Prophylactic antibiotics delivered via the respiratory tract to reduce ventilator-associated pneumonia: A systematic review, net-work meta-analysis, and Trial Sequential Analysis of Randomized Controlled Trials

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Table S1. Summary of previous meta-analysis.

Author	Included studies (study type)	Primary outcome	Results	Trial sequential analysis	Sensitivity analysis/ secondary analyses	Subgroup analyses	Network meta-analysis of indirect comparisons among different medicine	Network meta-analysis of indirect comparisons between nebulization and intratracheal instillation	Adverse events
Li et al*	Lode et al.,1988 (RCT) Rathgeber et al.,1993 (RCT) Wood et al.,2002 (RCT) Claridge et al.,2007 (RCT) Karvouniaris et al.,2015 (RCT) Kuzovlev et al.,2015 (RCT) Ehrmann et al.,2023 (RCT)	Incidence of VAP	A lower risk of VAP (RR 0·69, 95%CI [0·53–0·89]).	Required sample size was almost reached.	Confirmed by separately including two RCTs with a portion of non-intubated patients and two non-RCTs	The reduction in the risk of VAP due to intervention was more pronounced in subgroups where aminoglycosides or nebulization	Did not find any significant difference in-between those antibiotics in terms of VAP incidence. Rank probabilities assessment showed that inhaled colistin had the highest likelihood of reducing the risk of VAP	Did not find any significant difference in the incidence of VAP in-between those two modalities. Rank probabilities assessment showed that nebulization had the highest likelihood of reducing the risk of VAP	Two RCTs reported adverse events including bronchospasm, hypoxemia, and acute kidney injury, but their incidences were not significantly increased in the intervention group.
		Hospital mortality	No significant difference (RR 0·88 [0·75–1·03])	Required sample size was not reached.		No significant difference in hospital mortality were also found in subgroup analyses based on types of antibiotics and modalities of antibiotics administration through the respiratory tract	NR	NR	Five RCTs did not observe any adverse events, two RCTs and two non-RCTs did not report data on adverse events
Falagas et al.,2006[8]	Lode et al.,1988 (RCT) Rathgeber et al.,1993 (RCT) Wood et al.,2002 (RCT) Greenfield et al.,1973 (RCT, mechanically ventilated or not) Klatersky et al.,1974 (RCT, mechanically ventilated or not)	Incidence of ICU-acquired pneumonia	Less incidence of ICU-acquired pneumonia (OR = 0.49, 95% CI 0.32–0.76).	NR	Confirmed by including the three non-randomized comparative trials	NR	NR	NR	In five of the included studies no data regarding toxicity were reported. In two RCTs it was reported that no toxicity was observed during the trials, whereas in the remaining RCT the authors characterized the observed toxicity negligible, without reporting any further
		Mortality	No difference (OR = 0.86, 95% CI 0.55–1.32).	NR		NR	NR	NR	

									detail
Povoa et al.,2018[6]	Lode et al.,1988 (RCT) Wood et al.,2002 (RCT) Claridge et al.,2007 (RCT) Karvouniaris et al.,2015 (RCT) Klatersky et al.,1974 (RCT, mechanically ventilated or not) Rouby et al.,1994 (non-RCT)	Incidence of VAP	Lower incidence of VAP (OR 0.53; 95% CI 0.34–0.84).	NR	NR NR	NR	NR	NR	NR
		ICU mortality	No significant difference (OR 0.89; 95% CI 0.64–1.25)	NR		NR	NR	NR	
Zha et al.,2023[7]	Lode et al.,1988 (RCT) Rathgeber et al.,1993 (RCT) Wood et al.,2002 (RCT) Claridge et al.,2007 (RCT) Karvouniaris et al.,2015 (RCT) Klatersky et al.,1974 (RCT, mechanically ventilated or not) Rouby et al.,1994 (non-RCT)	Incidence of VAP	Lower incidence of VAP (OR 0.70; 95% CI 0.59–0.82)	NR	Sensitivity analyses were also conducted to assess the impact of each study on the pooled RR; the statistical results were not markedly altered after removing any study	NR	In the individual comparisons, no statistically difference was found between each antibiotics administered the respiratory tract. The assessment of rank probabilities indicated that aerosolized tobramycin presented the greatest likelihood of reducing the incidence of VAP	NR	NR
		ICU mortality	No difference (OR 0.94; 95% CI 0.76–1.16)	NR		NR	NR	NR	

*: This meta-analysis; NR, not reported; VAP, ventilator associated pneumonia; ICU, intensive care unit; OR, odds ratio; RR ,relative risk; CI, confidence interval

Search strategy

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("ventilator associated pneumonia" OR "ventilator-associated pneumonia" OR "vap" OR "nosocomial pneumonia" OR "hospital acquired pneumonia" OR "hospital-acquired pneumonia" OR "healthcare associated pneumonia" OR "healthcare-associated pneumonia" OR "health care associated pneumonia" OR "health care-associated pneumonia" OR "health-care associated pneumonia" OR "health-care-associated pneumonia" OR "icu acquired pneumonia" OR "icu-acquired pneumonia" OR "nosocomial bronchopneumonia") AND (antibacterial* OR "anti bacterial" OR "anti bacterials" OR "anti-bacterial" OR "anti-bacterials" OR antibiotic* OR aztreonam OR azthreonam OR urobactam OR azactam OR tobramycin OR obracin OR tobracin OR brulamycin OR nebcin OR nebicin OR "nebramycin factor six" OR "nebramycin factor 6" OR colisti* OR "polymyxin e" OR colimycin OR totazina OR ceftazidime OR fortaz OR fortum OR tazidime OR amika* OR yectamid OR biklin OR biclin OR amikin OR amiklin OR amukin OR gamikal OR kanbine OR oprad OR gentamicin* OR gentamycin* OR garamycin OR gentacycol OR gentavet OR genticin OR aminoglycoside* OR ciprofloxacin OR ciprinol OR amphotericin* OR fungizone OR amphocil OR caspofungin OR cancidas OR fluconazol* OR zonal OR beagyne OR diflucan OR "fluc hexal" OR flucobeta OR flucolich OR flunazul OR fungata OR lavisa OR loitin OR neofomiral OR oxifungol OR solacap OR triflucan OR posaconazole OR noxafil OR voriconazole OR vfend OR vancomycin* OR vancocin* OR diatracin OR meropenem OR merrem OR ronem OR penem OR ertapenem OR invanoz OR invanz OR imipenem OR imipemide OR "n-formimidoylthienamycin" OR "n formimidoylthienamycin" OR doripenem) AND (inhal* OR respirat* OR nebuli* OR vapor* OR vapour* OR atomi* OR aerosol* OR aeroli* OR endotracheal* OR intratracheal* OR "intra-tracheal" OR "intra tracheal" OR instillati*)

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Table S2. Summary of included non-randomized controlled trial studies in the meta-analysis.

Author	Country	Study design	Centers	ICU_type	Patients_type	Interventions	No. of Patients	Sex(F/M[a])	Age-yr	Medicine	Mode of administration	Days of administration
Rouby et al., 1994	France	prospective non-randomized	Unicenter	Surgical ICU	Adult	Usual care	251	124/127	51±12[b](survivors) 56±18[b](non- survivors)			
						Usual care+ topical use of antibiotics	347	168/179	53±16[b](survivors) 58±16[b](non- survivors)	Colistin,200000 U,q3h	Intratracheal instillation	15 days or until extubation
Klick et al.,1975	United States	prospective non-randomized	Unicenter	R-SICU	NR	topical use of 0.9% saline	370	NR	60[c]	0.9% saline,q4h	Intratracheal instillation	NR
						topical use of antibiotics	374	NR	57[c]	Polymyxin B, 2.5 mg/kg /day in 6 divided doses,q4h		

[a] F/M represents female/male.

[b] The value is a mean ± SD.

[c] The value is a mean

R-SICU,Respiratory-surgical ICU;NR,not reported;q3h,every 3 hours; q4h,every 4 hours.

Table S3. Summary of RCT studies which included a portion of mechanically ventilated patients in the meta-analysis

	Country	Centers	ICU_type	Patients_type	Group	No. of Patients	Sex(F/M[d])	Age-yr	Medicine	Mode of administration	Days of administration
Klastersky et al.,1974	Belgium	U[a]	Neurosurgical ICU	NR	IG[b]	43	14/29	51.2[e]	Gentamicin,80mg 0.9% saline	Intratracheal instillation, tid	NR
					CG[c]	42	4/38	43.5[e]			
Greenfield et al.1973	United States	U[a]	R-SICU	NR	IG[b]	33	15/18	20-39 15%[f] 40-59 24%[f] ≥60 61%[f]	Polymyxin B, 2.5 mg/kg /day in 6 divided doses	Intratracheal instillation, q4h	NR
					CG[c]	25	13/12	20-39 12%[f] 40-59 24%[f] ≥60 64%[f]			

[a] U represents unicenter.

[b] IG represents intervention group.

[c] CG represents control group.

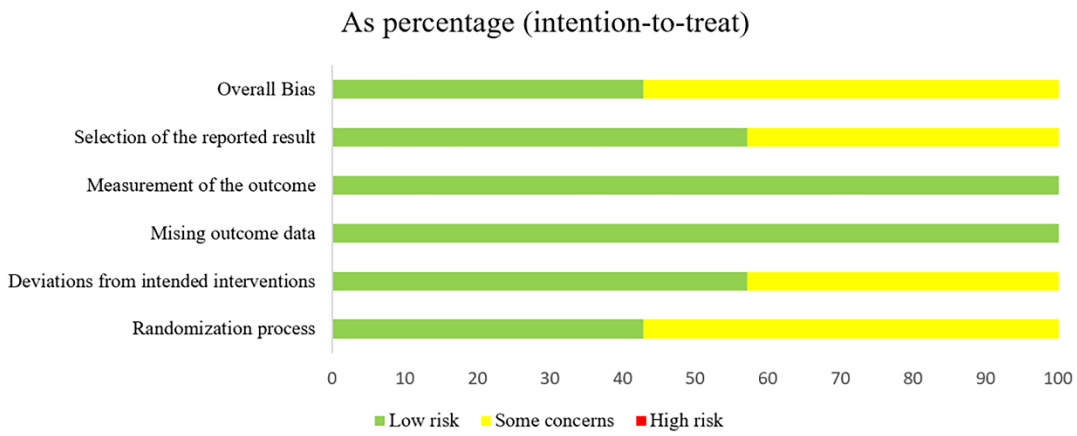
[d] F/M represents female/male.

[e] The value is a mean.

[f] This data represents the age group and proportion of patients.

R-SICU ,Respiratory-surgical ICU;NR, not reported; tid,three times a day; q4h,every four hours.

Figure S1. Assessment on risk of bias for included RCTs



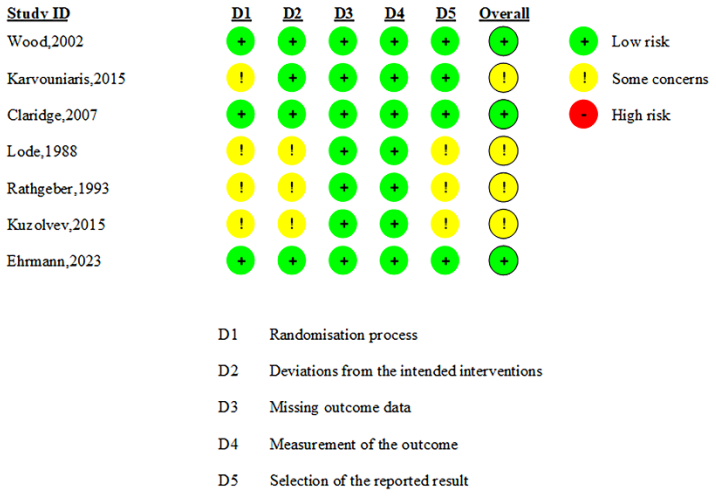


Table S4. Grading of recommendations, assessment, development and evaluations (GRADE).

Outcome	No of studies	Study design	No of participants		Certainty assessment					No of patients		Effect (Random effects model)		Certainty
			Topical use of antibiotics	Control	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias[m]	Topical use of antibiotics	Control	Relative risk (95% CI)	Absolute effect (95% CI)	
Incidence of VAP	7	RCT	715	730	Not serious[a]	Low[b]	Moderate[h]	Low	-	151/715 (21.1%)	219/730 (30.0%)	0.69 (0.53-0.89)	-	⨁⨁⨁◯ Moderate
Subgroup: Aminoglycosides	4	RCT	558	574	Not serious[a]	High[c]	Moderate[h]	Low	-	105/558 (18.8%)	155/574 (27.0%)	0.67 (0.47-0.97)		⨁⨁◯◯ Low
Subgroup: Ceftazidime	2	RCT	73	72	Not serious[a]	High[d]	Substantial[i]	Low	-	32/73 (43.8%)	39/72 (54.2%)	0.72 (0.35-1.49)		⨁◯◯◯ Very low[n]
Subgroup: Colistin	1	RCT	84	84	Not serious[a]	High[d]	NA[j]	Low	-	14/84 (16.7%)	25/84 (29.8%)	0.56 (0.31-1.00)		⨁◯◯◯ Very low[o]
Subgroup: Intratracheal instillation	1	RCT	85	77	Not serious[a]	High[d]	NA[j]	Low	-	29/85 (34.1%)	25/77 (32.5%)	1.05 (0.68-1.63)		⨁◯◯◯ Very low[o]
Subgroup: Nebulization	6	RCT	630	653	Not serious[a]	Low[e]	Low[k]	Low	-	122/630 (19.4%)	194/653 (29.7%)	0.64 (0.49-0.83)		⨁⨁⨁⨁ High
All-cause hospital mortality	7	RCT	715	730	Not serious[a]	High[d]	Low[k]	Low	-	192/715 (26.9%)	223/730 (30.5%)	0.88 (0.75-1.03)	-	⨁⨁⨁◯ Moderate
Subgroup: Aminoglycosides	4	RCT	558	574	Not serious[a]	High[d]	Low[k]	Low	-	153/558 (27.4%)	180/574 (31.4%)	0.83 (0.65-1.07)		⨁⨁⨁◯ Moderate
Subgroup: Ceftazidime	2	RCT	73	72	Not serious[a]	High[d]	Low[k]	Low	-	10/73 (13.7%)	12/72 (16.7%)	0.82 (0.37-1.81)		⨁⨁◯◯ Low[n]
Subgroup: Colistin	1	RCT	84	84	Not serious[a]	High[d]	NA[j]	Low	-	29/84 (34.5%)	31/84 (36.9%)	0.94 (0.62-1.40)		⨁◯◯◯ Very low[o]
Subgroup: Intratracheal instillation	1	RCT	85	77	Not serious[a]	High[d]	NA[j]	Low	-	23/85 (27.1%)	30/77 (39.0%)	0.69 (0.44-1.09)		⨁◯◯◯ Very low[o]
Subgroup: Nebulization	6	RCT	630	653	Not serious[a]	High[d]	Low[k]	Low	-	169/630 (26.8%)	193/653 (29.6%)	0.91 (0.77-1.08)		⨁⨁⨁◯ Moderate
Incidence of VAP on day 14	2	RCT	73	72	Not serious[a]	High[d]	Substantial[i]	Low	-	24/73 (32.9%)	35/72 (48.6%)	0.55 (0.18-1.64)	-	⨁◯◯◯ Very low[n]
Incidence of VAP on day 30	2	RCT	137	136	Not serious[a]	High[d]	Substantial[i]	Low	-	40/137 (29.2%)	51/136 (37.5%)	0.77 (0.45-1.33)	-	⨁◯◯◯ Very low[n]
VAP IDR	2	RCT	501	514	Not serious[a]	High[c]	Low[k]	Low	-	30.4/501 (6.1%)	52.6/514 (10.2%)	0.58 (0.36-0.93)	-	⨁⨁◯◯ Low[n]
Incidence of GNB VAP	2	RCT	501	514	Not serious[a]	Low[e]	Low[k]	Low	-	40/501 (8.0%)	82/514 (16.0%)	0.50 (0.35-0.71)	-	⨁⨁⨁◯ Moderate[n]
Incidence of Staphylococcus VAP	2	RCT	137	136	Not serious[a]	High[d]	Low[k]	Low	-	15/137 (10.9%)	14/136 (10.3%)	1.05 (0.54-2.05)	-	⨁⨁◯◯ Low[n]
Incidence of MDR VAP	2	RCT	137	136	Not serious[a]	High[d]	Substantial[l]	Low	-	21/137 (15.3%)	28/136 (20.6%)	0.71 (0.22-2.25)	-	⨁◯◯◯ Very low[n]
Incidence of VAP after VAT	2	RCT	501	514	Not serious[a]	High[d]	Low[k]	Low	-	29/501 (5.8%)	41/514 (8.0%)	0.85 (0.34-2.12)	-	⨁⨁◯◯ Low[n]
Time of VAP occurrence since randomization	2	RCT	501	514	Not serious[a]	High[f]	Substantial[l]	Low	-	501	514	-	3.97 days longer (1.17- 6.77)	⨁◯◯◯ Very low[n]
Duration of IMV	4	RCT	574	586	Not serious[a]	High[g]	Low[k]	Low	-	574	586	-	0.06 days shorter (-1.08-0.96)	⨁⨁⨁◯ Moderate
Duration of systemic antibiotics	2	RCT	437	450	Not serious[a]	High[g]	Substantial[i]	Low	-	437	450	-	3.45 days shorter (-8.72, 1.83)	⨁◯◯◯ Very low[n]
Need for tracheostomy	2	RCT	137	136	Not serious[a]	High[d]	Moderate[h]	Low	-	77/137 (56.2%)	68/136 (50%)	1.10 (0.81-1.49)	-	⨁◯◯◯ Very low[n]

ICU length of stay	5	RCT	601	613	Not serious[a]	High[g]	Substantial[l]	Low	-	601	613	-	0.41 days shorter (-4.96-4.13)	⊕⊕◯◯	Low
Hospital length of stay	3	RCT	554	566	Not serious[a]	High[g]	Low[k]	Low	-	554	566	-	0.74 days shorter (-3.08-1.60)	⊕⊕⊕◯	Moderate

[a]. According to Figure Assessment of risk of bias for RCTs, 3 studies did not mention random sequence generation, 2 studies did not mention allocation concealment, 2 studies were open-label trials.

[b]. The 95% CI of relative risk did not overlap a relative risk of 1.0 (no effect), trial sequential analysis showed that, while the required sample size of 1,449 was not quite reached, it was very close, and the cumulative Z-score did not fall within futility boundaries but crossed the O'Brian-Fleming boundaries.

[c]. Although the 95% CI of relative risk did not overlap a relative risk of 1.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

[d]. The 95% CI of relative risk overlapped a relative risk of 1.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

[e]. The 95% CI of relative risk did not overlap a relative risk of 1.0 (no effect). Trial sequential analysis supported the true positive conclusion by reaching the optimal information size.

[f]. Although the 95% CI of absolute effect did not overlap a mean difference of 0.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

[g]. The 95% CI of absolute effect overlapped a mean difference of 0.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

[h]. I^2 >30% and <60%, although heterogeneity test showed p-value > 0.05.

[i]. I^2 >50% and <90%, although heterogeneity test showed p-value > 0.05.

[j]. Only one study was included.

[k]. I^2 <40%, heterogeneity test showed p-value > 0.05.

[l].I^2 >50% and <90%, heterogeneity test showed p-value < 0.05.

[m]. For each outcome, the number of trials included is less than 10, so it is difficult to assess the publication bias by the Egos test.

[n]. It was downgraded by one level because only two studies were included and trial sequential analysis showed that the required sample size was far from being reached.

[o]. It was downgraded by one level because only one study was included and the imprecision was not available.

VAP, ventilator associated pneumonia; VAP IDR, adjudicated ventilator associated pneumonia incidence density per 1,000 days of invasive mechanical ventilation; GNB, gram negative bacteria; MDR,multi-drug resistance; VAT, ventilator associated tracheitis; IMV, intensive mechanical ventilation; CI, confidence interval; ICU, intensive care unit; RCT, randomized controlled trial; NA, not applicable.

Table S5. Assessment on risk of bias for included non-RCTs using Newcastle-Ottawa Scale.

Author, year	Selection			Comparability			Outcome			Quality[#]
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Controls for age, sex, and marital status	Controls of other factors	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Klick,1975		*	*	*			*	*	*	Poor
Rouby, 1994	*	*	*	*	*		*	*	*	Good

[#]The quality (good, fair, and poor) was defined based on the following criteria: Good - 3 or 4 stars in 'Selection' domain AND 1or 2 stars in 'Comparability' domain AND 2 or 3 stars in 'Outcome' domain; Fair - 2 stars in 'Selection' domain AND 1or 2 stars in 'Comparability' domain AND 2 or 3 stars in 'Outcome' domain; Poor - 0 or 1 star in 'Selection' domain OR 0 star in 'Comparability' domain OR 0 or 1 star in 'Outcome' domain. RCT, randomised controlled trial

Table S6. Summary of VAP definition from included RCTs in the meta-analysis.

Author	VAP definition
Ehrmann et al., 2023	1.Based on available routine clinical data, in case of new occurrence of any of the following: ①hyperleukocytosis (≥10,000 leucocytes/mm^3), ②leukopenia (≤ 4,000 leukocytes/mm^3), ③fever (≥38°C), ④purulent secretion, ⑤new chest X-ray infiltrate, ⑥significant respiratory compromise (decrease in PaO_2/FiO_2 ratio or increase in positive end expiratory pressure), ⑦significant cardiovascular compromise (shock) Move to VAP suspicion work up. 2.If not available obtain: Complete white blood, cell count, Temperature measurement, Semi-quantitative and qualitative secretion assessment, chest X-ray, blood gases, in case of : Definite or possible new chest X-ray infiltrate (or significant respiratory or cardiovascular compromise in patients suffering ARDS*) AND two among hyperleukocytosis (≥ 10,000 leukocytes/mm^3) or leukopenia (≤ 4,000 leukocytes/mm^3) OR fever (≥ 38°C) OR purulent secretion, Move to possible VAP work up. 3.Obtain bacteriological lung specimen (tracheal aspirate, bronchoalveolar lavage or distal protected specimen), File possible VAP case report form. Definite VAP diagnosis will be made a posteriori by an adjudication committee based on possible VAP case report form comprising clinical, microbiological data and original chest X-rays.
Karvouniaris et al., 2015	(a) the appearance of new or progressive and persistent pulmonary infiltrates on chest radiography and two of the following criteria: (b) abnormal temperature (>380C or <360C), (c) abnormal white blood cells (WBC) count, (d) purulent Tracheobroncheal Aspirates (TBA) with a positive culture. Confirmation of diagnosis required quantitative cultures of TBA, received within two days before or after clinical diagnosis, that were evaluated by microscopy and considered positive if grew ≥100000 Colony Forming Units (CFU)/mL
Kuzovlev et al., 2015	standard clinical and CPIS criteria (fever, leukocytosis, characteristics of sputum, arterial oxygenation, infiltrative changes on chest X-ray, and semi-quantitative analysis of tracheal aspirate and Gram staining).
Wood et al., 2002	Clinical (criteria for the systemic inflammatory response syndrome), and microbiological (quantitative cultures from BAL yielded at least 10^5 CFU).
Rathgeber et al., 1993	(a)New and persistent infiltrates on x-ray on one or more areas of the lungs, (b) purulent bronchial secretions, (c) detection of pathogen in the bronchial, (d) at least 2 of the following: signs of respiratory failure evident by increase of FiO_2 by at least 0.1, leukocytosis >10000/mm^3, rectal body temperature >38ºC
Claridge et al., 2007	Clinical (criteria for the systemic inflammatory response syndrome), and microbiological (quantitative cultures from BAL yielded > 100,000 CFU).
Lode et al., 1988	NR

NR, not reported.

Table S7. Summary of inclusion criteria in the 7 RCTs for the final meta-analysis.

Author	Age	Patient type	Invasive mechanical ventilation time	Others
Ehrmann et al., 2023	≥ 18 y	Intubated patients	≥ 72h	Negative pregnancy test
Karvouniaris et al., 2015	>18 y	Intubated patients	> 48 h	NR
Kuzovlev et al., 2015	NR	Intubated multiple trauma patients (ISS ≥30)	NR	NR
Wood et al., 2002	≥16 y	Intubated patients in Trauma ICU with at least 1 risk factor for "post-traumatic pneumonia"	Expected to receive MV for > 7 days	NR
Rathgeber et al., 1993	NR	Intubated patients	≥ 4 days	NR
Claridge et al., 2007	NR	Intubated patients in Trauma ICU expected to require prolonged intubation with a calculated probability of getting VAP of ≥ 0.25	NR	NR
Lode et al., 1988	NR	Intubated patients	≥ 4 days	NR

NR: not reported; ISS: Injury Severity Score; MV: Mechanical ventilation.

Table S8. Summary of exclusion criteria in the 7 RCTs for the final meta-analysis.

Author	Suspicion or confirmed pneumonia	Drug allergy	Pregnant women or breastfeeding women	Poor prognosis	Disease status	Current treatment	Others
Ehrmann et al., 2023	Suspicion or confirmed ventilator associated pneumonia the day of inclusion	Patients known at the time of inclusion to be allergic to aminoglycosides	Known pregnant women at the time of inclusion and breastfeeding women	NR	Stage 2 or 3 KDIGO classification acute kidney injury the day of inclusion. Patients undergoing renal replacement therapy or for whom decision has been made to initiate renal replacement therapy can be included whatever the KDIGO stage;Chronic kidney failure : baseline estimated glomerular filtration lower than 30 mL/min; Myasthenia gravis	Clinical indication for systemic aminoglycoside therapy the day of inclusion: as deemed necessary by the clinician in charge	Patient scheduled for extubation within the next 24h;Patient ventilated through an endotracheal tube for more than four consecutive days (96h);Patient ventilated through a tracheostomy;Known guardianship or trusteeship at the time of inclusion;Patients previously included in this study
Karvouniaris et al., 2015	Grossly purulent sputum or pneumonia on admission, new and persistent infiltrates on chest radiography within 48 h from admission	Allergy to colistin, and colonisation	Pregnancy	NR	Severe chronic obstructive pulmonary disease (COPD); infection with a strain resistant to colistin on admission	NR	NR
Kuzovlev et al., 2015	NR	NR	NR	NR	NR	NR	NR

Wood et al., 2002	NR	Allergy to betalactam	Pregnancy	Poor prognosis	Preexistent lung disease requiring long-term inhalation drug therapy ;human immunodeficiency virus infection, cancer,or white blood cell count less than $4 \times 10^3/mm^3$.	Current treatment for a lower respiratory tract infection, long-term therapy with corticosteroids or immunosuppressive drugs	NR
Rathgeber et al., 1993	Patients diagnosed with pneumonia within the first 24 hours of intubation	Known hypersensitivity to aminoglycoside antibiotics	NR	NR	NR	NR	NR
Claridge et al., 2007	NR	NR	NR	Patients with nonsurvivable injuries (predicted survival less than one week based on trauma/critical care surgeon assessment)	NR	NR	< 18 years old
Lode et al., 1988	NR	NR	NR	NR	NR	NR	NR

NR: not reported.

Figure S2. Trial sequential analysis of incidence of VAP for included RCTs.

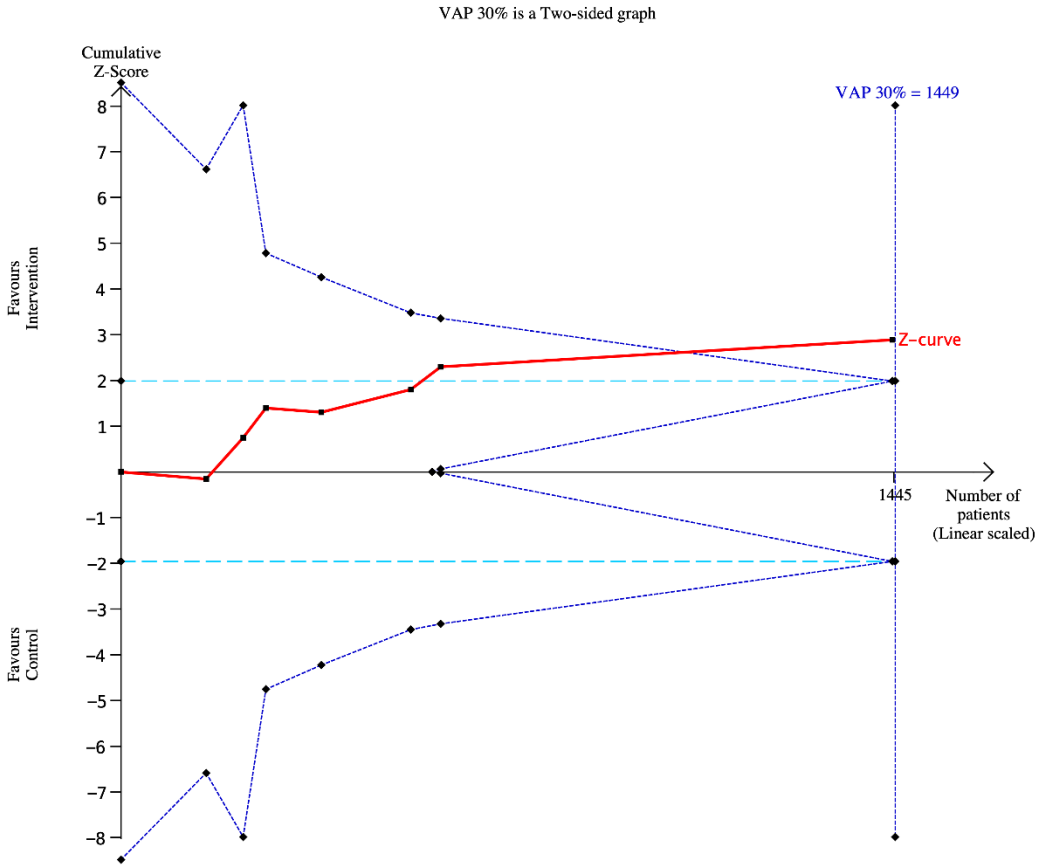


Figure S3. Sensitivity test of incidence of VAP for all RCT studies.

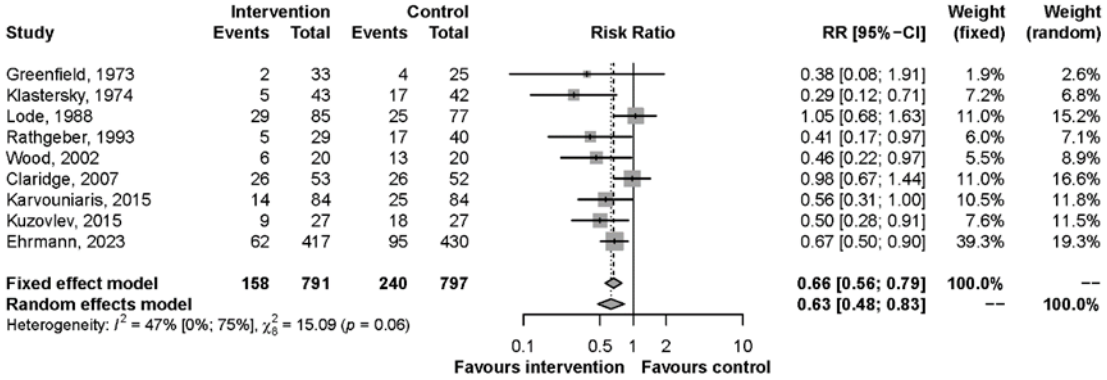


Figure S4. Sensitivity test of incidence of VAP for all RCT studies and non-RCT studies.

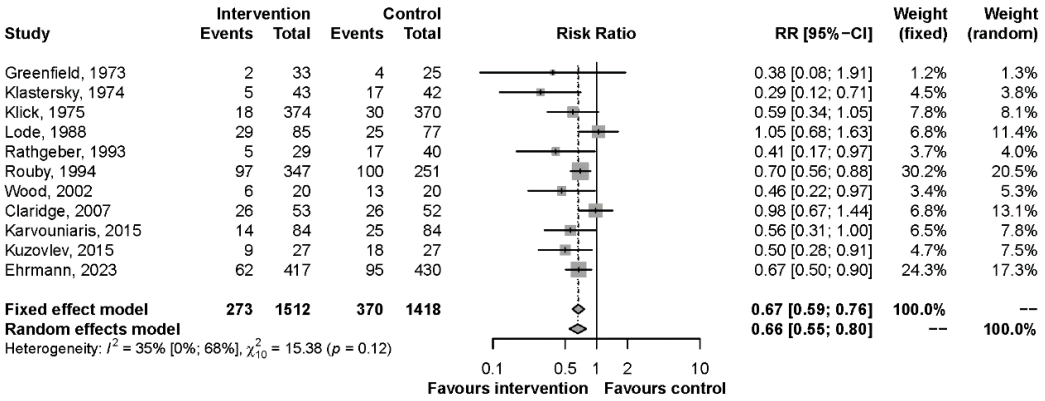


Figure S5. Risk of VAP incidence in RCTs reported microbiologically confirmed VAP

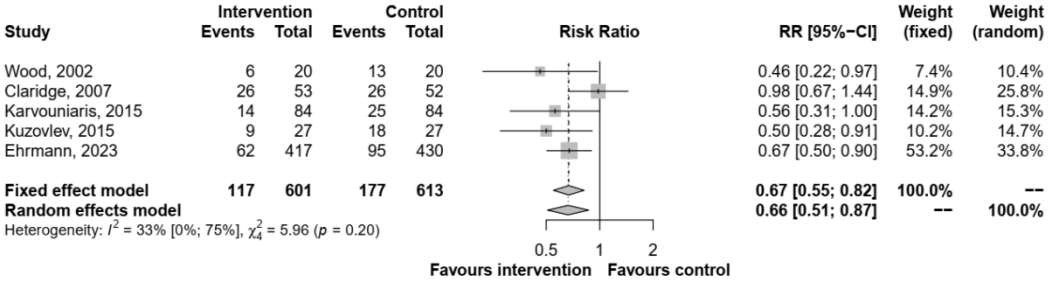


Figure S6. Trial sequential analysis of incidence of VAP in subgroups of nebulization for included RCTs

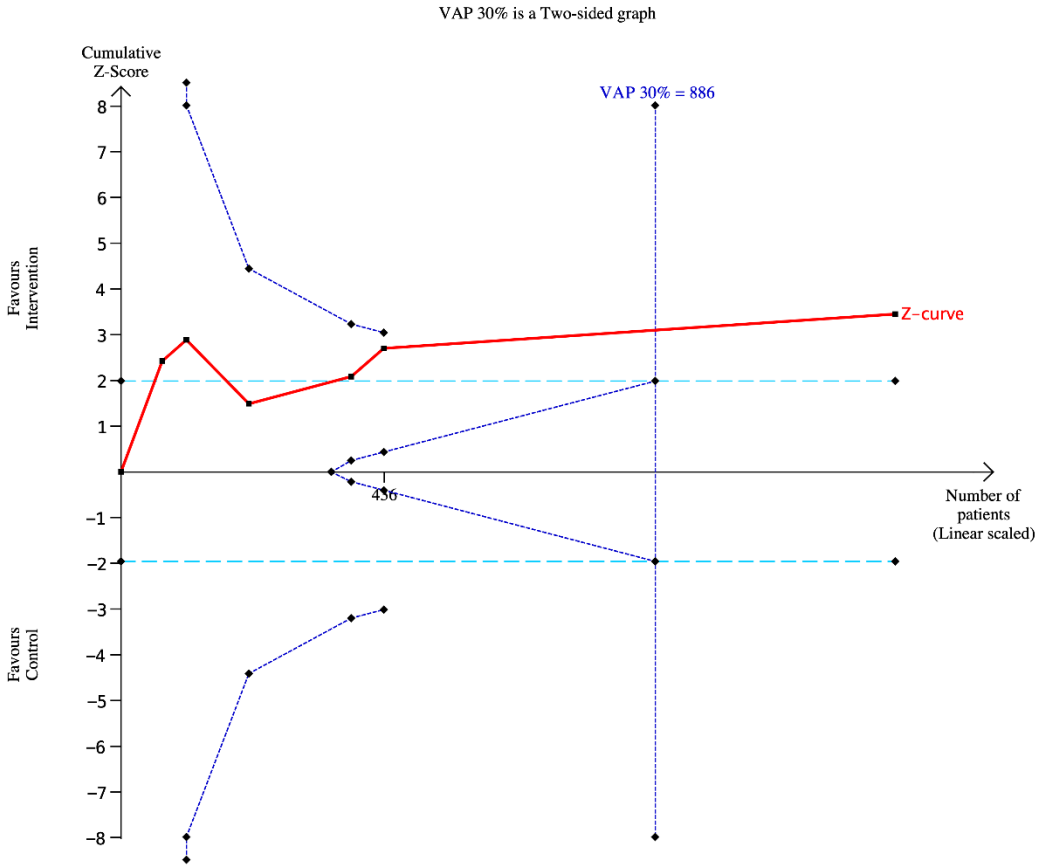


Figure S7. Trial sequential analysis of incidence of VAP in subgroups of aminoglycosides for included RCTs

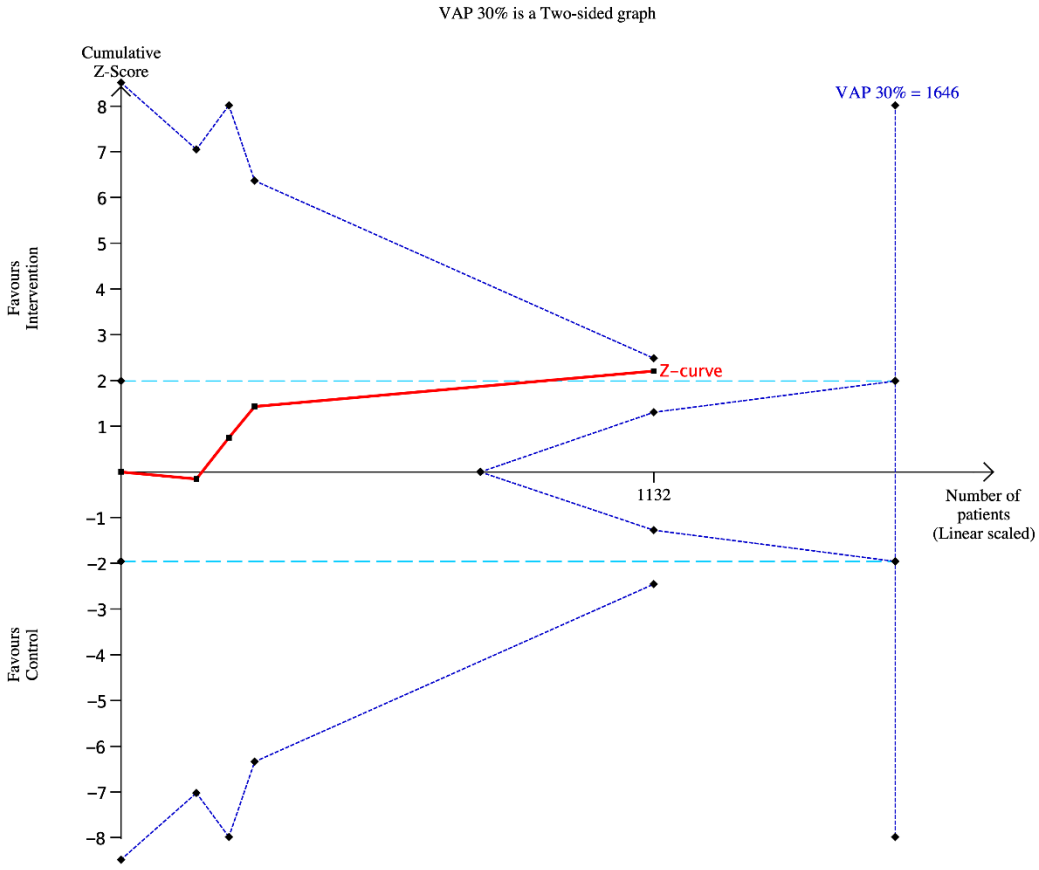


Figure S8. Network meta-analysis of indirect comparisons among aminoglycosides, ceftazidime, and colistin using Bayesian methodology

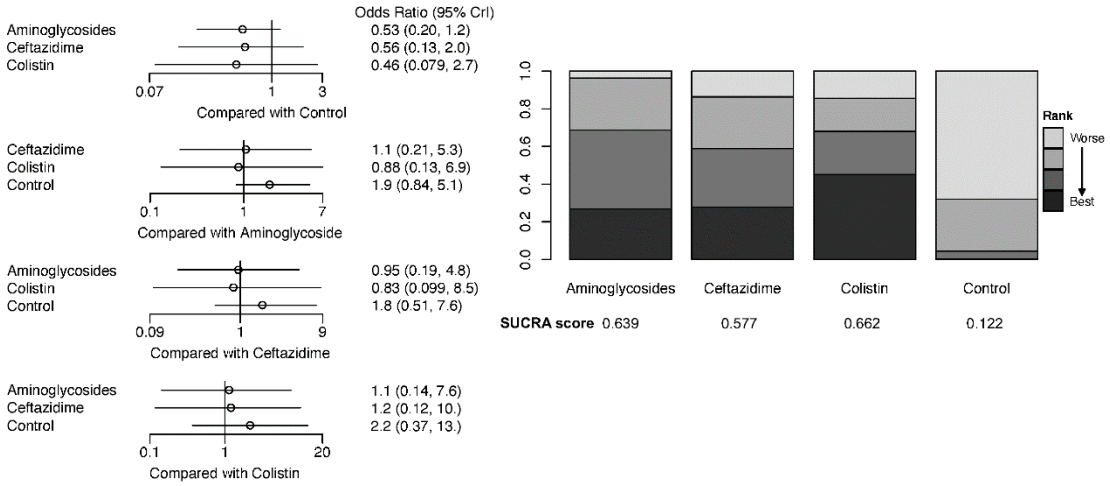


Figure S9. Network meta-analysis of indirect comparisons between nebulization and intratracheal instillation using Bayesian methodology

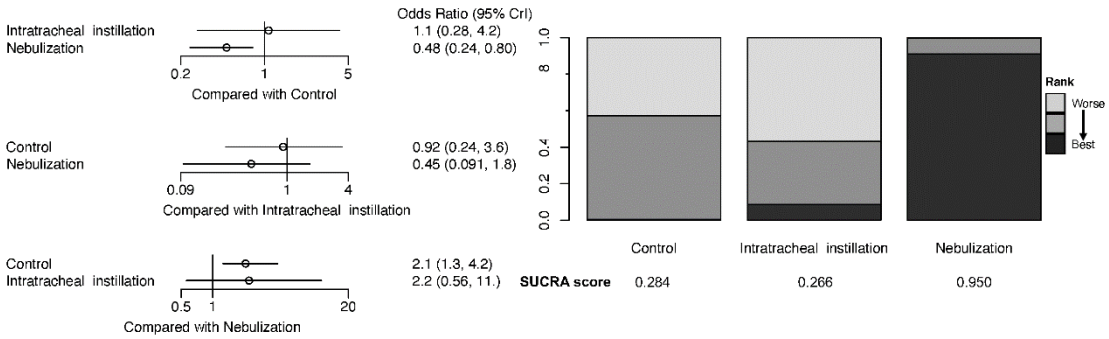


Figure S10. Meta analysis of the incidence density rate of VAP for included RCTs

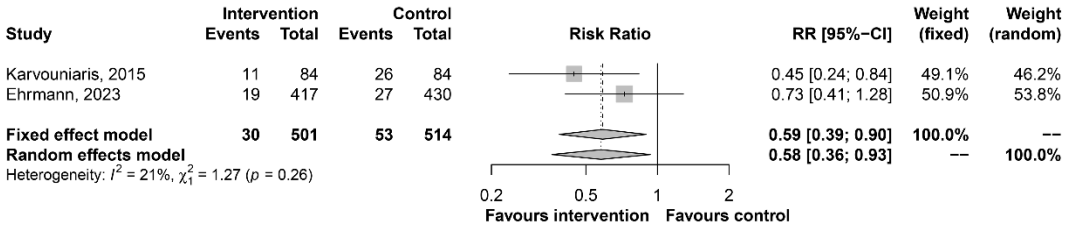


Figure S11. Meta analysis of the incidence of Gram-negative bacteria VAP for included RCTs

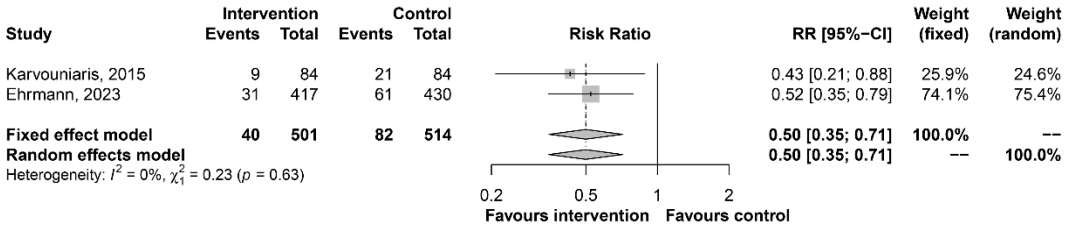


Figure S12. Meta analysis of the time from randomization to the occurrence of VAP for included RCTs

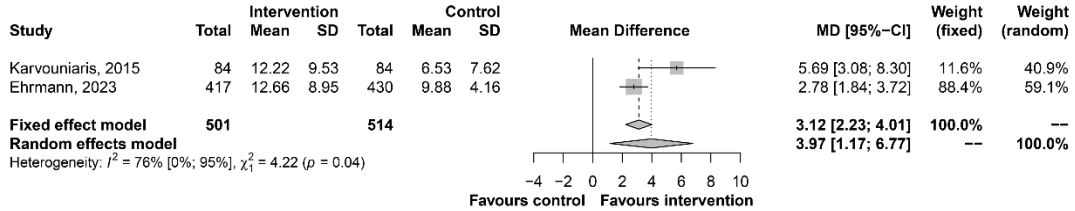


Figure S13. Meta analysis of incidence of VAP on day 14 for included RCTs

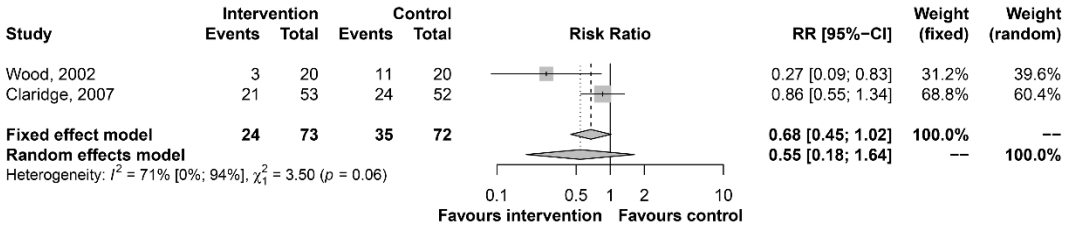


Figure S14. Meta analysis of incidence of VAP on day 30 for included RCTs

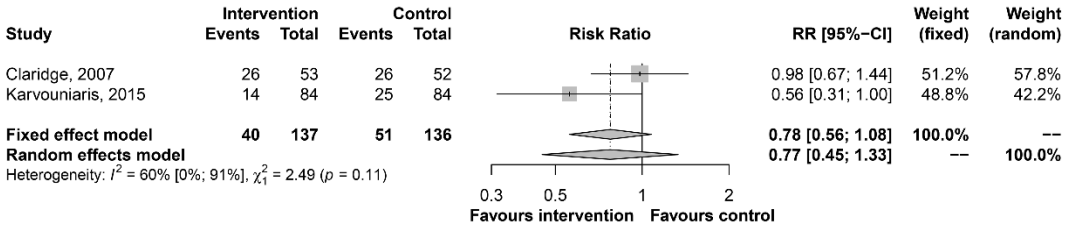


Figure S15. Meta analysis of incidence of VAP due to multidrug-resistant bacteria for included RCTs

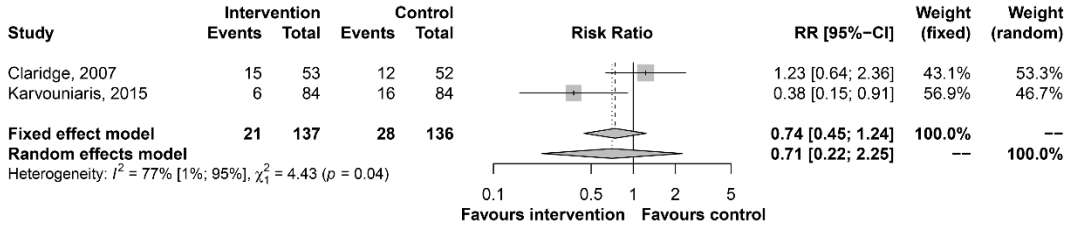


Figure S16. Meta analysis of incidence of VAP due to Staphylococcus species for included RCTs

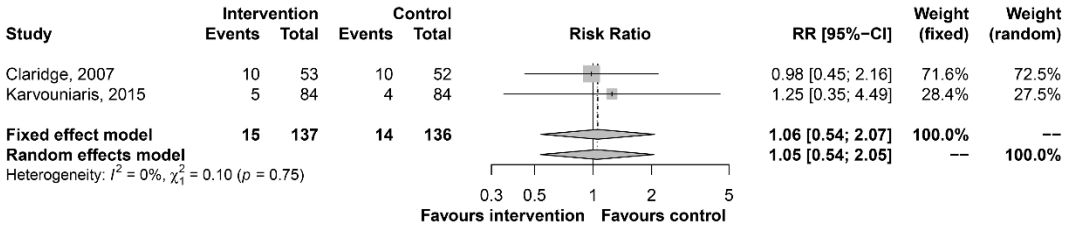


Figure S17. Meta analysis of incidence of VAP after VAT for included RCTs

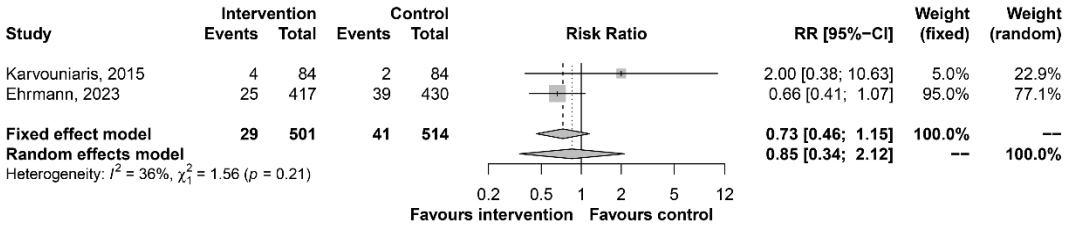


Figure S18. Trial sequential analysis of incidence of Gram-negative bacteria VAP for included RCTs

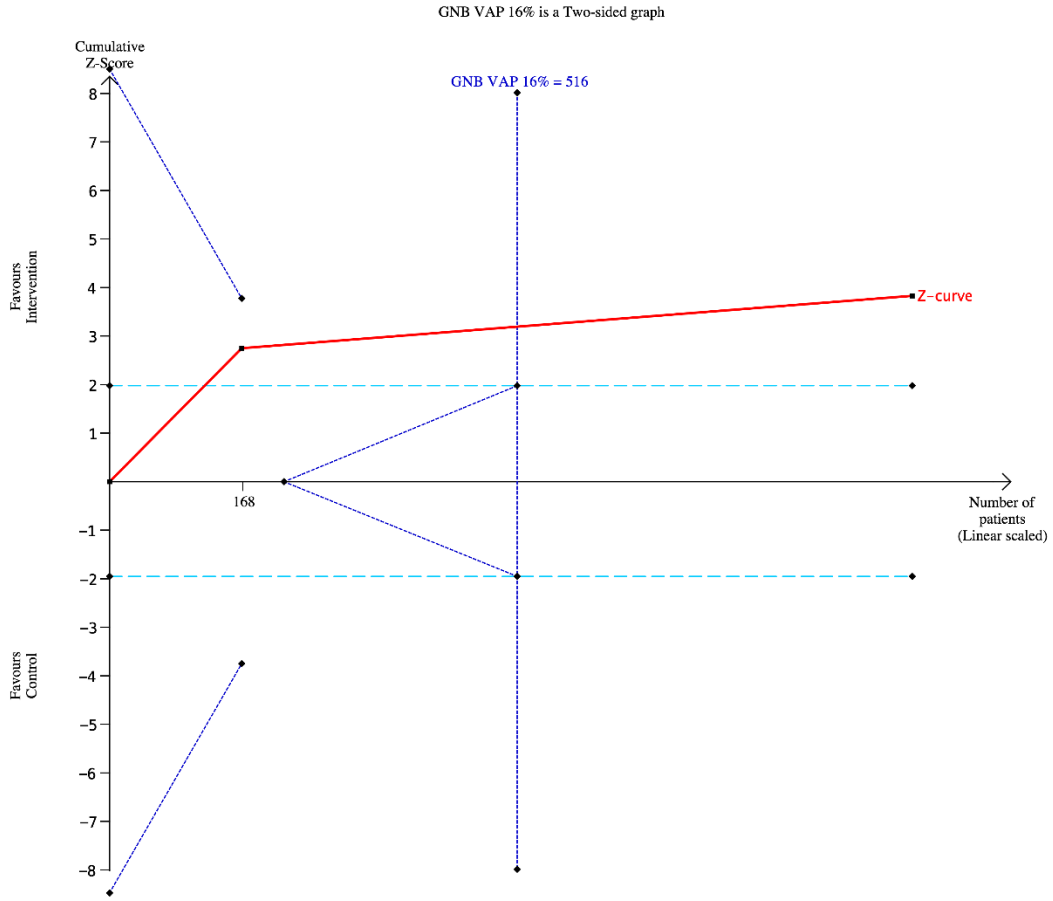


Figure S19. Trial sequential analysis of the incidence density rate of VAP for included RCTs

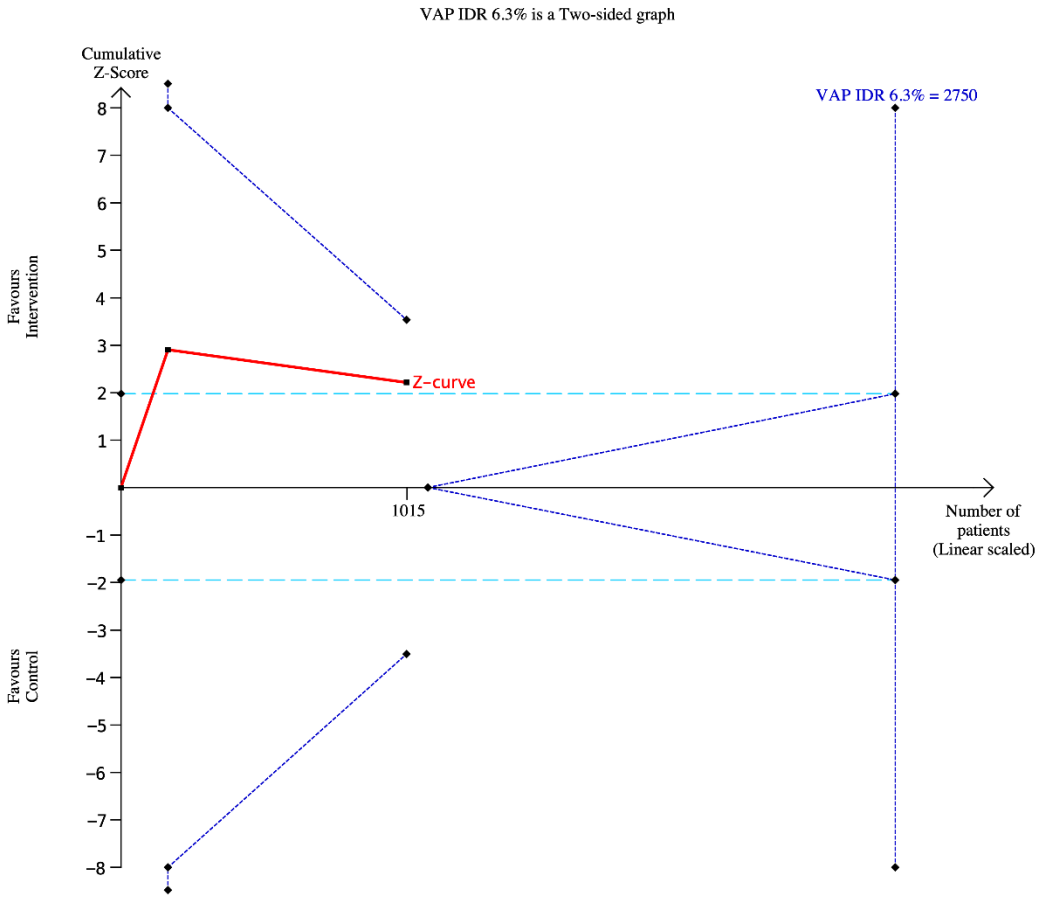


Figure S20. Trial sequential analysis of the time from randomization to the occurrence of VAP for included RCTs

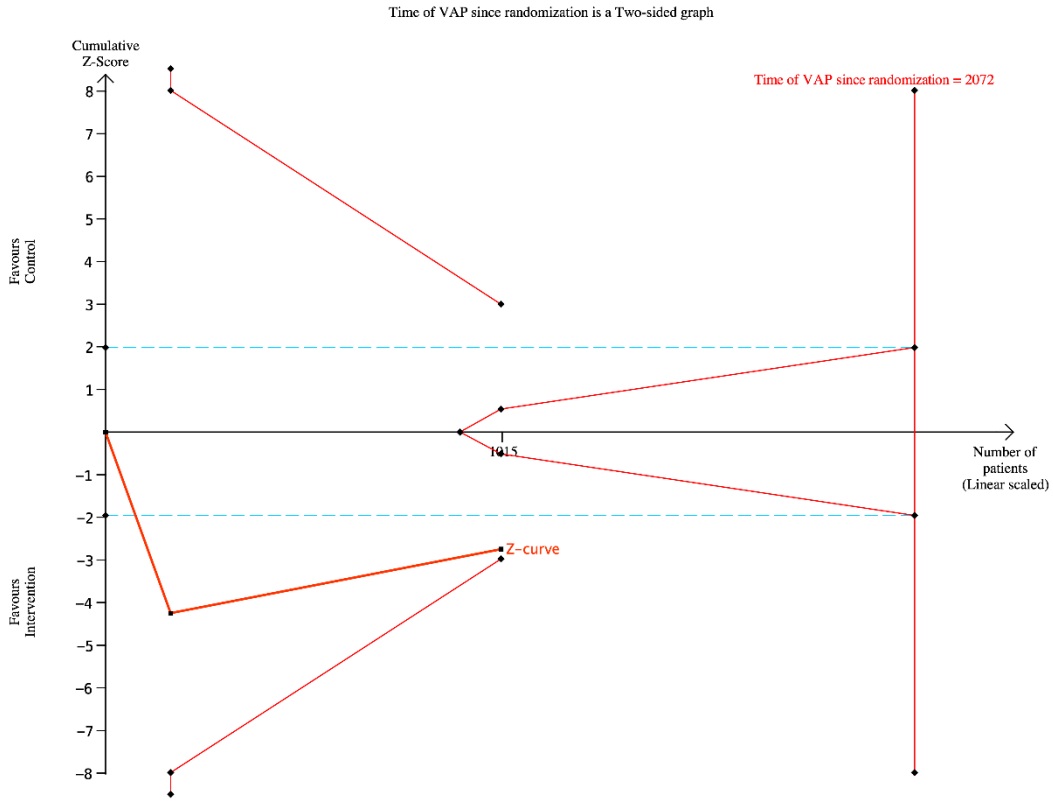


Figure S21. Trial sequential analysis of incidence of VAP on day 14 for included RCTs

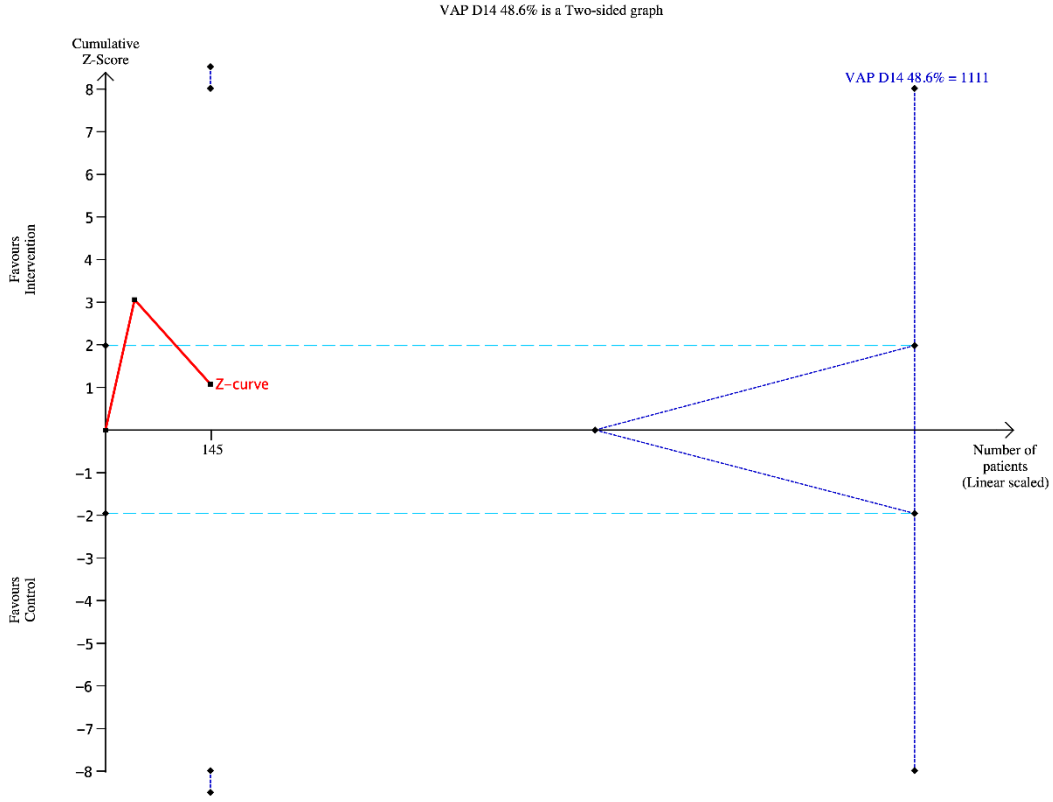


Figure S22. Trial sequential analysis of incidence of VAP on day 30 for included RCTs

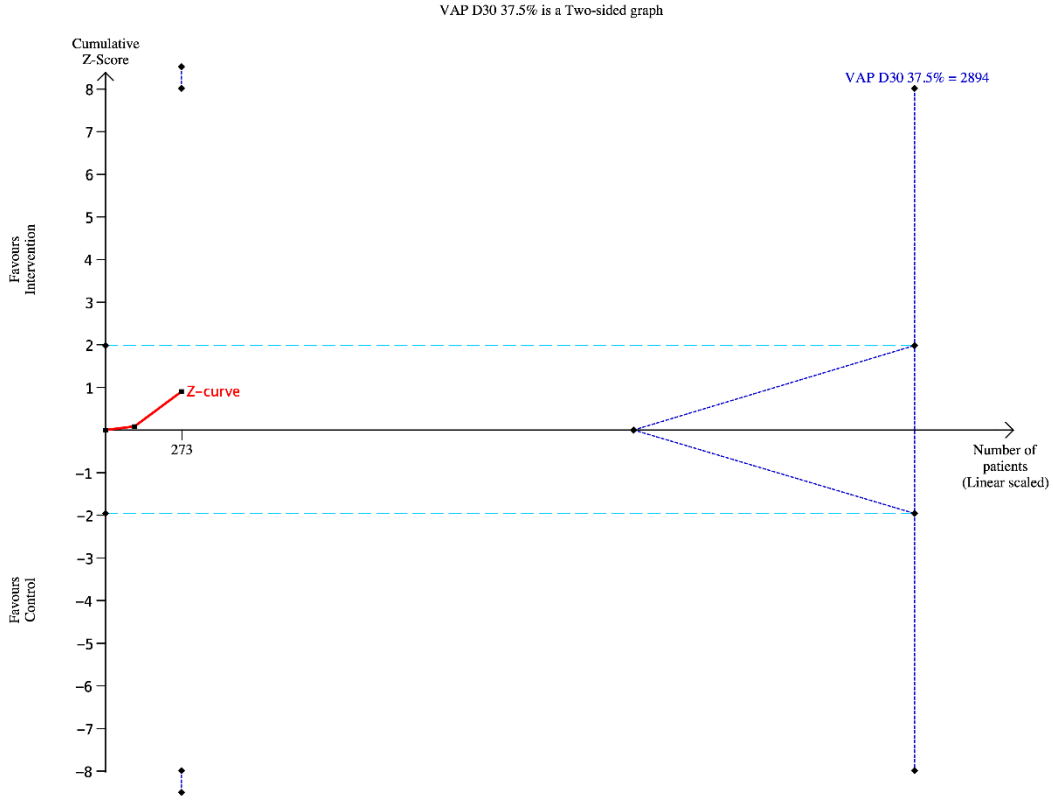


Figure S23. Trial sequential analysis of incidence of VAP due to multidrug-resistant bacteria for included RCTs

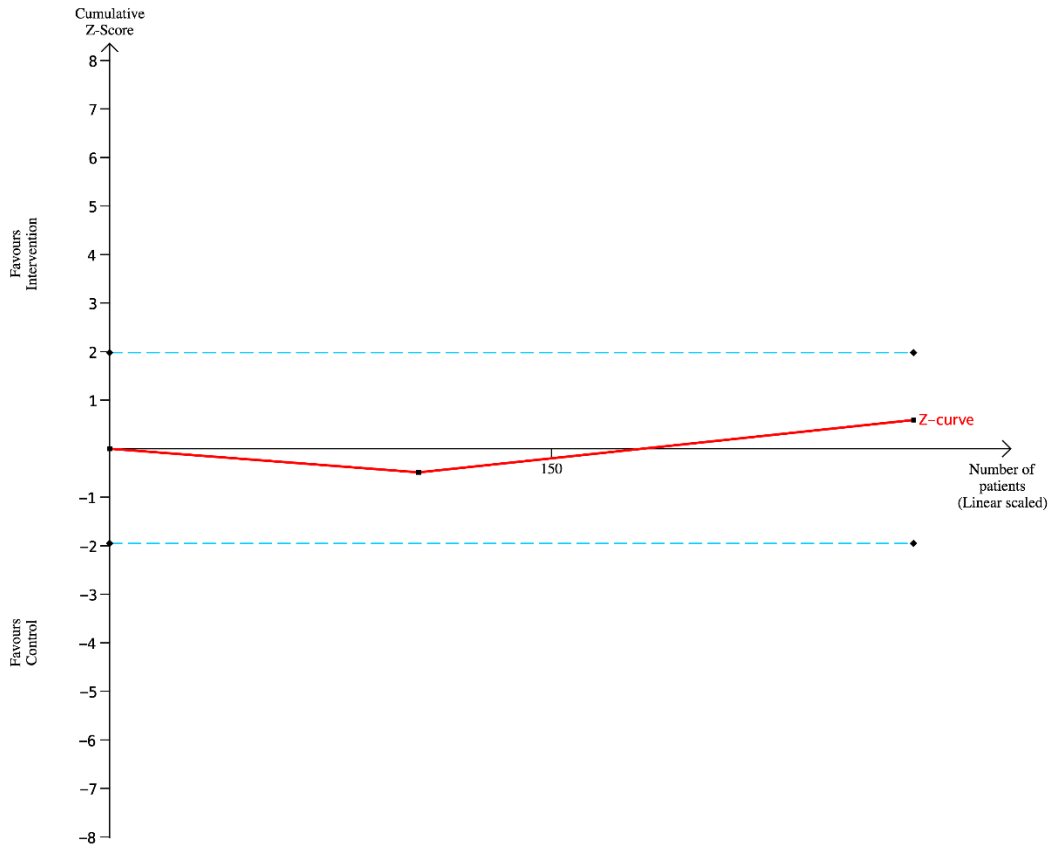


Figure S24. Trial sequential analysis of incidence of VAP due to Staphylococcus species for included RCTs

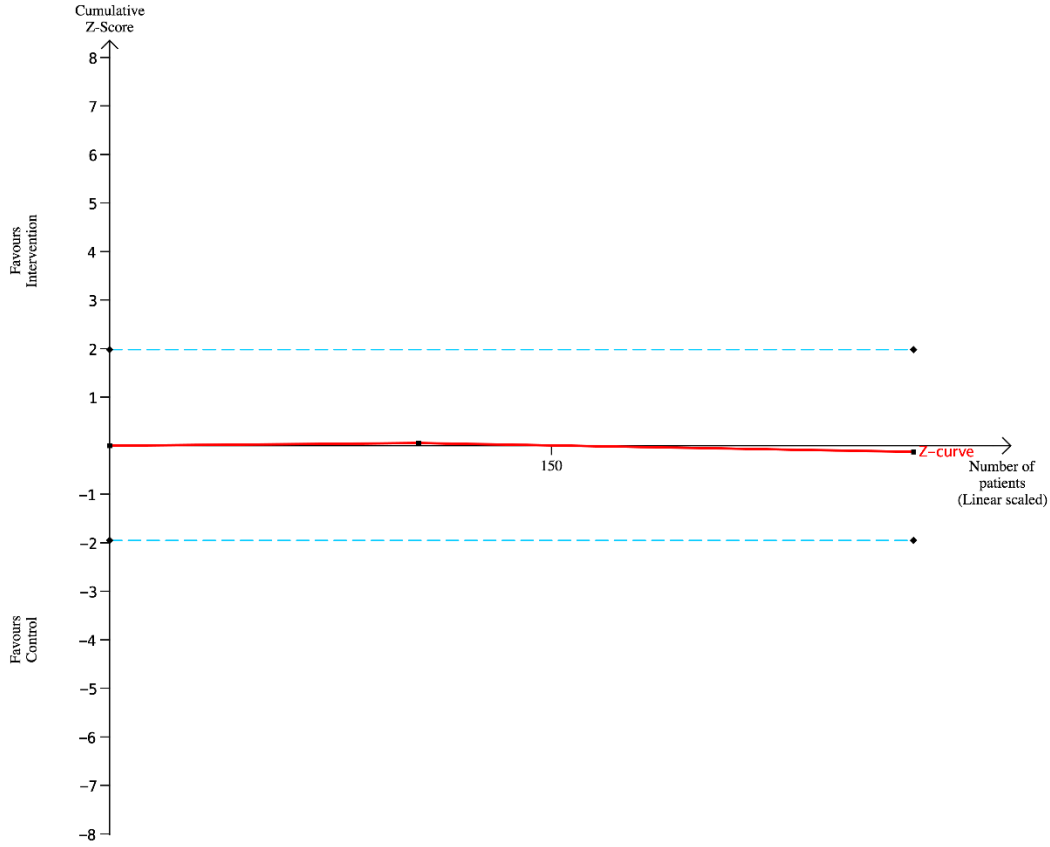


Figure S25. Trial sequential analysis of incidence of VAP after ventilator-associated tracheobronchitis for included RCTs

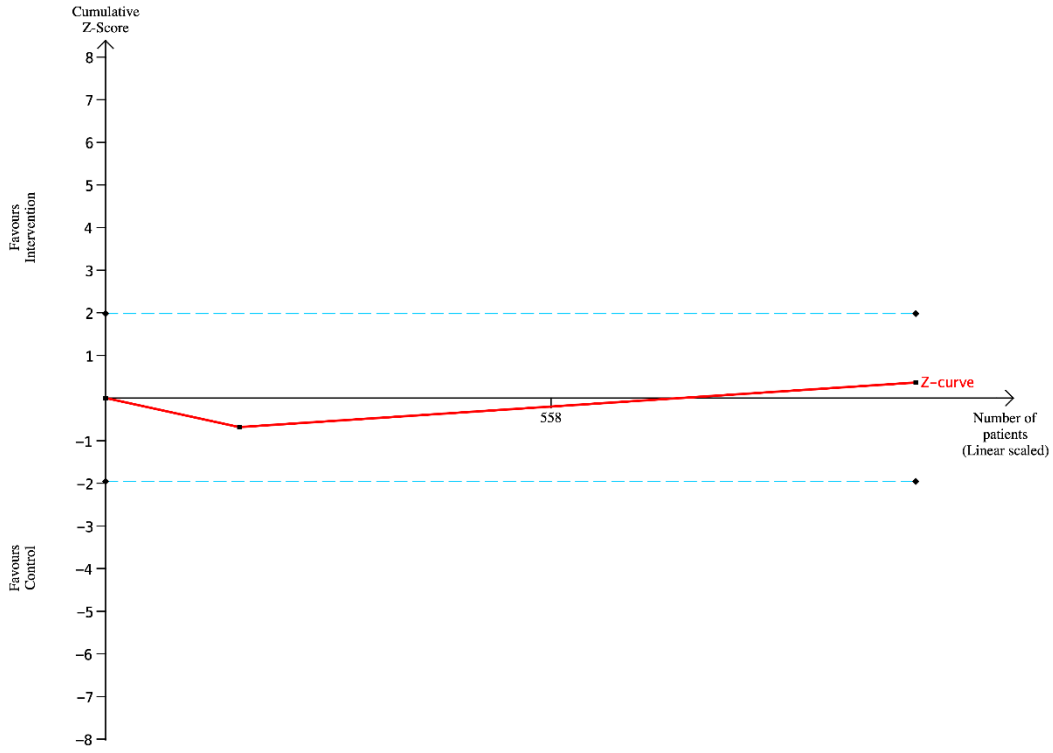


Figure S26. Trial sequential analysis of hospital mortality for included RCTs

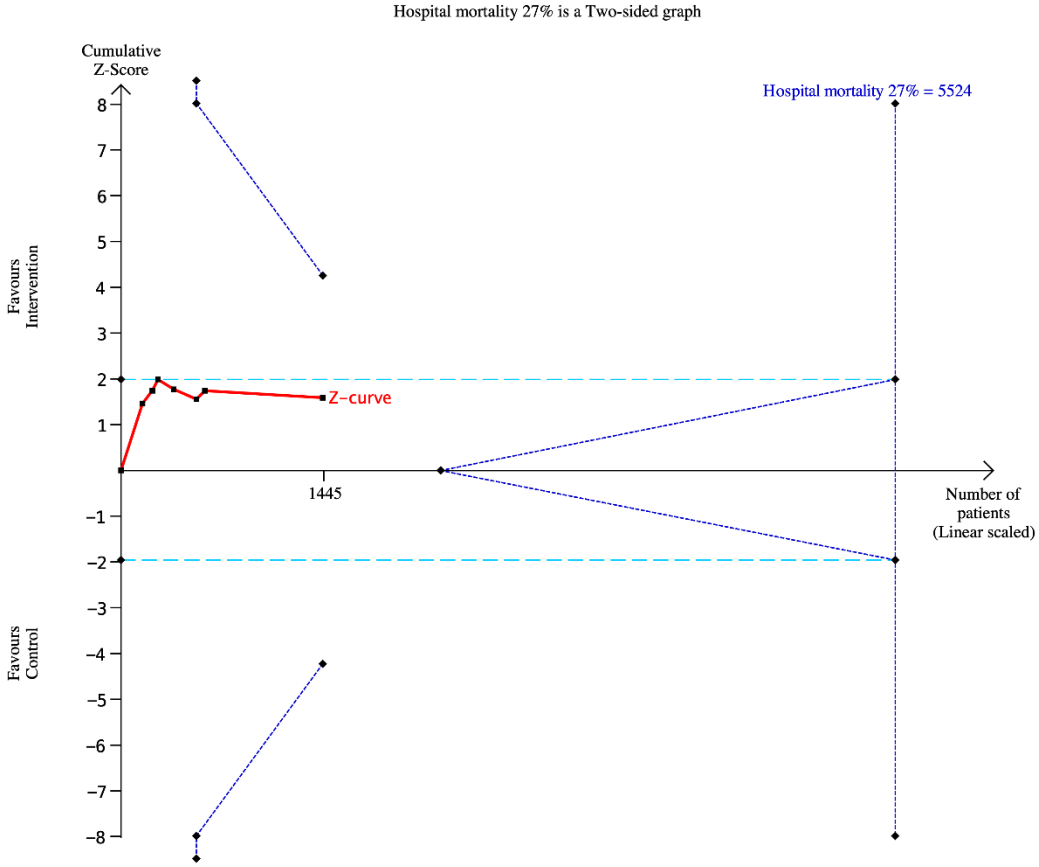


Figure S27. Trial sequential analysis of hospital mortality in subgroups of aminoglycosides for included RCTs

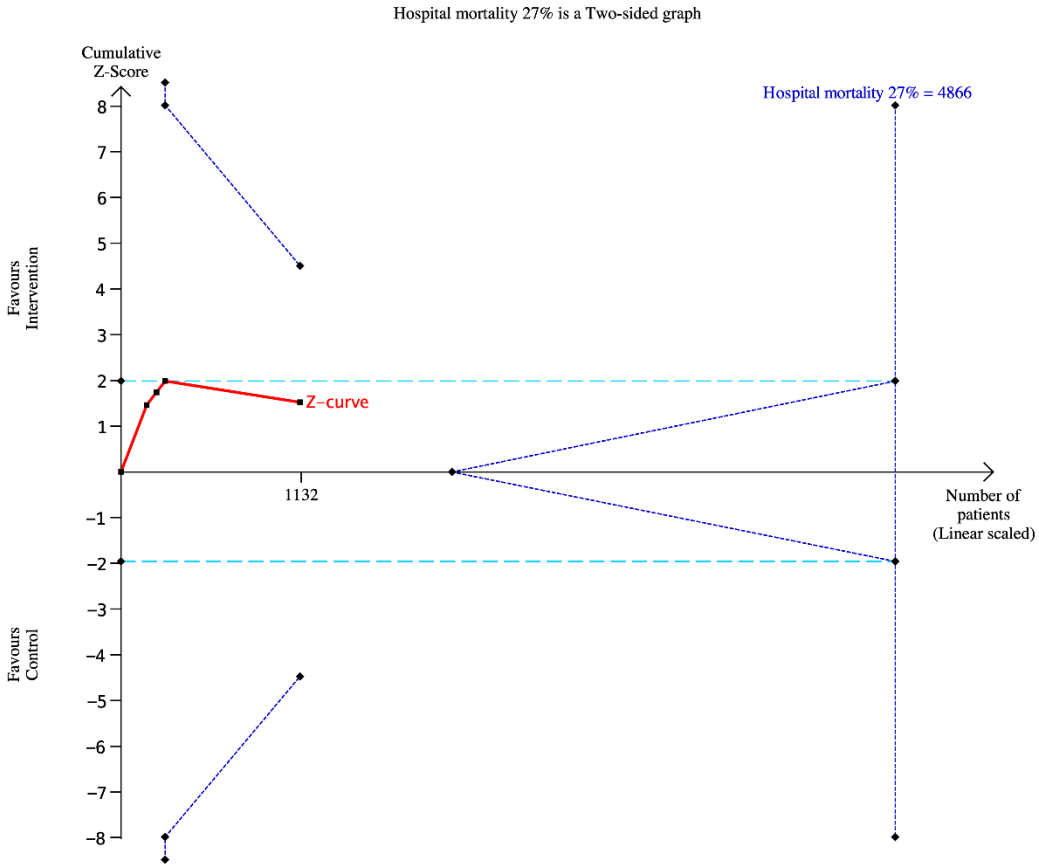


Figure S28. Trial sequential analysis of hospital mortality in subgroups of ceftazidime for included RCTs

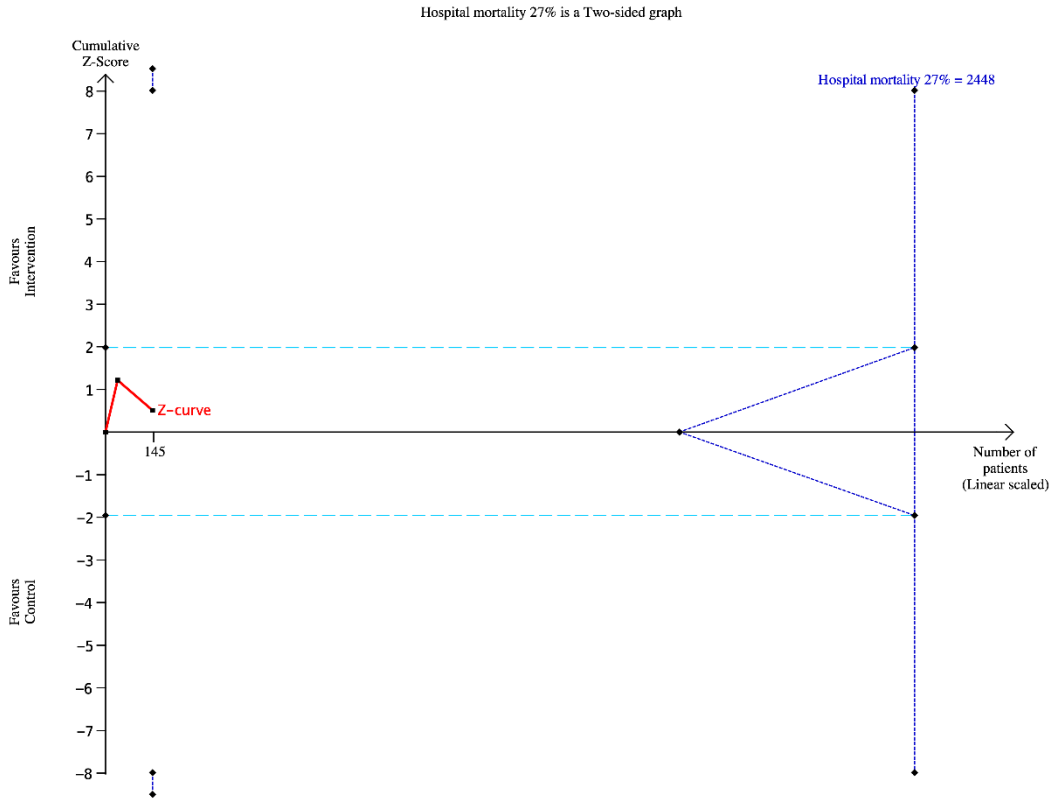


Figure S29. Trial sequential analysis of hospital mortality in subgroups of colistin for included RCTs

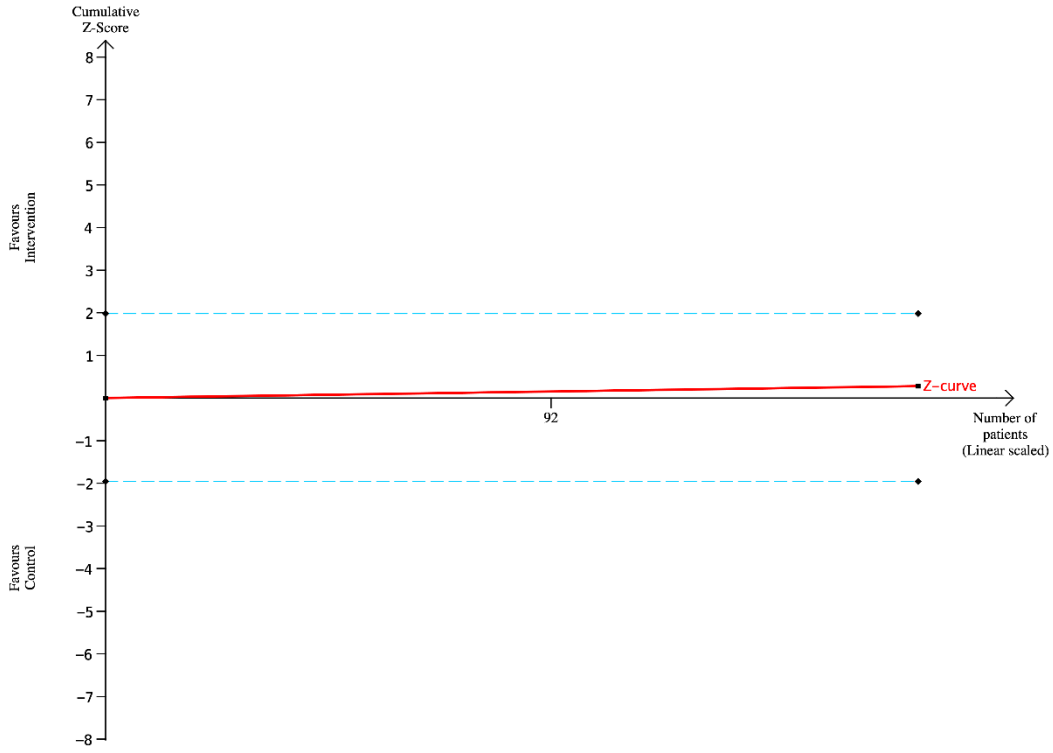


Figure S30. Trial sequential analysis of hospital mortality in subgroups of intratracheal instillation for included RCTs

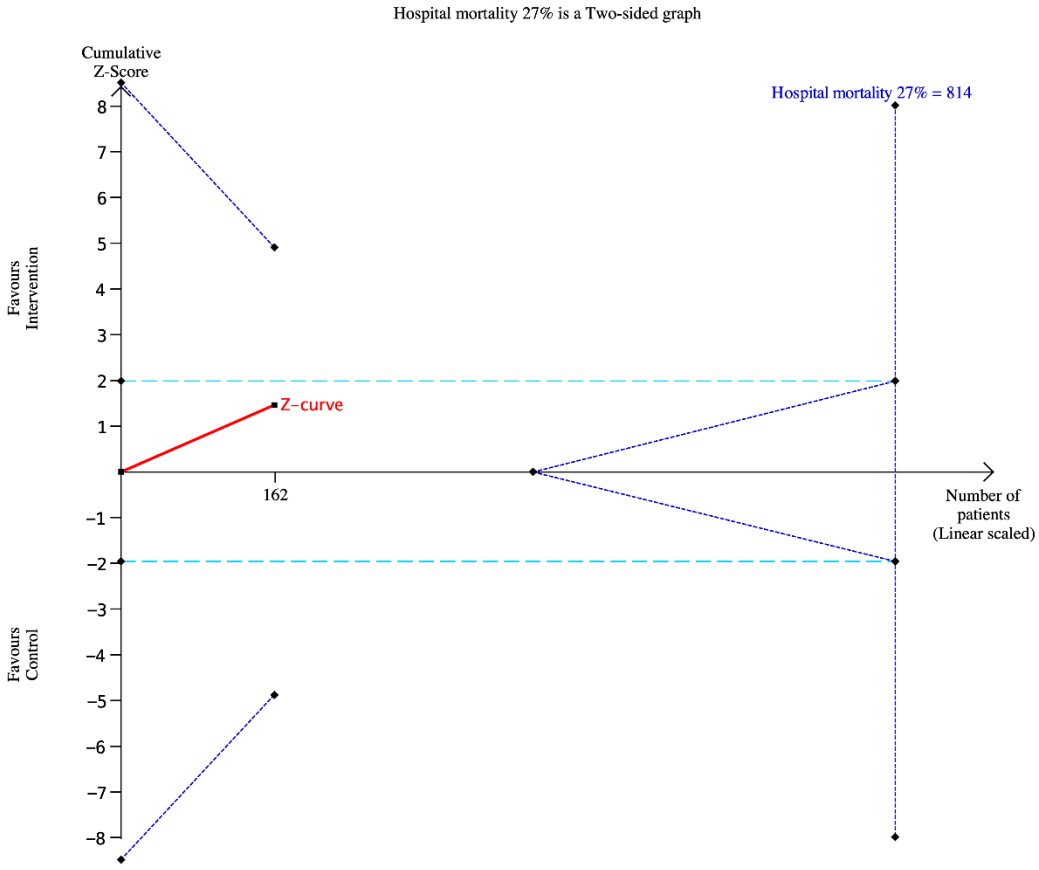


Figure S31. Trial sequential analysis of hospital mortality in subgroups of nebulization for included RCTs

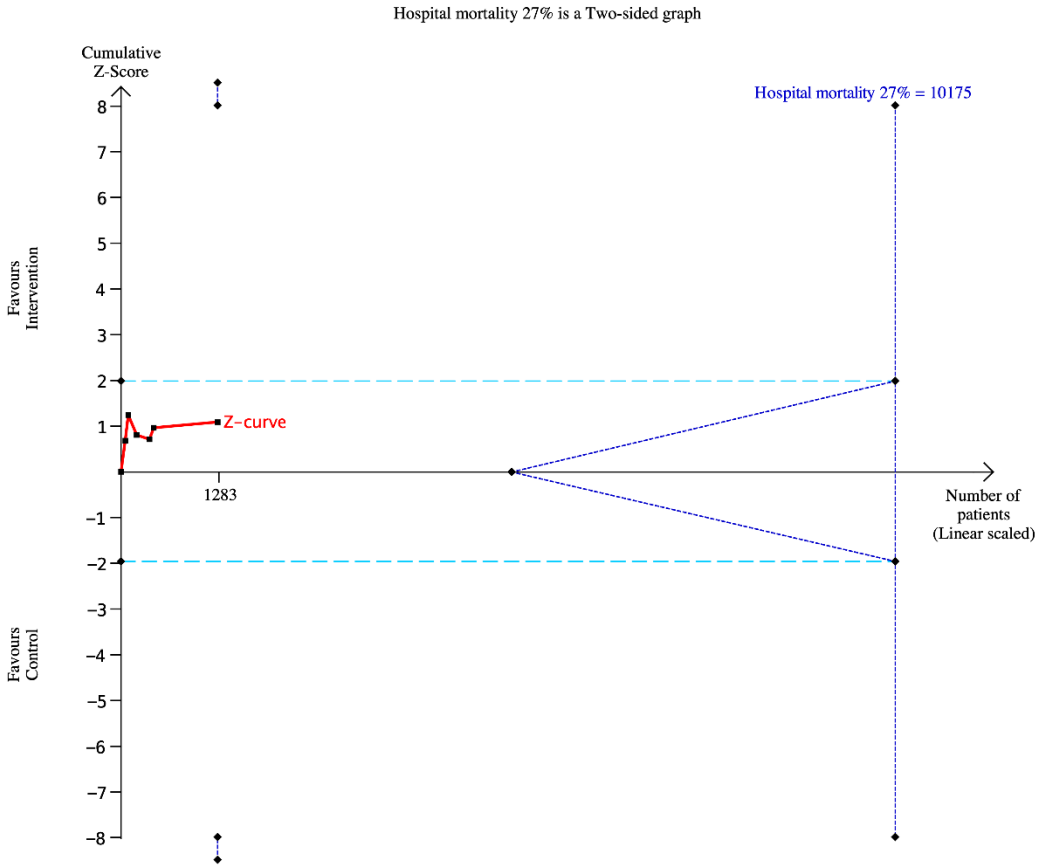


Figure S32. Sensitivity test of hospital mortality for all RCT studies.

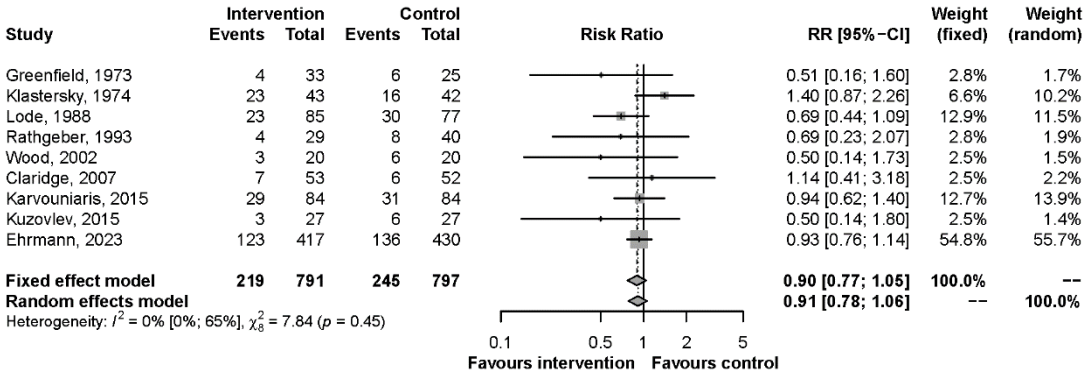


Figure S33. Sensitivity test of hospital mortality for all RCT studies and non-RCT studies.

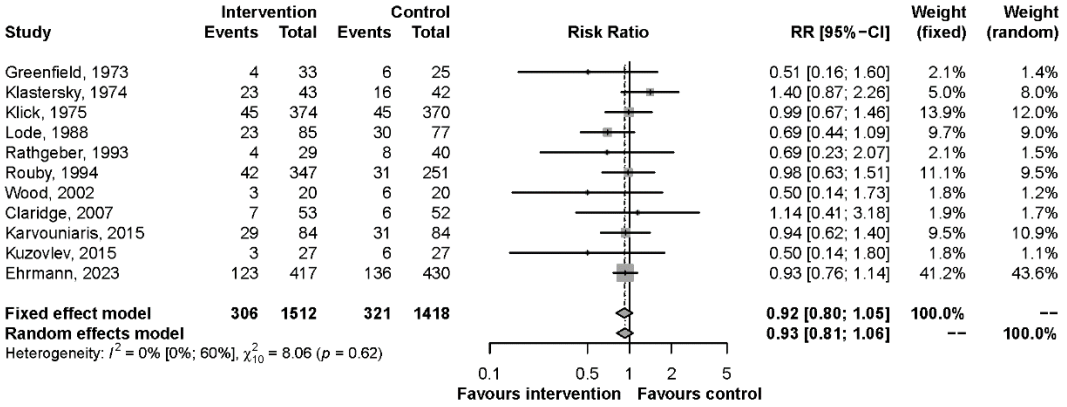


Figure S34. Meta analysis of duration of invasive mechanical ventilation for included RCTs

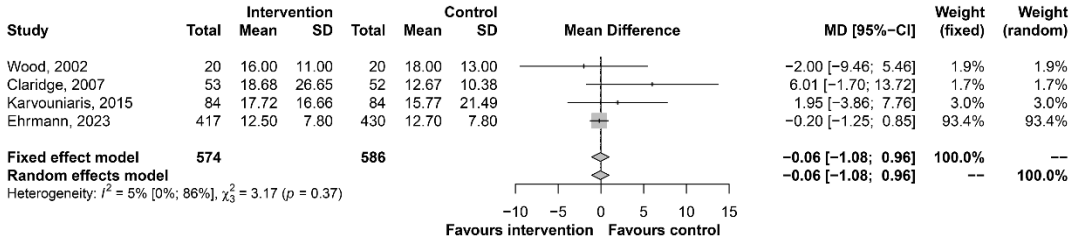


Figure S35. Meta analysis of duration of ICU length of stay for included RCTs

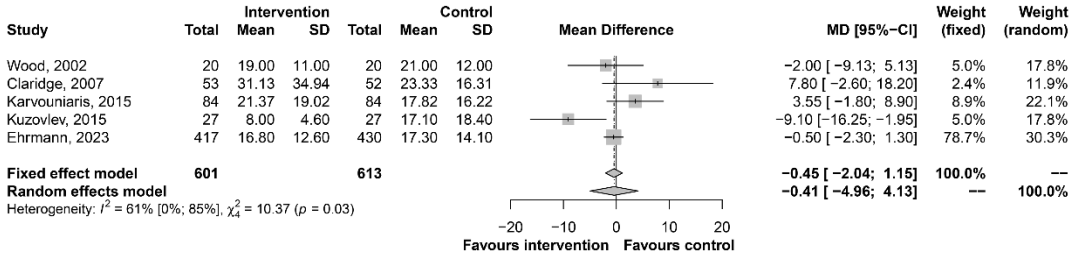


Figure S36. Meta analysis of duration of hospital length of stay for included RCTs

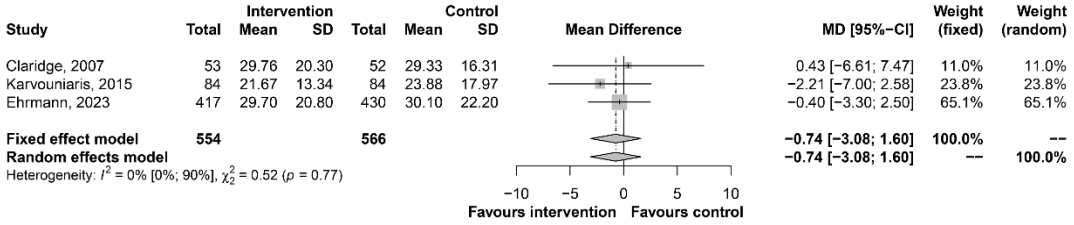


Figure S37. Meta analysis of duration of systematic antibiotic use for included RCTs

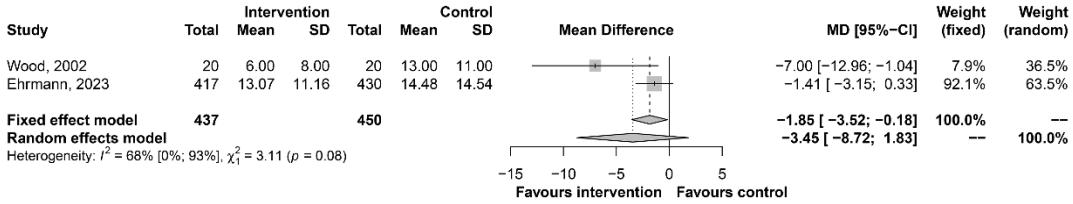


Figure S38. Meta analysis of the need for tracheostomy for included RCTs

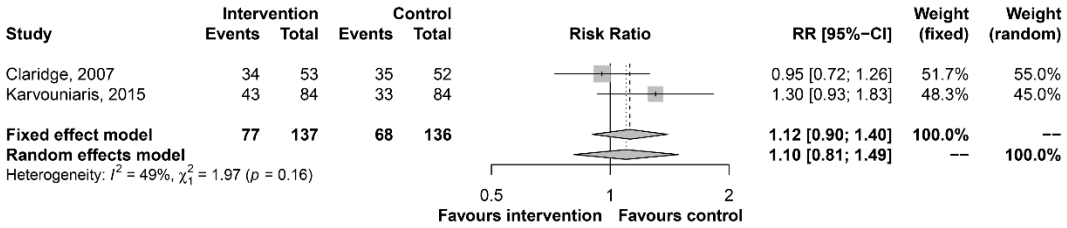


Figure S39. Trial sequential analysis of duration of invasive mechanical ventilation for included RCTs

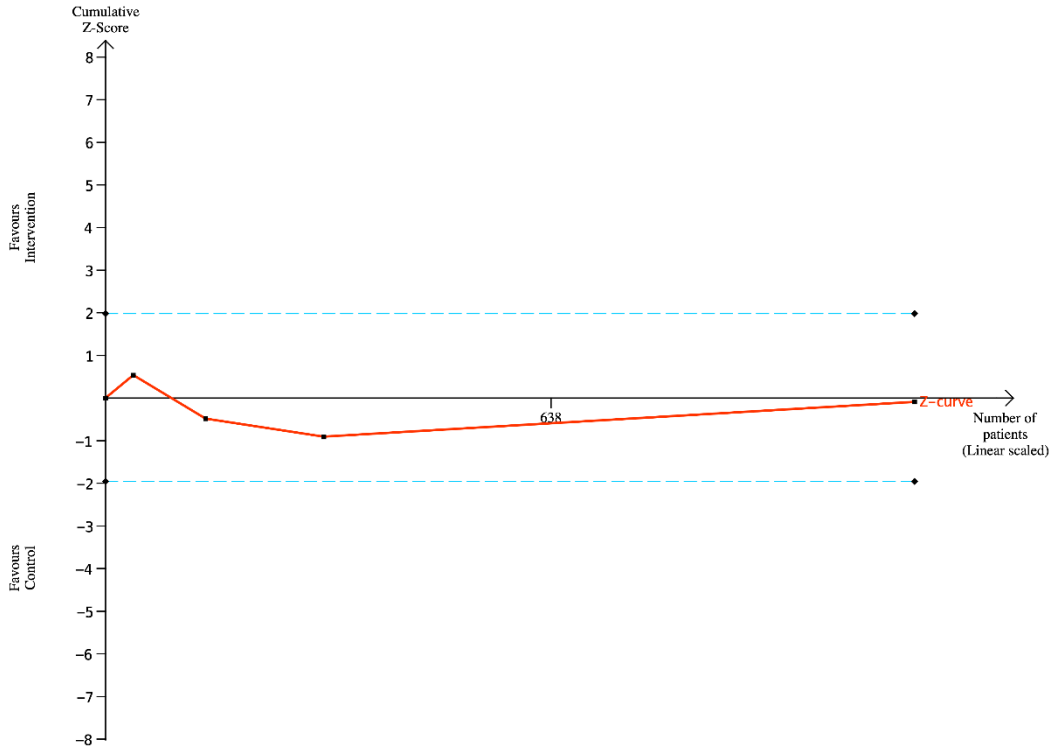


Figure S40. Trial sequential analysis of duration of ICU length of stay for included RCTs

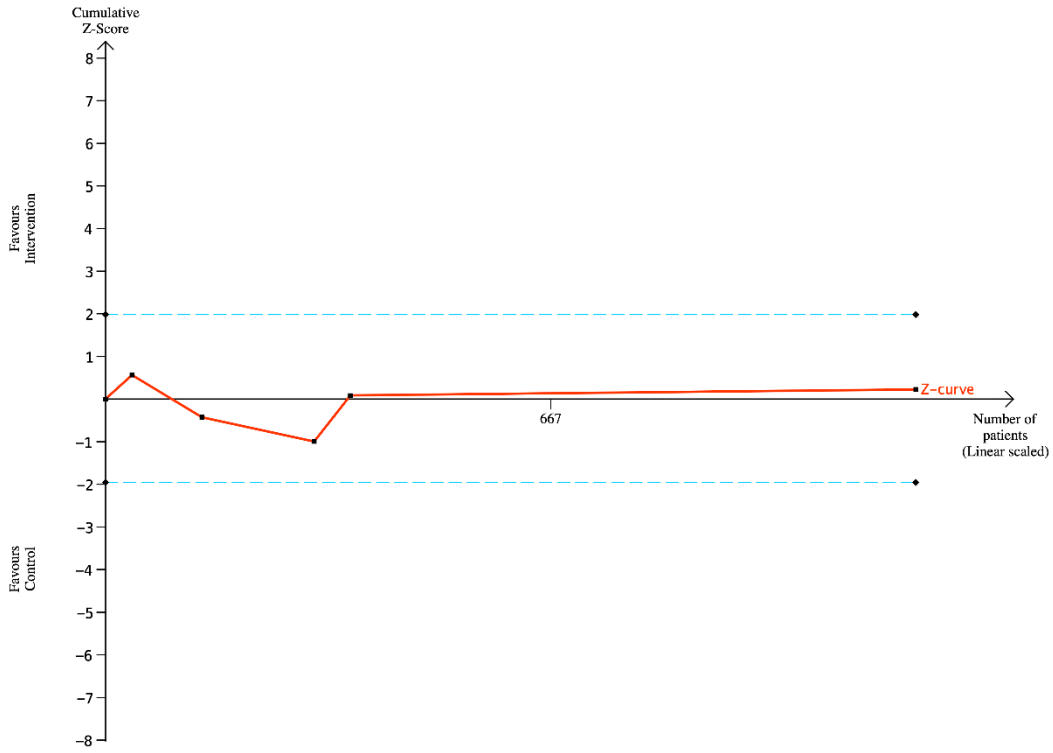


Figure S41. Trial sequential analysis of duration of hospital length of stay for included RCTs

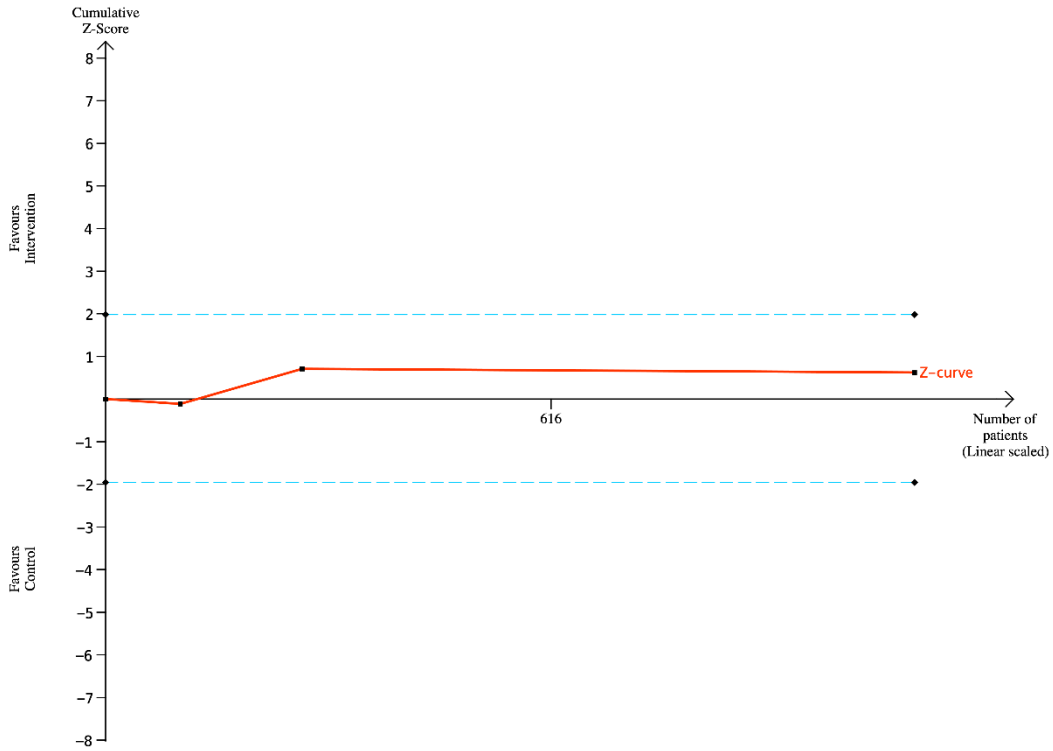


Figure S42. Trial sequential analysis of duration of systematic antibiotic use for included RCTs

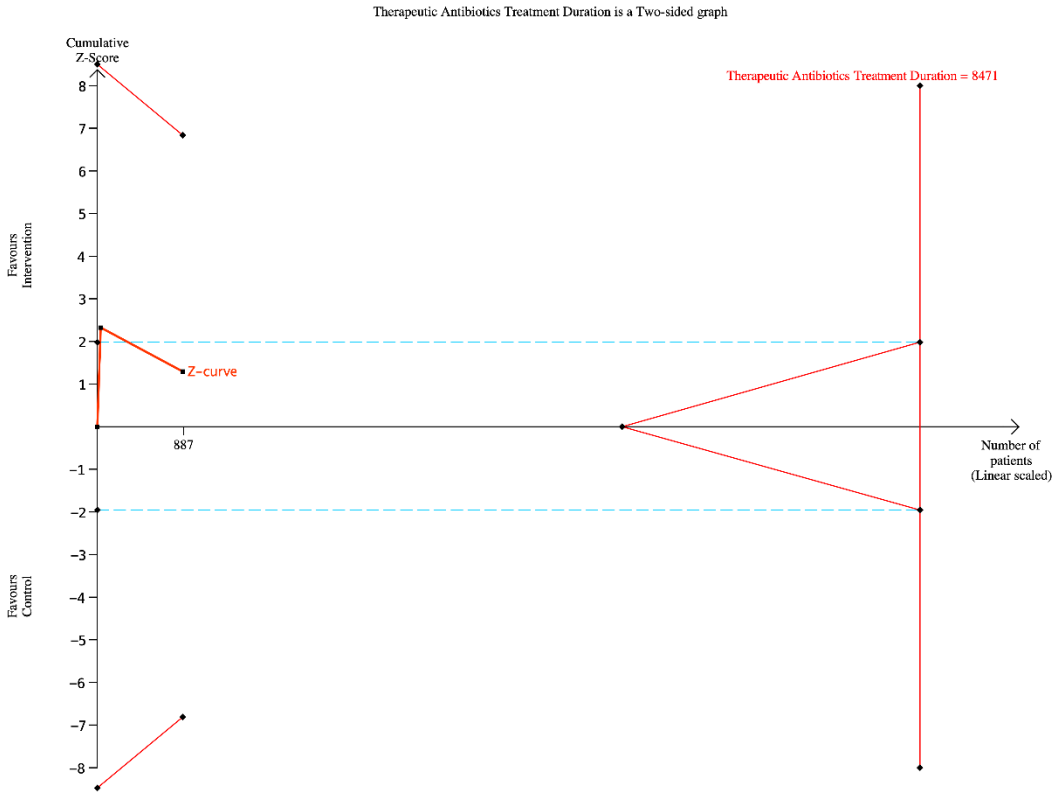


Figure S43. Trial sequential analysis of the need for tracheostomy for included RCTs

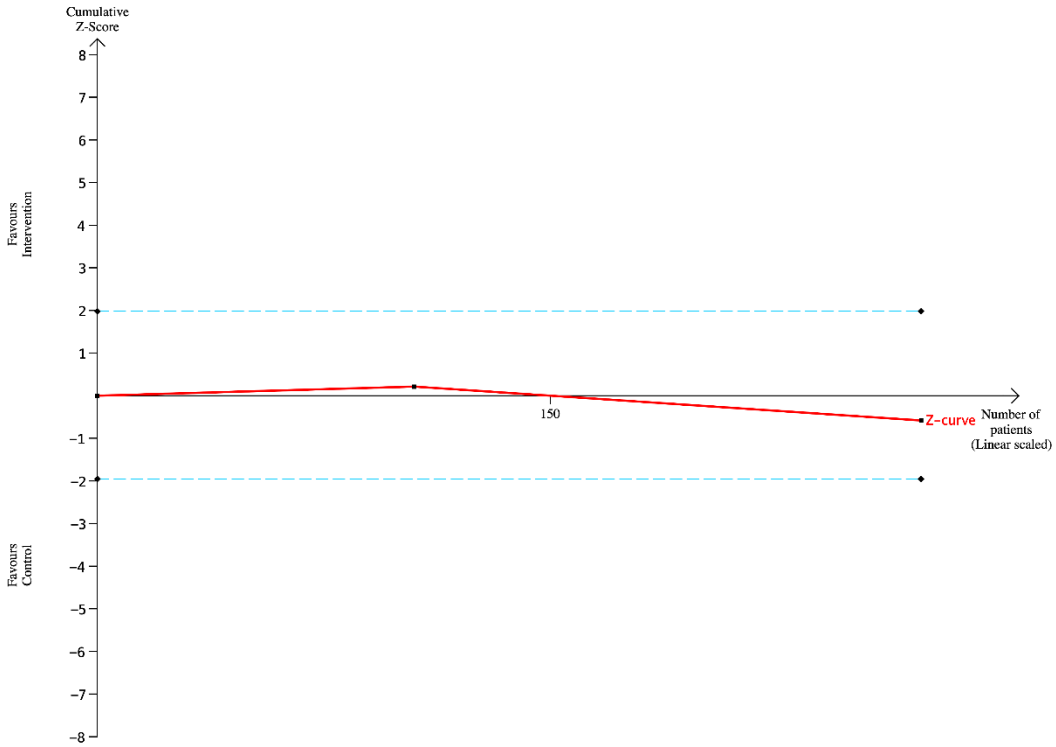


Table S9. Summary of adverse events of all RCTs and non-RCTs in the meta-analysis.

Author	Side effects
Ehrmann et al., 2023	Any serious adverse event (IG vs CG): 4% vs 3%; Respiratory tract–disorders event: 2% vs 2%; Serious adverse effect*: 2% vs 1%; Respiratory tract effect: 2% vs 1%; Acute kidney injury occurrence from randomization to day 28: 4% vs 8%
Karvouniaris et al., 2015	Bronchospasm (IG vs CG): 9.5% vs 3.4%
Kuzovlev et al., 2015	No side effects, such as bronchospasm, coughing up blood, ototoxicity, and nephrotoxicity, were observed.
Wood et al., 2002	No adverse events were reported.
Klastersky et al., 1974	In no case was there any suggestion of acoustic or vestibular dysfunction.
Rathgeber et al., 1993	No allergic reactions, increased respiratory pressures or bronchoconstrictions were observed.
Greenfield et al., 1973	Toxicity was not detected.
Claridge et al., 2007	Not mentioned.
Lode et al., 1988	Not mentioned.
Rouby et al., 1994	Not mentioned.
Klick et al., 1975	Not mentioned.

IG: intervention group; CG: control group.

*A serious adverse effect was a serious adverse event related to a trial procedure.