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Cost-effectiveness of selective digestive decontamination (SDD) versus selective oropharyngeal decontamination (SOD) in intensive care units with low levels of antimicrobial resistance: an individual patient data meta-analysis

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ABSTRACT

Objective To determine the cost-effectiveness of selective digestive decontamination (SDD) as compared to selective oropharyngeal decontamination (SOD) in intensive care units (ICUs) with low levels of antimicrobial resistance.

Design Post-hoc analysis of a previously performed individual patient data meta-analysis of two cluster-randomised cross-over trials.

Setting 24 ICUs in the Netherlands.

Participants 12 952 ICU patients who were treated with ≥1 dose of SDD (n=6720) or SOD (n=6232).

Interventions SDD versus SOD.

Primary and secondary outcome measures The incremental cost-effectiveness ratio (ICER; ie, costs to prevent one in-hospital death) was calculated by comparing differences in direct healthcare costs and in-hospital mortality of patients treated with SDD versus SOD. A willingness-to-pay curve was plotted to reflect the probability of cost-effectiveness of SDD for a range of different values of maximum costs per prevented in-hospital death.

Results The ICER resulting from the fixed-effect meta-analysis, adjusted for clustering and differences in baseline characteristics, showed that SDD significantly reduced in-hospital mortality (adjusted absolute risk reduction 0.0195, 95% CI 0.0050 to 0.0338) with no difference in costs (adjusted cost difference €62 in favour of SDD, 95% CI −€1079 to €935). Thus, SDD yielded significantly lower in-hospital mortality and comparable costs as compared with SOD. At a willingness-to-pay value of €33 633 per one prevented in-hospital death, SDD had a probability of 90.0% to be cost-effective as compared with SOD.

Conclusion In Dutch ICUs, SDD has a very high probability of cost-effectiveness as compared to SOD. These data support the implementation of SDD in settings with low levels of antimicrobial resistance.

Strengths and limitations of this study

- This is the largest cost-effectiveness analysis (CEA) comparing selective digestive decontamination (SDD) to the selective oropharyngeal decontamination (SOD) regimen thus far.
- Individual patient data were included of all randomised controlled trials that made a head-to-head comparison of SDD versus SOD in intensive care units (ICUs) with low prevalence of antibiotic resistance.
- Statistical analyses were adjusted for clustering within studies and hospitals and for baseline differences between intervention arms.
- This CEA was performed from a healthcare perspective and cost-effectiveness from a societal perspective could not be determined.
- The results of the current study are generalisable to ICU settings with low levels of antimicrobial resistance.

INTRODUCTION

Patients who are admitted to an intensive care unit (ICU) are prone to acquire nosocomial infections, which increase morbidity and mortality.[1–5] Besides detrimental effects on health status, ICU-acquired infections are also responsible for increased expenditure in an already costly healthcare setting, further supporting the importance of optimal prevention.[2 6–8] Selective oropharyngeal decontamination (SOD) and selective decontamination of the digestive tract (SDD) are two infection prevention strategies that aim to eradicate colonisation with aerobic Gram-negative bacteria, *Staphylococcus aureus* and yeasts, while leaving the anaerobic flora

intact. SOD comprises oropharyngeal application of bactericidal non-absorbable antibiotics, while in SDD this is supplemented with an intestinal suspension containing the same antibiotics (both applied until ICU discharge) *and* intravenous application of a third-generation cephalosporin during the first 4 days of ICU admission. Both selective decontamination regimens reduced ICU-acquired bacteremia and mortality rates in ICUs with low prevalence of antimicrobial resistance.[9–14] Both strategies are cost-effective as compared to no selective decontamination and are recommended as part of standard care in Dutch ICUs.[15 16]

Evidence that SDD is more effective than SOD in preventing ICU-acquired bacteremia and mortality is accumulating.[17–19] However, the SDD regimen includes more antibiotics and more microbiological surveillance and hence it is more expensive per patient day than SOD. Therefore, from a healthcare perspective, we aimed to evaluate the cost-effectiveness of SDD versus SOD in ICUs with low prevalence of antimicrobial resistance.

METHODS

Study selection

We performed a two-stage cost-effectiveness individual patient data meta-analysis (IPD-MA). Selection of studies was performed in a previous IPD-MA that aimed to assess whether the effect of selective decontamination differed between medical and surgical ICU patients.[19] Studies were included in the current cost-effectiveness analysis (CEA) if they performed a head-to-head comparison of the clinical effectiveness of SDD and SOD and if they were performed in ICU settings with low levels of antimicrobial resistance. Studies that only included either one of these strategies and compared it with usual care were excluded. This resulted in inclusion of patient-level data from two cluster-randomised cross-over (CRXO) trials in ICU patients who were included in the previous IPD-MA.[13 18] To assess the publication of any new trials that were published after the previous IPD-MA, the same systematic PubMed search was performed which included synonyms for domain and determinant (performed 11 December 2018, see original manuscript for search string).[19] One new trial was identified that made a head-to-head comparison of SDD and SOD.[20] This study was excluded for the current CEA because it did not meet criteria with regard to our domain, namely ICUs with low levels of antimicrobial resistance.

Description of included studies

Details of the two studies can be found elsewhere.[13 18] In short, in the first trial (De Smet *et al*), patients were included in 13 Dutch ICUs from May 2004 to July 2006.[13] Patients were eligible if they were admitted to the ICU with an expected duration of mechanical ventilation (MV) of more than 48 hours or an anticipated ICU length of stay (ICU-LOS) of more than 72 hours. Each ICU was assigned to a randomised order of 6-month periods in which standard care, SOD or SDD was applied. In the second CRXO trial (Oostdijk *et al*), patients were recruited in 16 Dutch ICUs from August 2009 to January 2011 and were eligible for inclusion if they had an expected ICU-LOS of at least 48 hours.[18] In this study, SOD and SDD were implemented in 12-month periods in a randomised order. In both trials, the SOD regimen consisted of four times per day application of an oropharyngeal paste consisting of polymyxin E or colistin, tobramycin and amphotericin B (2% concentration). In addition to the oropharyngeal paste, the SDD regimen contained four times per day application of 10 mL non-absorbable suspension of 100 mg polymyxin E or colistin, 80 mg tobramycin and 500 mg amphotericin B through a nasogastric tube, and intravenous (IV) application of a third-generation cephalosporin (cefotaxime 1000 mg four times per day or ceftriaxone 2000 mg once per day) during the first four days of ICU admission. Furthermore, microbiological surveillance for colonisation with Gram-negative bacteria of the respiratory tract (SOD and SDD) and rectum (SDD) was performed two times per week. In the first study individual informed consent was obtained for data collection, whereas in the second study the requirement for individual informed consent was waived by the institutional review boards.[13 18] As with the previous IPD-MA, we included only the first ICU admission of a patient within each hospital admission (further referred to as patients), from patients who received at least one dose of SOD or SDD.[19]

Patient and public involvement statement

Patients were not involved in the design and conduct of the current CEA.

Cost-effectiveness analysis

For the design and reporting of the CEA, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for health economic evaluations were followed.[21] The CEA was performed from a healthcare perspective considering only direct costs that reflect healthcare expenditure and the time horizon of the CEA was defined as the time from study inclusion on the ICU until hospital discharge or in-hospital death. SDD was considered the intervention and SOD the control treatment.

Measures of costs and effectiveness

Total healthcare costs were determined by multiplying healthcare resources used with corresponding unit costs (table 1). The following healthcare resources were included: number of days in the ICU, number of days on the hospital ward after the index ICU admission, study medication and microbiological investigations during ICU stay. For the latter, we considered both surveillance and clinical samples from the respiratory tract, intestinal tract and blood. Costs for ICU-LOS, microbiology and study medication were counted from study inclusion to ICU discharge. Dutch guidelines for health economic

Table 1 Costs per unit*

Hospital admission	Costs per unit
ICU admission day	€2061.64
Ward admission day	€487.02
Study medication	**Costs per day**
Oropharyngeal paste with non-absorbable AB†	€2.56
Suspension with non-absorbable AB‡	€14.18
Third-generation cephalosporin§	€20.92
Oropharyngeal paste with non-absorbable AB including amphotericin B¶	*€6.96*
*Suspension with non-absorbable AB including amphotericin B***	*€65.60*
Microbiological costs	**Costs per unit**
Blood culture	€28.93 + €5.70 order rate
Respiratory and rectum cultures	€32.17 + €5.70 order rate
Species determination bacteria and yeasts	€8.81
Antibiotic susceptibility testing (per isolate)	€55.04

Unit costs that are part of a sensitivity analysis are depicted in italic.
*All costs were indexed for the reference year 2017.
†Colistin/nystatin/tobramycin mouth paste (20 mg/100 000 E/20 mg/mL), 0.5 mL four times per day.
‡Colistin/nystatin/tobramycin suspension (10 mg/200 000 E/8 mg/mL), 10 mL four times per day (only part of the SDD regimen).
§Intravenous cefotaxime, 1 g four times daily (during first 4 days in ICU).
¶Colistin/amphotericin B/tobramycin mouth paste (20 mg/20 mg/20 mg/mL), 0.5 mL four times per day (sensitivity analysis 3).
**Colistin/amphotericin B/tobramycin suspension (8.75 mg/54.7 mg/11.75 mg/mL), 10 mL four times per day (sensitivity analysis 3, only part of the SDD regimen).
AB, antibiotics; ICU, intensive care unit; SDD, selective digestive decontamination.

evaluation were used to determine costs for days in the ICU and on the ward and included costs for storage, overhead and equipment.[22] For microbiological cultures, national reimbursement rates with overhead costs as advised by the Dutch Healthcare Authority were used,[23] whereas costs of study medication were retrieved from a Dutch database that includes average national reimbursement rates without overhead costs.[24] These average national reimbursement rates were preferred over exact cost-prices per hospital because of the heterogeneity and fluctuation in individual pricing agreements between different hospitals and pharmacies. Previous research has shown that nystatin is cheaper and has similar antifungal effectiveness as compared to amphotericin B. Currently, nystatin is common practice as the antifungal part of topical decontamination in a large part of Dutch ICUs.[25] Total costs for the topical antimicrobials were, therefore, based on costs for colistin, tobramycin and nystatin. Accordingly, the daily price of the topical study medication was €2.56 for SOD and €16.74 for SDD. Daily costs for the third-generation cephalosporin were based on the costs for four doses of 1 g IV cefotaxime per day (during the first four days in the ICU). The reference year for all costs was 2017. If needed, costs were corrected for inflation based on the Dutch price index.[26] We used the absolute risk reduction of in-hospital death as a measure of effectiveness. There was no discounting for costs or effects, since all costs and effects were measured in the first year after ICU admission.

Outcomes measures

Outcome of the CEA was the incremental cost-effectiveness ratio (ICER), defined as the ratio of the difference in mean costs and number of in-hospital deaths prevented per patient treated with SDD versus SOD. Consequently, the ICER is expressed as incremental costs per prevented in-hospital death.

Statistical analysis

A two-stage meta-analysis using individual patient data was performed to allow for optimal confounding adjustment within each study. We used separate generalised regression models per study to estimate costs and effects and took clustering on a hospital level into account by using a fixed effect per study centre. Linear regression was used to estimate the difference in costs between SDD and SOD. Similarly, logistic regression was performed to estimate an adjusted number of in-hospital deaths prevented with SDD versus SOD, with the absolute risk difference calculated by comparing the mean predicted probabilities per treatment arm. For comparison of these results with the previous IPD-MA, the pooled adjusted OR for in-hospital mortality was calculated as well.[19] Since CRXO trials are prone to selective inclusion, all analyses were corrected for possible confounders which were selected based on previous knowledge: centre, age, sex, APACHE II (De Smet study) or APACHE IV (Oostdijk study) score, admission type (medical or surgical) and MV at ICU admission (De Smet study, not available in Oostdijk study).

The definition of surgical admission type differed per study. In the De Smet study, this was defined as 'reason for ICU-admission is postoperative/surgical according to the treating ICU-physician' and for the Oostdijk study 'those who received any type of surgery in the week prior to ICU admission'. A random effect for cluster period did not improve model fit based on Akaike's Information Criterion in any of the four models and was therefore omitted. All analyses were performed on complete cases. Confidence intervals (CI) of non-parametric data and the ICER were calculated with the use of bootstrapping (10 000 repeats). A fixed-effect meta-analysis was used to obtain a pooled estimate of the ICER across the two trials, applying inverse variance weighting separately for costs and effects. The decision to use fixed-effect models was predefined and was based on the strong similarity of the two studies with regard to study design, ICU setting, inclusion and exclusion criteria and intervention.

The individual as well as the pooled results of the cost-effectiveness meta-analysis were plotted in a cost-effectiveness plane. Statistical heterogeneity was assessed by calculating the I^2 statistic. A willingness-to-pay plot was plotted to reflect the probability of cost-effectiveness of SDD versus SOD for a range of different values of the maximum incremental costs per averted in-hospital death. The curve represents the proportion of bootstrap samples that fall below the maximum acceptable incremental costs per averted in-hospital death (ie, the willingness-to-pay to prevent one in-hospital death). Subsequently, we calculated the minimum required number of quality-adjusted life-years (QALYs) gained per prevented in-hospital death, given the obtained incremental costs per prevented death for SDD compared to SOD, to reach cost-effectiveness in the context of the Dutch formal threshold of €80 000 per QALY for life-threatening illnesses. This was calculated by dividing the willingness-to-pay values corresponding to 90.0% and 95.0% probabilities of cost-effectiveness of SDD by €80 000.

Sensitivity analyses were performed to estimate the robustness of the cost-effectiveness of SDD in case of fluctuation in market-prices of the medication. We measured the effect of increasing costs of the SDD and SOD medication regimen (including the IV component of SDD) by factors 2 (scenario 1) and 5 (scenario 2). These factors were arbitrarily chosen. The third scenario included costs for amphotericin B instead of nystatin as the antifungal component of SDD and SOD (see table 1).

All analyses were performed with Statistical Package for Social Sciences V.25.0 (SPSS) and R V.3.4.1. Syntax for the cost-effectiveness meta-analysis is available at https://github.com/henrivanwerkhoven/meta2way.

RESULTS

Study population

A total of 3949 and 11 997 patients were included in the SDD and SOD groups in the original trials.[13 18] For the current analysis, 197 patients were excluded from the De Smet *et al*[13] study: 11 did not give permission to use clinical data, 1 was a duplicate, 176 were re-admissions within the same hospital admission and 9 patients had missing data for at least one variable in the regression analysis. 2797 patients were excluded from the Oostdijk *et al*[18] study: 18 were duplicates, 2206 were not treated with SDD or SOD, 567 were re-admissions within the same hospital admission and 6 patients had missing data for at least one variable in the regression analysis. This resulted in a total study population of 12 952 patients. Of these, 6720 and 6232 patients were treated with SDD and SOD, respectively.

Baseline characteristics were similar between the two studies except that patients were more often classified as surgical admission in the first trial (table 2). There were small differences within studies between treatment arms, similar to the reported differences in the original studies (table 2).[13 18]

Costs and effects

Patients in the first trial had a longer LOS in the ICU and hospital ward as compared to patients in the second trial (table 2). Within the first trial, LOS in the ICU was similar in the SDD and SOD group, and LOS in the hospital ward for SDD and SOD patients who survived the ICU was 13 days (IQR 6–25) and 12 days (IQR 2–26), respectively. In the second trial, SDD patients had shorter ICU-LOS compared to SOD patients (6 days (IQR 4–11) vs 7 days (IQR 4–12)). Average LOS on the hospital ward for ICU survivors was comparable between the treatment arms.

Crude average total healthcare costs per patient (ie, unadjusted for the CRXO design) were higher during the first trial compared to the second trial (table 3). Average healthcare costs from inclusion until hospital discharge for an SDD patient were €33 299 (95% CI €31 877 to €34 981) in the first trial and €27 705 (95% CI €26 921 to €28 574) in the second trial. Total healthcare costs from inclusion until hospital discharge for an SOD patient were on average €32 154 (95% CI €30 883 to 33 638) in the first trial and €28 276 (95% CI €27 446 to €29 140) in the second trial. Total healthcare costs were mainly determined by costs for ICU-LOS (75%) and hospital ward-LOS (23%). In the first trial, crude in-hospital mortality was higher among SDD patients compared with SOD patients, 32.0% and 30.6%, respectively (table 2). In the second trial, crude in-hospital mortality was lower in the SDD group than in the SOD group, 29.0% and 31.8%, respectively.

The adjusted paired bootstrapped ICERs of both trials as well as the results of the fixed-effect two-stage meta-analysis are depicted in a cost-effectiveness plane in figure 1. I^2 was 59.5% (95% CI 0% to 99%) and 69.7% (95% CI 0% to 99%) for costs and effects, respectively. In the meta-analysis, SDD significantly reduced in-hospital mortality (adjusted absolute risk reduction 0.0195, 95% CI 0.0050 to 0.0338) with no difference in costs (adjusted cost difference €62 in favour of SDD, 95% CI –€1079 to €935). The adjusted pooled OR for in-hospital

Table 2 Baseline characteristics, microbiological sampling and clinical outcomes

	De Smet *et al*[13]		Oostdijk *et al*[18]	
	SOD	SDD	SOD	SDD
	n=1803	n=1949	n=4429	n=4771
Baseline characteristics				
Mean age, years (±SD)	61.5 (16.4)	62.4 (16.0)	62.8 (15.6)	63.0 (15.6)
Male (%)	1144 (63.4)	1203 (61.7)	2710 (61.2)	2880 (60.4)
Admission type: surgical (%)	841 (46.6)	898 (46.1)	1593 (36.0)	1805 (37.8)
Mean APACHE II score (±SD)	19.5 (8.2)	19.6 (7.8)	NA	NA
Mean APACHE IV score (±SD)	NA	NA	82.2 (33.4)	81.7 (33.8)
MV at ICU admission (%)	1698 (94.2)	1814 (93.1)	NA	NA
Microbiological sampling				
Median number of cultures (IQR)				
Blood	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)
Respiratory	5 (2–9)	5 (3–9)	3 (1–6)	2 (1–5)
Rectum	0	2 (1–4)	0 (0–1)	1 (0–3)
Clinical outcomes				
Median LOS—ICU, days (IQR)	9 (6–15)	9 (5–15)	7 (4–12)	6 (4–11)
Median LOS—hospital ward, days (IQR)*	12 (5–26)	13 (6–25)	11 (4–22)	11 (5–21)
In-hospital death (%)	552 (30.6)	623 (32.0)	1410 (31.8)	1384 (29.0)

*For patients who were discharged from the ICU alive.
LOS, length of stay; MV, mechanical ventilation; NA, not available; SC, standard care; SDD, selective digestive decontamination; SOD, selective oropharyngeal decontamination.

mortality was 0.90 (95% CI 0.82 to 0.97) for SDD versus SOD, which was identical to the previous IPD-MA.[27] In the cost-effectiveness plane, these results were depicted in the different quadrants (figure 1). SDD was more effective (ie, lower in-hospital mortality) and was less costly in 54.6% of the bootstrap samples (ie, the lower right quadrant), compared to SOD. In 45.0% of the bootstrap samples, SDD was more effective, but was associated with higher costs (ie, the upper right quadrant). There was 90.0% and 95.0% probability that SDD was cost-effective at a willingness to pay value of €33 663 and €48 548 per prevented in-hospital death, respectively (figure 2). Accordingly, at least 0.42 and 0.61 QALYs would need to be gained per prevented in-hospital death in order to reach cost-effectiveness of SDD at the Dutch threshold of €80 000 per QALY, respectively.

Sensitivity analyses

Increasing SDD and SOD medication costs by factors 2 and 5 resulted in a reduction from 54.6% bootstrap samples being in the lower right quadrant (main analysis) to 37.8% and 5.7% of the bootstrap samples in the lower right quadrant, respectively (see scenarios 1 and 2 in the online supplementary material). The willingness-to-pay thresholds to prevent one in-hospital death corresponding to the 90.0% and 95.0% probabilities of cost-effectiveness of SDD were €47 360 and €65 607 for a doubling of medication costs of the SDD and SOD regimen, and €100 148

Table 3 Mean costs per patient

	De Smet *et al*[13]		Oostdijk *et al*[18]	
	SOD n=1803	SDD n=1949	SOD n=4429	SDD n=4771
LOS—ICU (95% CI)*	€24 278 (€23 111 to €25 544)	€24 851 (€23 576 to €26 343)	€21 539 (€20 842 to €22 291)	€20 409 (€19 737 to €21 129)
LOS—hospital ward (95% CI)	€7303 (€6860 to €7803)	€7472 (€7019 to €7958)	€6231 (€5960 to €6 513)	€6581 (€6287 to €6 907)
Microbiology cultures (95% CI)*	€544 (€516 to €577)	€698 (€663 to €736)	€479 (€460 to €500)	€473 (€455 to €491)
Study medication (95% CI)*	€30 (€29 to €32)	€279 (€269 to €291)	€27 (€26 to €28)	€242 (€236 to €248)
Total (95% CI)	**€32 154 (€30 832 to €33 618)**	**€33 299 (€31 839 to €34 929)**	**€28 276 (€27 464 to €29 099)**	**€27 705 (€26 888 to €28 537)**

*Costs were calculated for days on the ICU after study inclusion.
ICU, intensive care unit; LOS, length of stay; SC, standard care; SDD, selective digestive decontamination; SOD, selective oropharyngeal decontamination.

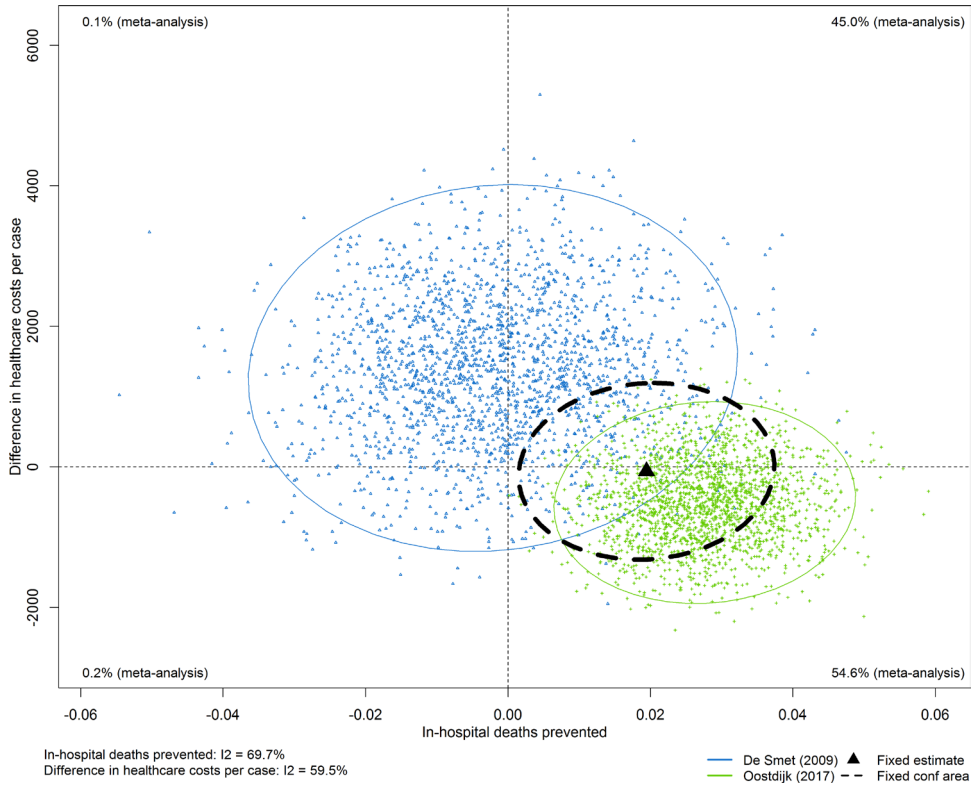

Figure 1 Cost-effectiveness plane of selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD). The blue and green points represent the bootstrapped incremental cost-effectiveness ratios (ICERs) of the De Smet and Oostdijk trials, respectively. The coloured ellipses around these points represent the 95% confidence ellipses of the corresponding study. **The bold black ellipse represents the 95% confidence ellipse for the fixed effect meta-analysis (ie, the pooled meta-analysis data).** The bootstrapped ICER points of the meta-analysis have been omitted from the figure to improve visuality of the plot. The proportions in each quadrant represent the proportion of bootstrap samples (ie, ICER points) of the meta-analysis in that quadrant. ICER points in the lower right quadrant are in favour of SDD in terms of costs and effects, ICER points in the upper right quadrant are in favour of SDD in terms of beneficial effects but not in terms of incremental costs. ICER points in the upper left quadrant are in favour of SOD in terms of effects and costs, and ICER points in the lower left quadrant are in favour of SOD in terms of effects but not in terms of costs.

and €134 849 for an increase in SDD and SOD medication by a factor 5, respectively. Choosing amphotericin B instead of nystatin as the antifungal component of the topical medication, against average national reimbursement rates, resulted in 18.4% of the bootstrap samples in the lower right quadrant (ie, SDD beneficial over SOD in terms of both costs and effects). In this scenario, the willingness-to-pay thresholds to prevent one in-hospital death were €68 924 and €94 591 for 90.0% and 95.0% probabilities of cost-effectiveness of SDD, respectively (see scenario 3 in the online supplementary material). The minimum number of QALYs gained per prevented in-hospital death in order for SDD to be cost-effective at the Dutch formal threshold of maximum €80 000 per QALY for the different scenarios can be found in the online supplementary material.

DISCUSSION

In this IPD-MA, SDD significantly reduced in-hospital mortality (adjusted absolute risk reduction 0.0195, 95% CI 0.0050 to 0.0338) with no difference in costs (adjusted cost difference €62 in favour of SDD, 95% CI –€1079 to €935) as compared to SOD. SDD had a 90.0% probability to be cost-effective compared to SOD at a willingness to pay of €33 663 to prevent one in-hospital death.

SDD and SOD are preventive regimens in a setting of critical care medicine. In the Netherlands, the willingness-to-pay threshold for one QALY gained is €80 000 in case of life-threatening illnesses.[28] According to our results, in order for SDD to be cost-effective with 90.0% and 95.0% probabilities, one would need to gain at least 0.42 and 0.61 QALYs, respectively, for each prevented in-hospital death. The Dutch National Intensive Care Evaluation (NICE) registry[29], in which 90% of all Dutch ICUs participate, was consulted to obtain life-expectancy data for ICU survivors. During the period 2006–2017, 111 608 patients who were admitted to the ICU for a minimum of 72 hours had left the hospital alive; of these patients, 65% were still alive at 4 years after ICU discharge (Dutch National Intensive Care Evaluation, unpublished data, 2018). This patient group was similar to our study population with respect to age (63.3±15 years), proportion of males (59.6%) and ICU-LOS (median 7.4 days, IQR 4.1–10.8) but had a lower mean APACHE IV score

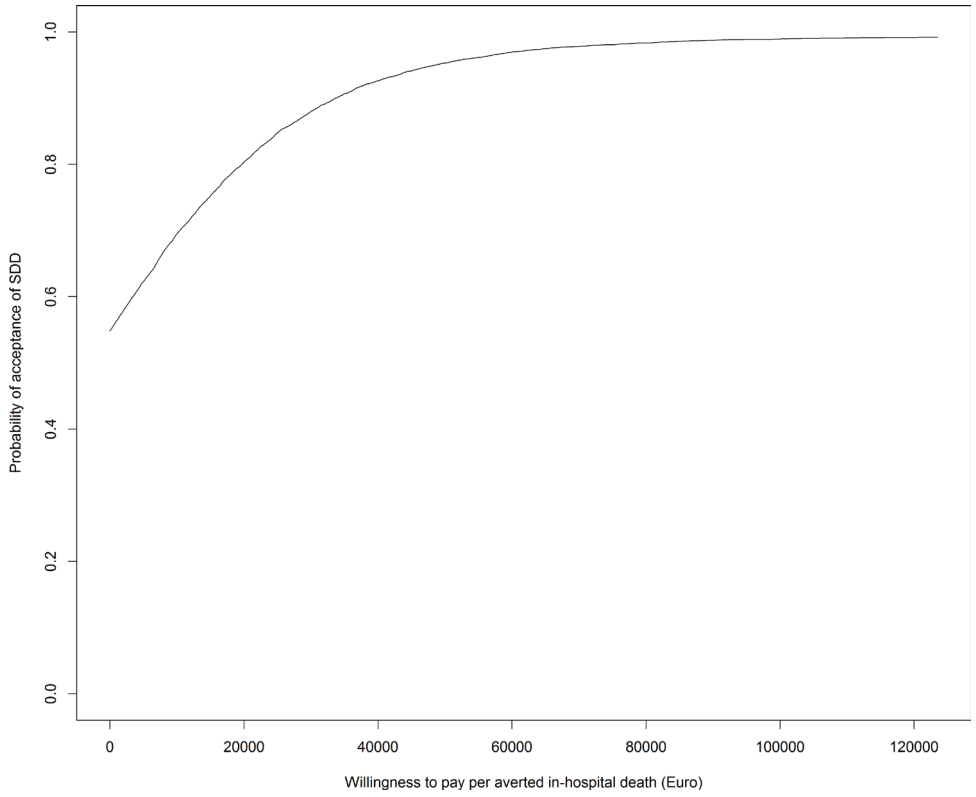

Figure 2 Willingness-to-pay plot. The curve represents the probability that selective digestive decontamination is below different thresholds of maximum willingness-to-pay values per one averted in-hospital death.

(70.9±27.5). A large Dutch single-centre study[30] that assessed long-term health-related QoL (HRQoL) of ICU patients found an HRQoL index 1 year after ICU admission of 0.71±0.26 for patients who were admitted to the ICU for 72 hours or more (Soliman, personal communication, 2018). So if we assume that those rescued by SDD have a similar life expectancy and HRQoL as the patients mentioned above, SDD has a very high probability of being cost-effective.

To the best of our knowledge, there is only one previous CEA on SDD and SOD which already showed cost-effectiveness of both SDD and SOD as compared to standard care.[15] That study was based on patient-level data of the De Smet *et al* study[13] only, thus included 29% of the patients in the current CEA. Yet, in that CEA, SOD was cost-effective compared with SDD, which is in contrast with the results of the current IPD-MA. There were important differences in our analysis methods as compared with the previous CEA. In the current CEA, additional costs for MV on the ICU were not included, because data were unavailable for the largest trial. Also, a different endpoint was chosen, namely incremental costs per prevented in-hospital death instead of incremental costs per life year gained, and the current analysis was corrected for clustering and differences in baseline characteristics between groups. Finally, in the current CEA, ICU re-admissions within one hospital admission were excluded, so patients could not be counted twice with relation to the occurrence of in-hospital mortality. The different result as compared with the previous CEA can also partly be explained by inclusion of the Oostdijk *et al*[18] study, in which SDD significantly improved in-hospital survival as compared to SOD (as opposed to the De Smet *et al* study[13], where there was no significant difference in clinical effectiveness between SDD and SOD). Also, in the Oostdijk *et al* study[18], the average ICU-LOS was shorter for patients treated with SDD in comparison to SOD, which was an important driver of the total healthcare costs per patient. As with any weighted meta-analysis, this larger study (n=9200) was assigned more weight in our meta-analysis as compared to the smaller first study (n=3752). As to date, it remains unclear why the first trial[13] did not show effectiveness of SDD over SOD in preventing in-hospital mortality. Inclusion criteria as well as the interventions were similar in both trials and both trials were performed in the same setting (Dutch ICUs with low levels of antimicrobial resistance). Although small differences in participating hospitals and patients between studies (and over time) cannot be ruled out, it is unlikely that such differences have modified the effectiveness of SDD and SOD to this extent. Therefore, we believe that chance is the best explanation for the statistical heterogeneity between the two trials.

In sensitivity analyses, doubling of medication costs for SDD and SOD had moderate impact on the cost-effectiveness, but a fivefold increase in medication costs would influence the cost-effectiveness estimates of SDD substantially. It is important to note that these scenarios were arbitrarily chosen to test the robustness of the cost-effectiveness estimate of SDD against fluctuation in

market prices, and that such a large increase in medication costs is not likely. Using amphotericin B instead of nystatin as the topical antifungal component would also reduce the cost-effectiveness of SDD, as nystatin is the cheaper option at present. Still, in all three scenarios, the minimum number of QALYs gained per prevented in-hospital death, in order for SDD to be cost-effective at the Dutch maximum willingness-to-pay value of €80 000 per QALY, is reached with high probability if we compare our results to currently available Dutch data on long-term survival and HRQoL of ICU survivors.

One of the reasons that SDD is not yet widely implemented in the Netherlands is the fear that prolonged selective antibiotic pressure increases antibiotic resistance rates. However, for ICUs with low prevalence of antibiotic resistance, there is no evidence that the use of SDD increases antibiotic resistance among Gram-negative bacteria, neither at ICU level nor at individual patient level, up to 10 days after ICU discharge.[31–34] Naturally, surveillance of respiratory and rectal carriage with Gram-negative bacteria, including assessment of colistin and tobramycin resistance, remains an essential part of the SDD regimen.

Strengths of the current analysis are the inclusion of individual patient data from 24 Dutch hospitals that participated in CRXO trials on SDD and SOD, and the adjustment for baseline differences and clustering in the statistical analyses, which is crucial when analysing data from studies without individual randomisation. Furthermore, patient characteristics were similar between the two studies, reflecting similar inclusion criteria and practices. This study also has some limitations. First, due to absence of post-hospital discharge data, health-economic evaluations could not be performed from a societal perspective, which is generally preferred by healthcare policymakers. However, we may assume that differences in costs after hospital discharge between SDD and SOD will be negligible. Second, we were not able to include costs for additional diagnostics, therapeutic antibiotics and other patient-level expenses that may have been influenced by the SDD and SOD strategy because these data were not available in one of the trials. Total absolute healthcare costs that were calculated in this study may therefore underestimate actual healthcare costs per patient. In the previous CEA that did include costs for therapeutic antibiotics, LOS still accounted for 98% of total costs.[15] Moreover, the analysis on antibiotic use in the study of De Smet *et al*[13] showed that overall antibiotic use was lower during treatment with SDD as compared to SOD (1.10 defined daily dosage vs 1.21 defined daily dosage per day in the ICU for SDD vs SOD) (De Smet, crude unpublished data, 2018). Also, in a post-hoc analysis, the proportion of patients on systemic antibiotics after day 5 of ICU admission (when IV cefotaxime per SDD protocol had stopped) was lower during SDD compared to SOD.[19] Therefore, it seems highly unlikely that including costs for therapeutic antibiotics would reduce the cost-effectiveness of SDD. Finally, it should be noted that both trials were performed in the Netherlands, where antimicrobial resistance levels in ICUs are low and selective decontamination has demonstrated clinical effectiveness. Therefore, the results of the current CEA may not be generalisable to countries with moderate to high antimicrobial resistance levels. In a recent CRXO trial in 13 European ICUs with moderate to high antibiotic resistance prevalence, SDD and SOD were not associated with statistically significant reductions in ICU-acquired bacteremias caused by multidrug-resistant Gram-negative bacteria or mortality, as compared to standard care.[20] In that study, baseline period prevalence of rectal colonisation with third-generation cephalosporin-resistant Enterobacterales and vancomycin-resistant enterococci (VRE) was 15.8% and 2.2%, respectively. The proportion of ICU-acquired bacteremia episodes caused by any highly resistant micro-organism (ie, multidrug-resistant Gram-negative bacteria, MRSA, VRE) and third-generation cephalosporin-resistant Enterobacterales was 25.5% and 15.1%, respectively. Results of the current study, therefore, apply to all patients with an expected LOS of>48 hours admitted to ICUs with low prevalence of antibiotic resistance. This critically ill population is at increased risk of ICU-acquired infections and subsequent in-hospital death. Results of the current study may assist healthcare policymakers and ICU physicians from settings with similar levels of antimicrobial resistance as the Netherlands in the allocation of their resources for infection prevention.

In conclusion, SDD has a very high probability of being cost-effective as compared to SOD in Dutch ICU patients. These data support the implementation of SDD in ICU settings with low levels of antimicrobial resistance.

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