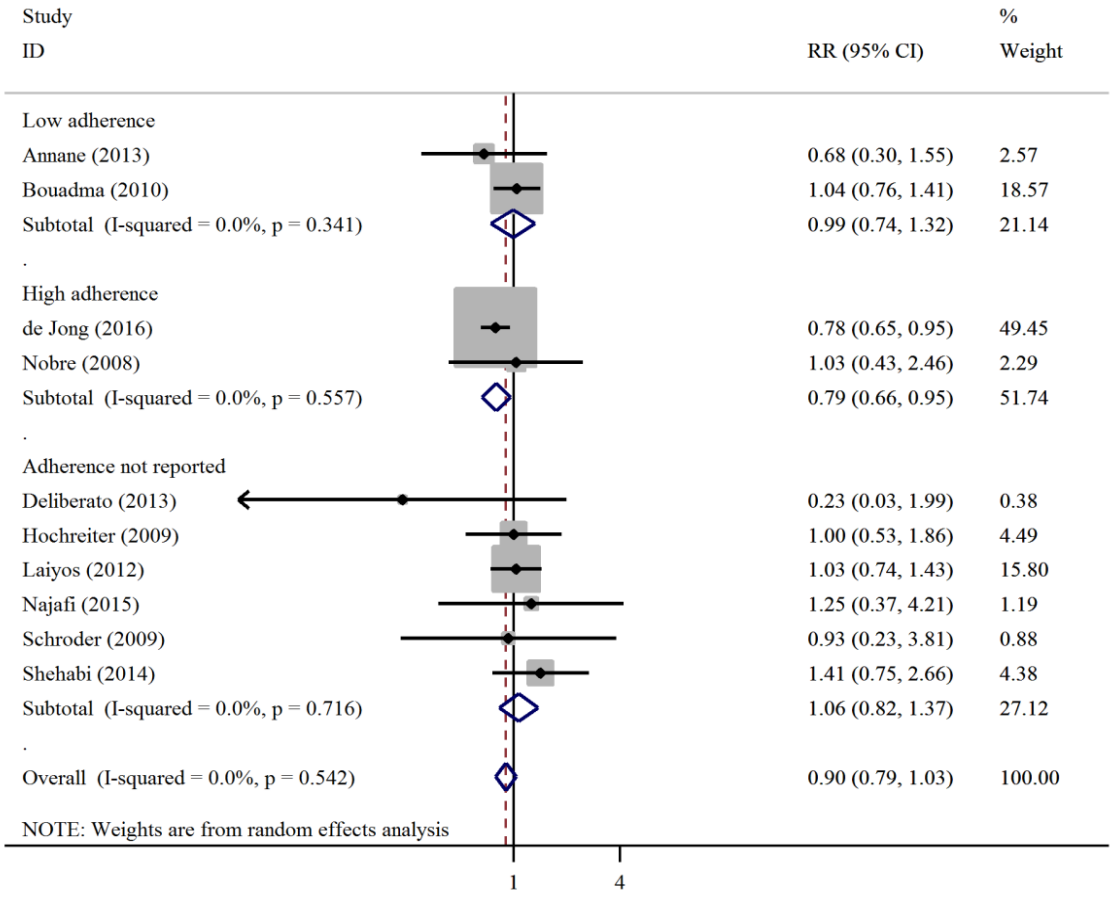
Mortality – Sepsis

Appendix 6 - 18: Risk of mortality (random effects model)



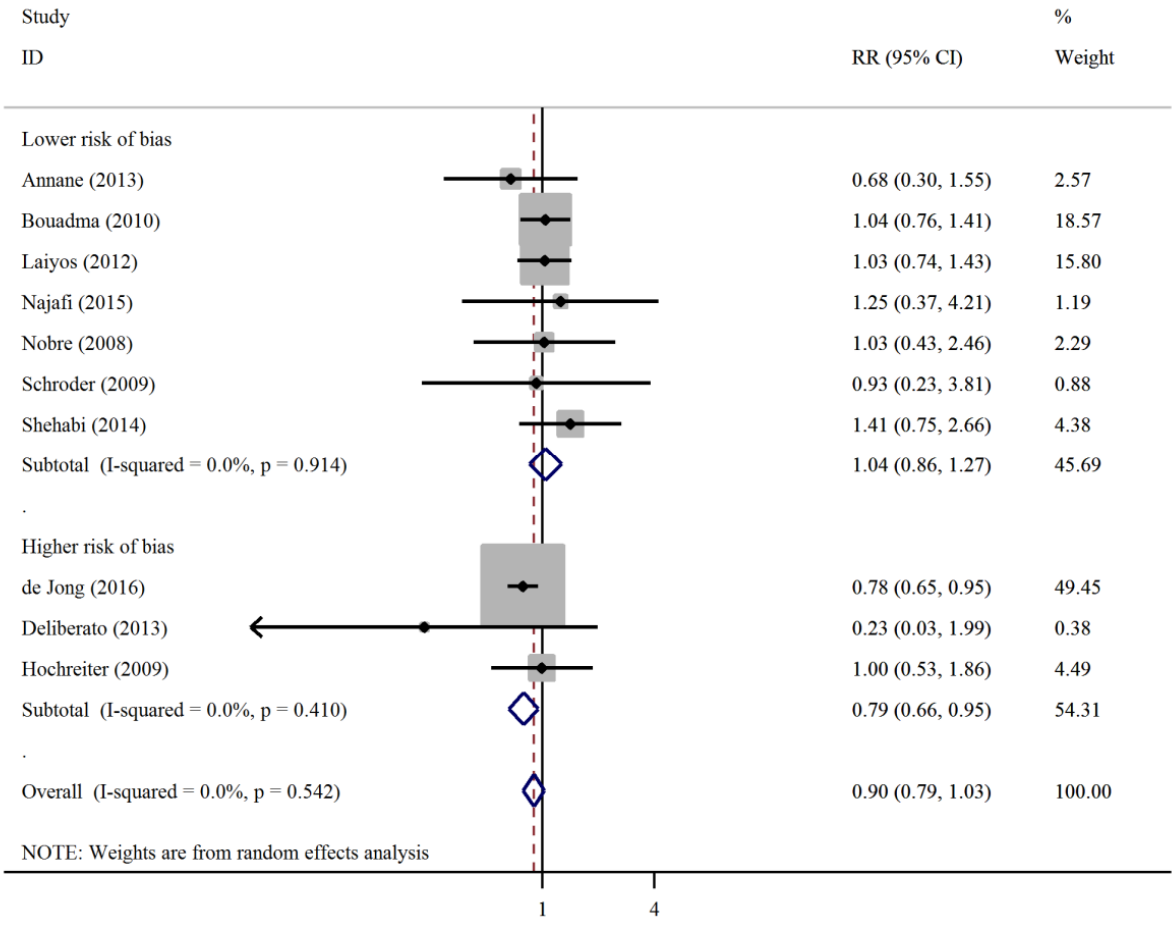
CI: confidence interval; RR: risk ratio

Appendix 6 - 19: Mortality stratified by adherence (random effects model)



CI: confidence interval; RR: risk ratio

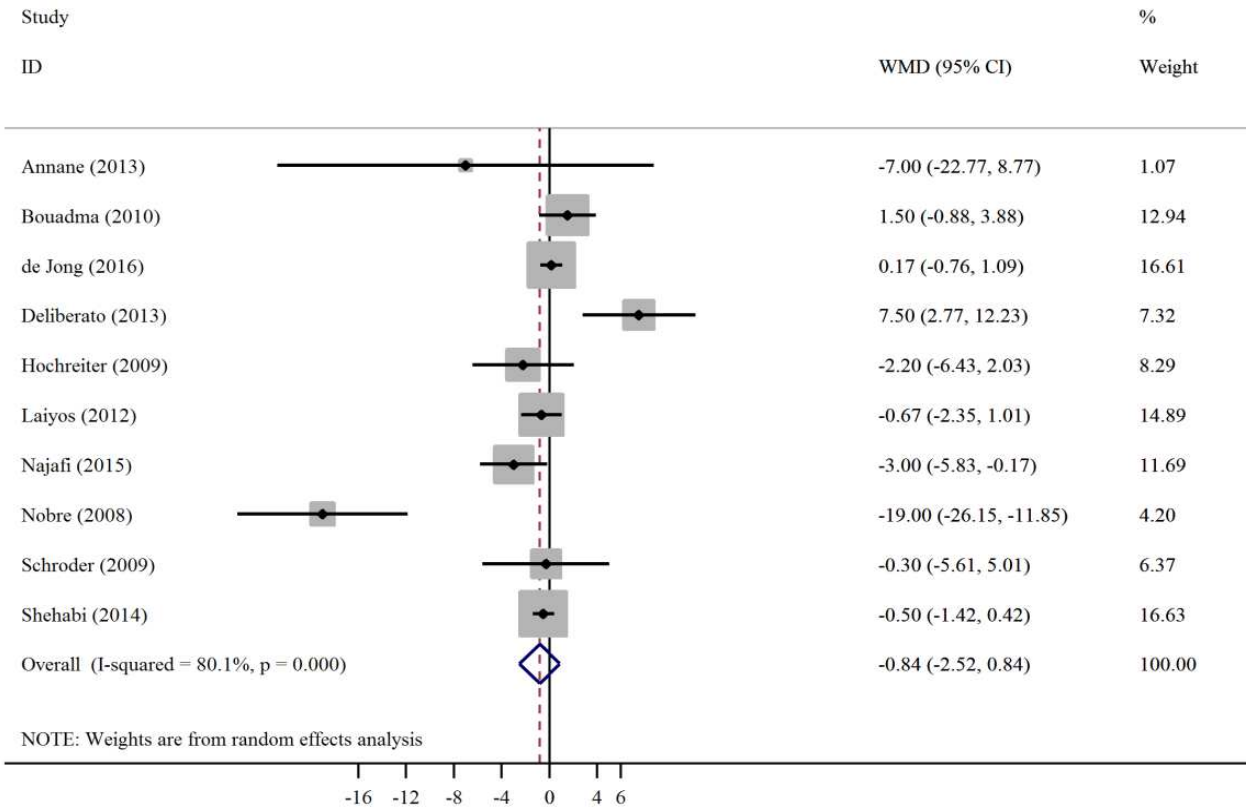
Appendix 6 - 20: Mortality stratified by risk of bias (random effects model)



CI: confidence interval; RR: risk ratio

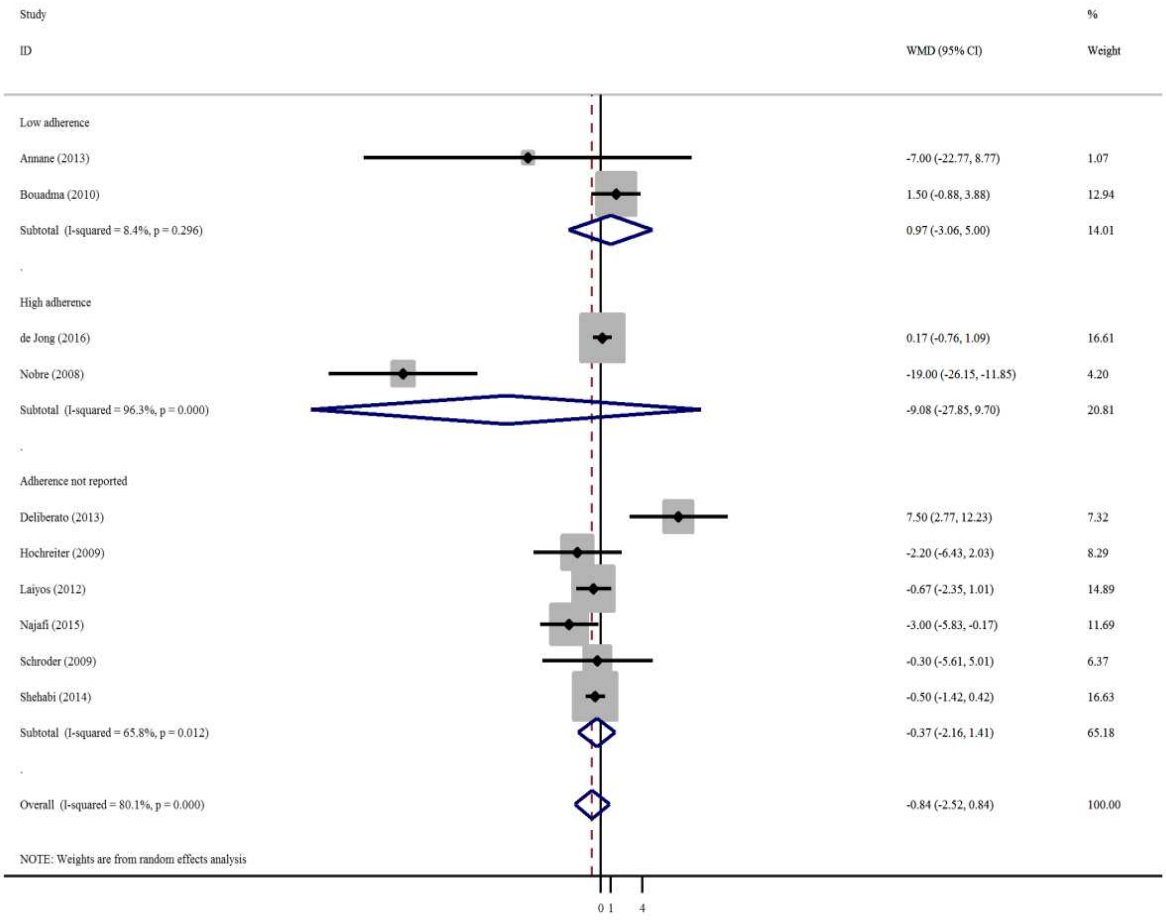
Length of ICU Stay – Sepsis

Appendix 6 - 21: Length of ICU stay (random effects model)



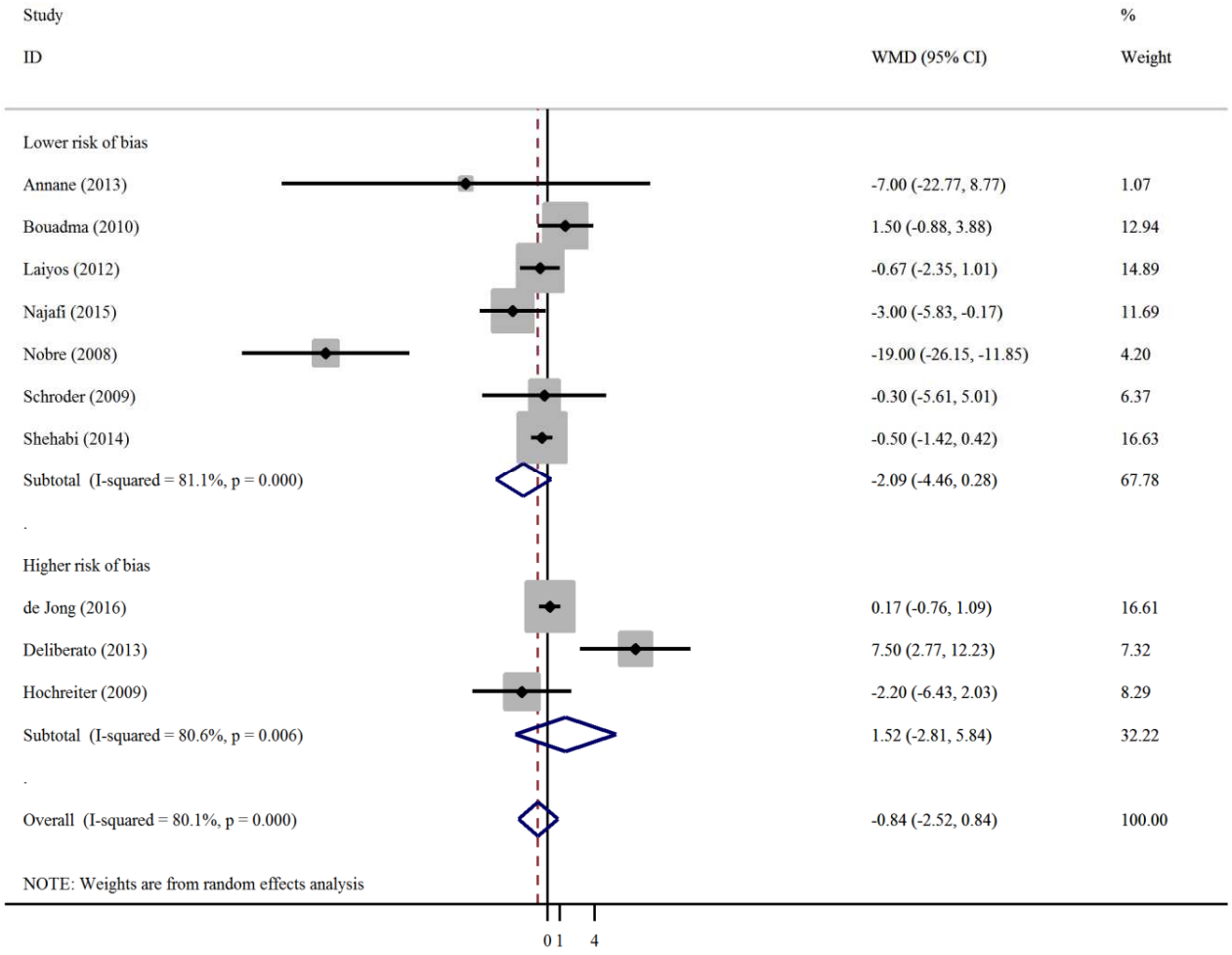
CI: confidence interval; WMD: weighted mean difference

Appendix 6 - 22: Length of ICU stay stratified by adherence (random effects model)



CI: confidence interval; WMD: weighted mean difference

Appendix 6 - 23: Length of ICU stay stratified by risk of bias (random effects model)



CI: confidence interval; WMD: weighted mean difference