

**Interventions to prevent the acquisition of resistant Gram-negative bacteria in critically ill patients-**

**A systematic review and meta-analysis**

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**Abstract**

**Interventions to prevent the acquisition of resistant Gram-negative bacteria in critically ill patients-  
A systematic review and meta-analysis**

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**Background:** The rising incidence of multidrug-resistant Gram negative bacterial infections acquired in intensive care units has prompted a variety of patient-level infection control efforts. However, there is yet no consensus on which measures are effective.

**Design:** Meta-analysis of studies to assess the efficacy of interventions in the prevention of colonization and infection with resistant Gram-negative bacteria in intensive care units.

**Methods:** PubMed, Cochrane, Embase and World of Science databases were searched. Interventional comparative studies were systematically analyzed.

**Results:** Comprehensive review of interventions with measureable outcomes resulted in 6 studies from a total of 631 potential studies meeting all inclusion criteria. 5 randomized and 1 observational interventional trial evaluating 6 patient-level interventions were quantitatively analyzed. 2 randomized studies lacked data on infection. Compared to control settings, the use of probiotics and selective digestive decontamination were associated with a significant reduction of colonization with multidrug-

resistant Gram negative bacteria (OR 0.39; 95%CI 0.16-0.95 and OR 0.54; 95%CI 0.38-0.77, respectively). No significant reduction in infection was observed by any patient-level intervention (pooled OR 1.24, 95% CI 0.94-1.64). Selective digestive decontamination was significantly associated with a reduction in intensive care unit mortality (OR 0.71; 95%CI 0.53-0.94).

**Conclusions:** Several interventions appear to be promising in reducing colonization but despite lower colonization rates associated with these efforts they did not translate to a reduction in hospital-acquired infections. Colonization may not be the only predecessor of infection in intensive care units. The use of probiotics and selective decontamination of the digestive tract should be studied in large randomized controlled trials.

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## Introduction

Antimicrobial resistance is an ever-growing problem in intensive care units. The number of Gram-negative bacteria resistant to one or more antibiotics is on the rise. For example, between 1986 and 2003, the proportion of *Enterobacteriaceae* resistant to third generation cephalosporins has increased by more than tenfold; resistant *Klebsiella Pneumoniae* and *Escherichia Coli* have increased by two fold [1]. The rate of antibiotic resistance has increased from 4% in 1986 to 7% in 2003 for *Pseudomonas Aeruginosa* [2] and *Acinetobacter* species [1]. Multidrug resistant Gram-negative bacteria (MDR-GNB) are responsible for a wide variety of infections encountered in the intensive care unit (ICU) such as ventilator-associated pneumonia (VAP), urinary tract infection (UTI), and vascular catheter-related infection (CRI).

Infection with MDR-GNB is associated with increased mortality [3], length of stay, and hospital costs [4]. In an attempt to prevent the transmission of drug resistant bacteria [5], the Center for Disease Control (CDC) and the Association of Professionals in Infection Control and Epidemiology (APICE) [6] have published guidelines that comprise hospital and ICU-based infection control strategies such as hand hygiene, and standard and contact precautions. However, several barriers impede the effectiveness of these measures for MDR-GNB:

- the continually changing pattern of antimicrobial resistance [7]
- the lack of sensitive and rapid laboratory tests to detect antimicrobial resistance [8]
- ongoing debate on which patient populations require the initiation of routine surveillance cultures and preventive infection control measures [9]
- the duration and number of negative cultures that should be obtained prior to termination of contact precautions [5]
- the debate about whether asymptomatic colonized patients should receive treatment (decolonization) [5]

The challenges in implementation of generalized infection control measures to prevent the transmission of MDR-GNB have fueled researchers to investigate complementary interventions targeting the prevention of specific infections. These patient-level interventions include pharmacologic and non-pharmacologic measures that target sites in the body that can act as a reservoir for bacterial colonization and infection. It is theorized that the implementation of patient-level interventions to prevent MDR-GNB colonization will be associated with a resultant reduction of infections. However, these interventions have only been studied in small underpowered studies with mixed results. For example, one study found that while administering prophylactic oral and parental antibiotics (also termed “selective digestive decontamination”(SDD)) was proven to be effective in eradication of colonization [10], another study [11] found employment of SDD ineffective in eradicating enteric MDR-GNB colonization, with an increase in the incidence of Gram-positive bacterial infections and a substantial increase in ICU costs.

This systematic review and meta-analysis has two objectives: First, to assess the range of patient-level interventions, beyond universal precautions, that have been evaluated for their effectiveness in reducing colonization. Second, to explore whether these interventions, targeted at reducing colonization, reduce downstream infections with MDR-GNB. The overall goal is to prioritize which patient-level interventions should be evaluated more extensively and implemented more broadly.

## Materials and methods

### Search Strategy:

We searched PubMed, EMBASE, World of Science, and Cochrane databases covering the time period from January 1, 2000 to April 14, 2010, using the following key words: '*Gram- negative bacteria*', AND '*intensive care unit*', AND '*adult*', AND either of '*multi-drug resistant*', OR '*drug resistant*'. These key words were combined with each of the following: '*colonization*', OR '*surveillance cultures*', OR '*hospital-acquired infection*', OR '*ventilator-associated pneumonia*', OR '*urinary tract infection*', OR '*soft tissue infection*', OR '*abdominal infection*', OR '*catheter-related blood stream infection*'. Searches included literature written in English, Spanish, Italian, and French.

### Study selection:

**Study population:** We included studies that had collected original data on adults in the ICU. We excluded animal studies and studies whose subjects were less than the age of 18 years, pregnant, or immunocompromised.

**Study design:** We included studies that reported details about MDR-GNB, including information about the site of colonization; method of diagnosis of infection; the name, number and method of detection of resistance to antibiotics; and the type of bacteria isolated from colonization or infection sites. We restricted the review to studies reporting on an intervention to prevent colonization or infection and those with appropriate comparison groups. Case reports, case series, abstracts from scientific meetings, and reviews were excluded.

### Data extraction:

Two authors screened titles (AZ, MT) and abstracts of all reports. All abstracts that did not explicitly meet our pre-defined inclusion criteria were excluded. Full text articles were then retrieved and the same authors scrutinized the retrieved reports to ensure all inclusion criteria were met. A final set of articles

was determined. Discrepancies were resolved by discussion among all authors to reach a consensus. Key information from each study was abstracted using a priori defined criteria in a systematic approach. Because studies often reported on multiple antibiotic resistant bacteria, we considered combined counts of subjects reported as colonized or infected with MDR-GNB along with subjects colonized or infected with other drug-resistant bacteria. Because studies reported various definitions of antibiotic resistance, such as Minimum Inhibitory Concentration (MIC) measured in the lab, we resorted to a study's original definition of antibiotic resistance. Because definitions were not standardized, we combined any report of colonization or infection based on the original study's definition. The term 'acquisition' was considered synonymous of 'colonization'. The number of patients included in the analysis was recorded. If the study reported the number of patients analyzed but did not report the number of patients originally enrolled, we assumed the study used an intent-to-treat approach and considered the reported number of patients in the analysis as corresponding to the number originally enrolled.

**Data collection:**

We attempted to describe as much patient information as possible across the studies including: average age and age range of study participants, gender, type of ICU population (medical versus surgical), colonization or infection site, type of pathogen, length of ICU stay, duration of mechanical ventilation, disease severity score, mortality, number and types of antibiotics, and frequency of use of vasoactive drugs.

**Definition of endpoints:**

The primary colonization endpoint was new acquisition of MDR-GNB. Colonization was defined as the isolation of MDR-GNB from the respiratory, gastrointestinal, urinary tracts, nose, rectum, intravascular catheters or urinary catheters in the absence of signs and symptoms of infection.

The secondary endpoint was progression to infection with MDR-GNB. This endpoint was defined as any event of VAP, catheter-related blood stream infection, UTI, abdominal infection, or soft tissue infection where the causative pathogens were MDR-GNB. When the original authors classified infections as “possible”, “probable” or “definitive”, only the latter two were considered as infections events.

#### **Internal validity of randomized trials:**

For randomized studies, we used the Jadad scale [12] to rate the quality of the study by examining details of randomization, generation of random numbers, the presence and appropriateness of double blinding procedure, information on withdrawals, and concealment of allocation [12]. This scale assigns one point for each of the above criteria: the maximum score is 5 [12].

#### **Pooled data analysis:**

We also explored the pooled effects of interventions in order to evaluate whether there was an effect on infection with MDR-GNB. The intent of this analysis was to account for the small size of many studies which were underpowered to evaluate whether reductions in colonization led to reductions in infection. Meta-analyses were performed using STATA version 12.1 (STATA Corp, College Station, TX). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using both the Mantel-Haenszel [13] fixed effects approach and the DerSimonian-Laird random effects model [14]. Three pooled analyses were conducted: one with colonization as the main endpoint, a second with an analysis with progression to infection as the endpoint, and a third combining studies that reported mortality differences between intervention and control groups. The heterogeneity in effect across studies was assessed using the chi-square test: a  $p$  value lower than 0.10 was defined to denote statistical significance in the analysis of heterogeneity. The reported odds ratios of the analyzed studies were weighted by the inverse of their variance.

## Results

### Search results:

The initial literature search identified 631 potential articles: 469 studies were excluded because they either did not contain an appropriate control group, did not measure outcomes associated with MDR-GNB, were conducted in a non-ICU setting, or lacked data on antibiotic resistance. We gathered this information from study abstracts and are confident that the missing information was not to be included in any further detail in full texts of these articles. Full text articles were retrieved for 162 studies. Of these, 155 (95.7%) did not meet inclusion criteria leaving 7 studies included in the final analysis. One study [15] appeared to meet the inclusion criteria; however, the results were reported as colonization and infection rates without details about the number of patients colonized or infected. Lack of information about study size variability interfered with calculation of pooled ORs and CIs. Additional data was requested from the primary author but was not available for this review. The reasons studies were excluded are described in Figure 1. Primary reasons for exclusion included lack of an appropriate comparison group, no report of colonization or infection endpoints, and missing patient information. The studies meeting all inclusion criteria included 6 randomized controlled trials: De Jonge [16], Forestier [17], Heyland [18], Oudhuis [19], and Topeli [20], et al, and one comparative observational study by Warren et al [21].

In assessing the quality of these studies, only the study by Forestier et al met all five Jadad criteria [12]. The studies by Heyland, Topeli, and De Jonge, et al received a Jadad score of 3 for lack of blinding. The study by Oudhuis et al was assigned a score of 2 for lack of blinding and early termination.

### Patient-level interventions:

These studies examined five types of patient-level interventions designed to prevent infection with MDR-GNB, all of which were implemented in addition to standard hospital-based infection control practices (Table 1). These five types included: closed endotracheal tube (ETT) suction for mechanically ventilated patients, empiric double antibiotic coverage for suspected late VAP, selective digestive decontamination

(SDD), administration of probiotics, and introduction of antibiotic cycling to prevent infection with MDR-GNB. Except for the study by Topeli et al which was conducted in a medical ICU, all other interventions were carried out in a combined medical/surgical ICU setting. MDR-GNB species most frequently studied were: *Pseudomonas Aeruginosa*, *Acinetobacter species* and *Enterobacteriaceae* (Table1). The studies by Heyland et al and De jonge et al only reported colonization as the study endpoint. The other studies reported both colonization and infections as endpoints, including VAP, UTI, CRI, and blood stream infections. Antibiotics for which resistance was identified varied among studies and included 2 or more of the following antibiotic classes:  $\beta$ -lactams, cephalosporins, imipenems, and flouroquinolones.

### **Characteristics of patients across studies (Table 2):**

Information about the study populations is described in Table 2. Sample sizes varied from 78 intervention and control subjects in the study by Topeli et al [20] to 1172 patients in the study by Warren et al [21]. The mean age ranged from 59-64 years. All studies enrolled more males than females. Ethnic background was only reported by Warren et al. As expected of studies conducted in the ICU, all studies included populations with high average severity scores. These were usually measured by Acute Physiology and Chronic Health Evaluation II (APACHEII) score. Studies inconsistently reported hospital days prior to enrollment, and total ICU and hospital days. For example, only Topeli et al reported hospitalization time prior to enrollment (mean = 5.2 days). Both ICU and hospital lengths of stay were reported only by Oudhuis et al (mean = 16.5, and 37.6 days, respectively). Forestier et al and Warren et al only reported mean length of ICU stay (13.7, and 8.2 days, respectively). De jonge, Heyland, and Topeli, et al did not report on either ICU or hospital length of stay. The use of resuscitation drugs was only reported by De jonge et al. History of antibiotics was reported only by Forestier et al. Only Topeli et al and Heyland et al exclusively included patients on mechanical ventilation. The remaining studies enrolled a large percentage of patients on mechanical ventilation (> 90%). Type of ICU admission was reported only by De jonge et al and Topeli et al. The latter only reported on admissions from the emergency room.

Individual patient co-morbid conditions were reported by all studies except those by Topeli et al and Forestier et al. Chronic renal failure was the co-morbid condition most consistently reported.

Studies varied in how they reported comparisons of characteristics of their intervention and control groups. De jonge et al and Heyland et al reported no statistical data on the baseline demographic differences between groups. Oudhuis et al reported no significant differences in the baseline demographics of groups. Topeli et al reported the intervention group was significantly older ( $p = 0.05$ ) and suffered from more metabolic diseases ( $p < 0.01$ ) compared with the control group. Warren et al reported significantly higher number of cancer patients in the post-intervention group compared with the baseline group ( $p < 0.001$ ). Forestier et al reported lower male gender representation in the intervention group compared with the control group ( $p < 0.05$ ).

### **Primary end points:**

#### **Colonization with MDR-GNB:**

All six studies reported the effect of their patient-level interventions on the incidence of colonization, with two studies (De jonge et al and Forestier et al) observing reductions in the incidence of colonization in the ICU population and four studies (Topeli, Heyland, Warren, and Oudhuis) finding no difference in incidence of colonization between the study groups (Table1). De jonge et al found SDD significantly reduced the incidence of colonization compared to the placebo group (relative risk, RR 0.61; 95% CI 0.46–0.81). Investigating the use of probiotics, Forestier et al found a significant reduction in the rate of gastric and respiratory colonization in the probiotics group compared with the placebo group ( $p < 0.05$ ). Examining closed (intervention) versus open ETT suction, Topeli et al found a significant increase in the rates of colonization by *Acinetobacter* and *Pseudomonas species* in the closed ETT suction group compared with the open suction group ( $p < 0.01$ , and  $p = 0.04$ , respectively). Examining the effects of double antibiotic coverage for suspected late VAP compared with monotherapy, Heyland et al found sputum colonization by MDR-GNB did not significantly differ between the intervention group and the

control group (RR 0.6; 95% CI 0.24-0.1). Interestingly, in a subgroup of 56 patients who were colonized at enrollment, there was a significant microbiological eradication (64.1% vs. 29.4%,  $P = 0.05$ ) in the combination therapy group compared with the monotherapy group. Using a comparative observational study of antibiotic cycling, Warren et al did not observe a significant difference in the enteric acquisition of *Pseudomonas species* (relative rate 0.96; 95% CI 0.47–2.16) and *Enterobacteriaceae* (relative rate 1.57; 95% CI 0.80 –3.43).

Three studies reported percent of patients colonized by MDR-GNB at enrollment: Warren (5%), De Jonge (9%), and Heyland (39%).

Sites of colonization and sampling were consistent among the 6 studies and included rectal, sputum, and urine with varying sampling frequency schemes. De Jonge, Heyland and Oudhuis, et al reported on Gram-positive resistant bacteria as well as MDR-GNB; the other studies [17, 20, 21] only reported colonization by MDR-GNB. Follow up cultures after baseline sampling were available on 733 out of 934 patients (De Jonge et al), 137 out of 254 patients (Oudhuis et al), and 42 out of 78 patients (Topeli et al). The remaining studies [17, 18, 21] did not report this information.

The results from pooled analysis are shown in Figure 2. The pooled effect size for all interventions combined did not show a reduction of colonization (pooled OR 0.86, 95% CI: (0.72-1.02)). In a secondary analysis that was restricted to RCTs only [16-20], the estimates showed a statistically significant effect of all intervention on reduction of MDR-GNB colonization (pooled OR 0.71; 95% CI: 0.58-0.88). Pooled analysis showed statistical heterogeneity (chi-squared = 18.29; d.f. = 5;  $p = 0.003$ ).

### **Infection with MDR-GNB:**

Four studies (Forestier [17], Oudhuis [19], Topeli [20], and Heyland [18]) reported the results of the patient-level interventions on the incidence of infection in the ICU populations (Figure 1). All four studies looked at the incidence of VAP, with Oudhuis et al [19] also examining UTI, CRI, and wound infections;

and Warren et al [21] examining blood stream infections in addition to VAP. None of the studies observed the expected decreases in the incidence of infection associated with the individual interventions: only the study by Forestier et al [17] reported a trend towards negative association suggesting that the intervention potentially decreased the incidence of infection. Three other studies (Topeli, Oudhuis, and Warren) showed positive associations suggesting the interventions potentially increased the incidence of infection, although the results were not significant for any individual study.

Forestier et al did not find a statistically significant difference in the incidence of VAP in the probiotics group compared with placebo despite a decrease in the rate of colonization of the respiratory tract (statistical data not reported). Topeli et al used development of VAP as the primary endpoint: there was no significant difference between closed and open ETT suction in the development of VAP ( $P = 0.47$ ). Using bivariate and multivariate analyses, sedation, rather than ETT suction type, was independently associated with VAP (OR 3.3; 95%CI 1-11.8). Oudhuis et al compared probiotics to SDD for the development of VAP, UTI, CRI, and wound infection. No significant differences in ICU-acquired infections were reported between the compared groups (OR 1.68; 95%CI: 0.91-3.08). The study was underpowered (370 patients were required to detect such differences). In addition, the study was prematurely terminated after the publication of other data [22] on increased mortality in patients with acute pancreatitis treated with probiotics. Warren et al compared a pre-antibiotic cycling period with a post- antibiotic cycling period for the development of VAP and blood stream infections. No significant differences were noted between periods ( $p = 0.15$ , and  $0.98$ , respectively).

Compared to controls, none of: probiotics (compared to placebo; OR 0.38; 95%CI 0.10-1.46, and to SDD; OR 1.39; 95%CI 0.8-2.42) and closed ETT suction (OR 1.44; 95%CI 0.53-3.92) were associated with a statistically significant reduction in the occurrence of infection by MDR-GNB (Figure 3). The pooled effect size of all interventions showed a lack of statistically significant effect on the relative odds of infection with MDR-GNB (pooled OR 1.24; 95%CI 0.94-1.64) that did not change after restricting the

analysis to RCTs (pooled OR 1.18; 95%CI: 0.76-1.85). Pooled analysis showed a statistical homogeneity (chi-squared = 3.27- d.f. = 3- p = 0.352).

### **Mortality**

Four studies (De jongs [16], Topeli [20], Heyland [18], and Warren [21]) reported the effect of their interventions on mortality outcomes including ICU, hospital, and overall 28-day mortality. De jongs et al [16] reported both ICU (OR 0.65; 95%CI 0.49–0.85) and hospital mortality (OR 0.78, 95%CI 0.63-0.96) were significantly lower in the SDD group compared with controls. In subgroup analyses, only mortality in patients admitted to the ICU for urgent causes remained statistically significant between both groups (OR 0.48; 95%CI 0.26-0.87). Topeli et al found ICU mortality rate was not significantly different (p = 0.87) between closed (65.9%) and open ETT suction (67.6%). This result was replicated using both bivariate and multivariate analyses. Heyland et al found no significant differences in mortality between combination and mono-empiric therapy for suspected late VAP (OR 1.05; 95%CI 0.78-1.42). Differences in mortality were not significantly altered by the diagnostic modality of VAP or by the time of acquisition of MDR-GNB. Warren et al found antibiotic cycling was not associated with a significant reduction in mortality compared with baseline antibiotic condition (p = 0.06). However, there was a trend towards an increase in mortality during the antibiotic cycling period (21%) compared with baseline (16%). Oudhuis et al reported that both ICU mortality (OR 0.99; 95%CI 0.51-1.92) and 28-day mortality (OR 1.31; 95%CI 0.68-2.53) were not significantly different between the probiotics group and the SDD group.

The overall effect of the 4 interventions combined did not show a significant effect on mortality (pooled OR 0.93; 95%CI 0.76-1.13). Pooled analysis showed a statistical heterogeneity (chi-squared = 8.79 -d.f. = 3- p = 0.032).

**Other Clinical Endpoints:****ICU length of stay:**

Topeli [20], Heyland, [18] and Warren [21] reported on the effect of patient-level interventions on ICU length of stay. Topeli et al reported no statistically significant differences between closed ETT versus open ETT suction on the days spent in the ICU (11.5 vs. 12.3,  $P = 0.64$ ). Heyland et al reported no significant differences between combination antibiotic therapy group versus monotherapy group (statistical data not reported). The results were not altered when a subgroup analysis of patients who were colonized from the beginning of enrollment was performed (statistical data not reported). Warren et al reported significantly longer ICU days in post antibiotic cycling group compared with baseline group (8.7 vs. 7.7,  $P = 0.01$ ). De jonge , Oudhuis and Forestier did not report on the effects of patient-level interventions on ICU length of stay. Poole analysis was not performed due to inconsistencies among studies in reporting ICU length of stay.

**Duration of mechanical ventilation:**

Topeli et al [20] and Heyland et al [18] reported no significant differences between the intervention and the control groups on the effect of patient-level interventions on the duration of mechanical ventilation. The duration of mechanical ventilation was 7.5 days in the open ETT suction group compared with 8.3 days in the closed ETT suction group ( $p = 0.55$ ), as reported by Topeli et al. Using a subgroup analysis of patients who were colonized by MDR-GNB, Heyland et al reported no significant differences in the duration of mechanical ventilation between combination and monotherapy for late suspected VAP (statistical data not reported). Pooled analysis was not performed due to incomplete data on the duration of mechanical ventilation among the studies.

## Discussion

While targeted patient-level interventions such as probiotics and antibiotic cycling have received considerable attention as potential infection control interventions against MDR-GNB in the ICU, our review observed that the few high quality studies testing these interventions have reported mixed results of their efficacy in reducing colonization, and little evidence that these interventions avoid infections and downstream consequences of MDR-GNB. Our review finds that oral probiotics and SDD are more promising patient-level interventions in preventing colonization with MDR-GNB compared to antibiotic cycling, closed ETT suction, and combination antibiotic coverage for suspected late VAP. Reduction in colonization did not translate to a reduction in infection with MDR-GNB. SDD was associated with a decrease in ICU and hospital mortality compared to closed ETT suction, antibiotic cycling, and combination antibiotic for suspected late VAP coverage.

We were unable to find evidence that reduction in colonization prevents infection with MDR-GNB. This finding might be explained by the lack of data on infection rates in the studies by Dejonge [16] and Heyland [18]. Lack of data from these studies might have underestimated the relationship between colonization and infection. Reduction in colonization not translating into a reduction in infection might also be explained by the fact that colonization might not be the only risk factor for infection in critically ill patients. In fact, multiple observational studies have identified other risk factors for ICU-acquired infections with MDR-GNB including duration of mechanical ventilation, length of hospital and ICU stay prior to infection, presence of central venous catheter, recent surgery, co-morbid patient conditions, such as Chronic Obstructive Pulmonary Disease (COPD), and antibiotic administration up to 90 days prior to ICU admission [23-27]. Limitations of these studies include small sample size, being single-centered, inconsistent implementation and reporting of hospital-based infection control measures, and non-standardized means for detecting resistant strains of MDR-GNB. Despite of the above-mentioned

limitations, the question of whether reduction of colonization leads to a reduction in downstream infection remains to be answered.

This review has only included 6 out of a pool of 631 studies. This relative discrepancy is due to the strict inclusion criteria of this review. We focused only on MDR-GNB because of the rising impact of these bacteria on ICU and hospital mortality and the lack of consensus on infection control measures specifically geared towards these bacteria. Furthermore, we only included interventional studies with appropriate control groups and endpoints. Studies that were excluded were not interventional, lacked important patient information, failed to report on appropriate patient outcomes, and were performed in non-ICU settings. In this venture, the largest randomized controlled trial was excluded from our analysis. In this study, Timsit and colleagues [15] demonstrated the non-inferiority of chlorohxidine-gluconate-impreganted catheter dressings (versus pivodine-iodine-based dressings) and less frequent (every 7 days versus every 3 day) central venous catheters dressing changes on the incidence of colonization and CRI. This study reported outcomes in terms of number of catheters rather than number of patients precluding the inclusion this study in our pooled analysis. By contacting the primary author, we were unable to procure patient data as well as data on MDR-GNB in this study.

While the use of probiotics and SDD were shown to decrease the acquisition of MDR-GNB compared to standard therapy [16, 17], they failed to demonstrate significant superiority when compared to each other [19]. The lack of a pronounced effect may be due to comparable beneficial effects of both interventions or it may be due to early discontinuation of the trial by Oudhuis et al [19].

Our finding of an association of patient-level interventions in the ICU on the incidence of colonization is similar to a recent meta –analysis by Siempos et al [28] focusing on probiotics. Siempos' review included 5 randomized controlled studies using different prescriptions of probiosis. Our review included only two studies on probiosis: Forestier et al [17] that compared oral probiotics to placebo and Oudhuis et al [19] that compared probiotics to SDD. Contrary to our review, the review by Siempos et al [28] did not focus on MDR-GNB, contained no data on antibiotic resistance, and did not target infections other than VAP.

Similar to Forestier et al, Siempos et al concluded that probiotics were associated with a reduction in the incidence of colonization of the respiratory tract by *Pseudomonas Aeruginosa* as well as a reduction in the incidence of VAP and shorter hospital length of stay. Similar to our review, Siempos et al did not observe a difference in mortality associated with probiotics administered in the ICU. A similar decrease in the incidence of VAP was found in a recent qualitative review[29]. In this review, the authors looked at the effects of both probiotics and SDD on the incidence of VAP. The authors reported a trend towards a reduction in the incidence of VAP by probiotics. However, the authors cautioned against making generalized conclusion based on these findings given multiple methodological weaknesses of the studies included in their review. Compared to this review, our review was quantitative and focused specifically on MDR-DRG. In contrast to reported beneficial effects of probiotics mentioned above, a multicenter randomized placebo-controlled trial found an increase in mortality in patients with predicted severe acute pancreatitis who were given probiotics species [30]. The trial included in our analysis did not contain patients with acute pancreatitis or organ failure who are prone to develop bowel ischemia. Since the mechanism of bowel ischemia in patients with acute severe pancreatitis is unknown, probiotics should not be administered in this group of patients. More adequately powered trials are needed to investigate the effects of probiotics on VAP and other hospital infections.

Several studies of the effect of patient-level interventions in ICU have concluded that SDD is associated with a reduction in the incidence of blood stream infections and VAP caused by Gram-negative bacteria. These studies were included in a Cochrane review [31] of 36 randomized controlled trials (6914 patients) that compared the use of prophylactic topical and systemic SDD with no treatment on the incidence of VAP and on mortality. A review by Silvestri et al [32] included 51 randomized controlled trials (8065 patients) that compared oropharyngeal and intestinal administration of antibiotics as part of SDD protocol, with or without systemic antibiotics with no treatment or placebo, on the incidence of blood stream infections and on mortality. Both reviews showed a significant reduction in mortality by SDD. The incidence of blood stream infections and VAP were significantly reduced in patients treated with SDD,

compared with controls. These reviews have made conclusions similar to ours. However, our review was exclusively focused on MDR-GNB.

Our study did not show a significant difference in the colonization rates of MDR GNB between empiric combination therapy of meropenem and ciprofloxacin vs. monotherapy with meropenem for late suspected VAP. On the contrary, there was a trend towards an increase in mortality and colonization with antibiotic cycling. The results of this review are similar to other reviews using different antibiotic combination. A meta-analysis [33] conducted by Paul et al found no significant difference in treatment failure, clinical failure, rate of emergence of resistant bacteria, and all-cause mortality between  $\beta$ -lactam-aminoglycoside combination therapy compared with  $\beta$ -lactams monotherapy for severe Gram-negative sepsis. The same study demonstrated a significantly higher incidence of nephrotoxicity in combination therapy compared monotherapy. Similar findings related to the same combination of antibiotics used by Paul et al were demonstrated by a Cochrane meta-analysis [34]. There is no current proven benefit of empiric combination antibiotic coverage for suspected late VAP.

The study by Warren and colleagues [21] demonstrated that antibiotic cycling was not associated with a significant reduction in infection, enteric colonization, or acquisition of MDR-GNB. The results of this study are not in agreement with a study by Gruson et al [35] which found a significant reduction in the incidence of early onset VAP during a 5-year period of antibiotic cycling. Several reasons may account for this disagreement. First, Gruson et al followed patients for a longer time period. Second, Gruson et al specifically targeted VAP rates rather than generalized hospital-acquired infections. Third, both studies were performed under infection control protocols specific only to 2 intensive care units, and hence precluding external validation. Taken together, antibiotic cycling should not supplant more effective infection control measures, such as hand hygiene and limited duration of empiric antibiotic coverage, to prevent infection with MDR-GNB.

Our finding that closed ETT suction is not associated with a reduction in the rate of colonization or infection with MDR-GNB is in accordance with a Cochrane meta-analysis [36]. The Cochrane meta-analysis consisted of 12 studies (1684 patients) including Topeli's study. The authors reported on more outcomes compared to our review in terms of costs, respiratory system outcomes (oxygen saturation), and hemodynamic outcomes (such as heart rate changes with the type of suction) compared to our analysis. All outcomes were not significantly different between closed and open ETT suction. A striking finding both in our review and in the Cochrane's is the significantly larger number of patients colonized by Gram-negative bacteria in the closed ETT suction group. Compared to our review, the Cochrane review was not specifically focused on MDR-GNB. The Cochrane meta-analysis reported on methodological weaknesses of the included studies such inadequate reporting of randomization methods, shorter length of follow up, variation among studies in time points when outcomes were measured. Despite the limitations, and the differences in reported endpoints, both reviews seem to agree on the efficacy of closed ETT suction. More studies with better methodological quality are required, particularly to clarify the hazard of bacterial colonization with closed ETT suction.

Our review has several limitations. First, we were able to identify only 6 studies that systematically reported outcomes associated with a targeted patient-level intervention against MDR GNB in the ICU. Because of the limited number of studies, we combined very different interventions to explore the general effect of patient-level interventions. Our pooled analysis does not allow us to comment on the effect of any individual intervention. Pooling these diverse studies may not detect important effects if some types of interventions are beneficial while others are not. Second, data were often reported inconsistently and we had to make several key assumptions, such as the appropriateness of each study's methods for defining antimicrobial resistance, documenting infections, and general follow-up assessment. It is possible that differences across studies in these methods may introduce potential biases. Third, some of the studies included in our analysis lacked data on either colonization or infection and hence a clear relationship could not be demonstrated. Fourth, some studies were conducted at one center with center-

specific protocols questioning the external validity of their results. Fifth, studies varied in their methodology for detecting antimicrobial resistance. Sixth, studies varied in their patient population, also affecting the external validation of their results.

**Conclusion**

Probiotics and SDD appear to be beneficial in reducing colonization with MDR-GNB in the ICU while closed ETT suction, combination antibiotic coverage for late suspected VAP and antibiotic cycling do not. Only one study (De Jonge et al) led to the avoidance of downstream infections and mortality.

Reductions in colonization may not be a sufficient intermediate endpoint of patient-level interventions, and future studies should be sufficiently powered to observe effects on infection and clinically meaningful outcomes.

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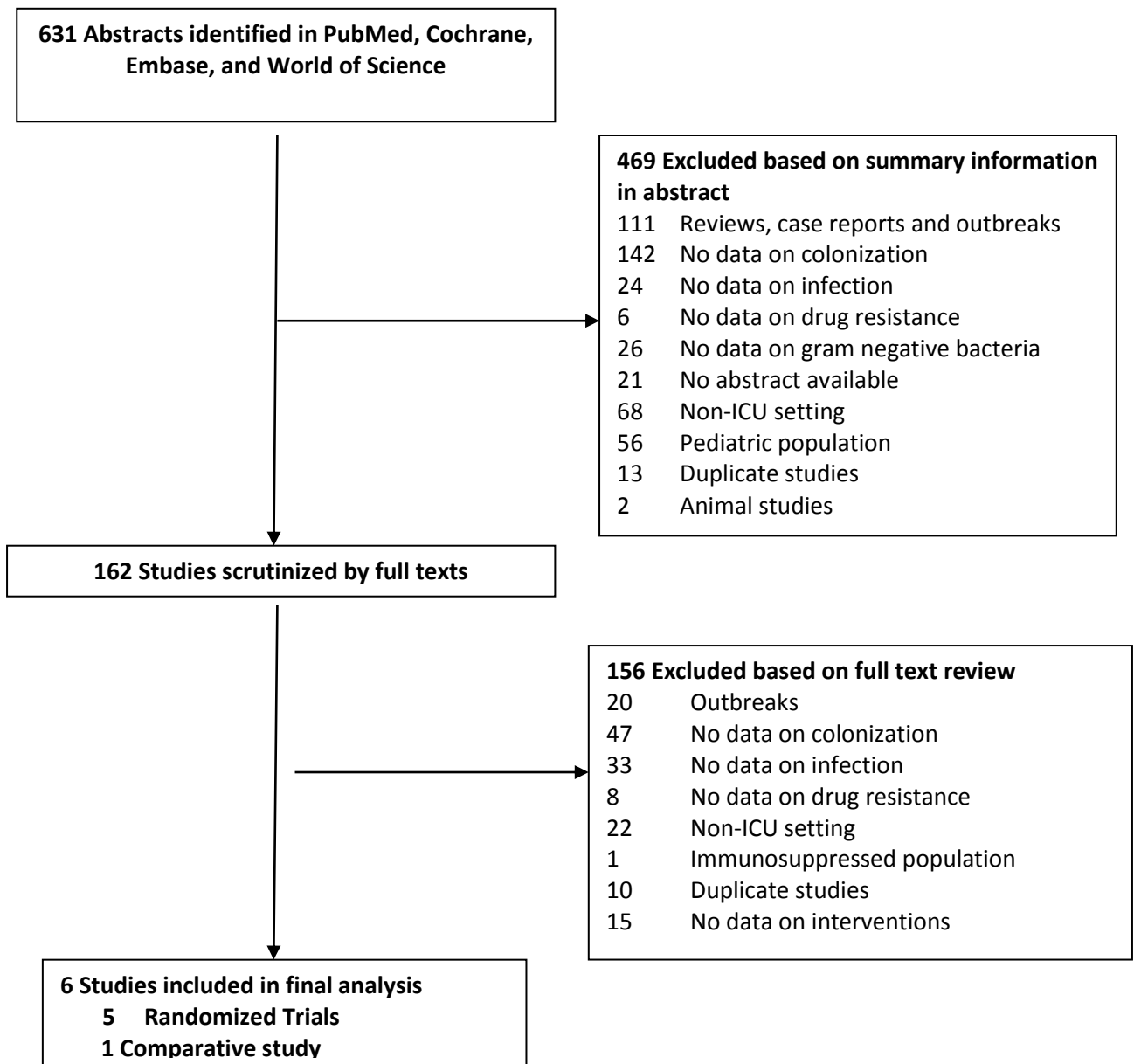
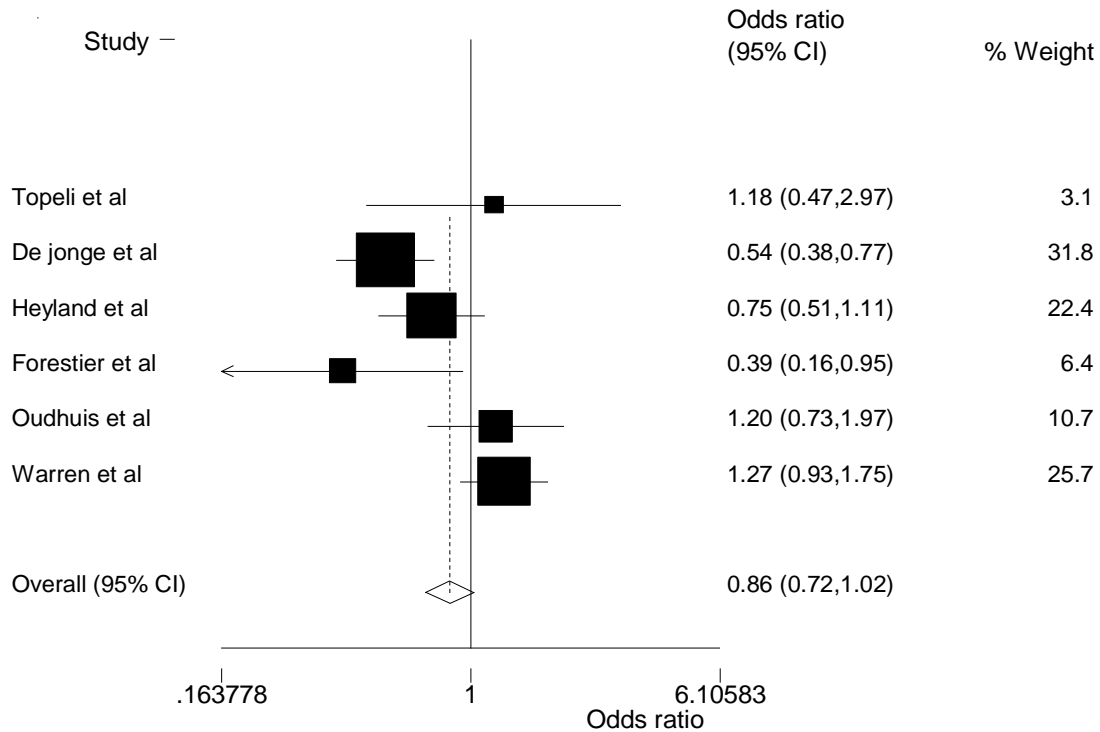
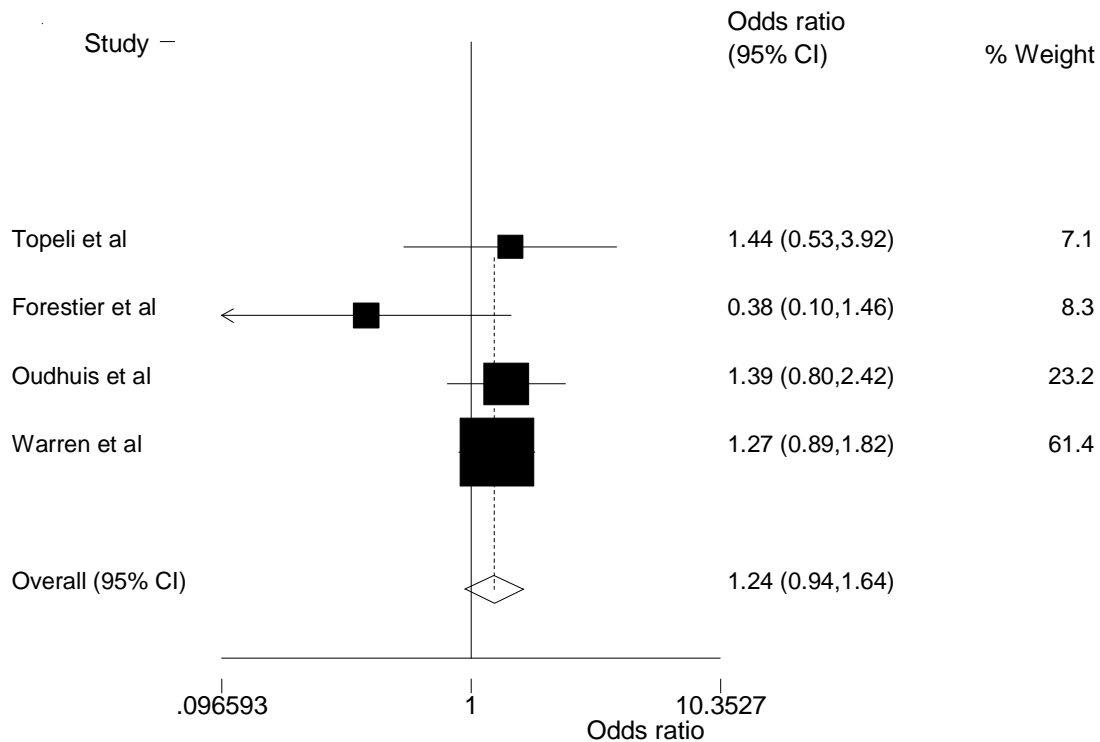


Figure 1. Flowchart of studies selected for meta-analysis



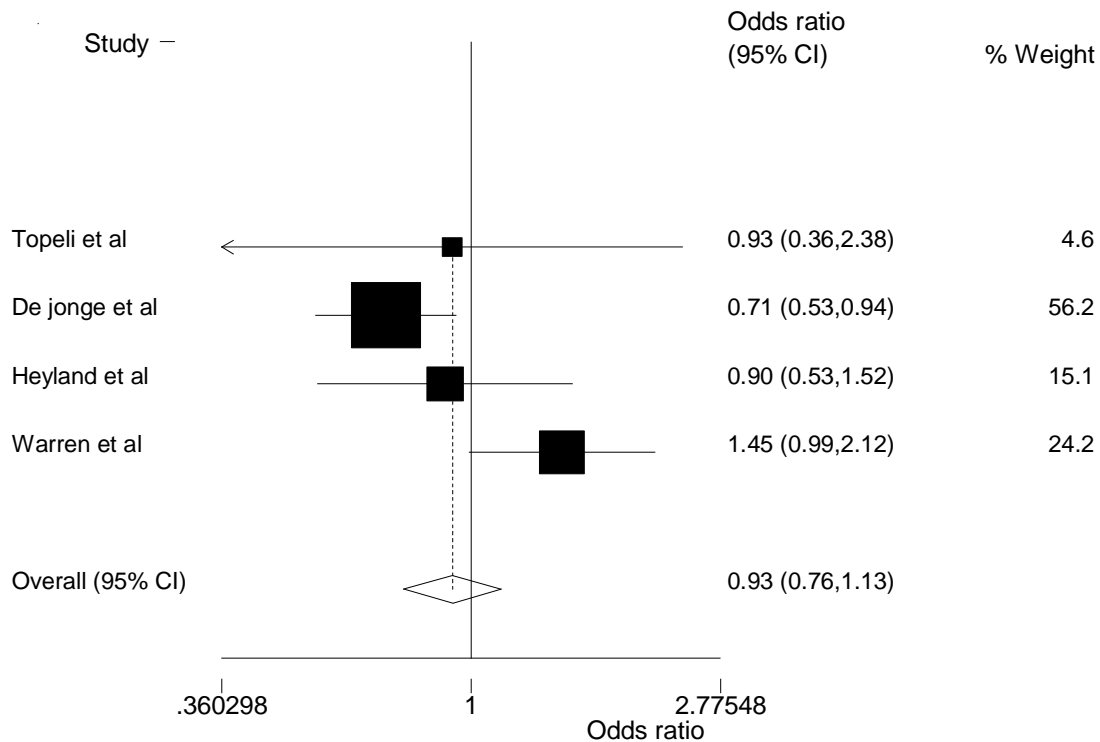
Heterogeneity chi-squared =18.29; d.f =5; p=0.003

**Figure 2. Odds ratios (ORs) of colonization in studies reporting relevant patient level data comparing patients undergoing prophylactic interventions versus controls. Vertical line - no differences between the 2 groups. OR-the size of each square denotes the proportion of information given by each study. Diamond- pooled OR; horizontal lines- 95% confidence intervals.**



Heterogeneity chi-squared = 3.27; d.f.= 3; p=0.352

**Figure 3. Odds ratios (ORs) of infection in studies reporting relevant patient level data comparing patients undergoing prophylactic interventions versus controls. Vertical line - no differences between the 2 groups. OR-the size of each square denotes the proportion of information given by each study. Diamond- pooled OR; horizontal lines- 95% confidence intervals.**



Heterogeneity chi-squared = 8.79; d.f. = 3; p=0.032

**Figure 4. Odds ratios (OR) of mortality in studies reporting relevant patient level data comparing patients undergoing prophylactic interventions versus controls. Vertical line - no differences between the 2 groups. OR-the size of each square denotes the proportion of information given by each study. Diamond- pooled OR; horizontal lines- 95% confidence intervals.**

**Table 1. Characteristics of studies included in the meta-analysis**

Author Name	Year	Study Design	ICU	Intervention N	Control N	MDR Bacteria Targeted	Infection Endpoints	Clinical Endpoints	Jadad score
De jonge [16]	2003	RCT	Med/ Surg	SDD 466	Placebo 468	<i>P. aeruginosa</i> , <i>Acinetobacter</i> , <i>Enterobacteriaceae</i> , <i>VRE</i> , <i>MRSA</i>	Colonization	ICU mortality, hospital mortality	3
Forestier [17]	2008	RCT	Med/ Surg	Oral probiotics 102	Placebo 106	<i>P. aeruginosa</i>	Colonization/ infection	<i>P.aeruginosa</i> colonization and infection of RT, GIT	5
Heyland [18]	2008	RCT	Med/ Surg	Combination ABx for late VAP 369	Mono- ABx 370	<i>P. aeruginosa</i> , <i>Acinetobacter</i> , <i>Enterobacteriaceae</i>	Colonization	28 day mortality	3
Oudhuis [19]	2011	RCT	Med/ Surg	Oral probiotics 130	SDD 124	<i>P. aeruginosa</i> , <i>Enterobacteriaceae</i>	Colonization/ VAP/UTI/CRI/ wound	Infection 'prematurely stopped'	2
Topeli [20]	2004	RCT	Med	Closed ETT suction 41	Open ETT suction 37	<i>Acinetobacter</i> , <i>P. aeruginosa</i>	Colonization, VAP	ICU mortality, LOS, duration of mechanical ventilation	3
Warren [21]	2004	Cohort	Med/ Surg	Baseline 242	Abx cycling 930	<i>P.aeruginosa</i> , <i>Enterobacteriaceae</i>	Colonization/ VAP,BSI	Infection by NDR GNB	NA

Med; medical, Surg; surgical, P; *Pseudomonas*, Abc; *Acinetbacter Braumnii*, UTI; urinary tract infection, HAI; hospital acquired infection, BSI; blood stream infection, CRI; catheter related infection, VAP; ventilator associated pneumonia, SDD; selective digestive decontamination, NA; not appreciated, NS; not stated, Abx; antibiotic, MDR; multidrug resistant GNB; Gram negative bacteria, R; treatment, CRI; vascular catheter-related infection

**Table 2. Demographic and clinical characteristics of patients included in meta-analysis**

<b>First Author</b>	<b>Characteristic</b>							
	<b>Age (Mean)</b>	<b>Gender (Male, %)</b>	<b>Severity score APACHEII (mean)</b>	<b>ICU days prior to enrollment (mean)</b>	<b>Hospital days prior to ICU admission (mean)</b>	<b>Patients on mechanical ventilation N (%)</b>	<b>Prior use of antibiotics N (%)</b>	<b>Use of vasoactive agent (%)</b>
Topeli [20]	64	53	24.7	NA	4.7	78 (100)	NA	NA
Dejonge [16]	59.5	59	18.7	NA	NA	79(85)	NA	629 (67.3)
Heyland [18]	59	69.3	30.7	7.9	NA	739(100)	252 (34.1)	NA
Forestier [17]	58.5	70	44.4*	13.7	NA	196(94)	206 (99)	NA
Oudhuis [19]	62.7	61	22	16.5	37.6	248(97)	NA	NA
Warren [21]	59.4	50	22.8	NA	NA	NA	NA	NA

APACHEII; Acute Physiology and Chronic Health Evaluation II score, NA; not appreciated, \* SAPS II; Simplified Acute Physiology II Score, ICU; intensive care unit, N; number.