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Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation (Review)

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Minozzi S, Pifferi S, Brazzi L, Pecoraro V, Montrucchio G, D'Amico R.
Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation.
Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD000022.
DOI: 10.1002/14651858.CD000022.pub4.

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TABLE OF CONTENTS

[Intervention Review]

Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2021.

Citation: Minozzi S, Pifferi S, Brazzi L, Pecoraro V, Montrucchio G, D'Amico R. Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No.: CD000022. DOI: 10.1002/14651858.CD000022.pub4.

ABSTRACT

Background

Patients treated with mechanical ventilation in intensive care units (ICUs) have a high risk of developing respiratory tract infections (RTIs). Ventilator-associated pneumonia (VAP) has been estimated to affect 5% to 40% of patients treated with mechanical ventilation for at least 48 hours. The attributable mortality rate of VAP has been estimated at about 9%. Selective digestive decontamination (SDD), which consists of the topical application of non-absorbable antimicrobial agents to the oropharynx and gastroenteric tract during the whole period of mechanical ventilation, is often used to reduce the risk of VAP. A related treatment is selective oropharyngeal decontamination (SOD), in which topical antibiotics are applied to the oropharynx only. This is an update of a review first published in 1997 and updated in 2002, 2004, and 2009.

Objectives

To assess the effect of topical antibiotic regimens (SDD and SOD), given alone or in combination with systemic antibiotics, to prevent mortality and respiratory infections in patients receiving mechanical ventilation for at least 48 hours in ICUs.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, PubMed, and Embase on 5 February 2020. We also searched the WHO ICTRP and ClinicalTrials.gov for ongoing and unpublished studies on 5 February 2020. All searches included non-English language literature. We handsearched references of topic-related systematic reviews and the included studies.

Selection criteria

Randomised controlled trials (RCTs) and cluster-RCTs assessing the efficacy and safety of topical prophylactic antibiotic regimens in adults receiving intensive care and mechanical ventilation. The included studies compared topical plus systemic antibiotics versus placebo or no treatment; topical antibiotics versus no treatment; and topical plus systemic antibiotics versus systemic antibiotics.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included a total of 41 trials involving 11,004 participants (five new studies were added in this update). The minimum duration of mechanical ventilation ranged from 2 (19 studies) to 6 days (one study). Thirteen studies reported the mean length of ICU stay, ranging from 11 to 33 days. The percentage of immunocompromised patients ranged from 0% (10 studies) to 22% (1 study).

The reporting quality of the majority of included studies was very poor, so we judged more than 40% of the studies as at unclear risk of selection bias. We judged all studies to be at low risk of performance bias, though 47.6% were open-label, because hospitals usually have standardised infection control programmes, and possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting. Regarding detection bias, we judged all included studies as at low risk for the outcome mortality. For the outcome RTIs, we judged all double-blind studies as at low risk of detection bias. We judged five open-label studies as at high risk of detection bias, as the diagnosis of RTI was not based on microbiological exams; we judged the remaining open-label studies as at low risk of detection bias, as a standardised set of diagnostic criteria, including results of microbiological exams, were used.

Topical plus systemic antibiotic prophylaxis reduces overall mortality compared with placebo or no treatment (risk ratio (RR) 0.84, 95% confidence interval (CI) 0.73 to 0.96; 18 studies; 5290 participants; high-certainty evidence). Based on an illustrative risk of 303 deaths in 1000 people this equates to 48 (95% CI 15 to 79) fewer deaths with topical plus systemic antibiotic prophylaxis. Topical plus systemic antibiotic prophylaxis probably reduces RTIs (RR 0.43, 95% CI 0.35 to 0.53; 17 studies; 2951 participants; moderate-certainty evidence). Based on an illustrative risk of 417 RTIs in 1000 people this equates to 238 (95% CI 196 to 271) fewer RTIs with topical plus systemic antibiotic prophylaxis.

Topical antibiotic prophylaxis probably reduces overall mortality compared with no topical antibiotic prophylaxis (RR 0.96, 95% CI 0.87 to 1.05; 22 studies, 4213 participants; moderate-certainty evidence). Based on an illustrative risk of 290 deaths in 1000 people this equates to 19 (95% CI 37 fewer to 15 more) fewer deaths with topical antibiotic prophylaxis. Topical antibiotic prophylaxis may reduce RTIs (RR 0.57, 95% CI 0.44 to 0.74; 19 studies, 2698 participants; low-certainty evidence). Based on an illustrative risk of 318 RTIs in 1000 people this equates to 137 (95% CI 83 to 178) fewer RTIs with topical antibiotic prophylaxis.

Sixteen studies reported adverse events and dropouts due to adverse events, which were poorly reported with sparse data. The certainty of the evidence ranged from low to very low.

Authors' conclusions

Treatments based on topical prophylaxis probably reduce respiratory infections, but not mortality, in adult patients receiving mechanical ventilation for at least 48 hours, whereas a combination of topical and systemic prophylactic antibiotics reduces both overall mortality and RTIs. However, we cannot rule out that the systemic component of the combined treatment provides a relevant contribution in the observed reduction of mortality. No conclusion can be drawn about adverse events as they were poorly reported with sparse data.

PLAIN LANGUAGE SUMMARY

Topical antibiotics to help reduce death and respiratory infections in people in intensive care receiving mechanical ventilation

Review question

We aimed to assess the effect of two topical antibiotic regimens (selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD)) in preventing deaths and respiratory infections in patients receiving mechanical ventilation for at least 48 hours in intensive care units (ICUs). In SDD, non-absorbable antibiotics are applied to the oropharynx (back third of the tongue, the soft palate, the side and back walls of the throat and tonsils), oesophagus, stomach, and intestine. SOD involves the application of non-absorbable antibiotics to the oropharynx only. These regimens may be given alone or in combination with systemic antibiotics.

Background

Infections acquired in ICUs are important complications of treatment with ventilation (invasive mechanical breathing support) in patients with very severe diseases who require such treatment. Some of these people will die because of these infections. One method that has been evaluated to reduce these complications is to use antibiotics as a preventative measure.

Search date

This review is current to 5 February 2020.

Study characteristics:

We included 41 trials involving a total of 11,004 patients mechanically ventilated in ICUs to find out whether giving topical antibiotics, alone or in combination with systemic antibiotics, prevents respiratory tract infections and reduces death. Antibiotics were administered either topically (e.g. antibiotics were applied directly to the oropharynx or to the stomach via a nasogastric tube) or systemically (e.g. intravenously (directly into the patient's vein)).

Study funding sources

Twenty-two studies (52.4%) did not report the funding source; 6 studies (14.3%) were supported by public institutional grants; and 13 studies (30.1%) were totally or partially funded by pharmaceutical companies.

Key results

In patients receiving the combination of topical plus systemic antibiotics, there were fewer deaths (data from 18 studies with 5290 patients) and probably fewer patients with respiratory tract infections (data from 17 studies with 2951 patients) compared to those who received no treatment or placebo, although we cannot exclude the possibility that the systemic component of the treatments contributed to the reduction in deaths. Assuming an illustrative risk of 303 deaths and of 417 cases of respiratory tract infections in 1000 people under mechanical ventilation, we expect 48 fewer death in patients who receive a combination of topical plus systemic antibiotics and 238 fewer cases of respiratory tract infections. When patients who received topical antibiotics only were compared with patients who received no treatment, or when patients who received topical plus systemic antibiotics were compared with patients who received systemic antibiotics alone, the number of deaths was probably similar (data from 22 studies with 4213 patients), although there may be fewer patients with respiratory tract infections in patients who received topical prophylaxis (data from 19 studies; 2698 patients). Adverse events were poorly reported, with limited data.

Certainty of the evidence

We judged the certainty of the evidence as high to moderate for deaths and respiratory tract infections and low to very low for adverse events.

SUMMARY OF FINDINGS

Summary of findings 1. Topical plus systemic prophylaxis versus placebo or no treatment in adults receiving mechanical ventilation for at least 48 hours

Topical plus systemic prophylaxis versus placebo or no treatment in adults receiving mechanical ventilation for at least 48 hours

Patient or population: adults receiving mechanical ventilation for at least 48 hours
Setting: ICU in The Netherlands, France, Spain, Germany, USA, UK, Egypt, Ireland, Tunisia, South Africa, Austria, Greece, Switzerland, Belgium, Australia and New Zealand
Intervention: topical and systemic antibiotic prophylaxis
Comparison: no prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no prophylaxis	Risk with topical plus systemic			
Overall mortality	Study population		RR 0.84 (0.73 to 0.96)	5290 (18 RCTs)	⊕⊕⊕⊕ HIGH
	303 per 1000	255 per 1000 (224 to 288)			
Respiratory tract infections	Study population		RR 0.43 (0.35 to 0.53)	2951 (17 RCTs)	⊕⊕⊕⊖ MODERATE[a]
	417 per 1000	179 per 1000 (146 to 221)			
Dropouts due to adverse events	Study population		RR 1.06 (0.30 to 3.76)	1287 (4 RCTs)	⊕⊕⊖⊖ LOW[b]
	6 per 1000	7 per 1000 (2 to 24)			
Gastrointestinal adverse events	Study population		RR 1.08 (0.57 to 2.04)	2637 (6 RCTs)	⊕⊕⊖⊖ LOW[b]
	44 per 1000	48 per 1000 (25 to 90)			
Allergic adverse events	Study population		RR 1.49 (0.09 to 25.33)	2981 (6 RCTs)	⊕⊕⊖⊖ LOW[b]
	0 per 1000	1 per 1000 (0 to 9)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **ICU:** intensive care unit; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level for suspected publication bias, as indicated by asymmetry in the funnel plot.
[b]Downgraded 2 levels due to very serious imprecision: sparse data.

Summary of findings 2. Topical prophylaxis versus no topical prophylaxis in adults receiving mechanical ventilation for at least 48 hours

Topical prophylaxis versus no topical prophylaxis in adults receiving mechanical ventilation for at least 48 hours

Patient or population: adults receiving mechanical ventilation for at least 48 hours
Setting: ICU in The Netherlands, France, Spain, Germany, USA, UK, Egypt, Ireland, Tunisia, South Africa, Austria, Greece, Switzerland, Belgium, Australia and New Zealand
Intervention: topical antibiotic prophylaxis
Comparison: no topical prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with topical			
Overall mortality	Study population		RR 0.96 (0.87 to 1.05)	4213 (22 RCTs)	⊕⊕⊕⊖ MODERATE[a]
	290 per 1000	279 per 1000 (253 to 305)			
Overall mortality - topical plus systemic prophylaxis versus systemic prophylaxis alone	Study population		RR 0.92 (0.72 to 1.18)	939 (7 RCTs)	⊕⊕⊖⊖ LOW[b,c]
	237 per 1000	218 per 1000 (171 to 280)			
Overall mortality - topical prophylaxis versus placebo or no treatment	Study population		RR 0.97 (0.87 to 1.07)	3274 (15 RCTs)	⊕⊕⊕⊖ MODERATE[d]
	305 per 1000	296 per 1000 (265 to 326)			
Respiratory tract infections	Study population		RR 0.57 (0.44 to 0.74)	2698 (19 RCTs)	⊕⊕⊖⊖ LOW[e,f,g]
	318 per 1000	181 per 1000			

		(140 to 235)			
Respiratory tract infections - topical plus systemic prophylaxis versus systemic prophylaxis alone	Study population		RR 0.82 (0.58 to 1.16)	850 (6 RCTs)	⊕⊕⊖⊖ LOW[b,c,f]
	303 per 1000	248 per 1000 (176 to 352)			
Respiratory tract infections - topical prophylaxis versus no treatment or placebo	Study population		RR 0.50 (0.36 to 0.69)	1848 (13 RCTs)	⊕⊕⊖⊖ LOW[f,h]
	324 per 1000	162 per 1000 (117 to 224)			
Dropouts due to adverse events	Study population		RR 2.20 (0.57 to 8.54)	1323 (7 RCTs)	⊕⊖⊖⊖ VERY LOW[c,i]
	9 per 1000	20 per 1000 (5 to 77)			
Gastrointestinal adverse events	Study population		RR 2.78 (0.26 to 29.50)	1859 (3 RCTs)	⊕⊕⊖⊖ LOW[i]
	22 per 1000	62 per 1000 (6 to 656)			
Allergic adverse events	Study population		RR 2.64 (0.34 to 20.69)	2357 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[i,j]
	1 per 1000	2 per 1000 (0 to 17)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **ICU:** intensive care unit; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]68% of studies at unclear risk and 1 study at high risk of selection bias.
[b]Optimal information size not met.
[c]All studies at unclear risk of selection bias.
[d]53.3% of studies at unclear risk and 1 study at high risk of selection bias.
[e]74% of studies at unclear risk and 1 study at high risk of selection bias.
[f]Downgraded 1 level for suspected publication bias, as indicated by the Funnel plot showing asymmetry.

[g] We decided against downgrading certainty of evidence of this outcome as, although there is heterogeneity among studies, the direction of all the results favours the experimental intervention.
[h] 62% of studies at unclear risk and 1 study at high risk of selection bias.
[i] Downgraded 2 levels due to very serious imprecision: sparse data.
[j] 50% of studies at unclear risk of selection bias.

BACKGROUND

Description of the condition

Patients admitted to intensive care units (ICUs) are prone to acquire nosocomial infections, which may increase morbidity and mortality (Adrie 2017; Melsen 2013).

Amongst respiratory tract infections (RTIs), ventilator-associated pneumonia (VAP) has been estimated to affect 5% to 40% of patients treated with mechanical ventilation for at least 48 hours. However, this estimate is highly variable depending on the country, the type of ICU, and the criteria used to define the VAP (American Thoracic Society 2005; Reignier 2016; Seguin 2014).

Data from the US report estimates of incidence of VAP in the order of 1 to 2 cases per 1000 days of ventilation (Dudeck 2013), whilst the European study EU-VAP/CAP has shown an incidence of 18.3 episodes of VAP per 1000 days of ventilation (Koulenti 2017). Higher incidences were also found in low- to middle-income countries compared to high-income countries (18.5 versus 9.0 per 1000 days of ventilation) (Bonell 2019). However, it should be noted that these differences are explained, at least partially, by the use of different definitions, and due to differences in microbiological sampling methods (Ego 2015). Incidence rates also vary according to the population studied, that is higher incidences have been reported in cancer patients, Stoclin 2020, and trauma patients (Cook 2010).

Based on aggregated results from 58 randomised studies on VAP prevention, the attributable mortality rate of VAP was reported as 9% (Melsen 2011). A competing risk survival analysis in a cohort of 4479 ICU patients in France reported that intensive care mortality attributable to VAP was approximately 1% on day 30 and 1.5% on day 60 (Bekaert 2011). Data from an individual patient meta-analysis including 24 studies (6284 patients) showed that mortality was higher in surgical patients and in those with medium-severity illness at ICU admission, when compared to traumatised and medical patients, or when compared to those with particularly high- or low-severity illness at admission (Melsen 2013).

ICU-acquired infections are also responsible for increased expenditure in an already costly healthcare setting. Interventions aimed at preventing these complications are therefore encouraged (Kollef 2012; Laupland 2006).

Description of the intervention

Selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD) are prophylactic antibiotic interventions used to eradicate colonisation of aerobic gram-negative bacteria, *Staphylococcus aureus*, and yeasts, whilst leaving the anaerobic flora intact.

SDD consists of the topical application of non-absorbable antimicrobial agents to the oropharynx and gastroenteric tract during the whole ICU stay, often in combination with a short initial course of intravenous antibiotics (usually intravenous second-generation cephalosporin during the first four days of ICU stay).

SOD comprises oropharyngeal application of bactericidal non-absorbable antibiotics.

Both interventions consist of enteral application of non-absorbable antimicrobial agents, most often amphotericin B, tobramycin or gentamycin, and colistin, aiming to eradicate yeasts, *S aureus*, and aerobic gram-negative bacteria.

Since the main goal of antibiotic prophylaxis is to prevent infections acquired in intensive care, the protocol was usually applied immediately after ICU admission and continued until ICU discharge or extubation (de Jonge 2003; de Smet 2009; Oostdijk 2014; Stoutenbeek 1984; Wittekamp 2018). The target population is patients admitted to ICU for at least 48 hours and undergoing invasive mechanical ventilation.

In early studies, antibiotic prophylaxis was assessed in the ICU setting to prevent VAP in trauma patients who received prolonged mechanical ventilation by using a four-component “classic” SDD regimen (Hurley 2020). Recent studies have broadened the inclusion criteria beyond trauma patients receiving invasive mechanical ventilation, tested different regimens, and used endpoints other than VAP. Variable definitions for some endpoints, such as VAP and bacteraemia, as well as variable study designs including blind or non-blind placebo-controlled groups, receiving or not receiving parenteral antibiotic prophylaxis, or even without any control group, have further clouded the picture. Although no relationship between the administration of SDD and antimicrobial resistance was detected (Daneman 2013), the real impact of SDD on the onset of antibiotic resistance remains, to date, not fully defined. This was mainly due to the fact that most of the studies assessed the effects of SDD at the patient level rather than at the ICU level, and with limited follow-up time (Sánchez-Ramírez 2018). Distinguishing ICUs with low prevalence of antibiotic resistance from ICUs with moderate to high prevalence of resistance, three cluster-randomised studies highlighted that in settings with low prevalence of antibiotic resistance, SDD has been consistently associated with improved patient outcome (de Jonge 2003; de Smet 2009; Oostdijk 2014). These benefits were not confirmed in a large international cluster-randomised study in settings with moderate-to-high prevalence of antibiotic resistance, where clinical relevance of SDD on patient outcomes remains to be seen (Wittekamp 2018).

How the intervention might work

The hypothesis behind antibiotic prophylaxis with SDD/SOD is that intestinal flora may represent the origin of potential pathogenic micro-organisms which, colonising the upper respiratory tract during hospitalisation, can induce an increased risk of VAP and infection-related ventilator-associated complication (IVAC) (Magill 2013).

SDD and SOD have been shown to reduce the incidence of RTIs, the colonisation with antibiotic-resistant gram-negative bacteria, and the incidence of nosocomial infections, and to improve patient survival (de Jonge 2018; de Smet 2009; Plantinga 2017; Vincent 2011). The prevention effect with antibiotic prophylaxis seems to exceed the VAP prevention effect of various non-decontamination methods evaluated in the mechanically ventilated patient group (Landelle 2018).

Why it is important to do this review

Antibiotic prophylaxis, especially SDD, has been discussed in intensive care literature for nearly 40 years (Stoutenbeek 1984). The diversity amongst the studies has fuelled controversy (Hurley 2020).

On the one hand, as early as 25 years ago, the summary evidence derived from more than 40 studies showed an apparent potent prevention effect against VAP, bacteraemia, and mortality (Hurley 1995). On the other hand, opinions regarding antibiotic prophylaxis have varied, even in the Netherlands, where many high-quality studies have been conducted (Bonten 2001), and where SDD is the standard of care (SWAB 2018).

Although high-quality evidence supports the use of SDD, its application is still a matter of debate, and it is not widely used in clinical practice (Reis 2015), due to the main concern that it may promote the emergence of antibiotic-resistant strains (Brink 2013; Halaby 2013).

Given the uncertainty on the efficacy of antibiotic prophylaxis, and in light of the worldwide challenge of multidrug resistance, we considered it necessary to revisit this meta-analysis, with the aim of redefining the role of the antibiotic prophylaxis in ICU patients requiring invasive mechanical ventilation.

OBJECTIVES

To assess the effect of topical antibiotic regimens (selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD)), given alone or in combination with systemic antibiotics, to prevent mortality and respiratory infections in patients receiving mechanical ventilation for at least 48 hours in intensive care units (ICUs).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and cluster-RCTs on antibiotic prophylaxis for the prevention of respiratory tract infections (RTIs) and death in adults on mechanical ventilation in intensive care unit (ICU) patients. We included both blinded and unblinded studies.

Types of participants

Adult (≥ 18 years) patients admitted to an ICU for at least 48 hours. We excluded studies where the majority of patients (> 50%) did not undergo mechanical ventilation for at least 48 hours. We also excluded studies if they considered only patients with a higher-than-usual risk of infection (e.g. liver transplantation, neutropenic patients).

Types of interventions

Experimental intervention

Topical antibiotic prophylaxis applied to nasopharynx (selective oropharyngeal decontamination (SOD)) or to oropharynx and gastric tube (selective decontamination of the digestive tract (SDD)) for the whole period of mechanical ventilation, given alone or in combination with systemic antibiotic prophylaxis.

Control intervention

Placebo, no prophylaxis, or systemic antibiotic prophylaxis alone.

Types of outcome measures

Primary outcomes

1. Overall mortality. We considered mortality at hospital discharge if this information was provided; otherwise we considered mortality in the ICU.
2. Respiratory tract infections. We made no restriction on the type of RTI considered (pneumonia and tracheobronchitis, ventilator-associated pneumonia (VAP), and infection-related ventilator-associated complication (IVAC)), nor on the RTI diagnostic criteria used. We considered both primary (diagnosed within 48 hours from admission) and acquired (diagnosed after 48 hours from admission) infections. In case both were reported, we considered data from the acquired group.

Secondary outcomes

1. Dropouts due to adverse events.
2. Participants with gastrointestinal adverse events.
3. Participants with allergic adverse events.

Search methods for identification of studies

Electronic searches

For this update, we searched the following databases up to 5 February 2020. We imposed no language, publication year, or publication status restrictions. We identified published, unpublished, and ongoing studies by searching the following databases from their inception.

1. Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, 2020 Issue 3 (searched 5 February 2020) (Appendix 1).
2. MEDLINE PubMed (up to 5 February 2020) (Appendix 2).
3. Embase Ovid (up to 5 February 2020) (Appendix 3).

We searched the following trials registries on 5 February 2020:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov); and
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

Details of the previous search strategies are shown in Appendix 4.

Searching other resources

We searched the reference lists of retrieved included studies, systematic reviews, and meta-analyses in order to identify other potentially eligible studies.

Data collection and analysis

Selection of studies

Two review authors (SP, SM) independently screened the titles and abstracts of all the references identified by the searches and retrieved and investigated all potentially relevant articles as full text to determine eligibility for inclusion in the review. Any disagreements were resolved by discussion or by involving a third review author (LB) if necessary.

Data extraction and management

Using a standardised data extraction form, three review authors (VP, SM and SP) collected the relevant study data, including study design, sample characteristics, description of the experimental and control interventions, outcomes, study funding, and conflicts of interest. Any disagreements were resolved by discussion. We contacted study authors for clarification when necessary.

Assessment of risk of bias in included studies

Two review authors (SM, VP) independently assessed the risk of bias using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The recommended approach for assessing risk of bias is a two-part tool, addressing the specific domains of sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). The first part of the tool involves describing what was reported to have occurred in the study, whilst in the second part a judgement is assigned relating to the risk of bias for each domain, that is low, high, or unclear risk. See Appendix 5 for details.

We assessed the risk of detection bias separately for mortality, RTIs, and adverse events.

Measures of treatment effect

We analysed dichotomous outcomes by calculating the risk ratio (RR) and its relative 95% confidence interval (CI).

Unit of analysis issues

In case of multi-arm studies, we combined all the relevant experimental or control groups into a single group to avoid double-counting of participants. In case of cluster-RCTs, we adjusted the raw data for the 'design effect' by using the effective sample size approach, as recommended in the updated version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

Dealing with missing data

Missing data are not a relevant issue in this setting and for our outcomes, as patients who meet the inclusion criteria are usually followed up until the end of the study, and outcome values are collected by the researchers.

Assessment of heterogeneity

We analysed heterogeneity using the I^2 statistic and the Chi^2 test. We considered heterogeneity as substantial if the I^2 was greater than 75%, or the P value was lower than 0.10 for the Chi^2 test for heterogeneity (Higgins 2020).

Assessment of reporting biases

We used the visual inspection of funnel plots (plots of the effect estimate from each study against the effect standard error) to evaluate possible publication bias if there were at least 10 studies included in the meta-analysis.

Data synthesis

We combined the outcomes from the individual trials through meta-analysis where possible (comparability of intervention and outcomes between trials), using a random-effects model, because we expected a certain degree of heterogeneity across trials. If the clinical or statistical heterogeneity was too high (i.e. 75% to 100%), we decided against pooling the data.

Subgroup analysis and investigation of heterogeneity

We did not perform subgroup analysis for type of drug because there were no data to assume a difference in effect amongst the considered prophylactic treatments. This obviously does not mean that all topical and systemic regimens are truly equivalent, but simply reflects our pragmatic working assumption.

Sensitivity analysis

To incorporate our assessment of risk of bias in the review process, we first plotted the intervention effect estimates stratified by risk of bias for allocation concealment (selection bias). We planned that if differences in the results were present amongst studies at different risks of selection bias, we would perform sensitivity analysis by excluding the studies at high risk of selection bias.

Summary of findings and assessment of the certainty of the evidence

We created two 'Summary of findings' tables (Summary of findings 1; Summary of findings 2) using the following outcomes: overall mortality, RTIs, dropouts due to adverse events, gastrointestinal adverse events and allergic adverse events. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), employing GRADEpro GDT software (GRADEpro GDT). We justified all decisions to down- or upgrade the quality of studies using footnotes, and made comments to aid the reader's understanding of the review where necessary.

The GRADE system uses the following criteria for assigning grades of evidence.

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

RESULTS

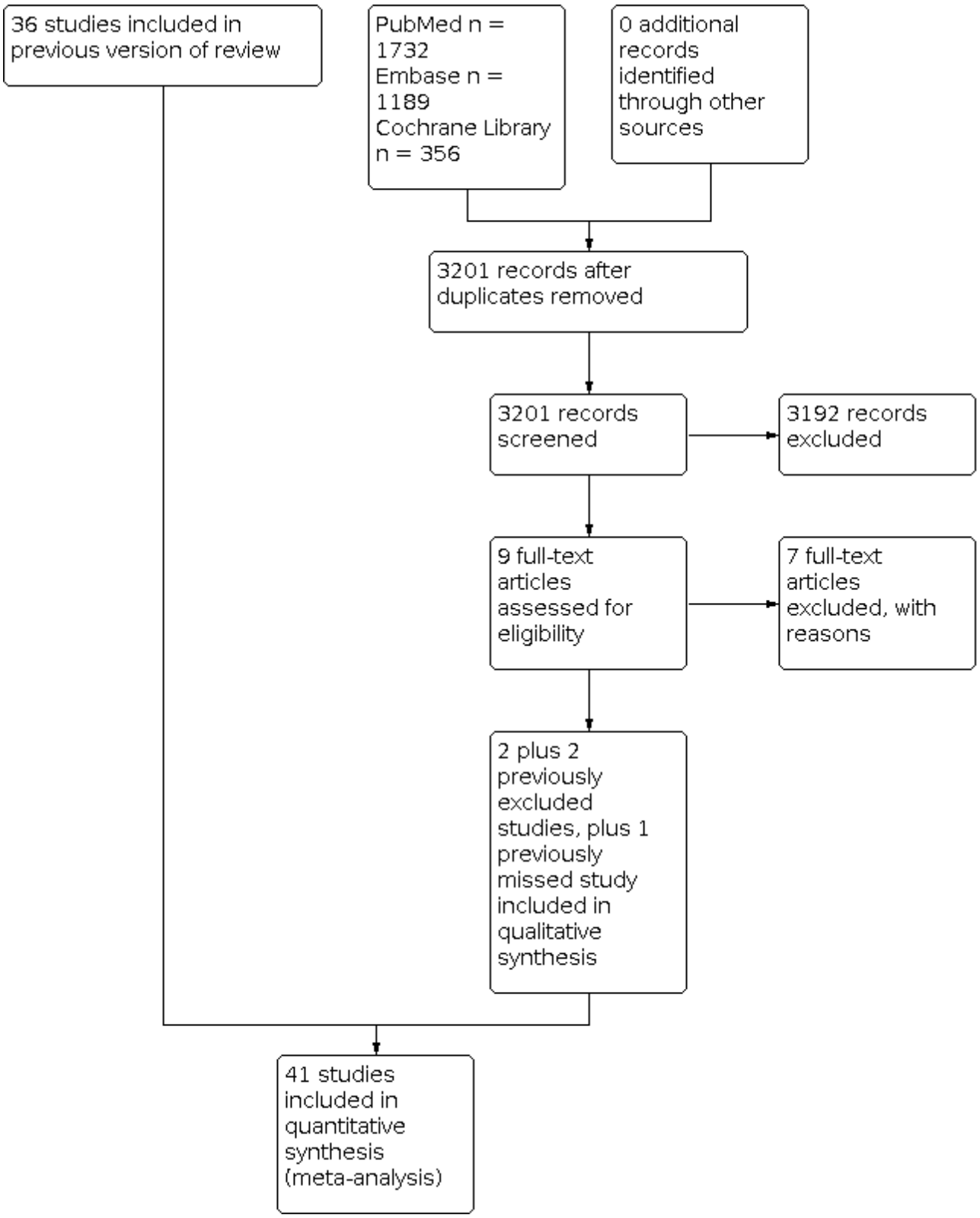
Description of studies

Results of the search

We included 36 trials involving 6914 people in the previous version of this review. In this 2020 update, we identified a total of 3201 records after de-duplication, of which nine studies were considered

as potentially relevant. We excluded seven studies and included two studies (Beshey 2014; Chaari 2014). We also decided to include two previously excluded studies (de la Cal 2005; de Smet 2009), and included one study that was missed in the previous version of the review (Koeman 2006). We identified two ongoing studies (IRCT20180110038298N1; NCT02389036). We included a total of 41 studies. See Figure 1.

Figure 1. Study flow diagram: 2020 update.



Included studies

We included 41 RCTs in this update. One study was a cluster-RCT (de Smet 2009). All of the trials were published, 39 as full reports, and two in abstract form (Boland 1991; Finch 1991). See Characteristics of included studies table.

Characteristics of participants

Overall, the trials included 16,329 participants. In our analyses, we considered 11,004 participants as fulfilling the inclusion criteria of a minimum duration of mechanical ventilation of at least 48 hours. The minimum duration of mechanical ventilation was two days in 19 studies, three days in seven studies, four days in three studies, five days in eight studies, and six days in one study. In two studies the minimum duration of mechanical ventilation was not stated.

The number of participants included in the studies ranged from 39 to 4035. The reasons for admission were surgical for 4726 (29%) participants, medical for 5305 (32.5%) participants, and trauma for 2609 (16%) participants.

Length of stay in ICU was reported as median in 18 studies, ranging from 3.5 to 19.5 days, and as mean in 13 studies, ranging from 11.3 to 33 days. Ten studies did not report this information.

In eight studies (Blair 1991; Brun-Buisson 1989; Cockerill 1992; de Jonge 2003; de la Cal 2005; de Smet 2009; Ulrich 1989; Winter 1992), not all participants were mechanically ventilated. Five studies did not report this information (Beshey 2014; Camus 2005; Cerra 1992; Finch 1991; Laggner 1994).

The percentage of immunocompromised participants ranged from 0% (10 studies) to 22% (1 study).

Characteristics of treatment regimens

Nineteen RCTs compared the combination of topical and systemic antibiotic prophylaxis versus no treatment or placebo (Abele-Horn 1997; Aerdts 1991; Blair 1991; Boland 1991; Cockerill 1992; de Jonge 2003; de la Cal 2005; de Smet 2009; Finch 1991; Jacobs 1992; Kerver 1988; Krueger 2002; Palomar 1997; Rocha 1992; Sanchez-Garcia 1998; Stoutenbeek 2007; Ulrich 1989; Verwaest 1997; Winter 1992); 16 RCTs compared topical prophylaxis alone to no treatment or placebo (Bergmans 2001; Beshey 2014; Brun-Buisson 1989; Camus 2005; Cerra 1992; de Smet 2009; Gastinne 1992; Georges 1994; Koeman 2006; Korinek 1993; Pneumatikos 2002; Pugin 1991; Quinio 1995; Rodriguez-Roldan 1990; Unertl 1987; Wiener 1995); and seven trials compared the combination of topical and systemic antibiotic prophylaxis versus systemic prophylaxis only (Chaari 2014; Ferrer 1994; Gaussorgues 1991; Hammond 1992; Laggner 1994; Lingnau 1997; Stoutenbeek 1996).

One study had three arms (de Smet 2009): one received the combination of topical and systemic antibiotic prophylaxis, one topical prophylaxis alone, and one arm received no prophylaxis.

Two studies were included in the 'topical SDD plus systemic antibiotic versus systemic antibiotic only' group (Gaussorgues 1991; Laggner 1994), though the use of systemic antibiotics was not explicitly stated in the description of interventions. However, all participants in both arms were treated with systemic antibiotics at admission.

Six studies had more than two arms and were analysed as follows. In two studies (Aerdts 1991; Verwaest 1997), the two control groups were pooled and compared to the treatment group. In Lingnau 1997, the participants in the two treatment arms were summarised and compared with the control arm. In two studies (Koeman 2006; Palomar 1997), one of the two control arms was excluded because the participants received only chlorhexidine and sucralfate, respectively. Another study was a four-arm factorial design in which we considered only two arms comparing antibiotic prophylaxis versus placebo (Camus 2005). In Chaari 2014, we considered three arms as the experimental group.

Eight studies were conducted in the Netherlands, seven in France, six in Spain, four in Germany, four in the USA, three in the UK, and one each in Egypt, Ireland, Tunisia, South Africa, Austria, Greece, Switzerland, and Belgium. One study was multicentric and was conducted in Europe, Australia, and New Zealand.

Twenty-two studies (52.4%) did not report the source of funding. Six studies (14.3%) were supported by public institutional grants. Thirteen studies (30.1%) were totally or partially funded by pharmaceutical companies.

Excluded studies

We excluded 33 trials (see Characteristics of excluded studies table). Grounds for exclusion were: only a subgroup of selected patients was included (12 studies); non-randomised design (two studies); experimental intervention not in the inclusion criteria (two studies); both groups received topical prophylaxis (five studies); control intervention not in the inclusion criteria (four studies); objective of the study was not to assess efficacy and safety of topical prophylaxis on clinical outcomes (one study); unclear description of the interventions being compared (one study); paediatric population (four studies); unpublished study, unable to contact study authors for feedback (one study); and data available only from other published meta-analyses so it was impossible to retrieve data from the original study (one study).

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

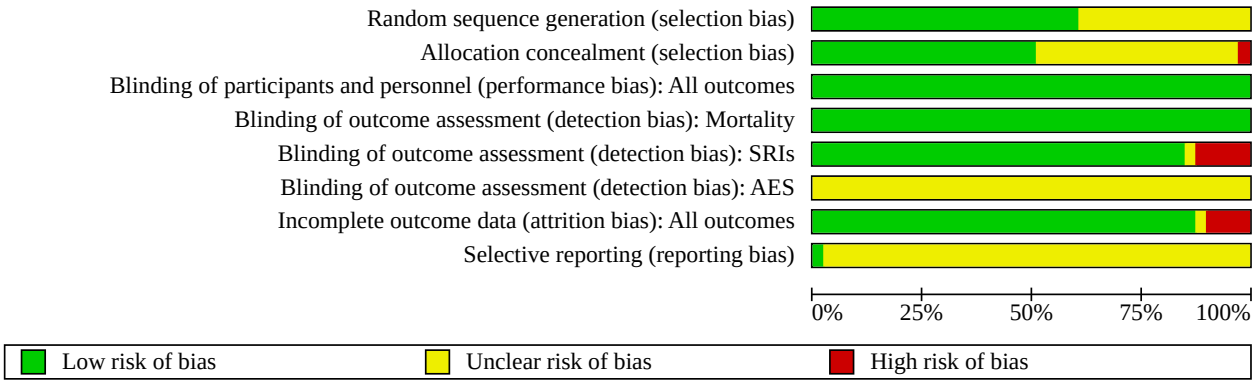


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

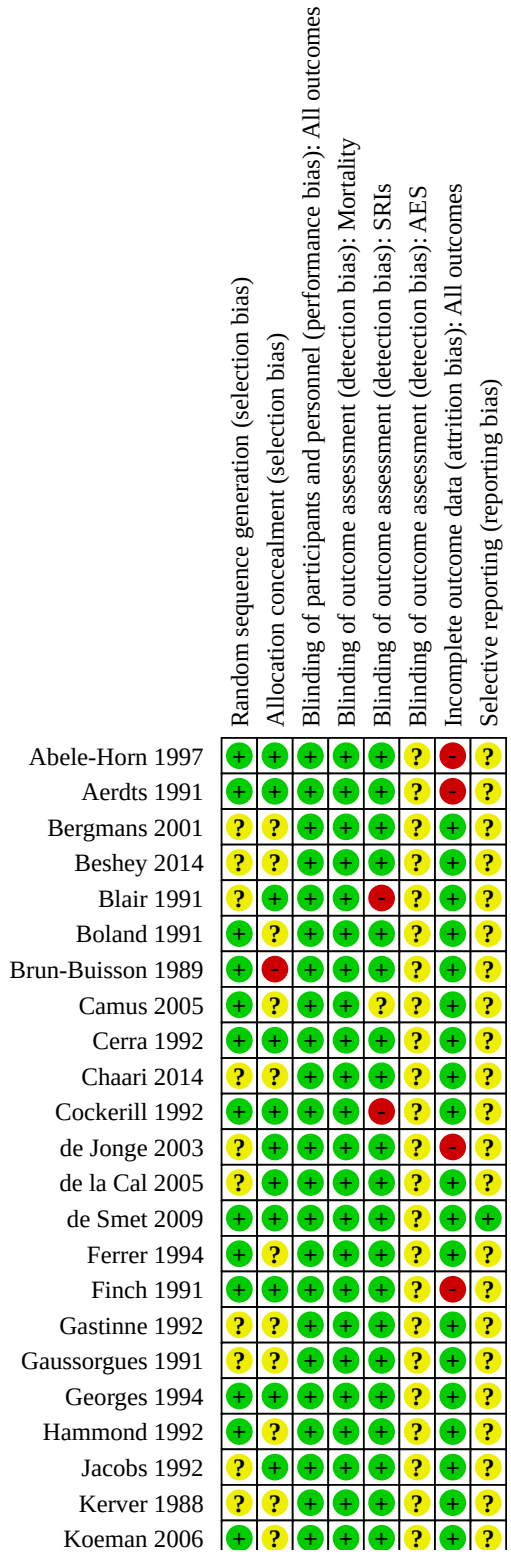
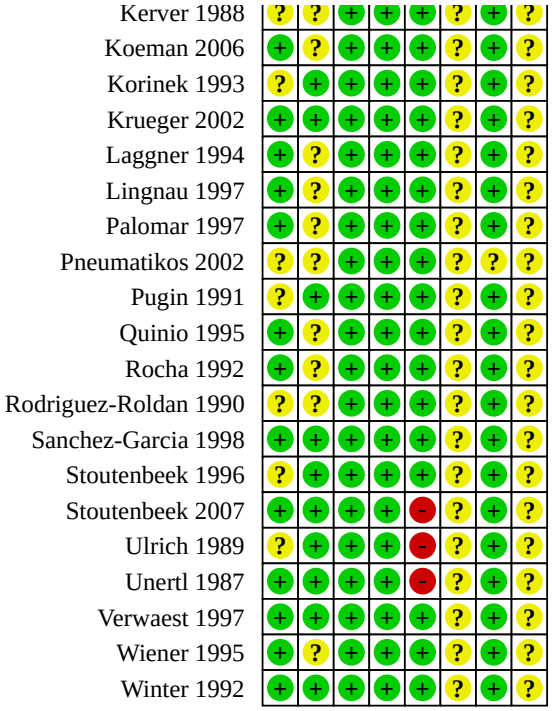


Figure 3. (Continued)



Allocation

Random sequence generation

We judged 25 studies (59.5%) as at low risk of bias. No information about the methods of sequence random generation was reported for the other 16 studies which were judged as at unclear risk of bias.

Allocation concealment

We judged 22 studies (52.4%) as at low risk of bias. One study was judged at high risk of bias (Brun-Buisson 1989). The remaining 18 studies did not report methods of allocation concealment and were therefore judged as at unclear risk of bias.

Blinding

Performance bias

We judged all of the included studies to be at low risk of bias. Twenty (47.6%) studies were open-label; however, hospitals usually have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies. Moreover, all ventilated patients are at high risk for infections independently of antibiotic prophylaxis, so knowledge of it does not change diagnostic workup.

Detection bias

Mortality: We judged all studies to be at low risk of bias.

RTIs: We judged all the double-blind studies as at low risk of bias. Twenty studies (47.6%) were open-label. We judged five open-label studies as at high risk of bias because the diagnosis of RTI was not based on microbiological exams (Blair 1991; Cockerill 1992; Stoutenbeek 2007; Ulrich 1989; Unertl 1987). We judged all the other open-label studies as at low risk of bias because a standardised set of diagnostic criteria, including results of microbiological exams, was used.

Adverse events (AEs): We judged all studies as at unclear risk of bias because methods for AEs collection were poorly reported, and AEs were heterogeneous.

Incomplete outcome data

We judged four studies as at high risk of bias because they excluded patients from the analyses for reasons that were not stated in the study exclusion criteria.

We judged the remaining 37 studies as at low risk of bias, as there were no dropouts. In 27 of these studies, the number of participants analysed was lower than that of those randomised; the authors of these studies decided to exclude from the analysis those participants who either died too soon after ICU admission, or who were extubated early. We did not judge these studies as at high risk of bias, as antibiotic prophylaxis is usually started on admission, whilst meeting the minimum stay in the ICU inclusion criterion can only be verified after at least 48 hours postrandomisation.

In 14 studies, the number of participants who were randomised and analysed was the same. In these cases, if not otherwise specified, we assumed that either no participants were excluded after randomisation, or that the study authors decided to consider as randomised and analysed only those participants who fulfilled the inclusion criteria after randomisation.

Selective reporting

The protocol was available only for one study (de Smet 2009), which was judged as at low risk of bias as the results for all the outcomes described in the protocol were reported in the final publication. We judged the remaining studies as at unclear risk of bias.

Effects of interventions

See: **Summary of findings 1** Topical plus systemic prophylaxis versus placebo or no treatment in adults receiving mechanical ventilation for at least 48 hours; **Summary of findings 2** Topical prophylaxis versus no topical prophylaxis in adults receiving mechanical ventilation for at least 48 hours

We grouped studies in the following comparisons:

1. topical plus systemic prophylaxis versus no treatment (19 studies); and
2. topical prophylaxis versus no topical prophylaxis (23 studies).

We further stratified the studies included in the comparison 'topical prophylaxis versus no topical prophylaxis' into two groups:

a. topical plus systemic prophylaxis versus systemic prophylaxis (7 studies); and
b. topical prophylaxis versus no treatment (16 studies).

Comparison 1: Topical plus systemic prophylaxis versus placebo or no treatment

See: Summary of findings 1

Primary outcomes

1. Overall mortality

We found a significant reduction in overall mortality amongst participants who received topical plus systemic prophylaxis compared to placebo or no treatment (risk ratio (RR) 0.84, 95% confidence interval (CI) 0.73 to 0.96; 18 studies; 5290 participants; high-certainty evidence; Analysis 1.1).

2. Respiratory tract infections

We found a significant reduction in the incidence of respiratory tract infections amongst participants who received topical plus systemic prophylaxis compared to placebo or no treatment (RR 0.43, 95% CI 0.35 to 0.53; 17 studies; 2951 participants; moderate-certainty evidence; Analysis 1.2).

Secondary outcomes

1. Dropouts due to adverse events

We did not find a significant difference in dropouts due to adverse events in participants who received topical plus systemic prophylaxis compared to placebo or no treatment (RR 1.06, 95% CI 0.30 to 3.76; 4 studies; 1287 participants; low-certainty evidence; Analysis 1.3).

2. Participants with gastrointestinal or allergic AEs

Gastrointestinal AEs

We did not find a significant difference in participants who received topical plus systemic prophylaxis compared to no treatment (RR 1.08, 95% CI 0.57 to 2.04; 6 studies; 2637 participants; low-certainty evidence; Analysis 1.4).

Allergic AEs

We did not find significant differences between groups (RR 1.49, 95% CI 0.09 to 25.33; 6 studies; 2981 participants; low-certainty evidence; Analysis 1.5).

Comparison 2: Topical prophylaxis versus no topical prophylaxis

See: Summary of findings 2

Primary outcomes

1. Overall mortality

We did not find a significant difference in overall mortality between participants who received and those who did not receive topical prophylaxis (RR 0.96, 95% CI 0.87 to 1.05; 22 studies, 4213 participants; moderate-certainty evidence; Analysis 2.1).

Topical plus systemic prophylaxis versus systemic prophylaxis alone

We did not find a significant difference between groups (RR 0.92, 95% CI 0.72 to 1.18; 7 studies; 939 participants; low-certainty evidence; Analysis 2.1).

Topical prophylaxis alone versus no treatment

We did not find a significant difference between groups (RR 0.97, 95% CI 0.87 to 1.07; 15 studies; 3274 participants; moderate-certainty evidence; Analysis 2.1).

2. Respiratory tract infections

We found a significant reduction in the incidence of respiratory tract infections in participants who received topical prophylaxis compared to those who did not receive topical prophylaxis (RR 0.57, 95% CI 0.44 to 0.74; 19 studies; 2698 participants; low-certainty evidence; Analysis 2.2).

Topical plus systemic prophylaxis versus systemic prophylaxis alone

We found no significant difference between groups (RR 0.82, 95% CI 0.58 to 1.16; 6 studies; 850 participants; low-certainty evidence; Analysis 2.2).

Topical prophylaxis alone versus no treatment

We found a significant reduction in the incidence of respiratory tract infections in favour of topical prophylaxis alone (RR 0.50, 95% CI 0.36 to 0.69; 13 studies; 1848 participants; low-certainty evidence; (Analysis 2.2).

Secondary outcomes

1. Dropouts due to adverse events

We did not find a significant difference in dropouts due to adverse events in participants who received topical prophylaxis compared to those who did not receive topical prophylaxis (RR 2.20, 95% CI 0.57 to 8.54; 7 studies; 1323 participants; very low-certainty evidence; Analysis 2.3).

2. Participants with gastrointestinal or allergic AEs

Gastrointestinal AEs

We did not find a significant difference in participants who received topical prophylaxis compared to those who did not receive topical prophylaxis (RR 2.78, 95% CI 0.26, to 29.50; 3 studies; 1859 participants; low-certainty evidence; Analysis 2.4).

Allergic AEs

We did not find a significant difference between groups (RR 2.64, 95% CI 0.34 to 20.69; 5 studies; 2357 participants; very low-certainty evidence; Analysis 2.5).

DISCUSSION

Since the introduction of selective digestive decontamination (SDD) as a preventive measure against the development of infections in critically ill patients (Stoutenbeek 1984), its use as an antibiotic prophylaxis has been controversial.

Initial studies aimed at quantifying the effectiveness of SDD in preventing ventilator-associated pneumonia (VAP) in intensive care units (ICUs) highlighted the difficulty in drawing solid conclusions regarding the effectiveness of the treatment, given the lack of a standardised protocol and the limited numbers of patients included in individual clinical trials (de Jonge 2018; de Smet 2009; Plantinga 2017; Vincent 2011). Concerns were even raised regarding the possible role of the SDD in inducing antimicrobial resistance, as well as the costs associated with its implementation. Furthermore, pneumonia, often considered the target outcome for evaluating efficacy of SDD, can be measured using different clinical, microbiological, and radiological criteria that are often difficult to apply in the ICU setting (Chahoud 2015; Waters 2015). Finally, ICU mortality depends on a number of factors only partially related to VAP.

As those enrolled in SDD trials gradually changed from trauma patients to other patient categories (surgical and medical, with complex medical histories and comorbidity, with prior antibiotic use in the presence of bacteria non-susceptible to cephalosporin), SDD regimens have varied over time. Endpoints have also changed in some clinical trials from VAP to bacteraemia or ICU mortality (Hurley 2020).

Compared to other published meta-analyses (Heyland 1994; Hurley 1995; Kollef 1994; Nathens 1999; SDD Group 1993; Vanderbrouk-Grauls 1991), we decided in our previously published review, D'Amico 2009, to separately analyse trials testing a combination of systemic and topical antibiotics, and those testing topical antibiotics alone. Though there is no consensus on the best way to classify antibiotic prophylaxis regimens, it seemed more appropriate to consider the two groups of trials as distinct approaches to antibiotic prophylaxis. We made this decision a priori, independent of knowing the results.

Summary of main results

We included 41 RCTs with a total of 11,004 participants who were mechanically ventilated for at least 48 hours. Nineteen RCTs compared the combination of topical and systemic antibiotic prophylaxis versus no treatment or placebo; 16 studies compared topical prophylaxis alone to no treatment or placebo; and seven trials compared the combination of topical and systemic antibiotic prophylaxis versus systemic antibiotic only.

Compared to no treatment or placebo, there was a significant reduction in overall mortality (high-certainty evidence) and a significant reduction of RTIs (moderate-certainty evidence) in participants receiving topical plus systemic prophylaxis. We also found low-certainty evidence that participants receiving topical antibiotic prophylaxis achieved a significant reduction of RTI, but moderate-certainty evidence that mortality did not change, when compared with placebo, no treatment, or systemic prophylaxis alone.

We found low-certainty evidence of no relevant differences in mortality and RTIs in the subgroup of studies comparing topical plus systemic prophylaxis versus systemic prophylaxis alone. In the subgroup of studies comparing topical prophylaxis alone versus placebo or no treatment, RTIs were significantly reduced (low-certainty evidence), whilst there was no difference in mortality rate (moderate-certainty evidence). Although these results could suggest that the systemic component of prophylaxis plays a key role in mortality reduction, caution is advised in interpreting such results on the basis of indirect comparisons. Moreover, as the certainty of the evidence was low, the contribution of adding topical to systemic prophylaxis remains uncertain.

The incidence of adverse events was reported in few studies with inconsistent and uninformative results (low- to very low-certainty evidence).

Overall completeness and applicability of evidence

Overall, the characteristics of participants and ICUs considered in the included studies represent well the actual ICU setting in high-income countries, although many of the studies were conducted more than 20 years ago. Despite the fact that modalities to prevent the development of infections have changed over time, as well as the characteristics of patients admitted to ICUs, RTIs are still an important cause of mortality.

One limitation of this meta-analysis is that the patient population, the antibiotic regimens, and the outcome definitions varied across studies. Nevertheless, we believe that it provides the best global picture of the effectiveness of the intervention, despite some recent criticisms on the quality of primary studies and their combination (van Nieuwenhoven 2001), which we feel we have convincingly addressed (Liberati 2001).

Quality of the evidence

Seventy-three per cent of the included studies were published before the 2001, the year in which the revised CONSORT statement was published and endorsed by many journals. This is the likely explanation for why the reporting of the majority of the studies was poor, which limited our ability to assess risk of bias. We judged more than 40% of the included studies as at unclear risk of selection bias, which led to the downgrading of the certainty of the evidence for the comparison 'topical antibiotic prophylaxis versus no prophylaxis'. In contrast, although about 48% of the studies were open-label, we judged all studies to be at low risk of performance bias, as hospitals usually have standardised infection control programmes, making subjective decisions on who should be tested for the presence or absence of RTIs unlikely. We judged only five studies as at high risk of detection bias, as they were open-label and did not use microbiological exams to diagnose RTIs. We judged all studies as at low risk of detection bias for the outcome mortality. We did not find any relevant inconsistency amongst trials. We found asymmetry in the funnel plot indicating possible publication bias for the outcome respiratory tract infection. Finally, we judged evidence for adverse events low or very low due to sparse data

Potential biases in the review process

We performed a comprehensive search without language or publication restrictions. The inspection of funnel plots did not show asymmetry suggestive of possible publication bias. See Figure 4 and Figure 5.

Figure 4. Funnel plot of comparison: 1 Topical plus systemic prophylaxis versus placebo or no treatment, outcome: 1.1 Overall mortality.

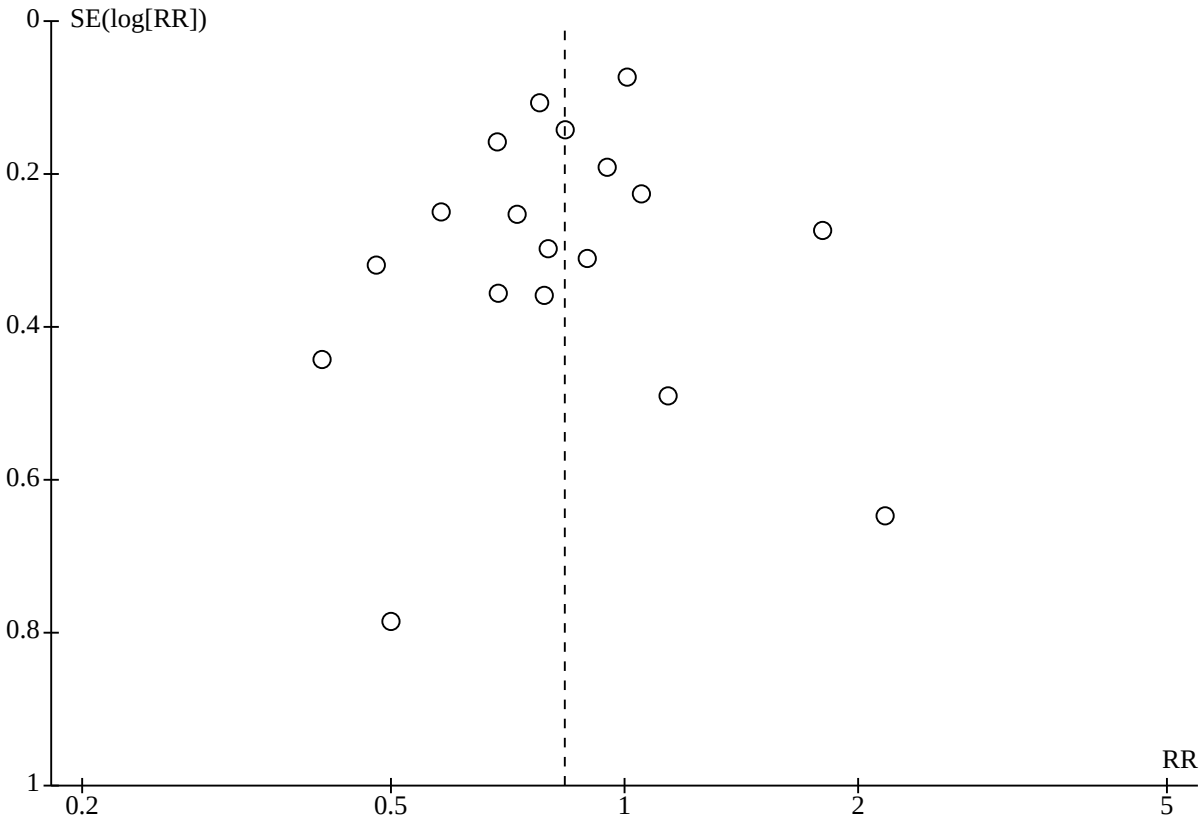
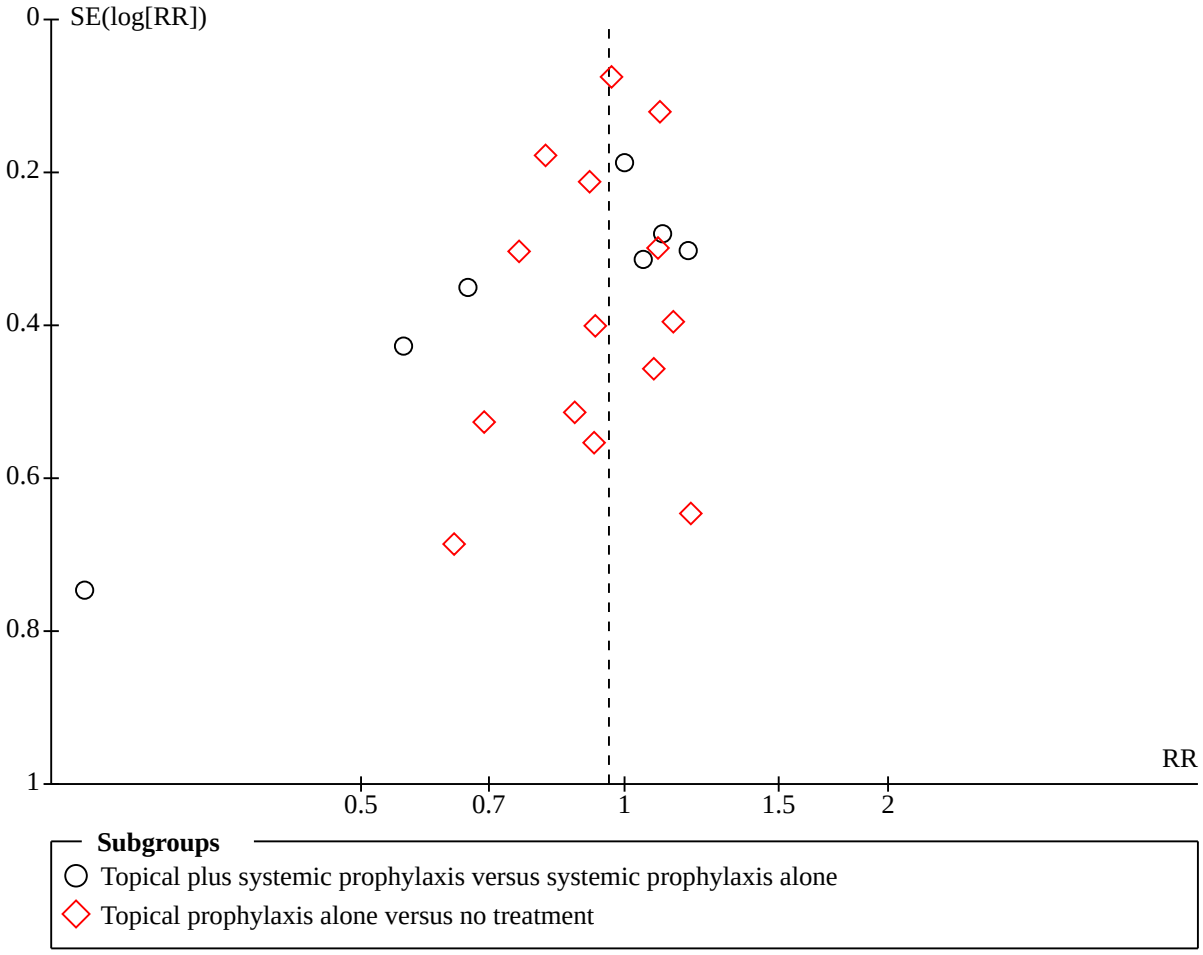


Figure 5. Funnel plot of comparison: 2 Topical prophylaxis versus no topical prophylaxis, outcome: 2.1 Overall mortality.



Agreements and disagreements with other studies or reviews

Prior to the publication of the previous version of this systematic review, several non-Cochrane Reviews and meta-analyses were published on the effect of SDD on RTIs and mortality (D'Amico 1998; Heyland 1994; Hurley 1995, Kollef 1994; Nathens 1999; Redman 2001; Silvestri 2007; SDD Group 1993; Vanderbrouk-Grauls 1991). Two systematic reviews were recently published (Price 2014; Righy 2017). All reviews assessing the incidence of RTIs supported the hypothesis that antibiotic prophylaxis is effective, though the magnitude of the treatment effect varied across reviews. The same results were observed in the majority of systematic reviews regarding mortality.

AUTHORS' CONCLUSIONS

Implications for practice

Treatments based on topical prophylaxis alone probably reduce respiratory tract infections, but not mortality, in adult patients receiving mechanical ventilation for at least 48 hours, whereas a combination of topical and systemic prophylactic antibiotics reduces both overall mortality and respiratory tract infections. However, it cannot be ruled out that the systemic component of the combined treatment provides a relevant contribution in the observed reduction of mortality. The risk of antimicrobial resistance occurring as a negative consequence of antibiotic use should be explored further using appropriate study designs. No conclusion can be drawn about adverse events as they were poorly reported with sparse data

Implications for research

The number of randomised controlled trials conducted on antibiotic prophylaxis to date is substantial and provides sufficient evidence to detect a moderate effect of the treatment on mortality. According to this systematic review, the combination of topical and systemic antibiotics should be the standard against which new treatments should be tested. A logical next step for future trials would be the comparison of this protocol against a regimen based on systemic antimicrobials only, as this design was addressed by only seven trials included in this review.

However, it is unlikely that one or more even large conventional trials will mitigate the concerns of those who fear that antimicrobial resistance may occur as a consequence of the widespread use

of antibiotics. A more precise definition of the type of drug treatment would also be desirable in order to clarify the possible clinical indications and the risks of resistance. The growing number of publications on this topic has underlined its relevant clinical importance. The lack of appropriately designed studies on microbial resistance leaves much room for future developments, in light of the ever-increasing complexity of therapies and patients; however, so far there does not seem to be a commercial interest by pharmaceutical companies to support such studies. Similarly, the intensivist community seems rather sceptical about the merits of the intervention and is not willing to embark on new, properly designed and conducted studies. A systematic analysis of the quality and reliability of existing data on antimicrobial resistance might result in a more comprehensive view of the effects of the treatment, especially in particular subgroups of patients.

ACKNOWLEDGEMENTS

We are greatly indebted to Alessandro Liberati, who inspired us to carry on this systematic review and to publish it in the Cochrane Library. Alessandro Liberati and Walter Torri are previous authors of this review.

We thank Tim Kenealy, Viviana Rodriguez Romero, Janet Wale, and Tom Fahey for commenting on the draft of this review update.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abele-Horn 1997

Study characteristics	
Methods	Randomised controlled trial Blinding: open-label Randomisation method: list block randomised assignments maintained by the main investigator Accrual period: not available Country: Germany
Participants	Eligibility criteria: intubation within 24 hours of admission, expected ventilation for at least 4 days, first microbial culture within 36 hours of admission Exclusion criteria: transfer from other hospitals, evidence of infection, prior antibiotic therapy, ARDS, leucopenia, myelosuppression Number of participants enrolled: 125 Number of participants randomised: not reported Number of patients excluded: 37 because they did not fulfil the inclusion criteria or protocol violation (12 study, 7 control) Number of participants analysed: 88 Percentage of ventilated participants: 100% Length of stay in ICU, mean days (SD): treatment group 18 (7.8), control group 22 (8.8) Diagnosis at admission: surgical unscheduled = 14 (16%); trauma = 29 (84%) Severity score on admission: APACHE II mean = 17; ISS not available Percentage of immunocompromised participants: not available Percentage of participants treated with systemic antibiotic therapy (not stated in protocol) in the first 3 days: not available Stress ulcer prophylaxis applied: sucralfate 1 g x 4 to all participants
Interventions	Treatment group, randomised = not reported, analysed = 58: • polymyxin 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied orally 4 times a day as a 2% paste during the ICU stay • cefotaxime 2 g x 3 iv x 3 days Control group, randomised = not reported, analysed = 30: • no prophylaxis Antibiotic prophylaxis was performed only for abdominal, orthopaedic, and neurologic surgery.
Outcomes	Respiratory infections (acquired pneumonia). Diagnosis was based on Clinical Pulmonary Infection Score as defined by Pugin 1991: new pulmonary infiltrate on X-ray, increasing amount of tracheal secretions containing > 3 x 10^4 granulocytes/µL and at least 2 of the following: temperature > 38.5 °C, WBC > 12,000/mm^3 or < 4000/mm^3, decrease in PaO_2 requiring an increase in FiO_2. Besides a bacteriological confirmation is required: tracheal aspirates yielding bacteria > 10^4 CFU/mL and granulocytes > 10/field Mortality: in ICU
Notes	Data for 37 excluded patients are not available. Conflict of interest: not reported Funding: not reported

Abele-Horn 1997 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed on the basis of a sequential list of block-randomised assignments maintained by the principal investigator.
Allocation concealment (selection bias)	Low risk	Randomisation was performed on the basis of a sequential list of block-randomised assignments maintained by the principal investigator.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Objective outcome unlikely to be biased by lack of blinding
Blinding of outcome assessment (detection bias) SRIs	Low risk	The chest X-ray was read by an independent radiologist who was unaware of the participant's randomisation.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	19 (15%) participants excluded for protocol violation (12 experimental, 7 control).
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Aerdts 1991

Study characteristics

Methods	Randomised study with 3 arms (1 treatment arm versus 2 control arms) Blinding: open-label Randomisation method: sealed envelopes, permuted block method Accrual period: from May 1986 to September 1987 Country: the Netherlands
Participants	Eligibility criteria: expected ventilation for at least 5 days, inclusion within 24 hours of admission Exclusion criteria: age < 16 years, pregnancy, allergy to 1 of the components of the regimen Number of participants enrolled: 88 Number of participants randomised: 88 Number of patients excluded: 32 because they did not receive mechanical ventilation for at least 5 days or for other reasons Number of participants analysed: 56 Percentage of ventilated participants: 100%

Aerdts 1991 *(Continued)*

	Length of stay in ICU, mean days (SD): treatment group 23 (13), control group A 30 (17), control group B 25 (11) Diagnosis at admission: medical = 14 (25%), surgical scheduled = 5 (9%), surgical unscheduled = 11 (20%), trauma = 23 (41%) Severity score on admission: APACHE II mean = 21.8, ISS not available Percentage of immunocompromised participants: 4.6% Percentage of participants treated with systemic antibiotic therapy (not stated in protocol) in the first 3 days: treatment = 35%, CTR = 80% Stress ulcer prophylaxis applied: antiacids until enteral feeding was possible
Interventions	Treatment group, randomised = 28, analysed = 17: • polymyxin E 200 mg, norfloxacin 50 mg, amphotericin B 500 mg applied enterally 4 times a day and (as a 2% paste) to the oropharynx until extubation • cefotaxime 500 mg x 3 iv x 5 days Infections of unknown origin were treated with cefotaxime + gentamicin and metronidazole if indicated. Control group A, randomised = 30, analysed = 18: • no prophylaxis Infections of unknown origin were treated with ampicillin + gentamicin Control group B, randomised = 30, analysed = 21: • no prophylaxis Infections of unknown origin were treated with cefotaxime + gentamicin and metronidazole if indicated.
Outcomes	Respiratory infections (acquired pneumonia and tracheobronchitis). Diagnosis of tracheobronchitis was based on positive culture of the tracheal aspirate and a Gram stain showing many leukocytes as well as the causative organism, associated with 2 of the following: temperature > 38 °C, WBC > 12,000/mm^3, purulent tracheal aspirate. Diagnosis of pneumonia was based on a new and persistent pulmonary infiltrate on X-ray and criteria of tracheobronchitis. Mortality: in ICU
Notes	Participants enrolled in both control groups were analysed together in the meta-analyses. Conflict of interest: not reported Funding: partially supported by an educational grant from Roussel by, Iloevelaken

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The severity of acute illness was assessed using the APACHE II score. Participants were stratified for APACHE II score: less than 10, 10 to 19, 20 to 29, and 30 or more. Within these strata, participants were randomly allocated to 1 of the treatment groups by means of the permuted block method.
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.

Aerdts 1991 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by the lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	A standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 and 3 (9%) participants from the control and experimental groups, respectively, were excluded for reasons other than the inclusion criteria.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Bergmans 2001

Study characteristics	
Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: randomisation was conducted per hospital Accrual period: from September 1994 to December 1996 Country: the Netherlands
Participants	Eligibility criteria: intubation within 24 hours of admission and need for mechanical ventilation with an expected duration > 2 days Exclusion criteria: age < 16 years Number of participants enrolled: 270 Number of participants randomised: 245 Number of patients excluded: 19 Number of participants analysed: 226 Percentage of ventilated participants: 100% Length of stay in ICU, median (range): treatment group 13 (4 to 54), control group A 15 (4 to 79), control group B 12 (4 to 108) Diagnosis at admission: medical = 78 (35%), surgery = 88 (39%), trauma = 43 (19%), neurology = 14 (6%), other = 3 (1%) Severity score on admission: APACHE II mean = 21.4, ISS not available Percentage of immunocompromised participants: 2% Percentage of participants treated with systematic antibiotic therapy at admission: treatment: 47%, control 42% Stress ulcer prophylaxis applied: treatment = 61%, control = 76%
Interventions	Treatment group, randomised = 92, analysed = 87. Orabase with 2% gentamicin, 2% colistin, and 2% vancomycin. Orabase was applied in the buccal cavities on a gloved finger every 6 hours. The application of Orabase was started within 24 hours of intubation. Application of treatment was limited to 21 days.

Bergmans 2001 *(Continued)*

	Control group A, randomised = 82, analysed = 78: no prophylaxis. This group was studied in ICU in which there were patients receiving topical antimicrobial prophylaxis. Control group B, randomised = 70, analysed = 61: no prophylaxis. This group was studied in ICU in which no topical antimicrobial prophylaxis was used.
Outcomes	Ventilator-associated pneumonia: diagnosis of VAP was established on the basis of positive quantitative cultures from BAL (cut-off point >= 10^4 CFU/mL) or protected specimen brush (cut-off point >= 10^3 CFU/mL), or a positive blood culture unrelated to another source of infection, or a positive culture from pleural fluid in the absence of previous pleural instrumentation. Mortality: in hospital
Notes	Conflict of interest: not available Funding: supported by Grant 28-2125-1 from the Praevention Foundation and a grant from Eli Lilly Netherland bv.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Randomisation was conducted per hospital and was executed by the Department of Clinical Pharmacy of the University Hospital Maastricht.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. No information about blinding of outcome assessor. However, outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. No information about blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	19 excluded because they did not fulfil inclusion criteria.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Beshey 2014

Study characteristics

Methods	Prospective, randomised, placebo-controlled trial

Beshey 2014 *(Continued)*

	Blinding: open-label Randomisation method: not available Accrual period: not reported Country: Egypt
Participants	Eligibility criteria: patients mechanically ventilated for at least 48 hours with an expectation to remain so for at least an additional 72 hours, based on admitting diagnosis, magnitude of haemodynamic instability, respiratory failure, and baseline medical condition and severity of illness according to APACHE II score Exclusion criteria: pregnancy, receipt of antifungal agents within 7 days before ICU admission, age younger than 18, an expectation that the patient would not survive more than 24 hours, and patients who did not complete the 15-day period of the study either due to discharge from ICU or death Number of participants enrolled: not reported Number of participants randomised: 75 Number of patients excluded: none Number of participants analysed: 75 Percentage of ventilated participants: not reported Length of stay in ICU: not reported Diagnosis at admission: not reported Severity score at admission: not reported Percentage of immunocompromised participants: not reported Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: not reported Stress ulcer prophylaxis applied: not reported
Interventions	Treatment group 1, randomised = 25, analysed = 25: participants who received SDD alone without fluconazole Treatment group 2, randomised = 2, analysed = 25: participants who received fluconazole as a part of their SDD Control group, analysed = 25, randomised = 25: placebo
Outcomes	Mortality at 15 days and number of positive *Candida* cultures
Notes	Conflict of interest: none Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.

Beshey 2014 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Blair 1991

Study characteristics	
Methods	Randomised study Blinding: open-label Randomisation method: sealed envelopes Accrual period: from September 1988 to January 1990 Country: Ireland
Participants	Eligibility criteria: all admitted patients who do not fulfil the exclusion criteria Exclusion criteria: patients discharged within 48 hours of ICU admission; admission from cardiac care unit; patients expected to die after 6 hours of ICU admission; patients with discharge anticipated within 48 hours but remaining more than 48 hours; drug overdose; security patients; age < 18 years; patients not randomised within 6 hours of admission; readmission to ICU; burns; miscellaneous Number of participants enrolled: 569 Number of participants randomised: 331 Number of patients excluded: 75 because length of stay was less than 48 hours Number of participants analysed: 256 Percentage of ventilated participants: 93% Length of stay in ICU, median days: 5 Diagnosis at admission: medical = 49 (14%), surgical scheduled = 109 (33%), surgical unscheduled = 43 (13%), trauma = 132 (40%) Severity score on admission: APACHE II mean = 14.4, ISS mean = 24.8 Percentage of immunocompromised participants: 1.8% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment 42%, control 74% Stress ulcer prophylaxis applied: all participants received ranitidine iv plus antiacid therapy if gastric pH was low
Interventions	Treatment group, randomised = 161, analysed = 126:

Blair 1991 *(Continued)*

	• polymyxin 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied enterally 4 times a day and as a 2% gel to the oropharynx • cefotaxime 50 mg/kg/day iv x 4 days Control group, randomised = 170, analysed: 130: • standard antibiotic therapy (no prophylaxis)
Outcomes	Respiratory infections (pneumonia acquired after 48 hours). Diagnosis of infection was based on the fulfilment of Criteria I or Criteria II: • Criteria I: temperature > 38.5 °C on 2 separate occasions, WBC > 12 x 10^9/L or < 4 x 10^9 and a new pulmonary infiltrate on X-ray • Criteria II: temperature > 37.5 °C, a new pulmonary infiltrate on X-ray, purulent sputum, and drop in PaO_2 Mortality: in ICU
Notes	Conflict of interest: not reported Funding: supported in part by Roussel Laboratories and Gelsdich Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	High risk	No blinding. The diagnosis of RTI was not based on microbiological exams.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	75 excluded because length of stay was less than 48 hours.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Boland 1991

Study characteristics	
Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: computer-generated randomisation directed by the pharmacy department Accrual period: from April 1989 to March 1991 Country: the USA
Participants	Eligibility criteria: all multiple traumatised patients, intubated at the time of admission and likely to stay intubated at least 5 days Exclusion criteria: patients who did not remain intubated for 5 days Number of participants enrolled: 62 Number of participants randomised: 62 Number of patients excluded: 32 because they did not remain intubated for 5 days Number of participants analysed: 30 Percentage of ventilated participants: 100% Length of stay in ICU, median: 8 days Diagnosis at admission: trauma = 100% Severity score on admission: APACHE II mean = 16.8, ISS not available Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 0%, control = 0% Stress ulcer prophylaxis applied: H2-blockers or sucralfate (78%)
Interventions	Treatment group, randomised = 32, analysed = 15: • polymyxin 100 mg, tobramycin 80 mg, nystatin 1,600,000 units applied enterally 4 times a day and, as a 2% paste plus 60,000 units of nystatin, to the oropharynx until extubation or discharge • cefotaxime 1 g x 3 iv for the first 3 days Control group, randomised = 32, analysed = 15: • placebo
Outcomes	Respiratory infections (acquired pneumonia and tracheobronchitis). Diagnosis of infection was based on positive sputum culture for bacteria, fever > 38 °C, and leukocytosis (> 10,000 WBC/mm^3 of blood). Mortality: in ICU
Notes	Personal contact with the main investigator provided data for 23 participants who were excluded from the published paper (20 early extubations, 3 early deaths); these data are considered in the analysis. Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation directed by the pharmacy department
Allocation concealment (selection bias)	Unclear risk	Not described

Boland 1991 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Stated as double-blind study, no information provided on blinding of outcome assessor. However, outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Stated as double-blind study, no information provided on blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 excluded because they did not remain intubated for 5 days.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Brun-Buisson 1989

Study characteristics	
Methods	Randomised trial Blinding: open-label Randomisation method: odd and even birth year technique Accrual period: from April 1987 to May 1987 Country: France
Participants	Eligibility criteria: patients with an admission SAPS > 2 and staying in the ICU more than 48 hours Exclusion criteria: patients with severe neutropenia routinely receiving oral antibiotic prophylaxis Number of participants enrolled: 123 Number of participants randomised: 123 Number of patients excluded: 47 because they did not match the inclusion criteria Number of participants analysed: 86 Percentage of ventilated participants: 59% Length of stay in ICU, median days: 3.5 Diagnosis at admission: medical 75%, surgical unscheduled 23%, trauma 2% Severity score on admission: SAPS mean = 10.4, ISS not available Percentage of immunocompromised participants: 12.8% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 41%, control = 53% Stress ulcer prophylaxis applied: none
Interventions	Treatment group, randomised = 65, analysed = 36: • polymyxin E 50 mg, neomycin 1 g, nalidixic acid 1 g, applied orally and enterally 4 times a day until discharge • oropharyngeal disinfectant in intubated participants

Brun-Buisson 1989 *(Continued)*

	Control group, randomised = 68, analysed = 50: • oropharyngeal disinfectant in intubated participants
Outcomes	Respiratory infections (pneumonia acquired in the ICU or within 48 hours from discharge). Diagnosis of infection was based on purulent sputum or tracheal aspirate associated with a new and persistent pulmonary infiltrate on X-ray and the culture of at least 10^9 CFU/L from a protected wedged catheter sample of bronchial aspirate, temperature > 38 °C, WBC > 10 x 10^9. Mortality: in ICU
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It is reported as "[...] newly admitted patients were allocated, on odd and even birth year to receive either no prophylaxis (group 2) or intestinal decontamination (group 3)".
Allocation concealment (selection bias)	High risk	It is reported as "[...] newly admitted patients were allocated, on odd and even birth year to receive either no prophylaxis (group 2) or intestinal decontamination (group 3)".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding, No information provided on blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	47 excluded because they did not match the inclusion criteria.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Camus 2005

Study characteristics

Methods	Randomised trial Blinding: double-blind

Camus 2005 *(Continued)*

	Randomisation method: performed by computer Accrual period: from April 1996 to October 1998 Country: France
Participants	Elegibility criteria: adults intubated for < 48 hours and likely to require mechanical ventilation for > 48 hours Exclusion criteria: patients with SAPS II > 80 and life expectancy of < 48 hours resulting from brain death of a palliative treatment, a polymorphonuclear count of < 500 cells/mm^3, severe diarrhoea, and anyone who had received either a prior decontamination regimen or was already participating in another ongoing clinical trial Number of participants enrolled: 4444 Number of participants randomised: 516 Number of patients excluded: 1 Number of participants analysed: 515 Of these 515 participants, 130 received polymyxin/tobramycin alone, 130 mupirocin/chlorhexidine alone, 129 both regimens, and 126 placebo. Pecentage of ventilated participants: not reported Length of stay in ICU: not reported Type of admission diagnosis: home/emergency department = 43%, hospital ward = 57% Severity score on admission: median SAPS II = 46 Percentage of immunocompromised participants: 3.9% Percentage of participants treated with systemic antibiotic therapy (not stated in protocol) in the first 3 days: none Stress ulcer prophylaxis applied: not reported
Interventions	Treatment group, randomised = 130, analysed = 130: solution containing 15 mg/mL polymyxin E and 10 mg/mL tobramycin Control group, randomised = 127, analysed = 126: placebo
Outcomes	Respiratory infections: acquired infections Mortality: in ICU
Notes	The study is a 4-arm, 2 x 2 factorial design. In this review we considered only the 2 arms comparing SDD regimen versus placebo. Conflict of interest: all the authors state that they have no financial interest to disclose. Funding: supported in part by the Programme Hospitalier de Recherche Clinique (Clinical Research Hospital Program) 94, Direction des Hôpitaux, Paris, France, and by a grant from GlaxoSmithKline. Some study drugs were provided by Astra-Zeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by a computer-generated list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.

Camus 2005 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	Stated as double-blind; no information on blinding of outcome assessor. However, outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Unclear risk	Stated as double-blind study, no information provided on blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 patient was excluded.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Cerra 1992

Study characteristics	
Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: sealed envelopes Accrual period: from September 1988 to January 1990 Country: the USA
Participants	Eligibility criteria: admission within 48 hours from surgery, trauma or other acute event, expected stay at least 5 days, hypermetabolisms (VO_2 > 140 mL/m^2 or urinary nitrogen excretion > 10 g/day) without progressive MOSF (normal transaminases, stable bilirubin and creatinine) Exclusion criteria: cirrhosis, allergy to used drugs, chemo-radiotherapy, progressive MOSF, gastrointestinal leak or fistula Number of participants enrolled: 48 Number of participants randomised: 48 Number of patients excluded: 2 because they stayed in the ICU less than 5 days Number of participants analysed: 46 Percentage of ventilated participants: not reported Lenght of stay in ICU: not reported Diagnosis at admission: surgical = 46 (96%), trauma = 2 (4%) Severity score on admission: not reported Percentage of immunocompromised participants: not reported Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: not reported Stress ulcer prophylaxis applied: not reported
Interventions	Treatment group, randomised = 25, analysed = 25: norfloxacin 500 mg x 3, nystatin 1 million units x 4 applied enterally until discharge Control group, randomised = 23, analysed 21: placebo
Outcomes	Respiratory infections: not possible to evaluate

Cerra 1992 *(Continued)*

	Mortality
Notes	Conflict of interest: not reported Funding: this study was supported by Public Health Service grant AI23484 and DK34931

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-derived random number generator
Allocation concealment (selection bias)	Low risk	The research pharmacist randomised the participants, then logged in the patient and dispensed the experimental drug or placebo sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind study; no information provided on blinding of outcome assessor. However, outcome is unlikely to be biased by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Stated as double-blind study, no information provided on blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 excluded because they stayed in the ICU less than 5 days.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Chaari 2014

Study characteristics

Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: not described Accrual period: from August 2011 to November 2011 Country: Tunisia
Participants	Eligibility criteria: age > 15 years, need for MV within the few hours after trauma, and predicted duration of MV > 48 hours Exclusion criteria: patients who received prior antibiotics for 48 hours, those who are known to be allergic to beta-lactams, and those with a contraindication of gastric tube were excluded Number of participants enrolled: 61

Chaari 2014 *(Continued)*

	Number of participants randomised: 44 Number of patients excluded: none Number of participants analysed: 44 Percentage of ventilated participants: 100% Lenght of stay in ICU: not reported Diagnosis at admission: trauma = 44 (100%). Severity score on admission: SAPS II mean 37 (13) Percentage of immunocompromised participants: not reported Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: not reported Stress ulcer prophylaxis applied: omeprazole
Interventions	Treatment group, randomised = not reported, analysed = 31: systemic antibiotic therapy (cefotaxime with a dose of 1 g 3 times a day for 4 consecutive days) in association with: • subglottic and gastric suspension (polymixin E 100 mg, vancomycin 1 g, and amphotericin B 500 mg); • gastric suspension and subglottic placebo; • gastric placebo and subglottic suspension. The suspension was administered orally (10 mL) for oropharyngeal decontamination and through a gastric tube (20 mL) for gastric decontamination. Control group, randomised = not reported, analysed = 13: systemic antibiotic prophylaxis plus subglottic and gastric placebo
Outcomes	Ventilator-associated pneumonia: the diagnosis was considered if the chest X-ray showed evidence of new and persistent (> 48 hours) pulmonary infiltrates with at least 2 of the following criteria: fever 38 °C or hypothermia, 35 °C, WBC 12,000 or 4000/mm^3, purulent respiratory secretion, and/or worsening of respiratory insufficiency Mortality Adverse events
Notes	Conflict of interest: the authors have no conflicts of interest to declare Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Randomisation was conducted per hospital and executed by the Department of Clinical Pharmacy of the Habib Bourguiba University Hospital.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	It is reported that: "only the study supervisor and the hospital pharmacist were aware of this inclusion scheme".
Blinding of outcome assessment (detection bias)	Low risk	It is reported that: "only the study supervisor and the hospital pharmacist were aware of this inclusion scheme".

Chaari 2014 *(Continued)*
SRIs

Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Cockerill 1992

Study characteristics	
Methods	Randomised study: intention-to-treat Blinding: open-label Randomisation method: randomisation table at a remote site in the pharmacy Accrual period: from 1986 to 1989 Country: the USA
Participants	Eligibility criteria: all patients admitted to the mixed ICU if their condition suggested a prolonged stay (> 3 days), age > 18 years Exclusion criteria: age < 18 years, pregnancy, allergy to 1 component of the regimen, infections, antibiotic therapy 24 hours before randomisation Number of participants enrolled: 150 Number of participants randomised:150 Number of patients excluded: none Number of participants analysed: 150 Percentage of ventilated participants: 85% Length of stay in ICU, median days: 4.5 Diagnosis at admission: medical = 261 (8%), surgical = 72 (48%), surgical unscheduled = 30 (20%), trauma = 22 (15%) Severity score on admission: APACHE II mean = 19.4, ISS mean = 24.3 Percentage of immunocompromised participants: 4% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 75%, control = 80% Stress ulcer prophylaxis applied: H2-blockers (80%)
Interventions	Treatment group, randomised = 75, analysed = 75: • gentamycin 80 mg, polymyxin B 100 mg, nystatin 2,000,000 units, applied enterally and as a 2% paste to the oropharynx 4 times a day during the ICU stay • cefotaxime 1 g/8 h iv for the first 3 days Control group, randomised = 75, analysed = 75: • no prophylaxis
Outcomes	Respiratory infections (only acquired infections)

Cockerill 1992 *(Continued)*

	• Diagnosis of pneumonia was based on clinical and laboratory criteria, a new or progressive pulmonary infiltrate, purulent secretions, isolation of a potential pathogen, and fever with or without leukocytosis. • Diagnosis of tracheobronchitis was based on the presence of increased purulent endotracheal secretions requiring frequent suctioning and the presence of a potential pathogen. Mortality: in hospital
Notes	Conflict of interest: not reported Funding: in part by Hoechst- Roussel Pharmaceutical, Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation tables
Allocation concealment (selection bias)	Low risk	It is reported as "Blocking within stratification with randomisation to the control or decontamination group was achieved using randomisation tables at a remote site by a neutral observer in the pharmacy".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	High risk	The diagnosis of RTI was not based on microbiological exams.
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 participants dropped out of the SDD group because of dislike or AEs. All included in the analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

de Jonge 2003

Study characteristics

Methods	Randomised study Blinding: open-label Randomisation method: computer-generated random number codes kept in sealed envelopes Accrual period: from September 1999 to December 2001

de Jonge 2003 *(Continued)*

	Country: the Netherlands
Participants	Eligibility criteria: adult patients admitted to ICU with an expected stay of at least 72 hours and an expected duration of mechanical ventilation of at least 48 hours Exclusion criteria: previous admission to ICU within 3 months, hypersensitivity to study medication, pregnancy, and perceived imminent death Number of participants enrolled: 1090 Number of participants randomised: 1090 Number of patients excluded: 102 because consent was denied or unable to ask consent Number of participants entered in the study: 934 Percentage of ventilated participants: 85% Length of stay in ICU: median days, treatment group 6.8 days, control group 8.5 Diagnosis at admission: elective surgery = 54 (17%), urgent surgery = 50 (21%), medical = 135 (35%) Severity score at admission: APACHE II mean = 18.7, SAPS II in SDD group mean = 17.9, SAPS II in control group mean = 17.1 Percentage of immunocompromised participants: SDD group = 2.4%, control group = 1.7% Information on prescribed antibiotics per 1000 patients available in the main publication. Stress ulcer prophylaxis by protocol: none
Interventions	Treatment group, randomised = 537, analysed = 466: topical plus systemic treatment • topical: oral paste containing 2% polymyxin E, 2% tobramycin, 2% amphotericin 500 mg amphotericin B through gastric tubes • systemic: cefotaxime 1000 mg 4 times daily for 4 days Control group, randomised = 533, analysed = 468: • no antibiotic prophylaxis; antibiotic treatment based on clinical needs
Outcomes	Colonisation, antibiotic resistance Mortality: in ICU and hospital
Notes	Participants were allocated to either an SDD or a control unit to prevent cross-colonisation between SDD and ICU control participants. Standard care was the same in the 2 units. Conflict of interest: none Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unless beds were available in 1 unit only, on admission participants were allocated to 1 of the 2 units, according to computer-generated random number codes kept in sealed envelopes.
Allocation concealment (selection bias)	Low risk	It is reported as "Which unit would be the SDD unit and which the control unit was randomly decided before the study. Patients were assigned to treatment groups by nursing staff not involved in the study".

de Jonge 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	102 excluded because consent was denied or unable to ask consent.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

de la Cal 2005

Study characteristics	
Methods	Randomised, placebo-controlled trial Blinding: double-blind Randomisation method: not described Accrual period: from May 1997 to January 2000 Country: Spain
Participants	Eligibility criteria: all patients > 14 years old with burns of > 20% of total body surface area and/or suspected inhalation injury and an interval between injury and burn ICU admission < 3 days were eligible Exclusion criteria: a stay in the burn ICU < 3 days, withdrawal of treatment within 3 days, immunosuppression, pregnancy, and inhalation injury not requiring mechanical ventilation within the first 3 days Number of participants enrolled: 117 Number of participants randomised: 117 Number of patients excluded: 10 because length of stay was less than 3 days Number of participants entered in the study: 107 Percentage of ventilated participants: 76% Length of stay in ICU, mean days: treatment 30.6 (30.9), control 33.6 (24.5) Diagnosis at admission: not available Severity score at admission: not available Percentage of immunocompromised participants: not available Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: not reported Stress ulcer prophylaxis applied: not available

de la Cal 2005 *(Continued)*

Interventions	Treatment group, randomised = 58, analysed = 53: • intravenous administration of cefotaxime (1 g 8 hours) for 4 days • topical application in the oropharynx using non-absorbable polymyxin E, tobramycin, and amphotericin B 0.5 g of a 2% paste 4 times a day • digestive administration of a 10 mL solution containing 100 mg of polymyxin E, 100 mg of tobramycin, and 500 mg of amphotericin B 4 times a day • surveillance samples of throat and rectum on admission and twice a week Control group, randomised = 59; analysed = 54: • placebo • isotonic 0.9% saline
Outcomes	Mortality Infection
Notes	Conflict of interest: not reported Funding: this study has been partially supported by 2 grants from Fondo de Investigación Sanitaria: FIS 02/1883 and Respira C 03/11

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	The randomisation result was introduced in a sealed envelope that was kept in the Department of Pharmacy. The hospital pharmacist was the only person to be informed regarding the identity of the study medication.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. The hospital pharmacist was the only person to be informed regarding the identity of the study medication.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. The hospital pharmacist was the only person to be informed regarding the identity of the study medication.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 excluded because length of stay was less than 3 days.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

de Smet 2009

Study characteristics	
Methods	Cluster-randomised study Blinding: open-label Randomisation method: computer software Accrual period: from May 2004 to July 2006 Country: the Netherlands
Participants	Eligibility criteria: patients admitted to the ICU with an expected duration of mechanical ventilation of more than 48 hours or an anticipated ICU stay of more than 72 hours were eligible Exclusion criteria: pregnant patients and patients with documented or presumed allergy to any component of the antimicrobial study regimens were excluded Number of participants enrolled: 6565 Number of participants randomised: 5939 Number of patients excluded: none Number of participants analysed: 5939 Percentage of ventilated participants: 91.5% Length of stay in ICU: not reported Diagnosis at admission: surgical = 2762 (47%), medical = 3165 (53%) Severity score on admission: APACHE II score mean: SDD 19.6 (7.8), SOD 19.5 (8.2), standard care 18.6 (7.9) Percentage of immunocompromised participants: 2.5% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: the median number of defined daily doses of systemic antibiotic agents per patient-day was reported Stress ulcer prophylaxis applied: none
Interventions	Treatment group: • SDD regimen, randomised = 2045, analysed = 2045: oropharyngeal application (every 6 h) of a paste containing polymyxin E, tobramycin, and amphotericin B each in a 2% concentration and administration (every 6 h) of a 10 mL suspension containing 100 mg polymyxin E, 80 mg tobramycin, and 500 mg amphotericin B • SOD regimen, randomised = 1904, analysed = 1904: oropharyngeal application of the same paste used for SDD, with surveillance cultures of endotracheal aspirates and oropharyngeal swabs obtained on admission and twice weekly thereafter Control group, randomised = 1990, analysed = 1990: • standard care
Outcomes	Mortality Adverse events
Notes	Conflict of interest: Dr Bonten reports receiving advisory board fees from Ipsat Therapies, 3M, and Novartis; consulting fees from Novartis, 3M, and Bayer; and lecture fees from Cepheid and Pfizer. Dr Kluytmans reports receiving consulting fees from 3M, NovaBay, and Wyeth and lecture fees from 3M and Becton Dickinson. Dr Cooper reports receiving a lecture fee from Novartis. Dr Voss reports receiving grants from 3M and Medica. No other potential conflicts of interest were reported. Funding: not reported

de Smet 2009 *(Continued)*

The study reported results in term of adjusted odds ratios (ORs) estimated using random logistic regression (de Smet 2009); covariates included in the model were scored on the Acute Physiology and Chronic Health Evaluation (APACHE II), intubation status, medical specialty (classified as surgical or other), age, and sex.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer software
Allocation concealment (selection bias)	Low risk	Randomisation was performed by a clinical pharmacist who was not involved in patient care in any of the participating units and who was unaware of the identity of each ICU.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs were poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout due to non-compliance: SOD: 4.3%, SDD 2.5%. All participants included in the analysis.
Selective reporting (reporting bias)	Low risk	ISRCTN registry number ISRCTN35176830. All outcomes listed in the protocol were reported in the final publication.

Ferrer 1994

Study characteristics

Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: computer-generated table Accrual period: from January 1991 to March 1992 Country: Spain
Participants	Eligibility criteria: all mechanically ventilated patients expected to remain intubated for more than 3 days Exclusion criteria: patients with HIV-related diseases or treated with antineoplastic chemotherapy as well as patients who had received transplants, extubation or death within 72 hours Number of participants enrolled: 101

Ferrer 1994 *(Continued)*

	Number of participants randomised: 101 Number of patients excluded: 21 because they were intubated less that 72 hours Number of participants analysed: 80 Percentage of ventilated participants: 100% Length of stay in ICU, median days: 7.5 Diagnosis at admission: medical = 66%, surgical scheduled = 6.9%, surgical unscheduled 6.9%, trauma = 19.8% Severity score on admission: SAPS mean = 12.1, ISS not available Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: not available Stress ulcer prophylaxis applied: sucralfate, except in participants with paralytic ileus or with upper gastrointestinal bleeding, who were treated with ranitidine
Interventions	Treatment group, randomised = 51, analysed = 39: • polymyxin E 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied enterally and as a 2% paste to the oropharynx 4 times a day until extubation or death • cefotaxime 2 g/day iv for the first 4 days or others if required* Control group, randomised = 50, analysed = 41: • placebo • cefotaxime 2 g/day iv for the first 4 days or others if required* *participants infected on admission received adequate antibiotic treatment instead of cefotaxime
Outcomes	Respiratory infections (pneumonia acquired after 4 days of mechanical ventilation). Diagnosis of infection was based on clinical criteria plus brush or BAL confirmation. Clinical criteria: new or progressive pulmonary X-ray infiltrate for at least 48 hours, purulent tracheal secretions, temperature > 38.5 °C, and leukocytosis >= 12 x 10^9 WBC/L or leukopenia <= 4 x 10^9 Mortality: in ICU
Notes	Personal contact with the main investigator provided data regarding 21 participants who were excluded from the published paper (14 early extubations, 6 early deaths, 1 transfer); these data are considered in the analysis. Conflict of interest: not reported Funding: in part by grant Hospital Clinic 1991, a grant from the Beques de Formaciod'Investigadors del Departament d'Ensenyament de la Generalitat de Catalunya 1992, and grant Fiss 92/0104

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was done using a computer-generated random number.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.

Ferrer 1994 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. Study authors were blinded in the recovery of the results.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. Study authors were blinded in the recovery of the results.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	21 excluded because they were intubated less that 72 hours.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Finch 1991

Study characteristics	
Methods	Randomised study Blinding: open-label Randomisation method: sealed envelopes. Randomisation series made available to the hospital pharmacy only. Accrual period: from August 1987 to September 1989 Country: the UK
Participants	Eligibility criteria: all patients whose length of stay was > 60 hours, age > 16 years Exclusion criteria: none Number of participants enrolled: 49 Number of participants randomised: not reported Number of patients excluded: 5 Number of participants analysed: 44 Percentage of ventilated participants: not reported Length of stay in ICU: not reported Diagnosis at admission: medical = 59%, surgical scheduled = 27%, surgical unscheduled = 10%, trauma = 4% Severity score on admission: SAPS mean = 10.5, ISS not available Percentage of immunocompromised participants: 22% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 58%, control = 68% Stress ulcer prophylaxis applied: not reported
Interventions	Treatment group A, randomised = 24, analysed = 20: • polymyxin B 100 mg, gentamicin 120 mg, amphotericin B 500 mg applied enterally and as a 2% paste to the oropharynx 4 times a day • cefotaxime 1 g x 3 iv for the first 4 days Control group B, randomised = 25, analysed = 24:

Finch 1991 *(Continued)*

	• conventional antibiotic therapy
Outcomes	Respiratory infections (acquired pneumonia). Diagnosis of pneumonia was based on tracheal aspirate with numerous leukocytes associated with any of the following: a single bacterial species with a growth density > 10^5 CFU, diagnosis of septicaemia, clinical signs of pulmonary infections (fever, leukocytosis, and appropriate radiological findings). Mortality: in ICU
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed envelopes
Allocation concealment (selection bias)	Low risk	Randomisation series made available to the hospital pharmacy by sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is unlikely to be biased due to lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs were poorly reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 49 participants were admitted, of whom 44 (90%) were evaluated; reasons for exclusion not provided.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Gastinne 1992

Study characteristics

Methods	Randomised, placebo-controlled, multicentre (15 ICUs) study. Intention-to-treat Blinding: double-blind Randomisation method: a randomised list of consecutive treatment assignments, performed separately in each unit Accrual period: from February 1990 to June 1990

Gastinne 1992 *(Continued)*

	Country: France
Participants	Eligibility criteria: all patients > 15 years of age who required mechanical ventilation and with intubation performed no more than 48 hours before randomisation Exclusion criteria: patients with ventilation for less than 24 hours, drug or alcohol overdose, neutropenia (WBC < 500/mm^3), SAPS > 24 or GCS < 4, chronic degenerative central nervous system disease or spinal cord injury above level of C4, acute severe enteropathy, pregnancy, participation in another ongoing clinical trial, refusal of consent, patients with conditions in which survival was strongly related to status on admission Number of participants enrolled: 445 Number of participants randomised: 445 Number of patients excluded: none Number of participants analysed: 445 Percentage of ventilated participants: 100% Length of stay in ICU, median: 12 days Diagnosis at admission: medical = 72%, surgical scheduled = 3%, surgical unscheduled = 10%, trauma = 15% Severity score on admission: SAPS mean = 13.5, ISS not available, GCS mean = 11.7 Percentage of immunocompromised participants: 18% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 89%, control = 84% Stress ulcer prophylaxis applied: sucralfate (43% participants), H2-blockers (13% participants)
Interventions	Treatment group, randomised = 220, analysed = 220: tobramycin 80 mg, polymyxin E 100 mg, amphotericin B 100 mg applied enterally and as a 2% paste to the oropharynx 4 times a day throughout the period of ventilation Control group, randomised = 225, analysed = 225: placebo
Outcomes	Respiratory infections (pneumonia diagnosed within 48 hours and acquired): diagnosis of infection was based on: purulent tracheal aspirate, temperature > 38.5 °C, peripheral leukocytosis (> 10,000 WBC/mm^3 of blood), and a new and persistent infiltrate on the chest film. Brushing was recommended but not mandatory. Mortality: in hospital
Notes	Conflict of interest: not reported Funding: supported in part by grants from Lilly France and the Commission de la Rocheeche Clinique de l'Assistance Publique Hopitaux de Paris

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	List of consecutive treatment assignment
Allocation concealment (selection bias)	Unclear risk	Performed separately in each centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.

Gastinne 1992 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. No information about blinding of outcome assessor. However, the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. No information about blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Gaussorgues 1991

Study characteristics	
Methods	Randomised study. Intention-to-treat Blinding: open-label Randomisation method: odd-even numbers Accrual period: from September 1988 to September 1989 Country: France
Participants	Eligibility criteria: all patients admitted to the ICU who required mechanical ventilation and inotropic drugs for haemodynamic reasons Exclusion criteria: neutropenia Number of participants enrolled: 118 Number of participants randomised: 118 Number of patients excluded: none Number of participants analysed: 118 Percentage of ventilated participants: 100% Length of stay in ICU: not reported Diagnosis at admission: medical = 83%, surgical scheduled = 17% (all participants were infected on admission) Severity score on admission: SAPS mean = 17.5 Percentage of immunocompromised participants: not reported Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 100%, control = 100% Stress ulcer prophylaxis applied: sucralfate 4 g to all participants
Interventions	Treatment group, randomised = 59, analysed = 59: • polymyxin E 36 mg, gentamicin 80 mg, vancomycin 50 mg, amphotericin B 500 mg applied enterally 4 times a day until extubation • amphotericin B, chlorhexidine applied orally 4 times a day • systemic antibiotic therapy

Gaussorgues 1991 *(Continued)*

	Control group, randomised = 59, analysed = 59: • amphotericin B, chlorhexidine applied orally 4 times a day • systemic antibiotic therapy
Outcomes	Respiratory infections: not possible to evaluate Mortality: in ICU
Notes	All participants were infected on admission. Data about respiratory infections are not provided. Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Georges 1994

Study characteristics

Methods	Randomised, placebo-controlled study Blinding: open-label Randomisation method: sealed envelopes

Georges 1994 *(Continued)*

	Accrual period: from June 1990 to April 1992 Country: France
Participants	Eligibility criteria: polytrauma, expected mechanical ventilation for at least 4 days, age > 18 years Exclusion criteria: hypersensitivity to the used agents, protocol violation, obesity, ventilation < 4 days, patients on mechanical ventilation 2 days before admission, severe maxillo-facial lesions Number of participants enrolled: 138 Number of participants randomised: 64 Number of patients excluded: none Number of participants analysed: 64 Length of stay in ICU, mean days: 33 Percentage of ventilated participants: 100%. Length of ventilation, mean: 16 days Diagnosis at admission: trauma 100% Severity score on admission: APACHE II mean = 15, ISS = 41 Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy in the first 3 days: almost 100% Stress ulcer prophylaxis: H2-blockers
Interventions	Treatment group, randomised = 31, analysed = 31: • polymyxin E 75 mg, netilmicin 150 mg, amphotericin B 400 mg applied enterally 4 times a day and as a 2% paste to the oropharynx until extubation • systemic antibiotic prophylaxis was free Control group, randomised = 33, analysed = 33: • placebo • systemic antibiotic prophylaxis was free
Outcomes	Respiratory infections (acquired pneumonia). Diagnosis of infection was based on: fever > 38.5 °C, leukocytosis > 12,000/mm^3, new infiltrates in the chest X-rays, purulent pulmonary secretions, positive bacteriologic findings (> 10^3 CFU/mL) obtained through a protected catheter Mortality: in ICU and hospital
Notes	Antibiotic prophylaxis was free, and almost all participants in both groups were treated with systemic antibiotics. Conflict of interest: not available Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin flip
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.

Georges 1994 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Hammond 1992

Study characteristics	
Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: computer-generated random numbers Accrual period: from January 1989 to December 1990 Country: South Africa
Participants	Eligibility criteria: expected intubation for longer than 48 hours and stay in ICU for at least 5 days Exclusion criteria: hypersensitivity to the study drugs, patients with asthma, drug overdose, and patients admitted electively after surgery Number of participants enrolled: 322 Number of participants randomised: 322 Number of patients excluded: 83 (80 short duration of ventilation, 3 protocol violations) Number of participants analysed: 239 Percentage of ventilated participants: 100% Length of stay in ICU, median days: 11 Diagnosis at admission: medical = 55%, surgical scheduled = 3%, surgical unscheduled = 11%, trauma = 31% Severity score on admission: APACHE II mean = 13.9, ISS mean = 28.7 Percentage of immunocompromised participants: 0.8% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 54%, control = 58% Stress ulcer prophylaxis applied: none, H2-blockers only to high-risk patients
Interventions	Treatment group, randomised = 162, analysed = 114: • polymyxin E 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied enterally and as a 2% gel to the oropharynx 4 times a day until 48 hours after extubation • cefotaxime 1 g x 3 iv for the first 3 days to participants untreated on admission Control group B, randomised = 160, analysed = 126:

Hammond 1992 *(Continued)*

	• placebo • cefotaxime 1 g x 3 iv for the first 3 days to participants untreated on admission
Outcomes	Respiratory infections (infections acquired after 48 hours) • Diagnosis of pneumonia was based on a new infiltrate on X-ray and purulent bronchial secretions with many leukocytes, temperature > 38 °C, WBC > 10^{10}/L, substantial number of organism on Gram stain with a pure growth culture from tracheal aspirate, deterioration of gas exchange of > 2 kPa. • Diagnosis of bronchial infection was based on all the previous criteria except the X-ray changes. Mortality: in hospital
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. No information about blinding of outcome assessor. However, the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. No information about blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs were poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	83 (80 short duration of ventilation, 3 protocol violations)
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Jacobs 1992

Study characteristics

Methods	Randomised study Blinding: open-label Randomisation method: sealed envelopes

Jacobs 1992 *(Continued)*

	Accrual period: from July 1989 to August 1990 Country: the UK
Participants	Eligibility criteria: expected stay in ICU > 3 days Exclusion criteria: none Number of participants enrolled: 91 Number of participants randomised: 91 Number of patients excluded: 11 length of stay shorter than 3 days, 1 suspected to be an HIV carrier Number of participants analysed: 79 Percentage of ventilated participants: 100% Length of stay in ICU, median days: SDD 9 (3 to 49), control 10 (3 to 52) Diagnosis at admission: medical = 25%, surgical = 57%, trauma = 18% (high percentage of neurologic and neurosurgical patients 52%) Severity score on admission: APACHE II mean = 17.5, ISS not available Percentage of immunocompromised participants: not available Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: next to 100% Stress ulcer prophylaxis applied: policy of maintenance a low gastric pH, H2-blockers only if peptic ulcer or steroid therapy (33%), sucralfate 4 g to all participants not on enteral feeding
Interventions	Treatment group, randomised = 45, analysed = 36: • polymyxin E 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied orally and enterally 4 times a day until extubation • cefotaxime 50 mg/kg/day iv x 4 days Control group, randomised = 46, analysed = 43: • no prophylaxis
Outcomes	Respiratory infections (acquired pneumonia). Diagnosis of infection was based on alveolar infiltrates on 2 or more chest X-rays, moderate or copious purulent tracheal aspirate, rectal temperature > 38.4 °C, leucocytosis > 13 x 10^9/L, a heavy growth of organisms from tracheal aspirate with a high polymorphonuclear leucocytes/epithelial cell ratio. Mortality
Notes	Almost 100% of participants received systemic antibiotic therapy on admission. Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Closed-envelope system
Blinding of participants and personnel (performance bias)	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlike-

Jacobs 1992 *(Continued)*

All outcomes		ly in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 excluded because length of stay shorter than 3 days, 1 suspected to be an HIV carrier.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Kerver 1988

Study characteristics	
Methods	Randomised study Blinding: open-label Randomisation method: odd/even numbers Accrual period: from January 1985 to May 1986 Country: the Netherlands
Participants	Eligibility criteria: all patients admitted to the surgical ICU who required care > 5 days Exclusion criteria: none Number of participants enrolled: not reported Number of participants randomised: 96 Number of patients excluded: none Number of participants analysed: 96 Percentage of ventilated participants: 100% Length of stay in ICU: not reported Diagnosis at admission: surgical = 60%, trauma = 28%, other = 12% Severity score on admission: APACHE II mean = 14.8, ISS not reported Percentage of immunocompromised participants: not reported Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: about 85% Stress ulcer prophylaxis applied: not reported
Interventions	Treatment group, randomised = 49, analysed = 49: • polymyxin E 200 mg, tobramycin 80 mg, amphotericin B 500 mg applied orally and enterally 4 times a day • oral disinfectant • cefotaxime 50 to 70 mg/kg/day iv x 5 to 7 days

Kerver 1988 *(Continued)*

	Control group, randomised = 47, analysed = 47: • oral disinfectant
Outcomes	Respiratory infections (primary pneumonia and pneumonia acquired after 48 h). Diagnosis of infection was based on X-ray findings and the presence of 3 of the following criteria on the same day: rectal temperature > 38.5 °C for at least 12 h, WBC count > 10 x 10^3 or < 4 x 10^3/µL, at least 3% band forming granulocytes, unexplained decrease in platelet count < 100,000/µL, deterioration of renal function due to acute tubular necrosis, unexplained decrease in systolic blood pressure of > 30 mmHg, progressive respiratory failure. Mortality
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. Outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Koeman 2006

Study characteristics

Methods	Randomised, placebo-controlled trial Blinding: double-blind

Koeman 2006 *(Continued)*

	Randomisation method: computerised randomisation schedule Accrual period: from February 2001 to March 2003 Country: the Netherlands
Participants	Eligibility criteria: consecutive adult patients (18 years of age) needing mechanical ventilation for at least 48 hours were included within 24 hours after intubation and start of mechanical ventilation Exclusion criteria: a preadmission immunocompromised status (defined as leucopenia < 3.10^9/L, cumulative dose of > 750 mg corticosteroids/year, or HIV), pregnancy, and if the physical condition did not permit oral application of study medication Number of participants enrolled: 385 Number of participants randomised: 385 Number of patients excluded: none Number of participants analysed: 385 Percentage of ventilated participants: 100% Length of stay in ICU, mean days: treatment 1 = 13.77, treatment 2 = 13.27, control = 12.45 Diagnosis at admission: trauma = 38 (10%), postoperative = 69 (18%), medical = 278 (72%) Severity score on admission APACHE II score, mean (SD): treatment 1 = 22.2 (7.02), treatment 2 = 23.7 (7.38), control = 21.8 (7.43) Percentage of immunocompromised participants: not available Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: not available Stress ulcer prophylaxis applied: not available
Interventions	Treatment group 1, randomised = 127, analysed = 127: chlorhexidine 2% in petroleum jelly (Vaseline) FNA, CHX 2% Treatment group 2, randomised = 128, analysed = 128: chlorhexidine 2% in petroleum jelly (Vaseline) FNA, CHX 2% with colistin 2% in Vaseline FNA, and Vaseline FNA Control group, randomised = 130, analysed = 130: placebo
Outcomes	Time to ventilator-associated pneumonia All-cause ICU mortality
Notes	Conflict of interest: "None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript." Funding: supported by ZonMw, the Netherlands Organisation for Health Research and Development (project number 2200.0046)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation schedule
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.

Koeman 2006 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind study. No information provided about blinding of assessor. However, outcome is unlikely to be biased due to lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind study. No information provided about blinding of assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs were poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study was discontinued in 6 participants: 5 participants (control group, 1 participant; treatment group 1, 2 participants; treatment group 2, 2 participants) refused to accept the oral paste, and 1 participant in treatment group 2 was prematurely withdrawn from the trial protocol due to tongue oedema on the second day. All participants included in the analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Korinek 1993

Study characteristics	
Methods	Randomised, placebo-controlled, dual-centre study Blinding: double-blind Randomisation method: randomisation performed by the hospital pharmacist on each unit separately Accrual period: from March 1989 to September 1990 Country: France
Participants	Eligibility criteria: all comatose patients with emergency admission to 2 neurosurgical ICUs and intubated within 24 hours for at least 5 days, age > 16 years Exclusion criteria: age < 16 years, known immunosuppression, antibiotic treatment during the 2 weeks preceding ICU admission, serious injury of oropharyngeal mucosa or epistaxis, abnormal chest X-ray on admission, extubation or infection occurring within the first 5 days of neurosurgical care Number of participants enrolled: 191 Number of participants randomised: 191 Number of patients excluded: 68 because length of stay shorter than 5 days Number of participants analysed: 123 Percentage of ventilated participants: 100% Length of stay in ICU, mean days: 26 Diagnosis at admission: surgical scheduled = 11%, surgical unscheduled = 39%, trauma = 50% Severity score on admission: SAPS mean = 10.9, ISS not available Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 0%, control = 0% Stress ulcer prophylaxis applied: sucralfate (32%), antiacids (14%), H2-blockers (20%) until enteral feeding was started
Interventions	Treatment group, randomised = 96, analysed = 63:

Korinek 1993 *(Continued)*

	• polymyxin E 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied enterally and as a 2% paste to the oropharynx 4 times a day for 15 days • vancomycin orally Control group, randomised = 95, analysed = 60: • placebo The non-absorbable antibiotics were discontinued if any infection requiring a parenteral antibiotic treatment occurred and at the time of participant's extubation.
Outcomes	Respiratory infections (pneumonia acquired after 5 days). Diagnosis of infection was based on fever > 38.5 °C, leukocytosis > 12,000 cells/mm^3, purulent sputum, new and persistent infiltrates on chest X-ray, and a culture of > 10^3 CFU/mL obtained with either brush or plugged telescoping catheter. Mortality: in ICU
Notes	Setting: neurosurgical ICU Conflict of interest: not reported Funding: the study was supported in part by Lilly-France

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Low risk	It is reported as "randomisation was performed on each unit separately by hospital's pharmacist, who delivered daily the placebo or treatment capsules for each patients".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. No information about blinding of outcome assessor. However, outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind study. No information provided about blinding of assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	68 excluded because length of stay shorter than 5 days.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Krueger 2002

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, double-centre study Randomisation method: computer-generated randomisation Accrual period: from April 1989 to March 1991 Country: Germany
Participants	Eligibility criteria: expected stay in ICU > 2 days and at least 1 risk factor for infection Exclusion criteria: patients expected to die within 48 hours or randomisation was not achieved within 12 hours after admission to ICU Number of participants enrolled: 546 Number of participants randomised: 546 Number of patients excluded: 19: withdrawal of consent (5 patients), violation of entry criteria (9 patients), and other reasons (5 patients) Number of participants analysed: 527 Percentage of ventilated participants: not reported Length of stay in ICU: not reported Diagnosis at admission: surgical Severity score on admission: APACHE II mean = 20, ISS not available Percentage of immunocompromised participants: not available Percentage of participants treated with systemic antibiotic therapy (not stated in protocol) in the first 3 days: not available Stress ulcer prophylaxis applied: sucralfate to all participants
Interventions	Treatment group, randomised = not reported, analysed = 265: • polymyxin B 50 mg, gentamicin 80 mg, applied nasally, orally, and enterally 4 times a day during the ICU stay • ciprofloxacin 400 mg x 2 iv x 4 days to uninfected participants Control group, randomised = not reported, analysed = 262: • placebo applied nasally, orally, and enterally • placebo iv to uninfected participants
Outcomes	Respiratory infections (acquired pneumonia) Mortality in ICU
Notes	Information about accrual period and severity score was reported in a previously published abstract. Conflict of interest: not reported Funding: grants from Bayer Vital GmbH, Leverkusen, and Merck, Darmstadt

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Sealed-envelope technique served for assignment to the treatment or placebo group.

Krueger 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind: "All data were noted on standardized documentation sheets and were exclusively collected by a study nurse and a medical doctor in each centre. None of these persons were involved in patient care or in diagnostic or therapeutic decisions"
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind: "All data were noted on standardized documentation sheets and were exclusively collected by a study nurse and a medical doctor in each centre. None of these persons were involved in patient care or in diagnostic or therapeutic decisions"
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs were poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	It is reported as "Nineteen (3.4%) patients were excluded after enrolment (8 of the prophylaxis group and 11 of the control group, all survived) because of withdrawal of consent (five patients), violation of entry criteria (nine patients), and other reasons (five patients)".
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Laggner 1994

Study characteristics	
Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: computer-generated randomisation in time blocks. Open Accrual period: from August 1987 to November 1990 Country: Germany
Participants	Eligibility criteria: expected ventilation for 5 days, age > 18 years and < 80 years, acute onset of respiratory failure Exclusion criteria: age < 18 years and > 80 years, bleeding of the nasopharynx and of the upper gastrointestinal tract on admission, stress ulcer prophylaxis with other drug therapy than sucralfate, mechanical ventilation for less than 5 days, patients on enteral nutrition or with known allergy to sucralfate or gentamicin Number of participants enrolled: 88 Number of participants randomised: 88 Number of patients excluded: 21 (18 participants ventilated for less than 5 days, 3 participants received enteral nutrition) Number of participants analysed: 67 Percentage of ventilated participants: 100% Length of stay in ICU, mean days: 28.8 Diagnosis at admission: medical = 88%, surgical scheduled = 9%, surgical unscheduled = 1%, trauma = 2% Severity score on admission: APACHE II mean = 23, ISS not available

Laggner 1994 *(Continued)*

	Percentage of immunocompromised participants: 15% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: 100% Stress ulcer prophylaxis applied: sucralfate
Interventions	Treatment group, randomised = not reported, analysed = 33: • gentamicin 40 mg, amphotericin B 100 mg applied to the oropharynx 4 times a day until extubation • oropharyngeal disinfectant • aminopenicillin and clavulanic acid or other appropriate regimens Control group, randomised = not reported, analysed = 34: • placebo • amphotericin B 100 mg • oropharyngeal disinfectant • aminopenicillin and clavulanic acid or other appropriate regimens
Outcomes	Respiratory infections (acquired pneumonia). Diagnosis of infection was based on: appearance of a new infiltrate on the chest film with concomitant tracheal colonisation, fever > 38 °C, and > 15,000 or < 5000 WBC/mm^3 of blood. Mortality: in ICU
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind study. No information about blinding of outcome assessor. However, outcome is unlikely to be biased due to lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind study. No information provided about blinding of assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	21 participants developed exclusion criteria during the first 5 days.

Laggner 1994 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available.

Lingnau 1997

Study characteristics	
Methods	Randomised, placebo-controlled study with 3 arms (1 control arm and 2 treatment arms) Intention-to-treat Blinding: double-blind Randomisation method: continuous random numbers assigned to blinded study drugs or vehicle by biometric department Accrual period: from August 1989 to January 1994 Country: Austria
Participants	Eligibility criteria: non-infected trauma patients, age > 18 years, expected ventilation for at least 2 days, expected ICU stay for at least 3 days, ISS > 16 and < 74, inclusion within 24 hours of admission Exclusion criteria: isolated brain injury, prior antibiotic treatment, history of infection Number of participants enrolled: 961 Number of participants randomised: 357 Number of patients excluded: 47 because they developed exclusion criteria Number of participants analysed: 310 Percentage of ventilated participants: 100% Length of stay in ICU, mean days: 20 Diagnosis at admission: trauma = 100% Severity score on admission: APACHE II mean = 15.6, ISS mean = 35.2 Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy (not stated in protocol) in the first 3 days: treatment 1 = 2%, treatment 2 = 2%, control = 6% Stress ulcer prophylaxis applied: free
Interventions	Treatment group 1, randomised = not reported, analysed = 80: • polymyxin E 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied orally and enterally 4 times a day during the ICU stay • ciprofloxacin 200 mg x 2 iv, for 4 days Treatment group 2, randomised = not reported, analysed = 82: • polymyxin E 100 mg, ciprofloxacin 50 mg, amphotericin B 500 mg applied orally and enterally 4 times a day during the ICU stay • ciprofloxacin 200 mg x 2 iv, for 4 days Control group, randomised = not reported, analysed = 148: • placebo • ciprofloxacin 200 mg x 2 iv, for 4 days
Outcomes	Respiratory infections (acquired pneumonia). Diagnosis of infection was based on concomitant occurrence of purulent sputum, positive cultures of bronchial secretions, and deterioration of lung function. Mortality: in ICU

Lingnau 1997 *(Continued)*

Notes	Conflict of interest: not available Funding: this study was funded in part by research grant BAY q 3939/0454 and grant of the Leopold Franzers University of Insbruck, Austria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out using random numbers in blocks of 20.
Allocation concealment (selection bias)	Unclear risk	The pharmacist prepared and dispensed all treatments according to the randomisation list.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. Red dye added by the hospital pharmacist to ensure blind protocol to clinicians and investigators.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. Red dye added by the hospital pharmacist to ensure blind protocol to clinicians and investigators.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	47 excluded because they developed exclusion criteria.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Palomar 1997

Study characteristics

Methods	Randomised, multicentric (10 ICUs) study with 3 arms (1 treatment arm and 2 control arms; 1 control arm was excluded from meta-analysis because it was the only study arm receiving sucralfate) Blinding: open-label Randomisation method: sealed envelopes Accrual period: from July 1989 to August 1991 Country: Spain
Participants	Eligibility criteria: patients requiring mechanical ventilation for more than 4 days, not infected at the time of entry, and not receiving antibiotic therapy Exclusion criteria: ARDS, leukopenia, pregnancy Number of participants enrolled: 151

Palomar 1997 *(Continued)*

	Number of participants randomised: 151 Number of patients excluded: 22: early extubation (10), early death (8), protocol violation (3), antibiotic hypersensitivity (1) Number of participants analysed: 129 Percentage of ventilated participants: 100% Length of stay in ICU, median days: 10 Diagnosis at admission: medical = 50 (40%), surgical = 14 (10%), trauma = 65 (50%) Severity score on admission: APACHE II mean = 16.8, ISS not available Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 0%, control = 6% Stress ulcer prophylaxis applied: sucralfate to 1 control group (excluded from meta-analysis), antiacids or H2-blockers to the 2 other groups
Interventions	Treatment group, randomised = 50; analysed = 41: • polymyxin E + B 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied enterally and as a 2% paste to the oropharynx 4 times a day until extubation • cefotaxime 1 g x 3 iv for the first 4 days Control group, randomised = 49, analysed = 42: • no prophylaxis Sucralfate group,* randomised = 52, analysed = 46: • cefotaxime 1 g x 3 iv for the first 4 days • sucralfate *this group was excluded from analysis because it was the only group receiving sucralfate
Outcomes	Respiratory infections (acquired infections). Diagnosis of pneumonia was based on the CDC criteria of 1980 (clinical or radiologic suspicion with: purulent sputum, organism isolated from blood culture, isolation of pathogen from tracheal aspirate, brush or biopsy). Bacteriologic evaluation was performed with brush or BAL in 50% of participants. Diagnosis of tracheobronchitis was based on the CDC criteria of 1980. Mortality: in ICU
Notes	Conflict of interest: not reported Funding: grant from Roussel Iberica Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.

Palomar 1997 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. However, outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	22 excluded because early extubation (10), early death (8), protocol violation (3), cefotaxime-related hypertensive reaction (1).
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Pneumatikos 2002

Study characteristics	
Methods	Randomised, placebo-controlled Blinding: outcome assessor Randomisation method: not stated Accrual period: not available Country: Greece
Participants	Eligibility criteria: patients with multiple trauma admitted to the ICU who required intubation and had an expected time of mechanical ventilation exceeding 5 days. Absence of cardiopulmonary disease, negative chest radiography, and a PaO_2/FiO_2 ratio higher than 300 mmHg Number of participants enrolled: 79 Number of participants randomised: 79 Number of patients excluded: 18 Number of participants analysed: 61 Percentage of ventilated participants: 100% Length of stay in ICU, median days: treatment = 16, control = 23 Diagnosis at admission: trauma = 100% Severity score on admission: APACHE II, treatment = 18.1, control = 19.1 Percentage of immunocompromised participants: not reported Percentage of participants treated with systemic antibiotic therapy: not stated Stress ulcer prophylaxis applied: H2 blockers or sucralfate: treatment = 26%, control = 19%
Interventions	Treatment group, randomised = 40, analysed = 31: • polymyxin 73 mg • tobramycin 73 mg, amphoteric in 500 mL in 0.9 saline solution at an infusion rate of 2 mL/h in the subglottic area for the entire period of the study

Pneumatikos 2002 *(Continued)*

	Control group, randomised = 39, analysed = 30: • placebo
Outcomes	Ventilator-associated pneumonia defined as presence of new and persistent pulmonary infiltrates plus 2 of the following criteria: body temperature > 38.3 °C, leukocytosis (> 12,000 leukocytes/mm3) or leukopenia (< 4000 leukocytes/mm^3), and purulent tracheal secretions. The diagnosis of VAP was confirmed by quantitative cultures. Mortality: not specified
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	It is reported as "chest physician, a radiologist, and a physician with experience in infectious diseases (blind to the patient's group assignment)".
Blinding of outcome assessment (detection bias) SRIs	Low risk	It is reported as "chest physician, a radiologist, and a physician with experience in infectious diseases (blind to the patient's group assignment)".
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	18 patients were excluded: 7 extubated, 4 developed pneumonia during the first 48 hours of mechanical ventilation, 1 underwent tracheotomy, and 6 died. It is not reported if these events occurred before or after the first 5 days of mechanical ventilation.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Pugin 1991

Study characteristics

Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: sealed envelopes

Pugin 1991 *(Continued)*

	Accrual period: from April 1989 to November 1989 Country: Switzerland
Participants	Eligibility criteria: all adult patients admitted to the surgical ICU, at high risk of developing pneumonia, and intubated for more than 48 hours Exclusion criteria: organ transplantation Number of participants enrolled: 79 Number of participants randomised: 79 Number of patients excluded: 27 due to early extubation or early death Number of participants analysed: 52 Percentage of ventilated participants: 100% Length of stay in ICU, mean days: 13.8 Diagnosis at admission: medical = 11%, surgical scheduled = 11%, surgical unscheduled = 22%, trauma = 56% Severity score on admission: APACHE II mean = 15.2, ISS not available Percentage of immunocompromised participants: not available Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 46%, control = 53% Stress ulcer prophylaxis applied: sucralfate (61%), ranitidine (11%)
Interventions	Treatment group, randomised = 38, analysed = 25: polymyxin B sulphate 150 mg, neomycin sulphate 1 g, vancomycin hydrochloride 1 g applied as a solution to the retropharynx 6 times a day within 24 hours after intubation until extubation or death Control group, randomised = 41, analysed = 27: placebo Withdrawal from the study was possible at any time if the treating physicians estimated that there was any problem related to administration of the drugs or side effects.
Outcomes	Respiratory infections (pneumonia acquired after 48 hours). Pneumonia was defined as a "clinical pulmonary infections score" (CPIS) ≥ 7 during the course of intubation and that remained elevated (= 7) for at least 3 days (i.e. for 2 consecutive measurements). Mortality: in hospital
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias)	Low risk	Double-blind. No information about blinding of outcome assessor. However, outcome is not likely to be influenced by lack of blinding.

Pugin 1991 *(Continued)*
Mortality

Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. No information about blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	27 patients excluded due to early extubation or early death.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Quinio 1995

Study characteristics	
Methods	Randomised, placebo-controlled study. Intention-to-treat Blinding: double-blind Randomisation method: randomisation made by the pharmacy service according to computer-generated random numbers Accrual period: from January 1991 to January 1993 Country: France
Participants	Eligibility criteria: trauma patients intubated within 24 h Exclusion criteria: age < 16 years, antibiotic treatment in the week preceding ICU admission, pregnancy Number of participants enrolled: 148 Number of participants randomised: 148 Number of patients excluded: none Number of participants analysed: 148 Percentage of ventilated participants: 100% Length of stay in ICU, mean days = 20.5 Diagnosis admission: medical = 2%, trauma = 98% Severity score on admission: SAPS mean = 11.2, ISS mean = 31.3, GCS mean = 6.5 Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 35%, control = 26% Stress ulcer prophylaxis applied: sucralfate until enteral feeding was effective, H2-blockers in high-risk patients
Interventions	Treatment group, randomised = 76, analysed = 76: polymyxin E 100 mg, gentamicin 80 mg, amphotericin B 500 mg applied enterally and in the nares and as a 2% paste to the oropharynx 4 times a day until extubation or start of enteral nutrition Control group: randomised = 72, analysed = 72: placebo
Outcomes	Respiratory infections (pneumonia acquired after 48 h). Diagnosis of infection was based on: purulent tracheal aspirate, fever > 38.5 °C, leukocytosis > 10,000 WBC/mm^3, new and persistent infiltrate on chest X-ray.

Quinio 1995 *(Continued)*

	Mortality: in ICU
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number
Allocation concealment (selection bias)	Unclear risk	Randomisation was performed by the hospital's pharmacists according to a randomised list of consecutive treatment assignments.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. No information about blinding of outcome assessor. However, the outcome measurement is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. No information about blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Rocha 1992

Study characteristics

Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: made by the pharmacy service according to computer-generated random numbers Accrual period: from September 1989 to October 1990 Country: Spain
Participants	Eligibility criteria: expected mechanical ventilation for more than 3 days, stay in ICU more than 5 days Exclusion criteria: infection or strong suspicion of infection at the start of ventilation, antibiotic treatment in the previous 7 days, neutropenia (WBC < 500/mm^3) and fever, pregnancy, history of hypersensitivity to the topical agents

Rocha 1992 *(Continued)*

	Number of participants enrolled: 151 Number of participants randomised: 151 Number of patients excluded: 50 (15 early extubations, 31 early deaths, 2 protocol violation, 2 other) Number of participants analysed: 101 Percentage of ventilated participants: 100% Length of stay in ICU, median days: 8 Diagnosis at admission: medical = 28%, surgical scheduled = 3%, surgical unscheduled = 1%, trauma = 68% Severity score on admission: APACHE II mean = 16.3, ISS not available, GCS mean = 9 Percentage of immunocompromised participants: 0.7% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 0%, control = 0% Stress ulcer prophylaxis applied: H2-blockers and antiacids
Interventions	Treatment group, randomised = 74, analysed = 47: • polymyxin E 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied enterally and as a 2% paste to the oropharynx 4 times a day • cefotaxime 6 g/day iv for the first 4 days Control group, randomised = 77, analysed = 54: • placebo • no systemic prophylaxis
Outcomes	Respiratory infections (acquired pneumonia). Diagnosis of infection was based on purulent pulmonary secretions, new infiltrates in the chest X-ray, and 1 of the following: fever/hypothermia, leukocytosis/leukopenia, positive physical examination, drop in arterial partial oxygen pressure. Bacteriologic diagnosis, even if performed (with brush in few participants), was not essential. Mortality: in ICU
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers table
Allocation concealment (selection bias)	Unclear risk	Made by the pharmacy service
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind study. No information about blinding of outcome assessor. However, outcome is unlikely to be biased due to lack of blinding.

Rocha 1992 *(Continued)*

Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. No information about blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	50 excluded (15 early extubations, 31 early deaths, 2 protocol violation, 2 other).
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Rodriguez-Roldan 1990

Study characteristics	
Methods	Randomised, placebo-controlled, dual-centre study Blinding: double-blind Randomisation method: odd and even numbers Accrual period: from June 1988 to December 1988 Country: Spain
Participants	Eligibility criteria: patients intubated and mechanically ventilated for more than 72 hours Exclusion criteria: patients whose chest X-rays were difficult to interpret, with suspected inflammatory images during the first 72 hours, patients ventilated for less time Number of participants enrolled: 28 Number of participants randomised: 28 Number of patients excluded: none Number of participants analysed: 28 Percentage of ventilated participants: 100% Length of stay in ICU, median days: 13.5 Diagnosis at admission: medical = 13 (42%), surgical = 5 (16%), trauma = 13 (42%) Severity score on admission: APACHE II mean = 17.1, ISS not available Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 36%, control = 35% Stress ulcer prophylaxis applied: sucralfate or alkaline agents plus ranitidine according to a randomised open protocol
Interventions	Treatment group: randomised = 13, analysed = 13: • polymyxin E, tobramycin or netilmicin, amphotericin B and antiseptic applied enterally and as a 2% paste to the oropharynx 4 times a day • antiseptic Control group: randomised = 15, analysed = 15: • placebo • antiseptic

Rodriguez-Roldan 1990 *(Continued)*

Outcomes	Respiratory infections (pneumonia acquired after 72 hours). Diagnosis of infection was based on the presence of at least 1 in each category of criteria: • clinical criteria: temperature > 38 °C, purulent bronchorrhoea, leukocytosis > 15,000 WBC/mm^3, increased alveolar-arterial oxygen gradient; • radiologic criteria: new and persistent infiltrate; • bacteriologic criteria: quantitative culture of tracheal aspirates > 10^3 CFU/mL (in 6 participants either bronchoscopy or a telescoped catheter was used to obtain the sample). Mortality: in ICU
Notes	Conflict of interest: not reported Funding: this study was supported in part by a grant from the Social Security Health Investigation Foundation of Spain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. No information about blinding of outcome assessor for mortality. However, the outcome is unlikely to be biased due to lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind chest radiographs were independently examined by 2 radiologists; independent microbiological surveillance.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Sanchez-Garcia 1998

Study characteristics

Methods	Randomised, placebo-controlled, multicentric (5 ICUs) study Blinding: double-blind

Sanchez-Garcia 1998 *(Continued)*

	Randomisation method: sealed envelopes Accrual period: not available Country: Spain
Participants	Eligibility criteria: expected ventilation for longer than 48 hours, age > 16 years Exclusion criteria: death or extubation before 48 hours, pregnancy, allergy to study antibiotics, organ transplantation, absence or contraindication to nasogastric tube Number of participants enrolled: 271 Number of participants randomised: 271 Number of patients excluded: none Number of participants analysed: 271 Percentage of ventilated participants: 100% Length of stay in ICU, median days: 13 Diagnosis at admission: medical = 191 (70%), surgical scheduled = 5 (3%), surgical unscheduled = 25 (9%), trauma = 45 (18%) Severity score on admission: APACHE II mean = 26.6, ISS not available Percentage of immunocompromised participants: 4.4% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 70%, control = 69% Stress ulcer prophylaxis applied: each group was randomised to receive either sucralfate or H2-blockers
Interventions	Treatment group, randomised = 131, analysed = 131: • polymyxin E 100 mg, gentamicin 80 mg, amphotericin B 500 mg applied orally and enterally 4 times a day until extubation • ceftriaxone 2 g/day iv x 3 days to uninfected participants Control group, randomised = 140, analysed = 140: • placebo • systemic placebo to uninfected participants
Outcomes	Respiratory infections (early- and late-acquired pneumonia). Diagnosis of infection was based on new and persistent infiltrate on chest X-ray and 3 of the following: temperature > 38.5 °C, leukocytosis > 12,000 WBC/mm^3 or leukopenia < 3000 WBC/mm^3, purulent tracheal aspirate with growth of a potentially pathogenic micro-organism. Mortality: in ICU
Notes	Personal contact with the main investigator provided data for 45 patients who were excluded from the published paper (12 early extubations, 12 early deaths, 17 protocol violation, 2 transferring, 2 other); these data are considered in the analysis. Conflict of interest: not reported Funding: supported in part by a grant from Productos Roche S.A., Spain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It is reported as "Patients were randomised through a computer-generated random-number table and were stratified by centre".

Sanchez-Garcia 1998 *(Continued)*

Allocation concealment (selection bias)	Low risk	Treatment codes were kept in individual sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. No information about blinding of outcome assessor for mortality. However, the outcome is unlikely to be biased due to lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. "The microbiologists who examined specimens for the study were blinded to the patient groups"
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs were poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Stoutenbeek 1996

Study characteristics	
Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: closed-envelope method (the code was known by the pharmacist only) Accrual period: from November 1984 to August 1986 Country: the Netherlands
Participants	Eligibility criteria: all patients admitted to the surgical ICU with blunt trauma and an HTI-ISS > 18, age > 18 years Exclusion criteria: patients mechanically ventilated for less than 5 days or discharged from ICU within 7 days and with an HTI-ISS < 18 after 24 hours Number of participants enrolled: 91 Number of participants randomised: 91 Number of patients excluded: 32 (27 early death or early extubations, 5 ISS < 18 after 24 hours) Number of participants entered in the study: 59 Percentage of ventilated participants: 100% Length of stay in ICU, mean days = 15 Diagnosis at admission: trauma = 100% Severity score on admission: APACHE II mean = 10.6, HTI-ISS mean = 35.1 Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 0%, control = 0%

Stoutenbeek 1996 *(Continued)*

	Stress ulcer prophylaxis applied: none, except for participants with history of pre-existing ulcer or on H2-blockers
Interventions	Treatment group, randomised = 49, analysed = 30: • polymyxin E 100 mg, tobramycin 80 mg, amphotericin 500 mg applied enterally and as a 2% paste to the oropharynx 4 times a day until ICU discharge • cefotaxime 50 to 100 mg/kg/day iv for the first 5 days Control group, randomised = 42, analysed = 29: • placebo • cefotaxime 50 to 100 mg/kg/day iv for the first 5 days The blinded medication was discontinued and topical prophylaxis started when a participant developed MOSF not responding to conventional therapy. The code was not broken, and the participant was further evaluated.
Outcomes	Respiratory infections (tracheobronchitis and pneumonia - early and late infections). Diagnosis of infection was based on clinical criteria: temperature > 38.5 °C, WBC > 12.5 x 10^9/L or leukopenia < 4 x 10^9/L, purulent secretions or X-ray changes and significant growth of bacteria. Mortality: in ICU
Notes	Conflict of interest: not reported Funding: this study was supported by a grant from Russel Netherland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Closed-envelope method. The code was known by the pharmacist only.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. No information about blinding of outcome assessor. However, the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. No information about blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs were poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	27 excluded due to early death or early extubations, 5 ISS < 18 after 24 hours.

Stoutenbeek 1996 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available.

Stoutenbeek 2007

Study characteristics	
Methods	Randomised, multicentre study. Intention-to-treat Blinding: open-label Randomisation method: randomisation lists prepared by the Biometrical Department and supplied with sealed envelopes Accrual period: from October 1991 to June 1994 Country: Europe, Australia, and New Zealand
Participants	Eligibility criteria: patients admitted within 24 hours after non-penetrating blunt trauma with an HTI-ISS >= 16, necessitating mechanical ventilation, age > 18 years Exclusion criteria: previous antibiotic use for more than 3 days at study entry, allergy to cefotaxime, referred patients from other hospital or secondary admissions with trauma having occurred > 24 hours before Number of participants enrolled: 405 Number of participants randomised: 405 Number of patients excluded: 4 (2 did not fulfil the inclusion criteria, data from 1 participant not available, 1 participant lost to follow-up after the 7th day) Number of participants analysed: 401 Percentage of ventilated participants: 100% Length of stay in ICU, median days: SDD = 13, control = 12 days Median duration of mechanical ventilation: SDD = 9 days, control = 8 days Type of admission diagnosis: trauma 100% Severity score on admission: APACHE II median: SDD = 15, control = 14; HTI-ISS median: SDD = 34, control = 29 Percentage of immunocompromised participants: 0% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 46%, control = 88% Stress ulcer prophylaxis applied: sucralfate, H2-blockers, omeprazole
Interventions	Treatment group, randomised = not reported, analysed = 201: • polymyxin E, tobramycin, amphotericin B administered through the nasogastric tube and applied to the buccal mucosa 4 times a day until discharge • cefotaxime 1 g every 6 hours for 4 days Control group, randomised = not reported, analysed = 200: • standard antibiotic prophylaxis used in each centre (no fluoroquinolones)
Outcomes	Primary: mortality from infection or multiple organ failure in ICU or up to 2 weeks after discharge Secondary: incidence of infection, multiple organ failure, and antibiotic usage The maximum observation period was 3 months. Patients dying within 24 hours after injury or dying from craniocerebral trauma were excluded.

Stoutenbeek 2007 *(Continued)*

	Diagnosis of pneumonia was based on any of the following: presence of a new and progressive pulmonary infiltrate on chest X-ray for >= 48 hours, purulent tracheal aspirate, fever > 38.5 °C, leukocytosis > 12,000/mL or leukopenia < 4000/mL. Diagnosis of tracheobronchitis was based on the same criteria except for the radiographic changes. Mortality: in ICU or up to 2 weeks after discharge
Notes	Conflict of interest: not reported Funding: this study was supported by a grant from Hoechst-Roussel International

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It is reported as "A randomisation schedule was prepared separately for each centre in balanced blocks of variable length by Medis GMBH".
Allocation concealment (selection bias)	Low risk	It is reported as "Each centre received a set of consecutively numbered sealed envelopes containing the treatment allocation guaranteeing adequacy of concealment of allocation sequence".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	It is reported as "Each death was audited by two independent investigators (R.L. and C.S.) who were blinded to the treatment arm, to confirm the statement of the treating physician about whether death resulted from cranio-cerebral trauma".
Blinding of outcome assessment (detection bias) SRIs	High risk	No blinding. The diagnosis of RTI was not based on microbiological exams.
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs were poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants were excluded from the final analysis after randomisation (2 did not fulfil the inclusion criteria, the data from 1 participant were not available, and 1 participant was lost to follow-up after the 7th day).
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Ulrich 1989

Study characteristics

Methods	Randomised, placebo-controlled study Blinding: open-label Randomisation method: sealed envelopes containing a random code for clusters of 4 patients Accrual period: from October 1986 to September 1987 Country: the Netherlands

Ulrich 1989 *(Continued)*

Participants	Eligibility criteria: patients expected to stay in the ICU more than 5 days and ventilated more than 48 hours Number of participants enrolled: 112 Number of participants randomised: 112 Number of patients excluded: 12 (early death) Number of participants analysed: 100 Percentage of ventilated participants: about 80% Length of stay in ICU, median days = 10 Diagnosis at admission: medical = 34 (34%), surgical scheduled = 19 (19%), surgical unscheduled = 31 (31%), trauma = 16 (16%) Severity score on admission: SAPS mean = 11.7, ISS mean = 36.9 Percentage of immunocompromised participants: 3% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 83%, control = 81% Stress ulcer prophylaxis applied: not available
Interventions	Treatment group, randomised = 55, analysed = 48: • polymyxin E 100 mg, norfloxacin 50 mg, amphotericin B 500 mg, applied enterally and as a 2% paste to the oropharynx 4 times a day • trimethoprim 500 mg iv Control group, randomised = 57, analysed = 52: • placebo
Outcomes	Respiratory infections (acquired pneumonia). Diagnosis of infection was based on clinical and radiologic signs of pulmonary infiltrations with fever and leukocytosis and a dense growth in cultures of sputum of tracheal aspirate. Mortality: in ICU
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Sealed envelopes containing a random code for clusters of 4 patients
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. However, outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	High risk	No blinding. The diagnosis of RTI was not based on microbiological exams.

Ulrich 1989 *(Continued)*
SRIs

Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 patients excluded because they died within 24 hours.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Unertl 1987

Study characteristics	
Methods	Randomised study Blinding: open-label Randomisation method: blocked randomisation scheme and sealed-envelope technique Accrual period: from May 1984 to January 1985 Country: Germany
Participants	Eligibility criteria: all patients admitted to the ICU with: intubation within 24 hours after the onset of an acute disease or surgery, expected ventilation > 6 days, interval between intubation and first microbiologic culture < 36 hours Exclusion criteria: patients with infection, systemic antibiotic treatment, respiratory distress syndrome, leukopenia and myelosuppression on admission, renal failure Number of participants enrolled: 39 Number of participants randomised: 39 Number of patients excluded: none Number of participants analysed: 39 Percentage of ventilated participants: 100% Length of stay in ICU: not reported Diagnosis at admission: medical = 20 (52%), surgical = 6 (15%), trauma = 13 (33%) Severity score on admission: SAPS mean = 12.5, GCS (75% of participants have GCS < 7) Percentage of immunocompromised participants: not available Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: not reported Stress ulcer prophylaxis applied: H2-blockers to all participants and antiacids if pH < 4
Interventions	Treatment group, randomised = 19, analysed = 19: • polymyxin B 50 mg, gentamicin 80 mg, applied orally, nasally, and enterally 4 times a day until extubation • amphotericin B 300 mg applied orally 4 times a day Control group, randomised = 20, analysed = 20: • no prophylaxis
Outcomes	Respiratory infections (acquired pneumonia). Diagnosis of infection was based on new "definite" infiltrate on chest X-ray together with increasing amounts of purulent tracheobronchial secretion containing > 3 x 10^4 granulocytes/µL and at least 2 of the following: new febrile spikes > 38.5 °C, blood leuko-

Unertl 1987 *(Continued)*

	cyte count > 12,000/µL or < 4000/µL, decrease of PaO_2 requiring an increase of the FiO_2 of at least 15% to maintain oxygen tension. "Definite" is an infiltrate confirmed by 2 blind independent radiologists and not reversible after chest physiotherapy. Mortality: in ICU
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation scheme
Allocation concealment (selection bias)	Low risk	Sealed-envelope technique
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. However, outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	High risk	No blinding. The diagnosis of RTI was not based on microbiological exams.
Blinding of outcome assessment (detection bias) AES	Unclear risk	Methods for collection of AEs were poorly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Verwaest 1997

Study characteristics

Methods	Randomised study with 3 arms (1 control arm and 2 treatment arms) Blinding: open-label Randomisation method: sealed envelopes with computer-generated random numbers Accrual period: from September 1989 to March 1991 Country: Belgium
Participants	Eligibility criteria: expected ventilation > 48 hours

Verwaest 1997 *(Continued)*

	Exclusion criteria: age < 18 years, pregnancy, recent organ transplantation, serious granulocytopenia (<= 500 WBC/mm^3), ventilation < 48 hours, death before 48 hours, missing of essential data in the clinical or bacteriological dossier Number of participants enrolled: 660 Number of participants randomised: 660 Number of patients excluded: 82 (33 early death, 9 early extubation, 40 missing data) Number of participants entered in the study: 578 Percentage of ventilated participants: 100% Length of stay in ICU, mean days = 19.6 Diagnosis at admission: medical = 10%, surgical = 67%, trauma = 23% Severity score on admission: APACHE II mean = 18.1, ISS not available Percentage of immunocompromised participants: not available Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment 1 = 34%, treatment 2 = 31%, control = 34% Stress ulcer prophylaxis applied: sucralfate 2 g x 4
Interventions	Treatment group 1, randomised = 220, analysed = 193: • ofloxacin 200 mg x 2, amphotericin B 500 mg x 4 applied enterally and as a 2% paste to the oropharynx 4 times a day until discharge • ofloxacin 200 mg iv x 4 days Control group, randomised = 220, analysed = 185: • no prophylaxis, antibiotic therapy was used only if an infection was suspected Treatment group 2, randomised = 220, analysed = 200: this group received non-absorbable antibiotics administered through a gastric tube as a combination of polymyxin, tobramycin, and amphotericin B. This group was not considered in the analyses. • orabase paste 4 times a day • cefotaxime (4 x 1 g/d) for 4 days
Outcomes	Respiratory infections (pneumonia acquired after 48 h). Diagnosis of infection was based on fever > 38.5 °C, leukocytosis > 10,000 cells/µL, luxuriant growth of potentially pathogenic micro-organisms in culture of bronchial aspirate, new and persistent infiltrate on chest X-ray. Mortality: in ICU
Notes	Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated randomly to 1 of 3 study groups, using a computer-generated randomisation scheme and the sealed-envelope technique.
Allocation concealment (selection bias)	Low risk	Participants were allocated randomly to 1 of 3 study groups, using a computer-generated randomisation scheme and the sealed-envelope technique.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.

Verwaest 1997 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. However, outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In 40 participants (6%), balanced between groups, a correct evaluation was impossible because important clinical or bacteriological data were missing.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Wiener 1995

Study characteristics	
Methods	Randomised, placebo-controlled study Blinding: double-blind Randomisation method: random number table in blocks of 6 patients Accrual period: 8 months Country: the USA
Participants	Eligibility criteria: expected intubation for more than 48 hours, inclusion within 18 hours of intubation, age > 18 years Exclusion criteria: refusal to consent, allergy to 1 of the components of the regimen, active inflammatory bowel disease Number of participants enrolled: 121 Number of participants randomised: 121 Number of patients excluded: 60 (31 early extubation, 20 early death, 4 transfer to general medical ward, 1 protocol violation) Number of participants entered in the study: 61 Percentage of ventilated participants: 100% Length of stay in ICU, mean days: 11.3 Diagnosis at admission: not available Severity score on admission: APACHE II mean = 27.2, ISS not available Percentage of immunocompromised participants: > 5% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 93%, control = 81% Stress ulcer prophylaxis applied: H2-blockers to most participants
Interventions	Treatment group, randomised = not reported, analysed = 30: polymyxin E 100 mg, gentamicin 80 mg, nystatin 2,000,000 U applied enterally 4 times a day and as a 2% paste to the oropharynx until extubation or tracheostomy Control group, randomised = not reported, analysed = 31: placebo

Wiener 1995 *(Continued)*

Outcomes	Respiratory infections (pneumonia acquired after 48 hrs). Diagnosis of infection was based on the presence of the following: persistence of a new or progressive infiltrate on chest-film, fever > 38.5 °C and/or leukocytosis > 12,000/mm^3, growth of > 10^3 bacteria from a quantitative culture of lower respiratory tract secretions obtained with a blind protected catheter. Mortality: in ICU
Notes	60 participants were excluded after randomisation (data not available). Conflict of interest: not reported Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised in block of 6 using a random number table to receive either the topical antibiotics or placebo.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Double-blind. No information about blinding of outcome assessor. However, outcome is unlikely to be biased due to lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	Double-blind. No information about blinding of outcome assessor. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	60 (31 early extubation, 20 early death, 4 transfer to general medical ward, 1 protocol violation)
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Winter 1992

Study characteristics

Methods	Randomised study Blinding: open-label Randomisation method: sealed envelopes based on a computer-generated table of random numbers Accrual period: from July 1988 to May 1990

Winter 1992 *(Continued)*

	Country: the UK
Participants	Eligibility criteria: patients likely to remain in the ICU for at least 48 hours Exclusion criteria: allergy to the antibiotics used, age > 85 years, pregnancy Number of participants enrolled: 267 Number of participants randomised: 267 Number of patients excluded: none Number of participants entered in the study: 267. Of these, 84 in the historical control group were not considered in the analysis. Percentage of ventilated participants: 92% Length of stay in ICU, median days: 4 Diagnosis at admission: medical = 40%, surgical scheduled = 10%, surgical unscheduled = 37%, trauma = 13% Severity score on admission: APACHE II mean = 15.3, ISS mean = 26.2 Percentage of immunocompromised participants: 2.2% Percentage of participants treated with systemic antibiotic therapy (not stated in the protocol) in the first 3 days: treatment = 47%, control = 64% Stress ulcer prophylaxis applied: all control participants received sucralfate; H2-blockers were used in participants in both groups with peptic ulcer or pancreatitis
Interventions	Treatment group, randomised = 91, analysed = 91: • polymyxin E 100 mg, tobramycin 80 mg, amphotericin B 500 mg applied enterally and as a 2% gel to the oropharynx 4 times a day • ceftazidime 50 mg/kg/day iv x 3 days Control group, randomised = 92, analysed = 92: • conventional infections treatment and prophylaxis
Outcomes	Respiratory infections (pneumonia acquired after 48 h). Diagnosis of infection was based on temperature > 38.5 °C 2 times in 24 hours, WBC < 4 or > 12 x 10^9/L, positive BAL, 2 of the following: new pulmonary infiltrates on chest X-ray, purulent sputum, increase of 15% in FiO_2 to maintain previous oxygenation. Mortality: in hospital
Notes	Few participants were excluded after randomisation (data not available). Conflict of interest: not reported Funding: Bristol and Weston Health Authority and Glaxo Research Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Suitable patients were allocated randomly to contemporaneous control or SDD group with consecutively numbered envelopes prepared by computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Suitable patients were allocated randomly to contemporaneous control or SDD group with consecutively numbered envelopes prepared by computer-generated random numbers.

Winter 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	ICUs have standardised infection control programmes. Possible subjective decisions on who should be tested for the presence or absence of RTIs are unlikely in an ICU setting because routine care includes daily laboratory tests and scheduled radiologic and microbiologic studies.
Blinding of outcome assessment (detection bias) Mortality	Low risk	No blinding. However, outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) SRIs	Low risk	No blinding. However, a standardised set of diagnostic criteria, including results of microbiological exams, were used.
Blinding of outcome assessment (detection bias) AES	Unclear risk	AEs not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

APACHE: Acute Physiology and Chronic Health Evaluation
ARDS: acute respiratory distress syndrome
BAL: bronchoalveolar lavage
CCU: coronary care unit
CDC: Centers for Disease Control and Prevention
CFU: colony-forming unit
CHX: chlorhexidine
CI: confidence interval
CTR: control group
FiO_2: fractional inspired oxygen
FNA: fine needle aspiration
GCS: Glasgow Coma Scale
HTI-ISS: Hospital Trauma Index-Injury Severity Score
ICU: Intensive care unit
ISS: injury severity score
iv: intravenous
MOSF: multiple organ system failure
MV: mechanical ventilation
OR: odds ratio
PaO_2:arterial oxygen partial pressure
RCT: randomised controlled trial
RD: risk difference
RR: risk ratio
RTI: respiratory tract infection
SAPS: simplified acute physiology score
SD: standard deviation
SDD: selective decontamination of the digestive tract
VAP: ventilator-associated pneumonia
VO_2: oxygen consumption
U: unit
WBC: white blood count

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arnow 1996	The study included a selected population of patients undergoing liver transplant.
Barret 2001	The study included only paediatric burns patients.
Bion 1994	The study included a selected population of patients undergoing liver transplant.
Bouter 2002	The study included a selected population undergoing cardiopulmonary bypass.
Camus 2011	Both groups received SDD.
Di Filippo 1999	Experimental intervention not in the inclusion criteria: endonasal mupirocin for only 3 days
Flaherty 1990	The study included a selected population of cardio-surgical patients.
Garbino 2002	The study tested the effectiveness of fluconazole, as both groups received SDD.
Godard 1990	Non-randomised study
Hellinger 2002	The study included only liver transplant patients.
Huang 2013	Comparison intervention not in the inclusion criteria: 1) screening and isolation of methicillin-resistant *Staphylococcus aureus* (MRSA) carriers; 2) screening, isolation, and decolonisation of MRSA carriers
Hunefeld 1989	Unclear description of the intervention compared
Jacobs 1995	This study, which was included in the previous version of our review as a personal contact with the principal investigator, has now been excluded due to lack of feedback from the trial author. To date, this study has never been published.
Lipman 1994	After contacting the principal investigator, it become apparent that it was not a randomised study.
Luiten 1995	The study included a selected population of patients affected by pancreatitis characterised by a low percentage of ICU admissions.
Martinez 1994	The study compared the effect of 2 different prophylactic regimens without a control group.
Martinez-Pellus 1993	The study included a selected population of cardio-surgical patients.
Nardi 2001	The study tested the effectiveness of mupirocin, as both groups received SDD.
Oostdijk 2014	Comparison intervention not in the inclusion criteria (selective oropharyngeal decontamination)
Oudhuis 2011	Comparison intervention not in the inclusion criteria (probiotics)
Rayes 2002	The study included only liver transplant patients.
Rios 2005	Data available only from other published meta-analyses; not possible to retrieve data from the original study.
Rolando 1996	The study included a selected population of patients with acute hepatic failure.
Ruza 1998	The study included only paediatric burns patients.
Saidel-Odes 2012	Objective of the study was not to assess efficacy and safety of SDD on clinical outcomes.

Study	Reason for exclusion
Schardey 1997	The study included a selected population of patients undergoing gastric surgery and characterised by a low percentage of ICU admission.
Silvestri 2004	Both groups received topical prophylaxis.
Smith 1993	The study included only paediatric liver transplant patients.
Tetteroo 1990	The study included a selected population of patients undergoing oesophageal resection and characterised by a short length of stay in ICU.
Wittekamp 2018	Comparison intervention not in the inclusion criteria (selective oropharyngeal decontamination, chlorhexidine)
Yilmazlar 2009	Intervention not in the inclusion criteria: SDD for only 3 days
Zobel 1991	The study only included paediatric patients.
Zwaveling 2002	The study only included liver transplant patients.

ICU: intensive care unit
SDD: selective decontamination of the digestive tract

Characteristics of ongoing studies *[ordered by study ID]*

IRCT20180110038298N1

Study name	Effect of oropharyngeal decontamination by topical antibiotics on the ventilator-associated pneumonia
Methods	Randomised, double-blind, placebo-controlled trial
Participants	100 patients between 18 and 65 years admitted to the ICU. Performed intubation in the first 24 hours and stay at least 72 hours
Interventions	SOD versus no prophylaxis: 2% concentration of polymyxin, nystatin and neomycin, prepared and combined by investigator administered with a syringe on the oral cavity versus saline solution
Outcomes	Ventilator-dependent pneumonia
Starting date	2018
Contact information	
Notes	Country: Iran

NCT02389036

Study name	Selective Decontamination of the Digestive Tract in ICU Patients (SuDDICU)
Methods	Cluster-randomised controlled trial
Participants	10,000 patients predicted to remain ventilated beyond the end of the calendar day after the day first ventilated

NCT02389036 *(Continued)*

Interventions	SDD oral paste, SDD gastric suspension, intravenous antibiotic versus standard care
Outcomes	All-cause mortality at time of hospital discharge
Starting date	2017
Contact information	jmyburgh@georgeinstitute.org.au
Notes	Country: Australia

ICU: intensive care unit
SDD: selective decontamination of the digestive tract
SOD: selective oropharyngeal decontamination

DATA AND ANALYSES

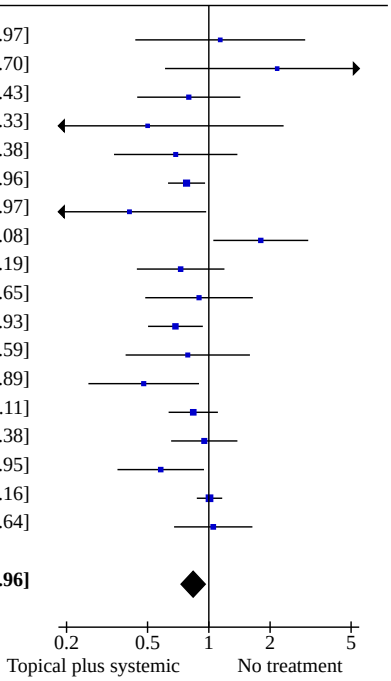
Comparison 1. Topical plus systemic prophylaxis versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall mortality	18	5290	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.73, 0.96]
1.2 Respiratory tract infections	17	2951	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.35, 0.53]
1.3 Dropouts due to adverse events	4	1287	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.30, 3.76]
1.4 Gastrointestinal adverse events	6	2637	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.57, 2.04]
1.5 Allergic adverse events	6	2981	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.09, 25.33]

Analysis 1.1. Comparison 1: Topical plus systemic prophylaxis versus placebo or no treatment, Outcome 1: Overall mortality

Study or Subgroup	Favours treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abele-Horn 1997	11	58	5	30	1.8%	1.14 [0.44 , 2.97]
Aerdts 1991	4	18	4	39	1.1%	2.17 [0.61 , 7.70]
Blair 1991	17	126	22	130	4.2%	0.80 [0.44 , 1.43]
Boland 1991	2	15	4	15	0.8%	0.50 [0.11 , 2.33]
Cockerill 1992	11	75	16	75	3.1%	0.69 [0.34 , 1.38]
de Jonge 2003	113	466	146	468	12.5%	0.78 [0.63 , 0.96]
de la Cal 2005	6	53	15	54	2.2%	0.41 [0.17 , 0.97]
Finch 1991	15	20	10	24	4.7%	1.80 [1.05 , 3.08]
Jacobs 1992	14	36	23	43	5.3%	0.73 [0.44 , 1.19]
Kerver 1988	14	49	15	47	3.9%	0.90 [0.49 , 1.65]
Krueger 2002	52	265	75	262	9.3%	0.69 [0.50 , 0.93]
Palomar 1997	10	41	13	42	3.1%	0.79 [0.39 , 1.59]
Rocha 1992	10	47	24	54	3.7%	0.48 [0.26 , 0.89]
Sanchez-Garcia 1998	51	131	65	140	10.2%	0.84 [0.63 , 1.11]
Stoutenbeek 2007	42	201	44	200	7.6%	0.95 [0.65 , 1.38]
Ulrich 1989	15	48	28	52	5.4%	0.58 [0.36 , 0.95]
de Smet 2009 (1)	258	805	249	783	14.9%	1.01 [0.87 , 1.16]
Verwaest 1997	34	193	31	185	6.2%	1.05 [0.68 , 1.64]
Total (95% CI)		**2647**		**2643**	**100.0%**	**0.84 [0.73 , 0.96]**
Total events:	679		789			

Heterogeneity: Tau² = 0.03; Chi² = 28.46, df = 17 (P = 0.04); I² = 40%
Test for overall effect: Z = 2.55 (P = 0.01)
Test for subgroup differences: Not applicable



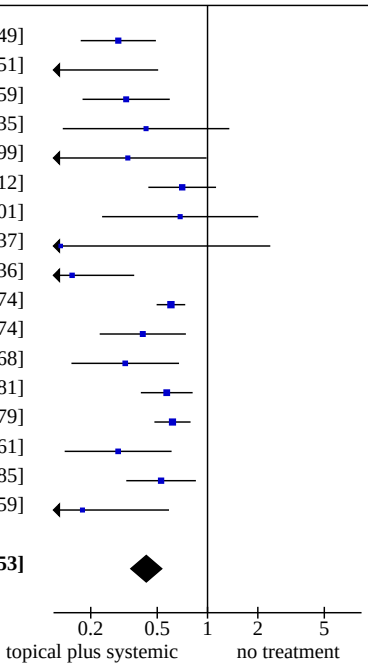
Footnotes

(1) We adjusted the sample size of the cluster-RCT by calculating the effective sample size according to #Section 23.1.4 of the Handbook

Analysis 1.2. Comparison 1: Topical plus systemic prophylaxis versus placebo or no treatment, Outcome 2: Respiratory tract infections

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abele-Horn 1997	13	58	23	30	7.7%	0.29 [0.17 , 0.49]
Aerdts 1991	1	18	29	39	1.1%	0.07 [0.01 , 0.51]
Blair 1991	12	126	38	130	6.6%	0.33 [0.18 , 0.59]
Boland 1991	3	15	7	15	2.8%	0.43 [0.14 , 1.35]
Cockerill 1992	4	75	12	75	3.0%	0.33 [0.11 , 0.99]
de la Cal 2005	18	53	26	54	8.4%	0.71 [0.44 , 1.12]
Finch 1991	4	20	7	24	3.1%	0.69 [0.23 , 2.01]
Jacobs 1992	0	36	4	43	0.5%	0.13 [0.01 , 2.37]
Kerver 1988	5	49	31	47	4.3%	0.15 [0.07 , 0.36]
Krueger 2002	91	265	149	262	12.6%	0.60 [0.50 , 0.74]
Palomar 1997	10	41	25	42	6.7%	0.41 [0.23 , 0.74]
Rocha 1992	7	47	25	54	5.2%	0.32 [0.15 , 0.68]
Sanchez-Garcia 1998	32	131	60	140	10.1%	0.57 [0.40 , 0.81]
Stoutenbeek 2007	62	201	100	200	11.9%	0.62 [0.48 , 0.79]
Ulrich 1989	7	48	26	52	5.2%	0.29 [0.14 , 0.61]
Verwaest 1997	22	193	40	185	8.2%	0.53 [0.33 , 0.85]
Winter 1992	3	91	17	92	2.6%	0.18 [0.05 , 0.59]
Total (95% CI)		**1467**		**1484**	**100.0%**	**0.43 [0.35 , 0.53]**
Total events:	294		619			

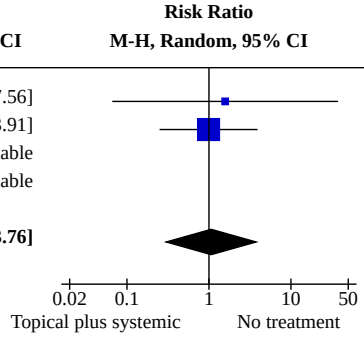
Heterogeneity: Tau² = 0.08; Chi² = 35.90, df = 16 (P = 0.003); I² = 55%
Test for overall effect: Z = 7.80 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Topical plus systemic prophylaxis versus placebo or no treatment, Outcome 3: Dropouts due to adverse events

Study or Subgroup	Topical plus systemic Events	Topical plus systemic Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Aerdts 1991	1	58	0	30	15.8%	1.58 [0.07 , 37.56]
Krueger 2002	4	265	4	262	84.2%	0.99 [0.25 , 3.91]
Sanchez-Garcia 1998	0	131	0	140		Not estimable
Stoutenbeek 2007	0	201	0	200		Not estimable
Total (95% CI)		**655**		**632**	**100.0%**	**1.06 [0.30 , 3.76]**
Total events:	5		4			

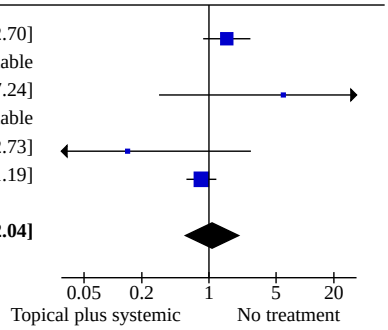
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Topical plus systemic prophylaxis versus placebo or no treatment, Outcome 4: Gastrointestinal adverse events

Study or Subgroup	Topical plus systemic Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cockerill 1992	23	75	15	75	40.8%	1.53 [0.87 , 2.70]
de Smet 2009 (1)	0	805	0	783		Not estimable
Finch 1991	2	20	0	24	4.2%	5.95 [0.30 , 117.24]
Sanchez-Garcia 1998	0	131	0	140		Not estimable
Stoutenbeek 2007	0	201	3	200	4.3%	0.14 [0.01 , 2.73]
Winter 1992	33	91	40	92	50.6%	0.83 [0.58 , 1.19]
Total (95% CI)		**1323**		**1314**	**100.0%**	**1.08 [0.57 , 2.04]**
Total events:	58		58			

Heterogeneity: Tau² = 0.18; Chi² = 6.24, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable

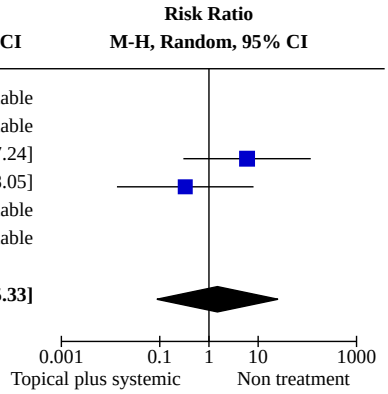


Footnotes
(1) We adjusted the sample size of the cluster-RCT by calculating the effective sample size according to #Section 23.1.4 of the Handbook

Analysis 1.5. Comparison 1: Topical plus systemic prophylaxis versus placebo or no treatment, Outcome 5: Allergic adverse events

Study or Subgroup	Topical plus systemic Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cockerill 1992	0	75	0	75		Not estimable
de Smet 2009 (1)	0	805	0	783		Not estimable
Finch 1991	2	20	0	24	52.1%	5.95 [0.30 , 117.24]
Krueger 2002	0	265	1	262	47.9%	0.33 [0.01 , 8.05]
Sanchez-Garcia 1998	0	131	0	140		Not estimable
Stoutenbeek 1996	0	201	0	200		Not estimable
Total (95% CI)		**1497**		**1484**	**100.0%**	**1.49 [0.09 , 25.33]**
Total events:	2		1			

Heterogeneity: Tau² = 1.71; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 0.27 (P = 0.78)
Test for subgroup differences: Not applicable



Footnotes
(1) We adjusted the sample size of the cluster-RCT by calculating the effective sample size according to #Section 23.1.4 of the Handbook

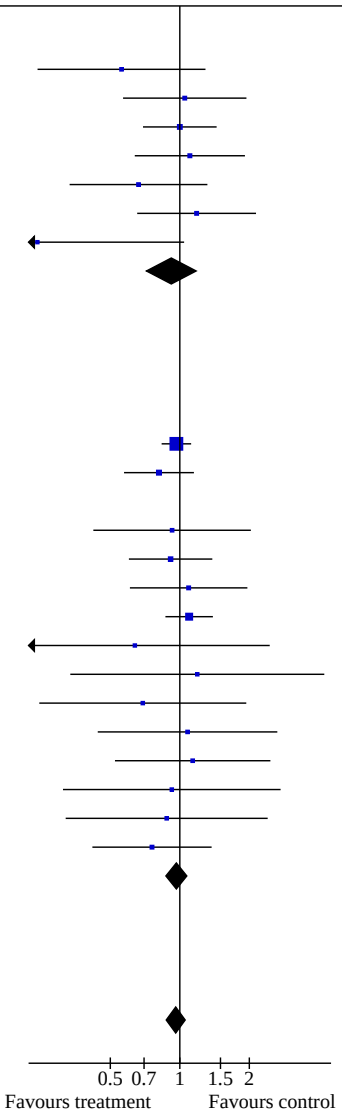
Comparison 2. Topical prophylaxis versus no topical prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Overall mortality	22	4213	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.05]
2.1.1 Topical plus systemic prophylaxis versus systemic prophylaxis alone	7	939	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.18]
2.1.2 Topical prophylaxis alone versus no treatment	15	3274	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Respiratory tract infections	19	2698	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.44, 0.74]
2.2.1 Topical plus systemic prophylaxis versus systemic prophylaxis alone	6	850	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.16]
2.2.2 Topical prophylaxis alone versus no treatment	13	1848	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.36, 0.69]
2.3 Dropouts due to adverse events	7	1323	Risk Ratio (M-H, Random, 95% CI)	2.20 [0.57, 8.54]
2.4 Gastrointestinal adverse events	3	1859	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.26, 29.50]
2.5 Allergic adverse events	5	2357	Risk Ratio (M-H, Random, 95% CI)	2.64 [0.34, 20.69]

Analysis 2.1. Comparison 2: Topical prophylaxis versus no topical prophylaxis, Outcome 1: Overall mortality

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Topical plus systemic prophylaxis versus systemic prophylaxis alone						
Chaari 2014	8	31	6	13	1.3%	0.56 [0.24 , 1.29]
Ferrer 1994	15	51	14	50	2.3%	1.05 [0.57 , 1.94]
Gaussorgues 1991	29	59	29	59	6.6%	1.00 [0.69 , 1.44]
Hammond 1992	21	114	21	126	2.9%	1.11 [0.64 , 1.91]
Laggner 1994	9	33	14	34	1.9%	0.66 [0.33 , 1.32]
Lingnau 1997	22	162	17	148	2.5%	1.18 [0.65 , 2.14]
Stoutenbeek 1996	2	30	8	29	0.4%	0.24 [0.06 , 1.04]
Subtotal (95% CI)		**480**		**459**	**18.0%**	**0.92 [0.72 , 1.18]**
Total events:	106		109			
Heterogeneity: Tau² = 0.02; Chi² = 6.93, df = 6 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.67 (P = 0.50)						
2.1.2 Topical prophylaxis alone versus no treatment						
de Smet 2009 (1)	235	765	254	799	41.0%	0.97 [0.83 , 1.12]
Bergmans 2001	30	87	59	139	7.3%	0.81 [0.57 , 1.15]
Beshey 2014	0	50	0	25		Not estimable
Brun-Buisson 1989	8	36	12	50	1.4%	0.93 [0.42 , 2.03]
Camus 2005	32	130	34	126	5.1%	0.91 [0.60 , 1.38]
Cerra 1992	13	25	10	21	2.6%	1.09 [0.61 , 1.96]
Gastinne 1992	88	220	82	225	15.9%	1.10 [0.87 , 1.39]
Georges 1994	3	31	5	33	0.5%	0.64 [0.17 , 2.45]
Korinek 1993	5	63	4	60	0.6%	1.19 [0.34 , 4.22]
Pneumatikos 2002	5	31	7	30	0.8%	0.69 [0.25 , 1.94]
Pugin 1991	7	25	7	27	1.1%	1.08 [0.44 , 2.64]
Quinio 1995	12	76	10	72	1.5%	1.14 [0.52 , 2.47]
Rodriguez-Roldan 1990	4	13	5	15	0.8%	0.92 [0.31 , 2.73]
Unertl 1987	5	19	6	20	0.9%	0.88 [0.32 , 2.40]
Wiener 1995	11	30	15	31	2.5%	0.76 [0.42 , 1.37]
Subtotal (95% CI)		**1601**		**1673**	**82.0%**	**0.97 [0.87 , 1.07]**
Total events:	458		510			
Heterogeneity: Tau² = 0.00; Chi² = 4.11, df = 13 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**2081**		**2132**	**100.0%**	**0.96 [0.87 , 1.05]**
Total events:	564		619			
Heterogeneity: Tau² = 0.00; Chi² = 11.12, df = 20 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.85 (P = 0.39)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%						

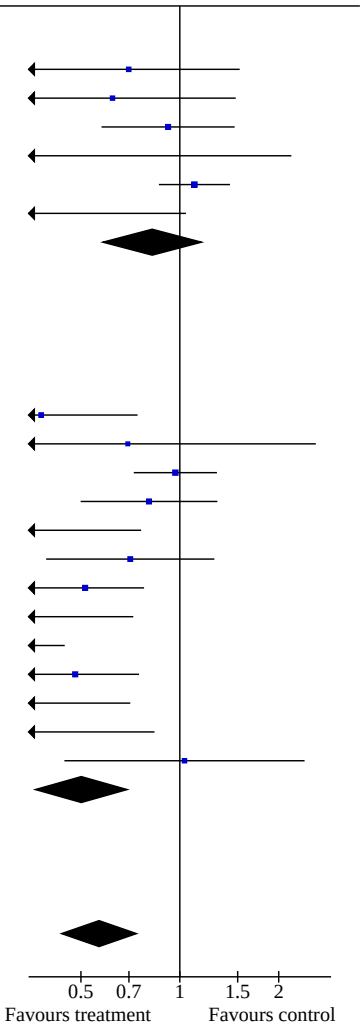


Footnotes

(1) We adjusted the sample size of the cluster-RCT by calculating the effective sample size according to #Section 23.1.4 of the Handbook

Analysis 2.2. Comparison 2: Topical prophylaxis versus no topical prophylaxis, Outcome 2: Respiratory tract infections

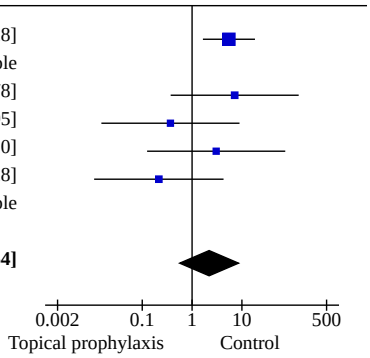
Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Topical plus systemic prophylaxis versus systemic prophylaxis alone						
Chaari 2014	10	31	6	13	5.3%	0.70 [0.32 , 1.52]
Ferrer 1994	7	51	11	50	4.8%	0.62 [0.26 , 1.48]
Hammond 1992	25	114	30	126	7.6%	0.92 [0.58 , 1.47]
Laggner 1994	1	33	4	34	1.3%	0.26 [0.03 , 2.19]
Lingnau 1997	72	162	71	177	9.2%	1.11 [0.86 , 1.42]
Stoutenbeek 1996	2	30	8	29	2.4%	0.24 [0.06 , 1.04]
Subtotal (95% CI)		**421**		**429**	**30.7%**	**0.82 [0.58 , 1.16]**
Total events:	117		130			
Heterogeneity: Tau² = 0.06; Chi² = 8.00, df = 5 (P = 0.16); I² = 38%						
Test for overall effect: Z = 1.10 (P = 0.27)						
2.2.2 Topical prophylaxis alone versus no treatment						
Bergmans 2001	9	87	38	139	6.0%	0.38 [0.19 , 0.74]
Brun-Buisson 1989	3	36	6	50	2.8%	0.69 [0.19 , 2.59]
Camus 2005	53	130	53	126	8.9%	0.97 [0.72 , 1.30]
Gastinne 1992	26	220	33	225	7.5%	0.81 [0.50 , 1.30]
Georges 1994	4	31	15	33	4.1%	0.28 [0.11 , 0.76]
Koeman 2006	16	128	23	130	6.7%	0.71 [0.39 , 1.27]
Korinek 1993	20	63	37	60	8.0%	0.51 [0.34 , 0.78]
Pneumatikos 2002	5	31	16	30	4.8%	0.30 [0.13 , 0.72]
Pugin 1991	4	25	24	27	4.6%	0.18 [0.07 , 0.45]
Quinio 1995	19	76	38	73	7.8%	0.48 [0.31 , 0.75]
Rodriguez-Roldan 1990	1	13	11	15	1.6%	0.10 [0.02 , 0.71]
Unertl 1987	1	19	9	20	1.5%	0.12 [0.02 , 0.84]
Wiener 1995	8	30	8	31	4.9%	1.03 [0.45 , 2.40]
Subtotal (95% CI)		**889**		**959**	**69.3%**	**0.50 [0.36 , 0.69]**
Total events:	169		311			
Heterogeneity: Tau² = 0.19; Chi² = 35.26, df = 12 (P = 0.0004); I² = 66%						
Test for overall effect: Z = 4.21 (P < 0.0001)						
Total (95% CI)		**1310**		**1388**	**100.0%**	**0.57 [0.44 , 0.74]**
Total events:	286		441			
Heterogeneity: Tau² = 0.18; Chi² = 55.08, df = 18 (P < 0.0001); I² = 67%						
Test for overall effect: Z = 4.23 (P < 0.0001)						
Test for subgroup differences: Chi² = 4.26, df = 1 (P = 0.04), I² = 76.5%						



Analysis 2.3. Comparison 2: Topical prophylaxis versus no topical prophylaxis, Outcome 3: Dropouts due to adverse events

Study or Subgroup	Topical prophylaxis Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Camus 2005	17	130	3	126	41.1%	5.49 [1.65 , 18.28]
Chaari 2014	0	31	0	13		Not estimable
Gastinne 1992	3	220	0	225	15.6%	7.16 [0.37 , 137.78]
Hammond 1992	0	114	1	126	13.9%	0.37 [0.02 , 8.95]
Koeman 2006	1	128	0	130	13.9%	3.05 [0.13 , 74.10]
Pugin 1991	0	25	2	27	15.4%	0.22 [0.01 , 4.28]
Rodriguez-Roldan 1990	0	13	0	15		Not estimable
Total (95% CI)		**661**		**662**	**100.0%**	**2.20 [0.57 , 8.54]**
Total events:	21		6			

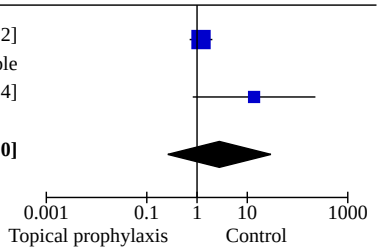
Heterogeneity: Tau² = 0.79; Chi² = 5.96, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 1.14 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Topical prophylaxis versus no topical prophylaxis, Outcome 4: Gastrointestinal adverse events

Study or Subgroup	Topical prophylaxis Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Camus 2005	26	130	21	126	65.5%	1.20 [0.71 , 2.02]
de Smet 2009 (1)	0	765	0	799		Not estimable
Unertl 1987	6	19	0	20	34.5%	13.65 [0.82 , 226.84]
Total (95% CI)		**914**		**945**	**100.0%**	**2.78 [0.26 , 29.50]**
Total events:	32		21			

Heterogeneity: Tau² = 2.15; Chi² = 3.02, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Not applicable



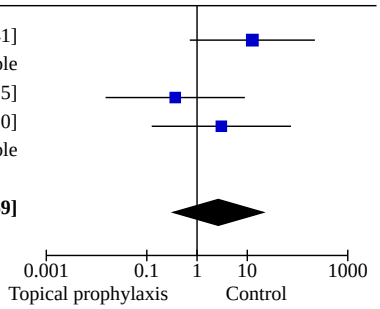
Footnotes

(1) We adjusted the sample size of the cluster-RCT by calculating the effective sample size according to #Section 23.1.4 of the Handbook

Analysis 2.5. Comparison 2: Topical prophylaxis versus no topical prophylaxis, Outcome 5: Allergic adverse events

Study or Subgroup	Topical prophylaxis Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Camus 2005	6	130	0	126	36.9%	12.60 [0.72 , 221.41]
de Smet 2009 (1)	0	765	0	799		Not estimable
Hammond 1992	0	114	1	126	31.5%	0.37 [0.02 , 8.95]
Koeman 2006	1	128	0	130	31.5%	3.05 [0.13 , 74.10]
Unertl 1987	0	19	0	20		Not estimable
Total (95% CI)		**1156**		**1201**	**100.0%**	**2.64 [0.34 , 20.69]**
Total events:	7		1			

Heterogeneity: Tau² = 0.84; Chi² = 2.68, df = 2 (P = 0.26); I² = 25%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable



Footnotes

(1) We adjusted the sample size of the cluster-RCT by calculating the effective sample size according to #Section 23.1.4 of the Handbook

APPENDICES

Appendix 1. Cochrane Library search strategy

#1 (“critical care” OR “intensive care” OR “burn unit” OR “burn units” OR “care unit” OR “care units” OR “recovery room” OR “recovery rooms” OR "critical illness" OR "mechanical ventilation" OR ventilator* OR "artificial respiration" OR respirator*):ti,ab 77406

#2 ("respiratory tract infection" OR "respiratory tract infections" OR pneumon* OR HAP OR VAP OR bronchopneumonia* OR pleuropneumonia* OR pharyngit* OR tracheit*):ti,ab 17417

#3 #1 and #2 8366

#4 'ventilator associated pneumonia':ti,ab 1410

#5 #3 or #4 8383

#6 antibiotic*:ti,ab 26080

#7 #5 and #6 1746

#8 "accession number" near pubmed 664007

#9 "accession number" near embase 538901

#10 #8 or #9 1001070

#11 #7 not #10 with Publication Year from 2012 to 2020, in Trials

Appendix 2. MEDLINE (PubMed) search strategy

#1 Search: "Intensive Care Units"[Mesh]) OR “critical care”[Title/Abstract] OR “intensive care”[Title/Abstract] OR “burn unit”[Title/Abstract] OR “burn units”[Title/Abstract] OR “care unit”[Title/Abstract] OR “care units”[Title/Abstract] OR “recovery room”[Title/Abstract] OR “recovery rooms”[Title/Abstract] OR "Critical Illness"[Mesh]) OR "critical illness"[Title/Abstract]) OR "Ventilators, Mechanical"[Mesh]) OR "mechanical ventilation”[Title/Abstract] OR ventilator*[Title/Abstract] OR "Respiration, Artificial"[Mesh]) OR "artificial respiration"[Title/Abstract] OR respirator*[Title/Abstract]

#2 Search: "Respiratory Tract Infections"[Mesh]) OR "respiratory tract infection"[Title/Abstract] OR "respiratory tract infections"[Title/Abstract] OR "Pneumonia"[Mesh]) OR pneumon*[Title/Abstract] OR HAP[Title/Abstract] OR VAP[Title/Abstract] OR bronchopneumonia*[Title/Abstract] OR pleuropneumonia*[Title/Abstract] OR "Pharyngitis"[Mesh]) OR pharyngit*[Title/Abstract] OR tracheit*[Title/Abstract]

#3 Search: #1 AND #2

#4 Search: "Pneumonia, Ventilator-Associated"[Mesh]

#5 Search: #3 OR #4

#6 Search: "Antibiotic Prophylaxis"[Mesh] OR "Anti-Bacterial Agents"[Mesh] OR antibiotic*[Title/Abstract])

#7 Search: #5 AND #6

#8 Search: #7 AND ("random*"[Title/Abstract] OR "placebo"[Title/Abstract] OR "trial*"[Title] OR "Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type])

#9 Search: ("2012/01/01"[Date - Entry]: "2020/05/21"[Date - Entry]

#10 Search: #8 AND #9

Appendix 3. Embase (Elsevier) search strategy

No.	Query
#23	#20 AND #21 AND [1-1-2012]/sd NOT [21-5-2020]/sd
#22	#20 AND #21
#21	[embase]/lim NOT [medline]/lim
#20	#16 AND #19
#19	#17 OR #18
#18	random*:ti,ab OR placebo*:ti,ab OR factorial*:ti,ab OR crossover*:ti,ab OR assign*:ti,ab OR allocat*:ti,ab OR volunteer*:ti,ab OR 'double blind':ti,ab OR 'double blinding':ti,ab OR 'double blinded':ti,ab OR 'single blind':ti,ab OR 'single blinded':ti,ab OR 'single blinding':ti,ab
#17	'crossover procedure'/exp OR 'single blind procedure'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp
#16	#14 AND #15
#15	'antibiotic prophylaxis'/exp OR 'antibiotic agent'/exp OR antibiotic*:ti,ab
#14	#12 OR #13
#13	'ventilator associated pneumonia'/exp OR 'ventilator associated pneumonia':ti,ab
#12	#6 AND #11
#11	#7 OR #8 OR #9 OR #10
#10	'artificial ventilation'/exp OR respirator*:ti,ab
#9	'ventilator'/exp OR ventilator*:ti,ab
#8	'critical illness'/exp OR 'critically ill':ti,ab OR 'critical illness':ti,ab
#7	'intensive care unit'/exp OR icu:ti,ab OR 'critical care':ti,ab OR 'intensive care':ti,ab OR 'burn unit':ti,ab OR 'burn units':ti,ab OR 'care unit':ti,ab OR 'care units':ti,ab OR 'recovery room':ti,ab OR 'recovery rooms':ti,ab

(Continued)

#6	#1 OR #2 OR #3 OR #4 OR #5
#5	'tracheitis'/exp OR tracheit*:ti,ab
#4	bronchit*:ti,ab OR bronchiolit*:ti,ab OR pharyngit*:ti,ab
#3	pneumon*:ti,ab OR hap:ti,ab OR vap:ti,ab OR bronchopneumonia*:ti,ab OR pleuropneumonia*:ti,ab
#2	'respiratory tract infection':ti,ab OR 'respiratory tract infections':ti,ab
#1	'respiratory tract infection'/exp OR 'bronchitis'/exp OR 'pharyngitis'/exp OR 'pneumonia'/exp

Appendix 4. Details of previous searches

MEDLINE was searched using the following search strategy in conjunction with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). The same strategy was used to search CENTRAL and adapted to search EMBASE.com. There were no language or publication restrictions.

MEDLINE (Ovid) search strategy

1 exp Respiratory Tract Infections/
2 respiratory tract infection*.tw.
3 exp Pneumonia/
4 pneumon*.tw.
5 (HAP or VAP).tw.
6 bronchopneumonia*.tw.
7 pleuropneumonia*.tw.
8 exp Bronchitis/
9 bronchit*.tw.
10 bronchiolit*.tw.
11 exp Pharyngitis/
12 pharyngit*.tw.
13 Tracheitis/
14 tracheit*.tw.
15 or/1-14
16 exp Intensive Care Units/
17 icu.tw.
18 exp Critical Care/
19 critical care.tw.
20 intensive care.tw.
21 burn unit*.tw.
22 care unit*.tw.
23 recovery room*.tw.
24 Critical Illness/
25 (critic* adj ill*).tw.
26 exp Ventilators, Mechanical/
27 mechanical ventilat*.tw.
28 ventilator*.tw.
29 Respiration, Artificial/
30 artificial respiration*.tw.
31 respirator*.tw.
32 or/16-31
33 15 and 32
34 Pneumonia, Ventilator-Associated/
35 33 or 34
36 Antibiotic Prophylaxis/
37 exp Anti-Bacterial Agents/
38 antibiotic*.tw.

39 or/36-38
40 35 and 39

EMBASE (Elsevier) search strategy

1. 'respiratory tract infection'/exp
2. 'respiratory tract infection':ti,ab OR 'respiratory tract infections':ti,ab
3. 'pneumonia'/exp
4. pneumon*:ti,ab
5. hap:ti,ab OR vap:ti,ab
6. bronchopneumonia*:ti,ab OR pleuropneumonia*:ti,ab
7. 'bronchitis'/exp
8. bronchit*:ti,ab OR bronchiolit*:ti,ab
9. 'pharyngitis'/exp
10. pharyngit*:ti,ab
11. 'tracheitis'/exp
12. tracheit*:ti,ab
13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14. 'intensive care unit'/exp
15. icu:ti,ab OR 'critical care':ti,ab OR 'intensive care':ti,ab OR 'burn unit':ti,ab OR 'burn units':ti,ab OR 'care unit':ti,ab OR 'care units':ti,ab OR 'recovery room':ti,ab OR 'recovery rooms':ti,ab
16. 'critical illness'/exp
17. 'critically ill':ti,ab OR 'critical illness':ti,ab
18. 'ventilator'/exp
19. ventilator*:ti,ab
20. 'artificial ventilation'/exp
21. respirator*:ti,ab
22. #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR # 21
23. #13 AND #22
24. 'ventilator associated pneumonia'/exp
25. 'ventilator associated pneumonia':ti,ab
26. #24 OR #25
27. #23 OR #26
28. 'antibiotic prophylaxis'/exp
29. 'antibiotic agent'/exp
30. antibiotic*:ti,ab
31. #28 OR #29 OR #30
32. #27 AND #31
33. 'randomized controlled trial'/exp
34. 'controlled clinical trial'/exp
35. 'single blind procedure'/exp
36. 'crossover procedure'/exp
37. random*:ti,ab OR placebo*:ti,ab OR factorial*:ti,ab OR crossover*:ti,ab OR assign*:ti,ab OR allocat*:ti,ab OR volunteer*:ti,ab OR 'double blind':ti,ab OR 'double blinding':ti,ab OR 'double blinded':ti,ab OR 'single blind':ti,ab OR 'single blinded':ti,ab OR 'single blinding':ti,ab
38. #33 OR #34 OR #35 OR #36 OR #37
39. #32 AND #38

Appendix 5. Criteria for 'Risk of bias' assessment

Item	Judgement	Description
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation.
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention.

(Continued)

	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	High risk	Investigators enrolling participants could possibly have foreseen assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit a judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to permit a definitive judgement.
Blinding of participants and providers (performance bias)	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding. Blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel was attempted, but it is likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit a judgement of low or high risk
Blinding of outcome assessor (detection bias)	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but it is likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit a judgement of low or high risk
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data. Reasons for missing outcome data are unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). Missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups.

(Continued)

		For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) amongst missing outcomes is not enough to have a clinically relevant impact on observed effect size. Missing data have been imputed using appropriate methods. All randomised participants are reported/analysed in the group to which they were allocated by randomisation irrespective of non-compliance and co-interventions (intention-to-treat).
	High risk	Reason for missing outcome data is likely to be related to true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is enough to induce clinically relevant bias in intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) amongst missing outcomes is enough to induce clinically relevant bias in observed effect size. 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
	Unclear risk	Insufficient information to permit a judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts not reported for each group)
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way. The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
	High risk	Not all of the study's prespecified primary outcomes have been reported. One or more primary outcomes are reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified. One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect). One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis. The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear risk	Insufficient information to permit a judgement of low or high risk

WHAT'S NEW

Date	Event	Description
5 February 2020	New search has been performed	Searches conducted 5 February 2020.
5 February 2020	New citation required but conclusions have not changed	Two review authors have been removed from the byline (Alessandro Liberati and Walter Torri), and three review authors have been added (Silvia Minozzi, Valentina Pecoraro, and Giorgia Montrucchio). We changed the inclusion criteria to include cluster-randomised controlled trials. We added three outcomes: 'dropouts due to adverse events', 'gastrointestinal adverse events', and 'allergic adverse events'. We included two new trials (Beshey 2014; Chaari 2014), and two previously excluded trials (de la Cal 2005; de Smet 2009). We included one study that was missed in the last update (Koeman 2006). We excluded seven new trials (Camus 2011; Huang 2013; Oostdijk 2014; Oudhuis 2011; Rios 2005; Saidel-Odes 2012; Wittekamp 2018). We identified two ongoing studies (IRCT20180110038298N1; NCT02389036).

HISTORY

Review first published: Issue 3, 1997

Date	Event	Description
13 March 2009	New citation required but conclusions have not changed	One study was included in this update (Camus 2005). Two studies whose data were reported in congress proceedings (Lenhart 1994) and were unpublished (Stoutenbeek 2) have been replaced by Krueger 2002 and Stoutenbeek 2007, which are their published versions in peer-reviewed journals. One study (Jacobs 1995) included in the previous version of this review as a personal contact with the principal investigator, has been excluded due to lack of feedback from the trial author. To date, this study has not been published.
13 March 2009	New search has been performed	Searches conducted.
30 January 2008	Amended	Converted to new review format
5 September 2003	New search has been performed	Searches conducted. Updated review published Issue 4, 2002.
5 December 1999	New search has been performed	Searches conducted. Review published Issue 3, 1997.
5 December 1995	New search has been performed	Searches conducted. Updated review published Issue 1, 2004.

CONTRIBUTIONS OF AUTHORS

Roberto D'Amico prepared the protocol and review, oversaw the data collection and critical appraisal of studies, and prepared the final version of the manuscript.
Luca Brazzi collaborated on the preparation of the protocol.
Silvia Pifferi and Silvia Minozzi screened the articles and selected studies for inclusion. Luca Brazzi contributed to screening in the case of doubt or disagreement.
Luca Brazzi, Silvia Pifferi, and Giorgia Montrucchio wrote the Background and the Discussion.
Silvia Minozzi, Silvia Pifferi, and Valentina Pecoraro contributed to the data extraction.
Silvia Minozzi performed the statistical analyses.
Valentina Pecoraro and Silvia Minozzi completed the 'Risk of bias' assessment and the assessment of the certainty of the evidence.
All review authors contributed to writing and revising the final report.

DECLARATIONS OF INTEREST

Silvia Minozzi: none known.
Silvia Pifferi: none known.
Luca Brazzi has been member of the advisory Board of the Prodigy trial sponsored by Medtronic.
Valentina Pecoraro: none known.
Giorgia Montrucchio: none known.
Roberto D'Amico: none known.

SOURCES OF SUPPORT

Internal sources

- Italian Cochrane Centre, Italy

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We modified the title to better reflect the topic of the review from 'Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care' to 'Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation'.

We changed the inclusion criteria to include cluster-randomised controlled trials. We checked included and excluded trials from previous versions of the review to verify the adherence of the inclusion and exclusion criteria.

We assessed risk of bias of the included studies using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We amended the Methods section to comply with Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards.

We added the outcomes dropouts due to adverse events, gastrointestinal adverse events, and allergic adverse events, as adverse events of a pharmacologic treatment are relevant outcomes.

We also included cluster-RCTs as they provide useful data to the question addressed in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Anti-Bacterial Agents [*administration & dosage] [adverse effects]; Antibiotic Prophylaxis [adverse effects] [*methods]; Bias; Critical Care; Cross Infection [mortality] [prevention & control]; Hospital Mortality; Pneumonia, Ventilator-Associated [mortality] [*prevention & control]; Randomized Controlled Trials as Topic; Respiration, Artificial [*adverse effects]; Respiratory Tract Infections [mortality] [*prevention & control]

MeSH check words

Adult; Humans