Effect of Selective Decontamination of the Digestive Tract on Hospital Mortality in Critically Ill Patients Receiving Mechanical Ventilation: A Randomized Clinical Trial

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ABSTRACT (419 words)

Importance: Whether selective decontamination of the digestive tract (SDD) reduces mortality in critically ill patients remains uncertain.

Objective: To determine whether SDD reduces in-hospital mortality in critically ill adults.

Design, Setting and Participants: A cluster, crossover, randomized clinical trial that recruited 5982 mechanically ventilated adults from 19 ICUs in Australia between April 2018 and May 2021 (final follow up August 2021). A contemporaneous ecological assessment recruited 8599 patients from participating ICUs between May 2017 and August 2021.

Interventions: ICUs were randomly assigned to adopt or not adopt a SDD strategy for two alternating 12-month periods, separated by a 3-month inter-period gap. Patients in the SDD group (N = 2791) received a six-hourly application of an oral paste and administration of a gastric suspension containing colistin, tobramycin and nystatin for the duration of mechanical ventilation, plus a four-day course of an intravenous antibiotic with a suitable antimicrobial spectrum. Patients in the control group (N = 3191) received standard care.

Main outcomes and measures: The primary outcome was hospital mortality. There were eight secondary outcomes, including the proportion of patients with new positive blood cultures, antibiotic resistant organisms (AROs) and *Clostridioides difficile* infections. For the ecological assessment, a non-inferiority margin of 2% was pre-specified for three outcomes including new cultures of AROs.

Results: Of 5982 patients (mean age 58.3 years, 36.8% women) enrolled from 19 ICUs; all patients completed the trial. There were 753 (27.0%) and 928 (29.1%) in-hospital deaths in the

SDD and standard care group respectively (mean difference [MD], -1.7%; -95% confidence interval [95% CI], -4.8% to 1.3%]; odds ratio [OR] 0.91, 95%CI 0.82 to 1.02, p=0.12). Of eight pre-specified secondary outcomes, six showed no significant differences.

In the SDD vs standard care groups, 23.1% vs 34.6% had new ARO cultures (absolute difference [AD] -11.0%, 95%CI -14.7 to -7.3), 5.6% vs 8.1% had new positive blood cultures (AD -1.95%, 95%CI -3.5 to -0.4), and 0.5% vs 0.9% had new *Clostridioides difficile* infections (AD -0.24%, 95%CI -0.6 to 0.1). In 8599 patients enrolled in the ecological assessment, the use of SDD was not shown to be non-inferior noninferior with regard to the change in the proportion of patients who developed new AROs (-3.3% vs -1.59%; MD -1.71%, one-sided 97.5%CI -∞ to 4.31, and 0.88% vs 0.55%; MD -0.32%, one-sided 97.5%CI -∞ to 5.47) in the first and second periods, respectively.

Conclusions and Relevance: Among critically ill patients receiving mechanical ventilation, SDD did not significantly reduce in-hospital mortality. However, the confidence interval around the effect estimate includes a clinically important benefit.

Trial Registration: Clinical Trials.gov registration number: NCT02389036

Key points

Question:

Among critically ill patients receiving mechanical ventilation, what is the effect of selective decontamination of the digestive tract (SDD) on hospital mortality?

Findings:

In this randomized clinical trial that included 5982 patients, SDD compared with standard care without SDD did not result in a significant difference in in-hospital mortality (27.0% vs 29.1%, respectively; odds ratio, 0.91).

Meaning:

Among critically ill patients receiving mechanical ventilation, SDD did not significantly reduce in-hospital mortality compared with standard care without SDD, although the confidence interval around the effect estimate includes a clinically important benefit.

INTRODUCTION (273/300 words, 14 references)

Selective decontamination of the digestive tract (SDD) was originally described in immunocompromised patients with haematological disease[1] and in patients with trauma[2,3] and extended to critically ill patients treated in intensive care units (ICUs) in the 1980s.[4,5]

SDD is the application of topical non-absorbable antibiotics and antifungal agents to the upper gastrointestinal tract combined with a short course of intravenous antibiotics to patients receiving mechanical ventilation via an endotracheal tube.[6]

The principal aim of SDD is to prevent the development of ventilator-associated pneumonia caused by pathogenic Gram-negative bacteria and secondary overgrowth with yeasts from the upper gastrointestinal tract. SDD usually consists of an oral paste and gastric suspension of three non-absorbed antimicrobial agents combined with a short course of an intravenous antibiotic with an appropriate antimicrobial spectrum.[5]

Although systematic reviews of published randomized clinical trials have reported that the use of SDD was associated with reductions in interval mortality rates and in the incidence of ventilator-associated pneumonia,[7-10] widespread international use of SDD as a standard of care remains low.[6,11,12] Clinician uncertainty may relate to concerns about the generalizability of the results of previous randomized clinical trials, weak recommendations about the use of SDD in international clinical practice guidelines[13] and that the use of SDD may increase the prevalence of antibiotic resistant organisms.[8,14]

To address this uncertainty, the Selective Decontamination of the Digestive Tract in the Intensive Care Unit (SuDDICU) trial was designed to test the hypothesis that adding SDD to

standard care would decrease hospital mortality in mechanically ventilated ICU adults compared to standard care. An observational evaluation of whether SDD was non-inferior to standard care in changes in microbiological ecology was conducted simultaneously.

METHODS

Consent

Ethical approval was obtained from Human Research Ethics Committees and Research Governance Offices at each site.

As SDD was implemented as an ICU-wide intervention, a waiver of individual patient consent up to hospital discharge was obtained. For patients in the control group and ecological assessment, a waiver of consent was also obtained as no intervention was offered.

Study design and oversight

This was a cross-over, cluster randomized clinical trial with a concomitant observational ecological assessment The protocol and statistical analysis plan are presented in Supplement 1 and Supplement 2 respectively and were pre-published.[15] The trial was originally planned as an international trial that would include sites outside Australia in Canada and the United Kingdom. Details of the evolution of the Australian trial are presented in the introduction of Supplement 3. Data were entered into an encrypted database for statistical analyses conducted at The George Institute for Global Health.

The SDD study drug preparations were manufactured by Verita Pharma® (Sydney, Australia) under licence from The George Institute for Global Health in accordance with the standards for Good Manufacturing Practice approved by the Therapeutic Goods Administration of Australia.

110 ***Trial participants***

111 Eligible ICUs were general medical and surgical facilities in Australia capable of treating
112 mechanically ventilated adults and able to implement the SDD protocol in all eligible patients.
113 ICUs were randomly assigned to adopt a SDD strategy or not for two alternating 12-month
114 periods, separated by a 3-month inter-period gap.

115 Eligible patients for the intervention periods were those i.) mechanically ventilated via an
116 endotracheal tube on admission to the ICU, ii.) who became ventilated during that admission
117 and iii.) who were predicted to remain ventilated for at least 48 hours. Patients who were
118 previously predicted not to be mechanically ventilated for more than 48 hours, but who
119 subsequently required ongoing ventilation were rescreened for recruitment.

120 For the ecological assessment that was conducted to determine changes in participating ICU
121 microbiological flora, data were collected for one full week of each month during five 3-month
122 ecology collection periods: the pre-trial period, inter-period gap and post-trial period; and the
123 final three months of each 12-month intervention period. During these periods, all patients
124 admitted to participating ICUs regardless of ventilation status, excluding mechanically ventilated
125 patients who were already enrolled in the intervention groups, were included in the ecology
126 assessment.

127 ***Randomization***

128 During the three-month pre-trial period, participating ICUs were stratified by size based on their
129 number of beds and then randomly assigned using a computer-generated program written in
130 SAS to deliver either SDD plus standard care (SDD group) or to continue standard care in the

first 12-month intervention period. The first intervention period was followed by a three-month inter-period gap, following which ICUs crossed over to the alternative group for a second 12-month period. This was followed by a three-month post-trial period. (Supplement 3: eFigure 1)

Interventions

SDD comprised i.) a six-hourly topical application of 0.5g of oral paste containing 10mg colistin, 10mg tobramycin and 125,000 international units of nystatin applied to the buccal mucosa and oropharynx; ii.) a six-hourly administration of 10mL of gastric suspension containing 100mg colistin, 80mg tobramycin and $2x10^6$ international units of nystatin to the upper gastrointestinal tract via a gastric or post-pyloric tube; iii.) a four-day course of an intravenous SDD-compliant antibiotic (e.g. a third-generation cephalosporin or ciprofloxacin) unless already treated with antibiotics with activity against Gram-negative bacteria during the first four days after enrolment, in which case additional antibiotics were not administered. Details of the SDD drug preparations are presented in Supplement 3: sections O to T.

The SDD oral paste and gastric suspension were administered as soon as possible from the time of admission to the ICU, if mechanically ventilated on admission and/or from the time of endotracheal intubation in the ICU and continued for the duration of mechanical ventilation via an endotracheal tube or until day 90, whichever came first. All other treatments, including the administration of antibiotics for prophylactic or therapeutic indications, were at the discretion of treating clinicians in accordance with respective institutional microbiological prescription polices. A list of SDD-compliant antibiotics is presented in Supplement 3: section J.

Data and Study Management

Data collected at baseline included demographics, admission diagnosis, the Acute Physiology and Chronic Health Evaluation (APACHE) score (a severity of illness score ranging from 0 to 71 [APACHE-II][16] or 0 to 299 [APACHE-III],[17] with higher scores indicating an increased risk of death) and specific risk factors for infection including prior receipt of oral chlorhexidine and intravenous antibiotics.

For patients treated in ICUs during the SDD intervention period, daily data documenting the delivery of SDD oral paste and gastric suspension were collected for the duration of mechanical ventilation up to 90 days and SDD-compliant antibiotics for 5 days. Adherence in administering the topical components of SDD was reported as the proportion of patients receiving at least one dose of an eligible SDD dose on a daily basis for the duration of mechanical ventilation.

For all trial participants, doses of all intravenous antibiotics were collected for 28 days. Data recorded daily for 90 days while still in the ICU included the duration of mechanical ventilation, ICU and hospital admission, all new organisms isolated from blood and non-blood cultures, any positive test for *Clostridioides difficile* and antibiotic resistant organisms from all cultures, as defined in Supplement 3: section K.

For the ecological assessment, data were collected for one full week of each month during five 3-month ecology collection periods: the pre-trial period, inter-period gap and post-trial period; and the final three months of each 12-month intervention period on all patients admitted to the participating ICU regardless of mechanical ventilation status, excluding mechanically ventilated patients already enrolled in the intervention periods.

Outcome Measures

The primary outcome was all-cause in-hospital mortality within 90 days of enrolment during the index hospital admission.

Clinical secondary outcomes were ICU mortality and days alive and free of mechanical ventilation, ICU admission, and hospitalization through 90 days

Microbiological secondary outcomes were the results from all new blood cultures; the incidence of new Clostridioides difficile infections; the incidence of pre-defined antibiotic resistant organisms from all blood, non-blood surveillance and clinical cultures and total antibiotic use, defined in daily defined doses.

Ecological assessment outcomes were the same as microbiological secondary outcomes, except that the outcome for total antibiotic use was excluded from the analysis.

Pre-specified additional analyses conducted during this trial, but are not included in this report, were a nested cohort microbial metagenomic analysis, a health economic analysis from a healthcare system perspective and an updated trial-level systematic review with Bayesian meta-analysis that included the results of this trial.

Sample size calculation

Based on data from a randomized clinical trial conducted in similar populations in Australia and available at the time of trial design,[18] a total of around 6000 patients from up to 20 Australian ICUs recruiting 150 patients per treatment period and assuming an intra-cluster correlation coefficient of 0.01 and an inter-period correlation of 0.005, provided at least 80% power to detect a 4.2 percentage point reduction in hospital mortality from a baseline mortality rate of 29% at an alpha of 0.05. This projected absolute reduction in mortality was considered to fall

within a range between 3.5 and 5.0 percentage points, representing a relative risk reduction between 12 and 17 percentage points and a number needed to treat between 20 and 29 that is consistent with other randomized clinical trials conducted in the Australian context[18,19] representing a plausible range for a detectable difference.

For the ecological assessment, the original sample size calculation was based on 40-50 sites recruiting 110-150 patients per period that would provide 80% power to reject a non-inferiority margin of 2%.[8] This calculation assumed a base incidence of antibiotic resistance of 10% (as defined in the original study protocol) using an inter-cluster coefficient of 0.01 and an inter-period coefficient of 0.005 as per the mortality analysis. Based on these assumptions, 20 Australian centres had 90% power to reject a non-inferiority margin of 3% for antibiotic resistance.

Statistical Analysis

Data were exported to SAS Enterprise Guide (version 8.3) for analysis. All patients were analyzed according to their randomization group, regardless of adherence. The primary analysis used all available data with no imputation for missing data.

The primary outcome of death in hospital within 90-days was analyzed using an individual-level hierarchical logistic regression model, including both a random cluster effect and a random cluster-period effect. The effect of the intervention is presented as the odds ratio (OR) for death and the 95% CI, adjusted by the Kenward-Roger correction.[20] Pre-specified sensitivity analyses were conducted without the Kenward-Roger correction and by fitting a linear regression at the cluster level;[21] and assessing the potential effect of missing data, using a

215 'worst case' and 'best case' scenario are presented in the statistical analysis plan. Adjusted
216 analyses of the primary outcome were conducted using the logistic regression model after
217 adding age, sex, severity of illness and operative vs. non-operative diagnosis as fixed covariates.
218 Post-hoc analyses included calculation of mean risk differences and its 95%CI for the primary
219 outcome (hospital mortality) and one clinical secondary outcome (death within the ICU);
220 secondary analyses excluding patients who were enrolled less than one hour from the time to
221 admission to the ICU; adding prior treatment with oral chlorhexidine and intravenous
222 antibiotics to the model and presenting the primary outcome for each participating site.

223 The primary outcome was also examined in five pre-specified subgroup pairs based on pre-
224 randomization age, sex, severity of illness, operative diagnosis and trauma. Heterogeneity
225 across subgroups was assessed by adding the subgroup variable as well as its interaction with
226 the intervention to the main analysis model.

227 Analyses of secondary duration outcomes were analysed as the number of days alive and free of
228 the outcome up to day 90, using a hierarchical linear regression model with the Kenward-Roger
229 correction. Intervention effects were reported as the adjusted mean difference (MD) and its
230 95% CI. No adjustments for baseline co-variates were made for secondary outcomes. Time to
231 discharge alive from ICU and hospital were summarized using cumulative incidence functions
232 treating mortality as a competing risk, censored at day 90. The intervention effect was
233 estimated as the hazard ratio (HR) and its 95% CI obtained from a cause-specific Cox model,
234 with a fixed effect of treatment and a random site effect. The proportionality assumption was
235 confirmed by visual inspection of the survival curves, given that the test cannot be conducted
236 using a frailty model.

Defined daily doses of antibiotics were defined according to the World Health Organisation Collaborating Centre for Drug Statistics Methodology[22] and presented as the mean cumulative daily defined dose for all antibiotics and for each antibiotic over the duration of each intervention period up to 28 days. Absolute differences (AD) between groups in mean cumulative daily defined doses were tested post-hoc using a hierarchical linear mixed model. Microbiological outcomes and adverse events were reported as proportions and compared between treatment groups using an analysis at the cluster-period level.

The statistical significance threshold for the primary outcome was a 2-sided p value of less than 0.05. For the four secondary clinical outcomes, a step-down Holm-Bonferroni approach was pre-specified to control the family-wise error rate.[23] All other tests were performed using a 2-sided level of 5%. Because of the potential for type one error due to multiple comparisons, findings for analyses of secondary endpoints were considered exploratory.

Ecological data were assessed using a non-inferiority comparison and with a non-inferiority margin set at 2%, assuming a base incidence of antibiotic resistance of 10%. An increase of 2% is half the increase in tobramycin resistance reported from a previous cluster randomized clinical trial of SDD[24] and was considered to represent an increase likely to affect the acceptability of SDD.[25,26] Data were analyzed from the five study periods using linear regression to model the proportion of events in each cluster and each period, presented as the mean proportion and its two-sided 95% CI (equivalent to a one-sided 97.5%CI). The main effect of the interventions was estimated as the change, expressed as the MD and its 95%CI (presented as a one-sided 97.5%CI) in new organisms and antibiotic resistant organisms isolated from all cultures and new *Clostridioides difficile* infections from the pre-trial period vs. the first intervention period and

inter-period gap period combined (first comparison) and from the inter-period gap vs. the second intervention period and post-trial period combined (second comparison). A p-value from a one-sided test of non-inferiority of <0.025 indicated that the non-inferiority margin of 2% was rejected. To declare non-inferiority of SDD compared to standard care, the upper bound of the 95% confidence interval around the absolute risk difference between SDD and standard care needed to be lower than 2%. Post hoc, a sensitivity analysis comparing the change in proportions from the pre-trial period and each of the two intervention periods was conducted.

One pre-specified interim analysis was conducted and reviewed by the Data and Safety Monitoring Committee after the completion of the first 12-month intervention period including day-90 follow-up data at all sites.

RESULTS

Study sites and patients

From May 2017 to November 2021, 19 ICUs in 17 hospitals in Australia recruited a total of 14581 participants, of which 5982 participants were enrolled in the intervention study and 8599 were enrolled in the ecological assessment (Supplement 3: Figure 1, eTable 1, eFigure 2, eFigure 3).

Intervention study

For the first intervention period, 3049 patients were recruited, 1393 (45.7%) in ICUs allocated to SDD and 1656 (54.3%) in ICUs allocated to standard care; for the second intervention period, 2933 patients were recruited, 1398 (47.6%) in SDD ICUS and 1535 (52.3%) in standard care ICUs.

The primary outcome was available for all patients, 2791 patients in the SDD group and 3191 in the standard care group.

There were no significant differences in baseline characteristics between the SDD and standard care groups, other than the median (IQR) time from ICU admission and enrolment (16.1 [3.5; 39.7] vs. 3.7 [0.0; 20.5] hours), prior treatment with oral chlorhexidine (778 [27.9%] vs. 526 [16.5%]), receipt of pre-enrolment intravenous antibiotics (2098 [75.2%] vs. 2176 [68.2%]) and receipt of intravenous antibiotics for more than 48 hours prior to randomization (689 [32.5%] vs. 600 [27.6%]) respectively. (Supplement 3: Table 1, eTables 2 and 3)

Study treatments and process measures

In the SDD group, the proportion of days of mechanical ventilation where patients received both the SDD oral paste and gastric suspension was 87.1% (Supplement 3: eFigure 4). The minimum and total number of eligible doses for the SDD preparations are presented in Supplement 3: eTable 4.

Over the first four days, SDD-compliant intravenous antibiotics were administered to 80.0% patients in the SDD group compared with 53.7% patients in the standard care group (Supplement 3: eFigure 5a and 5b).

Primary outcome

At hospital discharge, 753 of 2791 (27.0%) patients allocated to SDD and 928 of 3191 (29.1%) patients allocated to standard care had died, (MD -1.7%, 95%CI -4.8% to 1.3%; OR 0.91, 95% CI 0.82 to 1.02, P=0.12).Findings were similar without the Kenward-Roger correction and adjusting for pre-specified covariates. (Table 2). As all data were available for the primary outcome,

sensitivity analyses for missing data did not change the principal analysis. (Supplement 3: eTable 8). Post-hoc analyses excluding patients who were enrolled during the first hour after ICU admission (638/2361 [27.0%] vs. 577/1889 [30.5%], OR 0.85, 95%CI 0.68 to 1.06, p=0.13) and adjusting for baseline imbalances in chlorhexidine and intravenous antibiotic treatment (OR 0.91, 95% CI 0.75 to 1.11, P=0.28) did not significantly alter the analysis (Supplement 3: eTable 8); hospital mortality at each participating ICU is presented in Supplement 3: eTable 9.

Clinical secondary outcomes

There were no significant between-group differences in ICU mortality (MD -1.4%, 95%CI -3.5% to 0.7 OR 0.92 95% CI 0.79 to 1.08),, the number of days alive and free of mechanical ventilation (MD 2.09, 95% CI -0.35 to 4.53), ICU admission (MD 1.75 95% CI -0.62 to 4.12) and hospital admission (MD 1.34 95% CI -0.89 to 3.58). (Table 2). Given than none of the differences were significant at the 5% level, the pre-specified Holm-Bonferroni multiplicity correction was not applied. Proximate and underlying causes of death are presented in eTable 10. There were no significant between-group differences in the time to death (HR 0.93, 95% CI 0.84 to 1.02), time to ICU discharge (HR 1.05 95% CI 0.99 to 1.11) or time to hospital discharge (HR 1.01 95% CI 0.95 to 1.08, Supplement 3: Figure 2a, eFigures 8 and 9). There was no significant heterogeneity in the effect of intervention assignment on hospital mortality in any of the five pre-defined subgroup pairs (Figure 2b).

Microbiological secondary outcomes

During the intervention period, in the SDD and standard care groups, the number of patients with blood cultures collected was 1664 (59.6%) vs. 2163 (67.8%) and the number of patients

with non-blood cultures collected was 583 (20.9%) vs. 1036 (32.5%), respectively (Supplement 3: eTables 5 and 6). There was a statistically significant reduction in the proportion of patients from whom antibiotic resistant organisms were cultured (23.1% vs 34.6%; AD -11.0%, 95% CI -14.7 to -7.3) and new positive blood cultures (5.6% vs 8.1%; AD -1.95%, 95% CI -3.5 to -0.4) in the SDD group compared with the standard care group. There was no significant difference in the incidence of new *Clostridioides difficile* infection (0.5% vs 0.9%; AD 0.24%, 95%CI -0.6 to 0.1) between the two groups. (Table 2).

There was no significant difference in mean cumulative daily defined dose of all intravenous antibiotics administered over the first 28 days (MD -0.035 95% CI -0.13 to 0.06) (Table 2) and in the overall total daily defined dose (Supplement 3: eFigure 6) or for each antibiotic class (Supplement 3: eFigure 7) between the SDD and standard care groups.

Ecological assessment

Among 8599 patients recruited into the ecological assessment, there were no significant between-group differences in demographics, severity of illness scores, hospital mortality and microbiological cultures over the five 3-month assessment period (Supplement 3: eTable 11). The proportions of participants with development of antibiotic resistant organisms, new positive blood cultures, and *Clostridioides difficile* infections over the five 3-month assessment periods are presented in Table 3. For the pre-trial period vs. the first intervention period and inter-period gap period combined (first comparison) and from the inter-period gap vs. the second intervention period and post-trial period combined (second comparison), SDD was non-inferior to standard care for the change in the proportion of new positive blood cultures (-0.75% vs 0.30%; MD -1.05%, one-sided 97.5%CI -∞ to 0.47, non-inferiority $p<0.001$ and -0.90% vs -

0.86%; MD 0.04% one-sided 97.5%CI -∞ to 1.67, non-inferiority p=0.008) and for *Clostridioides difficile* infections (-0.19% vs 0.05%; MD -0.24%, one-sided 97.5%CI -∞ to 0.18, non-inferiority p<0.001 and 0.03% vs -0.03%; MD-0.05%, one-sided 97.5%CI -∞ to 0.37, non-inferiority p<0.001), but not for the change in proportions with positive cultures for antibiotic resistant organisms (-3.3% vs -1.59%; MD -1.71%, one-sided 97.5%CI -∞ to 4.31, non-inferiority p=0.11 and 0.88% vs 0.55%; MD -0.32%, one-sided 97.5%CI -∞ to 5.47, non-inferiority p=0.21) (Figure 3). A post hoc sensitivity analysis comparing the pre-trial period to each post-intervention period did not meaningfully alter the results. (Supplement 3: eTable 12, eFigure 10)

Adverse events and protocol deviations

Adverse and serious adverse reactions were not notably different between the SDD and standard care groups. (Table 2 and Supplement 3: eTable 13). Protocol deviations and valid reasons for not administering SDD interventions are presented in Supplement 3: eTables 14 and 15.

DISCUSSION

In this cross-over, cluster randomized clinical trial, the use of Selective Decontamination of the Digestive Tract in mechanically ventilated critically ill adults did not significantly reduce in-hospital mortality compared with standard care without SDD, although the confidence interval around the effect estimate includes a clinically important benefit.

The use of SDD did not significantly reduce ICU mortality, the duration of mechanical ventilation or the duration of ICU and hospital admission. There was a significant reduction in positive blood cultures and cultures of antibiotic resistant organisms and no significant increase in new

Clostridioides difficile infections in patients who received SDD. Overall antibiotic use was not increased in patients receiving SDD. In the ecology assessment, the use of SDD was non-inferior to standard care for the development of new positive blood cultures and *Clostridioides difficile* infections, but not for cultures of new antibiotic resistant organisms. The use of SDD was not associated with an increased incidence of adverse events.

This pragmatic randomized clinical trial has a number of strengths that include a large study population recruited from multiple ICUs under routine clinical care conditions that assessed the effect of SDD on a robust patient-centred outcome. Second, to our knowledge, the trial used the first mass-produced, commercially manufactured Good Manufacturing Practice-compliant SDD preparation that comprised the antimicrobial components previously identified to reduce the incidence of ventilator-associated pneumonia. Third, the trial was conducted according to a pre-published protocol and statistical analysis plan that included a hierarchical logistic regression model to adjust for the cluster size and a robust assessment of treatment adherence. Fourth, the trial had no loss to follow-up. Fifth, the observed baseline mortality rate of 29% confirms the high acuity of illness severity in the study population. Sixth, microbiological surveillance and antibiotic prescription were conducted in accordance with international practice standards within the context of a pragmatic trial. Seventh, the concurrent observational ecological assessment to evaluate changes in ICU microbiology, specifically antibiotic resistance over the trial period provides new contextual information about the effect of SDD on unit ecology.

A non-systematic analysis of patient-level data from selected randomized clinical trials conducted between 2000 and 2017[10] and the current Cochrane library systematic review[27] reported that SDD was associated with a statistically significant reduction in hospital mortality

compared to standard care with an absolute risk reduction in mortality that is similar to the point estimate from this trial.

Consistent with the results of this trial, previous randomized clinical trials conducted in environments of low endemic resistance did not report an increase in antibiotic resistance associated with the use of SDD.[5,10,28] A randomized clinical trial conducted in ICUs between 2013 and 2017 with moderate to high baseline rates of antibiotic resistance reported no statistically significant difference in the incidence of new bloodstream infections with multi-resistant Gram-negative bacteria (the primary outcome) and no significant differences in new highly resistant microorganisms or 28-day mortality between SDD and baseline standard care.[29]

While clinicians will need to consider the primacy of the effectiveness of SDD in improving patient-centred outcomes over the effect on microbiological outcomes, the use of SDD may confer benefits in specific patient populations such as those with trauma[3] and further trials are needed to confirm benefits in these patients, particularly in high endemic antibiotic resistance environments.

Limitations

This study had several limitations. First, due its nature, the intervention was unblinded, although this was mitigated by the objective primary outcome and the adoption of SDD as a standard of care administered to all eligible patients during the intervention period. Second, while more patients were recruited into the standard care group compared to the SDD group, this imbalance is likely due to greater reluctance to recruit patients to the intervention versus control group when doubt about their duration of ventilation or likelihood of surviving greater

than 12 hours existed. Third, while protocol adherence for the use of SDD approached 90% over the duration of the inception period and over 130000 doses of SDD were administered, prolonged use of SDD in long-term ventilated patients declined over time due to non-palatability of the oral paste and reduced access to the upper gastrointestinal tract for the gastric suspension. Fourth, reductions in antibiotic resistance and new blood cultures associated with SDD in the intervention trial may not represent the efficiency of SDD at an individual or institutional level within the context of an effectiveness trial. Fifth, due to the overall low rate of antimicrobial resistance and relatively short period of observation, the ecological assessment had limited power to confirm or refute non-inferiority of SDD compared to standard care and did not assess changes in microbiological outcomes at a hospital level or changes in ecology that might be associated with longer-term use of SDD.

Conclusions

Among critically ill patients receiving mechanical ventilation, SDD compared with standard care without SDD, did not significantly reduce in-hospital mortality. However, the confidence interval around the effect estimate includes a clinically important benefit.

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Access to Data Statement

Dr Myburgh and Dr Billot had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

See Supplement 5.

Role of the Sponsor and Funders

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preparation, review or approval of the manuscript; and the decision to submit the manuscript for publication. The Sponsor had no right of veto to publish this trial or to control the decision regarding to which journal the paper was submitted.

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Competing interests:

The George Institute for Global Health holds all intellectual property rights related to the SuDDICU study drugs, including component drug acquisition, manufacturing, packaging and distribution. None of the SuDDICU investigators have any direct or indirect financial or commercial interests relating to the development of the SuDDICU study drugs.

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Supervision: Billot, Correa, Finfer, Goodman, Hammond, Myburgh, Seppelt

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References

1. Schimpff SC. Infection prevention during profound granulocytopenia. New approaches to alimentary canal microbial suppression. Annals of Internal Medicine 1980;93:358-61.

2. Stoutenbeek CP, van Saene HK, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Medicine 1984;10:185-92.

3. Stoutenbeek CP, van Saene HK, Little RA, Whitehead A. The effect of selective decontamination of the digestive tract on mortality in multiple trauma patients: a multicenter randomized controlled trial. Intensive Care Medicine 2007;33:261-70.

4. van Saene HK, Stoutenbeek CP, Hart CA. Selective decontamination of the digestive tract (SDD) in intensive care patients: a critical evaluation of the clinical, bacteriological and epidemiological benefits. Journal of Hospital Infection 1991;18:261-77.

5. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. The New England Journal of Medicine 2009;360:20-31.

6. Wittekamp BHJ, Oostdijk EAN, Cuthbertson BH, Brun-Buisson C, Bonten MJM. Selective decontamination of the digestive tract (SDD) in critically ill patients: a narrative review. Intensive Care Medicine 2020;46:343-9.

7. 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. Critical Care Medicine 2010;38:1370-6.

8. Daneman N, Sarwar S, Fowler RA, Cuthbertson BH. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. The Lancet Infectious Diseases 2013;13:328-41.

9. Roquilly A, Marret E, Abraham E, Asehnoune K. Pneumonia prevention to decrease mortality in intensive care unit: a systematic review and meta-analysis. Clinical Infectious Diseases 2015;60:64-75.

10. Plantinga NL, de Smet A, Oostdijk EAN, et al. Selective digestive and oropharyngeal decontamination in medical and surgical ICU patients: individual patient data meta-analysis. Clinical Microbiology and Infection 2018;24:505-13.

11. Canter RR, Harvey SE, Harrison DA, Campbell MK, Rowan KM, Cuthbertson BH. Observational study of current use of selective decontamination of the digestive tract in UK critical care units. British Journal of Anaesthesia 2014;113:610-7.

12. Cuthbertson BH, Campbell MK, MacLennan G, et al. Clinical stakeholders' opinions on the use of selective decontamination of the digestive tract in critically ill patients in intensive care units: an international Delphi study. Critical Care 2013;17:R266.

13. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Medicine 2021;47:1181-247.

14. Oostdijk EAN, Kesecioglu J, Schultz MJ, et al. Effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs: a randomized clinical trial. JAMA 2014;312:1429-37.

15. The SuDDICU Investigators. Protocol summary and statistical analysis plan for the selective decontamination of the digestive tract in Intensive Care patients (SuDDICU) crossover, cluster randomised controlled trial. Critical Care and Resuscitation 2021;23:183-93.

16. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Critical Care Medicine 1985;13:818-29.

17. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100:1619-36.

18. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. The New England Journal of Medicine 2009;360:1283-97.

19. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. The New England Journal of Medicine 2018;378:797-808.

20. Kenward M.G. RJH. An improved approximation to the precision of fixed effects from restricted maximum likelihood. Computational statistics and data analysis 2009;53:2583-95.

21. Morgan KE, Forbes AB, Keogh RH, Jairath V, Kahan BC. Choosing appropriate analysis methods for cluster randomised cross-over trials with a binary outcome. Stat Med 2017;36:318-33.

22. https://www.who.int/tools/atc-ddd-toolkit/about-ddd . Accessed Sepember 7 2016

23. Holm S. Simple Sequentially Rejective Multiple Test Procedure. Scandinavian Journal of Statistics 1979;6:65-70.

24. Oostdijk EA, de Smet AM, Blok HE, et al. Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. American Journal of Respiratory and Critical Care Medicine 2010;181:452-7.

25. Duncan EM, Cuthbertson BH, Prior ME, et al. The views of health care professionals about selective decontamination of the digestive tract: an international, theoretically informed interview study. Journal of Critical Care 2014;29:634-40.

26. Wunderink RG. Welkommen to our world. Emergence of antibiotic resistance with selective decontamination of the digestive tract. American Journal of Respiratory and Critical Care Medicine 2010;181:426-7.

27. Minozzi S, Pifferi S, Brazzi L, Pecoraro V, Montrucchio G, D'Amico R. Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation. The Cochrane database of systematic reviews 2021;1:Cd000022.

28. 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;362:1011-6.

29. Wittekamp BH, Plantinga NL, Cooper BS, et al. Decontamination Strategies and Bloodstream Infections With Antibiotic-Resistant Microorganisms in Ventilated Patients: A Randomized Clinical Trial. JAMA 2018;320:2087-98.

565 **Figure Legends**

566

567 **Figure 1: Recruitment, randomization and patient flow**

568 SDD – Selective Decontamination of the Digestive Tract; ICUs – Intensive Care Units

569 **Figure 2:**

570 Panel A. Probability of survival to hospital discharge within 90-days

571 Panel B. Subgroup analysis for in-hospital death within 90-days.

572 Severity of illness was determined by the Acute Physiology and Chronic Health Evaluation
573 (APACHE) scores, ranging from 0 to 71 (APACHE-II)[16] or 0 to 299 (APACHE-III)[17] with higher
574 scores indicating an increased risk of death.

575 The median APACHE-II and APACHE-III scores were 20 and 70 respectively.

576 P-value is from the likelihood ratio test of the interaction term between the subgroup variable
577 and the intervention.

578

579 ***Figure 3: Ecological assessment outcomes.***

580 The change in mean proportions of microbiological outcomes between SDD and standard care
581 are presented from the pre-trial period vs. intervention period 1 and the inter-period gap
582 combined (first intervention) and the from inter-period gap vs. interventional period 2 and the
583 post-trial period combined (second intervention).

584 The pre-defined non-inferiority margin of 2% is presented as the red line.

The non-inferiority margin was rejected for new organisms isolated and Clostridioides difficile infection, but not for cultures of antibiotic resistance organisms, presented by the non-inferiority p-value.

590 **Tables**

591 **Table 1.**

592

Characteristic **All data N(%), unless stated**	**Selective Decontamination of the Digestive Tract (N=2791)**	**Standard care (N=3191)**
Age: mean (SD): years	58.2 (17.1)	58.5 (17.0)
Female sex	1012 (36.3)	1190 (37.3)
Male sex	1779 (63.7)	2001 (62.7)
ICU admission source		
Emergency Department	1119 (40.1)	1170 (36.7)
Admitted following emergency surgery	566 (20.3)	695 (21.8)
Hospital floor (wards)	517 (18.5)	575 (18.0)
Transfer from another hospital	236 (8.5)	314 (9.8)
Transfer from another ICU	189 (6.8)	209 (6.5)
Admitted following elective surgery	164 (5.9)	228 (7.1)
Time from ICU admission to enrolment: median (IQR): hours	16.1 (3.5;39.7)	3.7 (0.0;20.5)
APACHE diagnostic category: non-operative[a]	2061 (73.8)	2268 (71.1)
Admission diagnosis of trauma	378 (13.5)	425 (13.3)
Severity of illness score: (median [IQR])[b]		
APACHE II score	1479 (20.0 [15.0; 26.0])	2028 (20.0 [15.0; 25.0])
APACHE III Score	1312 (68.0 [49.0; 89.0])	1163 (73.0 [53.0; 95.0])
Comorbidities		
Diabetes	610 (21.9)	743 (23.3)
Systemic steroids	330 (11.8)	405 (12.7)
Immunosuppressed	231 (8.3)	279 (8.7)
Prior treatments		
Receiving intravenous antibiotics at enrolment	2098 (75.2)	2176 (68.2)
Receiving intravenous antibiotics for > 48 hours prior to enrolment	689 (32.5)	600 (27.6)
Use of oral chlorhexidine	778 (27.9)	526 (16.5)

593

Table 1. Baseline characteristics of the patients enrolled during in the intervention periods by group.

a The Acute Physiology and Chronic Health Evaluation (APACHE) diagnostic criteria are categorized into non-operative and operative groups and include pre-specifed organ system based criteria with each diagnostic group.

b Severity of illness was determined by the Acute Physiology and Chronic Health Evaluation (APACHE) scores, ranging from 0 to 71 (APACHE-II),[16] or 0 to 299 (APACHE-III)[17] with higher scores indicating an increased risk of death.

ICU – Intensive Care Unit; SD – standard deviation; IQR- interquartile range

604 **Table 2:**

605

606

	Selective Decontamination of the Digestive Tract (N=2791)	Standard care (N=3191)	Difference (%) (95% CI)	Odds ratio (95%CI)	p
Primary outcome[a,g,i,j,k,l]					
In-hospital death within 90-days: N (%)					
Primary analysis[b]	753 (27.0)	928 (29.1)	MD -1.7 (-4.38 to 1.3)	0.91 (0.82 to 1.02)	0.12
Adjusted analysis[c]				0.92 (0.75 to 1.11)	0.35
Clinical secondary outcomes[d,g]					
Death within ICU: N (%)	591 (21.2)	727 (22.8)	MD -1.4 (-3.5 to 0.7)	0.92 (0.79 to 1.08)	
Days alive and free of mechanical ventilation: (SD); median (IQR)	61.9 (36.1) 83 (18;87)	59.7 (37.1) 83 (7;87)	MD 2.09 (-0.35 to 4.53)		
Days alive and free of ICU admission mean (SD); median (IQR)	58.4 (35.7) 79 (6;85)	56.4 (36.4) 78 (2;85)	MD 1.75 (-0.62 to 4.12)		
Days alive and free of hospital admission[h] mean (SD); median (IQR)	45.3 (33.4) 59 (0;76)	44.0 (34.4) 57 (0;76)	MD 1.34 (-0.89 to 3.58)		
Microbiological secondary outcomes[g]					
Any antibiotic resistant organism found N (%)	583 (20.9)	1036 (32.5)	AD -11.0 (-14.7 to -7.3)		
Any blood organism found N (%)	156 (5.6)	259 (8.1)	AD -1.95 (-3.47 to -0.43)		
Positive for *Clostridioides Difficile* N (%)	14 (0.5)	29 (0.9)	AD-0.24 (-0.59 to 0.10)		
Defined daily dose of antibiotics[e]	0.81 (0.75 to 0.88)	0.85 (0.78 to 0.91)	MD -0.035 (-0.13 to 0.06)		

over 28 days (mean (95%CI)					
Adverse Events					
Adverse Medication Reactions	0 (0.0)	0 (0.0)			
Serious Adverse Medication Reactions	0 (0.0)	0 (0.0)			
Suspected Unexpected Serious Adverse Reactions	0 (0.0)	0 (0.0)			
Serious Adverse Events					
Any event	29 (1.0)	29 (0.9)			
Blocked gastric tube	7 (0.3)	0 (0.0)			
Other[f]	7 (0.3)	0 (0.0)			

Table 2. Clinical and microbiological outcomes and adverse events for intervention trial by group.

a Inter-cluster coefficient (ICC) for Primary Outcome = 0.007

b Hierarchical model with Kenward-Roger correction

c Adjusted analysis for age, sex, severity of illness, operative vs. non-operative diagnosis

d Given than none of the differences were significant at the 5% level for the 4 clinical secondary outcomes, the planned Holm-Bonferroni multiplicity correction was not applied

e Defined daily doses of antibiotics were defined as the assumed mean maintenance dose per day for a drug used for its main indication in adults according to the World Health Organisation Collaborating Centre for Drug Statistics Methodology[22]

f Other Serious adverse events were one case each of change in kidney function, persistent diarrhea, toxic epidermal necrolysis, persist fever, elevated creatinine kinase and two skin rashes

g Data were censored at day-90 after enrolment.

h The median time to hospital discharge was 16 days in the SDD group and 15 days in the standard care group.

i There was no significant interaction between treatment and period when analysing the primary outcome (p=0.76).

j No sensitivity analyses for missing data for the primary outcome was performed as there was 100% data available for analyses.

k Post hoc determination of the intra-cluster coefficient and inter-period correlation is presented in Supplement 3: eTable 7

l Post hoc sensitivity analyses adjusting the primary outcome for baseline imbalances for prior use of chlorhexidine and intravenous antibiotics are presented in Supplement 3: eTable 8

SD – standard deviation; IQR – interquartile range; MD – mean difference; AD – absolute difference

Table 3

	Pretrial period	Period 1 and inter-period gap	Intervention cross-over	Inter-period gap	Period 2 and post-trial period
New infections with antibiotic resistant organisms from all blood and non-blood cultures[a,b,c]					
SDD	108/915 (11.8)	184/1719 (10.7)	→Standard care	100/874 (11.4)	159/1589 (10.0)
Standard care	94/1012 (9.3)	149/1765 (8.4)	→SDD	79/912 (8.7)	136/1599 (8.5)
New positive blood cultures[a,b]					
SDD	26/915 (2.8)	40/1719 (2.3)	→Standard care	26/874 (3.0)	35/1589 (2.2)
Standard care	20/1012 (2.0)	43/1765 (2.4)	→SDD	29/912 (3.2)	26/1599 (1.6)
New infections with Clostridioides difficile[a,b]					
SDD	6/915 (0.7)	5/1719 (0.3)	→Standard care	2/874 (0.2)	5/1589 (0.3)
Standard care	2/1012 (0.2)	2/1765 (0.1)	→SDD	2/912 (0.2)	4/1599 (0.3)

Table 3: Ecological assessment outcomes.

All data presented as n/N (%)

a Three microbiological outcomes are presented for sites randomized to each intervention period.

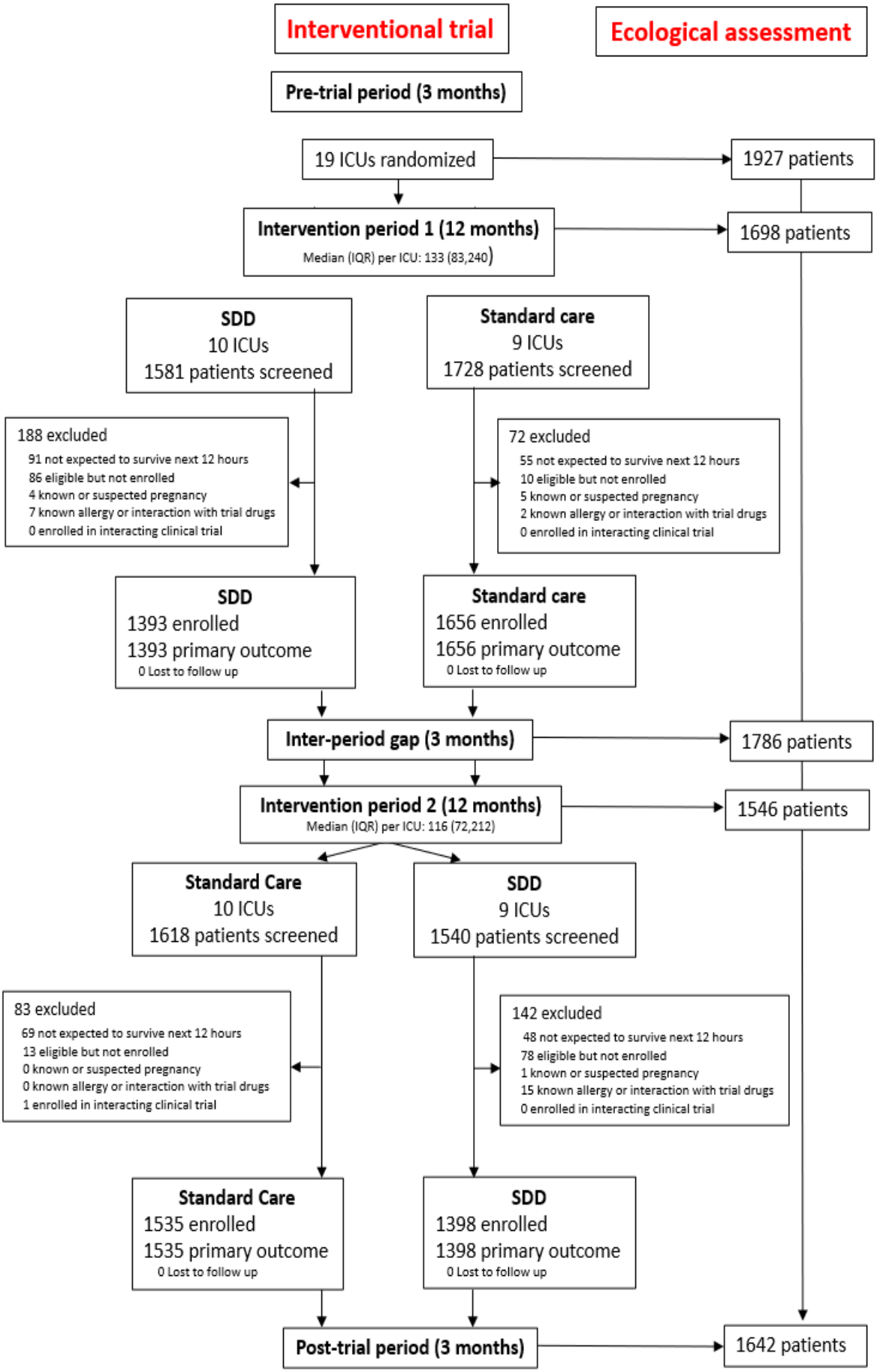
b Proportions of patients were obtained using linear regression to model the proportion of microbiological outcomes in each cluster and each period during the two comparative trial periods: pre-trial period vs. interventional period 1 and inter-period gap combined and the inter-period gap period vs. interventional period 2 and the post-trial period combined.

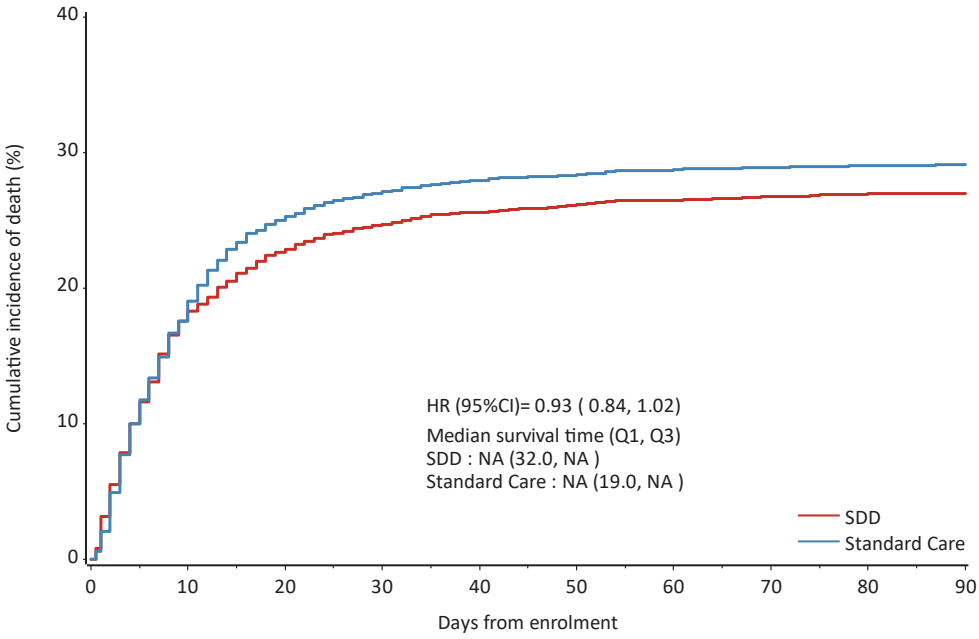
649 c Antibiotic resistant organisms were defined according to a modification of the Dutch

650 Nosocomial Infection Guidelines (Supplement 3: Section G).

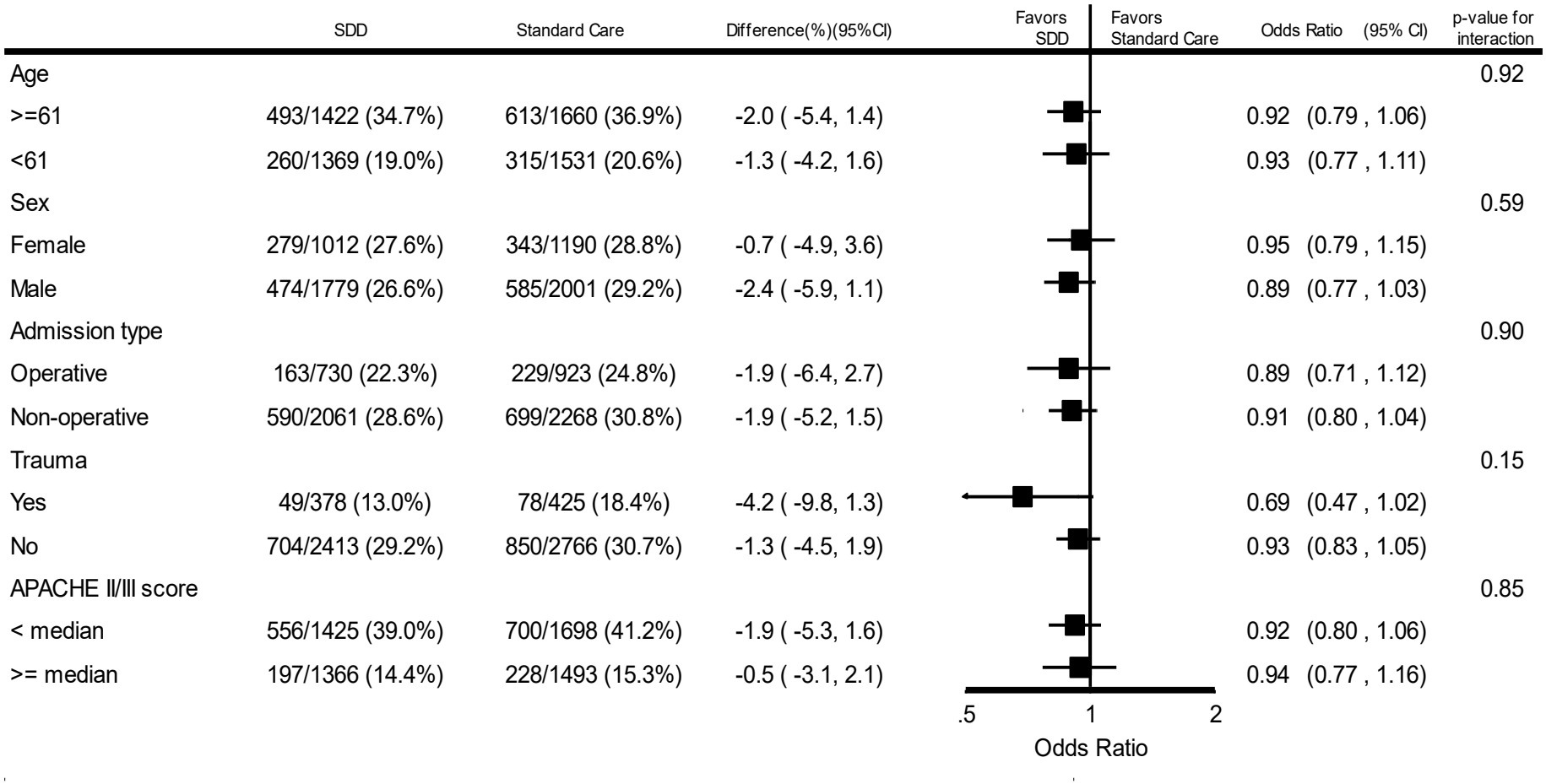
651 SDD – Selective Decontamination of the Digestive Tract

652


Interventional trial
Ecological assessment
Pre-trial period (3 months)
19 ICUs randomized
1927 patients
Intervention period 1 (12 months)
Median (IQR) per ICU: 133 (83,240)
1698 patients
SDD
10 ICUs
1581 patients screened
Standard care
9 ICUs
1728 patients screened
188 excluded
91 not expected to survive next 12 hours
86 eligible but not enrolled
4 known or suspected pregnancy
7 known allergy or interaction with trial drugs
0 enrolled in interacting clinical trial
72 excluded
55 not expected to survive next 12 hours
10 eligible but not enrolled
5 known or suspected pregnancy
2 known allergy or interaction with trial drugs
0 enrolled in interacting clinical trial
SDD
1393 enrolled
1393 primary outcome
0 Lost to follow up
Standard care
1656 enrolled
1656 primary outcome
0 Lost to follow up
Inter-period gap (3 months)
1786 patients
Intervention period 2 (12 months)
Median (IQR) per ICU: 116 (72,212)
1546 patients
Standard Care
10 ICUs
1618 patients screened
SDD
9 ICUs
1540 patients screened
83 excluded
69 not expected to survive next 12 hours
13 eligible but not enrolled
0 known or suspected pregnancy
0 known allergy or interaction with trial drugs
1 enrolled in interacting clinical trial
142 excluded
48 not expected to survive next 12 hours
78 eligible but not enrolled
1 known or suspected pregnancy
15 known allergy or interaction with trial drugs
0 enrolled in interacting clinical trial
Standard Care
1535 enrolled
1535 primary outcome
0 Lost to follow up
SDD
1398 enrolled
1398 primary outcome
0 Lost to follow up
Post-trial period (3 months)
1642 patients



No. at Risk										
SDD	2791	2300	2158	2103	2077	2063	2052	2045	2039	2038
Standard Care	3191	2630	2393	2329	2300	2287	2275	2268	2265	2263


SDD
Standard Care
Difference(%)(95%CI)
Favors SDD
Favors Standard Care
Odds Ratio (95% CI)
p-value for interaction
Age
0.92
>=61
493/1422 (34.7%)
613/1660 (36.9%)
-2.0 (-5.4, 1.4)
0.92 (0.79 , 1.06)
<61
260/1369 (19.0%)
315/1531 (20.6%)
-1.3 (-4.2, 1.6)
0.93 (0.77 , 1.11)
Sex
0.59
Female
279/1012 (27.6%)
343/1190 (28.8%)
-0.7 (-4.9, 3.6)
0.95 (0.79 , 1.15)
Male
474/1779 (26.6%)
585/2001 (29.2%)
-2.4 (-5.9, 1.1)
0.89 (0.77 , 1.03)
Admission type
0.90
Operative
163/730 (22.3%)
229/923 (24.8%)
-1.9 (-6.4, 2.7)
0.89 (0.71 , 1.12)
Non-operative
590/2061 (28.6%)
699/2268 (30.8%)
-1.9 (-5.2, 1.5)
0.91 (0.80 , 1.04)
Trauma
0.15
Yes
49/378 (13.0%)
78/425 (18.4%)
-4.2 (-9.8, 1.3)
0.69 (0.47 , 1.02)
No
704/2413 (29.2%)
850/2766 (30.7%)
-1.3 (-4.5, 1.9)
0.93 (0.83 , 1.05)
APACHE II/III score
0.85
< median
556/1425 (39.0%)
700/1698 (41.2%)
-1.9 (-5.3, 1.6)
0.92 (0.80 , 1.06)
>= median
197/1366 (14.4%)
228/1493 (15.3%)
-0.5 (-3.1, 2.1)
0.94 (0.77 , 1.16)
.5
1
2
Odds Ratio

	Mean proportion (95% CI) SDD -> Standard Care	Mean proportion (95% CI) Standard Care -> SDD	Mean difference (95% CI) SDD - Standard Care	Non-inferiority p-value
New organisms isolated				
First intervention	-0.75 (-1.94, 0.44)	0.30 (-0.65, 1.26)	-1.05 (-2.58 , 0.47)	<0.01
Second intervention	-0.90 (-2.09, 0.29)	-0.86 (-1.97, 0.25)	0.04 (-1.58 , 1.67)	<0.01
Antibiotic resistance				
First intervention	-3.30 (-8.17, 1.58)	-1.59 (-5.12, 1.94)	-1.71 (-7.73 , 4.31)	0.11
Second intervention	0.88 (-3.20, 4.96)	0.55 (-3.56, 4.67)	-0.32 (-6.12 , 5.47)	0.21
New Clostridioides difficile infection				
First intervention	-0.19 (-0.50, 0.12)	0.05 (-0.23, 0.32)	-0.24 (-0.66 , 0.18)	<0.01
Second intervention	0.03 (-0.28, 0.33)	-0.03 (-0.31, 0.26)	-0.05 (-0.47 , 0.37)	<0.01