Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis

Nick Daneman, Syed Sarwar, Robert A Fowler, Brian H Cuthbertson, on behalf of the SuDDICU Canadian Study Group

Lancet Infect Dis 2013; 13: 328–41

Published Online January 25, 2013 http://dx.doi.org/10.1016/S1473-3099(12)70322-5

See Comment page 282

Trauma, Emergency, and Critical Care Program (N Daneman MD, S Sarwar BSc, R A Fowler MD, B H Cuthbertson MD), **Division of Infectious Diseases, Department of Medicine** (N Daneman), **and Department of Critical Care Medicine** (R A Fowler, B H Cuthbertson), **Sunnybrook Health Sciences Centre, University of Toronto, ON, Canada**

Correspondence to: Dr Nick Daneman, Division of Infectious Diseases, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, ON, M4N 2M5, Canada **nick.daneman@sunnybrook.ca**

Summary

Background Many meta-analyses have shown reductions in infection rates and mortality associated with the use of selective digestive decontamination (SDD) or selective oropharyngeal decontamination (SOD) in intensive care units (ICUs). These interventions have not been widely implemented because of concerns that their use could lead to the development of antimicrobial resistance in pathogens. We aimed to assess the effect of SDD and SOD on antimicrobial resistance rates in patients in ICUs.

Methods We did a systematic review of the effect of SDD and SOD on the rates of colonisation or infection with antimicrobial-resistant pathogens in patients who were critically ill. We searched for studies using Medline, Embase, and Cochrane databases, with no limits by language, date of publication, study design, or study quality. We included all studies of selective decontamination that involved prophylactic application of topical non-absorbable antimicrobials to the stomach or oropharynx of patients in ICUs, with or without additional systemic antimicrobials. We excluded studies of interventions that used only antiseptic or biocide agents such as chlorhexidine, unless antimicrobials were also included in the regimen. We used the Mantel-Haenszel model with random effects to calculate pooled odds ratios.

Findings We analysed 64 unique studies of SDD and SOD in ICUs, of which 47 were randomised controlled trials and 35 included data for the detection of antimicrobial resistance. When comparing data for patients in intervention groups (those who received SDD or SOD) versus data for those in control groups (who received no intervention), we identified no difference in the prevalence of colonisation or infection with Gram-positive antimicrobial-resistant pathogens of interest, including meticillin-resistant *Staphylococcus aureus* (odds ratio 1·46, 95% CI 0·90–2·37) and vancomycin-resistant enterococci (0·63, 0·39–1·02). Among Gram-negative bacilli, we detected no difference in aminoglycoside-resistance (0·73, 0·51–1·05) or fluoroquinolone-resistance (0·52, 0·16–1·68), but we did detect a reduction in polymyxin-resistant Gram-negative bacilli (0·58, 0·46–0·72) and third-generation cephalosporin-resistant Gram-negative bacilli (0·33, 0·20–0·52) in recipients of selective decontamination compared with those who received no intervention.

Interpretation We detected no relation between the use of SDD or SOD and the development of antimicrobial-resistance in pathogens in patients in the ICU, suggesting that the perceived risk of long-term harm related to selective decontamination cannot be justified by available data. However, our study indicates that the effect of decontamination on ICU-level antimicrobial resistance rates is understudied. We recommend that future research includes a non-crossover, cluster randomised controlled trial to assess long-term ICU-level changes in resistance rates.

Funding None.

Introduction

Hospital-acquired infections affect a quarter of critically ill patients, and can double the risk of a patient dying.[1,2] Because hospital-acquired infections are preceded by colonisation with pathogenic bacteria, prophylactic antimicrobial treatment might have the potential to reduce the burden of pathogens in a patient's respiratory and gastrointestinal tract, and thereby prevent the onset of invasive infections such as ventilator-associated pneumonia.

Selective digestive decontamination (SDD) is defined as the prophylactic application of topical, non-absorbable antimicrobials in the oropharynx and stomach, with the goal of eradicating potentially pathogenic microorganisms but preserving the protective anaerobic microbiota. Selective oropharyngeal decontamination (SOD) is the application of such treatments to only the oropharynx. SDD is usually, and SOD is rarely, accompanied by systemic antimicrobials, which might also pre-emptively treat undetected infections. We refer to SDD, SOD, or both under the umbrella term of selective decontamination.

Selective decontamination is not a new idea; it has been assessed in more than 40 randomised controlled trials, with clinical benefits summarised in many meta-analyses.[3–11] This intervention has shown consistent reductions in hospital-acquired infection rates (most

notably ventilator-associated pneumonia), and might reduce overall mortality in intensive care units (ICUs).[5,12] However, there has been little uptake of selective decontamination in ICUs and little or no endorsement in guidelines issued by professional organisations.[13,14] The barriers to uptake of selective decontamination were explored in an international survey and Delphi panel of multidisciplinary expert stakeholders, including critical care and infectious diseases specialists.[15,16] The predominant concern expressed was that use of selective decontamination will promote the development of antimicrobial-resistant pathogens.

The possibility of promoting resistance is a serious concern, especially in view of ICUs already being the epicentre of antimicrobial use and resistance within most hospitals.[1] Calls for reduced antimicrobial use through improved antimicrobial stewardship are being made worldwide,[17,18] and have already shown some success in helping curtail antimicrobial resistance in some ICUs.[19,20] Proponents of selective decontamination counter that the body of research has not documented a clear signal of increased antimicrobial resistance, and that this intervention could even potentially reduce resistance rates.[21]

By contrast with meta-analyses assessing the effect of selective decontamination on infection and mortality rates, no such assessment has been done to measure the effect of selective decontamination on antimicrobial resistance. Therefore, we aimed to systematically review the effect of selective decontamination on rates of colonisation or infection with antimicrobial-resistant pathogens in patients in ICUs.

Methods

Search strategy and selection criteria

We did our systematic review and meta-analysis in accordance with the PRISMA guidelines.[22] To ensure that we captured all relevant studies we searched Medline, Embase, and Cochrane databases without any restriction on date of publication, language, country, sex, age, outcome measures, and study design or study quality. Search terms for selective decontamination included "digestive decontamination", "oral decontamination", "oropharyngeal decontamination", "bowel decontamination", "decontamination/methods*", "antibiotic prophylaxis*", "antibiotic prophylaxis/methods", "antibiotic prophylaxis/utilization*", "topical decontamination", "gastro* decontamination", "decontamination", "selective decontamination", "SDD", "SOD", or "antibacterial agent". Search terms for intensive care included "intensive care units", "critical care", "intensive care", "ICU", "critical illness", "critical care", "care unit*", "burn unit*", "recovery room*", "ventilators", "mechanical/, mechanical ventilat*", "ventilator*", "respiration", "artificial", or "artificial respiration*". We identified additional studies by scanning reference lists of relevant articles and previous meta-analyses on SDD or SOD, and by contacting subject experts.

We included all studies of selective decontamination that involved prophylactic application of topical non-absorbable antimicrobials to the stomach or oropharynx of patients in ICUs, with or without additional systemic antimicrobials. We excluded studies of interventions that used only antiseptic or biocide agents such as chlorhexidine, unless antimicrobials were also included in the regimen. We also excluded studies of antimicrobial prophylaxis to specifically prevent surgical-site infection or postsurgical infection, and studies focused on patients not in ICUs, patients receiving liver transplants, or other small populations of patients such as those with heart failure. We anticipated low numbers of randomised controlled trials with long-term follow-up in this subject, so we applied no predefined limitations on study design or study quality. Randomised controlled trials, non-randomised trials, quasiexperimental studies (before-and-after studies), cohort studies, case series, and case-control studies were all included. We excluded only case reports. We appraised the quality of included studies with the Cochrane risk of bias method for randomised controlled trials, and the Newcastle-Ottawa quality assessment scale for non-randomised studies. The Newcastle-Ottawa quality assessment scale assigns a maximum of four points for selection of patients, two points for comparability of intervention and control groups, and three points for outcome assessment.[23] We did not exclude repeat publications with the same populations of patients, as long as subsequent analyses explored different antimicrobial-resistance outcomes, to ensure that outcomes were not counted more than once.

One investigator (SS) did full searches on all the databases. Another investigator (ND) repeated the screening of articles for a 10% subset of citations. Agreement was measured via an unweighted κ score. Any disagreement was resolved by further discussion between the two investigators (SS and ND), with planned involvement of a third author (BHC) if consensus was not achieved.

Data extraction

We extracted a broad range of data from each study into a spreadsheet, including the author, year of publication, country, study design, number of patients enrolled, number of ICUs, total duration of study in months, total duration of intervention (SDD or SOD) in months, nature of topical agent with or without systemic drugs given during the study, use of routine surveillance swabs, antimicrobial use, and antimicrobial resistance outcomes.

The two general antimicrobial resistance outcomes of interest were differences in the incidence of colonisation or infection with antimicrobial-resistant organisms in intervention (SDD or SOD) versus control patients, and ICU-level changes in the incidence of colonisation or

infection with antimicrobial-resistant organisms with time. Individual antimicrobial-resistant pathogens of interest included meticillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and Gram-negative bacilli resistant to aminoglycosides, polymyxins, fluoroquinolones, third-generation cephalosporins, or carbapenems. For the purpose of our meta-analysis, antimicrobial resistance in patients included either colonisation (detection of bacteria by surveillance swabs without evidence of disease) or infection (detection of bacteria by clinical culture in the setting of invasive disease). Data for all antimicrobial resistance outcomes were abstracted irrespective of metric, but were only pooled for meta-analysis if they measured incidence per patient admitted rather than per bacterial isolate. Because of the small number of studies examining ICU-level changes in antimicrobial resistance over time and different analytical approaches and outcome measures used by these studies, these results could not be pooled. Additionally, total use of systemic antimicrobials in patients in intervention and control groups was extracted from all studies, as a potential mediator of differences in antimicrobial resistance levels.

Statistical analysis

Only data from studies that compared the detection of antimicrobial resistant pathogens per admitted patient in recipients of selective decontamination versus control were eligible for pooling. If different Gram-negative bacilli were analysed separated in the study results (eg, separate results reported for Enterobacteriaceae and non-Enterobacteriaceae), then we summed event rates for these subgroups before pooling. We used the Mantel-Haenszel model with random effects to calculate pooled odds ratios (ORs) and 95% CIs. We did sensitivity analyses with data obtained from only randomised controlled trials. Heterogeneity across studies was measured by I^2 statistics examining the percentage of heterogeneity due to variation between studies (0% suggest no heterogeneity; a value between 0–25% suggests very low heterogeneity; a value between 25–50% suggests low heterogeneity; a value between 50–75% suggests moderate heterogeneity; a value of >75% suggests high heterogeneity).[24] We used Review Manager (version 5.1) for data analysis. To assess whether heterogeneity in OR estimates might be associated with differences in the durations of included studies, we did a meta-regression with R statistical software (version 2.15.1).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 64 studies of selective decontamination,[12,25–87] 35 of which were included in our systematic analysis (figure 1 and table 1). The study selection criteria showed good reproducibility (unweighted κ score 0·92).

Studies of selective decontamination spanned from 1987 to 2012 (table 1). Of the 64 studies, the most common country of origin was the Netherlands (18 studies; 28%), but studies were also done in countries with higher baseline prevalences of antimicrobial resistance such as France (ten studies; 16%), Spain (seven studies; 11%), the

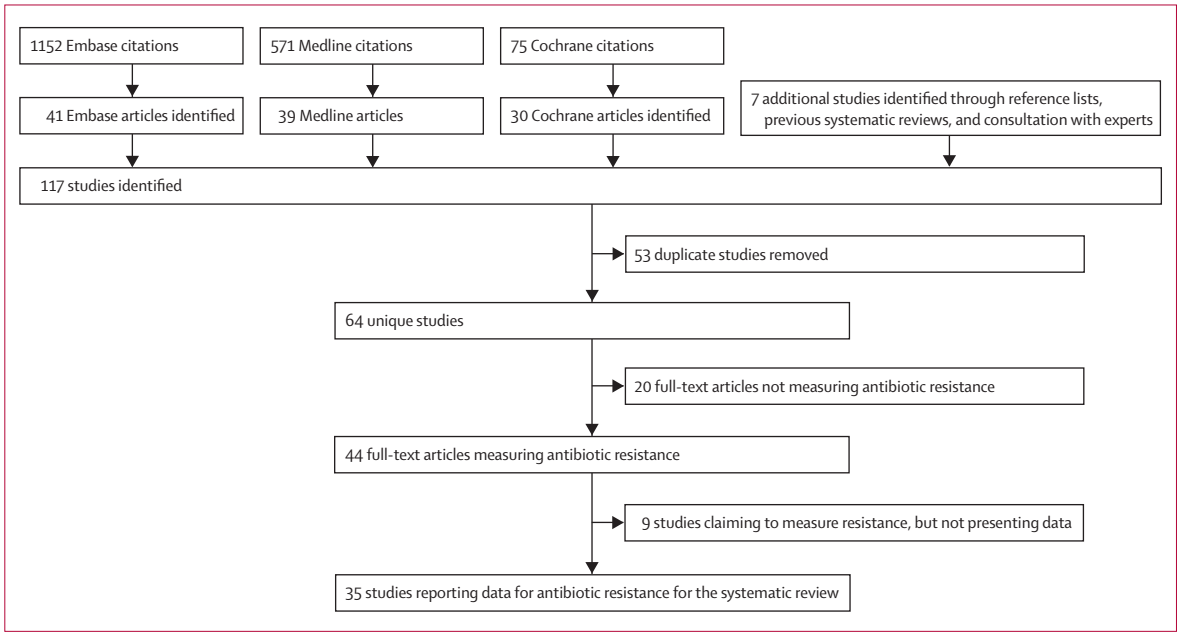

Figure 1: **Study selection**

	Year	Country	Study design	Number of ICUs	Number of patients			
					SDD	SOD	Control	Total
Melsen et al[85]*	2012	Netherlands	RCT (cluster/crossover)	13	2034	1904	1989	5927
Oostdijk et al[84]*	2011	Netherlands	RCT (cluster/crossover)	14	2667	2166	1945	6778
Ochoa Ardilla et al[83]	2011	Spain	Prospective cohort	1	1588	0	0	1588
De Smet et al[82]*	2011	Netherlands	RCT (cluster/crossover)	13	2034	1904	1989	5927
Abecasis et al[81]	2011	UK	Prospective cohort	1	39	0	0	39
Oudhuis et al[87]	2011	Netherlands	RCT (crossover)	1	124	0	130	254
Oostdijk et al[86]*	2010	Netherlands	Before and after	13	2034	1904	1989	5927
Benus et al[80]*	2010	Netherlands	RCT (cluster/crossover)	13	86	111	140	397
De Smet et al[12]*	2009	Netherlands	RCT (cluster/crossover)	NA	335	331	327	993
Koeman et al[78]	2008	Netherlands	RCT (parallel)	NA	0	128	257	385
De Smet et al[79]*	2008	Netherlands	RCT (cluster/crossover)	13	2034	1904	1989	5927
Heininger et al[76]	2006	Germany	Prospective cohort	1	1913	0	5357	7270
al Naeimi et al[77]	2005	Netherlands	Case series	1	4	0	0	4
Leone at al[75]‡	2005	France	Prospective cohort	1	159	0	0	159
de La Cal et al[74]†	2005	Spain	RCT (parallel)	1	53	0	54	107
Camus et al[73]	2005	France	RCT (parallel)	3	0	389	127	515
Van Der Voort et al[72]	2004	Netherlands	Before and after	1	529	0	513	1042
Garbino et al[64]	2004	Switzerland	RCT (parallel)	NA	110	0	110	220
de La Cal et al[71]†	2004	Spain	Before and after	1	401	0	398	799
Leone et al[70]‡	2003	France	Retrospective cohort	1	369	0	360	720
De Jonge et al[69]	2003	Netherlands	RCT (cluster)	2	466	0	468	934
Damjanovic et al[44]	2003	UK	Retrospective cohort	1	76	0	30	106
Rayes et al[67]	2002	Germany	RCT (parallel)	1	32	0	63	95
Pneumatikos et al[68]	2002	Greece	RCT (parallel)	1	30	0	31	61
Leone et al[66]‡	2002	France	Case control	1	159	0	163	324
Krueger et al[65]	2002	Germany	RCT (parallel)	2	265	0	262	527
Nardi et al[63]	2001	Italy	RCT (parallel)	1	223	0	0	223
Bergmans et al[62]	2001	Netherlands	RCT (cluster/parallel)	3	0	87	139	226
Barret et al[61]	2001	USA	RCT (parallel)	1	11	0	12	23
Dahms et al[60]	2000	USA	Retrospective cohort	1	54	0	542	596
Sanchez-Garcia et al[59]	1998	Spain	RCT (parallel)	5	131	0	140	271
Ruza et al[58]	1998	Spain	RCT (parallel)	1	116	0	110	226
Varwaest et al[57]	1997	Belgium	RCT (parallel)	1	393	0	185	578
Lingnau et al[56]	1997	Austria	RCT (parallel)	1	162	0	148	310
Abele-Horn et al[55]	1997	Germany	RCT (parallel)	1	0	58	30	88
Quinio et al[54]	1996	France	RCT (parallel)	1	76	0	72	148
Wiener et al[53]	1995	USA	RCT (parallel)	1	30	0	31	61
Luiten et al[51]	1995	Netherlands	RCT (parallel)	16	50	0	52	102
Hammond et al[52]	1995	South Africa	Before and after	1	719	0	809	1528
Georges et al[50]	1994	France	RCT (parallel)	1	31	0	33	64
Ferrer et al[49]	1994	Spain	RCT (parallel)	1	51	0	50	101
Bion et al[48]	1994	UK	RCT (parallel)	1	32	0	27	59
Tetteroo et al[46]	1993	Netherlands	Prospective cohort	1	97	0	0	97
Smith et al[47]	1993	USA	RCT (parallel)	1	18	0	18	36
Korinek et al[45]	1993	France	RCT (parallel)	2	63	0	60	123
Winter et al[43]	1992	UK	RCT (parallel)	1	91	0	85	176
Rocha et al[42]	1992	Spain	RCT (parallel)	1	47	0	52	101
Hammond et al[41]	1992	South Africa	RCT (parallel)	1	114	0	125	239
Gastinne et al[40]	1992	France	RCT (parallel)	15	220	0	225	445
Cockerill et al[39]	1992	USA	RCT (parallel)	NA	75	0	75	150

(Continues on next page)

	Year	Country	Study design	Number of ICUs	Number of patients			
					SDD	SOD	Control	Total
(Continued from previous page)								
Cerra et al[38]	1992	USA	RCT (parallel)	1	25	0	23	48
Zobel et al[37]	1991	Austria	RCT (parallel)	1	25	0	25	50
Pugin et al[36]	1991	Switzerland	RCT (parallel)	1	0	25	27	52
Fox et al[35]	1991	UK	Non-RCT	1	129	0	12	141
Aerdts et al[34]	1991	Netherlands	RCT (parallel)	1	21	17	18	56
Rodriguez-Roldan et al[33]	1990	Spain	RCT (parallel)	2	0	13	15	28
Godard et al[32]	1990	France	RCT (crossover)	1	112	0	97	209
Flaherty et al[31]	1990	USA	Non-RCT	1	0	51	56	107
Ulrich et al[30]	1989	Netherlands	RCT (parallel)	1	52	0	48	100
Brun-Buisson et al[29]	1989	France	RCT (parallel)	1	26	0	174	210
Ledingham et al[28]	1988	UK	Before and after	1	161	0	163	324
Kerver et al[27]	1988	Netherlands	RCT (parallel)	1	49	0	47	96
Unertl et al[26]	1987	Germany	RCT (parallel)	1	20	0	19	39
Stoutenbeek et al[25]	1987	Netherlands	Before and after	1	105	0	59	164

ICU=intensive care unit. NA=data not available. SDD=selective decontamination of the digestive tract. SOD=selective oropharyngeal decontamination. *Group of studies re-examining study population from De Smet et al.[79] †Group of studies re-examining study population from de La Cal et al.[71] ‡Group of studies re-examining study population from Leone et al.[66]

Table 1: **General characteristics of identified studies**

UK (six studies; 9%), the USA (six studies; 9%), and Germany (five studies; 8%). There were three groups of repeat studies examining different antimicrobial resistance outcomes in the same study populations, including follow-up studies from de Smet and colleagues,[12,79,80,82,84–86] Leone and colleagues,[66,70,75] and de La Cal and colleagues.[71,74] After removal of secondary publications from these datasets, there were a total of 28 852 unique patients; the median number of patients per study was 150 (IQR 76–324), including a median of 76 patients receiving SDD or SOD (IQR 34–146). Most studies (49 [77%]) were done in single intensive care units. 46 studies (72%) included systematic surveillance swabs as an adjunctive method of recording antimicrobial resistance—these surveillance swabs were collected at least once a week in 39 (85%) of the 46 studies.

47 (73%) of the 64 studies were randomised controlled trials, but we also identified non-randomised trials, cohort studies, and before-and-after studies (table 1). Of the 35 studies contributing data for antibiotic resistance, 24 were randomised controlled trials (69%). Most of these trials provided adequate data for sequence generation (19 of 24 studies) and allocation concealment (14 of 24 studies), but fewer than half (11 of 24 studies) were blinded. Only five (21%) of these 24 trials reported on all antimicrobial-resistant pathogens of interest either separately or as part of a composite outcome measure. So the potential of selective outcome reporting was not adequately addressed in 19 trials (79%). The 11 observational studies contributing data for antibiotic resistance had moderate-to-high Newcastle-Ottawa quality scores (mean 6·9, SD 0·8).

The typical regimen of non-absorbable antimicrobials used for selective decontamination was the combination of polymyxin E (colistin), tobramycin, and amphotericin B in 33 (52%) of the 64 studies (table 2). The other most common non-absorbable antibacterials were also polymyxins (polymyxin B) and aminoglycosides (gentamicin, neomycin, or netilmicin). The use of oral vancomycin was uncommon (used in only three studies). The only non-absorbable antifungal used in place of amphotericin B was nystatin, which was used in seven studies—in three of these studies, it was the only topical antimicrobial used. 44 (69%) of the 64 decontamination studies included systemic antimicrobials (parenteral or absorbable enteral antimicrobials; table 2). The most common drugs were intravenous third-generation cephalosporins (used in 32 studies) or oral fluoroquinolones (used in eight). Only one study used a systemic antifungal (fluconazole).[64] The median duration of studies was 18 months (IQR 10–29 months). The selective decontamination intervention (SDD or SOD) was applied for a median duration of 16 months (IQR 9–25 months; table 2).

20 studies (31%) reported the use of systemic antimicrobials in patients (either patients who received selective decontamination or those in control group; table 3). The amount of systemic antimicrobials was higher in the control groups in 13 studies, and higher in the intervention group in seven studies (table 3). Even in the seven studies that included the parenteral component of SDD in the calculations of use, five (71%) detected a net reduction in systemic antimicrobial use with SDD (table 3).[12,28,31,43,87] These included net reductions in total

	Topical agents									Systemic agents	Duration of intervention (months)	Duration of study (months)	Detection of antibiotic resistance
	Amphotericin B	Tobramycin	Polymixin E	Polymixin B	Gentamicin	Vancomycin	Neomycin	Nystatin	Netilmicin				
Melsen et al[85]	×	×	×	..	..	..	..	..	..	Cefotaxime	6	26	No
Oostdijk et al[84]	×	×	×	..	..	..	..	..	..	Cefotaxime	6	26	No
Ochoa Ardilla et al[83]	×	×	×	..	..	..	..	..	..	Cefotaxime	60	60	Yes
De Smet et al[82]	×	×	×	..	..	..	..	..	..	Cefotaxime	6	26	Yes
Abecasis et al[81]	×	..	×	..	×	..	..	..	..	Cefotaxime	4	10	Yes*
Oudhuis et al[87]	×	×	×	..	..	..	..	..	..	Cefotaxime	6	26	Yes
Oostdijk et al[86]	..	×	×	..	..	..	..	..	..	Cefotaxime	12	12	Yes
Benus et al[80]	..	×	×	..	..	..	..	..	..	Cefotaxime	NA	NA	Yes
De Smet et al[32]	×	×	×	..	..	..	..	..	..	Cefotaxime	6	26	No
Koeman et al[78]	..	..	×	..	..	..	..	..	..	None	25	25	No
De Smet et al[79]	×	×	×	..	..	..	..	..	..	Cefotaxime	6	26	Yes
Heininger et al[76]	×	×	×	..	..	..	..	..	..	None	60	60	Yes
al Naeimi et al[77]	×	×	×	..	..	..	..	..	..	Cefotaxime	5	5	Yes
Leone et al[75]	×		×	..	×	..	..	..	..	Cefazolin	48	48	No
de La Cal et al[74]	×	×	..	..	..	×	..	..	..	Cefotaxime	19	19	Yes
Camus et al[73]	..	×	×	..	..	..	..	..	..	None	30	30	Yes
Van Der Voort et al[72]	×	×	×	..	..	..	..	..	..	Cefotaxime	12	24	Yes
Garbino et al[64]	..	..	..	×	..	..	..	..	..	Fluconazole	30	30	No
de La Cal et al[71]	×	×	×	..	..	..	..	..	..	Cefotaxime	21	21	Yes
Leone et al[70]	×	..	×	..	×	..	..	..	..	Cefazolin	72	72	Yes
De Jonge et al[69]	×	×	×	..	..	..	..	..	..	Cefotaxime	27	27	Yes
Damjanovic et al[44]	..	..	..	..	..	..	..	×	..	None	14	14	No
Rayes et al[67]	×	×	×	..	..	..	..	..	..	Ceftriaxone	48	48	No
Pneumatikos et al[68]	×	×	×	..	..	..	..	..	..	None	NA	NA	Yes*
Leone et al[66]	×	..	×	..	×	..	..	..	..	Cefazolin	72	72	No
Krueger et al[65]	..	..	..	×	×	..	..	..	..	Ciprofloxacin	30	30	Yes
Nardi et al[63]	×	×	×	..	..	..	..	..	..	None	16	16	No
Bergmans et al[62]	..	..	×	..	×	×	..	..	..	None	16	16	Yes
Barret et al[61]	×	×	×	..	..	..	..	..	..	None	9	9	No
Dahms et al[60]	..	..	..	..	..	..	..	×	..	Norfloxacin	36	36	Yes
Sanchez-Garcia et al[59]	×	..	×	..	×	..	..	..	..	Ceftriaxone	NA	NA	Yes
Ruza et al[58]	..	×	×	..	..	..	..	×	..	None	24	24	No

(Continues on next page)

	Topical agents									Systemic agents	Duration of intervention (months)	Duration of study (months)	Detection of antibiotic resistance
	Amphotericin B	Tobramycin	Polymixin E	Polymixin B	Gentamicin	Vancomycin	Neomycin	Nystatin	Netilmicin				
(Continued from previous page)													
Varwaest et al[57]	×	..	..	..	..	..	..	..	..	Cefotaxime and ofloxacin	19	19	Yes
Lingnau et al[56]	×	×	×	..	..	..	..	..	..	Ciprofloxacin	53	53	No
Abele-Horn et al[55]	×	×	×	..	..	..	..	..	..	Cefotaxime	NA	NA	Yes
Quinio et al[54]	×	..	×	..	×	..	..	..	..	None	NA	NA	Yes
Wiener et al[53]	..	..	×	..	×	..	..	×	..	None	8	8	Yes
Luiten et al[51]	×	..	×	..	..	..	..	..	..	Cefotaxime and norfloxacin	36	36	Yes*
Hammond et al[52]	×	×	×	..	..	..	..	..	..	Cefotaxime	24	48	Yes
Georges exl[50]	×	..	×	..	..	..	..	..	×	Cefotaxime	22	22	No
Ferrer et al[49]	×	×	×	..	..	..	..	..	..	Cefotaxime	12	12	Yes
Bion et al[48]	×	×	×	..	..	..	..	..	..	Cefotaxime	18	18	Yes
Tetteroo et al[46]	×	..	×	..	..	..	..	..	..	Norfloxacin	18	18	Yes
Smith et al[47]	×	×	×	..	..	..	..	..	..	None	12	12	No
Korinek et al[45]	×	×	×	..	..	..	..	..	..	None	18	18	Yes*
Winter et al[43]	×	×	×	..	..	..	..	..	..	Ceftazidime	16	22	Yes
Rocha et al[42]	×	×	×	..	..	..	..	..	..	Cefotaxime	14	14	Yes
Hammond et al[41]	×	×	×	..	..	..	..	..	..	Cefotaxime	24	24	Yes
Gastinne et al[40]	×	×	×	..	..	..	..	..	..	None	5	5	No
Cockerill et al[39]	..	..	..	×	×	..	..	×	..	Cefotaxime	36	36	Yes
Cerra et al[38]	..	..	..	..	..	..	..	×	..	Cefotaxime, ceftazidime, norfloxacin	NA	NA	Yes*
Zobel et al[37]	×	..	×	..	×	..	..	..	..	Cefotaxime	18	18	Yes*
Pugin et al[36]	..	..	..	×	..	×	×	..	..	None	7·5	7·5	Yes*
Fox et al[35]	×	×	×	..	..	..	..	..	..	None	4	8	No
Aerdts et al[34]	×	..	×	..	..	..	..	..	..	Cefotaxime and norfloxacin	16	16	No
Rodriguez-Roldan et al[33]	×	×	×	..	..	..	..	..	..	None	7	7	Yes*
Godard et al[32]	..	×	×	..	..	..	..	..	..	None	3	6	Yes
Flaherty et al[31]	..	..	×	..	×	..	..	×	..	Cefazolin	8	8	Yes
Ulrich et al[30]	×	×	×							Trimethoprim	11	11	Yes
Brun-Buisson et al[29]	..	..	×	..	..	..	×	..	..	None	2	4.5	Yes
Ledingham et al[28]	×	×	×	..	..	..	..	..	..	Cefotaxime	9	16	Yes
Kerver et al[27]	×	×	×	..	..	..	..	..	..	Cefotaxime	16	16	No
Unertl et al[26]	..	..	..	×	×	..	..	..	..	None	9	9	Yes
Stoutenbeek et al[25]	×	×	×	..	..	..	..	..	..	Cefotaxime	24	36	No

NA=data not available. *Claimed to measure antibiotic resistance but did not report data.

Table 2: **Composition and duration of study interventions**

defined daily doses of antibiotics in one study,[12] defined daily doses per 100 patient-days in one study,[87] and total days of antibiotic treatment in three studies.[28,31,43]

Only one group of investigators examined a composite endpoint that included all major antibiotic-resistant bacterial pathogens of interest, which they termed highly resistant microorganisms.[12,82] These investigators detected a statistically significant reduction of highly resistant bacteraemia in patients who received SDD (OR 0·41, 95% CI 0·18–0·94) and those who received SOD (0·37, 0·16–0·85) compared with patients in the control group.[82] Respiratory tract colonisation with highly resistant microorganisms was also less common in patients who received SDD (0·58, 0·43–0·78) or SOD (0·65, 0·49–0·87) versus control groups.[82] Most studies examined antimicrobial-resistant organisms separately. Therefore, the effect of selective decontamination on the incidence of individual antimicrobial resistant organism was assessed (figures 2–4).

Meticillin-resistant *Staphylococcus aureus* (MRSA) was assessed in 16 studies (25%). Of these studies, nine reported the incidence of MRSA per admitted patient in recipients versus non-recipients of selective decontamination (figure 2). There was low heterogeneity and no statistically significant difference (figure 2).

Vancomycin-resistant enterococci were examined in seven studies (11%), of which only five reported the incidence per patient in recipients versus non-recipients of SDD or SOD (figure 3). We identified no heterogeneity and no statistically significant difference with selective decontamination (figure 3).

Aminoglycoside resistance was the most commonly studied pattern of resistance in Gram-negative bacilli in 13 (20%) of the 64 studies. In nine studies reporting incidence per patient, there was no statistically significant difference in aminoglycoside-resistant Gram-negative bacilli in recipients of SDD or SOD versus non-recipients, with moderate heterogeneity across studies (figure 4). Polymyxin E or B resistance was assessed in six studies with low heterogeneity across studies (figure 4). Polymyxin resistance was lower in selective decontamination recipients than it was in controls (figure 4). Fluoroquinolone resistance was investigated in three studies, with all three studies reporting incidence per patient in selective decontamination recipients versus non-recipients. The results of these studies showed a high degree of heterogeneity and we identified no statistically significant difference in fluoroquinolone-resistant Gram-negative bacilli in selective decontamination recipients versus non-recipients (figure 4). Third-generation cephalosporin-resistant Gram-negative bacilli were

	Systemic antimicrobial use in decontamination recipients	Systemic antimicrobial use in control patients	Unit of measurement	p value
Oudhuis et al[87]	108·7*	141·7	Defined daily doses per 100 patient-days	<0·01
De Smet et al[12]	29 981*†	33 688	Defined daily doses	NA
Koeman et al[78]	36	32	Percentage of patients receiving antibiotics	<0·001
De Jonge et al[69]	14 496*	6269	Defined daily doses per 1000 patients	NA
Krueger et al[65]	68	79	Percentage of patients receiving antibiotics	0·006
Bergmans et al[62]	0·95	1·30	Mean antibiotic courses per patient	0·02
Quinio et al[54]	54	84	Percentage of patients receiving antibiotics	<0·001
Wiener et al[53]	8·6	7·2	Mean duration of antibiotic treatment in days	NS
Hammond et al[52]	1367*	743	Total number of antibiotic courses	NA
Winter et al[43]	112*	317	Days of antibiotic treatment	NA
Rocha et al[42]	0·8	1·7	Mean antibiotic courses per patient	<0·05
Gastinne et al[40]	10·5	11·7	Length of antibiotic treatment courses	NA
Cockerill et al[39]	9	4	Mean antibiotic courses per patient	0·001
Cerra et al[38]	13	20	Mean antibiotic courses per patient	NS
Aerdts et al[34]	13	42	Mean antibiotic days per patient	0·001
Flaherty et al[31]	358*	451	Days of antibiotic treatment	NA
Ulrich et al[30]	36·5	11·1	Days of antibiotic treatment per patient	NA
Brun-Buisson et al[29]	4·4	4	Mean antibiotic days per patient	NA
Ledingham et al[28]	916*	1136	Days of antibiotic treatment	NA
Kerver et al[27]	27·6	29·9	Days of antibiotic treatment per patient	<0·001

NA=data not available. NS=not significant (p>0·05). *Comparison includes the systemic antimicrobial given as part of the decontamination intervention. †The average of total antibiotic use during selective decontamination of the digestive tract intervention months (29 663 defined daily doses) and selective oropharyngeal decontamination intervention months (30 299 defined daily doses).

***Table 3*: Use of systemic antibiotics in selective decontamination recipients and controls**

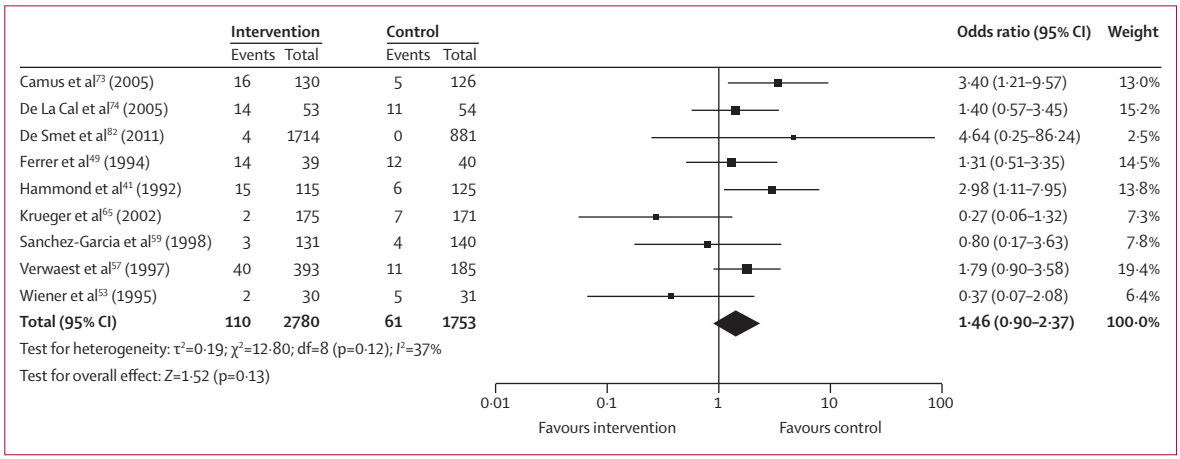

Figure 2: **Prevalence of MRSA infection or colonisation in patients in intensive care**
Patients in the intervention groups received selective decontamination, those in control groups did not. Includes only studies examining MRSA rates per patient admitted to intensive care. Excludes studies examining MRSA rates per *Staphylococcus aureus* isolates and studies with no MRSA detected in either group. MRSA=meticillin-resistant *Staphylococcus aureus*. df=degrees of freedom.

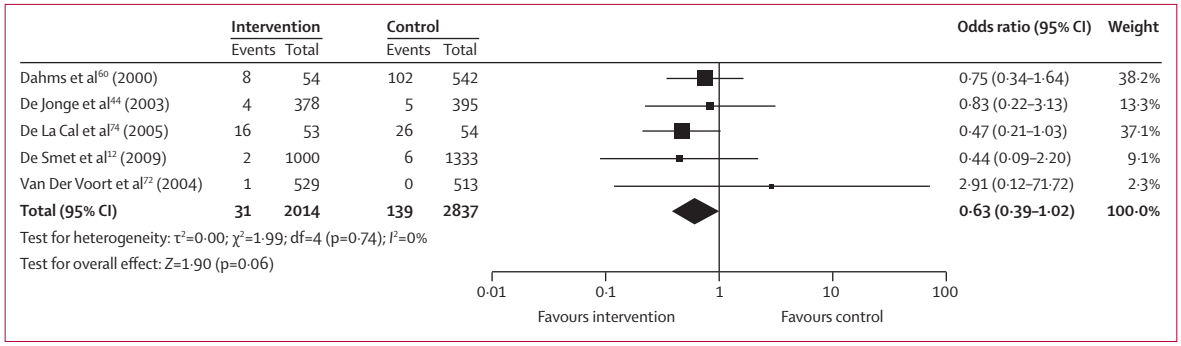

Figure 3: **Prevalence of VRE infection or colonisation in patients in intensive care**
Patients in the intervention groups received selective decontamination, those in control groups did not. Includes only studies examining VRE rates per patients admitted to intensive care. Excludes studies examining VRE rates per enterococcus isolates, and studies with no VRE detected in either group. VRE=vancomycin-resistant enterococci. df=degrees of freedom.

investigated in six studies, and in the four of these studies that reported incidence per patient, we recorded moderate heterogeneity and a reduction in resistance in decontamination recipients (figure 4).

Only two studies compared carbapenem-resistance between *Pseudomonas* spp and other Gram-negative bacilli.[69,70] We identified substantial heterogeneity between the findings of these studies (I^2=83%) and no difference in prevalence between decontamination recipients and non-recipients (OR 0·29, 95% CI 0·05–1·75).

We did sensitivity analyses including only randomised controlled trials and recorded very similar findings to the main analyses for MRSA, vancomycin-resistant enterococci, and Gram-negative bacilli resistance profiles (appendix), but, by contrast with the main analysis, the results from randomised controlled trials that assessed vancomycin-resistant enterococci were statistically significant with respect to a reduction in the prevalence of such enterococci in recipients of selective decontamination compared with patients in control groups (OR 0·53, 95% CI 0·28–0·99; appendix). Several studies examined antimicrobial resistance per bacterial isolate (rather than per admitted patient), and so their results could not be pooled in this meta-analysis. However, the findings of these studies were much the same as the included studies, with no overall findings that suggested increased antimicrobial resistance in selective decontamination recipients versus non-recipients (data not shown).

Meta-regression detected no association of study duration with the odds ratio estimate for MRSA rates, vancomycin-resistant enterococci rates, or rates of aminoglycoside, polymyxin, fluoroquinolone, or cephalosporin resistance among Gram-negative bacilli in selective decontamination versus control patients. However, each additional study month was associated with an increase in the OR estimate for the prevalence of vancomycin-resistant enterococci in patients who received selective decontamination versus those in the control groups (OR 1·2 per month, 1·1–1·3; p<0·0001).

See Online for appendix

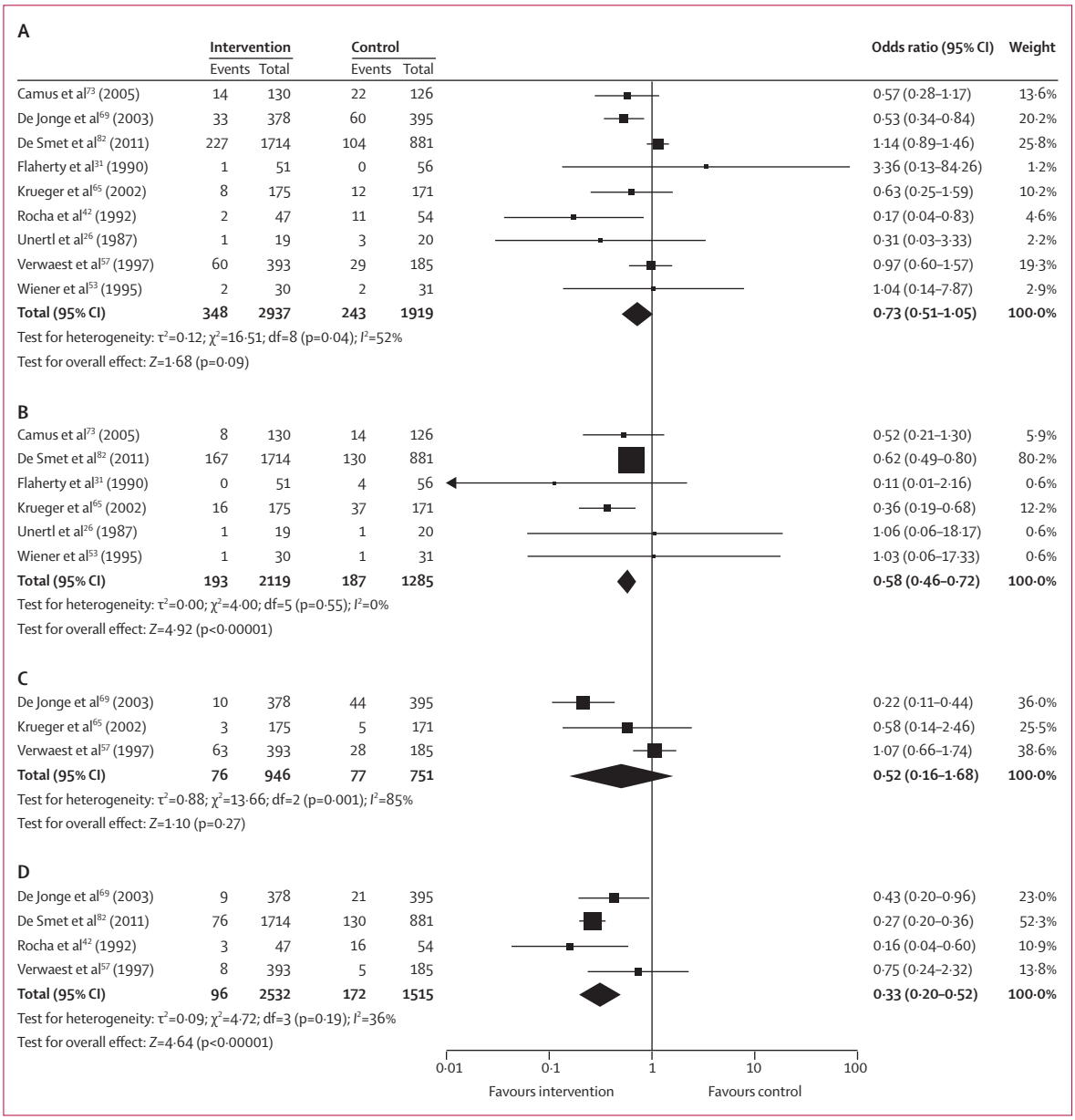

Figure 4: **Prevalence of Gram-negative bacilli resistant to selected antibiotics in patients in intensive care**
Prevalence of Gram-negative bacilli resistant to aminoglycosides (A), polymyxin E or B (B), fluoroquinolones (C), and third-generation cephalosporins (D). Patients in the intervention groups received selective decontamination, those in control groups did not. Includes studies examining rates of resistant organisms per patient admitted to intensive care. Excludes studies examining rates per isolate. df=degrees of freedom.

Only five studies (8%) assessed ICU-level changes in antimicrobial resistance over time.[52,60,76,83,86] Although these studies examined lengthy durations of SDD intervention (6 months,[86] 2 years,[52] 3 years,[60] and 5 years[76,83]), only two compared the difference in antimicrobial resistance rates over time between recipients of selective decontamination versus non-recipients,[60,76] and only one assessed this difference in patients treated in separate ICUs.[76]

Heininger and colleagues[76] did a 5 year prospective study of antimicrobial resistance in a German ICU that used SDD routinely (n=4597 isolates), and compared temporal trends in resistance with those documented in the 33 non-SDD ICUs contributing standardised data to the same national surveillance system (n=46 346 isolates), The incidence density of MRSA was stable over time, and lower in the study ICU than in reference ICUs. Aminoglycoside resistance in *Escherichia coli* was higher in the study ICU than it was in reference ICUs, but was stable for other Gram-negative bacilli in the study ICU. Vancomycin-resistant enterococci incidence was higher

in the study ICU than it was in reference ICUs in years 4 and 5, because of a hospital-wide outbreak of *Enterococcus faecium*.[76]

A Spanish group also assessed resistance rates prospectively for 5 years in an ICU that used SDD, but without control ICUs for comparison.[83] They noted a temporal decrease in the incidence of acquired antimicrobial-resistant bacteria (a composite of Enterobacteriaceae resistant to cefotaxime, aminoglycosides, or ciprofloxacin; *Pseudomonas aeruginosa* resistant to ceftazidime, aminoglycosides, ciprofloxacin, or imipenem; MRSA; or any isolate of *Acinetobacter* spp; Spearman regression coefficient –0·72, p=0·01). The investigators recorded no increase in resistance to components of the SDD regimen, although they did record an increase in β-lactam resistance in *P aeruginosa*.[83]

A retrospective cohort study in a surgical ICU that used SDD, detected an increase in vancomycin-resistant enterococci from 1·1% to 2·1% of admissions over 4 years (p=0·05).[60] In this ICU, very few patients received SDD (54 of 6152 patients), but the OR for the development of vancomycin-resistant enterococci was higher for patients who received SDD and vancomycin during ICU stay (OR 10·9, 95% CI 2·4–46·9) than it was for those who received vancomycin alone (4·3, 2·6–7·0).[60]

Finally, two groups of investigators followed up cohorts from RCTs of SDD[12,41] with before-and-after studies[52,86] examining changes in resistance rates before introduction of the SDD intervention and after removal of SDD after the trial. A 2 year trial in a South African ICU[41] detected a reduction in cefotaxime-resistant Enterobacteriaceae (p=0·02), and no statistically significant changes in MRSA or aminoglycoside-resistant Gram-negative bacilli.[52] By contrast with these findings, an ecological analysis of the 6 months after versus the 6 month before an SDD intervention in a large crossover RCT in the Netherlands showed an increase in intestinal colonisation with resistant Gram-negative bacilli; ceftazidime resistance increased from 5% to 15%, tobramycin resistance increased from 7% to 13%, and ciprofloxacin resistance increased from 7% to 13% (p<0·05 for all comparisons).[86]

Discussion

We did not detect an increased incidence of colonisation or infection with antimicrobial resistant pathogens in recipients of selective decontamination compared with non-recipients in an ICU setting. For all pathogens other than MRSA, the pooled OR estimate showed a lower level of antibiotic-resistance in patients who received selective decontamination compared with patients who did not. This reduction in resistance was statistically significant for polymyxin-resistant and third-generation cephalosporin-resistant Gram-negative bacilli. These results seemingly contradict the well established relation between antimicrobial use and selection of antimicrobial resistance.

What, then, are some potential mechanisms by which selective decontamination antimicrobials might not result in increased rates of antimicrobial-resistant organisms in the ICU? One possibility is that by preventing hospital-acquired infections, the use of prophylactic selective decontamination antimicrobials could lead to reductions in the need for therapeutic antimicrobials. If the overall net use of antimicrobials is unchanged (or even decreased) with selective decontamination, then there would be no increased antimicrobial selection pressure. Although five trials noted net reductions in systemic antimicrobial use in recipients of selective decontamination,[12,28,31,43,87] other studies detected increases in antibiotic use, and most trials did not study this idea. Another possibility is that by decreasing the total burden of colonisation with Gram-positive cocci and Gram-negative bacilli, as has been shown in a previous systematic review,[3] selective decontamination might reduce the total denominator of pathogens, so that even if the proportion of resistant pathogens increases, the incidence of antimicrobial-resistant pathogens per patient might still decrease. A third potential explanation would be that selective decontamination might decrease the burden of bacterial colonisation, and thereby lead to less transmission of pathogens (including antimicrobial-resistant pathogens) in patients, but these studies had no data with which to further test this hypothesis.

However, an absence of detection of antimicrobial resistance associated with selective decontamination could also relate to limitations identified in the included studies. First, and most importantly, the effect of selective decontamination on ICU-level antimicrobial resistance rates over time is largely unstudied. The median duration of selective decontamination intervention was 16 months, which should be sufficient time for exertion of selection pressure. However, only five studies examined temporal trends in resistance, only two compared the difference in antimicrobial resistance rates over time in recipients of selective decontamination versus non-recipients, and only one assessed this difference in patients treated in separate ICUs. Therefore, existing studies of selective decontamination have not answered the question of how selective decontamination affects ICU-level antimicrobial resistance rates over time.

Second, the quality of the individual RCTs in this field is variable,[3–6,8,10,11] and selective reporting cannot be ruled out because most studies examined only a subset of important antimicrobial-resistant organisms. Antibiotic resistance rates varied substantially between control groups in different studies in different countries, and even between control ICUs within individual studies. Also, differential microbiological sampling of patients in intervention and control groups could have led to systematic differences in outcome detection. Since most studies examined recipients of selective decontamination and non-recipients in the same ICU concurrently or with crossover designs, the signal of antimicrobial resistance could have been diluted by cross-contamination of

control patients by antimicrobial-resistant pathogens from recipients of selective decontamination.

The absence of a strong signal of increased antimicrobial resistance despite nearly three decades of selective decontamination research and practice suggests that the perceived risk of long-term harm related to selective decontamination cannot be justified by available data. Further research is needed to substantiate our findings and overcome the limitations of previous studies on this subject. In particular, we recommend a large multinational, non-crossover, cluster randomised trial design, which would examine individual-level, and, even more importantly, ICU-level, changes in antimicrobial resistance rates over an extended period in recipients of SDD and controls in separate ICUs. Such a trial is urgently needed to assess whether this potentially life-saving intervention can be given to critically ill patients without causing harm to future patients.

Contributors

ND, RAF, and BHC were involved in the inception of the research question and study design. ND and SS did the literature search, data abstraction, data analysis, and prepared the paper. ND, SS, RAF, and BHC were involved in data interpretation and editing and revision of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

ND is supported by a Clinician Scientist Award from the Canadian Institutes of Health Research. RAF is a clinician scientist at the Heart and Stroke Foundation. We acknowledge biostatistician Ruxandra Pinto for doing the meta-regression. The SuDDICU international collaboration is a collaboration of the Canadian Critical Care trials group and the Australia and New Zealand Clinical Trials Group, and is supported by both organisations (see appendix for members of the SuDDICU Canada collaboration).

References

1 Vincent JL, Rello J, Marshall J, et al, and the EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302:** 2323–29.

2 Bueno-Cavanillas A, Delgado-Rodríguez M, López-Luque A, Schaffino-Cano S, Gálvez-Vargas R. Influence of nosocomial infection on mortality rate in an intensive care unit. *Crit Care Med* 1994; **22:** 55–60.

3 Silvestri L, van Saene HK, Casarin A, Berlot G, Gullo A. Impact of selective decontamination of the digestive tract on carriage and infection due to Gram-negative and Gram-positive bacteria: a systematic review of randomised controlled trials. *Anaesth Intensive Care* 2008; **36:** 324–38.

4 Pileggi C, Bianco A, Flotta D, Nobile CG, Pavia M. Prevention of ventilator-associated pneumonia, mortality and all intensive care unit acquired infections by topically applied antimicrobial or antiseptic agents: a meta-analysis of randomized controlled trials in intensive care units. *Crit Care* 2011; **15:** R155.

5 Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *Cochrane Database Syst Rev* 2009; **4:** CD000022.

6 D'Amico R, Pifferi S, Leonetti C, Torri V, Tinazzi A, Liberati A. Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. *BMJ* 1998; **316:** 1275–85.

7 Safdar N, Said A, Lucey MR. The role of selective digestive decontamination for reducing infection in patients undergoing liver transplantation: a systematic review and meta-analysis. *Liver Transpl* 2004; **10:** 817–27.

8 Silvestri L, van Saene HK, Milanese M, Gregori D. Impact of selective decontamination of the digestive tract on fungal carriage and infection: systematic review of randomized controlled trials. *Intensive Care Med* 2005; **31:** 898–910.

9 Silvestri L, van Saene HK, Zandstra DF, Marshall JC, Gregori D, Gullo A. Impact of selective decontamination of the digestive tract on multiple organ dysfunction syndrome: systematic review of randomized controlled trials. *Crit Care Med* 2010; **38:** 1370–76.

10 Silvestri L, van Saene HK, Weir I, Gullo A. Survival benefit of the full selective digestive decontamination regimen. *J Crit Care* 2009; **24:** e7–14.

11 Silvestri L, van Saene HK, Milanese M, Gregori D, Gullo A. Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients. Systematic review of randomized, controlled trials. *J Hosp Infect* 2007; **65:** 187–203.

12 de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 2009; **360:** 20–31.

13 Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008; **34:** 17–60.

14 Muscedere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D, and the VAP Guidelines Committee and the Canadian Critical Care Trials Group. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. *J Crit Care* 2008; **23:** 126–37.

15 Cuthbertson BH, Francis J, Campbell MK, MacIntyre L, Seppelt I, Grimshaw J, and the SuDDICU study groups. A study of the perceived risks, benefits and barriers to the use of SDD in adult critical care units (the SuDDICU study). *Trials* 2010; **11:** 117.

16 Bastin AJ, Ryanna KB. Use of selective decontamination of the digestive tract in United Kingdom intensive care units. *Anaesthesia* 2009; **64:** 46–49.

17 Dellit TH, Owens RC, McGowan JE Jr, et al, and the Infectious Diseases Society of America, and the Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; **44:** 159–77.

18 Carlet JM, Artigas A, Niederman MS, Torres A, and on behalf of the World Alliance against Antibiotic Resistance. The Barcelona Declaration from the World Alliance against Antibiotic Resistance: engagement of intensivists. *Crit Care* 2012; **16:** 145.

19 Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. *J Antimicrob Chemother* 2011; **66:** 1223–30.

20 Elligsen M, Walker SA, Pinto R, et al. Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. *Infect Control Hosp Epidemiol* 2012; **33:** 354–61.

21 Silvestri L, van Saene HK. Selective decontamination of the digestive tract does not increase resistance in critically ill patients: evidence from randomized controlled trials. *Crit Care Med* 2006; **34:** 2027–29.

22 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; **151:** W65–94.

23 The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. http://www ohri ca/programs/clinical_epidemiology/oxford htm 2012 (accessed Sept 30, 2012).

24 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions (version 5.1.0). http://www.cochrane.org/training/cochrane-handbook (accessed Aug 31, 2012).

25 Stoutenbeek CP, van Saene HK, Miranda DR, Zandstra DF, Langrehr D. The effect of oropharyngeal decontamination using topical nonabsorbable antibiotics on the incidence of nosocomial respiratory tract infections in multiple trauma patients. *J Trauma* 1987; **27:** 357–64.

26 Unertl K, Ruckdeschel G, Selbmann HK, et al. Prevention of colonization and respiratory infections in long-term ventilated patients by local antimicrobial prophylaxis. *Intensive Care Med* 1987; **13:** 106–13.

27 Kerver AJ, Rommes JH, Mevissen-Verhage EA, et al. Prevention of colonization and infection in critically ill patients: a prospective randomized study. *Crit Care Med* 1988; **16:** 1087–93.

28 Ledingham IM, Alcock SR, Eastaway AT, McDonald JC, McKay IC, Ramsay G. Triple regimen of selective decontamination of the digestive tract, systemic cefotaxime, and microbiological surveillance for prevention of acquired infection in intensive care. *Lancet* 1988; **1:** 785–90.

29 Brun-Buisson C, Legrand P, Rauss A, et al. Intestinal decontamination for control of nosocomial multiresistant gram-negative bacilli. Study of an outbreak in an intensive care unit. *Ann Intern Med* 1989; **110:** 873–81.

30 Ulrich C, Harinck-de Weerd JE, Bakker NC, Jacz K, Doornbos L, de Ridder VA. Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections: a prospective randomized study. *Intensive Care Med* 1989; **15:** 424–31.

31 Flaherty J, Nathan C, Kabins SA, Weinstein RA. Pilot trial of selective decontamination for prevention of bacterial infection in an intensive care unit. *J Infect Dis* 1990; **162:** 1393–97.

32 Godard J, Guillaume C, Reverdy ME, et al. Intestinal decontamination in a polyvalent ICU. A double-blind study. *Intensive Care Med* 1990; **16:** 307–11.

33 Rodríguez-Roldán JM, Altuna-Cuesta A, López A, et al. Prevention of nosocomial lung infection in ventilated patients: use of an antimicrobial pharyngeal nonabsorbable paste. *Crit Care Med* 1990; **18:** 1239–42.

34 Aerdts SJ, van Dalen R, Clasener HA, Festen J, van Lier HJ, Vollaard EJ. Antibiotic prophylaxis of respiratory tract infection in mechanically ventilated patients. A prospective, blinded, randomized trial of the effect of a novel regimen. *Chest* 1991; **100:** 783–91.

35 Fox MA, Peterson S, Fabri BM, van Saene HK. Selective decontamination of the digestive tract in cardiac surgical patients. *Crit Care Med* 1991; **19:** 1486–90.

36 Pugin J, Auckenthaler R, Lew DP, Suter PM. Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia. A randomized, placebo-controlled, double-blind clinical trial. *JAMA* 1991; **265:** 2704–10.

37 Zobel G, Kuttnig M, Grubbauer HM, Semmelrock HJ, Thiel W. Reduction of colonization and infection rate during pediatric intensive care by selective decontamination of the digestive tract. *Crit Care Med* 1991; **19:** 1242–46.

38 Cerra FB, Maddaus MA, Dunn DL, et al. Selective gut decontamination reduces nosocomial infections and length of stay but not mortality or organ failure in surgical intensive care unit patients. *Arch Surg* 1992; **127:** 163–67.

39 Cockerill FR 3rd, Muller SR, Anhalt JP, et al. Prevention of infection in critically ill patients by selective decontamination of the digestive tract. *Ann Intern Med* 1992; **117:** 545–53.

40 Gastinne H, Wolff M, Delatour F, Faurisson F, Chevret S, and the The French Study Group on Selective Decontamination of the Digestive Tract. A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. *N Engl J Med* 1992; **326:** 594–99.

41 Hammond JM, Potgieter PD, Saunders GL, Forder AA. Double-blind study of selective decontamination of the digestive tract in intensive care. *Lancet* 1992; **340:** 5–9.

42 Rocha LA, Martín MJ, Pita S, et al. Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract. A randomized, double blind, placebo-controlled study. *Intensive Care Med* 1992; **18:** 398–404.

43 Winter R, Humphreys H, Pick A, MacGowan AP, Willatts SM, Speller DC. A controlled trial of selective decontamination of the digestive tract in intensive care and its effect on nosocomial infection. *J Antimicrob Chemother* 1992; **30:** 73–87.

44 Damjanovic V, Connolly CM, van Saene HK, et al. Selective decontamination with nystatin for control of a Candida outbreak in a neonatal intensive care unit. *J Hosp Infect* 1993; **24:** 245–59.

45 Korinek AM, Laisne MJ, Nicolas MH, Raskine L, Deroin V, Sanson-Lepors MJ. Selective decontamination of the digestive tract in neurosurgical intensive care unit patients: a double-blind, randomized, placebo-controlled study. *Crit Care Med* 1993; **21:** 1466–73.

46 Tetteroo GW, Wagenvoort JH, Mulder PG, Ince C, Bruining HA. Decreased mortality rate and length of hospital stay in surgical intensive care unit patients with successful selective decontamination of the gut. *Crit Care Med* 1993; **21:** 1692–98.

47 Smith SD, Jackson RJ, Hannakan CJ, Wadowsky RM, Tzakis AG, Rowe MI. Selective decontamination in pediatric liver transplants. A randomized prospective study. *Transplantation* 1993; **55:** 1306–09.

48 Bion JF, Badger I, Crosby HA, et al. Selective decontamination of the digestive tract reduces gram-negative pulmonary colonization but not systemic endotoxemia in patients undergoing elective liver transplantation. *Crit Care Med* 1994; **22:** 40–49.

49 Ferrer M, Torres A, González J, et al. Utility of selective digestive decontamination in mechanically ventilated patients. *Ann Intern Med* 1994; **120:** 389–95.

50 Georges B, Mazerolles M, Decun JF. Decontamination digestive selective resultats d'une etude chez le polytraumamatise. *Relen Urg* 1994; **3:** 621–27.

51 Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. *Ann Surg* 1995; **222:** 57–65.

52 Hammond JM, Potgieter PD. Long-term effects of selective decontamination on antimicrobial resistance. *Crit Care Med* 1995; **23:** 637–45.

53 Wiener J, Itokazu G, Nathan C, Kabins SA, Weinstein RA. A randomized, double-blind, placebo-controlled trial of selective digestive decontamination in a medical-surgical intensive care unit. *Clin Infect Dis* 1995; **20:** 861–67.

54 Quinio B, Albanèse J, Bues-Charbit M, Viviand X, Martin C. Selective decontamination of the digestive tract in multiple trauma patients. A prospective double-blind, randomized, placebo-controlled study. *Chest* 1996; **109:** 765–72.

55 Abele-Horn M, Dauber A, Bauernfeind A, et al. Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal decontamination (SOD). *Intensive Care Med* 1997; **23:** 187–95.

56 Lingnau W, Berger J, Javorsky F, Lejeune P, Mutz N, Benzer H. Selective intestinal decontamination in multiple trauma patients: prospective, controlled trial. *J Trauma* 1997; **42:** 687–94.

57 Verwaest C, Verhaegen J, Ferdinande P, et al. Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients in a multidisciplinary intensive care unit. *Crit Care Med* 1997; **25:** 63–71.

58 Ruza F, Alvarado F, Herruzo R, et al. Prevention of nosocomial infection in a pediatric intensive care unit (PICU) through the use of selective digestive decontamination. *Eur J Epidemiol* 1998; **14:** 719–27.

59 Sánchez García M, Cambronero Galache JA, López Diaz J, et al. Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients. A randomized, double-blind, placebo-controlled, multicenter trial. *Am J Respir Crit Care Med* 1998; **158:** 908–16.

60 Dahms R, Carlson M, Lohr B, Beilman G. Selective digestive tract decontamination and vancomycin-resistant enterococcus isolation in the surgical intensive care unit. *Shock* 2000; **14:** 343–46.

61 Barret JP, Jeschke MG, Herndon DN. Selective decontamination of the digestive tract in severely burned pediatric patients. *Burns* 2001; **27:** 439–45.

62 Bergmans DC, Bonten MJ, Gaillard CA, et al. Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med* 2001; **164:** 382–88.

63 Nardi G, Di Silvestre AD, De Monte A, et al. Reduction in gram-positive pneumonia and antibiotic consumption following the use of a SDD protocol including nasal and oral mupirocin. *Eur J Emerg Med* 2001; **8:** 203–14.

64 Garbino J, Lew DP, Romand JA, Hugonnet S, Auckenthaler R, Pittet D. Prevention of severe Candida infections in nonneutropenic, high-risk, critically ill patients: a randomized, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination. *Intensive Care Med* 2002; **28:** 1708–17.

65 Krueger WA, Lenhart FP, Neeser G, et al. Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: a prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2002; **166:** 1029–37.

66 Leone M, Bourgoin A, Giuly E, et al. Influence on outcome of ventilator-associated pneumonia in multiple trauma patients with head trauma treated with selected digestive decontamination. *Crit Care Med* 2002; **30:** 1741–46.

67 Rayes N, Seehofer D, Hansen S, et al. Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. *Transplantation* 2002; **74:** 123–27.

68 Pneumatikos I, Koulouras V, Nathanail C, Goe D, Nakos G. Selective decontamination of subglottic area in mechanically ventilated patients with multiple trauma. *Intensive Care Med* 2002; **28:** 432–37.

69 de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet* 2003; **362:** 1011–16.

70 Leone M, Albanese J, Antonini F, Nguyen-Michel A, Martin C. Long-term (6-year) effect of selective digestive decontamination on antimicrobial resistance in intensive care, multiple-trauma patients. *Crit Care Med* 2003; **31:** 2090–95.

71 de la Cal MA, Cerdá E, van Saene HK, et al. Effectiveness and safety of enteral vancomycin to control endemicity of methicillin-resistant Staphylococcus aureus in a medical/surgical intensive care unit. *J Hosp Infect* 2004; **56:** 175–83.

72 van der Voort PHJ, van Roon EN, Kampinga GA, et al. A before-after study of multi-resistance and cost of selective decontamination of the digestive tract. *Infection* 2004; **32:** 271–77.

73 Camus C, Bellissant E, Sebille V, et al. Prevention of acquired infections in intubated patients with the combination of two decontamination regimens. *Crit Care Med* 2005; **33:** 307–14.

74 de La Cal MA, Cerdá E, García-Hierro P, et al. Survival benefit in critically ill burned patients receiving selective decontamination of the digestive tract: a randomized, placebo-controlled, double-blind trial. *Ann Surg* 2005; **241:** 424–30.

75 Leone M, Delliaux S, Bourgoin A, et al. Risk factors for late-onset ventilator-associated pneumonia in trauma patients receiving selective digestive decontamination. *Intensive Care Med* 2005; **31:** 64–70.

76 Heininger A, Meyer E, Schwab F, Marschal M, Unertl K, Krueger WA. Effects of long-term routine use of selective digestive decontamination on antimicrobial resistance. *Intensive Care Med* 2006; **32:** 1569–76.

77 Al Naiemi N, Heddema ER, Bart A, et al. Emergence of multidrug-resistant Gram-negative bacteria during selective decontamination of the digestive tract on an intensive care unit. *J Antimicrob Chemother* 2006; **58:** 853–56.

78 Koeman M, van der Ven AJ, Hak E, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2006; **173:** 1348–55.

79 de Smet AM, Hopmans TE, Minderhoud AL, et al. Decontamination of the digestive tract and oropharynx: hospital acquired infections after discharge from the intensive care unit. *Intensive Care Med* 2009; **35:** 1609–13.

80 Benus RF, Harmsen HJ, Welling GW, et al. Impact of digestive and oropharyngeal decontamination on the intestinal microbiota in ICU patients. *Intensive Care Med* 2010; **36:** 1394–402.

81 Abecasis F, Sarginson RE, Kerr S, Taylor N, van Saene HK. Is selective digestive decontamination useful in controlling aerobic gram-negative bacilli producing extended spectrum beta-lactamases? *Microb Drug Resist* 2011; **17:** 17–23.

82 de Smet AM, Kluytmans JA, Blok HE, et al. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. *Lancet Infect Dis* 2011; **11:** 372–80.

83 Ochoa-Ardila ME, García-Cañas A, Gómez-Mediavilla K, et al. Long-term use of selective decontamination of the digestive tract does not increase antibiotic resistance: a 5-year prospective cohort study. *Intensive Care Med* 2011; **37:** 1458–65.

84 Oostdijk EA, de Smet AM, Kesecioglu J, Bonten MJ, and the Dutch SOD-SDD Trialists Group. The role of intestinal colonization with gram-negative bacteria as a source for intensive care unit-acquired bacteremia. *Crit Care Med* 2011; **39:** 961–66.

85 Melsen WG, de Smet AM, Kluytmans JA, Bonten MJ, and the Dutch SOD-SDD Trialists' Group. Selective decontamination of the oral and digestive tract in surgical versus non-surgical patients in intensive care in a cluster-randomized trial. *Br J Surg* 2012; **99:** 232–37.

86 Oostdijk EA, de Smet AM, Blok HE, et al. Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. *Am J Respir Crit Care Med* 2010; **181:** 452–57.

87 Oudhuis GJ, Bergmans DC, Dormans T, et al. Probiotics versus antibiotic decontamination of the digestive tract: infection and mortality. *Intensive Care Med* 2011; **37:** 110–17.