VIDAS® B•R•A•H•M•S PCT™ for Procalcitonin (PCT) Guided Antibiotic Therapy

November 10, 2016

bioMérieux

Meeting of the Microbiology Devices Panel

Urgent Need for Biomarkers for Appropriate Antibiotic Use and Reducing Antibiotic Resistance

Mark Miller, MD

Chief Medical Officer

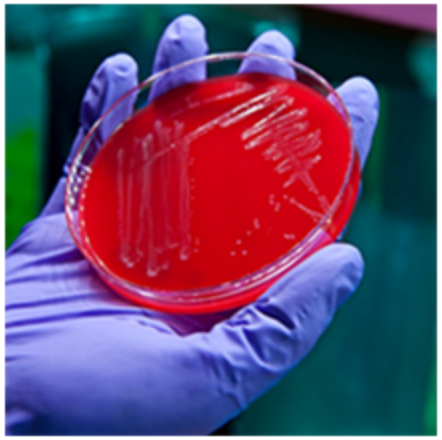
bioMérieux

Serious and Growing Threat to U.S. and Global Public Health

- Antibiotic overuse, inappropriate initiation and prolonged use
- Safety risk to patients and contributed to rise of antibiotic resistance
- 2 million illnesses and ~23,000 deaths per year in U.S.[1]

1. Centers for Disease Control and Prevention (CDC)

Diagnosing Bacterial Infection that Requires Antibiotics is Difficult



- Bacterial cultures can take 2-3 days to perform
- Often provide false positive or false negative results

- Faster, more accurate indicators of infection needed to make critical antibiotic decisions
- Diagnostic tests can support antimicrobial stewardship

Photo by Centers for Disease Control and Prevention

50% of the 69 Million Antibiotic Prescriptions for Acute Respiratory Conditions are Unnecessary

34.3 Million
Antibiotic prescriptions unnecessary

34.6 Million
Antibiotic prescriptions appropriate

Fleming-Dutra et al. *JAMA* 2016; 315:1864-13

When Used Inappropriately, Antibiotics Carry Risks without Benefit

- Side effects and toxicity[1]
  - Allergic reactions, diarrhea, other GI issues
- Collateral damage[2]
  - Such as *Clostridium difficile* infections
- Antibiotic resistance[3]
- Spread of drug-resistant pathogens[4]

1. NHS. *Antibiotics – side effects*
2. Lessa et al. *NEJM* 2015;372:825-34
3. Laxminarayan et al. *Lancet Infect Dis* 2013;13:1057-98
4. WHO Fact Sheet: www.who.int/mediacentre/factsheets/fs194/en/

Increasing Number of Drug-Resistant Infections

- More serious illness and disability
- Higher death rate
- Need for more complex therapeutic options
- Extended hospitalizations

https://www.cdc.gov/drugresistance/about.html; http://www.who.int/mediacentre/factsheets/fs194/en/

PCT Assay to Help Guide Appropriate Antibiotic Use in LRTI and Sepsis

- Lower respiratory tract infection
  - Whether to ***start*** antibiotics
  - When to ***stop*** antibiotics
- Sepsis
  - When to ***stop*** antibiotics

LRTI: Whether to Start Antibiotics Difficult to Determine

- 78-year-old male in ER
  - Fever, cough, chest pain
- Examination: Fever, abnormal chest sounds, elevated white blood cell count, abnormal chest X-ray
- Diagnosis: Community acquired pneumonia?
  - Not definitively bacterial or viral

Physicians will often prescribe antibiotics "just in case"

Sepsis: When to Discontinue Antibiotics Difficult to Determine

- 50-year-old female in ICU
  - Shock of undetermined origin
- Examination: Fever, multiple lung abnormalities on X-ray and CT scan of chest
- Diagnosis: Sepsis from pneumonia?
  - Started on antibiotics, ventilation

Unclear when/if she stops benefitting from continued antibiotic treatment

Current Use: VIDAS B•R•A•H•M•S PCT Assay

Two current FDA-cleared uses

1. To aid in risk assessment for sepsis and septic shock on first day of ICU admission
2. To aid in assessing the cumulative 28-day risk of all-cause mortality for patients with severe sepsis or septic shock in the ICU using change of PCT levels over time

Two New Proposed Indications: VIDAS B•R•A•H•M•S PCT Assay

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 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.*

Existing Evidence from Randomized Controlled Trials Supports Indications for Use

- Nearly two dozen RCTs have evaluated safety and effectiveness of PCT guidance for antibiotic therapy for LRTI and sepsis
- Plan for systematic reviews and meta-analyses discussed through interactive discussions with FDA
- Goal: Determine whether antibiotic use could be safely reduced

Presentation Overview

- Biology of PCT and role as a host-response biomarker stimulated by bacterial infection
- Results of meta-analyses: PCT-guided treatment decisions can reduce antibiotic use without compromising safety
- VIDAS B•R•A•H•M•S PCT can improve the appropriate use of antibiotics with no added risk

Agenda

Diagnostic Utility of PCT	**Sam Bozzette, MD, PhD** Vice President, Medical Affairs – Americas bioMérieux
Meta-Analysis Methodology	**Noam Kirson, PhD** Vice President Analysis Group, Inc.
Meta-Analysis Results	**Philipp Schuetz, MD, MPH** Chief Physician of Endocrinology and Internal Medicine University of Basel
Benefit-Risk Profile	**Mark Miller, MD** Chief Medical Officer bioMérieux

Diagnostic Utility of Procalcitonin

Sam Bozzette, MD, PhD

Vice President, Medical Affairs – Americas

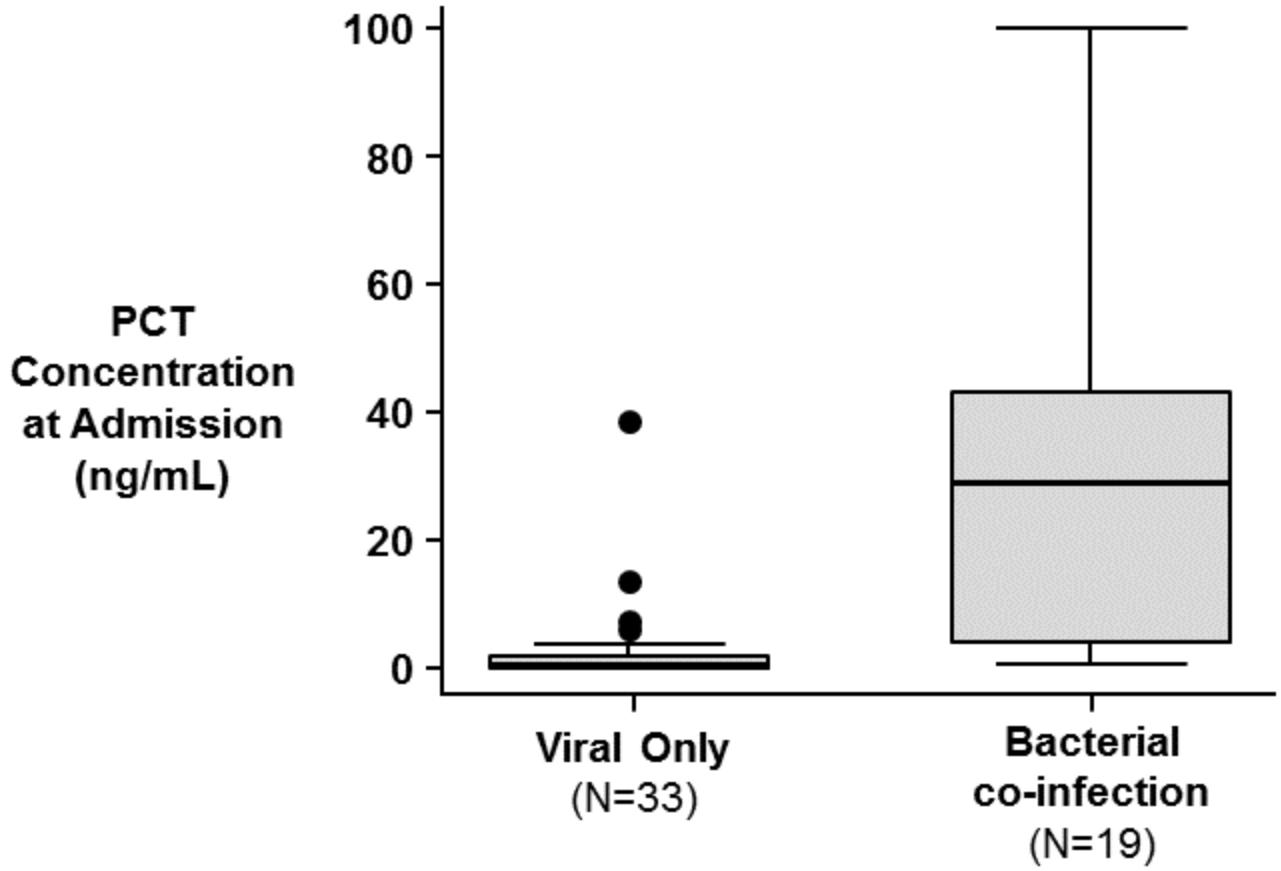
bioMérieux

PCT is a Host-Response Biomarker Stimulated by Bacterial Infection

- PCT is a precursor of calcitonin
- C cells of thyroid produce PCT, convert to calcitonin
- PCT also produced by neuroendocrine cells
  - Normal serum concentrations <0.05 ng/mL
- Bacterial infection stimulates PCT production[1-3]
  - Concentrations typically >0.25 ng/mL
  - Can rise 1000-fold in septic shock

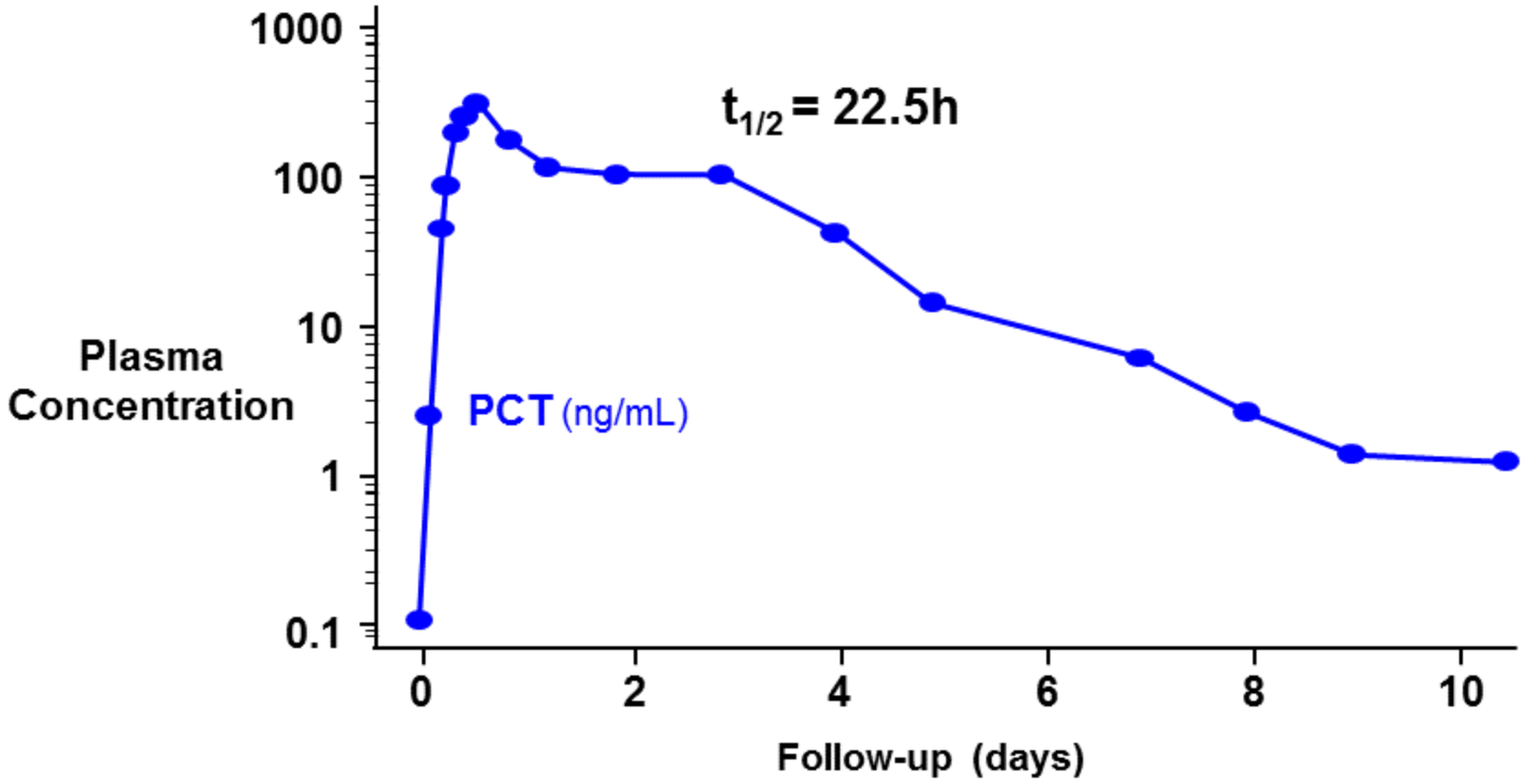
1. Linscheid P et al. *Crit Care Med* 2004;32:1715-21
2. Linscheid P et al. *Endocrinology* 2003;144:5578-84
3. Linscheid P et al. *Endocrinology* 2005;146:2699-708

PCT Levels Significantly Higher in Patients with Bacterial Co-Infection



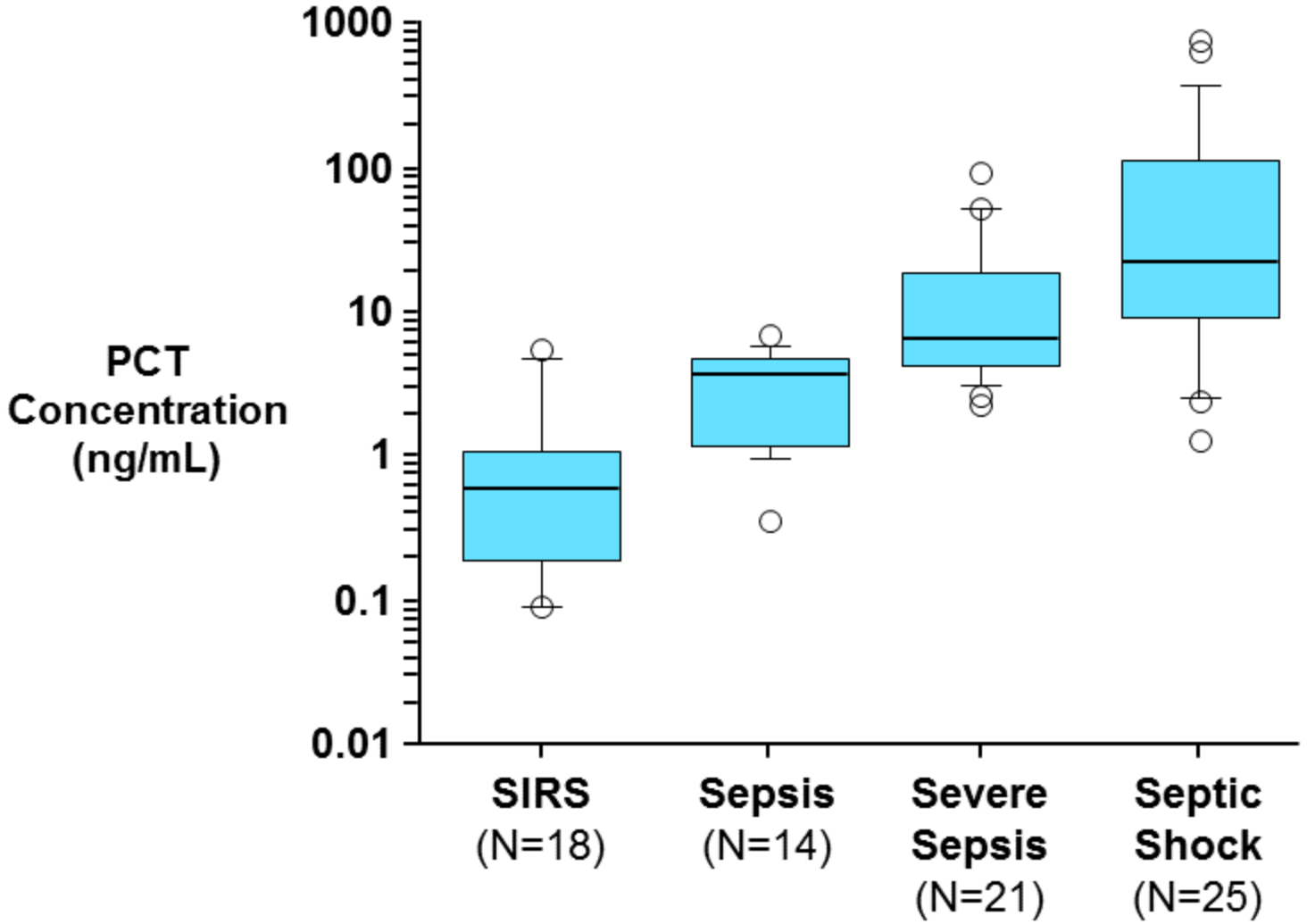
Cuquemelle et al. *Intensive Care Med* 2011;37:796

PCT Properties Favorable for Antibiotic Decision Making



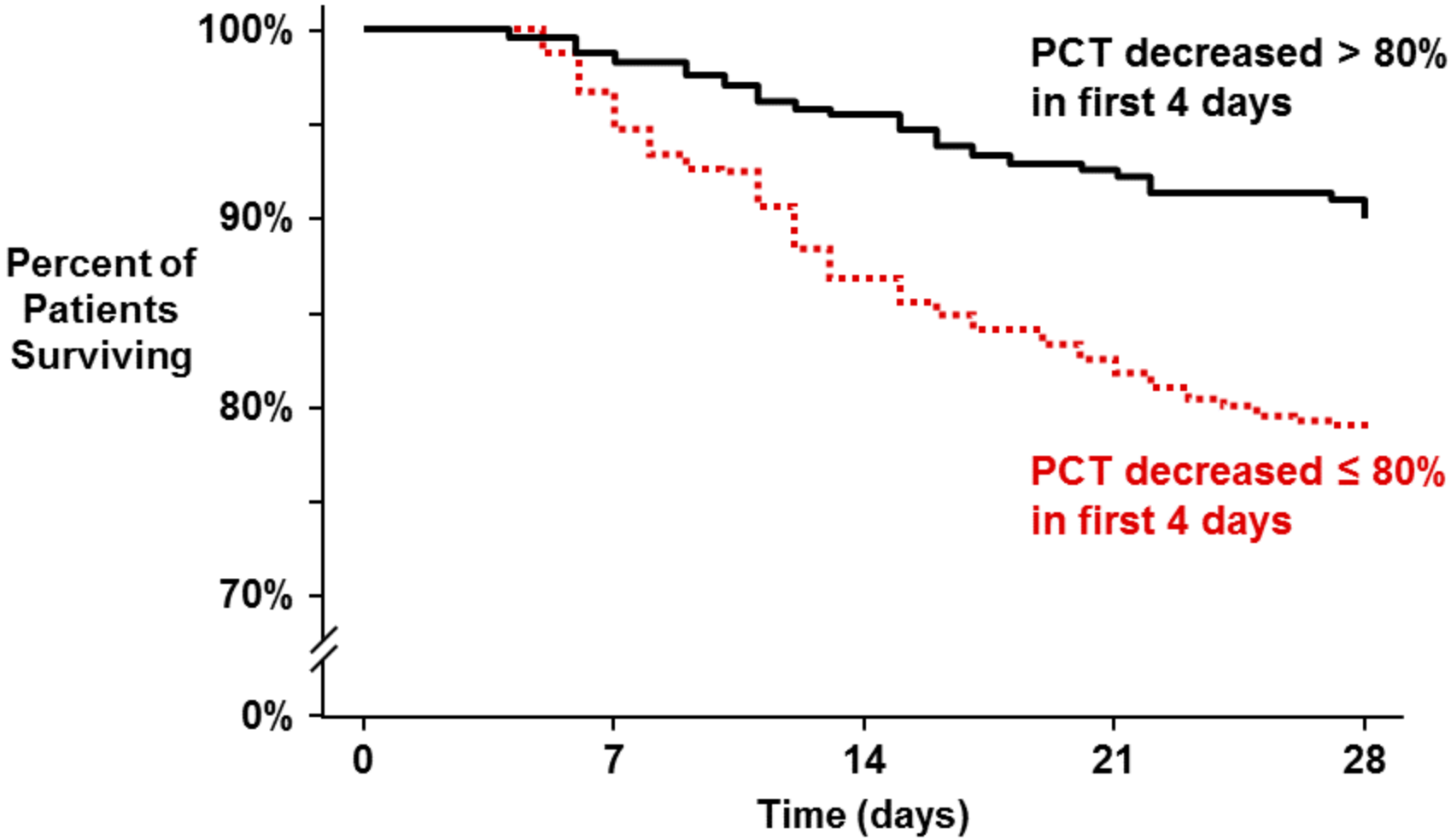
Brunkhorst et al. *Intensive Care Med* 1998;24:888-9

PCT Levels Correlate with Disease Severity



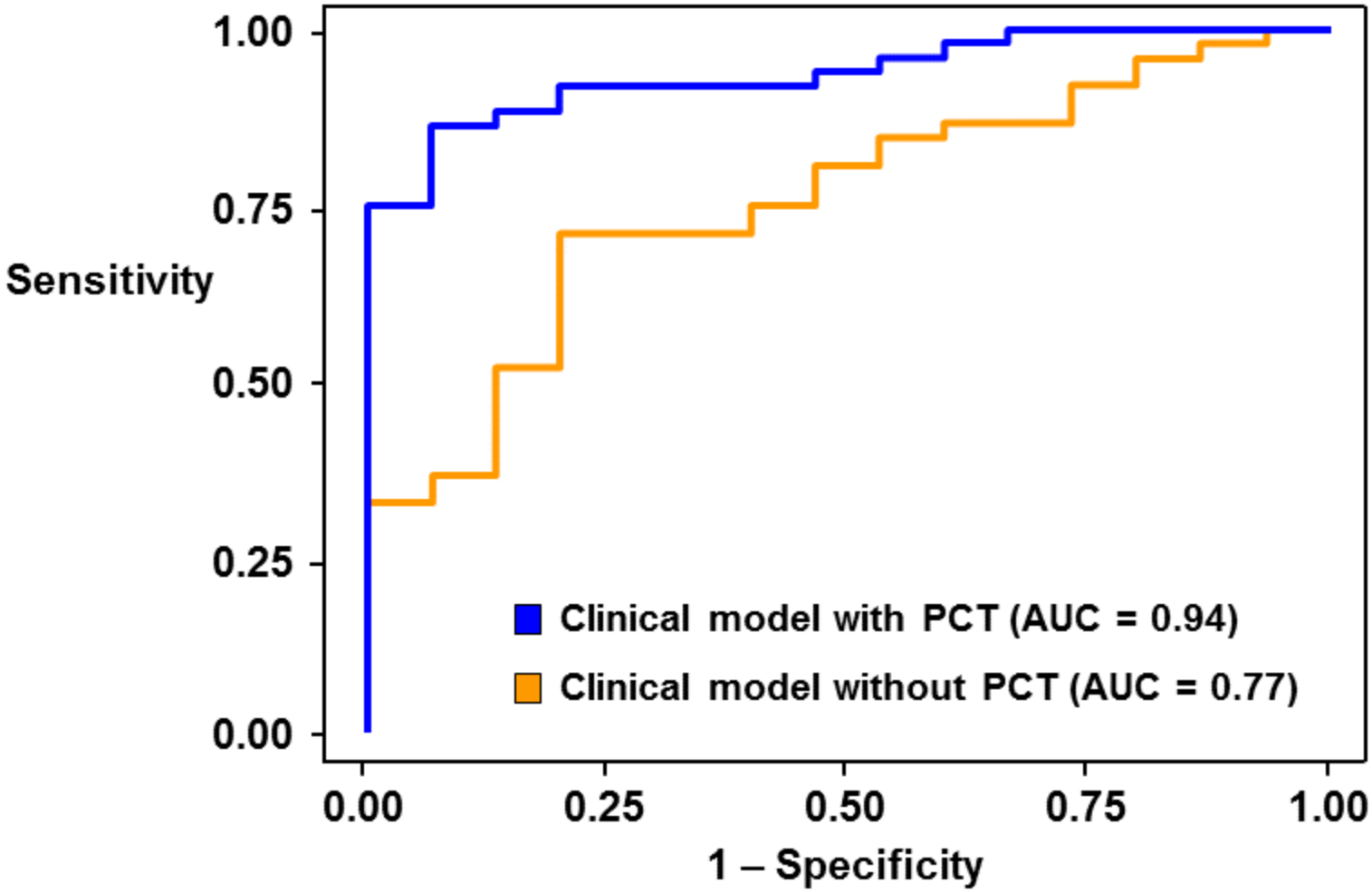
Harbath et al. *Am J Respir Crit Care Med* 2001;164:396-402

Changes in PCT Levels Have Prognostic Significance in Sepsis Patients



VIDAS B•R•A•H•M•S PCT Package Insert

PCT with Clinical Judgment Superior to Clinical Judgment Alone in Sepsis



Harbath et al. *Am J Respir Crit Care Med* 2001;164:396-402.

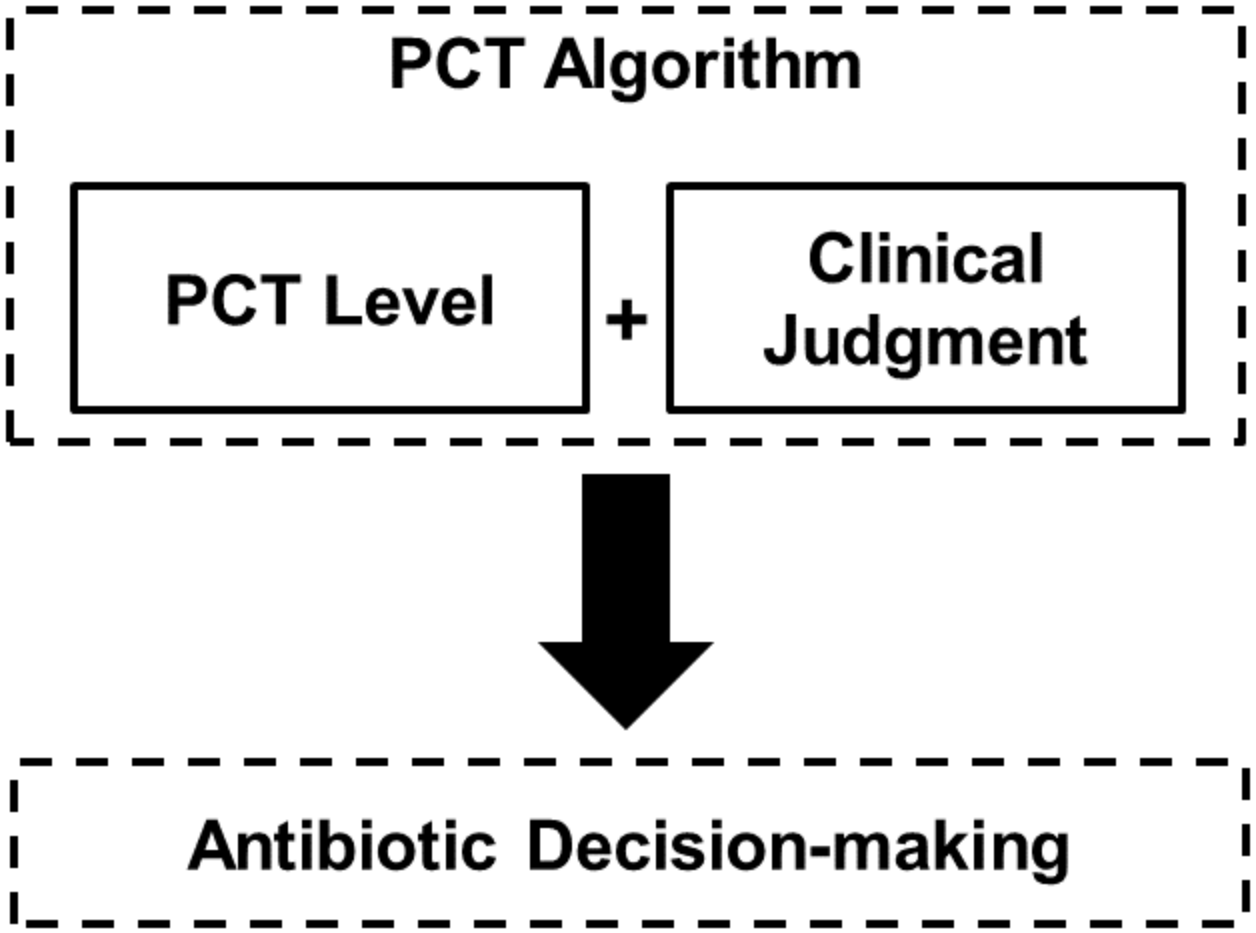
PCT Levels Have a High Negative Predictive Value in LRTI

- NPV = probability condition is absent given negative test

	Endpoint (Prevalence)	Sensitivity	Specificity	PPV	NPV
Rodriguez[1]	Confirmed bacterial co-infection (20%)	90%	31%	25%	92%
Stolz[2]	Need for antibiotics (24%)	84%	98%	93%	94%

1. Rodriguez et al. *J Infect* 2016;72:143-51
2. Stolz et al. *Swiss Med Wkly* 2006;136:434-40

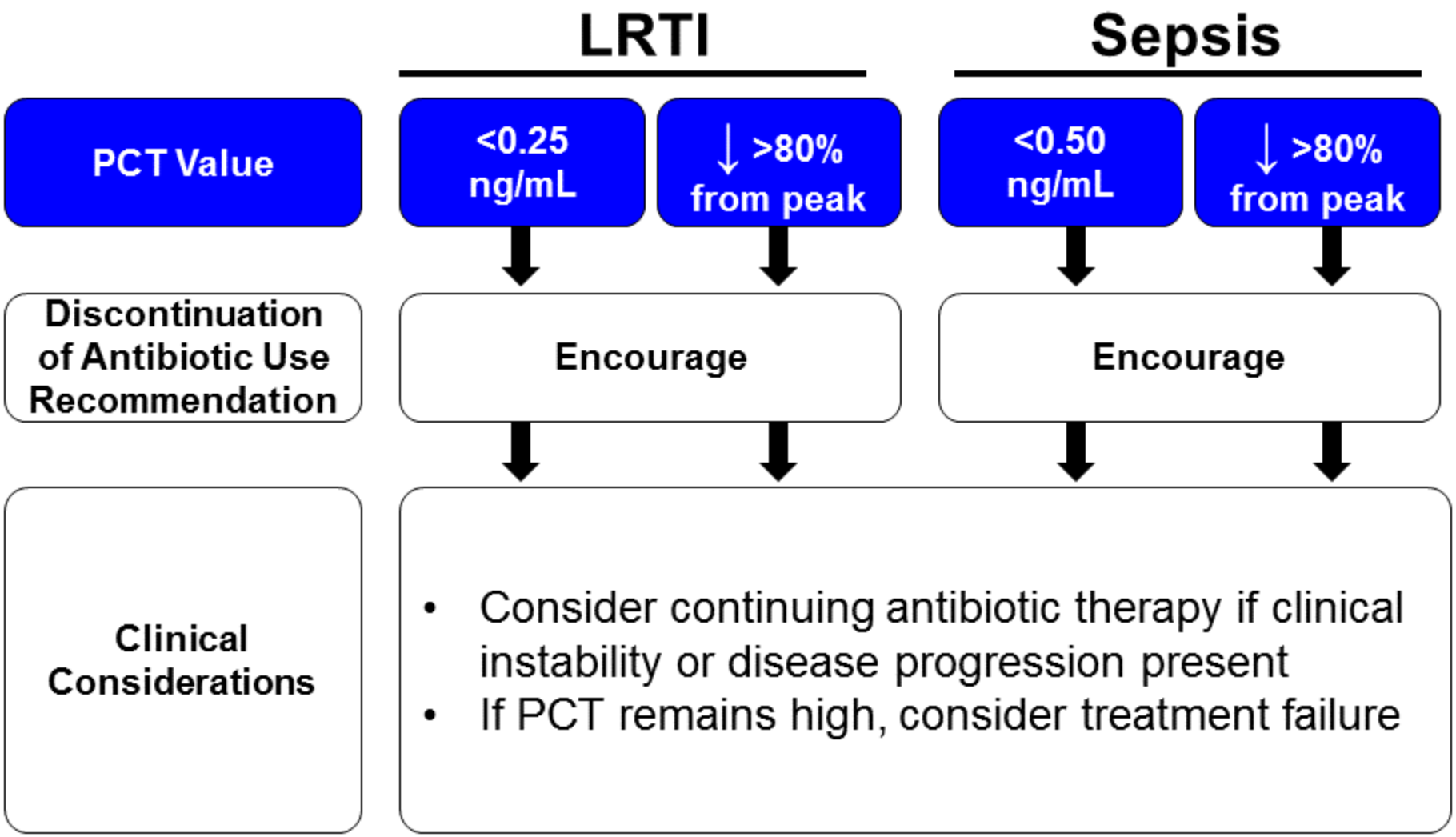
bioMérieux Antibiotic Management Algorithms: Two Components



LRTI: bioMérieux Proposed Antibiotic Initiation Algorithm

PCT Value	<0.1 ng/mL	0.1 – 0.25 ng/mL	0.26 – 0.5 ng/mL	>0.5 ng/mL
Initiation of Antibiotic Use Recommendation	Strongly Discourage	Discourage	Encourage	Strongly Encourage
Clinical Considerations	• Inpatients: If antibiotics are withheld, repeat measurement within 6-24 hours • Outpatients: reassess and/or repeat test if symptoms persist/worsen • Antibiotic therapy should be considered if clinical context indicates it is warranted		Follow-up samples should be tested at regular intervals and antibiotic therapy may be adjusted using algorithm for discontinuation	

LRTI and Sepsis: bioMérieux Proposed Antibiotic Discontinuation Algorithms



PCT Guidance is Widely Used

- PCT in use clinically for 10 years
- ~50% of U.S. hospitals use PCT[1]
- PCT guidance incorporated in several treatment guidelines, for example:
  - *International Guidelines for the Management of Severe Sepsis and Septic Shock*
  - *European Respiratory Society Guidelines*
  - *IDSA Guidelines for Antibiotic Stewardship Programs*
- >36 million PCT determinations worldwide in 2015[2]

1. Kadri et al. Epidemiology of Procalcitonin Use in United States Hospitals. *Submitted.*
2. Thermo-Fisher

VIDAS B•R•A•H•M•S PCT

- Automated, individual test
- Assay takes 20 minutes
- Two components:
  - VIDAS B•R•A•H•M•S PCT kit
  - VIDAS family of instruments

VIDAS B•R•A•H•M•S PCT Produces Accurate Results

- Performed on serum or lithium heparinate plasma
- Detection limit: 0.03 ng/mL
- Quantitative linear range: 0.05-200 ng/mL

PCT is a Useful, Reliable Biomarker for Detecting Bacterial Infection

- PCT levels
  - Rise rapidly after bacterial insult (4-6 hours)
  - Decline rapidly with control of infection (half-life of ~24 hours)
  - Correlate with severity of illness
- Aids in assessing risk and prognosis

PCT is Useful Tool for Antibacterial Decision Making

- High NPV for bacterial infection
- Adds to clinical judgment
- Widely accepted and cited in international treatment guidelines
- Measured in the VIDAS system with accuracy and precision

Meta-Analysis Methodology

Noam Kirson, PhD
Vice President
Analysis Group, Inc.

Meta-Analysis Evaluated Safety and Effectiveness of PCT-Guided Approach

- Worked with FDA to develop meta-analysis approach
- Compared PCT guided therapy to standard of care for LRTI and sepsis
- Two primary goals:
  - Evaluate reduction in antibiotic use
  - Evaluate impact of PCT guidance on safety

Meta-Analyses Summarize the State of Published Literature

- Provide greater precision in estimating effects than individual trials
- Different RCTs reflect various clinical factors
- Leverages variation to best capture effect
- Averages effect across multiple RCTs
  - Give different weights to different studies

Random Effects Model Accounts for Variation in Effect Size

- Different study characteristics can result in differences in treatment effects
  - Researchers, settings, patients, etc.
- Confidence intervals appropriately account for variation

Design of RCTs Included in Meta-Analysis

Patients with LRTI or sepsis randomized to:

- Control group
  - Treatment based on clinical judgment under standard of care
- PCT group
  - Treatment based on clinical judgment plus results of PCT assay

Two Types of Meta-Analyses

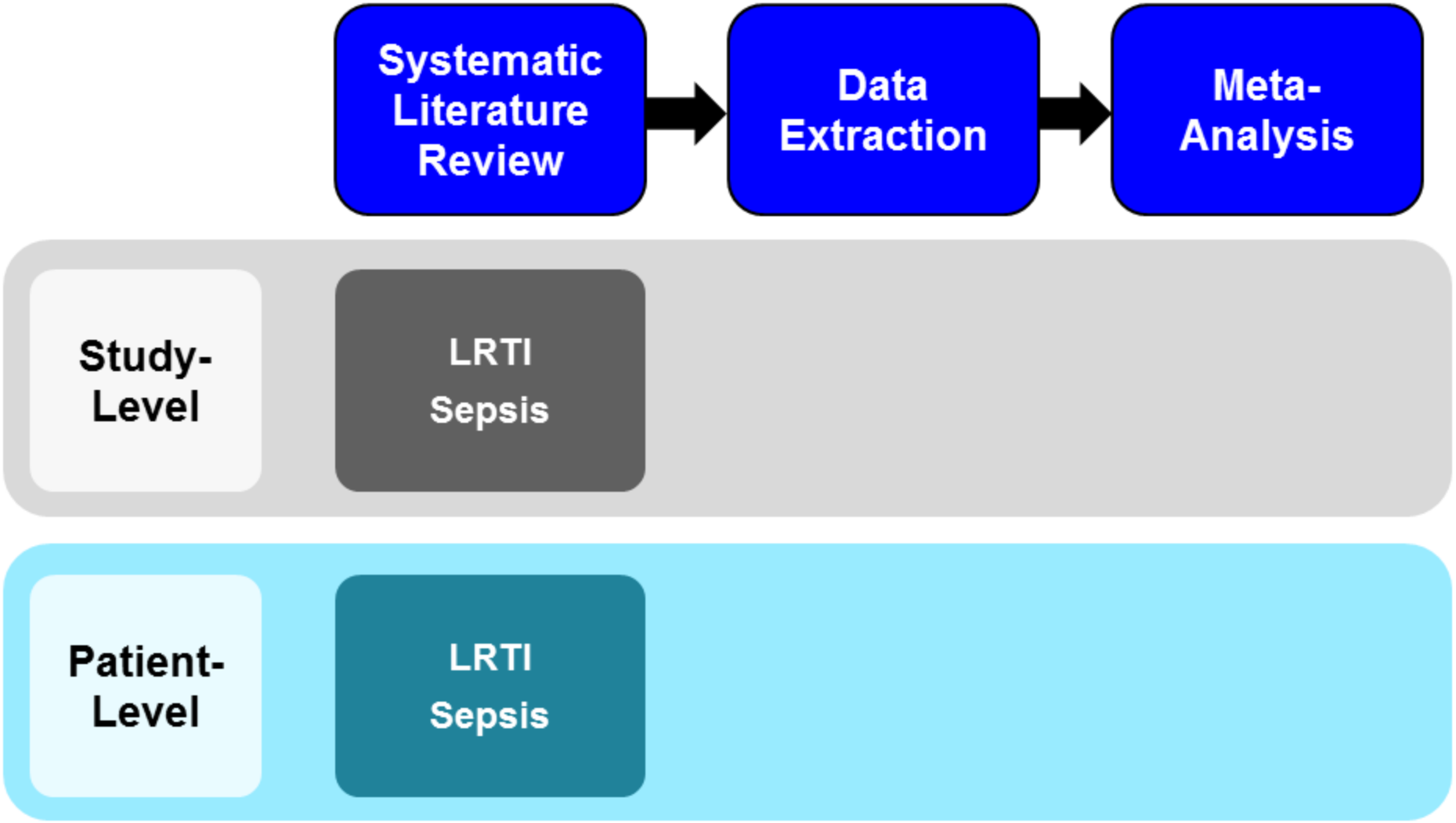
Study-Level

- Combines aggregate study-level information (e.g., mean differences, odds ratios)
- Limited ability to account for patient-level characteristics (e.g., age, gender)

Patient-Level

- Combines individual-level information
- Access to raw datasets
- Greater flexibility to address heterogeneity in patient characteristics

Established Predefined Methodology: Systematic Literature Review



Study-Level Search Procedures

- Databases searched
  - PubMed
  - Cochrane Database of Systematic Reviews
- Keywords prospectively identified
- Publications selected on pre-defined criteria
- 2 reviewers independently screened all articles

Patient-Level Search Procedures

- Literature identified in prior systematic review conducted in 2011 on PCT and acute respiratory infection[1]
- Databases searched
  - Cochrane Controlled Trials Registry
  - MEDLINE
  - Embase
- Publications selected on pre-defined criteria
- 2 reviewers independently screened all articles

1. Schuetz et al. *Clin Infect Dis* 2012;55:651

Study-Level Literature Review Results

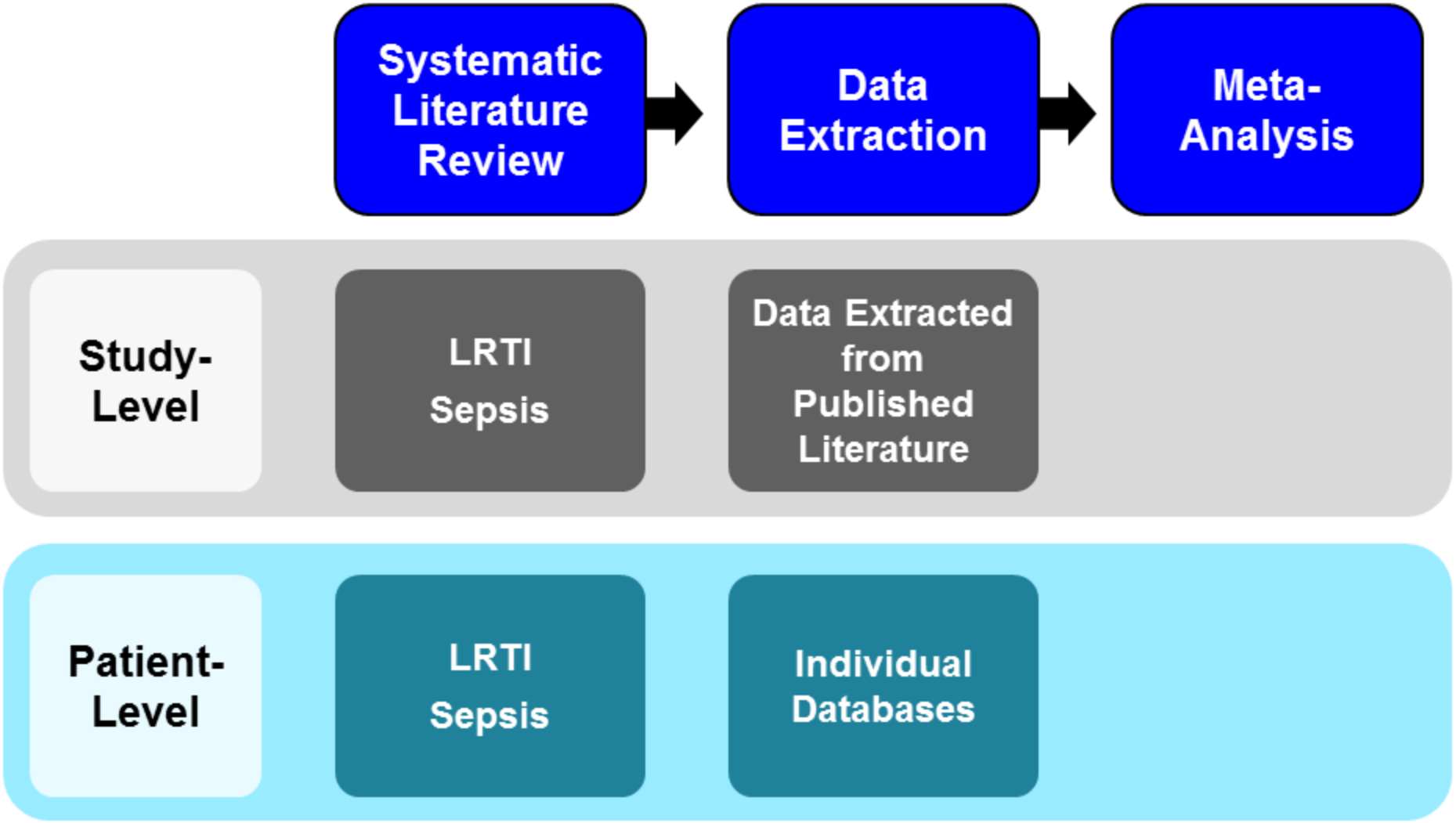
	LRTI	Sepsis
Articles screened based on abstracts	263	340
No original data (e.g., review, editorial)	*(136)*	*(148)*
PCT not measured for intended purpose	*(55)*	*(100)*
PCT not measured in target population	*(20)*	*(57)*
Other	*(41)*	*(25)*
Retained for meta-analysis	11	10
Total patients in analyses	N=4090	N=3489

Patient-Level Literature Review Results

	Articles
Search of database	327
Not RCTs	*(283)*
Ongoing trials	*(14)*
Duplicates	*(4)*
Other	*(12)*
Retained for meta-analysis	14

	LRTI	Sepsis
RCTs in final analyses	13	5
Total patients in analyses	N=3142	N=598

Established Predefined Methodology: Data Extraction



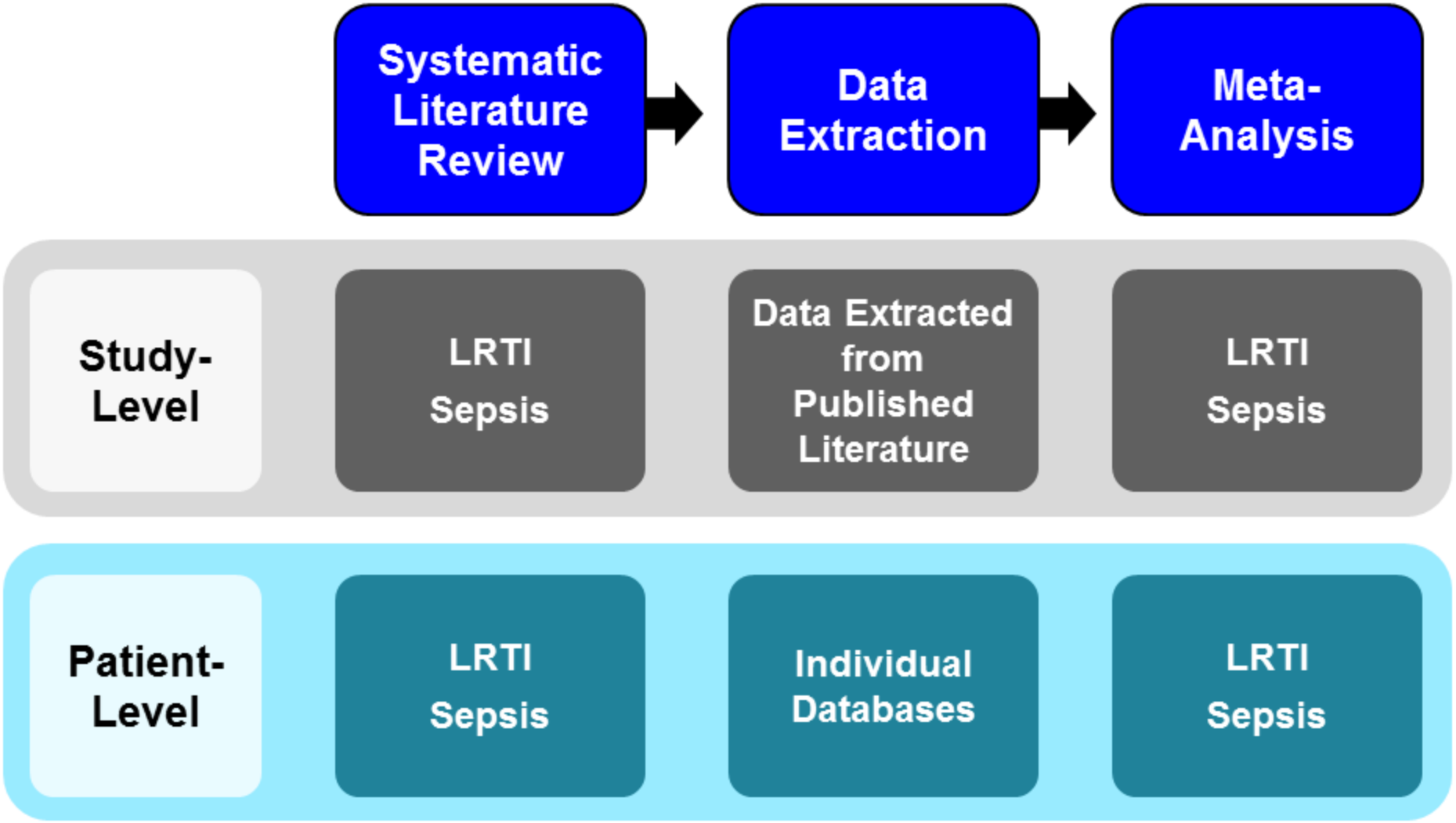
Study-Level Analysis: Data Extraction

- Data extraction completed independently by 2 reviewers
- Study characteristics and outcomes were extracted into standardized data form
- Discrepancies between reviewers resolved by consensus

Patient-Level Analysis: Data Extraction

- All data from original acute respiratory infection dataset
- LRTI dataset included patients with:
  - Community-acquired pneumonia (CAP)
  - Acute bronchitis
  - Acute exacerbation of chronic obstructive pulmonary disease (AECOPD)
- Sepsis dataset included patients in ICU with pulmonary infection

Established Predefined Methodology: Meta-Analysis



Effectiveness Endpoints Evaluated in Meta-Analyses

	LRTI		Sepsis	
	Study-Level	Patient-Level	Study-Level	Patient-Level
Antibiotic Initiation	✓	✓		
Duration of Therapy	✓	✓	✓	✓
Exposure to Antibiotics	✓	✓	✓	✓

- **Duration**: Time on antibiotics among patients initiating treatment
- **Exposure**: Time on antibiotics among all patients

Example of Duration vs. Exposure

Patient	Time on Antibiotics (days)	Duration (days)	Exposure (days)
#1	0	n/a	0
#2	0	n/a	0
#3	4	4	4
#4	5	5	5
#5	6	6	6
	Average	**5 days**	**3 days**

- Duration more relevant to patient benefit
- Exposure more relevant to public health benefit

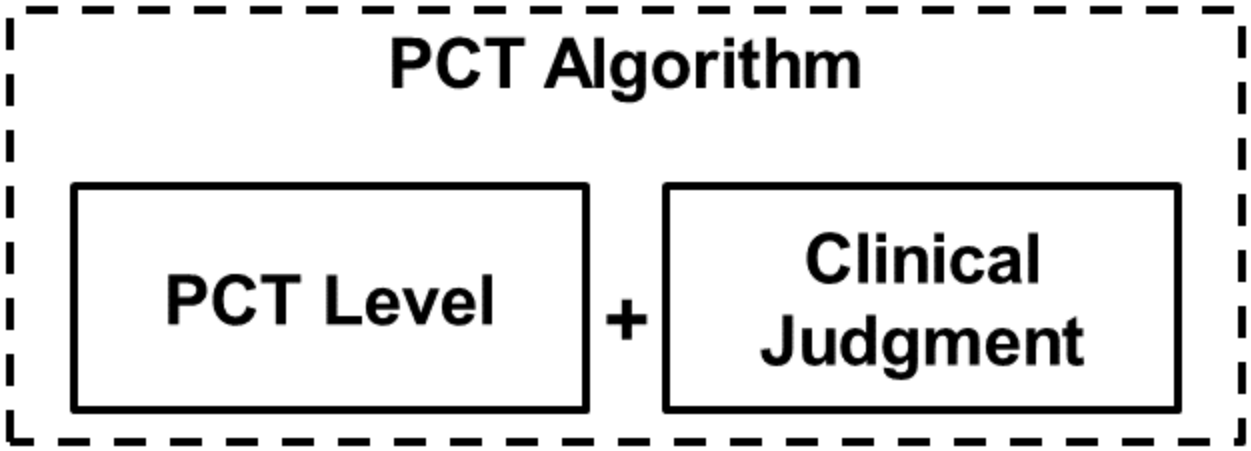
Safety Endpoints Evaluated in Meta-Analyses

	LRTI		Sepsis	
	Study-Level	Patient-Level	Study-Level	Patient-Level
Mortality	✓	✓	✓	✓
Complications		✓		
Hospital Length of Stay	✓	✓		✓
ICU Length of Stay			✓	✓

Statistical Methods and Bias Assessment

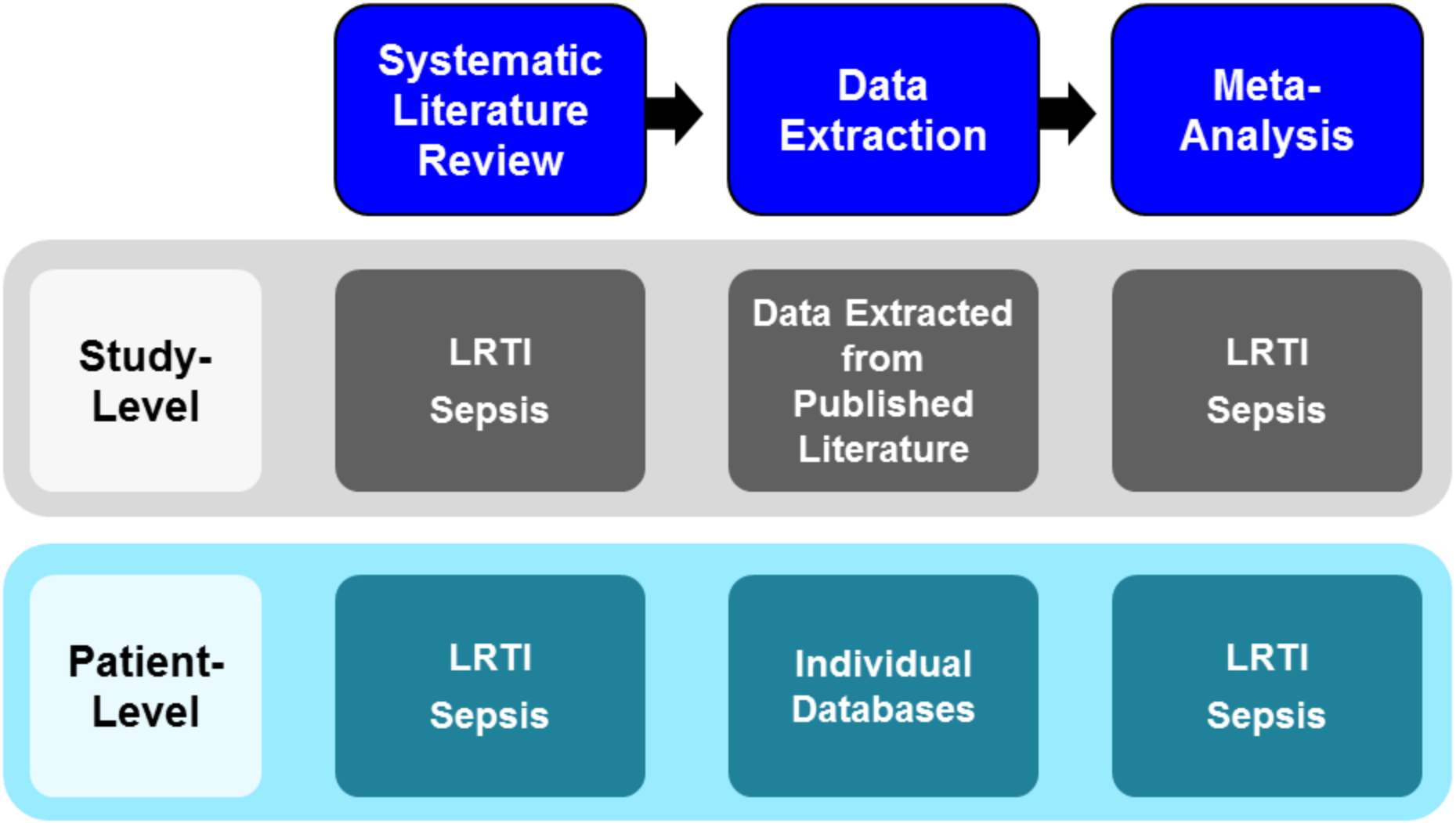
- Random-effects models
  - Study-level: No adjustment for covariates
  - Patient-level: Adjustment for age
- Subgroup analyses and stratifications performed
  - Study-level: LRTI type, risk of bias, level of adherence
  - Patient-level: LRTI type, PCT level, age, gender, inpatient vs. outpatient setting
- Risk of bias assessed using Cochrane Handbook

Definition of Adherence in Study-Level Meta-Analyses



- Example of non-adherence:
  - LRTI patient with PCT=0.12 ng/mL
  - AB treatment initiated

Meta-Analyses Used Best Practices



Results of Meta-Analyses

Philipp Schuetz, MD, MPH

Chief Physician of Endocrinology and Internal Medicine

University of Basel

Outline for Meta-Analysis Results

LRTI	**Baseline Characteristics**
	Effectiveness: Initiation of Antibiotics
	Effectiveness: Antibiotic Duration/Exposure
	Safety
Sepsis	Baseline Characteristics
	Effectiveness: Antibiotic Duration/Exposure
	Safety

Baseline Characteristics Similar Between Groups in LRTI Patient-Level Meta-Analysis

Characteristic	PCT Group (N=1536)	Control Group (N=1606)
Age (years), median (IQR)	66 (50, 79)	66 (49, 78)
Female, n (%)	671 (44%)	744 (46%)
Diagnosis, n (%)		
CAP	999 (65%)	1028 (64%)
Acute Bronchitis	249 (16%)	282 (18%)
AECOPD	288 (19%)	296 (18%)
PCT value at initiation (ng/mL), median (IQR)	0.23 (0.10, 0.96)	0.21 (0.09, 1.04)

Outline for Meta-Analysis Results

LRTI	Baseline Characteristics
	Effectiveness: Initiation of Antibiotics
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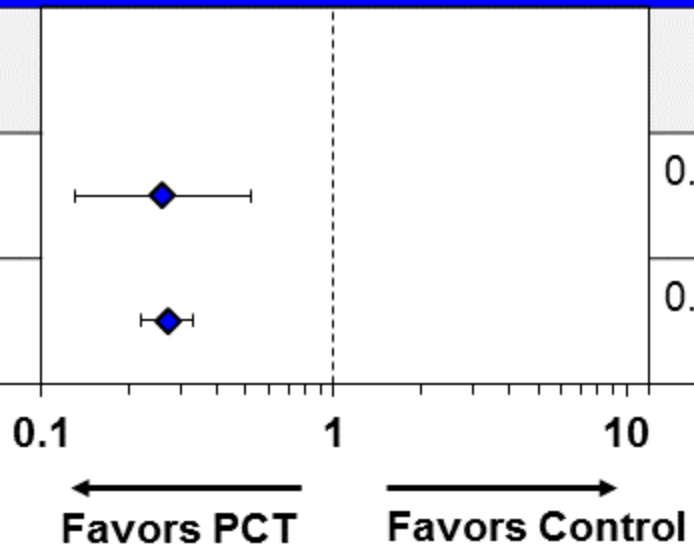
	Safety
Sepsis	Baseline Characteristics
	Effectiveness: Antibiotic Duration/Exposure
	Safety

PCT Guidance Significantly Reduced Antibiotic Initiation

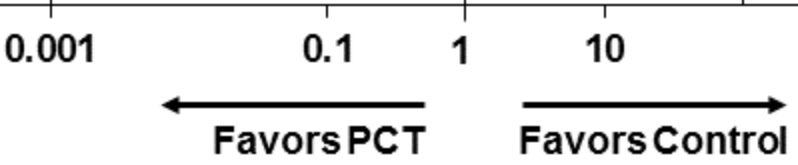
Endpoint	PCT # studies or n/N (%)	Control # studies or n/N (%)	Odds Ratio (95% CI)	Odds Ratio (95% CI) *p*-value
Initiation of Antibiotics				
Study-Level	Data from 10 RCTs			0.26 (0.13, 0.52) *p*<0.001
Patient-Level	1096/1536 (71.4%)	1420/1606 (88.4%)		0.27 (0.22, 0.33) *p*<0.001



- Relative reduction = (88% - 71%) ÷ 88% = 19%

Study-Level Findings for Antibiotic Initiation in LRTI

Endpoint Study	Percent Weight	Odds Ratio (95% CI)
Antibiotic Initiation in LRTI	I^2=93%, p<0.001	
Overall	**100%**	**0.26 (0.13, 0.52)**
Branche (2015)	10.9%	1.21 (0.77, 1.92)
Briel (2008)	10.0%	0.01 (0.00, 0.02)
Burkhardt (2010)	11.0%	0.31 (0.20, 0.48)
Christ-Crain (2004)	10.6%	0.16 (0.09, 0.29)
Christ-Crain (2006)	7.7%	0.07 (0.02, 0.32)
Corti (2016)	10.1%	0.48 (0.22, 1.05)
Kristoffersen (2009)	10.3%	1.52 (0.74, 3.12)
Long (2011)	7.5%	0.15 (0.03, 0.67)
Schuetz (2009)	11.2%	0.43 (0.32, 0.58)
Stolz (2007)	10.7%	0.27 (0.15, 0.47)

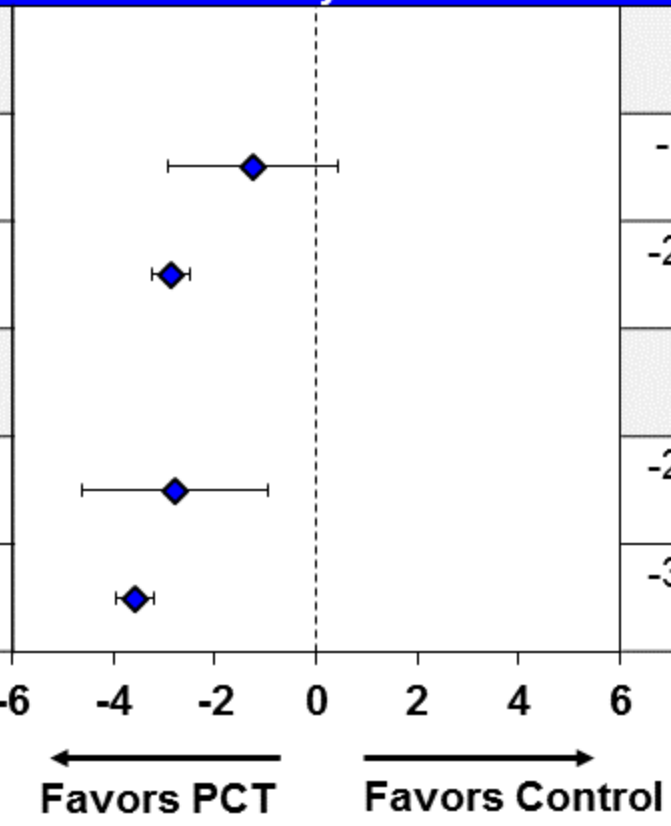


Outline for Meta-Analysis Results

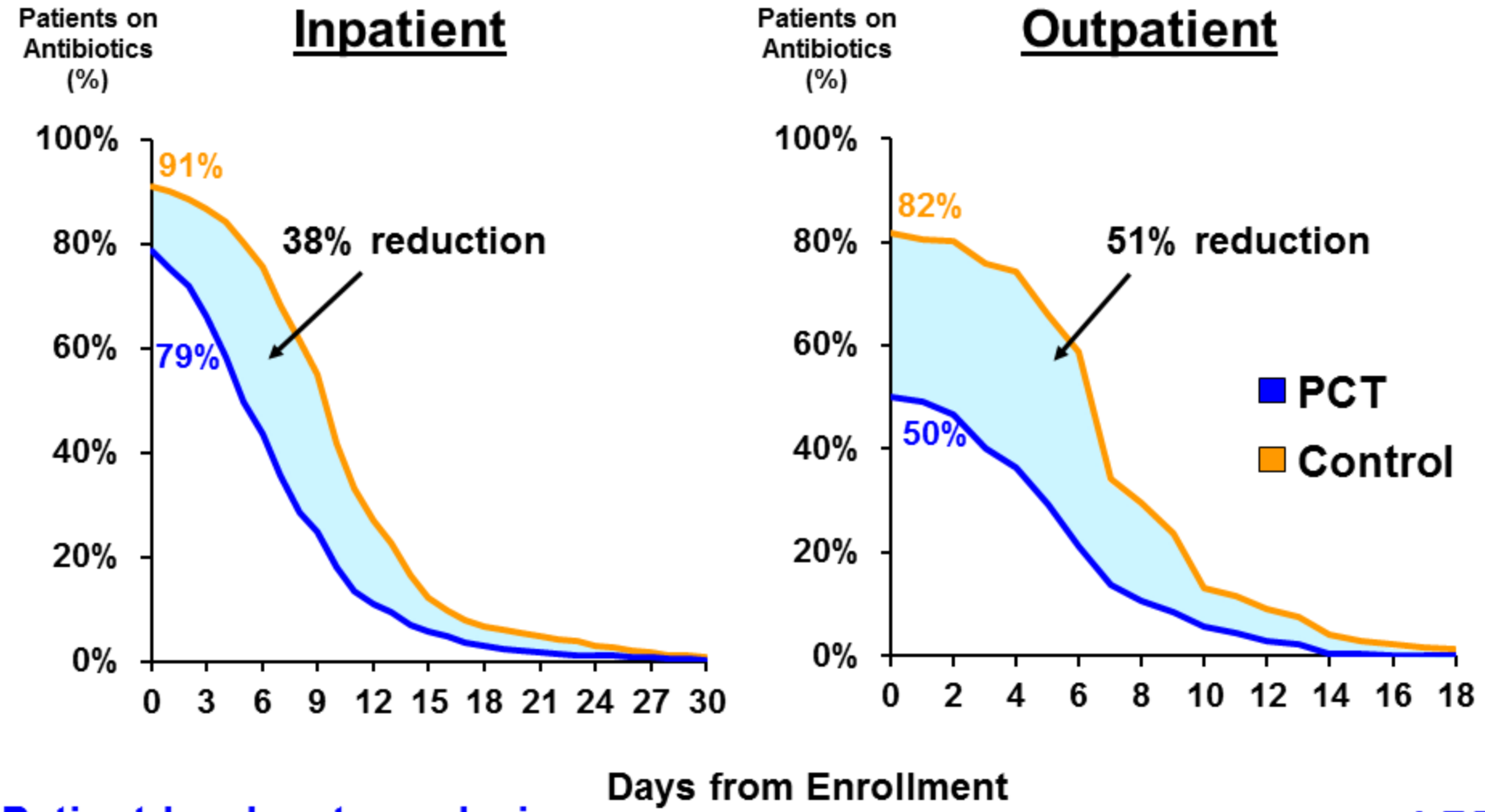
LRTI	Baseline Characteristics
	Effectiveness: Initiation of Antibiotics
	Effectiveness: Antibiotic Duration/Exposure
	Safety
Sepsis	Baseline Characteristics
	Effectiveness: Antibiotic Duration/Exposure
	Safety

PCT Guidance Significantly Reduced Duration and Exposure to Antibiotics

Endpoint	PCT # studies or Median (IQR)	Control # studies or Median (IQR)	Mean Difference (95% CI) Days	Mean Difference (95% CI) *p*-value
Duration of antibiotics (days)				
Study-Level	Data from 3 RCTs			-1.3 (-2.9, 0.4) *p*=0.14
Patient-Level	7 (4, 10)	10 (7, 12)		-2.9 (-3.3, -2.5) *p*<0.001
Total antibiotic exposure (days)				
Study-Level	Data from 5 RCTs			-2.8 (-4.6, -1.0) *p*=0.003
Patient-Level	5 (0, 8)	9 (6, 12)		-3.6 (-4.0, -3.2) *p*<0.001



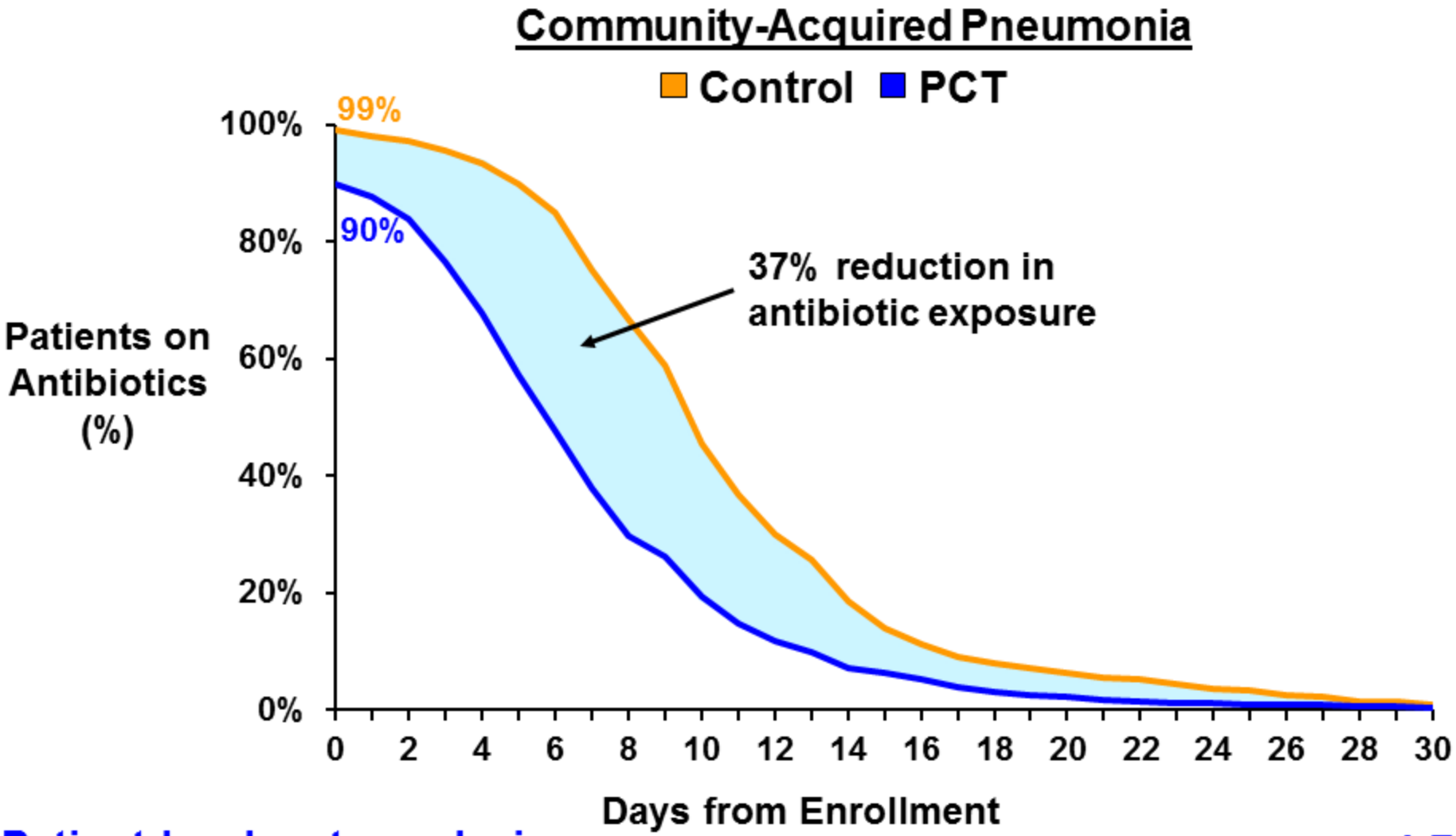
Large Reductions in Antibiotic Exposure in Inpatient and Outpatient Settings



Patient-level meta-analysis

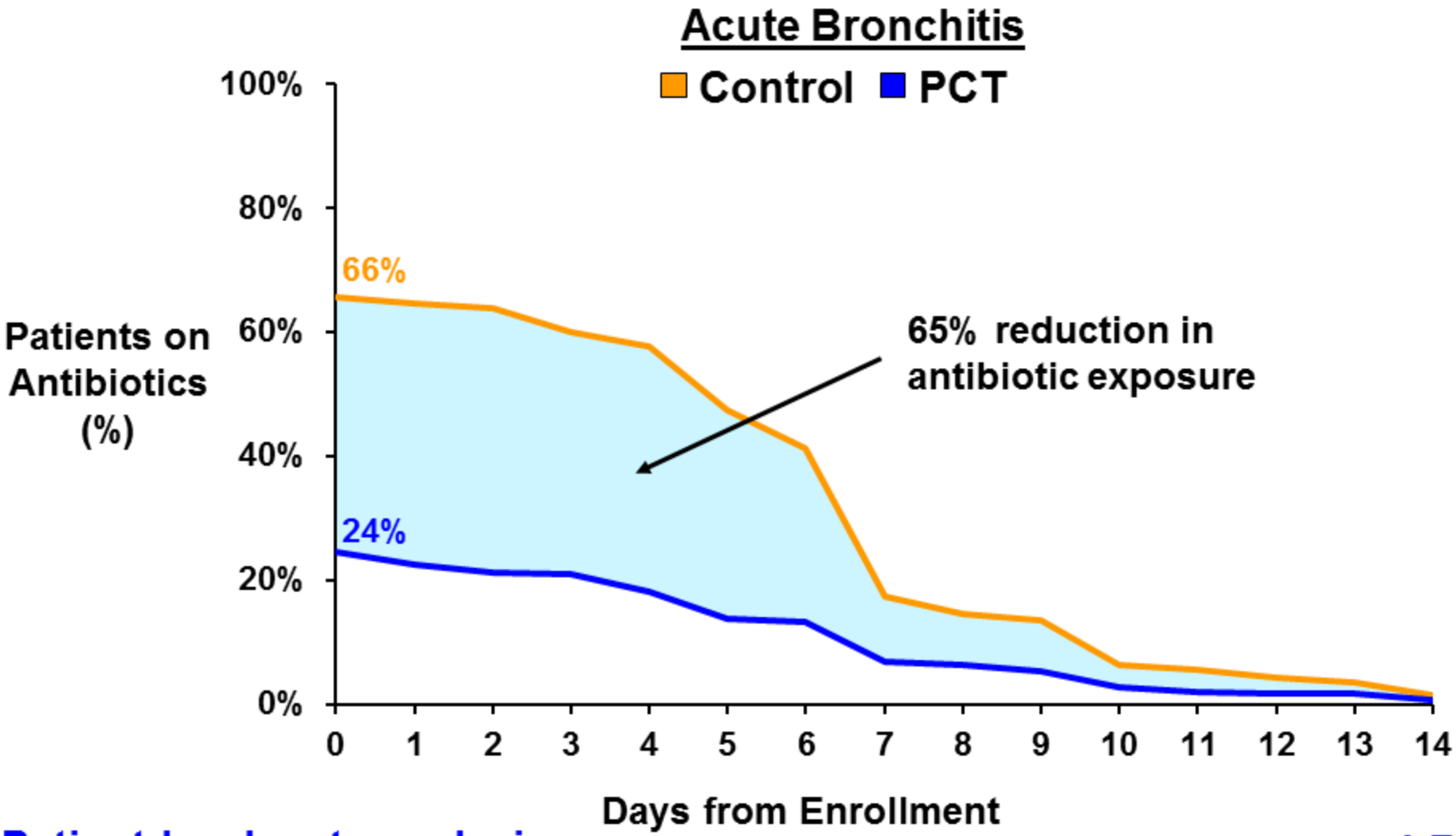
LRTI

Fewer Patients with CAP in PCT Group on Antibiotics Throughout Follow-up



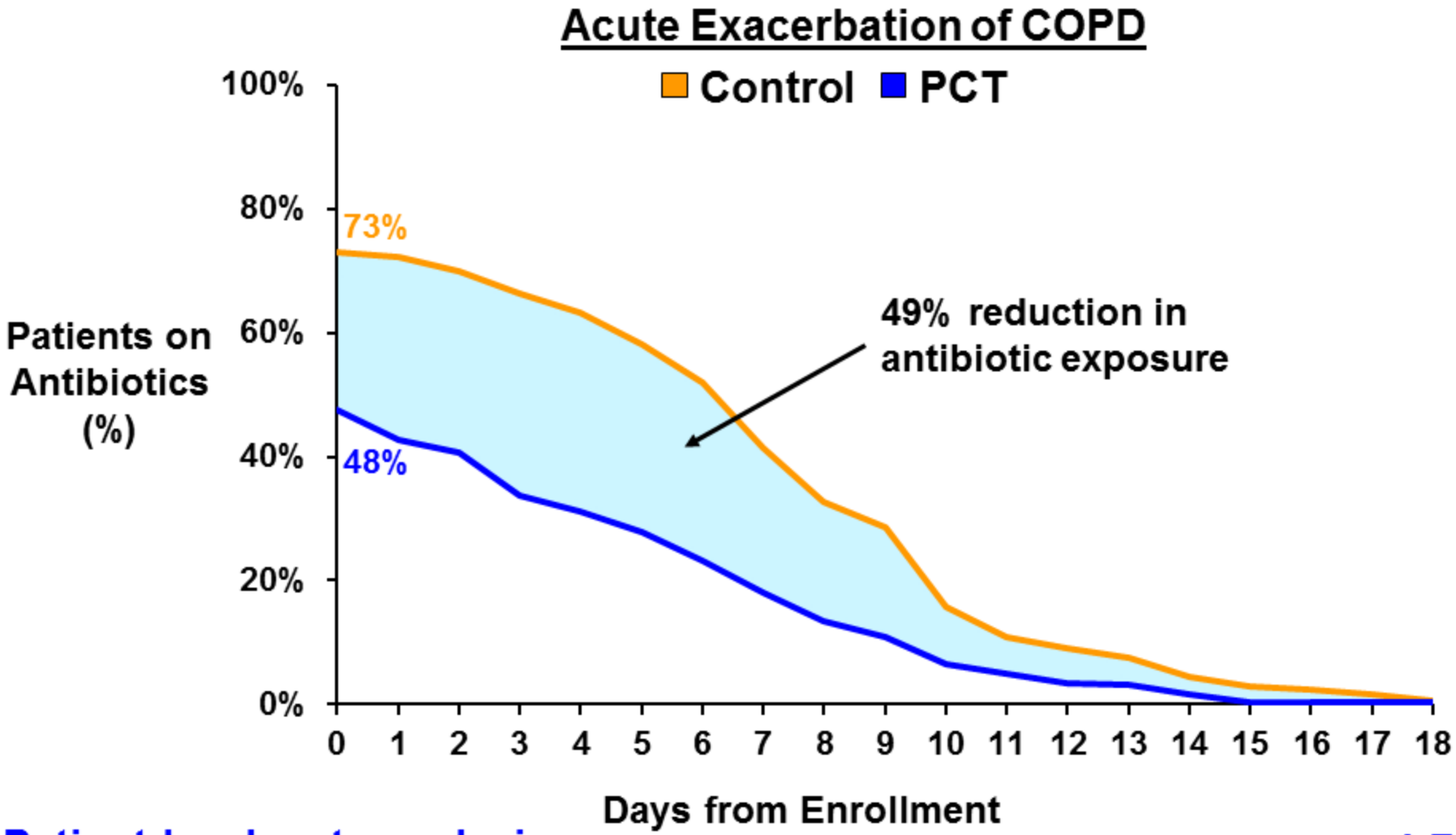
Patient-level meta-analysis

Fewer Patients with Acute Bronchitis in PCT Group on Antibiotics Throughout Follow-up



Patient-level meta-analysis

Fewer Patients with AECOPD in PCT Group on Antibiotics Throughout Follow-Up



Patient-level meta-analysis

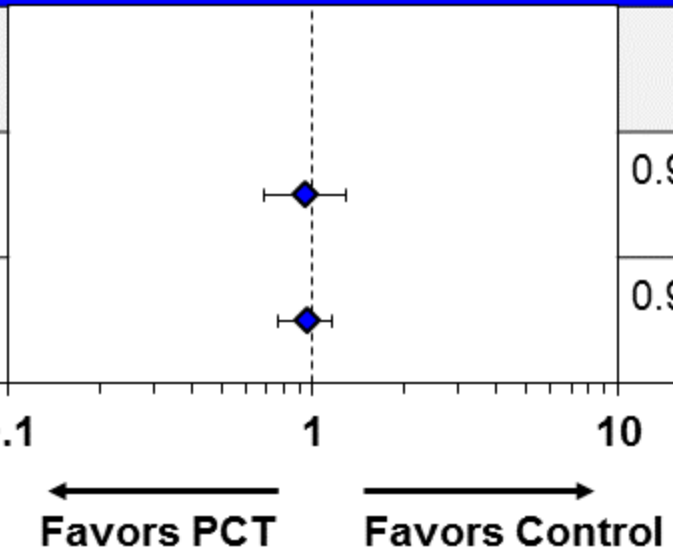
LRTI

Outline for Meta-Analysis Results

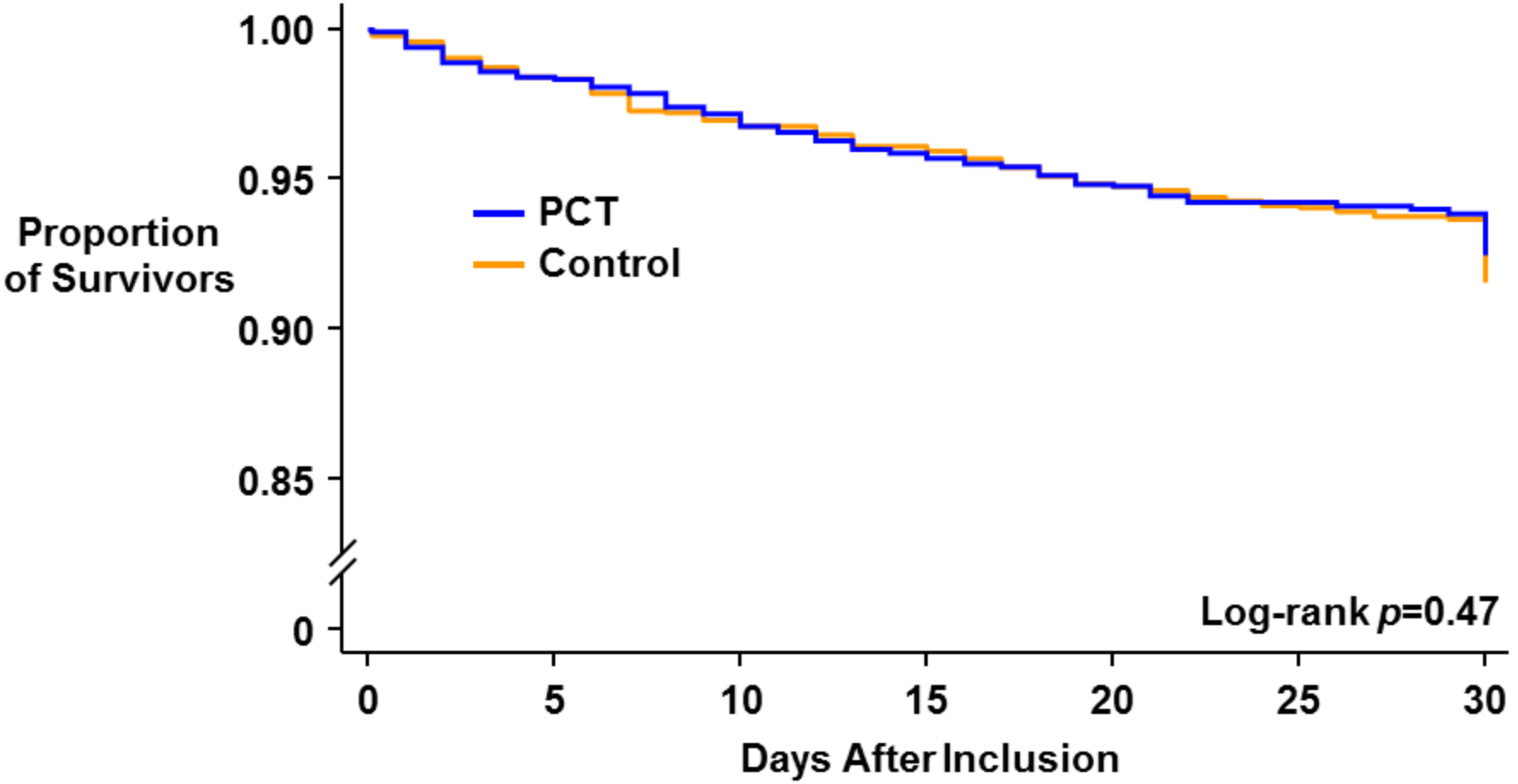
LRTI	Baseline Characteristics
	Effectiveness: Initiation of Antibiotics
	Effectiveness: Antibiotic Duration/Exposure
	Safety
Sepsis	Baseline Characteristics
	Effectiveness: Antibiotic Duration/Exposure
	Safety

No Adverse Mortality Signal Associated with PCT Guidance for LRTI

Endpoint	PCT # studies or n/N (%)	Control # studies or n/N (%)	OR/RR (95% CI)	OR/RR (95% CI) *p*-value
Mortality				
Study-Level	Data from 9 RCTs			0.94 (0.69, 1.28) *p*=0.68
Patient-Level	103/1536 (6.7%)	119/1606 (7.4%)		0.95 (0.77, 1.16) *p*=0.62



Similar Rates of Mortality in LRTI Patient-Level Meta-Analysis

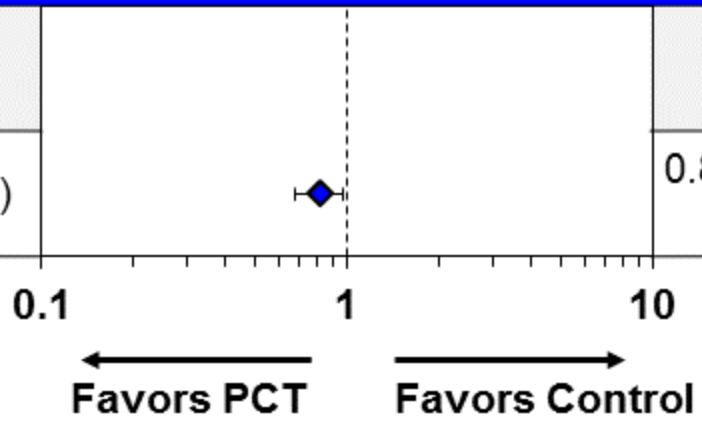


Number at Risk

PCT	1536	1477	1404	1330	1281	1248	1020
Control	1606	1553	1477	1395	1338	1297	1058

PCT-Guided Therapy Associated with Lower Incidence of Complications

Endpoint	PCT (N=1536) n (%)	Control (N=1606) n (%)	Odds Ratio (95% CI) *p*-value
Complications			
Patient-Level	276 (18.0%)	339 (21.1%)	0.82 (0.68, 0.99) *p*=0.03

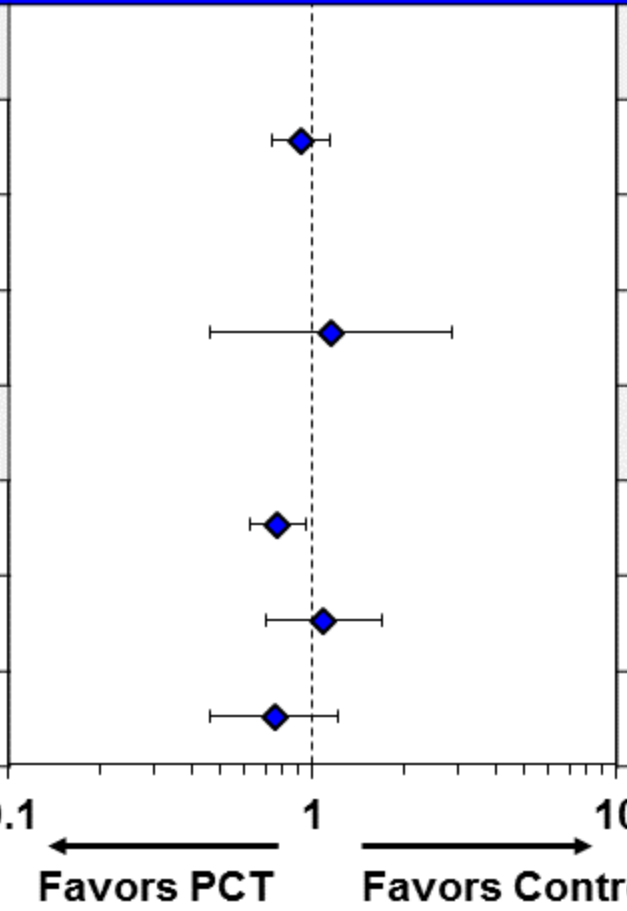


Complications:

- Death
- ICU admission
- Hospitalization or re-hospitalization
- Acute respiratory infection-specific complications
- Recurrent or worsening infection

30-Day Mortality and Complication Profile of PCT Guidance Consistent Across Subgroups

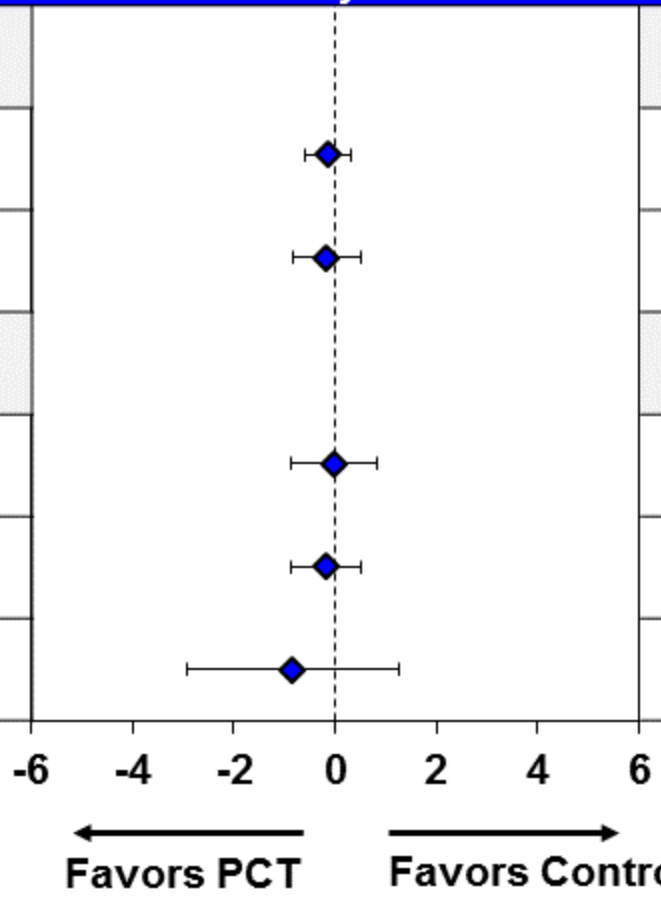
Endpoint	PCT (N=1536) n (%)	Control (N=1606) n (%)	Odds Ratio (95% CI) *p*-value
30-day mortality (Patient-Level)			
CAP	92 (9.2%)	111 (10.8%)	0.92 (0.74, 1.15) *p*=0.47
Acute Bronchitis	2 (0.8%)	0 (0.0%)	*Could not be estimated*
AECOPD	9 (3.1%)	8 (2.7%)	1.15 (0.46, 2.89) *p*=0.76
Complications (Patient-Level)			
CAP	190 (19.0%)	240 (23.3%)	0.77 (0.62, 0.96) *p*=0.02
Acute Bronchitis	51 (20.5%)	54 (19.1%)	1.09 (0.70, 1.70) *p*=0.71
AECOPD	35 (12.2%)	45 (15.2%)	0.75 (0.46, 1.22) *p*=0.25



LRTI

Similar Lengths of Hospital Stay in Both Groups Overall and by LRTI Type

Endpoint	PCT # studies or Median (IQR)	Control # studies or Median (IQR)	Mean Difference (95% CI) Days	Mean Difference (95% CI) *p*-value
Length of hospital stay (days)				
Study-Level	Data from 7 RCTs			-0.2 (-0.6, 0.3) *p*=0.51
Patient-Level	7 (0, 12)	6 (0, 13)		-0.2 (-0.9, 0.5) *p*=0.61
Subgroup analysis by type of LRTI (Patient-Level)				
CAP	8 (2, 14)	8 (2, 13)		0.0 (-0.9, 0.8) *p*=0.96
Acute Bronchitis	0 (0, 2)	0 (0, 2)		-0.2 (-0.9, 0.5) *p*=0.62
AECOPD	8 (3, 14)	8 (3, 13)		-0.8 (-2.9, 1.3) *p*=0.44



LRTI

Summary of Findings from LRTI Meta-Analyses

- PCT-guided antibiotic treatment for LRTI associated, on average, with:
  - ~19% relative reduction in antibiotic initiation
  - 1 to 3-day reduction in duration of therapy
  - 3 to 4-day reduction in total exposure
- Across LRTI types, 37-65% reduction in exposure
- No signal for increase in short-term mortality, complications, or length of hospital stay
- Safety and effectiveness findings consistent across subgroups

Outline for Meta-Analysis Results

LRTI	Baseline Characteristics
	Effectiveness: Initiation of Antibiotics
	Effectiveness: Antibiotic Duration/Exposure
	Safety
Sepsis	**Baseline Characteristics**
	Effectiveness: Antibiotic Duration/Exposure
	Safety

Baseline Characteristics Similar Between Groups in Sepsis Patient-Level Meta-Analysis

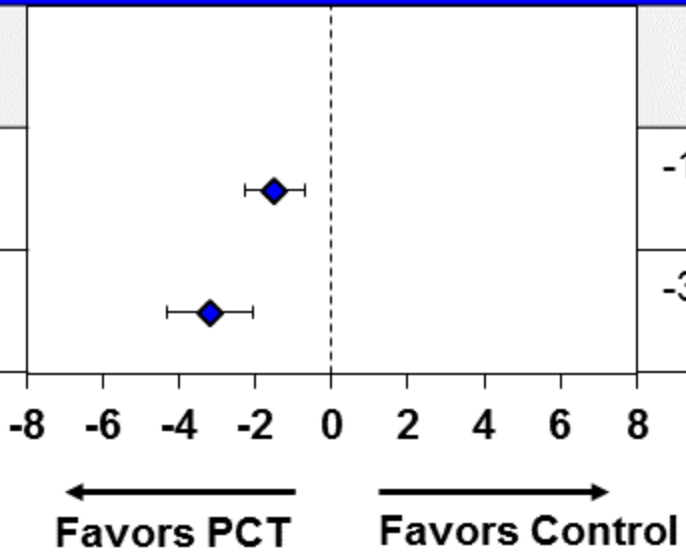
Characteristic	PCT Group (N=287)	Control Group (N=311)
Age (years), median (IQR)	62 (50, 74)	65 (53, 75)
Female, n (%)	79 (28%)	95 (31%)
PCT value at initiation (ng/mL), median (IQR)	1.42 (0.39, 5.78)	1.20 (0.34, 4.74)

Outline for Meta-Analysis Results

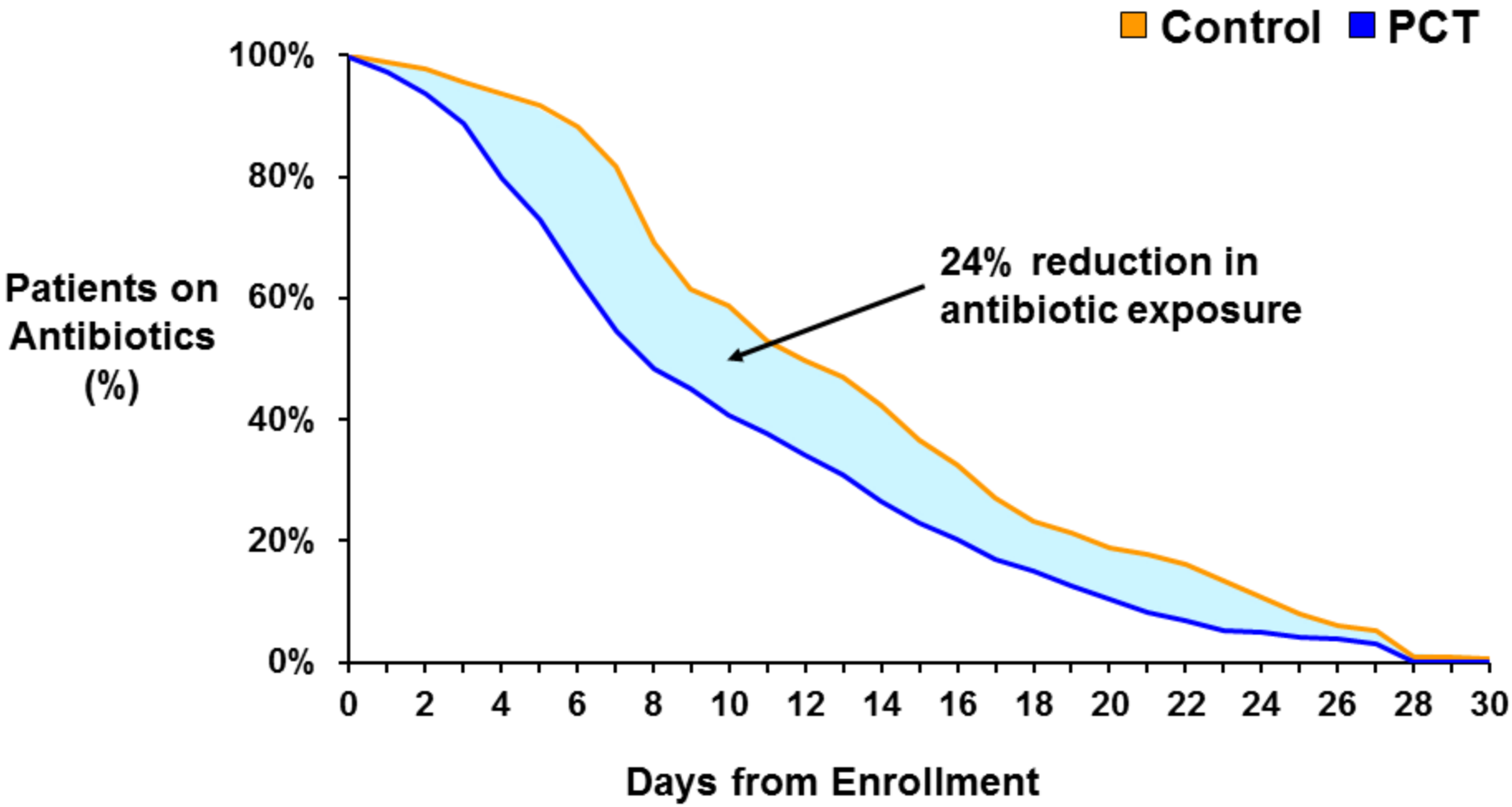
LRTI	Baseline Characteristics
	Effectiveness: Initiation of Antibiotics
	Effectiveness: Antibiotic Duration/Exposure
	Safety
Sepsis	Baseline Characteristics
	Effectiveness: Antibiotic Duration/Exposure
	Safety

PCT Guidance Significantly Reduced Duration and Exposure to Antibiotics for Patients with Sepsis

Endpoint	PCT # studies or Median (IQR)	Control # studies or Median (IQR)	Mean Difference (95% CI) Days	Mean Difference (95% CI) *p*-value
Duration / Exposure to antibiotics (days)				
Study-Level	Data from 8 RCTs			-1.5 (-2.3, -0.7) *p*<0.001
Patient-Level	8 (5, 15)	12 (8, 18)		-3.2 (-4.3, -2.1) *p*<0.001



Patients with Sepsis in PCT Group Discontinued Antibiotics Earlier than Control Group



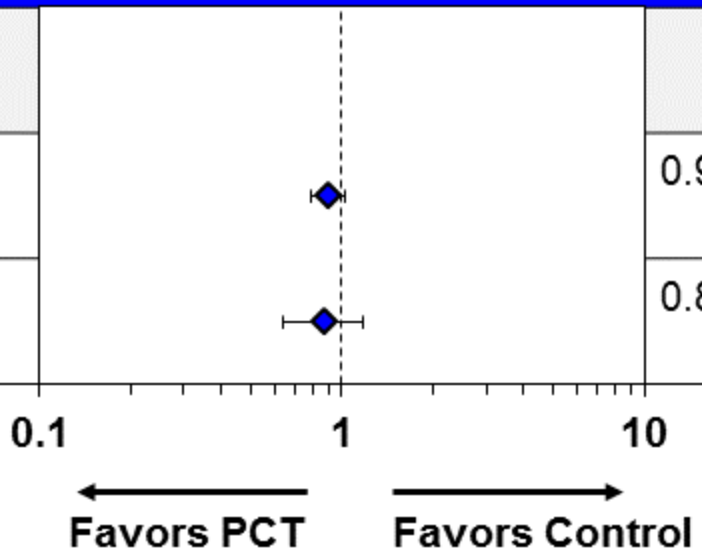
Patient-level meta-analysis

Outline for Meta-Analysis Results

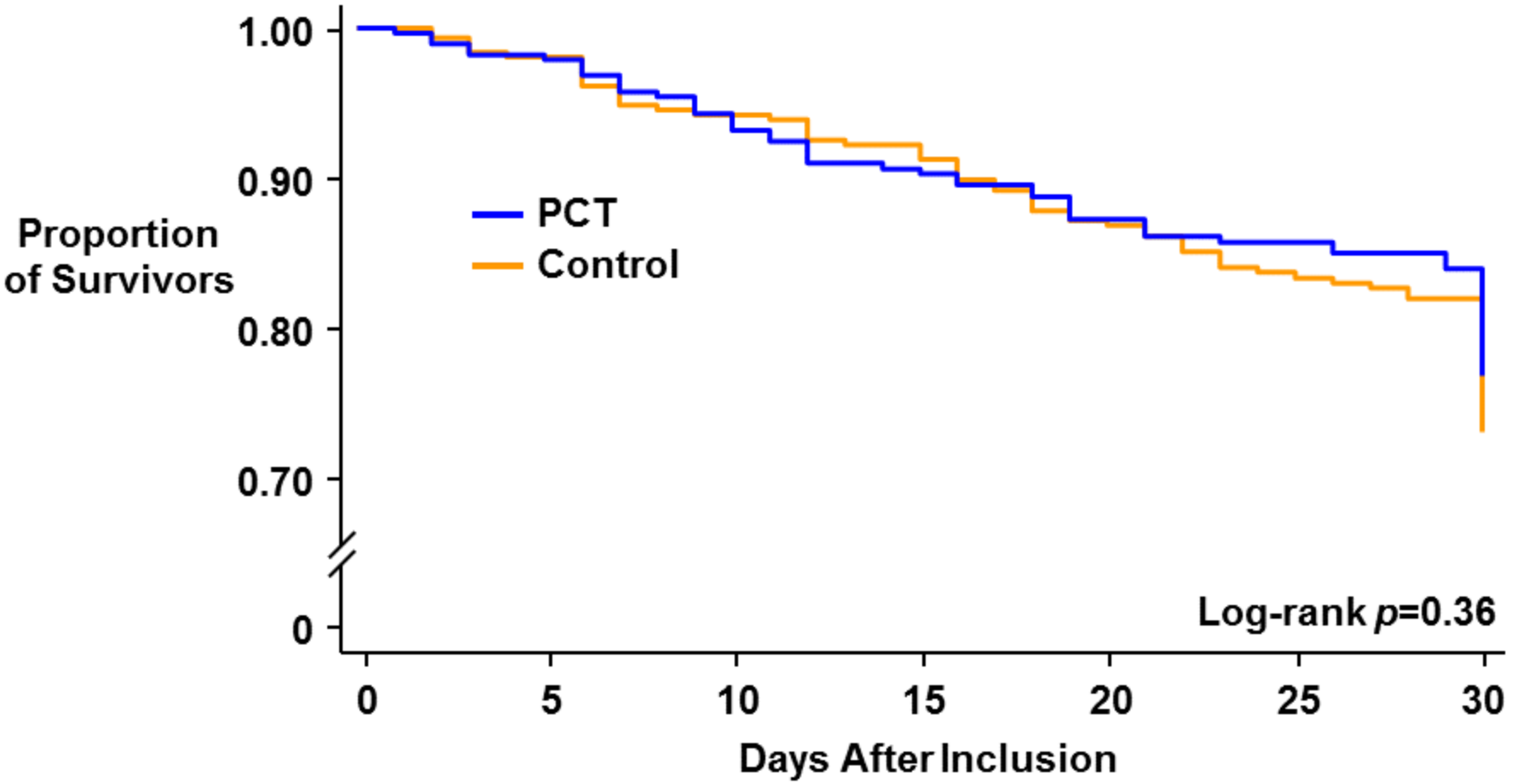
LRTI	Baseline Characteristics
	Effectiveness: Initiation of Antibiotics
	Effectiveness: Antibiotic Duration/Exposure
	Safety
Sepsis	Baseline Characteristics
	Effectiveness: Antibiotic Duration/Exposure
	Safety

No Adverse Mortality Signal Associated with PCT Guidance for Sepsis

Endpoint	PCT # studies or n/N (%)	Control # studies or n/N (%)	OR/RR (95% CI)	OR/RR (95% CI) *p*-value
Mortality				
Study-Level	Data from 10 RCTs			0.90 (0.79, 1.03) *p*=0.11
Patient-Level	57/287 (19.9%)	74/311 (23.8%)		0.87 (0.64, 1.18) *p*=0.36



Similar Rates of Mortality in Sepsis Patient-Level Meta-Analysis

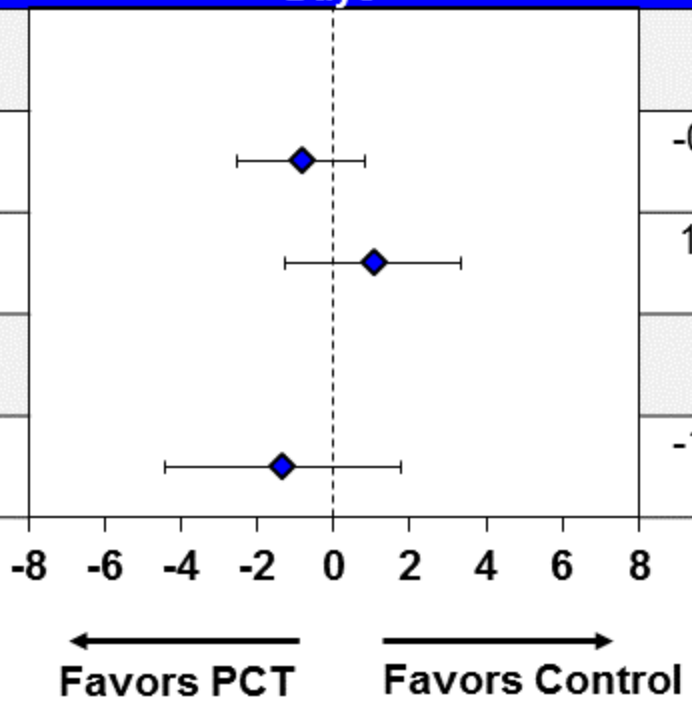


Number at Risk

PCT	287	278	257	244	229	221	164
Control	311	305	288	274	253	239	183

Length of ICU Stay and Hospital Length of Stay Similar Between Groups

Endpoint	PCT # studies or Median (IQR)	Control # studies or Median (IQR)	Mean Difference (95% CI) Days	Mean Difference (95% CI) *p*-value
Length of ICU stay (days)				
Study-Level	Data from 10 RCTs			-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



Summary of Findings from Sepsis Meta-Analyses

- PCT-guided antibiotic treatment for sepsis associated, on average, with:
  - ~1.5 to 3-day reduction in antibiotic use
  - 24% reduction in antibiotic exposure
- Similar mortality rate compared to control
- Similar length of ICU stay and hospital stay compared to control

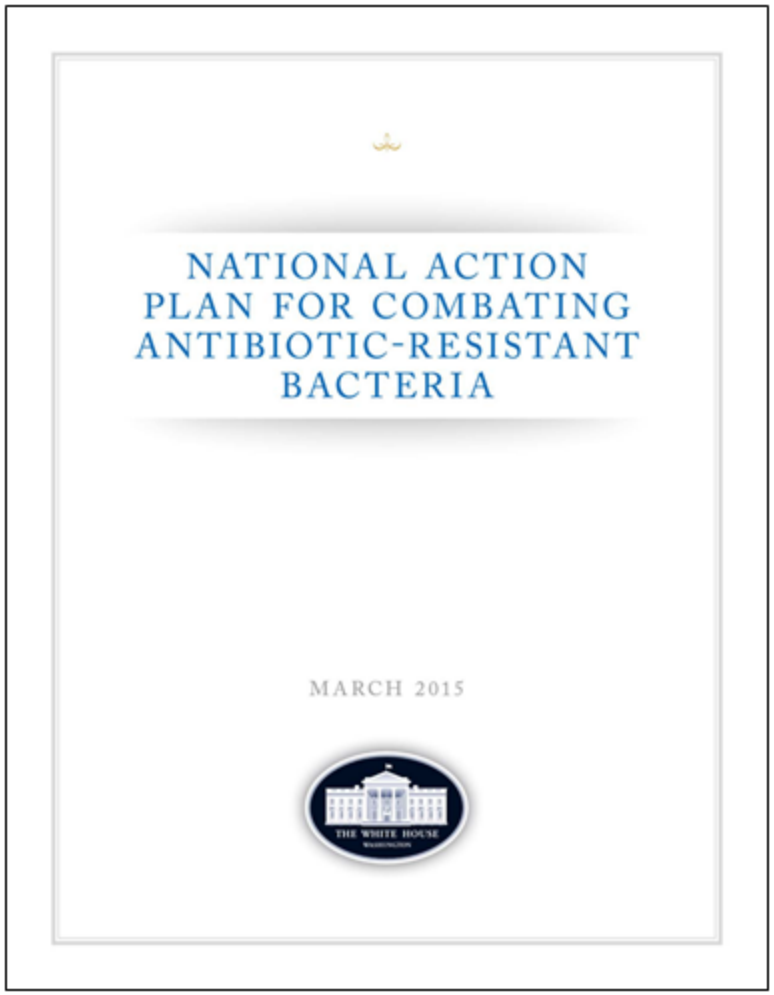
Summary and Clinical Benefit-Risk Assessment

Mark Miller, MD

Chief Medical Officer

bioMérieux

A Global Public Health Emergency



PCT Levels Better Inform Decisions on Antibiotic Use for LRTI and Sepsis

- 78-year-old male: Possible CAP
  - Initial PCT low, 0.11 ng/mL
  - CT scan found pulmonary emboli
- 50-year-old female: Suspected sepsis
  - Initial PCT low, 0.15 ng/mL
  - Consider diagnosis of heart failure
  - Day 4: PCT 0.05 ng/mL
  - Discontinued antibiotic, good outcome

Rapid PCT Detection Can Help Guide Clinicians on Antibiotic Use

- VIDAS B•R•A•H•M•S PCT guides clinicians to significantly, safely reduce antibiotic use
  - Used with other clinical assessments
  - Can inform decision on initiation or continuation of therapy

Leveraged Knowledge Base of RCTs Evaluating PCT-Guided Approach

- 23 RCTs and more than 7,800 patients
- Evaluated safety and effectiveness of PCT-guided antibiotic decision-making
- Meta-analysis study design is robust
  - Provides greater external validity and generalizability than single RCT
  - Responsive to urgent need for improved antimicrobial stewardship

Summary of Results for LRTI: PCT Guidance Effective and Safe

LRTI	Study-Level	Patient-Level
Effectiveness		
Initiation	OR = 0.26, $p<0.001$	19% relative reduction
Duration	1.3-day mean reduction	2.9-day mean reduction
Exposure	2.8-day mean reduction	3.6-day mean reduction
Safety		
Mortality	No safety signal detected	
Complications	*not evaluated*	15% relative reduction
Length of hospital stay	No safety signal detected	

- Consistent safety profile by age, gender, initial PCT level, inpatient vs. outpatient setting, and type of LRTI

Summary of Results for Sepsis: PCT Guidance Effective and Safe

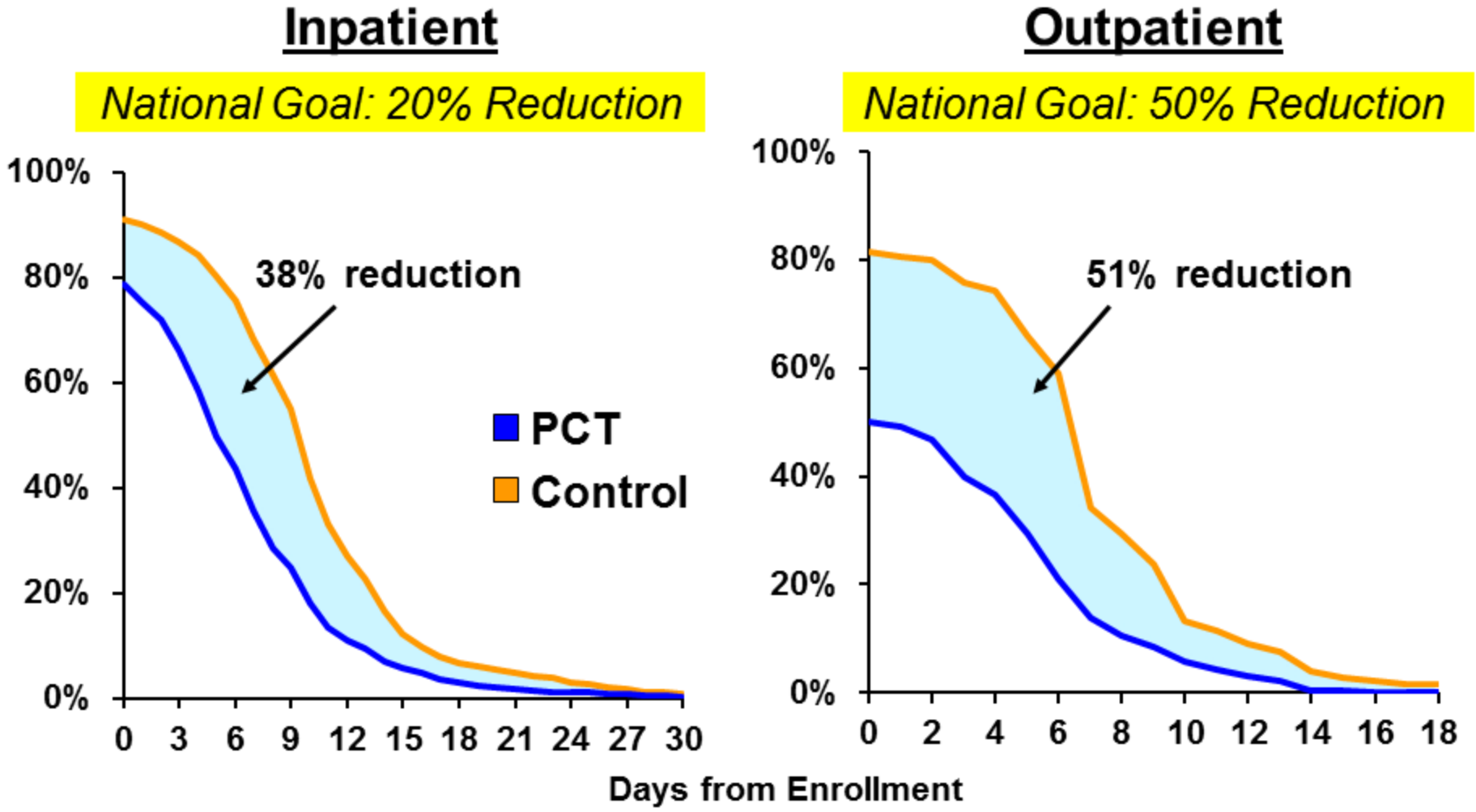
Sepsis	Study-Level	Patient-Level
Effectiveness		
Duration/Exposure	1.5-day mean reduction	3.2-day mean reduction
Safety		
Mortality	No safety signal detected	
Length of ICU stay	No safety signal detected	
Length of hospital stay	*not evaluated*	No safety signal detected

- Consistent safety profile by age, gender, and initial PCT level

Antimicrobial Stewardship Goal: Right Patient, Right Time, Right Duration

- VIDAS B•R•A•H•M•S PCT can help improve antimicrobial stewardship
- PCT-guided therapy
  - Reduce antibiotic use in LRTI patients with no increased risk
  - Decrease antibiotic exposure in sepsis patients with no impact on safety

Reductions in Antibiotic Exposure with PCT Guidance Exceeds National Goals



LRTI: Patient-level meta-analysis

VIDAS B•R•A•H•M•S PCT: Better, Evidence-Based Decisions

- PCT assay and other clinical information helps
  - Prevent and slow emergence of resistant bacteria
  - Avoid side effects of unnecessary antimicrobials
- Benefits patients and healthcare system

VIDAS® B•R•A•H•M•S PCT™ for Procalcitonin (PCT) Guided Antibiotic Therapy

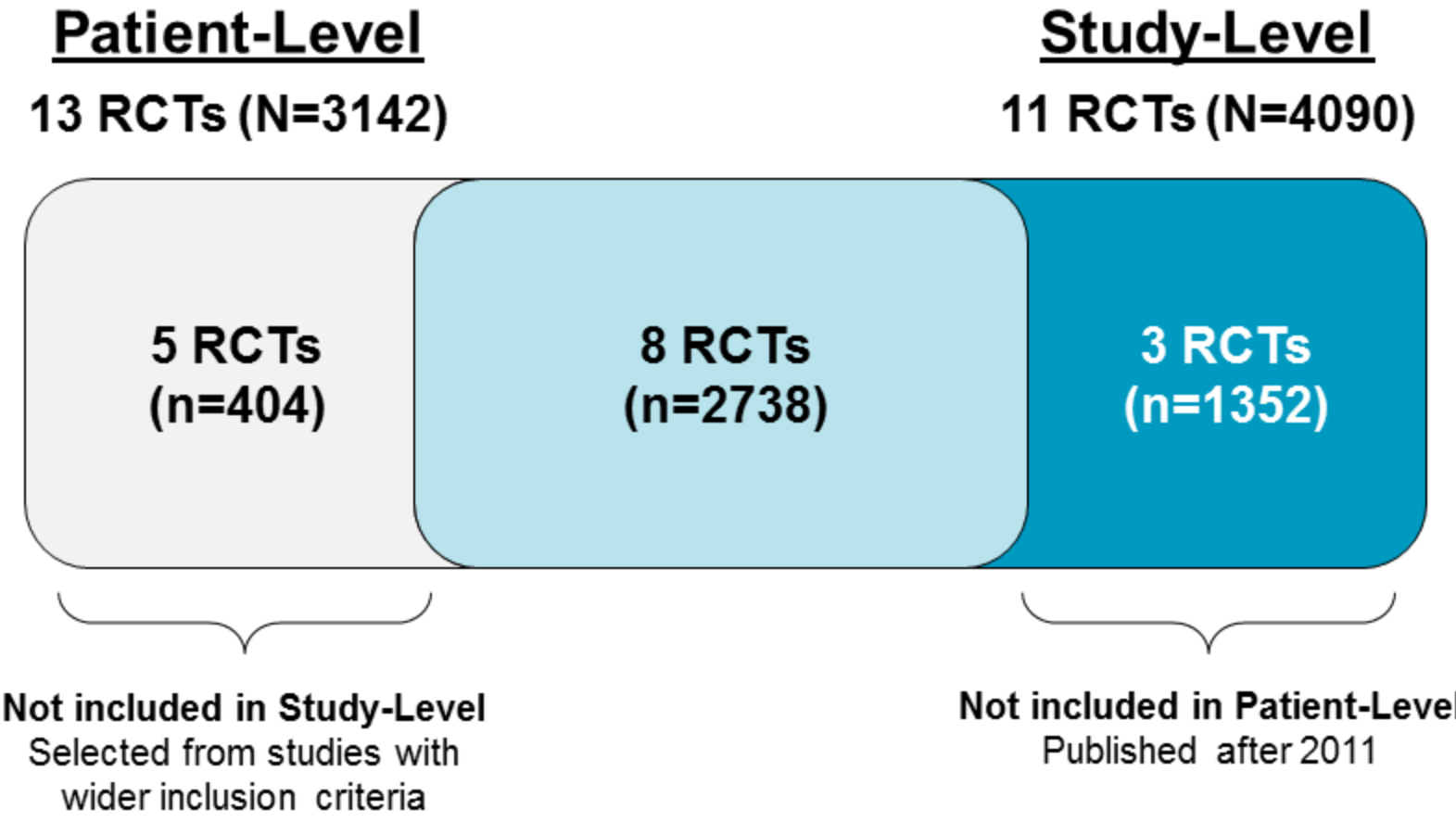
November 10, 2016

bioMérieux

Meeting of the Microbiology Devices Panel

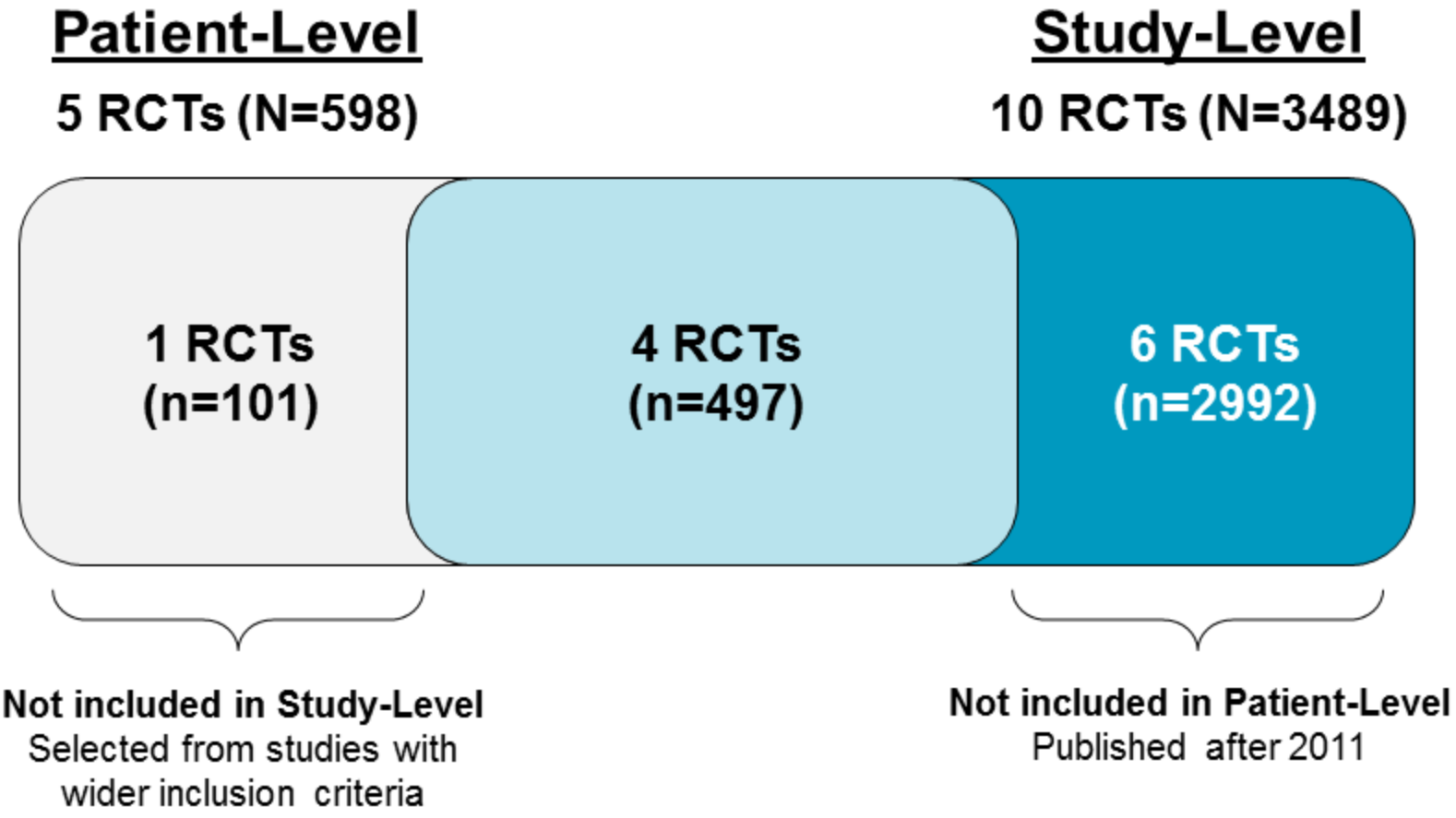
Backup Slides

Overlap between Study-Level and Patient-Level MA for LRTI



Total: 16 unique RCTs - 4494 unique patients

Overlap Between Study-Level and Patient-Level MA for Sepsis

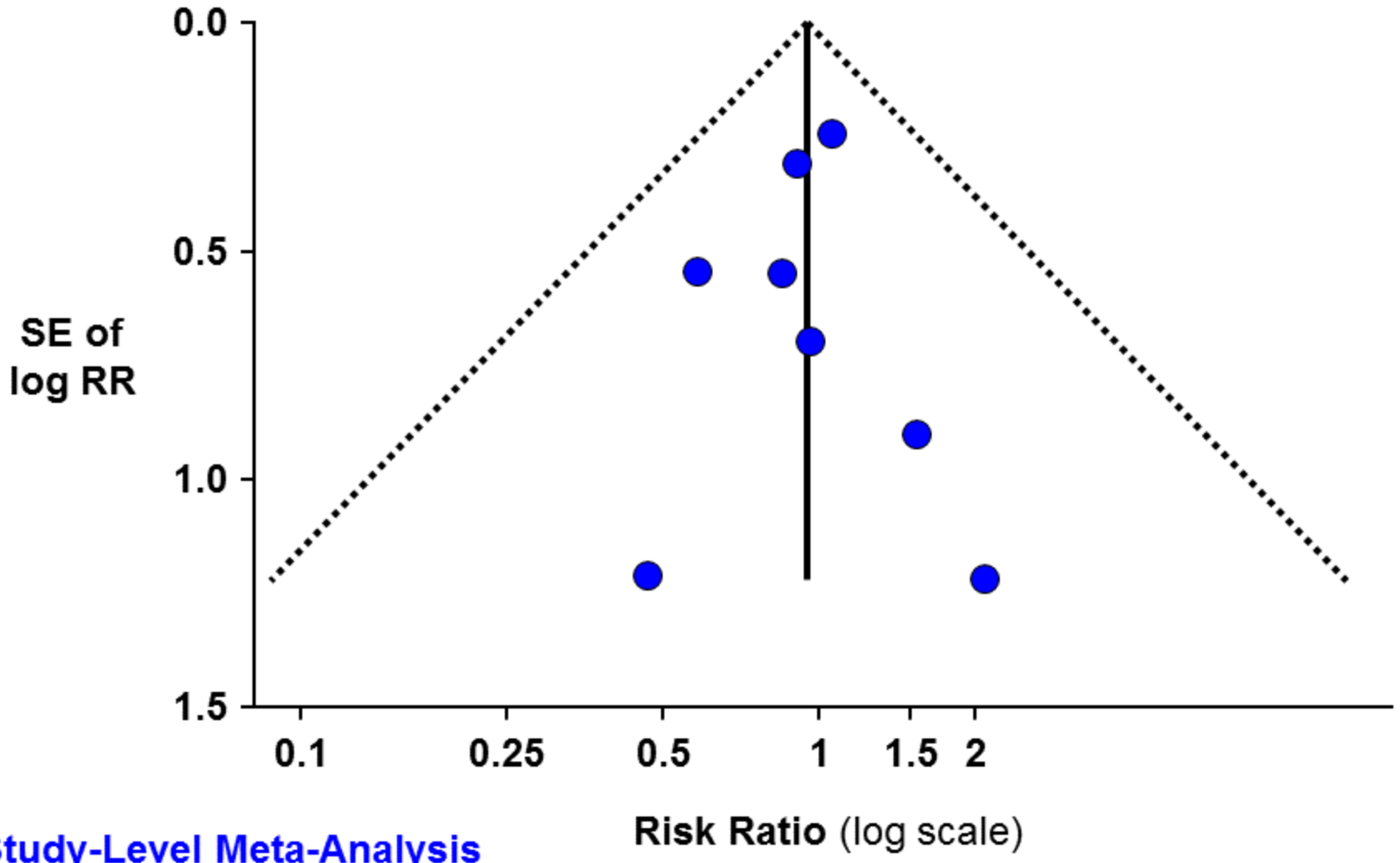


Total: 11 unique RCTs - 3590 unique patients

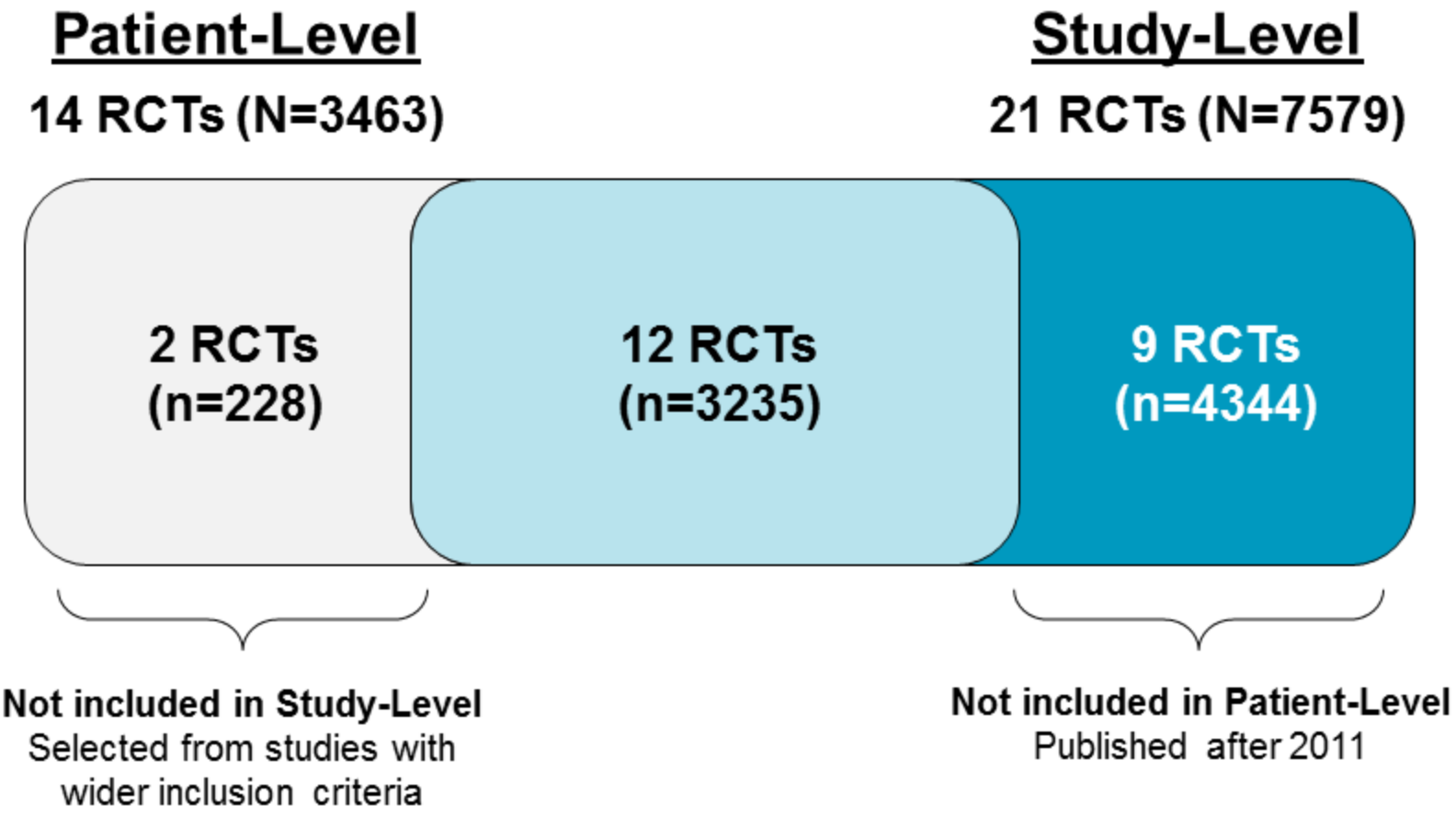
LRTI Antibiotic Initiation: Cut-Offs (ng/mL) Used in Retained RCTs

Study	Antibiotics Strongly Discouraged	Antibiotics Discouraged	Antibiotics Encouraged	Antibiotics Strongly Encouraged
Branche (2015)	≤ 0.1	< 0.25	≥ 0.25	≥ 0.5
Briel (2008)	< 0.1	≤ 0.25	> 0.25	-
Burkhardt (2010)	-	< 0.25	≥ 0.25	-
Christ-Crain (2004)	≤ 0.1	≤ 0.25	> 0.25	≥ 0.5
Christ-Crain (2006)	< 0.1	≤ 0.25	> 0.25	> 0.5
Corti (2016)	≤ 0.15	≤ 0.25	> 0.25	-
Kristoffersen (2009)	-	< 0.25	≥ 0.25	> 0.5
Long (2009)	-	< 0.25	≥ 0.25	-
Long (2011)	< 0.1	≤ 0.25	> 0.25	-
Schuetz (2009)	< 0.1	≤ 0.25	> 0.25	> 0.5
Stolz (2007)	< 0.1	≤ 0.25	> 0.25	-
BMX Proposal	< 0.1	≤ 0.25	> 0.25	> 0.5

Funnel Plot – LRTI Mortality



Overlap Between Study-Level and Patient-Level MA for LRTI and Sepsis



Total: 23 unique RCTs - 7807 unique patients

VIDAS B.R.A.H.M.S PCT is a Precise Assay at the Cut-Offs

Sample	Mean (ng/mL)	Repeatability CV*	Total Precision CV*
1	0.10	9.7%	15.9%
2	0.22	4.3%	6.8%
3	0.52	3.8%	6.1%
4	2.06	2.0%	4.9%

*Coefficient of Variation

Performed on VIDAS 3
According to CLSI Guidelines

Number of Studies Using VIDAS

- Study-level for LRTI (N=2 studies)
  - Corti, Branche: VIDAS exclusively

- Study-level for Sepsis: (N=3 studies)
  - Deliberato: VIDAS exclusively
  - De Jong, Shehabi : Multiple assays (VIDAS, Kryptor, Roche)

Concordance Study: VIDAS vs KRYPTOR Overall Agreement Ranging 87-99%

	Overall Agreement (95% CI)	Kappa
0.10 ng/mL	**86.7%** (81.2, 91.0)	**0.7309**
0.25 ng/mL	**97.5%** (94.3, 99.2)	**0.9380**
0.50 ng/mL	**99.0%** (96.5, 99.9)	**0.9710**
2.00 ng/mL	**97.5%** (94.3, 99.2)	**0.8702**

PCT and Renal Dysfunction

- PCT half-life-time is not significantly altered during renal dysfunction (26.1-33.1 h, vs. 22.3-28.9 h in normal population)[1]
- Renal elimination is not a major mechanism for PCT removal from blood[2]
- Renal failure occurs often in sepsis but PCT algorithm still effective

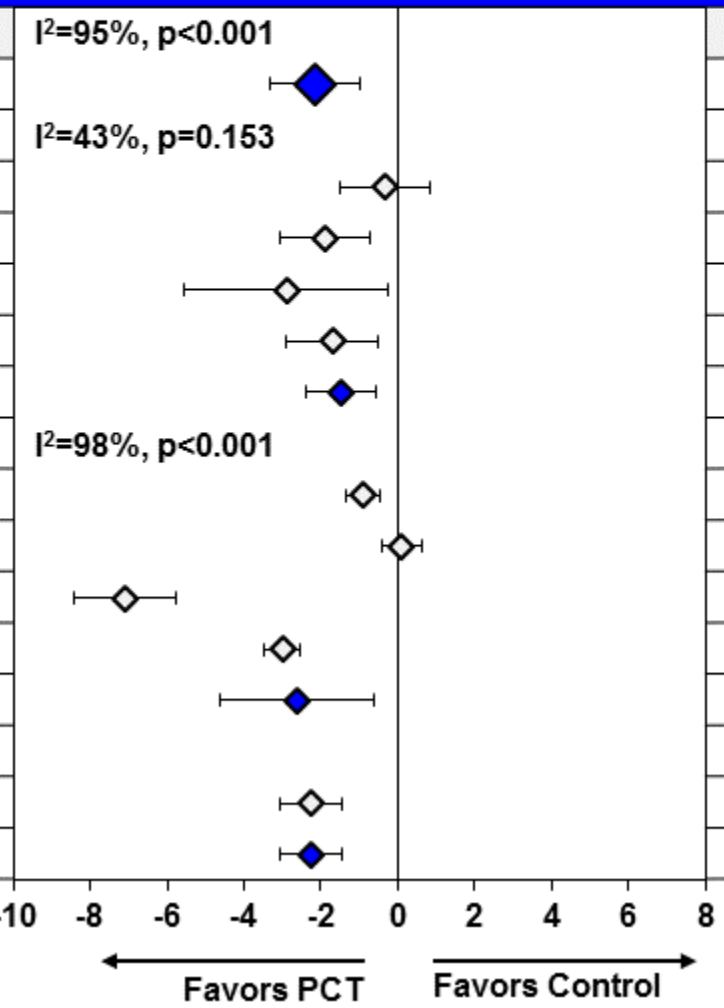
1. Meisner et al., Intens Care Med 2000
2. Meisner et al., Eur J Anaesthesiol 2001

Reported Adherence in Study-Level Meta-Analyses

Author	Adherence	
LRTI		
Kristoffersen	59%	Median = 82%
Corti	61%	
Branche	64%	
Christ-Crain (2004)	78%	
Briel	85%	
Burkhardt	87%	
Christ-Crain (2006)	87%	
Schuetz	91%	
Sepsis		
Bouadma	47%	Median = 72%
Annane	63%	
Nobre	81%	
de Jong	93%	

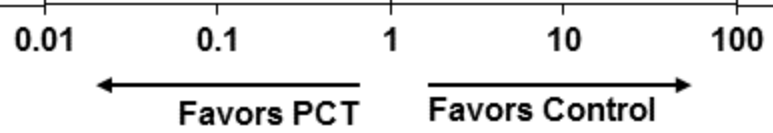
LRTI: Antibiotic Duration by PCT Adherence

Endpoint Study	Percent Weight	Mean Difference (95% CI)
Antibiotic Duration by PCT Adherence	I^2=95%, p<0.001	
Overall	**100%**	**-2.15 (-3.30, -0.99)**
Low Adherence	I^2=43%, p=0.153	
Branche (2015)	11.1%	-0.33 (-1.52, 0.85)
Christ-Crain (2004)	11.1%	-1.90 (-3.07, -0.73)
Corti (2016)	7.5%	-2.90 (-5.55, -0.25)
Kristoffersen (2009)	11.0%	-1.70 (-2.90, -0.50)
Subtotal	**40.7%**	**-1.47 (-2.39, -0.55)**
High Adherence	I^2=98%, p<0.001	
Briel (2008)	12.3%	-0.90 (-1.33, -0.47)
Burkhardt (2010)	12.2%	0.10 (-0.41, 0.61)
Christ-Crain (2006)	10.7%	-7.10 (-8.44, -5.76)
Schuetz (2009)	12.3%	-3.00 (-3.48, -2.52)
Subtotal	**47.5%**	**-2.62 (-4.61, -0.64)**
Adherence Not Reported		
Long (2011)	11.8%	-2.25 (-3.06, -1.44)
Subtotal	**11.8%**	**-2.25 (-3.06, -1.44)**



LRTI: Mortality by PCT Adherence

Endpoint Study	Percent Weight	Risk Ratio (95% CI)
Mortality by PCT Adherence	I^2=0%, p=0.957	
Overall	**100%**	**0.94 (0.69, 1.28)**
Low Adherence	I^2=0%, p=0.853	
Branche (2015)	8.4%	0.85 (0.29, 2.46)
Christ-Crain (2004)	5.1%	0.96 (0.25, 3.75)
Corti (2016)	1.7%	0.47 (0.04, 5.02)
Kristoffersen (2009)	1.7%	2.08 (0.19, 22.57)
Subtotal	**16.9%**	**0.91 (0.43, 1.92)**
High Adherence	I^2=0%, p=0.727	
Briel (2008)	0.9%	0.32 (0.01, 7.93)
Christ-Crain (2006)	26.9%	0.90 (0.50, 1.63)
Schuetz (2009)	43.7%	1.06 (0.66, 1.69)
Subtotal	**71.6**	**0.98 (0.68, 1.41)**
Adherence Not Reported	I^2=0%, p=0.352	
Stolz (2007)	8.5%	0.58 (0.20, 1.66)
Verduri (2015)	3.1%	1.53 (0.26, 8.96)
Subtotal	**11.6%**	**0.75 (0.30, 1.85)**

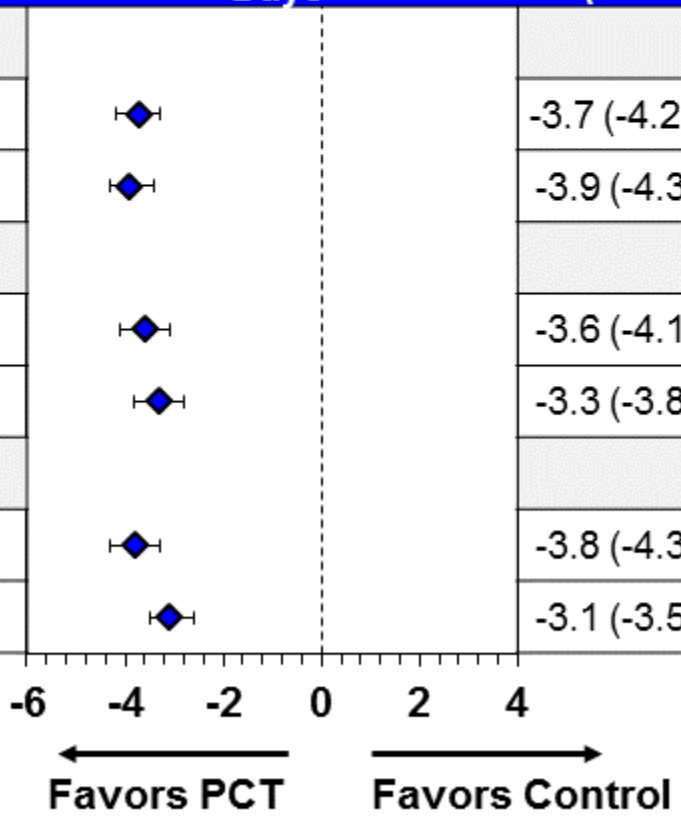


Extensive Training and Materials will Guide Appropriate Use of PCT Assay

- Laboratory training
- Physician and other healthcare provider in-service education (ISE)
- Interpretation of results materials
- Physician to Physician education
- Webinars and other ISE as requested by each healthcare system
- ISE by Nurses trained in Critical Care medicine and PCT

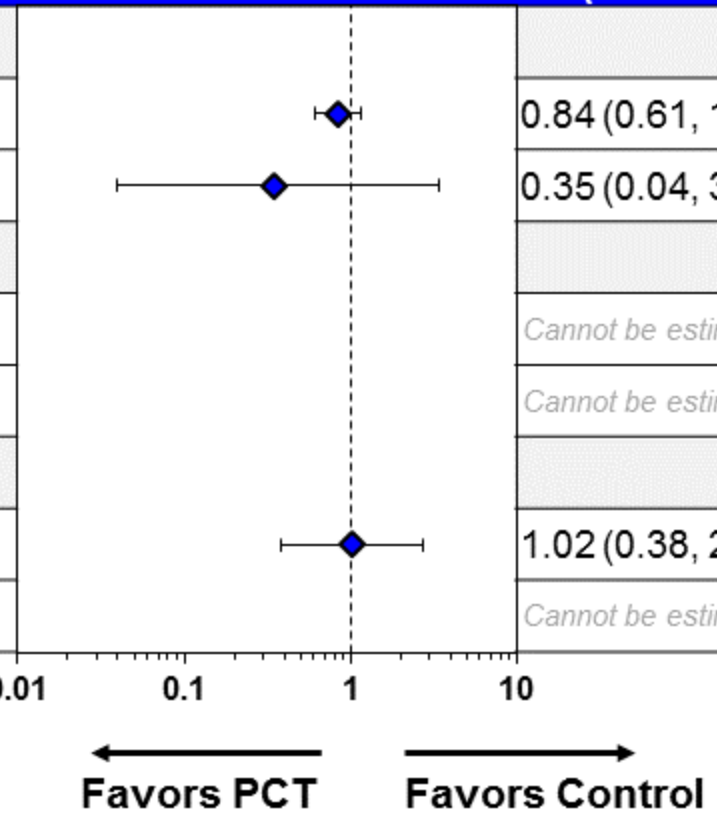
LRTI: Total Antibiotic Exposure in Patient-Level Analyses by Type of LRTI Stratified by Inpatient vs Outpatient

Endpoint	PCT Median (IQR) [n]	Control Median (IQR) [n]	Mean Difference (95% CI) Days	Mean Difference (95% CI)
CAP				
Inpatient	7 (4, 10) [750]	11 (9, 14) [769]		-3.7 (-4.2, -3.3,)
Outpatient	5 (2, 7) [207]	8 (6, 10) [217]		-3.9 (-4.3, -3.4)
Acute Bronchitis				
Inpatient	0 (0, 1) [70]	4 (0, 7) [79]		-3.6 (-4.1, -3.1)
Outpatient	0 (0, 0) [179]	6 (0, 7) [203]		-3.3 (-3.8, -2.8)
AECOPD				
Inpatient	0 (0, 7) [244]	6 (0, 10) [249]		-3.8 (-4.3, -3.3)
Outpatient	0 (0, 5) [44]	7 (2, 10) [47]		-3.1 (-3.5, -2.6)

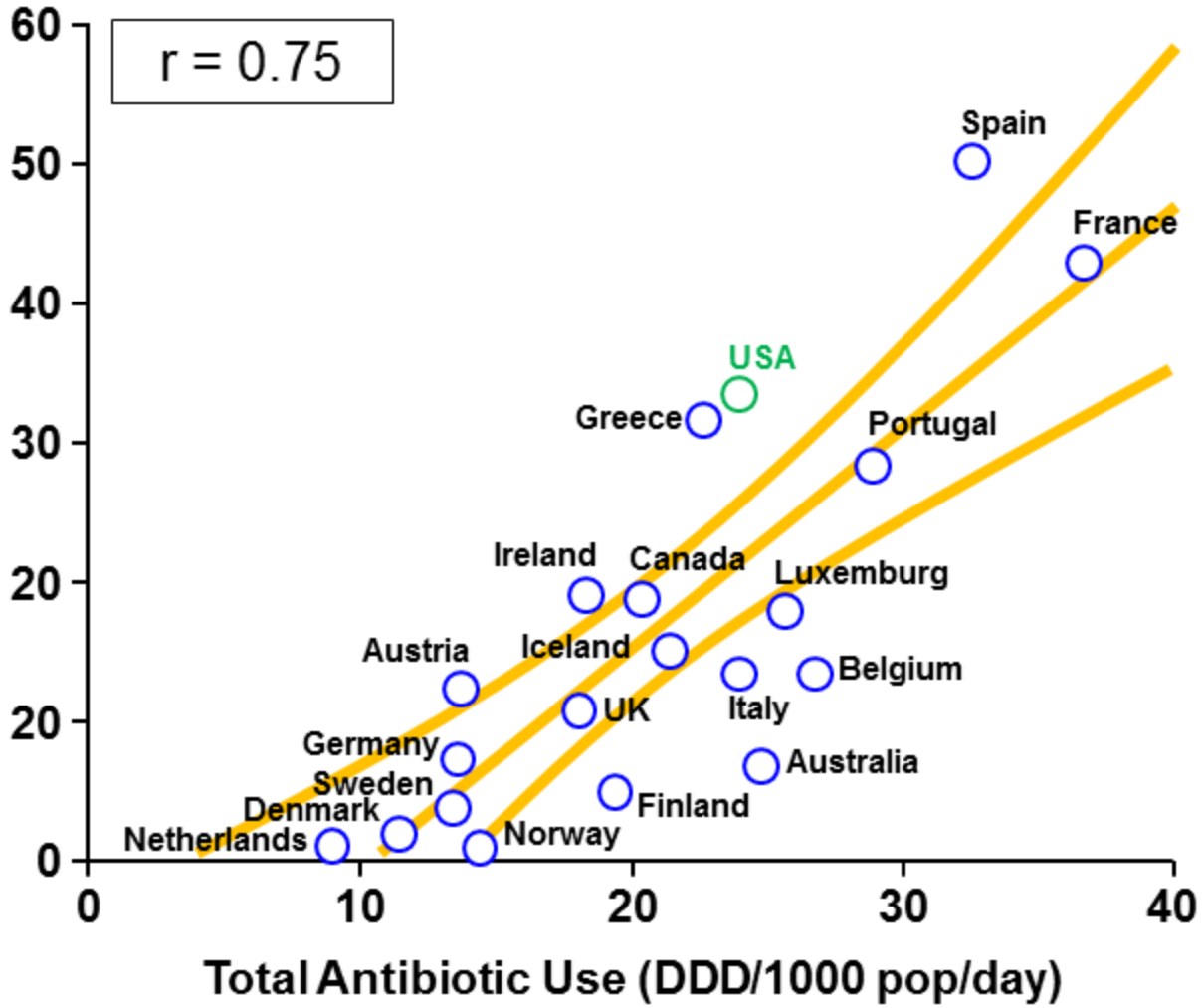


LRTI: Mortality in Patient-Level Analyses by Type of LRTI Stratified by Inpatient vs Outpatient

Endpoint	PCT n / N (%)	Control n / N (%)	OR/RR (95% CI)
CAP			
Inpatient	81 / 750 (10.8%)	97 / 769 (12.6%)	0.84 (0.61, 1.15)
Outpatient	1 / 207 (0.5%)	3 / 217 (1.4%)	0.35 (0.04, 3.40)
Acute Bronchitis			
Inpatient	2 / 70 (2.9%)	0 / 79 (0%)	*Cannot be estimated*
Outpatient	0 / 179 (0%)	0 / 203 (0%)	*Cannot be estimated*
AECOPD			
Inpatient	8 / 244 (3.3%)	8 / 249 (3.2%)	1.02 (0.38, 2.77)
Outpatient	1 / 44 (2.3%)	0 / 47 (0%)	*Cannot be estimated*



Possible Harm of Over-Treatment



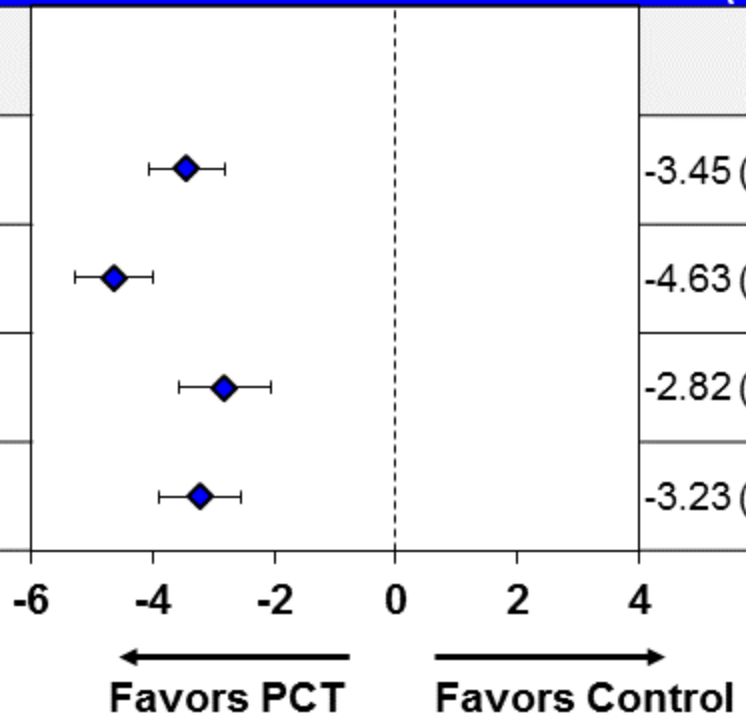
Albrich WC, Emerg Inf Dis 04

PCT Stability

- The sera or plasma separated from the clot can be stored at 2-8°C in stoppered tubes for up to 48 hours
- >48 hours longer storage is required, freeze at -25 ± 6°C
- Six-month storage of frozen samples does not affect the quality of results
- Three freeze/thaw cycles were validated.

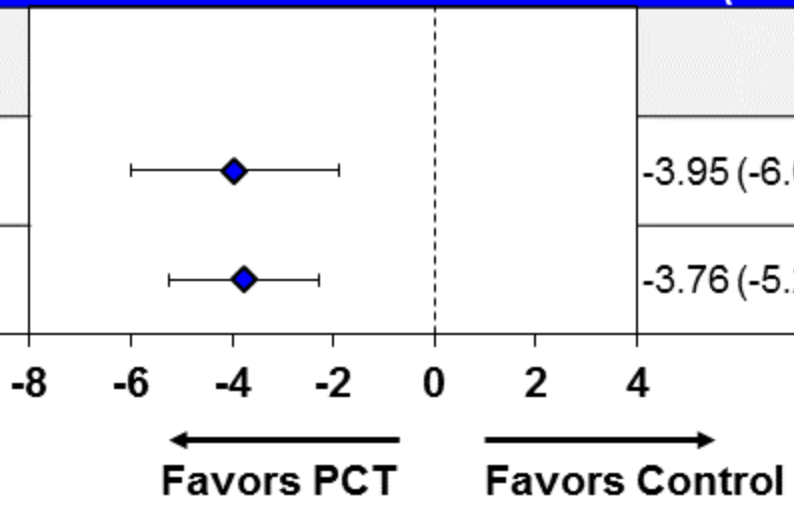
LRTI - Antibiotic Exposure by Initial PCT Level: Patient-Level Meta-Analysis

Endpoint Initial PCT Level	PCT Median (IQR)	Control Median (IQR)	Patient-Level Results	Mean Difference (95% CI)
LRTI - Antibiotic Exposure (days)				
<0.10 ng/mL	0 (0, 4)	7 (0, 10)		-3.45 (-4.07, -2.83)
0.10 – 0.25 ng/mL	2 (0, 6)	8 (5, 10)		-4.63 (-5.27, -3.99)
>0.25 – 0.50 ng/mL	5 (4, 8)	9 (6, 12)		-2.82 (-3.58, -2.05)
>0.50 ng/mL	8 (5, 11)	11 (8, 14)		-3.23 (-3.91, -2.54)



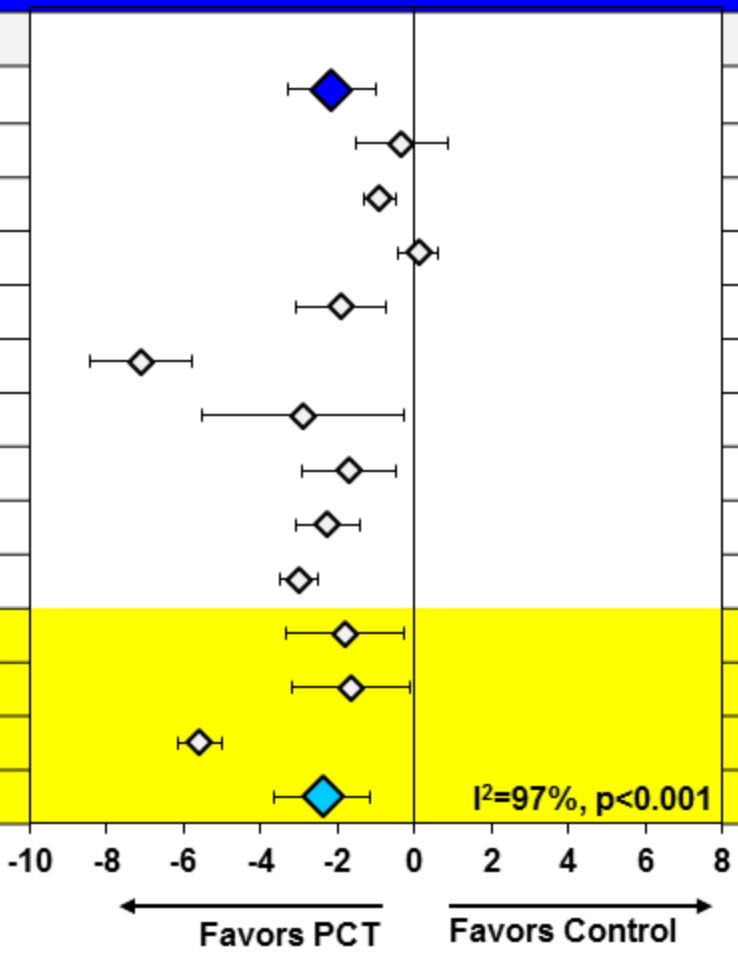
Sepsis - Antibiotic Exposure by Initial PCT Level: Patient-Level Meta-Analysis

Endpoint Initial PCT Level	PCT Median (IQR)	Control Median (IQR)	Patient-Level Results	Mean Difference (95% CI)
Sepsis - Antibiotic Exposure (days)				
≤ 0.50 ng/mL	7 (4, 12)	10 (8, 18)		-3.95 (-6.00, -1.90)
> 0.50 ng/mL	9 (6, 15)	14 (8, 20)		-3.76 (-5.24, -2.28)



LRTI: Antibiotic Exposure/Duration (Including Pediatrics)

Endpoint Study	Percent Weight	Mean Difference (95% CI)
Antibiotic Exposure/Duration		
Overall Adult Only		**-2.15 (-3.30, -0.99)**
Branche (2015)	8.4%	-0.33 (-1.52, 0.85)
Briel (2008)	9.0%	-0.90 (-1.33, -0.47)
Burkhardt (2010)	9.0%	0.10 (-0.41, 0.61)
Christ-Crain (2004)	8.4%	-1.90 (-3.07, -0.73)
Christ-Crain (2006)	8.2%	-7.10 (-8.44, -5.76)
Corti (2016)	6.4%	-2.90 (-5.55, -0.25)
Kristoffersen (2009)	8.3%	-1.70 (-2.90, -0.50)
Long (2011)	8.7%	-2.25 (-3.06, -1.44)
Schuetz (2009)	8.9%	-3.00 (-3.48, -2.52)
Baer (2013) – Pediatrics	8.0%	-1.80 (-3.32, -0.28)
Bao (2015) – Pediatrics	8.0%	-1.67 (-3.21, -0.12)
Esposito (2011) - Pediatrics	8.9%	-5.59 (-6.16, -5.02)
Overall Adult & Pediatrics	**100%**	**-2.40 (-3.64, -1.17)**



PEDIATRIC DATA
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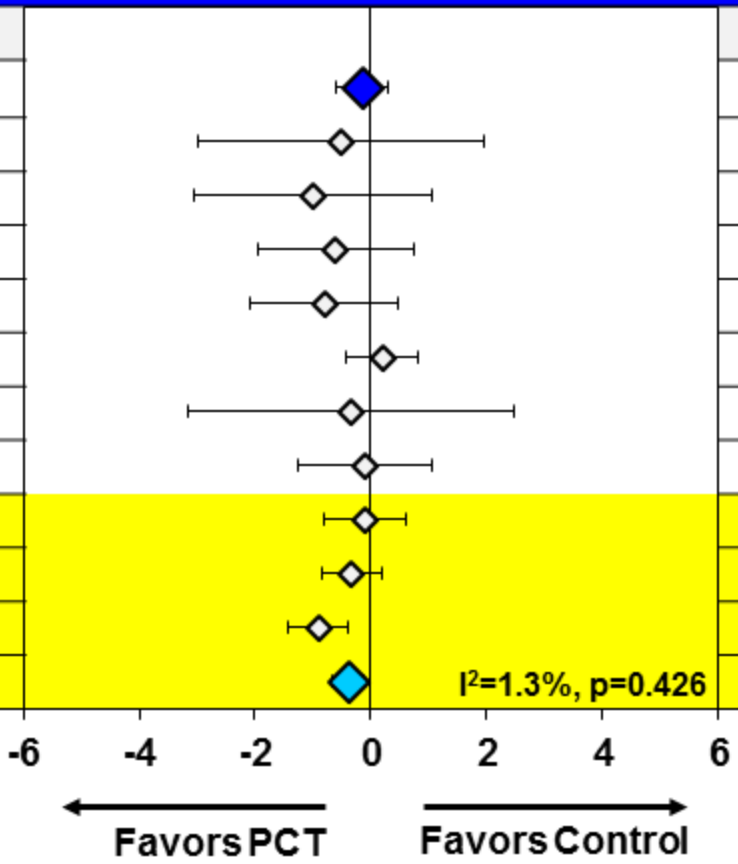
LRTI: Hospital Length of Stay (Including Pediatrics)

Endpoint Study	Percent Weight	Mean Difference (95% CI)
Length of Hospital Stay		
Overall Adult Only		**-0.15 (-0.60, 0.30)**
Christ-Crain (2004)	1.2%	-0.50 (-2.97, 1.97)
Christ-Crain (2006)	1.7%	-1.00 (-3.04, 1.04)
Corti (2016)	3.8%	-0.60 (-1.96, 0.76)
Kristoffersen (2009)	4.4%	-0.80 (-2.07, 0.47)
Schuetz (2009)	17.4%	0.20 (-0.43, 0.83)
Stolz (2007)	0.9%	-0.33 (-3.15, 2.49)
Verduri (2015)	5.2%	-0.10 (-1.26, 1.06)
Baer (2013) – Pediatrics	13.6%	-0.10 (-0.82, 0.62)
Bao (2015) – Pediatrics	25.6%	-0.33 (-0.85, 0.18)
Esposito (2011) - Pediatrics	26.3%	-0.91 (-1.42, -0.40)
Overall Adult & Pediatrics	**100%**	**-0.39 (-0.66, -0.13)**



PEDIATRIC DATA
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