Selective decontamination of the digestive tract in mechanically ventilated patients in the intensive care unit: a systematic review with Bayesian meta-analysis

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Key Points

Question: In mechanically ventilated adults in the intensive care unit, does the use of Selective Decontamination of the Digestive Tract (SDD) reduce hospital mortality compared to standard care?

Findings: In this systematic review and meta-analysis of 32 randomised trials that included 24 389 participants, there was an 99.3% posterior probability that SDD was associated with reduced hospital mortality compared with standard care (risk ratio 0.91, 95% credible intervals 0.82 to 0.99, moderate certainty).

Meaning: The use of SDD probably reduces hospital mortality in mechanically ventilated adults in the ICU.

Abstract

Importance: The effectiveness of Selective Digestive Decontamination (SDD) in mechanically ventilated critically ill adults is uncertain.

Objective: To determine whether SDD reduces the risk of death in mechanically ventilated adults in Intensive Care Units (ICUs) compared to standard care.

Data sources: The primary search was conducted using MEDLINE, EMBASE and CENTRAL databases until December 2021

Study selection: Randomized clinical trials (RCTs) including adults receiving mechanical ventilation in the ICU comparing SDD to standard care or placebo.

Data extraction and synthesis: Data extraction and risk of bias assessments were performed in duplicate. The primary analysis was conducted using a Bayesian framework.

Main Outcomes and Measures: The primary outcome was hospital mortality. Subgroups included SDD with an intravenous (IV) agent compared to SDD without. Secondary outcomes included incidence of ventilator associated pneumonia (VAP), ICU acquired bacteraemia, and incidence of positive cultures of antimicrobial resistant organisms (ARO).

Results: From 32 RCTs, including 24,389 participants, 30 trials (24,034 participants) contributed data to the primary outcome. The estimated relative risk (RR) for mortality for SDD compared to standard care was 0.91 (95% credible interval (CrI) 0.82 to 0.99, I^2=33.9%, moderate certainty) with a 99.3% posterior probability that SDD reduced hospital mortality. The beneficial effect of SDD was evident in trials with an IV agent (RR 0.84, 95% CrI 0.74 to 0.94), but not in trials without (RR 1.01, 95% CrI 0.91 to 1.11). SDD was associated with reduced risk of VAP (RR 0.44, 95% CrI 0.36 to 0.54), and ICU acquired bacteraemia (RR 0.68, 95% CrI 0.57 to 0.81). Available data regarding the incidence of positive cultures of antimicrobial resistant organisms was of very low certainty.

Conclusion and relevance

The use of SDD probably reduces hospital mortality in mechanically ventilated adults in ICU. Evidence regarding its effect on antimicrobial resistance is of very low certainty.

Background

Selective Decontamination of the Digestive Tract (SDD) is a preventive infection control strategy that usually comprises the administration of non-absorbable, topical antimicrobial agents to the oropharynx and upper gastrointestinal tract, with or without the administration of a short-term course of broad-spectrum intravenous antibiotics.

Since the 1980s, advocates have encouraged the use of SDD in mechanically ventilated patients treated in the Intensive Care Unit (ICU), primarily to reduce the incidence of ventilator-associated pneumonia.[1] While a body of evidence suggesting reductions in hospital mortality and ventilator associated pneumonia exist[2,3] concerns regarding the impact of SDD on the development of antibiotic resistance have left international guideline panels[4-6] reluctant to recommend SDD and clinicians reluctant to implement in practice.[7,8] Evidence from randomized clinical trials (RCTs), including the Ecological Effects of Decolonisation Strategies in Intensive Care (RGNOSIS)[9] study and the Selective Decontamination of the Digestive Tract in the Intensive Care Unit (SuDDICU) study have recently added substantive weight to the body of evidence.[10] To provide an updated summary of current evidence, we conducted a systematic review and meta-analysis addressing the effect of SDD compared to standard care on hospital mortality and other relevant outcomes in mechanically ventilated patients treated in the ICU.

Methods

We conducted a systematic review according to a pre-specified published protocol,[11] registered at the international prospective register of systematic reviews (PROSPERO CRD42022309825) and report the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[12]

Eligibility criteria

We included RCTs and cluster-randomized controlled trials (cRCTs) that recruited ICU patients of whom ≥75% were invasively ventilated and compared the administration of SDD using antibacterial and/or antifungal agents to the upper gastrointestinal tract, stomach or proximal small bowel, with or without the administration of systemic antibiotics to standard care or placebo. Trials that administered only oral antiseptic agents as the intervention were excluded. Trials that included the routine use of topical antiseptic agents were included in the standard care comparator. We included all reports including studies only reported as abstracts, with no language restriction.

Search Strategy

We systematically searched MEDLINE, EMBASE, and the Cochrane Central Register of Clinical Trials (CENTRAL), from inception to December 20, 2021.

The search strategy included multiple medical subject heading (MESH) terms and keywords to identify critically ill patients, mechanical ventilation and Selective Digestive Decontamination (SDD) or Selective Oral Decontamination (SOD), combined with sensitive filters to identify randomized clinical trials[13] including cluster and cross over randomized controlled trials. We limited the search to adult human studies. We contacted experts and conducted manual searches of reference lists of included studies and other systematic reviews. The supplement provides details of the electronic search strategy.

Study selection

Using the COVIDENCE reference management system[14], a minimum of two investigators independently screened all identified references for inclusion based on the study title and abstract. A minimum of two reviewers reviewed for inclusion the full text of articles deemed possibly eligible. We resolved disagreement during the review process by discussion or if necessary, consultation with a third reviewer.

Data collection

Three investigators independently extracted data from each included trial using a standardized data collection form. We extracted all available data as outlined in the protocol, including characteristics of the included studies, design (RCT or cRCT), details of the enrolled population including demographics, illness severity, details of the intervention including oral and systemic agents, dose and duration and comparison group information including use of topical antiseptics. We did not impute missing data. Continuous variables presented in formats not readily amenable to pooling were converted to mean and standard deviation according to published methods.[15] For the SuDDICU trial[10], we had access to the study data prior to publication. We resolved discrepancies in the data extracted by discussion or, if necessary, adjudication by a fourth reviewer.

Risk of bias assessment

Two investigators with no affiliation with the included trials independently assessed risk of bias of for each of the included trials using the DistillerSR, 'Tool to Assess Risk of Bias in Randomized Controlled Trials'[16] modified to include items specific to cluster randomized trials developed by three of the authors (AD, NEH, GG) and reported in the supplement.

Disagreements were resolved by discussion and if necessary, consultation with a third reviewer.

Outcomes

The primary outcome was hospital mortality. For trials where hospital mortality was not reported, we used the closest approximation reported. Data were collected for the following secondary outcomes: mortality at longest follow-up, incidence of ventilator associated pneumonia, duration of mechanical ventilation, ICU and hospital length of stay. We attempted to collect data regarding the incidence of positive cultures of antibiotic resistant organisms using data as reported in the included trials and the incidence of *Clostridioides difficile* at both a unit level and an individual patient level.

Subgroup analyses

There were three pre-specified subgroups for the primary outcome.[11] We compared trials where the intervention consisted of SDD with oral and/or enteral agents only compared with SDD that included oral, enteral, and intravenous agents, with the specified hypothesis that there would be a greater reduction in mortality in trials that included intravenous agents as a component of the intervention. We compared trials conducted in surgical ICUs vs. medical ICUs vs. trauma ICUs vs. mixed population/ICUs, with the specified hypothesis that there would be a greater reduction in mortality in trials conducted in surgical ICUs. We also compared individual patient compared to unit level randomization (i.e., cluster and cluster/cluster-cross-over) with the specified hypothesis that there would be a greater reduction mortality in trials that randomized individual patients. When results suggested possible subgroup effects, we used the ICEMAN[17] guidelines to assess their credibility.

Data synthesis

The primary analysis used a Bayesian random effects model. We performed sensitivity analyses examining treatment effects using different priors including vague and weakly-informative priors on effect and heterogeneity parameters[18] and, in addition, a frequentist random-effects model using Hartung-Knapp-Sidik-Jonkman[19] and Der-Simonian Laird estimates of the between-study variance. The full description of priors has been reported in the protocol.[11]

As some of the included trials are cluster randomized trials, we prospectively adjusted the raw data for the design effect by using an effective sample size approach, defined as the original sample size divided by the design effect.[20]

We present results as risk ratios (RR) for binary outcomes and mean differences (MD) for continuous outcomes. Along with the pooled estimates of effect sizes and 95% credible intervals (CrI) for the Bayesian meta-analysis, we reported 95% confidence intervals (CI) for the frequentist model.

We assessed quantitative heterogeneity by reporting the posterior estimates of the heterogeneity parameter (tau) with its 95% credible interval, the prediction interval[21] of the intervention pooled effect size and evaluating the proportion of total variability due to heterogeneity rather than due to sampling error (I^2).

Small-study effects were assessed by visual assessment of the contour-enhanced funnel plots and formal Egger's regression test.

All statistical analyses were performed using R (for the Bayesian meta-analysis using the package bayesmeta[22]) and Stata 17 (StataCorp LLC, College Station, TX, USA).

Confidence in the cumulative evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the overall certainty of evidence that SDD compared with standard care improves each outcome measure to any degree.[23] We rated certainty in non-zero effects of SDD.

Results

We retrieved 6,569 records. Figure 1 presents the results of the search and reasons for trial exclusion. The 32 eligible trials[9,10,24-53] included 24,389 participants. Table 1 (and Table S1) present the characteristics of included trials.

Risk of Bias

Table S2 presents the risk of bias assessments. No trials were adjudicated as low risk of bias in all domains. The risk of bias was adjudicated as low for 28/30 trials contributing data regarding hospital mortality. We rated down the certainty in other outcomes due to risk of bias (Table S2 and Table 3).

Primary outcome

There were 30 trials (24,034 participants) that contributed data to the primary outcome. Using a Bayesian random effects model with vague priors, the pooled estimated risk ratio for hospital mortality for SDD was 0.91 (95% CrI 0.82 to 0.99, Tau=0.10, I^2=33.9%) compared to standard care, with an 99.3% posterior probability that SDD was associated with lower hospital mortality (Figure 2, Table 2). The certainty in the evidence was adjudicated as

moderate (Table 3). The results were similar for the sensitivity analyses using semi-informative priors and the specified frequentist methods (Figure 2, Table 2; Table S3). There was no evidence of small study effects on visual inspection of the funnel plot (Figure S1a) or the Egger test (Figure S1a).

Subgroup analysis

The primary outcome of hospital mortality was assessed in three subgroups (Table 2, and Figures S2-S4). There was evidence that the pooled estimate for mortality was different for trials that included an intravenous agent as a component of SDD (RR 0.84, 95% CrI 0.74 to 0.94) compared to those with no intravenous agents (RR 1.01, 95% CrI 0.91 to 1.11) as shown in Figure S2. We judged the credibility of the potential effect modification as moderate to high certainty. There was evidence that the pooled estimate for mortality was different for cluster-randomized (RR 1.0, 95% CrI 0.79 to 1.2) compared versus individual patient randomized trials (RR 0.85, 95% CrI 0.77 to 0.94) as shown in Figure S3. We judged the credibility of the potential effect modification as low. Details of the credibility assessments are presented in the supplement. There was no evidence of a differential estimate of treatment effect in trials comparing surgical, trauma, and mixed ICU populations, with no data available from medical ICUs (Figure S4). Data were not available to permit an assessment of the potential differential effect of study design (cluster randomized compared to individual patient randomized trials) on the estimated incidence of positive cultures for antimicrobial resistant organisms.

Secondary outcomes

Table 2, Table 3, and Table S3 present the results of all secondary outcomes with assessment of small study effects presented in Figure S1b-k. Compared to standard care, SDD was associated with a reduced risk of VAP (RR 0.44, 95% CrI 0.36 to 0.54, very low certainty (Figure S5)), a reduced risk of ICU acquired bacteraemia (RR 0.68 95% CrI 0.57 to 0.81, low certainty (Figure S6)), a reduction in the duration of MV (mean difference -0.73 days, 95% CrI -1.3 to -0.09 days, moderate certainty (Figure S7)), and duration of ICU admission (mean difference -0.86, 95% CrI -1.73 to 0 days, low certainty (Figure S8)). There was no effect on duration of hospital stay (mean difference -0.52 days, 95%CrI -2.2 to 1.2 days, moderate certainty (Figure S9)).

The pooled estimated risk ratio for mortality at longest follow-up for SDD compared to standard care was 0.93 (95% CrI 0.86 to 1.00) (Figure S10). Only two trials[26,33] provided additional data regarding mortality beyond hospital discharge.

Data were unavailable at a unit level to facilitate a pooled analysis of the effect of SDD on the emergence of antimicrobial resistant organisms; available data are qualitatively summarised in Table S4. None of the three cluster randomised trials[9,10,25] reported an increase in positive cultures of antimicrobial resistant organisms at a unit level.

Of the studies that reported data at an individual patient level, data were available to provide a pooled estimate of the incidence of positive cultures of antimicrobial resistant organisms, (estimated RR 0.65, 95% CrI 0.46 to 0.92, very low certainty, Figure S11)), incidence of positive cultures of methicillin resistant staphylococcus aureus (estimated RR 1.06, 95% CrI 0.56 to 1.98, very low certainty, (Figure S12)), and vancomycin resistant enterococcus (estimated RR 0.62, 95% CrI 0.18 to 2.1, very low certainty, (Figure S13)). The pooled estimated RR for Clostridioides difficile was 0.52 (95% CrI 0.15 to 1.80, (Figure S14).

Table S4 summarizes data not amenable to pooling. Fourteen trials [26,29-33,37,38,41,45,46,49,50,53] reported no increase in detection of antimicrobial resistant organisms from clinical or surveillance cultures, six[34,35,39,42,48,51] reported an increase in antimicrobial resistant organisms detected, and nine[24,27,28,36,40,43,44,47,52] did not report the incidence of detection of antimicrobial resistant organisms.

Discussion

In this systematic review and meta-analysis, we found that the use of SDD in mechanically ventilated patients in the ICU is probably associated with a reduced risk of hospital mortality. This reduction in mortality was evident in trials that included an intravenous agent as a component of the intervention. We also found evidence that the use of SDD may result in a reduced incidence of ventilator-associated pneumonia, and ICU acquired bacteraemia, however this evidence was of lower certainty. We found that SDD was probably associated with a small reduction in the duration of mechanical ventilation, but little or no reduction in the duration of ICU admission. We found no evidence that SDD was associated with an increase in the incidence of antimicrobial resistant organisms, however the effect of SDD on the emergence of antimicrobial resistant organisms remains very uncertain.

The findings of reduced risk of mortality and incidence of ventilator-associated pneumonia are consistent with the results of a recent Cochrane review.[3] The addition of two recent trials has more than doubled the sample size, increasing confidence in the primary finding of a reduction in mortality associated with the use of SDD. Concern that the widespread use of

broad spectrum antibiotics might promote antimicrobial resistant organisms has been a barrier to the adoption of SDD.[7,8] In keeping with previous literature,[7,9] we found no evidence to support the concern, but the available evidence is of very low certainty and is insufficient to rule out that possibility.

Our review has several strengths. We followed current best practice guidelines for the conduct and reporting of systematic reviews.[12,17,23] The inclusion of recent large trials has substantially increased the number of included participants, allowing the assessment of a broader range of outcomes than have been previously reported.[3] Limitations of our review relate primarily to the identification of antimicrobial resistant organisms. Consistent with previous trials,[9,25] the prevalence of antimicrobial resistance was uniformly low, consequently the results may not be applicable in healthcare settings with a higher rate of antimicrobial resistance.

Our results present clinicians with evidence that the use of SDD is probably associated with a reduction in mortality. The absence of evidence of increased antimicrobial resistance with the use of SDD in these trials, the majority of which have a relatively short duration of follow-up does not exclude such an effect in the longer term. For those clinicians or health policy decision makers planning to implement SDD as a standard of care, caution is required to ensure that this is done in conjunction with systematic microbiological surveillance and monitoring of resistance patterns. Future research should focus on quantifying any effect on antimicrobial resistance; clearly defining the risks and benefits of a potentially life-saving intervention.

Conclusions

The use of SDD probably reduces hospital mortality in mechanically ventilated adults in the ICU. Available evidence regarding its effect on antimicrobial resistance is of very low certainty.

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Author contributions

Concept and design: Hammond, Myburgh, Di Tanna, Garside, Vlok, Mahendran, Adigbli, Finfer, Goodman, Guyatt, Venkatesh, Seppelt, Delaney

Acquisition, analysis or interpretation of the data: Hammond, Garside, Vlok, Mahendran, Adigbli, Gao, Yao, Delaney

Drafting of the manuscript: Hammond, Myburgh, Finfer, Seppelt, Venkatesh, DiTanna, Guyatt, Delaney

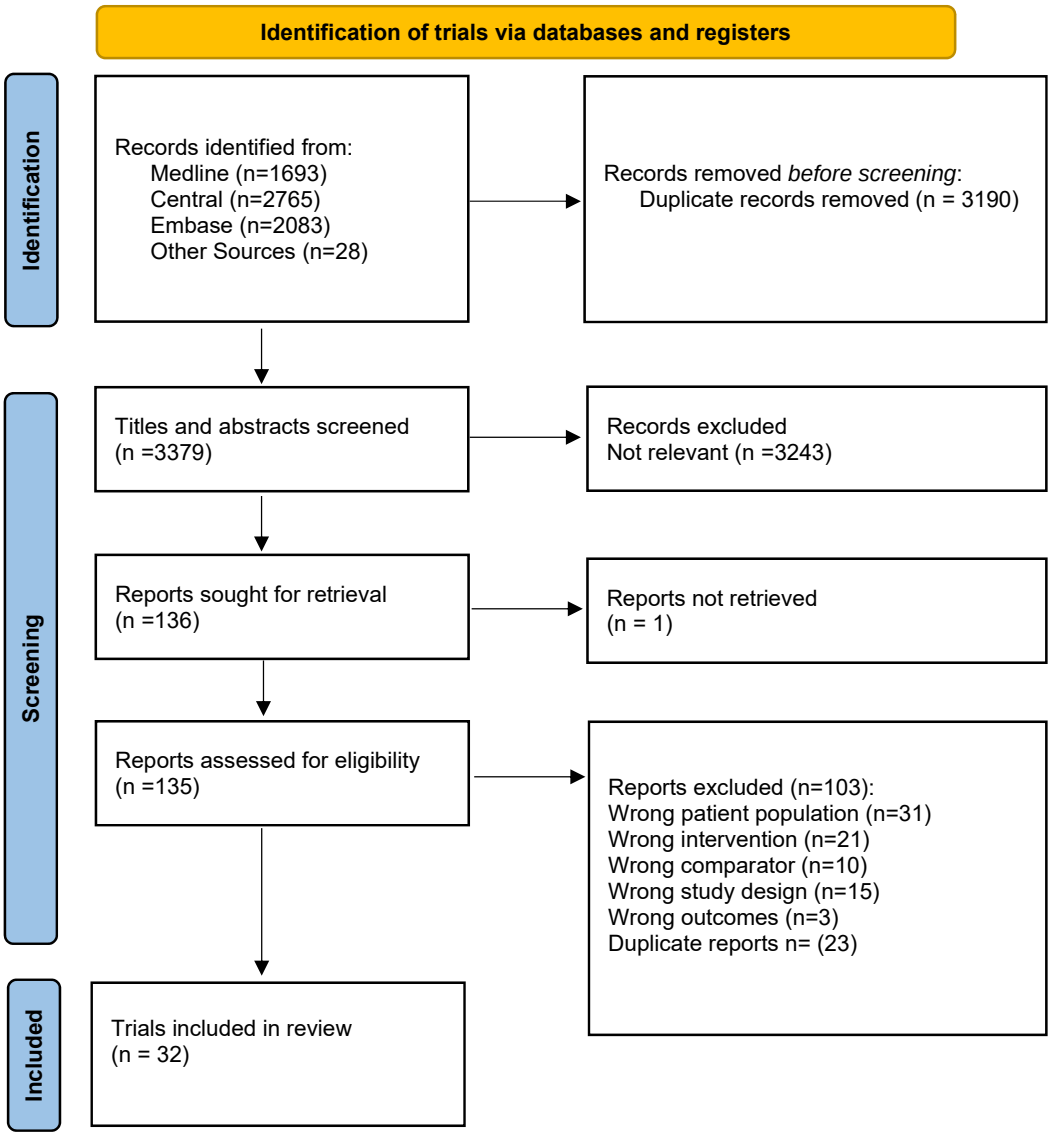
Critical revision of the manuscript for important intellectual content: Hammond, Myburgh, Garside, Vlok, Mahendran, Adigbli, Gao, Yao, Santos, Finfer, Goodman, Guyatt, Venkatesh, Seppelt, Di Tanna, Delaney

Statistical analysis: Di Tanna, Santos, Delaney

Supervision: Delaney, Di Tanna, Myburgh, Hammond

Anthony Delaney and Gian Luca Di Tanna had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

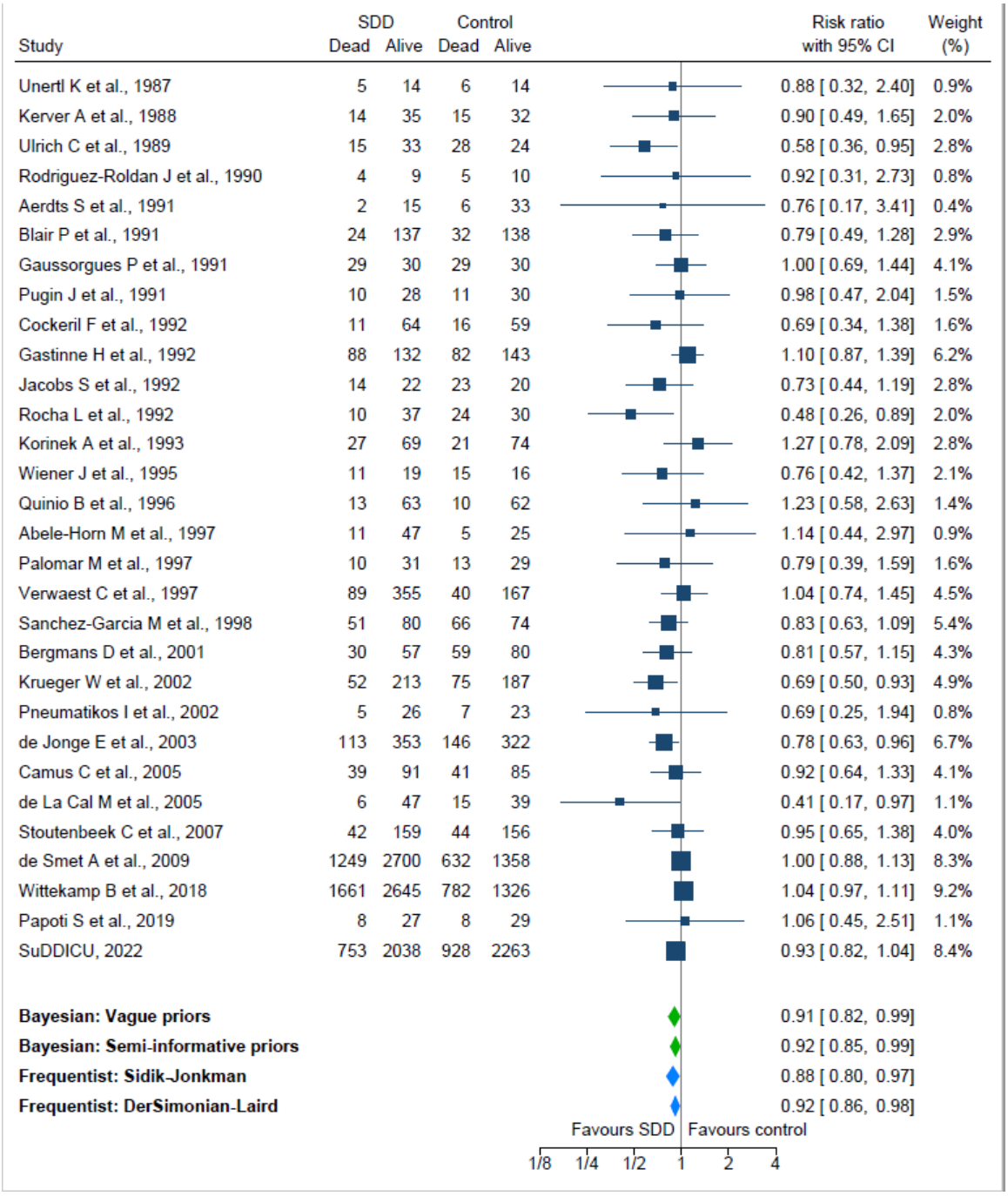
Figure 1: PRISMA flow diagram of search strategy and included studies



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

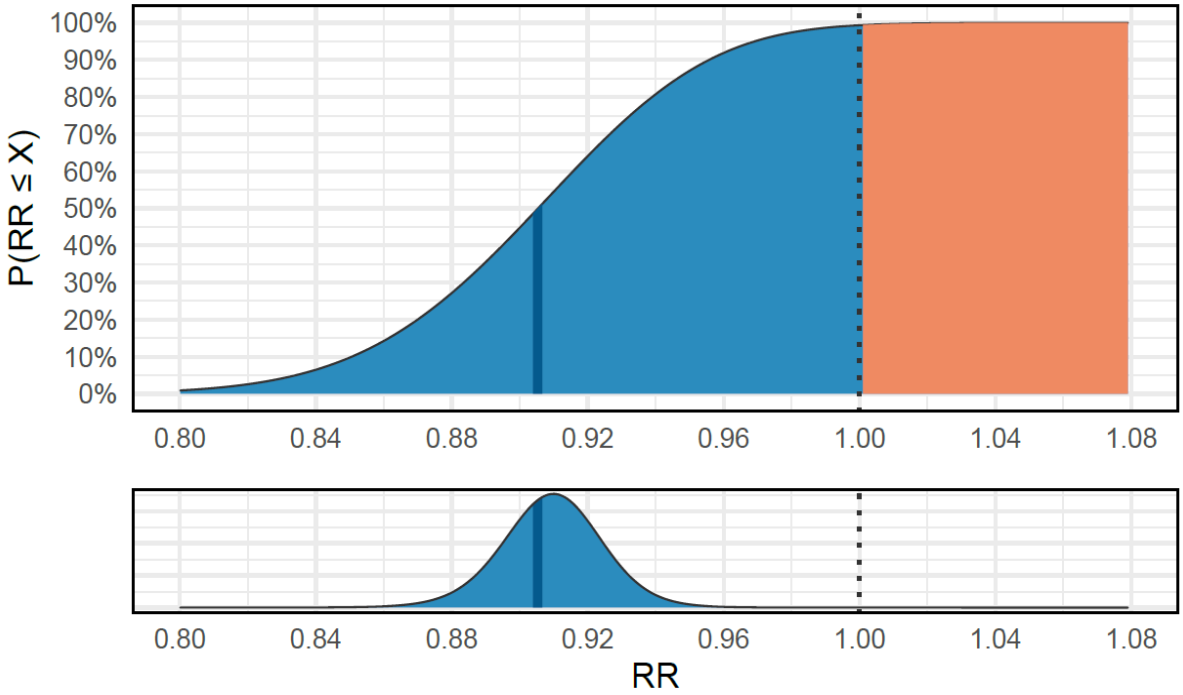
Figure 2: Forest Plot for hospital mortality for the comparison between SDD v Standard care (a). Cumulative incidence plot for the posterior probability of the RR for mortality for SDD compared to Standard care (b)

a)



SDD: Selective Digestive Decontamination. CI: Confidence intervals (Credible intervals for Bayesian estimates). Dark blue box represents point estimate. Dark blue line represents confidence intervals. Green and light blue diamond: the width represents all trials pooled estimate confidence interval and the middle point the point estimate.

b)



The upper subplots display the cumulative posterior distribution, with the y-axis corresponding to the probability the RR is less than or equal to the value on the x-axis sizes. The lower subplot displays the entire posterior distribution, with the bold, vertical line indicating the median value and the area highlighted in blue indicating the percentile-based 95% credible interval.

400 **Table 1: Included study characterisitcs**

Study	Year	Design	Centres	Participants	Population	SDD	Control	Ventilated	Primary Outcome
Unertl	1987	Individual patient RCT	1	39	Mixed medical surgical	**Oral**: q6h for duration of intubation • polymyxin B 15mg, gentamicin 24mg, amphotericin B 300mg **Enteral**: q6h for duration of intubation • polymyxin B 25mg, gentamicin 40mg	Standard care	100%	Colonization and respiratory infection
Kerver	1988	Individual patient RCT	1	96	Mixed medical surgical	**Oral**: q6h until orophryangeal and tracheal cultures negative • polymyxin E 2%, tobramycin 2%, amphotericin 2% **Enteral:** q6h until orophryangeal and tracheal cultures negative • Polymxin E 200mg, tobramycin 80 mg, amphotericin B 200mg **Intravenous**: 5 days • Cefotaxime 50-70mg/kg/day	Standard care	100%	Prevention of colonization
Ulrich	1989	Individual patient RCT	1	100	Mixed medical surgical	**Oral**: qid until potentially pathogenic organism could no longer be isolated • polymyxin E 2% norfloxacin 2%, amphotericin 2% **Enteral:** qid until potentially pathogenic organism could no longer be isolated • polymyxin E 100mg, tobramycin 80mg, amphotericin 500mg I**ntravenous**: daily until potentially pathogenic organism could no longer be isolated • Trimethoprim 500mg	Standard care	80%	Prevention of ICU acquired infection
Rodriguez-Roldan	1990	Individual patient RCT	1	28	Mixed medical surgical	**Oral**: q6h • Polymyxin E 2%, tobramycin or netilmicin 2%, amphotericin B 2%	Placebo	100%	Colonization and infection in the respiratory system
Aerdts	1991	Individual patient RCT	1	56	Mixed medical surgical	**Oral**: 1g q6h • Amphotericin 2%, Norfloxacin 2%, Polymixin E 2% **Enteral**: qid via NGT	Standard Care	100%	Lower respiratory tract infection

						• Polymxin E 200mg, Norfloxacin 50mg, amphotericin B 500mg **Intravenous**: tds for 3 days • Cefotaxime 500mg			
Blair	1991	Individual patient RCT	1	331	Mixed medical surgical	**Oral:** qid for duration of ICU • ORAL Polymxin, 2% tobramycin, 2% amphotericin 2% **Enteral:** qid for duration of ICU • Polymxin 100mg, Tobramycin 80mg, amphotericin 500mg **Intravenous**: 4 days • Cefotaxime 50mg/kg/day	Standard care	93%	Infection
Gaussorgues	1991	Individual patient RCT	1	118	Mixed medical surgical	**Enteral:** qid for duration of ventilation • gentamicin 20mg, colistin 36mg, vancomycin 50mg, amphotericin B 500mg	Standard care	100%	Nosocomial bacteraemia
Pugin	1991	Individual patient RCT	1	79	Surgical	**Oral:** 6 times daily for duration of ventilation • Polymyxin B sulfate 37.5mg, neomycin 250mg, vancomycin 250mg	Placebo	100%	Ventilator associated pneumonia
Cockerill	1992	Individual patient RCT	1	150	Mixed medical surgical	**Oral:** qid for duration of ICU • Gentamicin 2%, polymxin B 2%, nystatin $1x10^5$U/g **Enteral:** qid for duration of ICU • Gentamicin 80mg, Polymyxin B 100mg, Nystatin 2 million units **Intravenous:** tds for 3 days • Cefotaxime 1g	Standard care	84.7%	Infection rates
Gastainne	1992	Individual patient RCT	15	445	Mixed medical surgical	**Oral:** 3g qid for duration of ventilation • colistin sulfate 2%, tobramycin 2%, amphotericin B 2% **Enteral:** qid for duration of ventilation colistin sulfate 100mg, tobramycin 80mg, amphotericin B qid100mg	Placebo	100%	Mortality at day 60
Jacobs	1992	Individual patient RCT	1	76	Mixed medical surgical	**Oral:** qid for duration of ventilation • polymyxin E 2%, tobramycin 2%, amphotericin 2%	Standard care	100%	Nosocomial pneumonia

						Enteral: qid for duration of ventilation • polymyxin E 100mg, tobramycin 80mg, amphotericin 500mg **Intravenous:** tds for 4 days • Cefotaxime 50mg/kg/day			
Rocha	1992	Individual patient RCT	1	101	Mixed medical surgical	**Oral:** qid for duration of ICU • Polymyxin E 2%, tobramycin 2%, amphotericin B 2% **Enteral:** qid for duration of ICU • polymyxin E 100mg, tobramycin 80mg, amphotericin 500mg **Intravenous:** 4 days • Cefotaxime 2g/day	Placebo	100%	Prevention of nosocomial infection in the ICU
Korinek	1993	Individual patient RCT	2	191	Neurosurgical	**Oral:** qid for duration of ventilation (max. 15 days) • polymyxin E 2%, Tobramycin 2%, amphotericin 2%, vancomycin 2% **Enteral:** qid for duration of ventilation (max. 15 days) polymyxin E 100mg, tobramycin 80mg, amphotericin 500mg	Placebo	100%	Infection rate
Langlois-Karaga	1995	Individual patient RCT	1	97	Trauma	**Oral:** qid for duration of ventilation or commencement of enteral nutrition • colistin, gentamicin, amphotericin B **Enteral:** qid for duration of ventilation or commencement of enteral nutrition • colistin, gentamicin, amphotericin B	Placebo	100%	Duration of hospitalization and cost of antibiotherapy
Wiener	1995	Individual patient RCT	1	61	Mixed medical surgical	**Oral:** qid for duration of intubation • polymyxin E 2%, gentamicin 2%, nystatin 100,000 units **Enteral:** qid for duration of intubation polymyxin E 100mg, gentamicin 80mg, nystatin 2 x 10^6U	Placebo	100%	Nosocomial infection
Quinio	1996	Individual patient RCT	1	148	Trauma	**Oral:** 15ml qid until 24 hours post extubation or commencement of enteral feeding • Colistin sulfate 2%, gentamicin 2%,	Placebo	100%	Nosocomial infection

						amphotericin B 2% **Enteral:** qid until 24 hours post extubation or commencement of enteral feeding • Colistin sulfate100mg, gentamicin 80mg, amphotericin B 500mg			
Abele-Horn	1997	Individual patient RCT	1	88	Mixed medical surgical	**Oral:** q6h for duration of ventilation • Amphotericin 2%, Tobramycin 2%, Polymyxin E 2% **Intravenous:** tds for 3 days • Cefotaxime 2g	Standard care	100%	Colonisation and infection rates
Palomar	1997	Individual patient RCT	10	83	Mixed medical surgical	**Oral:** q6h for duration of ventilation or 40 days • polymyxin E 2%, tobramycin 2%, amphotericin 2% **Enteral:** q6h for duration of ventilation or 40 days • polymyxin E 2%, tobramycin 2%, amphotericin 2% **Intravenous:** tds for 4 days • Cefotaxime 1g	Standard care	100%	The prophylaxis of nosocomial infection
Verwaest	1997	Individual patient RCT	1	578	Surgical	**Oral**: qid for duration of ICU • Ofloxacin 2%, amphotericin B2% OR • polymyxin 2%, tobramycin 2%, amphotericin 2% **Enteral**: duration of ICU • ofloxacin 200mg bd and amphotericin 500mg qid OR • Polymyxin E 1 MU, tobramycin 80mg, amphotericin 500mg **Intravenous**: for 4 days • Ofloxacin 200mg OR cefotaxime 1g qid	Standard care	100%	Colonization, incidence of infection and mortality
Sanchez-Garcia	1998	Individual patient RCT	5	271	Mixed medical surgical	**Oral:** q6h • gentamicin 2%, Polymyxin E 2%, amphotericin B 2% **Enteral:** q6h • gentamicin 80mg, polymyxin E 100mg,	Placebo	100%	Ventilator associated pneumonia

						amphotericin 500mg **Intravenous:** daily for 3 days • Ceftriaxone 2g			
Bergmans	2001	Individual patient RCT	3	226	Mixed medical surgical	**Oral:** q6h • Gentamicin 2%, Colistin 2%, Vancomycin 2%	Placebo	100%	Ventilator associated pneumonia
Krueger	2002	Individual patient RCT	2	527	Surgical	**Oral:** q6h for duration of ICU • gentamicin 24mg, polymyxin B 15mg, ± vancomycin 37.5mg **Enteral:** q6h for duration of ICU • gentamicin 40mg, polymyxin B 25mg, ± vancomycin 62.5mg **Intravenous:** bd for 4 days • Ciprofloxacin 400mg	Placebo	92.6%	Incidence and time of onset of infection, incidence and time of onset of severe organ dysfunctions and mortality
Pneumatikos	2002	Individual patient RCT	1	61	Trauma	**Oral:** Continuous infusion of 2ml/hr • polymyxin E 73mg, tobramycin 73mg, amphotericin B 500mg in 500ml 0.9% saline	Placebo	100%	Tracheal colonization and ventilator associated pneumonia
De Jonge	2003	Individual patient RCT	1	934	Mixed medical surgical	**Oral:** qid 0.5g • Polymyxin E 2%, Tobramycin 2%, Amphotericin B 2% **Enteral:** qid • Polymyxin E 100mg, Tobramycin 80mg, Amphotericin B 500mg **Intravenous:** qid for 4 days • Cefotaxime 1g	Standard care	85.3%	Acquired colonization by any resistant strain and mortality
Camus	2005	Individual patient RCT	3	256	Mixed medical surgical	**Oral:** qid for duration of ventilation • 45mg Polymyxin E, 30mg Tobramycin **Enteral:** qid for duration of ventilation • 75mg Polymyxin E, 50mg Tobramycin	Placebo	100%	Acquired infection
de La Cal	2005	Individual patient RCT	1	107	Burns	**Oral:** qid 0.5g • Polymyxin E 2%, tobramycin 2%, amphotericin B 2% **Enteral:** qid 10ml • Polymyxin B 100mg, Tobramycin 100mg, Amphotericin B 500mg	Placebo	76.6%	Mortality and endogenous pneumonia

						Intravenous: tds for 4 days • Cefotaxime 1g			
Koeman	2006	Individual patient RCT	5	258	Mixed medical surgical	**Oral:** 0.5g qid • Colistin 2% chlorhexidine 2%	Standard care	100%	Time to ventilator associated pneumonia
Stoutenbeek	2007	Individual patient RCT	17	401	Trauma	**Oral:** 0.5g qid • Polymyxin E 2%, tobramycin 2% amphotericin B 2% **Enteral:** 10mLs qid • polymyxin E 100mg, tobramycin 80mg, amphotericin 500mg **Intravenous:** qid for 4 days • Cefotaxime 1g	Standard Care	100%	Mortality at 3 months
deSmet	2009	Cluster cross over	13	5939	Mixed medical surgical	**Oral:** qid • Polymyxin E 2%, Tobramycin 2%, Amphotericin B 2% **Enteral:** qid • Polymyxin E 100mg, Tobramycin 80mg, Amphotericin B 500mg **Intravenous**: qid for 4 days • Cefotaxime 1g (SDD group only)	Standard care	91.5%	28-day mortality
Wittekamp	2018	Cluster Cross-Over	13	6414	Mixed medical surgical	**Oral:** qid • 0.19 million units of colistin sulfate, 10 mg of tobramycin sulfate, and 0.1 million units of nystatin **Enteral:** qid • 1.9 million units of colistin sulfate, 80 mg of tobra- mycin sulfate, and 2.0 million units of nystatin	Standard Care	100%	Incidence of ICU-acquired BSI with multi-drug resistant Gram-negative bacteria
Papoti	2019	Individual patient RCT	1	72	Mixed medical surgical	**Oral:** tds for 10 days • Colistine, fluconazole	Standard care	100%	Prevention of infection related ventilator associated complications and VAP
SuDDICU	2022	Cluster Cross-	19	5982	Mixed medical	**Oral:** q6h for duration of ventilation • 0.5g of oral paste containing 10mg colistin,	Standard care	100%	Hospital mortality

		Over			surgical	10mg tobramycin and 125,000 international units of nystatin **Enteral:** q6hr • 100mg colistin, 80mg tobramycin and 2x106 international units of nystatin **Intravenous:** daily for 4 days • third-generation cephalosporin or ciprofloxacin			

RCT: Randomised clinical trial. VAP: ventilator associated pneumonia. BSI: Blood stream infections. Qid: four times a day. Q6h: every 6 hours. Participant number for Wittekamp reported as numbers used from CHX arm (control) and SDD/SOD arms. Control arm for Wittekamp was the randomised CHX arm as most sites used this as standard of care prior to randomisation.

403 **Table 2: Outcomes**

	Trials	Participants	I^2	Effect measure	95% CrI
Primary outcome					
Hospital mortality (BMA – Vague priors)	30	24,034	33.9%	RR = 0.91	0.82 to 0.99
Hospital mortality (BMA – semi-informative priors)	30	24,034	31.2%	RR = 0.92	0.85 to 0.99
Hospital mortality (Hartung-Knapp-Sidik-Jonkman)	30	24,034	56.4%	RR = 0.88	0.80 to 0.97*
Hospital mortality (Der Simonian-Laird)	30	24,034	20.3%	RR = 0.92	0.86 to 0.98*
Secondary Outcomes					
Mortality at longest time point	30	24,034	22.9%	RR = 0.93	0.86 to 1.00
Duration of MV (days)	20	20,733	22.2%	MD = - 0.73	-1.32 to -0.09
ICU length of stay (days)	24	23,198	52.1%	MD = -0.86	-1.73 to 0
Hospital length of stay (days)	5	18,592	2.1%	MD = -0.52	-2.2 to 1.2
Incidence of VAP	22	3619	36.2%	RR = 0.44	0.36 to 0.54
Incidence of ICU acquired bacteraemia	21	22,076	18.9%	RR= 0.68	0.57 to 0.81
C. Diff infection	3	12,322	7.0%	RR = 0.52	0.15 to 1.80
Culture of any ARO	5	12,841	16.1%	RR = 0.64	0.45 to 0.91
Positive MRSA culture	5	13,240	30.4%	RR = 1.06	0.52 to 2.11
Positive VRE culture	3	13,287	6.1%	RR = 0.62	0.18 to 2.1
Subgroup analysis for the primary outcome					
Cluster cross-over	3	18,335	70.6%	RR = 1.0	0.79 to 1.2
Individual patient randomised	27	5699	12.3%	RR = 0.85	0.77 to 0.94
SDD with no intravenous agent[+]	14	11,037	9.4%	RR = 1.01	0.91 to 1.11
SDD with intravenous agent[+]	17	12,997	30.4%	RR = 0.84	0.74 to 0.94
Surgical ICUs	5	1,544	44.2%	RR = 0.92	0.67 to 1.30
Trauma ICUs	4	717	34.8%	RR =0.84	0.48 to 1.37
Mixed population ICUs	21	21,773	40.2%	RR = 0.91	0.81 to 1.0

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405 RR: Risk Ratio; MD: Mean Difference; *Confidence Interval; MV: Mechanical ventilation; ICU: Intensive care unit; C-Diff: Clostridioides difficile; VAP: Ventilator associated pneumonia; ARO: Antibiotic
406 resistant micro-organisms. No data in medical ICUs. [+]Total number of trials is 31 as de Smet contributes both IV and non-IV data. Participant numbers for the control group have been split evenly
407 between IV and non-IV group so they remain the same as the main publication (i.e. not double counted).

409 **Table 3: GRADE Summary of Findings Table**

Selective decontamination of the digestive tract in mechanically ventilated patients in the intensive care unit					
Population	Mechanically ventilated patients treated in the ICU				
Intervention	Selective decontamination of the digestive tract				
Comparison	Standard care				
Outcome Timeframe	**Effect estimate** (95% CrI) Number of trials Number of participants	**Absolute effect estimates**		**Certainty of Evidence** (Quality of the evidence)	**Plain language summary***
		Standard Care	**SDD** **(95% CrI)**		
Mortality in hospital	Relative risk 0.91 (0.82 to 0.99) 30 trials 24,034 participants	316 per 1000	287 per 1000 29 fewer per 1000 (4 fewer to 55 fewer)	**Moderate** Due to inconsistency[1]	The use of SDD probably reduces the risk of in-hospital mortality
Ventilator associated pneumonia	Relative risk 0.44 (0.36 to 0.54) 22 trials 3,619 participants	298 per 1000	132 per 1000 166 fewer per 1000 (137 fewer to 192 fewer)	**Very Low** Due to inconsistency, indirectness and risk of bias[2]	The evidence is very uncertain about the effect of SDD on the reduction in VAP
Incidence of ICU acquired bacteraemia	Relative risk 0.68 (0.57 to 0.81) 21 trials 22,076 participants	101 per 1000	69 per 1000 32 fewer per 1000 (19 fewer to 44 fewer)	**Low** Due to indirectness and risk of bias[3]	The use of SDD may result in a reduction in ICU acquired bacteraemia
Incidence of participants with positive cultures of antimicrobial resistant organisms	Relative risk 0.64 (0.45 to 0.91) 5 trials 12,841 participants	205 per 1000	131 per 1000 94 fewer per 1000 (17 fewer to 113 fewer)	**Very Low** Due to inconsistency, indirectness, risk of bias[4]	The evidence is uncertain about the effect of SDD on the emergence of antimicrobial resistant organisms
Incidence of participants with positive culture for MRSA	Relative risk 1.06 (0.52 to 2.11) 5 trials 13,240 participants	20 per 1000	21 per 1000 1 more per 1000 (10 fewer to 22 more)	**Very Low** Due to inconsistency, indirectness, risk of bias [5]	The evidence is very uncertain about the effect of SDD on the incidence of positive cultures ofMRSA
Incidence of participants with positive culture for VRE	Relative risk 0.62 (0.18 to 2.1) 3 trials 13,287 participants	3 per 1000	2 per 1000 1 fewer per 1000 (3 fewer to 2 more)	**Very Low** Due to inconsistency, indirectness, risk of bias [6]	The evidence is very uncertain about the effect of SDD on the

					incidence of positive cultures of VRE
Duration of mechanical ventilation	Mean difference -0.73 days (-1.32 to -0.09 days) 20 trials 20,733 participants	9.2 days	8.5 days (7.9 days to 9.1 days)	**Moderate** Due to indirectness[7]	The use of SDD probably results in a small reduction in the duration of ventilation
Duration of ICU admission	Mean difference -0.86 days (-1.73 to 0 days) 24 trials 23,198 participants	12.9 days	12.1 days (11.2 days to 12.9 days)	**Low** Due to indirectness and imprecision[8]	The use of SDD may have little to no difference in the duration of ICU admission
Duration of hospital admission	Mean difference -0.52 days (-2.2 to 1.2 days) 5 trials 18,592 participants	26.6 days	26.1 days (24.2 days to 27.8 days)	**Moderate** Due to imprecision[9]	The use of SDD probably results in little to no difference in the duration of hospital admission

* Judgement is based on the intervention reducing the outcome by any amount. ICU = Intensive Care unit, CrI = credible intervals from primary Bayesian analysis with vague priors, SDD = Selective digestive decontamination, MRSA = methicillin resistant Staphylococcus aureus, VRE = vancomycin resistant Enterococcus.

1. Downgraded for inconsistency due to differences in the components of the intervention (Table 1), and differences in standard care in the included trials.

2. Downgraded due to indirectness as VAP is not a patient important outcome, there is significant variation in standards for diagnosis as shown in Table S1 and risk of bias in adjudication of these outcomes in the included trials (Table S2).

3. Downgraded due to indirectness as ICU acquired bacteraemia is not a patient important outcome, and risk of bias in adjudication of these outcomes in the included trials (Table S2).

4. Downgraded due to inconsistency in the definition of antimicrobial resistant organisms and the threshold for testing, indirectness as not a patient important outcome, risk of bias in adjudication of this outcome in the included trials (Table S2) and imprecision as the 95% credible intervals include values that may be of direct value to patients .

5. Downgraded due to inconsistency in the indication for testing, indirectness regarding patient importance and risk of bias in the adjudication of this outcome in the included trials (Table S2)

6. Downgraded due to inconsistency in the indication for testing, indirectness regarding patient importance of this outcome and risk of bias in the adjudication of this outcome in the included trials (Table S2)

7. Downgraded due to indirectness as duration of ventilation not directly a patient important outcome

8. Downgraded due to indirectness as duration of ICU not directly a patient important outcome, imprecision as evidence by high heterogeneity in the I^2

9. Downgraded due to imprecision as the 95% credible intervals include values that may be of direct value to patients

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