APPENDIX

I. PROTOCOL

Population: Acute pancreatitis cases.

Acute Necrotizing Pancreatitis: Acute pancreatitis cases with >30% necrosis and/or serum CRP >100 mg/dL in abdominal CT.

Intervention and Comparison: Carbapenem prophylaxis (imipenem, meropenem, doripenem, ertapenem) and placebo or standard therapy without antibiotic therapy.

Outcome

***Mortality*:** In-hospital mortality.

***Surgical intervention*:** Cases with pancreatitis complications who underwent surgical intervention.

***Peri-pancreatic infection*:** Infection with microbiological evidence in peripancreatic tissue (in samples taken by surgery or fine needle aspiration).

***Non-pancreatic infections*:** Non-pancreatic infection proven by microbiological culture.

Types of Trials Included: Randomized control trials.

Inclusion Criteria

- Full-text or abstract available, English-written articles.
- Articles published up to December 2022.
- Articles including the intervention (carbapenems)-comparison (placebo or standard therapy) groups in acute pancreatitis cases.

Exclusion Criteria

- Articles comparing carbapenems with other antibiotic groups in acute pancreatitis.

Review process

The systematic review was conducted in accordance with the PRISMA guidelines. Three reviewers searched the literature and retrieved all publications that met the inclusion criteria.

Each publication was evaluated for methodological quality using the Cochrane Collaboration's risk assessment tool for risk of bias for RCTs.

Literature Search Databases: PUBMED database.

Literature Search Keywords

- Pancrea* and carbapenem
- Pancrea* and imipenem
- Pancrea* and meropenem
- Pancrea* and ertapenem
- Pancrea* and doripenem

Data Analysis and Recording: Cases characteristics (necrotizing or non-necrotizing pancreatitis), treatment regimens (Type of carbapenems, duration, starting time), outcomes (mortality, surgical intervention, peri-pancreatic or non-pancreatic infections and their definitions), follow-up periods were controlled and recorded.

Bias Assessment for Studies: Bias assessment for RCTs was made according to version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), 22 August 2019.

II. CHARACTERISTICS AND OUTCOMES OF STUDIES INCLUDED IN THE SYSTEMATIC REVIEW AND META-ANALYSIS

Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet. 1993;176(5):480-3.		
Methods	Randomized controlled trial Multicenter study ***Allocation method:*** Casual number table (pre-printed random tables) ***Blinding:*** Open	
Including criteria	Acute pancreatitis cases	
Excluding criteria	Not stated	
Number of total cases	74 patients	
Intervention	41 patients received medical treatment with prophylactic antibiotics (imipenem 0.5 g every 8 hours for 14 days	
Control	33 patients received medical treatment without prophylactic antibiotics	
Outcomes	- Mortality - Surgery - Peripancreatic infections - Non-pancreatic infections - Adverse events	
Follow-up duration	Not stated	
Bias	**Authors' judgement**	**Reason for judgement**
Random sequence generation	Low risk	Casual number table
Allocation concealment	Unclear risk	Not available
Blinding of participants and personnel	Unclear risk	Not available
Blinding of outcome	Unclear risk	Not available
Incomplete outcome data	Low risk	There were post-randomization dropouts
Selective reporting	Low risk	Outcome results, including adverse events, were reported
Other bias	Low risk	No other risk of bias

Nordback I, Sand J, Saaristo R, Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis--a single-center randomized study. J Gastrointest Surg. 2001;5(2):113-8; discussion 118-20. [CrossRef]	
Methods	Randomized controlled trial Monocenter study ***Allocation method:*** Not stated ***Blinding:*** Open
Including criteria	Patients with severe acute pancreatitis and pancreatic necrosis (Severity based on CRP concentration > 150 mg/L and computerized tomography [CT])
Excluding criteria	- Patients who had already been started on antibiotics - Patients admitted directly to the intensive care unit (ICU) with multiorgan failure

	- Patients suspected to have a reaction to study drugs	
Number of total cases	58 patients	
Intervention	25 patients received medical treatment with prophylactic antibiotics (Imipenem 1g every 8 hours; therapy duration was not stated)	
Control	33 patients received medical treatment without prophylactic antibiotics	
Outcomes	- Mortality - ICU or hospital stay - Adverse event	
Follow-up duration	Not stated	
Bias	**Authors' judgement**	**Reason for judgement**
Random sequence generation	Unclear risk	Not available
Allocation concealment	Unclear risk	Not available
Blinding of participants and personnel	Unclear risk	Not available
Blinding of outcome	Unclear risk	Not available
Incomplete outcome data	High risk	There were post-randomization dropouts (32 cases)
Selective reporting	High risk	Adverse events were not reported
Other bias	Low risk	No other risk of bias

Hejtmankova S, Cech P, Hoskovec D, Kostka R, Leffler J, Kasalicky M, et al. Antibiotic prophylaxis in severe acute pancreatitis: Randomized multicenter prospective study with meropenem. Gastroenterology. 2003;124(4):A85. [CrossRef]		
Methods	Randomized controlled trial Multicenter study ***Allocation Method:*** Not stated ***Blinding:*** Open	
Including criteria	Patients with severe acute pancreatitis	
Excluding criteria	- < 18 years of age - More than 48 hours from the onset of symptoms - Pancreatitis following surgery or endoscopic retrograde cholangiopancreatography (ERCP) - Infectious complications - Already receiving antibiotics for the previous two weeks	
Number of total cases	41	
Intervention	21 participants received medical treatment with prophylactic antibiotics (Meropenem 0.5 g every 8 hours for 10 days)	
Control	20 participants received medical treatment without antibiotics	
Outcomes	- Mortality - Surgery - Peripancreatic infection stay	
Follow-up duration	**???**	
Bias	**Authors' judgement**	**Reason for judgement**
Random sequence generation	Unclear risk	Not available
Allocation concealment	Unclear risk	Not available
Blinding of participants and personnel	Unclear risk	Not available
Blinding of outcome	Unclear risk	Not available

Incomplete outcome data	Unclear risk	Not available
Selective reporting	Low risk	Outcome results, including adverse events, were reported
Other bias	Low risk	No other risk of bias

Manes G, Uomo I, Menchise A, Rabitti PG, Ferrara EC, Uomo G. Timing of antibiotic prophylaxis in acute pancreatitis: a controlled randomized study with meropenem. Am J Gastroenterol. 2006;101(6):1348-53. [CrossRef]		
Methods	Randomized controlled trial Multicenter study ***Allocation method:*** Computer-generated list ***Blinding:*** Open	
Including criteria	- Patients older than 18 years - Diagnosis of AP, admission within 48 hours of onset of symptoms - No intake of antibiotics in the 3 days before admission	
Excluding criteria	- Referred patients - Immunocompromised patients - Patients with underlying chronic pancreatitis	
Number of total cases	59	
Intervention	30 participants received medical therapy with prophylactic antibiotic (500 g every 8 hours for at least 14 days)	
Control	29 participants received medical therapy without prophylactic antibiotic	
Outcomes	- Mortality - Surgery - Peripancreatic infection - Non-pancreatic infection - Multiorgan failure - Systemic complications (acute renal failure, acute respiratory distress syndrome, pleuropericardial effusion, diabetic ketoacidosis, hypocalcemia, cardiac arrhythmia, gastrointestinal bleeding) - Local complications (portal/mesenteric, thrombosis, pancreatic fistula, pseudocysts, pancreatic ascites) -Hospitalization days	
Follow-up duration	Not Stated	
Bias	**Authors' judgement**	**Reason for judgement**
Random sequence generation	Low risk	Computer generated list
Allocation concealment	Unclear risk	Not available
Blinding of participants and personnel	Unclear risk	Not available
Blinding of outcome	Unclear risk	Not available
Incomplete outcome data	Low risk	There were no post-randomization dropouts
Selective reporting	High risk	Adverse events were not reported.
Other bias	Low risk	No other risk of bias

Røkke O, Harbitz TB, Liljedal J, Pettersen T, Fetvedt T, Heen LØ, et al. Early treatment of severe pancreatitis with imipenem: a prospective randomized clinical trial. Scand J Gastroenterol. 2007;42(6):771-6. [CrossRef]	
Methods	Randomized controlled trial Multicenter study

	Allocation method: Computer-based randomization without stratification ***Blinding:*** Open	
Including criteria	- Patients with severe acute pancreatitis - Necrosis on CT and CRP>120 first 24 hours or CRP>200 first 48 hours - Duration of symptoms of less than 72 hours and	
Excluding criteria	- Age below 18 years - Ongoing antibiotic treatment - Previous episodes of acute pancreatitis - Post-ERCP pancreatitis - Concomitant bacterial infection such as cholangitis or cholecystitis - Allergy to imipenem - Pregnancy	
Number of total cases	73	
Intervention	36 patients received early antibiotic treatment with imipenem (0.5 g, every 8 hours, for 5-7 days)	
Control	37 patients received medical therapy without antibiotics	
Outcomes	- Mortality - Surgery - Peripancreatic infection - Non-pancreatic infection - Organ failure - ICU and hospital stay - Adverse events	
Follow-up duration	1 month	
Bias	**Authors' judgement**	**Reason for judgement**
Random sequence generation	Low risk	Computer-based randomization
Allocation concealment	Unclear risk	Not available
Blinding of participants and personnel	High risk	Unblinded
Blinding of outcome	High risk	Unblinded
Incomplete outcome data	Low risk	There were no post-randomization dropouts
Selective reporting	High risk	Adverse events were not reported.
Other bias	Low risk	No other risk of bias

Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg. 2007;245(5):674-83. [CrossRef]	
Methods	Randomized controlled trial Multicenter study ***Allocation method:*** Computer-based randomization ***Blinding:*** Double-blind
Including criteria	- Patients with 30% necrosis of the pancreas confirmed by contrast-enhanced CT or who had non-contrast scans with extensive or multiple peripancreatic fluid collections of either CRP > 120 mg/L or multiple organ dysfunction (MOD)>2 - Patients within 120 hours of the onset of symptoms
Excluding criteria	- Patients diagnosed with a concurrent pancreatic or peripancreatic infection - Patients received an investigational drug 30 days before enrollment - Antimicrobial therapy for 48 hours before randomization - Patients who had an allergy to beta-lactam antimicrobial agents

	- Patients who received or were likely to require probenecid - Progressing underlying disease, neutropenia, or cirrhosis - Pregnant or lactating females	
Number of total cases	100	
Intervention	50 participants received medical treatment with meropenem (1g every 8 hours, for 2-21 days)	
Control	50 received medical treatment without antibiotic	
Outcomes	- Mortality - Surgery - Peripancreatic infection. - Non-pancreatic infection - Adverse events	
Follow-up duration	42 days	
Bias	**Authors' judgement**	**Reason for judgement**
Random sequence generation	Low risk	Computer-based randomization
Allocation concealment	Low risk	Random numbers
Blinding of participants and personnel	Low risk	Double-blind
Blinding of outcome	Low risk	Double-blind
Incomplete outcome data	Low risk	There were no post-randomization dropouts
Selective reporting	Low risk	Outcomes including adverse events were reported
Other bias	Low risk	No other risk of bias

Xue P, Deng LH, Zhang ZD, Yang XN, Wan MH, Song B, et al. Effect of antibiotic prophylaxis on acute necrotizing pancreatitis: results of a randomized controlled trial. J Gastroenterol Hepatol. 2009;24(5):736-42. [CrossRef]	
Methods	Randomized controlled trial Multicenter study ***Allocation method:*** Computer-derived random number sequence ***Blinding:*** Open
Including criteria	- Patients older than 18 years - Patients with 30% or more necrosis of the pancreas, as proven by contrast-enhanced computerized tomography (CECT), - Patients within 72 hours after the onset of the symptoms
Excluding criteria	-Concurrent sepsis or (peri)pancreatic infection caused by a second disease -Direct transfer to the ICU due to multiple organ failure -Recurrent or ERCP, or traumatic or operative pancreatitis -Pregnancy, malignancy or immunodeficiency -History of allergy to imipenem-cilastatin -History of antibiotic administration within 48 hours before enrollment -Possible death within 48 hours after enrollment.
Number of total cases	56
Intervention	29 participants received medical therapy with the antibiotic Imipenem (0.5 g every 8 hours, for 7-14 days)
Control	27 participants received medical therapy without antibiotic
Outcomes	- Mortality - Surgery - Peri-pancreatic infection - Non-pancreatic infection - Adverse events

Follow-up duration	**Not stated**	
Bias	**Authors' judgement**	**Reason for judgement**
Random sequence generation	Low risk	Computer-derived random number sequence
Allocation concealment	Unclear risk	Not available
Blinding of participants and personnel	Unclear risk	Not available
Blinding of outcome	Unclear risk	No available
Incomplete outcome data	High risk	There were post-randomization dropouts
Selective reporting	Low risk	Outcomes, including adverse events, were reported
Other bias	Low risk	No other risk of bias

Poropat G, Goričanec K, Lacković A, Kresović A, Lončarić A, Marušić M. Systematic review with trial sequential analysis of prophylactic antibiotics for acute pancreatitis. antibiotics (Basel). 2022;11(9):1191. [CrossRef]		
Methods	Randomized controlled trial Multicenter study ***Allocation method:*** Computer-generated random number sequence ***Blinding:*** Double-blind	
Including criteria	- Patients older than 18 years - First episode of AP and a calculated acute physiology and chronic health evaluation II (APACHE II) score of ≥8, regardless of etiology - Patients presented at the hospital within 72 hours of symptoms onset.	
Excluding criteria	- Active and documented infection at admission - Concomitant antibiotic treatment or antibiotic treatment present within 72 hours before enrollment - AP diagnosed at surgery - Active malignancy - Known immune deficiency - Chronic pancreatitis - Pregnant and breastfeeding women - Patients unwilling to participate	
Number of total cases	98	
Intervention	Patients received prophylactic antibiotics (500g, every 8 hours)	
Control	Patients received placebo	
Outcomes	- Mortality - Surgery - Peripancreatic infection - Non-pancreatic infection - Serious adverse events	
Follow-up duration	Not Stated	
Bias	**Authors' judgement**	**Reason for judgement**
Random sequence generation	Low risk	Computer-based randomization
Allocation concealment	Low risk	Random numbers
Blinding of participants and personnel	Low risk	Double-blind

Blinding of outcome	Low risk	Double-blind
Incomplete outcome data	Low risk	There were no post-randomization dropouts
Selective reporting	Low risk	Outcomes, including adverse events, were reported.
Other bias	Low risk	No other risk of bias

III. RESULTS OF THE META-ANALYSIS

PICO 1: Does the use of prophylactic carbapenem reduce the risk of mortality in acute pancreatitis cases?

P: Acute pancreatitis cases

I: Carbapenem

C: Placebo or standard therapy

O: In-hospital mortality

Figure 1a. Forest plot for mortality in all studies

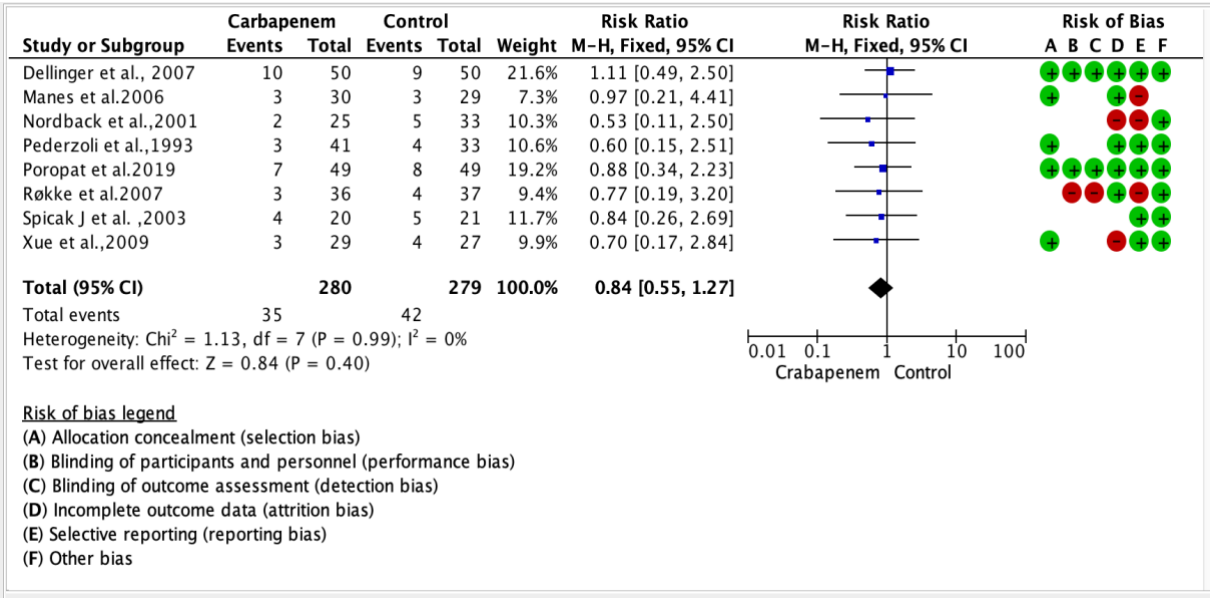


Figure 1b. Forest plot for mortality in studies only included acute necrotizing pancreatitis

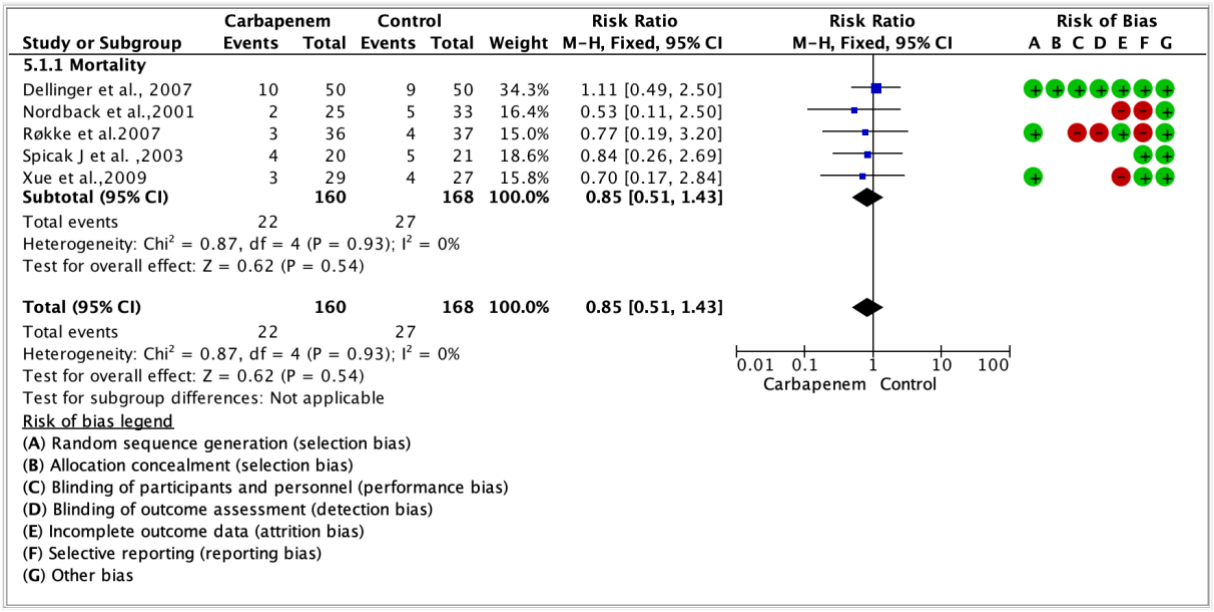


Figure 1c. Forest plot for mortality in studies compared imipenem and placebo/standard therapy

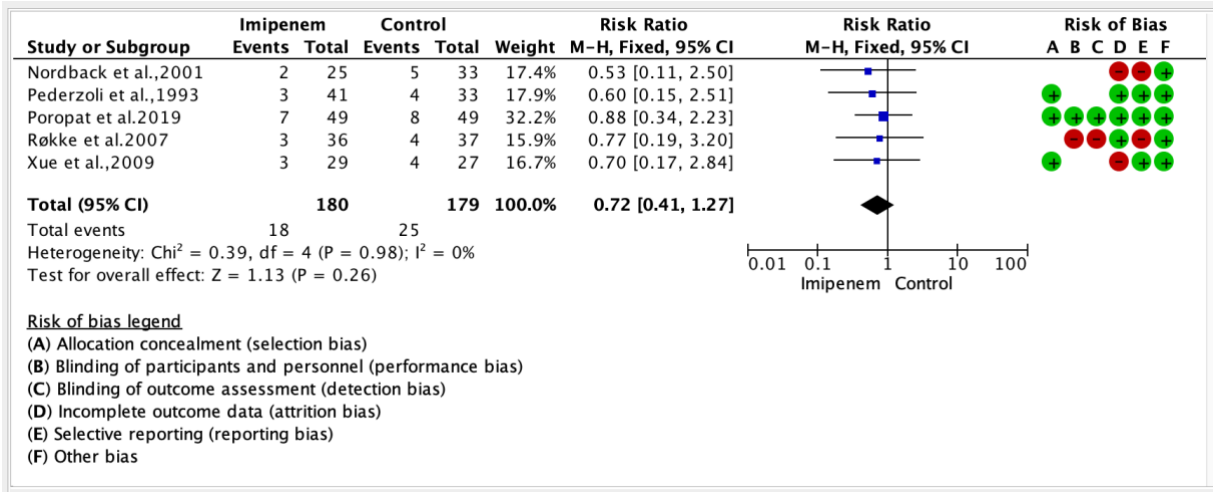


Figure 1d. Forest plot for mortality in high-quality studies

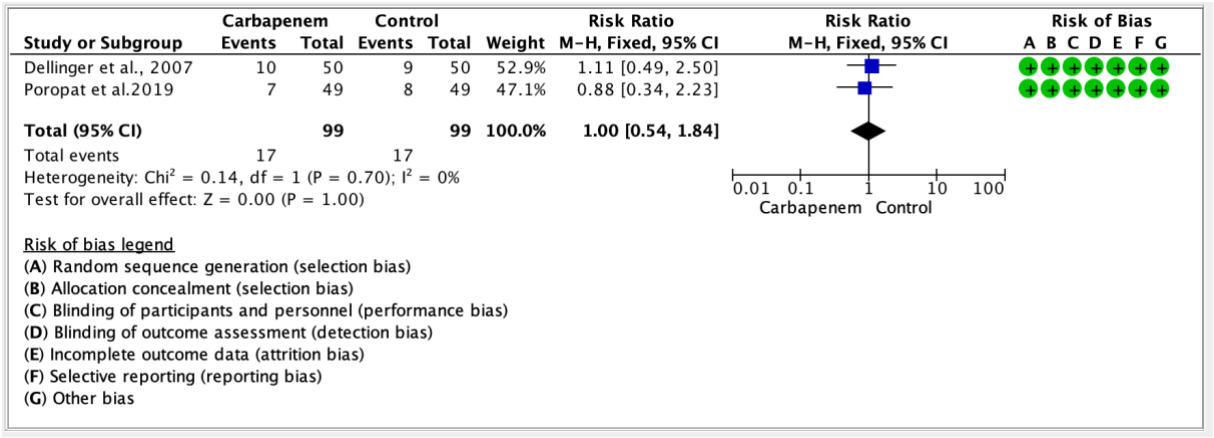
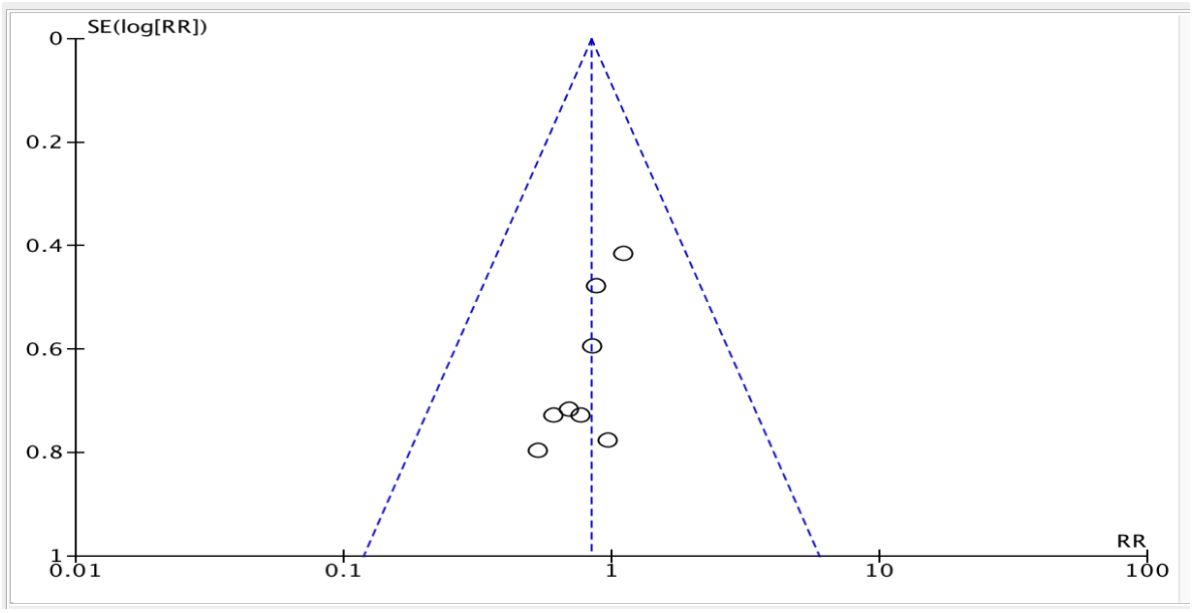


Figure 1f. Funnel plot for mortality studies



PICO 2: Does the use of prophylactic carbapenem reduce the risk of surgical intervention in acute pancreatitis cases?

P: Acute pancreatitis cases

I: Carbapenem

C: Placebo or standard therapy

O: Surgical intervention

Figure 2a. Forest plot for surgical intervention in all studies.

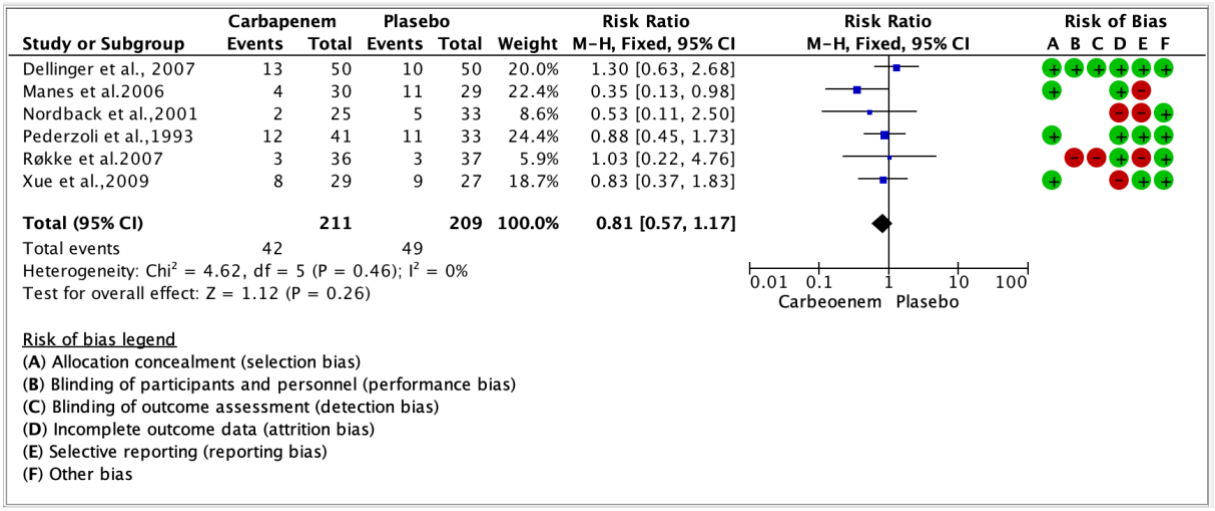


Figure 2b. Forest plot for surgical intervention in studies only included acute necrotizing pancreatitis.

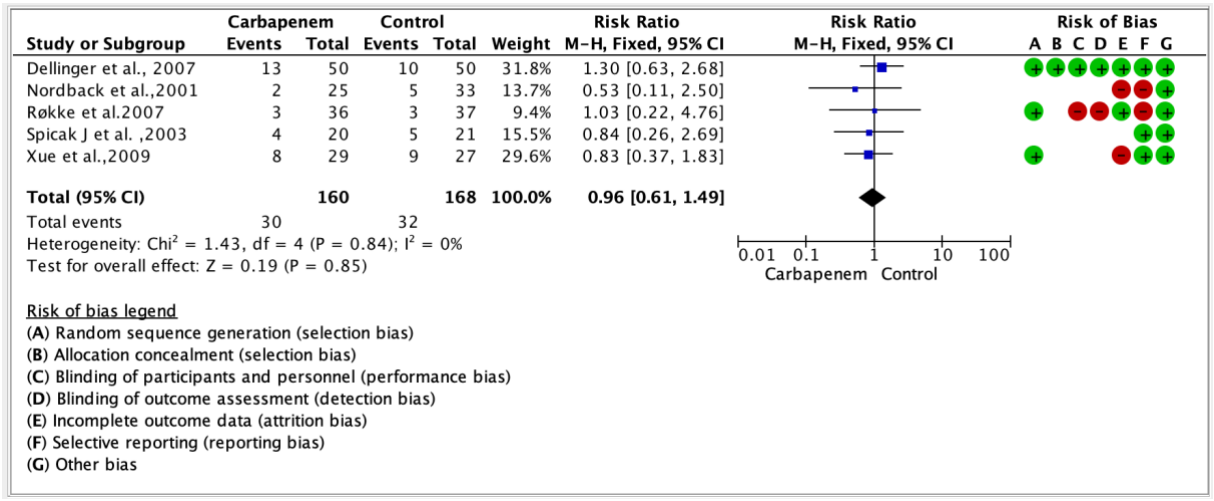


Figure 2c. Forest plot for surgical intervention in studies compared imipenem and placebo/standard therapy.

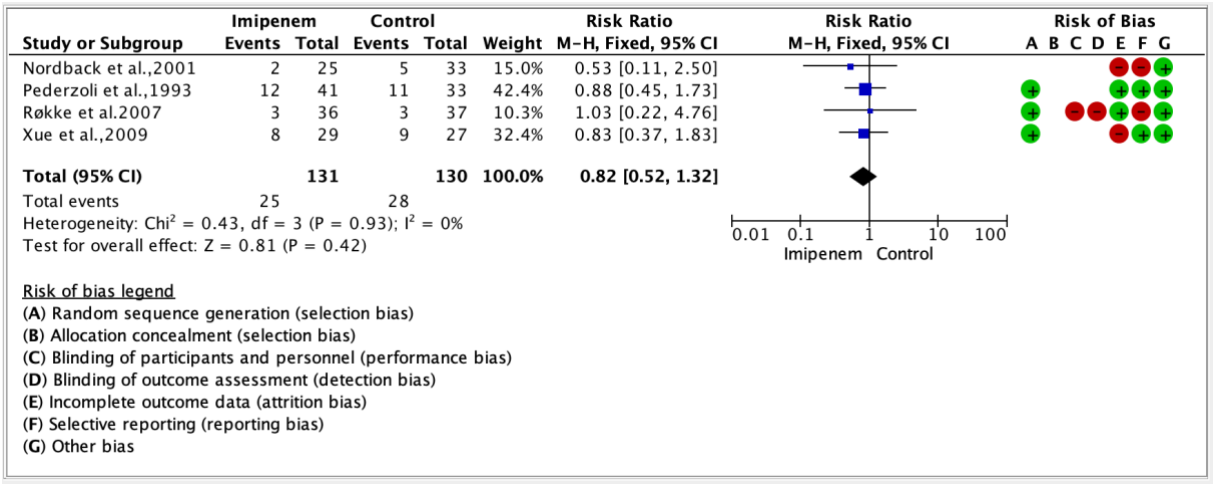
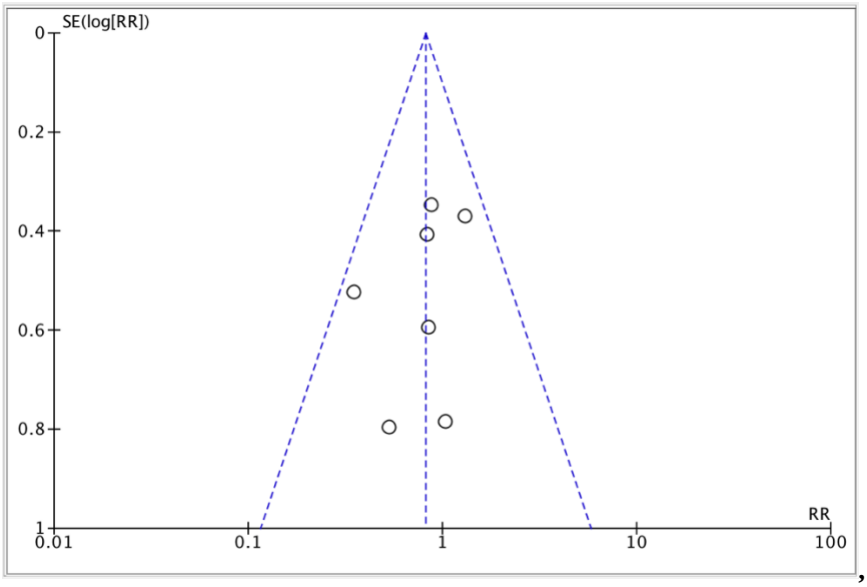


Figure 2d. Funnel plot for surgical intervention studies.



PICO 3: Does the use of prophylactic carbapenem reduce the risk of peripancreatic infection in acute pancreatitis cases?

P: Acute pancreatitis cases

I: Carbapenem

C: Placebo or standard therapy

O: Peripancreatic infection

Figure 3a. Forest plot for peripancreatic infection in all studies.

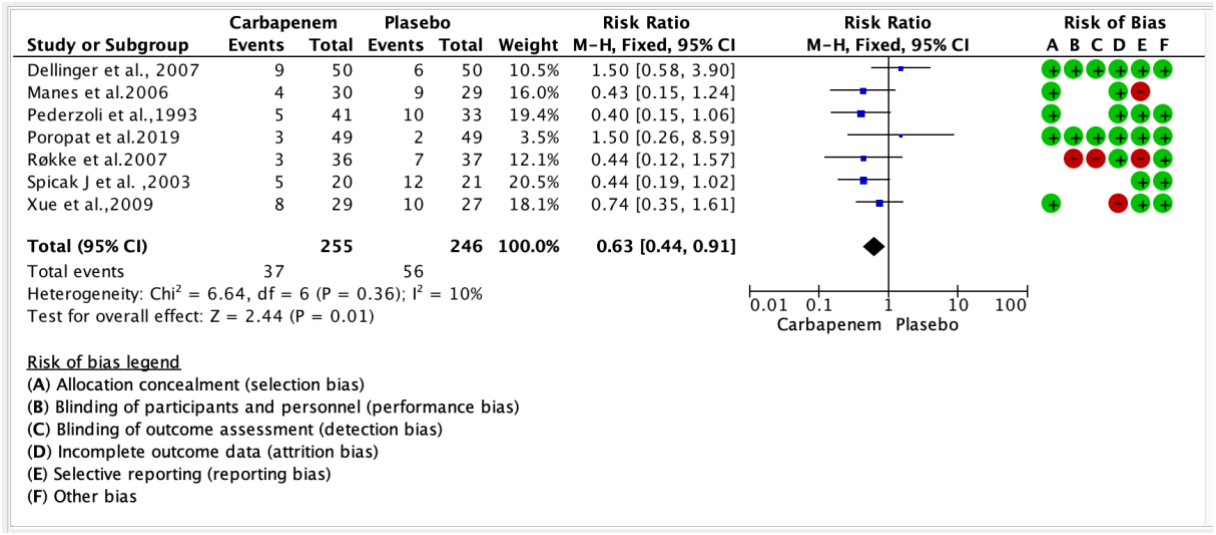


Figure 3b. Forest plot for peripancreatic infections in studies only included acute necrotizing pancreatitis.

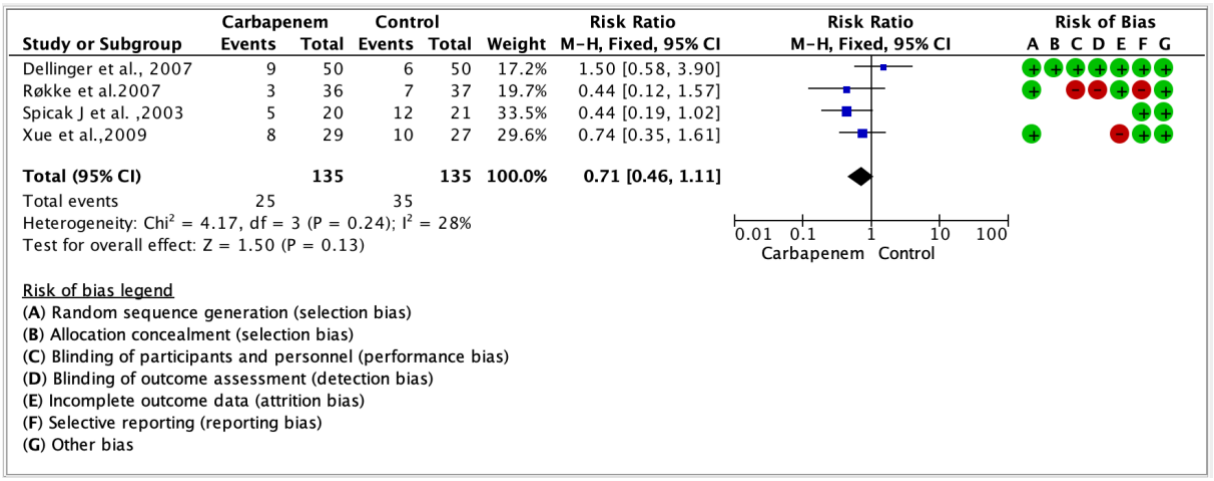


Figure 3c. Forest plot for peripancreatic infections in studies compared imipenem and placebo/standard therapy.

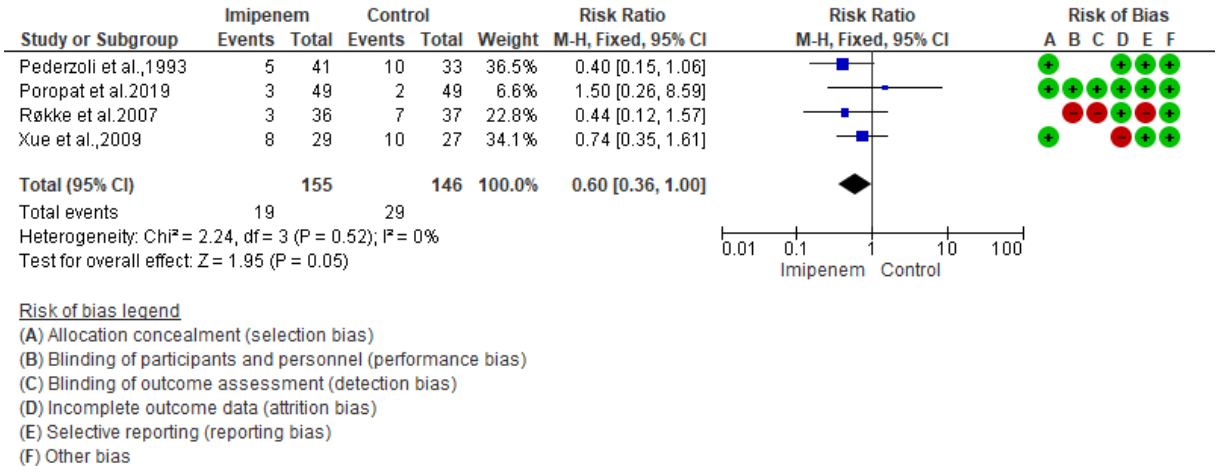


Figure 3d. Forest plot for peripancreatic infections in high-quality studies.

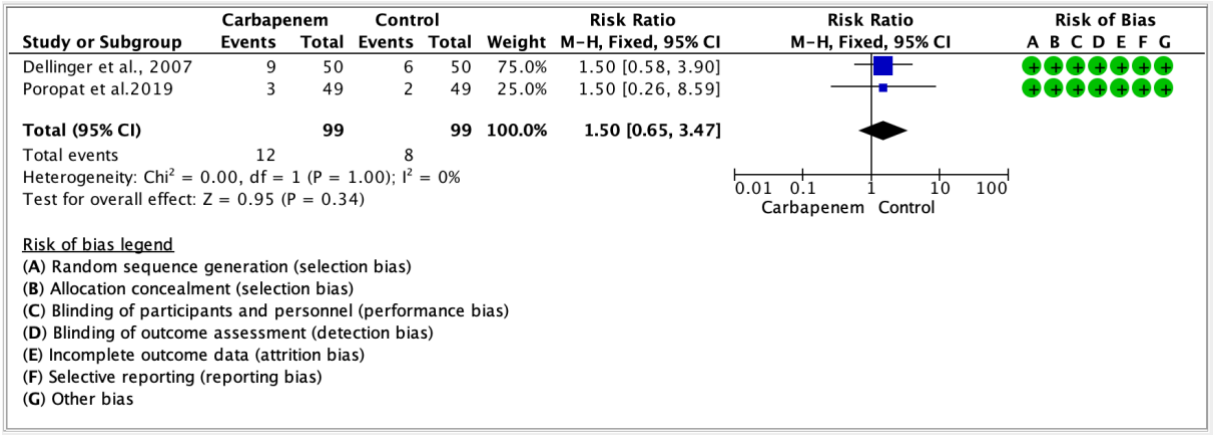
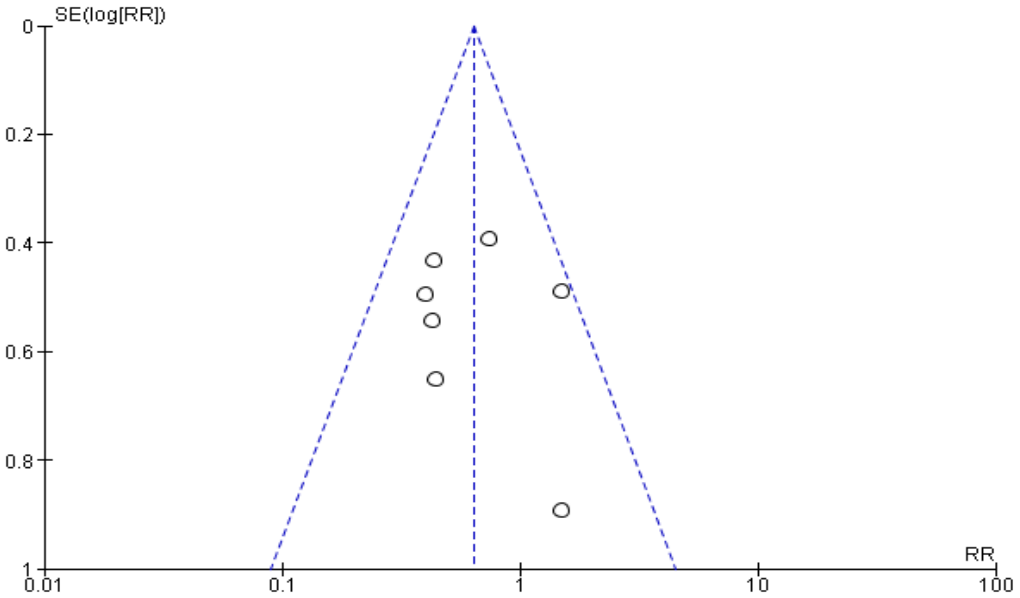


Figure 3e. Funnel plot for peripancreatic infection studies.



PICO 4: Does the use of prophylactic carbapenem reduce the risk of non-pancreatic infection in acute pancreatitis cases?

P: Acute pancreatitis cases

I: Carbapenem

C: Placebo or standard therapy

O: Non-pancreatic infection

Figure 4a. Forest plot for non-pancreatic infection in all studies.

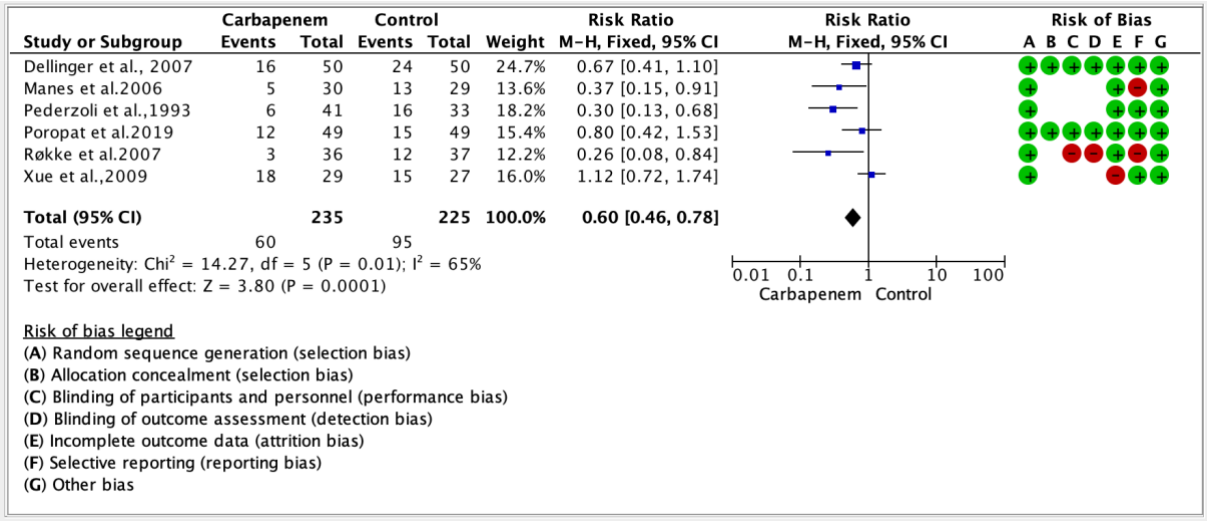


Figure 4b. Forest plot for non-pancreatic infection in studies only included acute necrotizing pancreatitis.

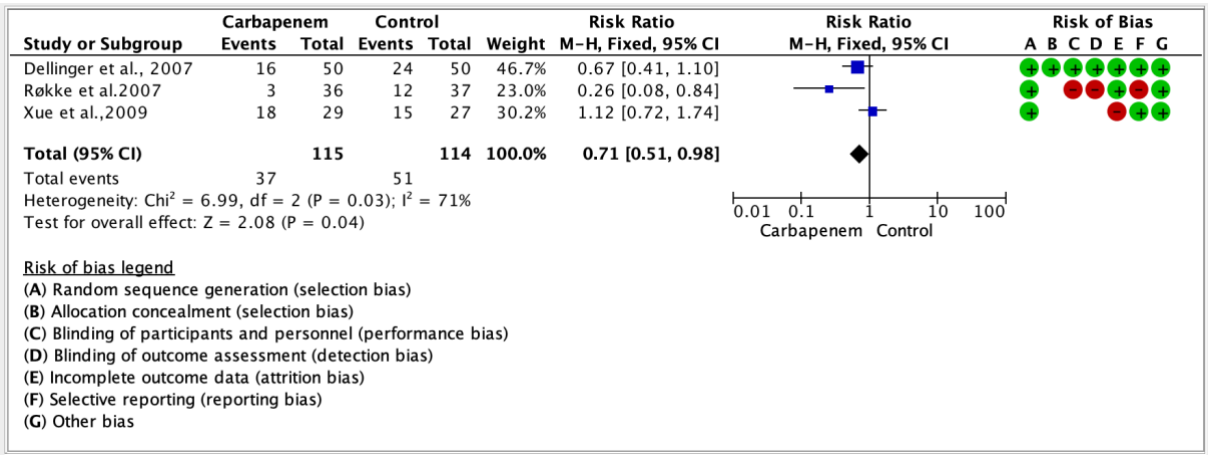


Figure 4c. Forest plot for non-pancreatic infection in studies compared imipenem and placebo/standard therapy.

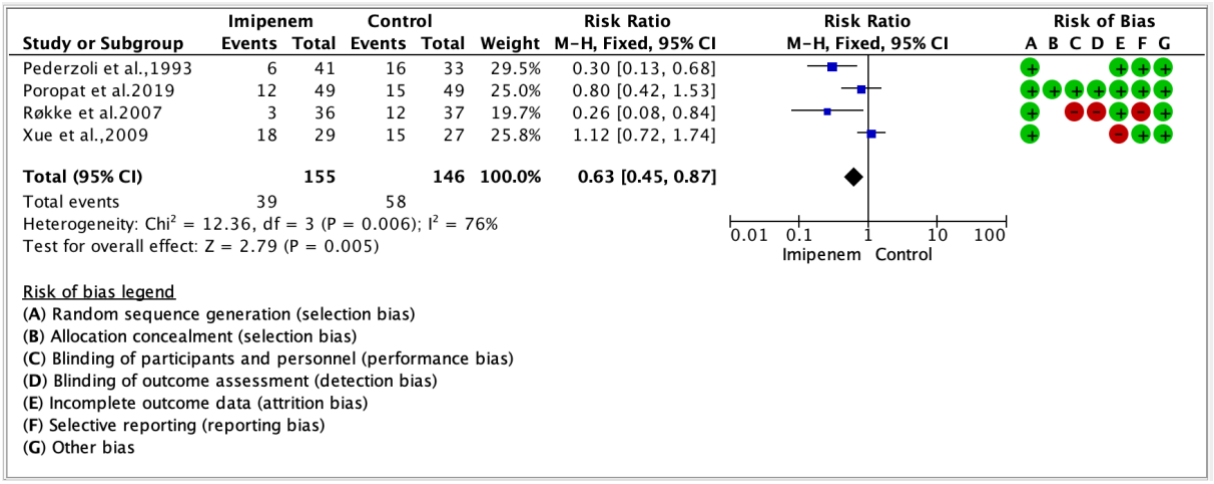


Figure 4d. Forest plot for non-pancreatic infections in high-quality studies.

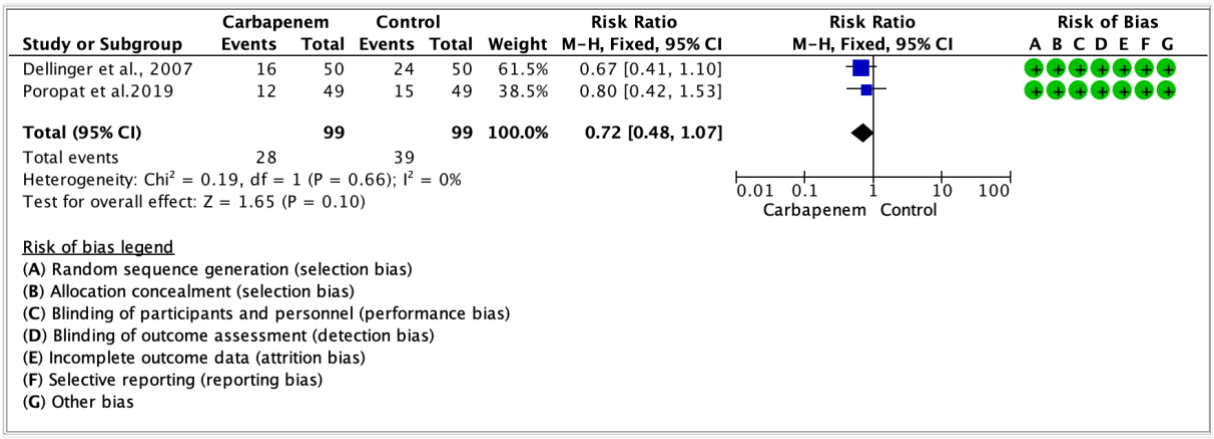


Figure 4e. Funnel plot for non-pancreatic infection studies.

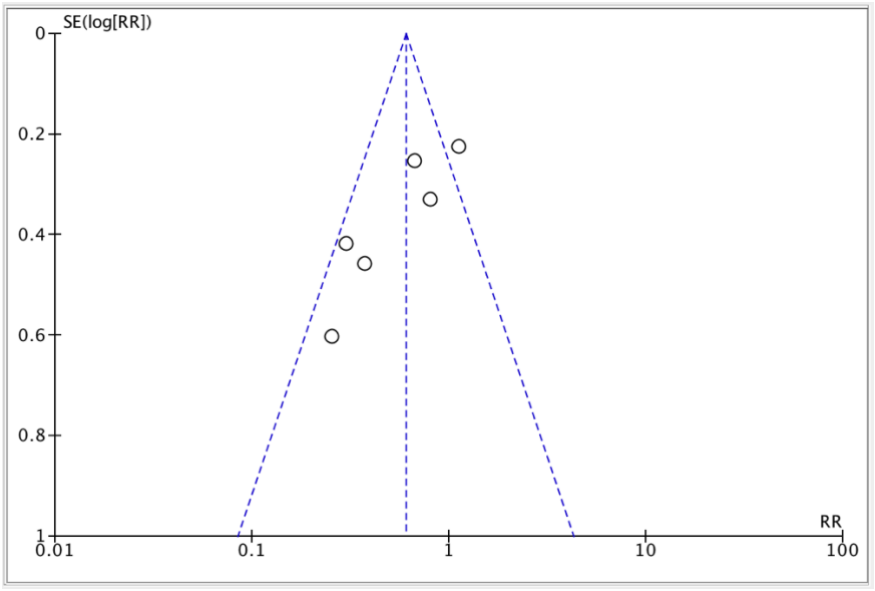


Table 1. Summary of findings.

Results	Patients (studies)	Relative effect (95% CI)	Absolute effect	
			The risk with placebo or standard therapy	The expected difference in risk with carbapenem therapy (95% CI)
Mortality	559 (8)	0.85 (0.55-1.27)	150/1000 cases	26 fewer/1000 cases (-83 - +32)
Surgical intervention	420 (6)	0.81 (0.57-1.17)	234/1000 cases	35 fewer/1000 cases (-114 - +43)
Peripancreatic infection	501 (7)	0.60 (0.41-0.87)	228/1000 cases	90 fewer/1000 cases (-158 - -23)
Non-pancreatic infection	460 (6)	0.60 (0.46-0.78)	422/1000 cases	167 fewer/1000 cases (-252 - -82)