

Selective Decontamination of the Digestive Tract and Selective Oropharyngeal Decontamination in ICU patients: a cost-effectiveness analysis

Journal:	BMJ Open
Manuscript ID:	bmjopen-2012-002529
Article Type:	Research
Date Submitted by the Author:	21-Dec-2012
Complete List of Authors:	Oostdijk, Evelien; University Medical Center Utrecht, Department of Medical Microbiology; University Medical Center Utrecht, Department of Intensive Care Medicine Wit, Ardine; Julius Center for Health Sciences and Primary Care; Center for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bakker, Marina; University Medical Center Utrecht, Department of Medical Microbiology De Smet, Anne Marie; University Medical Center Groningen, Department of Critical Care Medicine Bonten, Marc; UMC Utrecht; University Medical Centre Utrecht, Julius Center for Health Sciences and Primary Care
Primary Subject Heading :	Health economics
Secondary Subject Heading:	Infectious diseases, Intensive care
Keywords:	HEALTH ECONOMICS, Epidemiology < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

SCHOLARONE[™] Manuscripts

BMJ Open

1	Selective Decontamination of the Digestive Tract and Selective Oropharyngeal Decontamination in
2	ICU patients: a cost-effectiveness analysis
3	
Z	E.A.N. Oostdijk MD ^{1,2} , G.A. de Wit PhD ^{3,4} , M. Bakker MSc ¹ , A.M.G.A. de Smet MD PhD ⁵ , M.J.M.
5	Bonten ^{1,3} MD PhD on behalf of the Dutch SOD-SDD trialists group
6	
7	¹ Department of Medical Microbiology, ² Department of Intensive Care Medicine and ³ Julius Center for Health
8	Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The
ç	Netherlands
10	⁴ Center for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM),
11	Antonie van Leeuwenhoeklaan 9, 3721 MA, Bilthoven, The Netherlands
12	⁵ Department of Critical Care Medicine, University Medical Center Groningen, Hanzeplein 1, 9713 GZ,
13	Groningen, The Netherlands
14	
15	
16	
17	This work was presented in part at the 25th Annual Congress of the European Society of Intensive
18	Care Medicine, Lisbon, Portugal, October 13-17, 2012.
19	Words: 3089
20	Words: 3089
21	
22	
23	
24	
25	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

	26	Tjip S. van der Werf, Jan P. Arends, University Medical Center, Groningen; Johannes G. van der
:	27	Hoeven, Peter Pickkers, Patrick D.J. Sturm, Andreas Voss, Radboud University, Nijmegen Medical
:	28	Center, Nijmegen; Alexandra T. Bernards, Ed J. Kuijper, Hubertus I.J Harinck, Leiden University
	29	Medical Center, Leiden; Alexander .J.G.H. Bindels, Arjan R. Jansz, Catharina Hospital, Eindhoven;
	30	Ronald M.J. Wesselink, Bartelt M de Jongh, St. Antonius Hospital, Nieuwegein; Paul J.W. Dennesen,
	31	Gerard J. van Asselt, Medical Center Haaglanden, The Hague; Leonard F. te Velde, Ine H.M.E. Frenay,
	32	Albert Schweitzer Hospital, Dordrecht; Mat van Iterson, Steven F.T. Thijsen, Diakonessen Hospital,
	33	Utrecht; Georg H. Kluge, Slotervaart Hospital, Amsterdam; Jacob W. de Vries, Jan A. Kaan, Mesos
	34	Medical Center, Utrecht — all in the Netherlands.
	35	
	36	Corresponding author: E.A.N. Oostdijk
:	37	Mailing address: Department of Medical Microbiology, University Medical Center Utrecht, G04.614,
	38	PO box 85500, 3508 GA Utrecht, The Netherlands.
:	39	Phone: +31 88 7555006. Fax +31 88 7555132; Email: E.A.N.Oostdijk@umcutrecht.nl
	40	
	41	Keywords: SDD, SOD, Intensive Care, cost-effectiveness, economic evaluation
	42	
4	43	

BMJ Open

2 3	44	Article summary:	
4			
5 6	45	Article Focus	
7 8	46	Selective digestive tract decontamination (SDD) and selective oropharyngeal	
9 10	47	decontamination (SOD) are prophylactic antibiotics used as infection prevention strategy in	
11 12	48	Intensive Care Units (ICU)	
13 14	49	• In a Dutch 13-center study, SDD and SOD were associated with relative risk reductions of	
15 16	50	mortality at day 28 of 13% and 11%, respectively, as compared to standard care (i.e. no SDD	1
17 18 19	51	or SOD) and with lower incidence of ICU-acquired bacteremia and ICU-acquired colonization	1
20 21	52	of the respiratory tract with multi-resistant bacteria	
22 23	53	• This paper describes the costs and effects of SDD and SOD from the healthcare perspective	
24 25	54	in Dutch ICUs	
26 27	55	Key Messages	
28 29 30	56	Both SDD and SOD were cheaper and more beneficial as compared to standard care and	
31 32	57	these findings were insensitive to changes in discount rates and extra costs for ventilation	
33 34	58	days	
35 36	59	• SOD, but not SDD, was still dominant (i.e. cheaper and more beneficial) over standard care	
37 38 39	60	to current tenfold higher market-prices of the topical components (\in 40/day for SOD and	
40 41	61	€400/day for SDD)	
42 43	62	Strengths and Limitations.	
44 45	63	• This is the first head-to-head comparison of the costs and benefits of SDD and SOD and the	
46 47	64	first comparison of both interventions versus standard care using data from a multi-center	
48 49	65	trial including 5,939 patients	
50 51 52	66	Baseline differences were present between the three study groups	
53 54	67	Only direct medical costs were included in the analysis and cost data were restricted to	
55 56	68	health care settings	
57 58 59 60	69		3

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

70	ABSTRACT
71	Objective: To determine costs and effects of Selective digestive tract decontamination (SDD) and
72	selective oropharyngeal decontamination (SOD) as compared to standard care (i.e. no SDD/SOD (SC))
73	from a healthcare perspective in Dutch ICUs
74	Design: A post-hoc analysis of a previously performed cluster-randomized trial (NEJM 2009;360:20).
75	Setting: 13 Dutch ICUs
76	Participants: Patients with ICU-stay of >48 hours that received SDD (n=2,045), SOD (n=1,904) or SC
77	(n=1,990).
78	Interventions: SDD or SOD.
79	Primary and secondary outcome measures: Effects were based on hospital survival, expressed as
80	crude Life Years Gained (cLYG). The incremental cost effectiveness ratio (ICER) was calculated, with
81	corresponding cost acceptability curves. Sensitivity analyses were performed for discount-rates,
82	costs of SDD, SOD and mechanical ventilation.
83	Results: Total costs per patient were €41,941 for SC (95%Cl €40,184-€43,698), €40,433 for SOD
84	(95%Cl €38,838-€42,029) and €41,183 for SOD (95%Cl €39,408-€42,958). SOD and SDD resulted in
85	crude LYG of +0.04 and +0.25, respectively, as compared to SC, implying that both SDD and SOD are
86	dominant (i.e. cheaper and more beneficial) over SC. In cost-effectiveness acceptability curves
87	probabilities for cost-effectiveness, compared to standard care, ranged from 89% to 93% for SOD
88	and from 63% to 72% for SDD, for acceptable costs for 1 LYG ranging from €0 to €20,000. Sensitivity
89	analysis for mechanical ventilation and discount rates did not change interpretation. Yet, if costs of
90	the topical component of SDD of SOD would increase tenfold to €400/day and €40/day (maximum
91	values based upon free market prices in 2012), the estimated ICER as compared to SC for SDD would
92	be €21,590 per LYG. SOD would remain cost-saving.
93	Conclusions SDD and SOD were both effective and cost-saving in Dutch ICUs
94	
95	

BMJ Open

96	Introduction
97	Many patients in Intensive Care Units (ICU) are affected by nosocomial infections. ¹ These infections
98	are associated with increased mortality and morbidity, and considerable extra costs. ² Selective
99	oropharyngeal decontamination (SOD) and selective decontamination of the digestive tract (SDD)
100	are prophylactic antibiotic regimens, that consist of topical antibiotics applied to the oropharynx and
101	the intestinal tract to prevent colonization of gram-negative bacteria, Staphylococcus aureus and
102	yeasts. During SOD topical antibiotics are exclusively applied to the oropharynx throughout ICU-stay.
103	During SDD topical antibiotics are applied to the oropharynx but also to the intestinal tract
104	throughout ICU-stay, in combination with intravenous administration of cefotaxime during the first
105	four days in ICU, to pre-emptively treat infections with commensal respiratory tract bacteria. ³ SDD
106	has been a widely evaluated but highly controversial intervention in ICU. ⁴ Many, but not all, studies
107	reported statistically significant reductions in the incidence of Ventilator-Associated Pneumonia
108	(VAP), but only few were able to demonstrate outcome benefits such as reduced mortality and
109	length of ICU-stay. ⁵ In the absence of indisputably documented outcome benefits, the fear for
110	selection of antibiotic resistance has prevailed and SDD has not been recommended in most
111	infection prevention guidelines. ⁶⁻⁹ In a cluster-randomized study in 13 Dutch ICUs, SDD and SOD
112	were associated with relative risk reductions of mortality at day 28 of 13% and 11%, respectively, as
113	compared to standard care (i.e. no SDD or SOD). ³ Although SOD and SDD are currently widely used in
114	Dutch ICUs, the costs and effects of both regimens have not yet been determined. We, therefore,
115	conducted a cost-effectiveness analysis (CEA), comparing Standard Care, SOD and SDD using data
116	from the Dutch multi-center trial.
117	
118	Methods
119	Data collection
120	A post-hoc analysis was performed of the cluster randomized crossover trial comparing SOD and

121 SDD to standard care (SC). The trial was conducted in 13 Dutch ICUs and included 5,939 patients

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

Page 6 of 27

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

BMJ Open

(2,045 received SDD, 1,904 received SOD and 1,990 were treated according to SC). All centers were
assigned to all three regimens during periods of six months, however, the order of implementation
of SC, SOD and SDD was randomized per center.³

SOD and SDD have been described in detail elsewhere.³ In short, SOD consists of a paste applied to the oropharynx, containing polymyxin E, tobramycin and amphotericin B (all in a 2% concentration, applied every 6h). SDD consists, besides of the paste used in SOD, also of a 10 mL suspension of 100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B that is applied via a nasogastric tube, every 6h, and of cefotaxime (1000 mg, every 6h) applied intravenously during the first four days of ICU-admission. The topical antibiotics of both regimens are applied until ICU-discharge. During the trial there were no restrictions to systemic antibiotic use during SC and SOD. During SDD, the use of antibiotics with anti-anaerobic activity was discouraged. This resulted in a marked increase of cephalosporin use and lower usage of penicillins, carbapenem and clindamycin.³ Surveillance cultures of endotracheal aspirates, oropharynx and rectum were obtained on admission and twice weekly during SDD. During SOD surveillance cultures of endotracheal aspirates and the oropharynx were obtained on admission and twice weekly thereafter. During SC no surveillance cultures were obtained. Clinical cultures were obtained on clinical suspicion of infection in all three periods.

139 Approach for economic evaluation

We performed a cost-effectiveness analysis (CEA) from a healthcare perspective, hence, only including direct medical costs.¹⁰⁻¹² The time horizon of the study was the period from ICU-admission until hospital-discharge. Life Years Gained (LYG) was used as effectiveness measure. The outcome of the CEA was the incremental cost effectiveness ratio (ICER), expressed as cost per life year gained (LYG). The informal Dutch threshold for cost-effectiveness is €20,000 per LYG.^{13 14} Data were collected on patient-level. The CEA was performed post-hoc, however, using data that were prospectively collected in Case Report Forms during the trial. Total direct medical costs of the three regimens consisted of three main categories: Length of Stay (LOS), antibiotic use and microbiology

Page 7 of 27

BMJ Open

148	costs (table 1). LOS was based on the length of ICU-stay and the number of days on a hospital ward
149	after ICU-discharge. Costs for days in ICU and other hospital days were based upon the Dutch
150	guidelines for costing research in health economic studies. ¹¹ Days in ICU were categorized in days
151	with and without mechanical ventilation; days with mechanical ventilation were considered to be
152	15% more expensive than ICU-days without mechanical ventilation. ¹⁵⁻¹⁷ Antibiotic use consisted of
153	the topical components of the SDD and SOD-regimen, hereafter referred to as study medication, and
154	of all systemic antibiotics used in ICU during all periods, including the four days cefotaxime during
155	SDD as part of the SDD-protocol. The price of study medication was €0.87 and €10.48 per day, for
156	SOD and SDD respectively. Costs of systemic antibiotics were based upon prices per Defined Daily
157	Dose (DDD) provided by the Dutch information project on medication and medical devices (Genees-
158	en hulpmiddelen Informatie Project (GIP)-database ¹⁸). For microbiology costs blood cultures,
159	broncheoalveolar lavages (BAL), sputum-, throat- and rectal cultures were considered. Rectal
160	cultures were only obtained during SDD as part of SDD-surveillance. Cultures obtained from the
161	other sites were either obtained as part of surveillance (throat- and sputum cultures during
162	SDD/SOD) or as part of daily clinical practice. Microbiological costs were obtained as the internal
163	tariffs applied within the University Medical Center Utrecht. These costs included costs for the
164	microbiological culture, order tariff and extra costs for species determination and susceptibility
165	resistance testing in case of relevant bacterial growth, irrespective of the species. The year 2009 was
166	taken as the reference year for all costs. Costs that were not available for 2009 were corrected for
167	inflation (with respect to 2009) based on the price index. ¹¹ An overview of all unit costs used in the
168	analysis is provided in table 1. LYG were discounted at 1.5% a year, following Dutch guidelines for
169	health economic evaluation. ¹⁹ Discounting of costs was not necessary, as all costs occurred within
170	the first year after inclusion. ²⁰
171	

172 Analysis

173 Life Years Gained (LYG) were determined by calculating Life Years Lost (LYL) of the patients who

Page 8 of 27

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

BMJ Open

174	deceased in the hospital, using life tables for the Dutch population combined with age and sex, ²¹
175	with LYG defined as the difference in LYL between regimens. The ICER was defined as the
176	incremental difference between the mean cost of treatment regimens, divided by the incremental
177	difference in mean effect between treatment regimens. To estimate confidence limits for the ICER,
178	bootstrapping (25,000 repeats) was performed, as this does not depend on parametric assumptions
179	about the distribution of the data. ^{22 23} Results of the bootstrap procedure were plotted in a cost-
180	effectiveness plane that graphically represents the cost-difference and effect difference between
181	either SDD or SOD and SC, and for SDD versus SOD, for each of the bootstrap replications. Cost-
182	effectiveness acceptability curves (CEAC) were plotted to express the probability that treatment
183	regimens were cost-effective as compared to standard care, for a range of willingness to pay levels
184	for one life year gained (λ). ²⁴ The curves display the proportion of bootstrapped ICER-pairs that are
185	cost-effective, meaning that they either fall within the south-east quadrant of the cost-effectiveness
186	plane or remain below the λ threshold in the north-east and south-west quadrants of the plane.
187	Additionally, sensitivity analyses were performed: The discounted results (at 1.5% a year) were
188	compared to results without discounting and to a discount rate of 3% a year; costs for ICU-days with
189	mechanical ventilation were analyzed for 0% and 30% extra per ICU-day as compared to 15%
190	additional costs in basecase analysis; daily costs of study medication were analyzed with maximum
191	values based upon free market prices in 2012 (€40 for SOD and €400 for SDD). Mann-Whitney U test
192	was used to calculate P-values. P-value < 0.05 was considered to denote statistical significance and all
193	reported p-values are two-sided. All analyses were performed using Statistical Package for Social
194	Sciences version 20 (SPSS, Chicago, IL) version 17.0 and R version 2.14.2.
195	

196 Results

In this cluster-randomized trial 5,939 patients were included; 1,990 patients in the SC group, 1,904
received SOD and 2,045 received SDD. For this post-hoc analysis 19 patients were excluded (3
patients during SC, 3 during SOD and 13 during SDD). Twelve patients declined permission to use

BMJ Open

2 3	200	clinical data. Seven additional patients were excluded because data on hospital discharge and/or
4 5 6	201	hospital mortality was missing, as reported previously. ³
7 8	202	Patients receiving SDD were on average 62.4 (\pm 15.8) years old, compared to 61.4 (\pm 16.3) and 61.4
9 10	203	(±16.2) years for patients receiving SOD and SC, respectively (Table 2). Patients receiving SC had a
11 12	204	lower mean APACHE II score (18.6) than those receiving SOD (19.6) and SDD (19.9), and were less
13 14	205	likely to be on mechanical ventilation (88.1% for SC vs. 94.2% and 92.9% for SOD and SDD,
15 16	206	respectively).
17 18	207	Mean LOS in ICU and in hospital and mean duration of mechanical ventilation did not differ
19 20 21	208	significantly between SC, SOD and SDD. These data differ somewhat from original LOS data reported
22 23	209	previously ³ , which included only data of patients who were alive at day 28.
24 25	210	In all, 7,609 daily doses of study medication were used in the SOD group and 8,068 during SDD, with
26 27	211	average numbers of 4.0 doses/day for SOD patients and 3.95 for SDD patients. The average number
28 29	212	of DDD of systemic antibiotics during ICU-stay was lowest during SDD with absolute numbers of
30 31	213	33,688 DDDs during SC, 30,299 during SOD and 29,663 during SDD.
32 33 34	214	
35 36	215	Cost analysis
37 38	216	Average total costs per patient were €41,941 for SC (95%Cl €40,184-€43,698), €40,433 for SOD
39 40	217	(95%CI €38,838-€42,029) and €41,183 for SDD (95%CI €39,408-€42,958) (Table 3). LOS accounted for
41 42	218	approximately 98% of total costs, and these costs were highest for patients during SC. Mean costs
43 44	219	per patient for study medication were €3.48 and €41.35 during SOD and SDD, respectively. Mean
45 46 47	220	costs of systemic antibiotics per patient were €358.29 (95%CI €321.34 - €395.24) during SC, €317.65
48 49	221	(95%CI €280.89 - €354.42) during SOD and €439.14 (95%CI €406.69 - €471.59) during SDD (P<0.01
50 51	222	for SDD vs SC and SOD). Mean costs for microbiology cultures were highest for SDD (€ 371.72), as
52 53	223	compared to SOD (€287.27) and SC (€220.05) (P<0.01 for SDD vs SC and SOD) .
54 55	224	Hospital mortality was 31.8%, 30.7% and 32.3% during SC, SOD and SDD respectively. The difference
56 57 58 59	225	in hospital mortality for SDD, as compared to reported mortality previously, ³ (32.3% vs 32.6%)

Page 10 of 27

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

BMJ Open

1
2
3 1
5
6
7
8
9
10
11
12
13
14
15
16
17
10 10
20
$\begin{array}{c}2\\3\\4\\5\\6\\7\\8\\9\\1\\1\\1\\2\\3\\4\\5\\6\\7\\8\\9\\1\\1\\1\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\3\\3\\3\\3$
22
23
24
25
26
27
28
29
30
31
32
33
34
30
30 27
38
30
40
41
42 43
44
45
46
47
48
49
50
51 52
52 53
53 54
54 55
55 56
50 57
58
59
60

226	results from inclusion of outcome data from the twelve patients that declined permission to use
227	clinical (not mortality) data in the main analysis. Estimated life years lost were, on average, 6.07
228	years for SC patients, 5.62 years for SOD patients and 5.97 years for SDD patients. Effects were
229	discounted with 1.5% a year resulting in life years gained (LYG) of +0.25 years for SOD and +0.04
230	years for SDD as compared to SC (table 4). SOD resulted in +0.21 LYG when compared to SDD. In the
231	cost-effectiveness plane, point estimates of the differences in costs and effects indicated that both
232	SOD and SDD were beneficial and cheaper (i.e. south-east quadrant) over SC. As depicted in figure 1,
233	SOD and SDD were dominant (i.e. southeast quadrant of plane) in 77.5% and 40.1% of the bootstrap
234	estimates respectively. When comparing SOD vs SDD, SOD dominates SDD in 60.2% of the bootstrap
235	replicates. If only cost aspects were taken into account (i.e. combining the south-east and south-
236	west quadrants), 89.3% and 72.4% of the bootstrap replicates were cheaper than SC during SOD and
237	SDD, respectively. In addition, bootstrap results were graphically displayed in cost-effectiveness
238	acceptability curves showing the probability that a treatment is cost-effective in comparison with
239	another treatment, given a certain threshold value for the willingness to pay for one life year gained.
240	These probabilities varied for values ranging from €0 to €20,000, between 89% and 93% for SOD and
241	between 63% and 72% for SDD (figure 1). For SOD vs SDD, these probabilities varied from 73% to
242	87%.
243	In the cost-analysis, €69.59 per one DDD of cefotaxime was used as reference price ¹⁸ and average
244	costs of systemic antibiotics were highest during SDD. ³ The price of 1 DDD cefotaxime should be
245	€39.37 and €19.07 to balance costs for systemic antibiotics between SDD and SC and SDD and SOD
246	respectively.
247	Sensitivity analyses on mechanical ventilation costs and discount rates did not change the
248	interpretation of results (table 5, figure 1). Yet, daily costs of €10 and €400 for study medication in
249	SOD and SDD resulted in an ICER of €21,590 per LYG for SDD vs SC whereas SOD remained dominant
250	over SC. For all situations, SOD was more effective and cheaper than SDD (table 4 and 5). To stay

BMJ Open

251	below the Dutch threshold of €20,000 per life year gained, the maximum daily price for the topical
252	SDD-components should be €375.
253	
254	Discussion
255	This post-hoc analysis of a large cluster-randomized trial performed in 13 Dutch ICUs including 5,920
256	patients revealed that both SOD and SDD are cost-saving and more effective as compared to
257	standard care. These findings were insensitive to changes in discount rates and extra costs for
258	ventilation days. Furthermore, for SOD, but not for SDD, these findings were insensitive to current
259	(higher) market-prices of the topical components. The probabilities that SOD and SDD are cost-
260	effective for a willingness to pay threshold of €20,000 per life year gained as compared to standard
261	care, were 93% and 63%, respectively.
262	This is the first head-to-head comparison of the costs and benefits of SDD and SOD and the first
263	comparison of both interventions versus standard care. Strengths of the present study include the
264	large study size and the completeness of data collection.
265	Limitations of the study are the baseline differences between the three study periods. Patients
266	receiving standard care were younger, had lower APACHE II scores and were less likely to receive
267	mechanical ventilation and, therefore, seemed to have a better prognosis. In the original trial
268	random effects logistic regression modelling was applied to adjust for these differences. ³ Here we
269	have used crude data, without any adjustments for baseline differences. Our analysis points at
270	superiority of SOD and SDD when compared to standard care, despite the somewhat more
271	favourable prognosis at the time of ICU-admission of patients receiving standard care. Our findings
272	on the cost-effectiveness of both interventions are, therefore, conservative estimates. Furthermore,
273	patients receiving SOD were, on average, one year younger than those receiving SDD, which may
274	have affected the difference in life years lost between both interventions. Other limitations are the
275	restriction of cost data to the health care setting and the absence of antibiotic and microbiology cost
276	data after ICU-discharge, which could not be obtained retrospectively. Finally, this trial was

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

performed in ICU-settings with low endemicity of antibiotic resistance, which may limit generalizability to other settings. The main contributor to the total costs was length of stay, which was composed of stay in ICU and hospital after ICU-discharge. The other costs, microbiology and antibiotics, were highest for SDD, which had been reported previously.²⁵ Some, relatively small single-centre studies, also determined the effects of SDD on costs of days in ICU or in the hospital. In a German study SOD with cefotaxime prophylaxis resulted in lower average costs for antibiotic therapy and for days on ventilation than during standard care.²⁶ In a French study of trauma patients both daily ICU-costs as well as mean antibiotic costs, including SDD treatment, were lower during SDD compared to standard care.²⁷ In a Spanish study mean costs of systemic antibiotics were lower and less diagnostic procedures for infections were performed during SDD, compared to standard care, which resulted in a 21% reduction of total costs per survivor in the SDD-treated group.²⁸ Yet, in none of these studies a formal cost-effectiveness analysis was performed. VAP incidences were not determined in the Dutch SDD-SOD trial³ because of the perceived difficulties in uniformly diagnosing VAP in 13 ICUs. Yet, both SDD and SOD have been associated with reduced incidences of VAP, as compared to standard care.^{5 29} In addition to SDD and SOD there are other preventive measures that have been associated with reductions in the incidence of VAP, such as the use of silver-coated endotracheal tubes and continuous subglottic suctioning. In a large multi-centre randomized controlled trial silver-coated endotracheal tubes were associated with a relative risk reduction of the incidence of VAP of 35.9%, without discernible beneficial effects on patient outcome.³⁰ In a cost-effectiveness analysis of this trial the use of silver-coated tubes, although 45-fold more expensive than normal tubes (\$90 vs \$2 per tube), yielded savings of \$12,840 per episode of VAP prevented.³¹ Continuous subglottic suctioning (CSS) was, in a recent meta-analysis of 13 randomized trials, associated with a 45% reduction in the incidence of VAP (RR 0.55 (95%CI 0.46-0.66), but also without discernible beneficial effects on patient outcome (RR 1.01 (95%CI 0.85-1.20).³² The intervention appeared cost saving in two studies, saving \$4,992 and €1,176 per episode

BMJ Open

303	of VAP prevented. ^{33 34} However, these analyses were based on extrapolated costs per episode of
304	VAP, rather than on the true costs generated during the trials. Other widely recommended measures
305	to prevent VAP, such as the semi-recumbent patient position and different bundle approaches have
306	not been associated with documented improvements in patient outcome and have not been
307	evaluated with formal cost-effectiveness analyses.
308	In conclusion, both SOD and SDD appeared more beneficial and cost saving as compared to standard
309	care and even if the costs of both measures would increase tenfold SOD will remain cost-saving and
310	the incremental cost effectiveness ratio of SDD will be around the Dutch threshold for cost-
311	effectiveness of €20,000 per life year gained. The higher price for medication follows from the higher
312	costs for amphotericine B, which could be alleviated by replacing amphotericine B by nystatin, which
313	has also good antifungal activity in topical application. ³⁵ With 1,180 ICU-beds in a country of 16.6
314	million inhabitants (year 2010), extrapolation of our findings suggests that nationwide
315	implementation of SOD or SDD in ICUs, as occurred after the trial, has saved, per year, 18-36 million
316	euros.
316 317	euros. The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower
317	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower
317 318	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-
317 318 319	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria, ³⁷ effective eradication of
317 318 319 320	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria, ³⁷ effective eradication of intestinal carriage with cephalosporin-resistant Enterobacteriaceae, ³⁸ and low rates of resistance
 317 318 319 320 321 	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria, ³⁷ effective eradication of intestinal carriage with cephalosporin-resistant Enterobacteriaceae, ³⁸ and low rates of resistance development to colistin ³⁹ . Importantly, these beneficial effects were obtained in ICUs with low levels
 317 318 319 320 321 322 	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria, ³⁷ effective eradication of intestinal carriage with cephalosporin-resistant Enterobacteriaceae, ³⁸ and low rates of resistance development to colistin ³⁹ . Importantly, these beneficial effects were obtained in ICUs with low levels of antibiotic resistance, reflected by incidence rates of bloodstream infections caused by methicillin-
 317 318 319 320 321 322 323 	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria, ³⁷ effective eradication of intestinal carriage with cephalosporin-resistant Enterobacteriaceae, ³⁸ and low rates of resistance development to colistin ³⁹ . Importantly, these beneficial effects were obtained in ICUs with low levels of antibiotic resistance, reflected by incidence rates of bloodstream infections caused by methicillin-resistant <i>S. aureus</i> , vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of
 317 318 319 320 321 322 323 324 	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria, ³⁷ effective eradication of intestinal carriage with cephalosporin-resistant Enterobacteriaceae, ³⁸ and low rates of resistance development to colistin ³⁹ . Importantly, these beneficial effects were obtained in ICUs with low levels of antibiotic resistance, reflected by incidence rates of bloodstream infections caused by methicillin-resistant <i>S. aureus</i> , vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of <0.1, <0.1 and 0.5 per 1,000 patient at risk, respectively. ³⁷ Whether these benefits can be realized in
 317 318 319 320 321 322 323 324 325 	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria, ³⁷ effective eradication of intestinal carriage with cephalosporin-resistant Enterobacteriaceae, ³⁸ and low rates of resistance development to colistin ³⁹ . Importantly, these beneficial effects were obtained in ICUs with low levels of antibiotic resistance, reflected by incidence rates of bloodstream infections caused by methicillin-resistant <i>S. aureus</i> , vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of <0.1, <0.1 and 0.5 per 1,000 patient at risk, respectively. ³⁷ Whether these benefits can be realized in ICUs with different bacterial ecology remains to be determined, ⁴⁰ but given the potential gains

2	
3	
4	
5	
6	
7	
/ 0	
0	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
$2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 101 \\ 12 \\ 13 \\ 14 \\ 15 \\ 16 \\ 17 \\ 18 \\ 9 \\ 201 \\ 22 \\ 22 \\ 22 \\ 22 \\ 22 \\ 22 \\ 2$	
23	
24	
25	
26	
27	
28	
20	
29	
21	
20	
ა∠ ეე	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
52	
53 54	
54 55	
22	
56	
57	
58	
59	
60	

32	9	Acknowledgment
33	0	Contributors: AMdS and MJMB conceived the study. EO, AdW and MJMB designed the study. The
33	1	SDD-SOD trialist group and AMdS collected the trial data. EO, AdW, MB and MJM analyzed and
33	2	interpreted the data. EO, MB and MJMB drafted the manuscript and AdW, AMdS and The SDD-SOD
33	3	trialist group critically revised the manuscript for important intellectual content. All the authors had
33	4	full access to the data and approved the final manuscript. EO is the guarantor.
33 33 33	6	Ethical approval: Ethical approval for the trial was granted by the institutional review board at each participating hospital, as published previously (NEJM 2009;360:20). The requirement for informed consent was waived.
33 33 34	9	Data sharing: statistical code is available from the corresponding author
34	1	Obtained funding: no financial support was provided
34		
34	3	Funding: None

BMJ Open

References	e d, ed tice
1. Vincent JL. Nosocomial infections in adult intensive-care units. <i>Lancet</i> 2003;361(9374):2068	8-77
2. Bearman GM, Munro C, Sessler CN, Wenzel RP. Infection control and the prevention of	5-77.
nosocomial infections in the intensive care unit. Semin Respir Crit Care Med 2006;27(<u>م</u> ع)·310- ح
24.	
3. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, et al.	
Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med	
2009;360(1):20-31.	с. Д
4. Wunderink RG. Welkommen to our world. Emergence of antibiotic resistance with selective	e
decontamination of the digestive tract. Am J Respir Crit Care Med 2010;181(5):426-7.	
5. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce	
respiratory tract infections and mortality in adults receiving intensive care. Cochrane	
Database Syst Rev 2009(4):CD000022.	pen
6. American Thoracic Society. Guidelines for the management of adults with hospital-acquired	d,
ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care M	ed N
2005;171(4):388-416.	Ċ
7. Dodek P, Keenan S, Cook D, Heyland D, Jacka M, Hand L, et al. Evidence-based clinical pract	tice
guideline for the prevention of ventilator-associated pneumonia. Ann Intern Med	
2004;141(4):305-13.	= 0
8. Healthcare Infection Control Practices Advisory Committee, Centers for Disease Control and	d s
Prevention (U.S.). Guidelines for preventing health-care-associated pneumonia, 2003	
recommendations of the CDC and the Healthcare Infection Control Practices Advisory	
Committee. Respir Care 2004;49(8):926-39.	
9. Torres A, Carlet J. Ventilator-associated pneumonia. European Task Force on ventilator-ass	ociated
pneumonia. Eur Respir J 2001;17(5):1034-45.	
10. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. <i>Methods for the ecor</i>	
evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press, 2005. 11. Hakkaart-Van Roijen L, Tan SS, Bouwmans CA. <i>Handleiding voor kostenonderzoek. Method</i>	· ā
standaard kostprijzen voor economische evaluaties in de gezondheidszorg., 2011.	
12. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, con	duct =
analysis, and reporting. <i>Bmj</i> 2011;342:d1548.	
13. Boersma C, Carides GW, Atthobari J, Voors AA, Postma MJ. An economic assessment of lo	sartan-
based versus atenolol-based therapy in patients with hypertension and left-ventricula	ar 🤤
hypertrophy: results from the Losartan Intervention For Endpoint reduction (LIFE) stu	idv d
adapted to The Netherlands. <i>Clin Ther</i> 2007;29(5):963-71.	
14. Simoens S. Health economic assessment: a methodological primer. Int J Environ Res Public	c Health
2009;6(12):2950-66.	
15. Al Maiwenn MJ, Hakkaart L, Tan SS, Bakker J. Cost-consequence analysis of remifentanil-b	ased
analgo-sedation vs. conventional analgesia and sedation for patients on mechanical	
ventilation in the Netherlands. <i>Crit Care</i> 2010;14(6):R195.	=
16. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the	ů, V
contribution of mechanical ventilation. Crit Care Med 2005;33(6):1266-71.	
17. Tan SS, Hakkaart-van Roijen L, Al MJ, Bouwmans CA, Hoogendoorn ME, Spronk PE, et al. A	۱ +
microcosting study of intensive care unit stay in the Netherlands. J Intensive Care Med	d g
2008;23(4):250-7.	
18. The Dutch Drug Information System of the Health Care Insurance Board.	
http://www.gipdatabank.nl/.	
19. Gravelle H, Smith D. Discounting for health effects in cost-benefit and cost-effectiveness a	analysis.
Health Econ 2001;10(7):587-99.	
20. De Wit GA, Tariq, L., Van Gils, P.F. and Panneman, M.J.M. Handleiding voor economisch	Š S
evaluatieonderzoek bij gezondheidsbevordering: Over Euro en Effect, 2010.	
	analysis.
	15 -
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2		
2	395	21. Centraal Bureau Voor de Statistiek. Levensverwachting; geslacht en leeftijd, 2012.
4	396	22. Obenchain RL. Resampling and multiplicity in cost-effectiveness inference. <i>J Biopharm Stat</i>
5	397	1999;9(4):563-82.
6	398	23. O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: an
7	399	introduction to statistical issues and methods. Stat Methods Med Res 2002;11(6):455-68.
8	400	24. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curvesfacts, fallacies and
9	401	frequently asked questions. Health Econ 2004;13(5):405-15.
10 11	402	25. van der Voort PH, van Roon EN, Kampinga GA, Boerma EC, Gerritsen RT, Egbers PH, et al. A
12	403	before-after study of multi-resistance and cost of selective decontamination of the digestive
13	404	tract. Infection 2004;32(5):271-7.
14	405	26. Abele-Horn M, Dauber A, Bauernfeind A, Russwurm W, Seyfarth-Metzger I, Gleich P, et al.
15	406	Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal
16	407	decontamination (SOD). Intensive Care Med 1997;23(2):187-95.
17	408	27. Langlois-Karaga A, Bues-Charbit M, Davignon A, Albanese J, Durbec O, Martin C, et al. Selective
18	409	digestive decontamination in multiple trauma patients: cost and efficacy. Pharm World Sci
19	410	1995;17(1):12-6.
20	411	28. Sanchez Garcia M, Cambronero Galache JA, Lopez Diaz J, Cerda Cerda E, Rubio Blasco J, Gomez
21 22	412	Aguinaga MA, et al. Effectiveness and cost of selective decontamination of the digestive
22	413	tract in critically ill intubated patients. A randomized, double-blind, placebo-controlled,
24	414	multicenter trial. Am J Respir Crit Care Med 1998;158(3):908-16.
25	415	29. Bergmans DC, Bonten MJ, Gaillard CA, Paling JC, van der Geest S, van Tiel FH, et al. Prevention of
26	416	ventilator-associated pneumonia by oral decontamination: a prospective, randomized,
27	417	double-blind, placebo-controlled study. <i>Am J Respir Crit Care Med</i> 2001;164(3):382-8.
28	418	30. Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, et al. Silver-coated
29	419	endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT
30 31	420	randomized trial. <i>Jama</i> 2008;300(7):805-13.
32	421 422	31. Shorr AF, Zilberberg MD, Kollef M. Cost-effectiveness analysis of a silver-coated endotracheal
33	422	tube to reduce the incidence of ventilator-associated pneumonia. <i>Infect Control Hosp</i> Epidemiol 2009;30(8):759-63.
34	423 424	32. Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion
35	424	drainage for the prevention of ventilator-associated pneumonia: a systematic review and
36	426	meta-analysis. Crit Care Med 2011;39(8):1985-91.
37	427	33. Hallais C, Merle V, Guitard PG, Moreau A, Josset V, Thillard D, et al. Is continuous subglottic
38	428	suctioning cost-effective for the prevention of ventilator-associated pneumonia? <i>Infect</i>
39	429	Control Hosp Epidemiol 2011;32(2):131-5.
40 41	430	34. Shorr AF, O'Malley PG. Continuous subglottic suctioning for the prevention of ventilator-
41	431	associated pneumonia: potential economic implications. <i>Chest</i> 2001;119(1):228-35.
43	432	35. Normand S, Francois B, Darde ML, Bouteille B, Bonnivard M, Preux PM, et al. Oral nystatin
44	433	prophylaxis of Candida spp. colonization in ventilated critically ill patients. Intensive Care
45	434	Med 2005;31(11):1508-13.
46	435	36. Oostdijk EA, de Smet AM, Blok HE, Thieme Groen ES, van Asselt GJ, Benus RF, et al. Ecological
47	436	effects of selective decontamination on resistant gram-negative bacterial colonization. Am J
48	437	Respir Crit Care Med 2010;181(5):452-7.
49 50	438	37. de Smet AM, Kluytmans JA, Blok HE, Mascini EM, Benus RF, Bernards AT, et al. Selective digestive
50 51	439	tract decontamination and selective oropharyngeal decontamination and antibiotic
52	440	resistance in patients in intensive-care units: an open-label, clustered group-randomised,
53	441	crossover study. Lancet Infect Dis 2011;11(5):372-80.
54	442	38. Oostdijk EA, de Smet AM, Kesecioglu J, Bonten MJ. Decontamination of cephalosporin-resistant
55	443	Enterobacteriaceae during selective digestive tract decontamination in intensive care units. J
56	444	Antimicrob Chemother 2012;67(9):2250-3.
57		
58 50		
59 60		
00		16

1		
2 3	445	39. Oostdijk EA, Smits L, de Smet AM, Leverstein-van Hall MA, Kesecioglu J, Bonten MJ. Colistin
3 4	446	resistance in gram-negative bacteria during prophylactic topical colistin use in intensive care
5	447	units. Intensive Care Med 2012.
6	448	40. Walden AP, Bonten MJ, Wise MP. Should selective digestive decontamination be used in critically
7	449	ill patients? <i>Bmj</i> 2012;345:e6697.
8	450	41. Ioannidis JP, Garber AM. Individualized cost-effectiveness analysis. PLoS Med
9	451	2011;8(7):e1001058.
10 11	452	42. Internal Revenue Service.
12	453	
13	454	
14	455	
15		
16		
17 18		
10		
20		
21		
22		
23		
24 25		
25 26		
27		
28		
29		
30		
31 32		
33		
34		
35		
36		
37		
38 39		
40		
41		
42		
43		
44		
45 46		
40		
48		
49		
50		
51 52		
52 53		
53 54		
55		
56		
57		
58 50		
59 60		17
~~~		17

Category		Prices per unit		
Length of Stay	Day in ICU	€2,183 ¹¹		
	Day in hospital ward	€505 ¹¹		
	Mechanical ventilation, additional costs	€327.45 ¹⁵⁻¹⁷		
Topical antibiotics	Cost of SOD per day	€0.87 ³⁴²		
	Cost of SDD per day	€10.48 ³⁴²		
Microbiology	Blood culture	€11.89 per culture + €12.90 order rate		
	Throat culture	€7.78 per culture + €12.90 order rate		
	Sputum culture	€7.78 per culture + €12.90 order rate		
	Bronchoalveolar lavage	€7.78 per sample + €12.90 order rate		
	Rectum culture	€7.78 per sample + €12.90 order rate		
	Species determination	Extra €13.00 per isolate + €18.52 *		
	Resistance profile determination	8.96 per isolate		
Antibiotics		According to GIP database ¹⁸		

458 Table 1: Costs used per unit

459 SOD, selective oropharyngeal decontamination ; SDD selective decontamination of the Digestive tract; SC,

- 460 standard care
- 461 * UMCU costs

		SC	SOD	SDD
		N=1,987	N=1,901	N=2,032
Baseline characteristics				
Age, years (mean (SD)) *#		61.4 ± 16.2	61.4 ± 16.3	62.4 ± 15.8
Male sex (no (%))		1219 (61.3)	1211 (63.7)	1242 (63.7)
Apache II score (mean (SD)) **		18.6 ± 7.9	19.6 ± 8.8	19.9 ± 8.9
Mechanical ventilation (no (%)) †	*	1,751 (88.1)	1,790 (94.2)	1,888 (92.9)
Clinical outcome **		8		
Length of MV, days (median (IQR	))	6 (9)	7 (8)	6 (9)
Length of stay ICU, days (median	(IQR))	8 (11)	9 (9)	9 (10)
Length of stay hospital, days (me	dian (IQR)) ***	15 (23)	15 (22)	15 (21)
Resource use				
Study medication, DDD (total (me	ean))	0	7,609 (4.0)	8,068 (3.95)
Systemic antibiotics, DDD (total (	mean))	33,688 (5.9)	30,299 (6.2)	29,663 (5.2)
Microbiology (total (mean))	Rectal	0	0	7,247 (3.8)
	BAL	263 (1.3)	221 (1.3)	253 (1.3)
	Sputum	5,430 (3.7)	7,467 (4.3)	8,073 (4.4)
	Throat	431 (2.7)	6,277 (3.5)	7,176 (3.8)
	Blood	4,113 (3.7)	4,849 (4.1)	4,461 (4.1)

Table 2: Baseline characteristics, clinical outcomes and resource use of patients

SDD, Selective Decontamination of the Digestive tract; SOD, Selective Oropharyngeal Decontamination; SC, Standard Care; IQR, inter quartile range; DDD, defined daily

doses; MV, mechanical ventilation; ICU, Intensive Care Unit; BAL, Brancheoalveolar Lavage

P value <0.05 for: † SC vs SOD ; * SC vs SDD ; # SOD vs SDD

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

** Values differ from previously reported values as not all patients could be included in the present analysis

*** Duration in the hospital is the number of days in the hospital after ICU-discharge, for patients who were discharged from the ICU alive

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.136/bmjopen-2012.002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

		SC	SOD	SDD
		N=1990	N=1904	N=2045
Length of Stay	ICU	€29,553.45 (€28,152.40 - €30,954.49)	€28,684.46 (€27,412.05 - €29,956.87)	€29,069.78 (€27,636.40 - €30,503.16)
	Hospital	€8,621.85 (€8,059.10 - €9,184.61)	€7,830.55 (€7,345.91 - €8,315.20)	€7,963.94 (€7,476.75 - €8,451.13)
	MV	€3,225.06 (€3,045.61 – €3,404.51)	€3,316.36 (€3,151.14 – €3,481.58)	€3,308.18 (€3,116.09 – €3,500.27)
	Total	€41,400.36 (€39,672.04 -€43,128.68)	€39,831.37 (€38,261.92 - €41,400.82)	€40,341.90 (€38,599.66 - €42,084.14)
Study medication		-	€3.48 (€3.47 - €3.49)	€41.35 (€41.07 – €41.62)*
Systemic Antibiot	ics	€358.29 (€321.34 - €395.24)	€317.65 (€280.89-€354.42)	€439.14 (€406.69-€471.59)
Microbiology	Rectal swabs	-	-	€102.75 (€97.64 – €107.86)
	BAL	€6.44 (€5.42 – €7.46)	€4.70 (€3.92 – €5.49)	€4.77 (€4.01 – €5.53)
	Sputum	€114.83 (€106.87 – €122.79)	€135.85 (€127.99 – €143.71)	€117.57 (€110.78 – €124.36)
	Throat	€8.12 (€6.39 – €9.84)	€86.66 (€83.07 – €90.25)	€89.65 (€85.68 – €93.63)
	Blood	€52.61 (€48.74 – €56.49)	€53.72 (€49.64 – €57.79)	€45.45 (€41.87 – €49.04)
	Total	€182.15 (€170.60 – €193.69)	€280.93 (€267.00 – €294.87)	€360.73 (€343.69 – €377.76)
Total		€41,940.79	€40,433.42	€41,183.12
		(€40,183.93 – €43,697.66)	(€38,837.50 - €42,029.35)	(€39,408.39 - €42,957.85)

*Excluding cefotaxim. Cefotaxim use is included in total systemic antibiotic use.

SDD, Selective Decontamination of the Digestive tract; SOD, Selective Oropharyngeal Decontamination; SC, Standard Care; MV, mechanical ventilation; ICU, Intensive Care

Unit; BAL, Brancheoalveolar Lavage

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

1	
2 3 4	
4 5	
5 6 7	
7 8 9	
10	
11 12	
13	
14 15	
16 17	
13 14 15 16 17 18 19	
20	
21 22	
23 24	
25	
26 27	
28 29	
30	
31 32	
33 34	
35 36	
32 33 34 35 36 37 38	
38 39	
40 41	
42	
43 44	
45 46	
47	
48 ⊿q	

	LYG*	Cost difference	ICER	-
SOD vs SC (95% CI)	+ 0.25 (-0.05 – 0.55)	-€1507.37 (-€3,186.45 – €171.72)	SOD dominates SC	-
SDD vs SC (95% CI)	+ 0.04 (-0.26 – 0.34)	-€757.67 (-€2,522.56 – €1,007.21)	SDD dominates SC	
SOD vs SDD (95% CI)	+ 0.21 (-0.09 – 0.51)	-€749.69 (-€2,439.35 – €939.97)	SOD dominates SDD	
Table 4: Outcomes of cc	ost-effectiveness comparisons across	groups		-
* Effects are discounted	at 1.5% a year			
LYG, life years gained ;	95% CI, 95% confidence intervals	; SDD, Selective Decontamination of the Digestive	e tract; SOD, Selective Oropharyngeal	Decontamination; SC,
Standard Care; ICER, inc	remental costs effectiveness ratio (c	costs/LYG)		
		osts/LYG)		

		SC	SOD	SDD	ICER analyses	ICER analyses	ICER analyses
					SC vs SOD	SC vs SDD	SDD vs SOD
Sensitivity analysis	BC	4.27	4.02	4.23	SC = dominated by	SC = dominated by	SDD = dominated b
discounting effects (Life	+1.5%	(3.96 – 4.57)	(3.72 – 4.32)	(3.94 – 4.53)	SOD	SDD	SOD
years lost)	+0%	6.07	5.62	5.97	SC = dominated by	SC = dominated by	SDD = dominated b
		(5.58 – 6.55)	(5.15 – 6.08)	(5.50 – 6.44)	SOD	SDD	SOD
	+3%	2.82	2.68	2.82	SC = dominated by	SC = dominated by	SDD = dominated b
		(2.63 – 3.01)	(2.49 – 2.87)	(2.63 – 3.00)	SOD	SDD	SOD
Sensitivity analysis	BC	€41,940.79	€40,433.42	€41,183.12	SC = dominated by	SC = dominated by	SDD = dominated b
mechanical ventilation*	+15%	(€40,183.93 -	(€38,837.50 -	(€39,408.39 –	SOD	SDD	SOD
		€43,697.66)	€42,029.35)	€42,957.85)			
	+ 0%	€38,715.73	€37,117.07 🧹	€37,874.94	SC = dominated by	SC = dominated by	SDD = dominated b
		(€37,112.32 -	(€35,659.90 –	(€36,270.73 –	SOD	SDD	SOD
		€40,319.14)	€38,574.24)	€39,479.15)			
	+30%	€45,165.85	€43,749.78	€44,491.30	SC = dominated by	SC = dominated by	SDD = dominated b
		(€43,251.01 -	(€42,010.47 –	(€42,542.03 -	SOD	SDD	SOD
		€47,080.69)	€45,489.09)	€46,440.57)			
Sensitivity analysis price		€41,940.79	€40,493.15	€42,720.23	SC = dominated by	ICER 21,590	SDD = dominated b
study regimen*#		(€40,183.93 -	(€38,996.62 -	(€40,943.82 -	SOD		SOD
		€43,697.66)	€42,189.67)	€44.496.65)		P	

Table 5: Sensitivity analysis

# Price SOD €40 and SDD €400 per day * Effects are discounted 1.5% a year

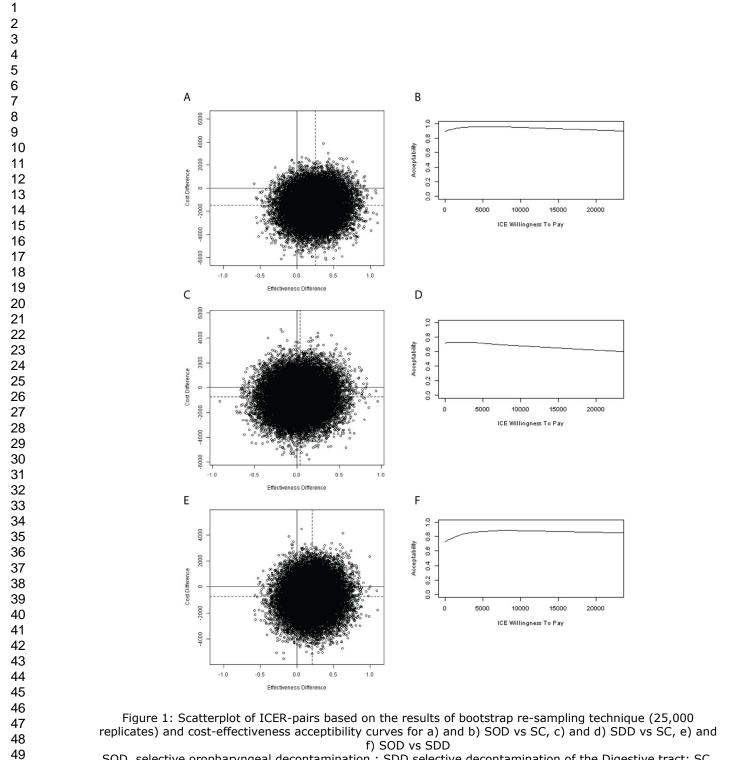
BC base case results ; SDD Selective Decontamination of the Digestive tract, SOD Selective Oropharyngeal Decontamination, SC Standard Care, ICER incremental costs

effectiveness ratio (costs/LYG)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

BMJ Open



SOD, selective oropharyngeal decontamination ; SDD selective decontamination of the Digestive tract; SC, standard care 187x251mm (150 x 150 DPI)

1
2
2 3 4 5 6
4
5
5
6
7
8
g
10
10
11
12
13
1/
45
15
16
17
18
19
20
20
21
22
23
21
7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 32 4 25 26 27 28 9 30 132 33 4 35 6 37 8 9
25
26
27
28
20
29
30
31
32
33
24
34
35
36
37
38
30
39
40
41
42
43
43 44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
20
59
<u>^</u>

		-
Study design	Item	Page
1	The research question is stated	5
2	The economic importance of the research question is stated	5
3	The viewpoint(s) of the analysis are clearly stated and justified	5
4	The rationale for choosing the alternative programmes or interventions compared is stated	5
5	The alternatives being compared are clearly described	5,6
6	The form of economic evaluation used is stated	6
7	The choice of form of economic evaluation is justified in relation to the questions addressed	6
Data		
collection		
8	The source(s) of effectiveness estimates used are stated	8
9	Details of the design and results of effectiveness study are	5
5	given (if based on a single study)	5
10	Details of the method of synthesis or meta-analysis of	Na
	estimates are given (if based on an overview of a number	
	of effectiveness studies)	
11	The primary outcome measure(s) for the economic	6
	evaluation are clearly stated	
12	Methods to value health states and other benefits are	8
	stated	
13	Details of the subjects from whom valuations were obtained are given	Na
14	Productivity changes (if included) are reported separately	Na
15	The relevance of productivity changes to the study question is discussed	Na
16	Quantities of resources are reported separately from their unit costs	17,19
17	Methods for the estimation of quantities and unit costs are described	6,7
18	Currency and price data are recorded	7
19	Details of currency of price adjustments for inflation or currency conversion are given	7
20	Details of any model used are given	Na
20	The choice of model used and the key parameters on	Na
	which it is based are justified	
Analysis and		
Analysis and		
interpretation of results		
22	Time horizon of costs and benefits is stated	6
23	The discount rate(s) is stated	7
24	The choice of rate(s) is justified	7
25	An explanation is given if costs or benefits are not discounted	7
26	Details of statistical tests and confidence intervals are given for stochastic data	8
27	The approach to sensitivity analysis is given	8
28	The choice of variables for sensitivity analysis is justified	8
29	The ranges over which the variables are varied are stated	8
30	Relevant alternatives are compared	Na
	neletant alternatives are compared	



# Selective Decontamination of the Digestive Tract and Selective Oropharyngeal Decontamination in ICU patients: a cost-effectiveness analysis

Journal:	BMJ Open
Manuscript ID:	bmjopen-2012-002529.R1
Article Type:	Research
Date Submitted by the Author:	27-Jan-2013
Complete List of Authors:	Oostdijk, Evelien; University Medical Center Utrecht, Department of Medical Microbiology; University Medical Center Utrecht, Department of Intensive Care Medicine Wit, Ardine; Center for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), ; Julius Center for Health Sciences and Primary Care Bakker, Marina; University Medical Center Utrecht, Department of Medical Microbiology De Smet, Anne Marie; University of Groningen, University Medical Center Groningen, Department of Critical Care Bonten, Marc; UMC Utrecht; University Medical Centre Utrecht, Julius Center for Health Sciences and Primary Care
<b>Primary Subject Heading</b> :	Health economics
Secondary Subject Heading:	Infectious diseases, Intensive care
Keywords:	HEALTH ECONOMICS, Epidemiology < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

SCHOLARONE[™] Manuscripts

## **BMJ Open**

1	Selective Decontamination of the Digestive Tract and Selective Oropharyngeal Decontamination in
2	ICU patients: a cost-effectiveness analysis
3	
Z	E.A.N. Oostdijk MD ^{1,2} , G.A. de Wit PhD ^{3,4} , M. Bakker MSc ¹ , A.M.G.A. de Smet MD PhD ⁵ , M.J.M.
5	Bonten ^{1,3} MD PhD on behalf of the Dutch SOD-SDD trialists group
e	
7	¹ Department of Medical Microbiology, ² Department of Intensive Care Medicine and ³ Julius Center for Health
8	Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The
ç	Netherlands
10	⁴ Center for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM),
11	Antonie van Leeuwenhoeklaan 9, 3721 MA, Bilthoven, The Netherlands
12	⁵ Department of Critical Care, University of Groningen, University Medical Center Groningen, Hanzeplein 1,
13	9713 GZ, Groningen, The Netherlands
14	
15	
16	
17	This work was presented in part at the 25th Annual Congress of the European Society of Intensive
18	Care Medicine, Lisbon, Portugal, October 13-17, 2012.
19	
20	
21	
22	
23	
24	
25	

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

26	Tjip S. van der Werf, Jan P. Arends, University Medical Center, Groningen; Johannes G. van der
27	Hoeven, Peter Pickkers, Patrick D.J. Sturm, Andreas Voss, Radboud University, Nijmegen Medical
28	Center, Nijmegen; Alexandra T. Bernards, Ed J. Kuijper, Hubertus I.J Harinck, Leiden University
29	Medical Center, Leiden; Alexander .J.G.H. Bindels, Arjan R. Jansz, Catharina Hospital, Eindhoven;
30	Ronald M.J. Wesselink, Bartelt M de Jongh, St. Antonius Hospital, Nieuwegein; Paul J.W. Dennesen,
31	Gerard J. van Asselt, Medical Center Haaglanden, The Hague; Leonard F. te Velde, Ine H.M.E. Frenay,
32	Albert Schweitzer Hospital, Dordrecht; Mat van Iterson , Steven F.T. Thijsen, Diakonessen Hospital,
33	Utrecht; Georg H. Kluge, Slotervaart Hospital, Amsterdam; Jacob W. de Vries, Jan A. Kaan, Mesos
34	Medical Center, Utrecht — all in the Netherlands.
35	
36	Corresponding author: E.A.N. Oostdijk
37	Mailing address: Department of Medical Microbiology, University Medical Center Utrecht, G04.614,
38	PO box 85500, 3508 GA Utrecht, The Netherlands.
39	Phone: +31 88 7555006. Fax +31 88 7555132; Email: E.A.N.Oostdijk@umcutrecht.nl
40	
41	Keywords: SDD, SOD, Intensive Care, cost-effectiveness, economic evaluation
42	
43	

## **BMJ Open**

2 3	44	Article summary:
4 5 6	45	Article Focus
7 8	46	Selective digestive tract decontamination (SDD) and selective oropharyngeal
9 10	47	decontamination (SOD) are prophylactic antibiotics used as infection prevention strategy in
11 12	48	Intensive Care Units (ICU)
13 14 15	49	• In a Dutch 13-center study, SDD and SOD were associated with relative risk reductions of
16 17	50	mortality at day 28 of 13% and 11%, respectively, as compared to standard care (i.e. no SDD
18 19	51	or SOD) and with lower incidence of ICU-acquired bacteremia and ICU-acquired colonization
20 21	52	of the respiratory tract with multi-resistant bacteria
22 23	53	• This paper describes the costs and effects of SDD and SOD from the healthcare perspective
24 25	54	in Dutch ICUs
26 27 28	55	Key Messages
29 30	56	Both SDD and SOD were cheaper and more beneficial as compared to standard care and
31 32	57	these findings were insensitive to changes in discount rates and extra costs for ventilation
33 34	58	days
35 36	59	• SOD, but not SDD, was still dominant (i.e. cheaper and more beneficial) over standard care
37 38 20	60	to current tenfold higher market-prices of the topical components ( $\in$ 40/day for SOD and
39 40 41	61	€400/day for SDD)
42 43	62	Strengths and Limitations.
44 45	63	• This is the first head-to-head comparison of the costs and benefits of SDD and SOD and the
46 47	64	first comparison of both interventions versus standard care using data from a multi-center
48 49	65	trial including 5,939 patients
50 51 52	66	Baseline differences were present between the three study groups
53 54	67	Only direct medical costs were included in the analysis and cost data were restricted to
55 56	68	health care settings
57 58 59 60	69	3

70	ABSTRACT
71	Objective: To determine costs and effects of Selective digestive tract decontamination (SDD) and
72	selective oropharyngeal decontamination (SOD) as compared to standard care (i.e. no SDD/SOD (SC))
73	from a healthcare perspective in Dutch ICUs
74	Design: A post-hoc analysis of a previously performed cluster-randomized trial (NEJM 2009;360:20).
75	Setting: 13 Dutch ICUs
76	Participants: Patients with ICU-stay of >48 hours that received SDD (n=2,045), SOD (n=1,904) or SC
77	(n=1,990).
78	Interventions: SDD or SOD.
79	Primary and secondary outcome measures: Effects were based on hospital survival, expressed as
80	crude Life Years Gained (cLYG). The incremental cost effectiveness ratio (ICER) was calculated, with
81	corresponding cost acceptability curves. Sensitivity analyses were performed for discount-rates,
82	costs of SDD, SOD and mechanical ventilation.
83	Results: Total costs per patient were €41,941 for SC (95%Cl €40,184-€43,698), €40,433 for SOD
84	(95%Cl €38,838-€42,029) and €41,183 for SOD (95%Cl €39,408-€42,958). SOD and SDD resulted in
85	crude LYG of +0.04 and +0.25, respectively, as compared to SC, implying that both SDD and SOD are
86	dominant (i.e. cheaper and more beneficial) over SC. In cost-effectiveness acceptability curves
87	probabilities for cost-effectiveness, compared to standard care, ranged from 89% to 93% for SOD
88	and from 63% to 72% for SDD, for acceptable costs for 1 LYG ranging from €0 to €20,000. Sensitivity
89	analysis for mechanical ventilation and discount rates did not change interpretation. Yet, if costs of
90	the topical component of SDD and SOD would increase tenfold to €400/day and €40/day (maximum
91	values based upon free market prices in 2012), the estimated ICER as compared to SC for SDD would
92	be €21,590 per LYG. SOD would remain cost-saving.
93	Conclusions SDD and SOD were both effective and cost-saving in Dutch ICUs
94	
95	

### **BMJ Open**

96	Introduction
97	Many patients in Intensive Care Units (ICU) are affected by nosocomial infections. ¹ These infections
98	are associated with increased mortality and morbidity, and considerable extra costs. ² Selective
99	oropharyngeal decontamination (SOD) and selective decontamination of the digestive tract (SDD)
100	are prophylactic antibiotic regimens, that consist of topical antibiotics applied to the oropharynx and
101	the intestinal tract to prevent colonization of gram-negative bacteria, Staphylococcus aureus and
102	yeasts. During SOD topical antibiotics are exclusively applied to the oropharynx throughout ICU-stay.
103	During SDD topical antibiotics are applied to the oropharynx but also to the intestinal tract
104	throughout ICU-stay, in combination with intravenous administration of cefotaxime during the first
105	four days in ICU, to pre-emptively treat infections with commensal respiratory tract bacteria. ³ SDD
106	has been a widely evaluated but highly controversial intervention in ICU. ⁴ Many, but not all, studies
107	reported statistically significant reductions in the incidence of Ventilator-Associated Pneumonia
108	(VAP), but only few were able to demonstrate outcome benefits such as reduced mortality and
109	length of ICU-stay. ⁵ In the absence of indisputably documented outcome benefits, the fear for
110	selection of antibiotic resistance has prevailed and SDD has not been recommended in most
111	infection prevention guidelines. ⁶⁻⁹ In a cluster-randomized study in 13 Dutch ICUs, SDD and SOD
112	were associated with relative risk reductions of mortality at day 28 of 13% and 11%, respectively, as
113	compared to standard care (i.e. no SDD or SOD). ³ Although SOD and SDD are currently widely used in
114	Dutch ICUs, the costs and effects of both regimens have not yet been determined. We, therefore,
115	conducted a cost-effectiveness analysis (CEA), comparing Standard Care, SOD and SDD using data
116	from the Dutch multi-center trial.
117	
118	Methods
119	Data collection
120	A post-hoc analysis was performed of the cluster randomized crossover trial comparing SOD and

121 SDD to standard care (SC). The trial was conducted in 13 Dutch ICUs and included 5,939 patients

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

Page 6 of 53

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

### **BMJ Open**

(2,045 received SDD, 1,904 received SOD and 1,990 were treated according to SC). All centers were assigned to all three regimens during periods of six months, however, the order of implementation of SC, SOD and SDD was randomized per center.³

SOD and SDD have been described in detail elsewhere.³ In short, SOD consists of a paste applied to the oropharynx, containing polymyxin E, tobramycin and amphotericin B (all in a 2% concentration, applied every 6h). SDD consists, besides of the paste used in SOD, also of a 10 mL suspension of 100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B that is applied via a nasogastric tube, every 6h, and of cefotaxime (1000 mg, every 6h) applied intravenously during the first four days of ICU-admission. The topical antibiotics of both regimens are applied until ICU-discharge. During the trial there were no restrictions to systemic antibiotic use during SC and SOD. During SDD, the use of antibiotics with anti-anaerobic activity was discouraged. This resulted in a marked increase of cephalosporin use and lower usage of penicillins, carbapenem and clindamycin.³ Surveillance cultures of endotracheal aspirates, oropharynx and rectum were obtained on admission and twice weekly during SDD. During SOD surveillance cultures of endotracheal aspirates and the oropharynx were obtained on admission and twice weekly thereafter. During SC no surveillance cultures were obtained. Clinical cultures were obtained on clinical suspicion of infection in all three periods.

Approach for economic evaluation

We performed a cost-effectiveness analysis (CEA) from a healthcare perspective, hence, only including direct medical costs.¹⁰⁻¹² The time horizon of the study was the period from ICU-admission until hospital-discharge. Life Years Gained (LYG) was used as effectiveness measure. The outcome of the CEA was the incremental cost effectiveness ratio (ICER), expressed as cost per life year gained (LYG). The informal Dutch threshold for cost-effectiveness is €20,000 per LYG.^{13 14} Data from all individual patients were used for analyses. The CEA was performed post-hoc, however, using data that were prospectively collected in Case Report Forms during the trial. Total direct medical costs of the three regimens consisted of three main categories: Length of Stay (LOS), antibiotic use and

Page 7 of 53

### **BMJ Open**

148	microbiology costs (table 1). LOS was based on the length of ICU-stay and the number of days on a
149	hospital ward after ICU-discharge. Costs for days in ICU and other hospital days were based upon the
150	Dutch guidelines for costing research in health economic studies. ¹¹ Days in ICU were categorized in
151	days with and without mechanical ventilation; days with mechanical ventilation were considered to
152	be 15% more expensive than ICU-days without mechanical ventilation. ¹⁵⁻¹⁷ Antibiotic use consisted
153	of the topical components of the SDD and SOD-regimen, hereafter referred to as study medication,
154	and of all systemic antibiotics used in ICU during all periods, including the four days cefotaxime
155	during SDD as part of the SDD-protocol. The price of study medication was €0.87 and €10.48 per day,
156	for SOD and SDD respectively. Costs of systemic antibiotics were based upon prices per Defined Daily
157	Dose (DDD) provided by the Dutch information project on medication and medical devices (Genees-
158	en hulpmiddelen Informatie Project (GIP)-database ¹⁸ ). For microbiology costs blood cultures,
159	broncheoalveolar lavages (BAL), sputum-, throat- and rectal cultures were considered. Rectal
160	cultures were only obtained during SDD as part of SDD-surveillance. Cultures obtained from the
161	other sites were either obtained as part of surveillance (throat- and sputum cultures during
162	SDD/SOD) or as part of daily clinical practice. Microbiological costs were obtained as the internal
163	tariffs applied within the University Medical Center Utrecht. These costs included costs for the
164	microbiological culture, order tariff and extra costs for species determination and susceptibility
165	resistance testing in case of relevant bacterial growth, irrespective of the species. The year 2009 was
166	taken as the reference year for all costs. Costs that were not available for 2009 were corrected for
167	inflation (with respect to 2009) based on the price index. ¹¹ An overview of all unit costs used in the
168	analysis is provided in table 1. LYG were discounted at 1.5% a year, following Dutch guidelines for
169	health economic evaluation. ¹⁹ Discounting of costs was not necessary, as all costs occurred within
170	the first year after inclusion. ²⁰
171	
172	Analysis

Life Years Gained (LYG) were determined by calculating Life Years Lost (LYL) of the patients who

### Page 8 of 53

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

### **BMJ Open**

3	
3 4 5 6	
5	
6	
7	
<i>'</i>	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
7 8 9 10 11 12 13 14 15 16 17 18 19 20 12 22 32 42 56 7 28 9 30 1 32 33 43 56 37 88 90 44	
22 22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
30	
10	
40	
41	
42	
43	
44	
45	
46	
47	
48	
40 49 50	
50	
50 51 52 53 54 55 56 57 58 59 60	
52	
53	
54	
55	
56	
57	
50	
50	
59 60	
00	

1

2

deceased in the hospital, using life tables for the Dutch population combined with age and sex.²¹ 174 175 with LYG defined as the difference in LYL between regimens. The ICER was defined as the 176 incremental difference between the mean cost of treatment regimens, divided by the incremental 177 difference in mean effect between treatment regimens. To estimate confidence limits for the ICER, 178 bootstrapping (25,000 repeats) was performed, as this does not depend on parametric assumptions about the distribution of the data.^{22 23} Results of the bootstrap procedure were plotted in a cost-179 180 effectiveness plane that graphically represents the cost-difference and effect difference between 181 either SDD or SOD and SC, and for SDD versus SOD, for each of the bootstrap replications. Cost-182 effectiveness acceptability curves (CEAC) were plotted to express the probability that treatment 183 regimens were cost-effective as compared to standard care, for a range of willingness to pay levels for one life year gained ( $\lambda$ ).²⁴ The curves display the proportion of bootstrapped ICER-pairs that are 184 185 cost-effective, meaning that they either fall within the south-east quadrant of the cost-effectiveness 186 plane or remain below the  $\lambda$  threshold in the north-east and south-west quadrants of the plane. 187 Additionally, sensitivity analyses were performed: The discounted results (at 1.5% a year) were 188 compared to results without discounting and to a discount rate of 3% a year; costs for ICU-days with 189 mechanical ventilation were analyzed for 0% and 30% extra per ICU-day as compared to 15% 190 additional costs in basecase analysis; daily costs of study medication were analyzed with maximum 191 values based upon free market prices in 2012 (€40 for SOD and €400 for SDD). Mann-Whitney U test 192 was used to calculate P-values. P-value <0.05 was considered to denote statistical significance and all 193 reported p-values are two-sided. All analyses were performed using Statistical Package for Social 194 Sciences version 20 (SPSS, Chicago, IL) version 17.0 and R version 2.14.2. 195

196 Results

197 In this cluster-randomized trial 5,939 patients were included; 1,990 patients in the SC group, 1,904 198 received SOD and 2,045 received SDD. For this post-hoc analysis 19 patients were excluded (3 199 patients during SC, 3 during SOD and 13 during SDD). Twelve patients declined permission to use

### **BMJ Open**

<u>^</u>		
2 3	200	clinical data. Seven additional patients were excluded because data on hospital discharge and/or
4 5 6	201	hospital mortality was missing, as reported previously. ³
7 8	202	Baseline characteristics differed among the three groups (table 2). Patients receiving SDD were on
9 10	203	average 62.4 (±15.8) years old, compared to 61.4 (±16.3) and 61.4 (±16.2) years for patients
11 12	204	receiving SOD and SC, respectively. Patients receiving SC had a lower mean APACHE II score (18.6)
13 14	205	than those receiving SOD (19.6) and SDD (19.9), and were less likely to be on mechanical ventilation
15 16	206	(88.1% for SC vs. 94.2% and 92.9% for SOD and SDD, respectively).
17 18	207	Mean LOS in ICU and in hospital and mean duration of mechanical ventilation did not differ
19 20	208	significantly between SC, SOD and SDD. These data differ somewhat from original LOS data reported
21 22 23	209	previously ³ , which included only data of patients who were alive at day 28.
23 24 25	210	In all, 7,609 daily doses of study medication were used in the SOD group and 8,068 during SDD, with
26 27	211	average numbers of 4.0 doses/day for SOD patients and 3.95 for SDD patients. The average number
28 29	212	of DDD of systemic antibiotics during ICU-stay was lowest during SDD with absolute numbers of
30 31	213	33,688 DDDs during SC, 30,299 during SOD and 29,663 during SDD.
32 33	214	
34		
35 36	215	Cost analysis
37 38	216	Average total costs per patient were €41,941 for SC (95%CI €40,184-€43,698), €40,433 for SOD
39 40	217	(95%CI €38,838-€42,029) and €41,183 for SDD (95%CI €39,408-€42,958) (Table 3). LOS accounted for
41 42	218	approximately 98% of total costs, and these costs were highest for patients during SC. Mean costs
43 44 45	219	per patient for study medication were €3.48 and €41.35 during SOD and SDD, respectively. Mean
46 47	220	costs of systemic antibiotics per patient were €358.29 (95%CI €321.34 - €395.24) during SC, €317.65
48 49	221	(95%CI €280.89 - €354.42) during SOD and €439.14 (95%CI €406.69 - €471.59) during SDD (P<0.01
50 51	222	for SDD vs SC and SOD). Mean costs for microbiology cultures were highest for SDD (€ 371.72), as
52 53	223	compared to SOD (€287.27) and SC (€220.05) (P<0.01 for SDD vs SC and SOD) .
54 55	224	Hospital mortality was 31.8%, 30.7% and 32.3% during SC, SOD and SDD respectively. The difference
56 57 58 59	225	in hospital mortality for SDD, as compared to reported mortality previously, 3 (32.3% vs 32.6%)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

# Page 10 of 53

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

# **BMJ Open**

1
2
3 1
5
6
7
8
9
10
11
12
13
14
15
16
17
10 10
20
$\begin{array}{c}2\\3\\4\\5\\6\\7\\8\\9\\1\\1\\1\\2\\3\\4\\5\\6\\7\\8\\9\\1\\1\\1\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\3\\3\\3\\3$
22
23
24
25
26
27
28
29
30
31
32
33
34
30
30 27
38
30
40
41
42 43
44
45
46
47
48
49
50
51 52
52 53
53 54
54 55
55 56
50 57
58
59
60

1

226	results from inclusion of outcome data from the twelve patients that declined permission to use
227	clinical (not mortality) data in the main analysis. Estimated life years lost were, on average, 6.07
228	years for SC patients, 5.62 years for SOD patients and 5.97 years for SDD patients. Effects were
229	discounted with 1.5% a year resulting in life years gained (LYG) of +0.25 years for SOD and +0.04
230	years for SDD as compared to SC (table 4). SOD resulted in +0.21 LYG when compared to SDD. In the
231	cost-effectiveness plane, point estimates of the differences in costs and effects indicated that both
232	SOD and SDD were beneficial and cheaper (i.e. south-east quadrant) over SC. As depicted in figure 1,
233	SOD and SDD were dominant (i.e. southeast quadrant of plane) in 77.5% and 40.1% of the bootstrap
234	estimates respectively. When comparing SOD vs SDD, SOD dominates SDD in 60.2% of the bootstrap
235	replicates. If only cost aspects were taken into account (i.e. combining the south-east and south-
236	west quadrants), 89.3% and 72.4% of the bootstrap replicates were cheaper than SC during SOD and
237	SDD, respectively. In addition, bootstrap results were graphically displayed in cost-effectiveness
238	acceptability curves showing the probability that a treatment is cost-effective in comparison with
239	another treatment, given a certain threshold value for the willingness to pay for one life year gained.
240	These probabilities varied for values ranging from €0 to €20,000, between 89% and 93% for SOD and
241	between 63% and 72% for SDD (figure 1). For SOD vs SDD, these probabilities varied from 73% to
242	87%.
243	In the cost-analysis, €69.59 per one DDD of cefotaxime was used as reference price ¹⁸ and average
244	costs of systemic antibiotics were highest during SDD. ³ The price of 1 DDD cefotaxime should be
245	€39.37 and €19.07 to balance costs for systemic antibiotics between SDD and SC and SDD and SOD
246	respectively.
247	Sensitivity analyses on mechanical ventilation costs and discount rates did not change the
248	interpretation of results (table 5, figure 1). Yet, daily costs of €10 and €400 for study medication in
249	SOD and SDD resulted in an ICER of €21,590 per LYG for SDD vs SC whereas SOD remained dominant
250	over SC. For all situations, SOD was more effective and cheaper than SDD (table 4 and 5). To stay

### **BMJ Open**

251	below the Dutch threshold of €20,000 per life year gained, the maximum daily price for the topical
252	SDD-components should be €375.
253	
254	Discussion
255	This post-hoc analysis of a large cluster-randomized trial performed in 13 Dutch ICUs including 5,920
256	patients revealed that both SOD and SDD are cost-saving and more effective as compared to
257	standard care. These findings were insensitive to changes in discount rates and extra costs for
258	ventilation days. Furthermore, for SOD, but not for SDD, these findings were insensitive to current
259	(higher) market-prices of the topical components. The probabilities that SOD and SDD are cost-
260	effective for a willingness to pay threshold of €20,000 per life year gained as compared to standard
261	care, were 93% and 63%, respectively.
262	This is the first head-to-head comparison of the costs and benefits of SDD and SOD and the first
263	comparison of both interventions versus standard care. Strengths of the present study include the
264	large study size and the completeness of data collection.
265	Limitations of the study are the baseline differences between the three study periods. Patients
266	receiving standard care were younger, had lower APACHE II scores and were less likely to receive
267	mechanical ventilation and, therefore, seemed to have a better prognosis. In the original trial
268	random effects logistic regression modelling was applied to adjust for these differences. ³ Here we
269	have used crude data, without any adjustments for baseline differences. Our analysis points at
270	superiority of SOD and SDD when compared to standard care, despite the somewhat more
271	favourable prognosis at the time of ICU-admission of patients receiving standard care. Our findings
272	on the cost-effectiveness of both interventions are, therefore, conservative estimates. Furthermore,
273	patients receiving SOD were, on average, one year younger than those receiving SDD, which may
274	have affected the difference in life years lost between both interventions. Other limitations are the
275	restriction of cost data to the health care setting and the absence of antibiotic and microbiology cost
276	data after ICU-discharge, which could not be obtained retrospectively. Finally, this trial was

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

performed in ICU-settings with low endemicity of antibiotic resistance, which may limit generalizability to other settings. The main contributor to the total costs was length of stay, which was composed of stay in ICU and hospital after ICU-discharge. The other costs, microbiology and antibiotics, were highest for SDD, which had been reported previously.²⁵ Some, relatively small single-centre studies, also determined the effects of SDD on costs of days in ICU or in the hospital. In a German study SOD with cefotaxime prophylaxis resulted in lower average costs for antibiotic therapy and for days on ventilation than during standard care.²⁶ In a French study of trauma patients both daily ICU-costs as well as mean antibiotic costs, including SDD treatment, were lower during SDD compared to standard care.²⁷ In a Spanish study mean costs of systemic antibiotics were lower and less diagnostic procedures for infections were performed during SDD, compared to standard care, which resulted in a 21% reduction of total costs per survivor in the SDD-treated group.²⁸ Yet, in none of these studies a formal cost-effectiveness analysis was performed. VAP incidences were not determined in the Dutch SDD-SOD trial³ because of the perceived difficulties in uniformly diagnosing VAP in 13 ICUs. Yet, both SDD and SOD have been associated with reduced incidences of VAP, as compared to standard care.^{5 29} In addition to SDD and SOD there are other preventive measures that have been associated with reductions in the incidence of VAP, such as the use of silver-coated endotracheal tubes and continuous subglottic suctioning. In a large multi-centre randomized controlled trial silver-coated endotracheal tubes were associated with a relative risk reduction of the incidence of VAP of 35.9%, without discernible beneficial effects on patient outcome.³⁰ In a cost-effectiveness analysis of this trial the use of silver-coated tubes, although 45-fold more expensive than normal tubes (\$90 vs \$2 per tube), yielded savings of \$12,840 per episode of VAP prevented.³¹ Continuous subglottic suctioning (CSS) was, in a recent meta-analysis of 13 randomized trials, associated with a 45% reduction in the incidence of VAP (RR 0.55 (95%CI 0.46-0.66), but also without discernible beneficial effects on patient outcome (RR 1.01 (95%CI 0.85-1.20).³² The intervention appeared cost saving in two studies, saving \$4,992 and €1,176 per episode 

### **BMJ Open**

303	of VAP prevented. ^{33 34} However, these analyses were based on extrapolated costs per episode of
304	VAP, rather than on the true costs generated during the trials. Other widely recommended measures
305	to prevent VAP, such as the semi-recumbent patient position and different bundle approaches have
306	not been associated with documented improvements in patient outcome and have not been
307	evaluated with formal cost-effectiveness analyses.
308	In conclusion, both SOD and SDD appeared more beneficial and cost saving as compared to standard
309	care and even if the costs of both measures would increase tenfold SOD will remain cost-saving and
310	the incremental cost effectiveness ratio of SDD will be around the Dutch threshold for cost-
311	effectiveness of €20,000 per life year gained. The higher price for medication follows from the higher
312	costs for amphotericine B, which could be alleviated by replacing amphotericine B by nystatin, which
313	has also good antifungal activity in topical application. ³⁵ With 1,180 ICU-beds in a country of 16.6
314	million inhabitants (year 2010), extrapolation of our findings suggests that nationwide
315	implementation of SOD or SDD in ICUs, as occurred after the trial, has saved, per year, 18-36 million
316	euros.
317	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower
318	antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-
319	acquired colonization of the respiratory tract with multi-resistant bacteria, ³⁷ effective eradication of
320	intestinal carriage with cephalosporin-resistant Enterobacteriaceae, ³⁸ and low rates of resistance
321	development to colistin ³⁹ . Importantly, these beneficial effects were obtained in ICUs with low levels
322	of antibiotic resistance, reflected by incidence rates of bloodstream infections caused by methicillin-
322 323	of antibiotic resistance, reflected by incidence rates of bloodstream infections caused by methicillin- resistant <i>S. aureus</i> , vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of
323	resistant S. aureus, vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of
323 324	resistant <i>S. aureus</i> , vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of <0.1, <0.1 and 0.5 per 1,000 patient at risk, respectively. ³⁷ Whether these benefits can be realized in
323 324 325	resistant <i>S. aureus</i> , vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of <0.1, <0.1 and 0.5 per 1,000 patient at risk, respectively. ³⁷ Whether these benefits can be realized in ICUs with different bacterial ecology remains to be determined, ⁴⁰ but given the potential gains

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

329	Acknowledgment
330	Contributors: AMdS and MJMB conceived the study. EO, AdW and MJMB designed the study. The
331	SDD-SOD trialist group and AMdS collected the trial data. EO, AdW, MB and MJM analyzed and
332	interpreted the data. EO, MB and MJMB drafted the manuscript and AdW, AMdS and The SDD-SOD
333	trialist group critically revised the manuscript for important intellectual content. All the authors had
334	full access to the data and approved the final manuscript. EO is the guarantor.
335	Ethical approval: Ethical approval for the trial was granted by the institutional review board at each
336	participating hospital, as published previously (NEJM 2009;360:20). The requirement for informed
337	consent was waived.
338	
339	Data sharing: statistical code is available from the corresponding author
340	
341	Obtained funding: no financial support was provided
342	Obtained funding: no financial support was provided

# **BMJ Open**

2		
3	343	References
4	344	1. Vincent JL. Nosocomial infections in adult intensive-care units. Lancet 2003;361(9374):2068-77.
5	345	2. Bearman GM, Munro C, Sessler CN, Wenzel RP. Infection control and the prevention of
6 7	346	nosocomial infections in the intensive care unit. Semin Respir Crit Care Med 2006;27(3):310-
8	347	24.
9	348	3. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, et al.
10	349	Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med
11	350	2009;360(1):20-31.
12	351	4. Wunderink RG. Welkommen to our world. Emergence of antibiotic resistance with selective
13	352	decontamination of the digestive tract. <i>Am J Respir Crit Care Med</i> 2010;181(5):426-7.
14	353	5. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce
15	354	respiratory tract infections and mortality in adults receiving intensive care. <i>Cochrane</i>
16	355	Database Syst Rev 2009(4):CD000022.
17	356	6. American Thoracic Society. Guidelines for the management of adults with hospital-acquired,
18	350	ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med
19	358	2005;171(4):388-416.
20	358	
21		7. Dodek P, Keenan S, Cook D, Heyland D, Jacka M, Hand L, et al. Evidence-based clinical practice
22	360	guideline for the prevention of ventilator-associated pneumonia. Ann Intern Med
23	361	2004;141(4):305-13.
24 25	362	8. Healthcare Infection Control Practices Advisory Committee, Centers for Disease Control and
25 26	363	Prevention (U.S.). Guidelines for preventing health-care-associated pneumonia, 2003
20	364	recommendations of the CDC and the Healthcare Infection Control Practices Advisory
28	365	Committee. <i>Respir Care</i> 2004;49(8):926-39.
29	366	9. Torres A, Carlet J. Ventilator-associated pneumonia. European Task Force on ventilator-associated
30	367	pneumonia. <i>Eur Respir J</i> 2001;17(5):1034-45.
31	368	10. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. <i>Methods for the economic</i>
32	369	evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press, 2005.
33	370	11. Hakkaart-Van Roijen L, Tan SS, Bouwmans CA. Handleiding voor kostenonderzoek. Methoden en
34	371	standaard kostprijzen voor economische evaluaties in de gezondheidszorg., 2011.
35	372	12. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct,
36	373	analysis, and reporting. <i>Bmj</i> 2011;342:d1548.
37	374	13. Boersma C, Carides GW, Atthobari J, Voors AA, Postma MJ. An economic assessment of losartan-
38	375	based versus atenolol-based therapy in patients with hypertension and left-ventricular
39 40	376	hypertrophy: results from the Losartan Intervention For Endpoint reduction (LIFE) study
40 41	377	adapted to The Netherlands. <i>Clin Ther</i> 2007;29(5):963-71.
42	378	14. Simoens S. Health economic assessment: a methodological primer. <i>Int J Environ Res Public Health</i>
43	379	2009;6(12):2950-66.
44	380	15. Al Maiwenn MJ, Hakkaart L, Tan SS, Bakker J. Cost-consequence analysis of remifentanil-based
45	381	analgo-sedation vs. conventional analgesia and sedation for patients on mechanical
46	382	ventilation in the Netherlands. <i>Crit Care</i> 2010;14(6):R195.
47	383	16. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the
48	384	contribution of mechanical ventilation. Crit Care Med 2005;33(6):1266-71.
49	385	17. Tan SS, Hakkaart-van Roijen L, Al MJ, Bouwmans CA, Hoogendoorn ME, Spronk PE, et al. A
50	386	microcosting study of intensive care unit stay in the Netherlands. J Intensive Care Med
51	387	2008;23(4):250-7.
52	388	18. The Dutch Drug Information System of the Health Care Insurance Board.
53	389	http://www.gipdatabank.nl/.
54 55	390	19. Gravelle H, Smith D. Discounting for health effects in cost-benefit and cost-effectiveness analysis.
55 56	391	Health Econ 2001;10(7):587-99.
56 57	392	20. De Wit GA, Tariq, L., Van Gils, P.F. and Panneman, M.J.M. Handleiding voor economisch
58	393	evaluatieonderzoek bij gezondheidsbevordering: Over Euro en Effect, 2010.
59		
60		15

2	
3	39
4	39
5	39
6	39
7	39
8 9	39
9 10	40
11	40
12	40
13	40
14	40
15	40
16	40
17	40
18 19	40
20	40
21	41
22	41 41
23	41 41
24	41
25	41
26	41
27	41
28 29	41
30	41
31	42
32	42
33	42
34	42
35	42
36 37	42
38	42
39	42
40	42
41	42
42	43
43	43
44	43
45 46	43
40 47	43
48	43 43
49	43 43
50	
51	43 43
52	43 44
53	44 44
54 55	44 44
55 56	44
56 57	44
58	
59	
60	

1

394 205	21. Centraal Bureau Voor de Statistiek. Levensverwachting; geslacht en leeftijd, 2012.
395 396	22. Obenchain RL. Resampling and multiplicity in cost-effectiveness inference. <i>J Biopharm Stat</i> 1999;9(4):563-82.
397	23. O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: an
398	introduction to statistical issues and methods. Stat Methods Med Res 2002;11(6):455-68
399	24. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curvesfacts, fallacies and
400	frequently asked questions. <i>Health Econ</i> 2004;13(5):405-15.
401	25. van der Voort PH, van Roon EN, Kampinga GA, Boerma EC, Gerritsen RT, Egbers PH, et al. A
402 403	before-after study of multi-resistance and cost of selective decontamination of the diges tract. <i>Infection</i> 2004;32(5):271-7.
404	26. Abele-Horn M, Dauber A, Bauernfeind A, Russwurm W, Seyfarth-Metzger I, Gleich P, et al.
405	Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal
406	decontamination (SOD). Intensive Care Med 1997;23(2):187-95.
407	27. Langlois-Karaga A, Bues-Charbit M, Davignon A, Albanese J, Durbec O, Martin C, et al. Selecti
408	digestive decontamination in multiple trauma patients: cost and efficacy. <i>Pharm World</i> S
409	1995;17(1):12-6.
410	28. Sanchez Garcia M, Cambronero Galache JA, Lopez Diaz J, Cerda Cerda E, Rubio Blasco J, Gom
411	Aguinaga MA, et al. Effectiveness and cost of selective decontamination of the digestive
412	tract in critically ill intubated patients. A randomized, double-blind, placebo-controlled,
413	multicenter trial. Am J Respir Crit Care Med 1998;158(3):908-16.
414	29. Bergmans DC, Bonten MJ, Gaillard CA, Paling JC, van der Geest S, van Tiel FH, et al. Preventio
415	ventilator-associated pneumonia by oral decontamination: a prospective, randomized,
416	double-blind, placebo-controlled study. Am J Respir Crit Care Med 2001;164(3):382-8.
417	30. Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, et al. Silver-coated
418	endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT
419	randomized trial. <i>Jama</i> 2008;300(7):805-13.
420	31. Shorr AF, Zilberberg MD, Kollef M. Cost-effectiveness analysis of a silver-coated endotrachea
421	tube to reduce the incidence of ventilator-associated pneumonia. Infect Control Hosp
422	Epidemiol 2009;30(8):759-63.
423	32. Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion
424	drainage for the prevention of ventilator-associated pneumonia: a systematic review and
425	meta-analysis. Crit Care Med 2011;39(8):1985-91.
426	33. Hallais C, Merle V, Guitard PG, Moreau A, Josset V, Thillard D, et al. Is continuous subglottic
427	suctioning cost-effective for the prevention of ventilator-associated pneumonia? Infect
428	Control Hosp Epidemiol 2011;32(2):131-5.
429	34. Shorr AF, O'Malley PG. Continuous subglottic suctioning for the prevention of ventilator-
430	associated pneumonia: potential economic implications. <i>Chest</i> 2001;119(1):228-35.
431	35. Normand S, Francois B, Darde ML, Bouteille B, Bonnivard M, Preux PM, et al. Oral nystatin
432	prophylaxis of Candida spp. colonization in ventilated critically ill patients. Intensive Care
433 434	Med 2005;31(11):1508-13. 36. Oostdijk EA, de Smet AM, Blok HE, Thieme Groen ES, van Asselt GJ, Benus RF, et al. Ecologica
434 435	effects of selective decontamination on resistant gram-negative bacterial colonization. A
435	Respir Crit Care Med 2010;181(5):452-7.
430 437	37. de Smet AM, Kluytmans JA, Blok HE, Mascini EM, Benus RF, Bernards AT, et al. Selective dige
438	tract decontamination and selective oropharyngeal decontamination and antibiotic
438 439	resistance in patients in intensive-care units: an open-label, clustered group-randomised
440	crossover study. Lancet Infect Dis 2011;11(5):372-80.
440 441	38. Oostdijk EA, de Smet AM, Kesecioglu J, Bonten MJ. Decontamination of cephalosporin-resista
442	Enterobacteriaceae during selective digestive tract decontamination in intensive care un
443	Antimicrob Chemother 2012;67(9):2250-3.

1 2		
- 3 4 5	444 445 446	39. Oostdijk EA, Smits L, de Smet AM, Leverstein-van Hall MA, Kesecioglu J, Bonten MJ. Colistin resistance in gram-negative bacteria during prophylactic topical colistin use in intensive care units. <i>Intensive Care Med</i> 2012.
6	447	40. Walden AP, Bonten MJ, Wise MP. Should selective digestive decontamination be used in critically
7	448	ill patients? Bmj 2012;345:e6697.
8 9	449	41. Ioannidis JP, Garber AM. Individualized cost-effectiveness analysis. <i>PLoS Med</i>
10	450	2011;8(7):e1001058. 42. Internal Revenue Service.
11	451 452	42. Internal Revenue Service.
12	453	
13 14	454	
15		
16		
17		
18 19		
20		
21		
22		
23 24		
25		
26		
27		
28 29		
30		42. Internal Revenue Service.
31		
32		
33 34		
34 35		
36		
37		
38		
39 40		
41		
42		
43 44		
44 45		
46		
47		
48		
49 50		
50 51		
52		
53		
54 55		
55 56		
57		
58		
59		
60		17

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

2
2
3
4
5
6
7
8
ğ
10
10
11
12
13
14
15
16
17
10
10
19
$\begin{array}{c} 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 1 \\ 1 \\ 1 \\ 2 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$
21
22
23
24
27
20
26
27
28
29
30
31
22
3Z
33
34
35
36
37
38
20
39
40
41
42
43
44
45
46
45 46 47 48
47
48
49 50 51
50
51 52 53
52
53
54
04 57
55
56
57 58
58
59
60
00

1

_		
Category		Prices per unit
Length of Stay	Day in ICU	€2,183 ¹¹
	Day in hospital ward	€505 ¹¹
	Mechanical ventilation, additional costs	€327.45 ¹⁵⁻¹⁷
Topical antibiotics	Cost of SOD per day	€0.87 ³⁴²
	Cost of SDD per day	€10.48 ³⁴²
Microbiology	Blood culture	€11.89 per culture + €12.90 order rate*
	Throat culture	€7.78 per culture + €12.90 order rate *
	Sputum culture	€7.78 per culture + €12.90 order rate *
	Bronchoalveolar lavage	€7.78 per sample + €12.90 order rate *
	Rectum culture	€7.78 per sample + €12.90 order rate *
	Species determination	Extra €13.00 per isolate + €18.52 *
	Resistance profile determination	8.96 per isolate
Antibiotics		According to GIP database ¹⁸

456

457 Table 1: Costs used per unit

458 SOD, selective oropharyngeal decontamination ; SDD selective decontamination of the Digestive tract; SC,

- 459 standard care
- 460 * UMCU costs

		SC	SOD	SDD
		N=1,987	N=1,901	N=2,032
Baseline characteristics				
Age, years (mean (SD)) *#		61.4 ± 16.2	61.4 ± 16.3	62.4 ± 15.8
Male sex (no (%))		1219 (61.3)	1211 (63.7)	1242 (63.7)
Apache II score (mean (SD)) **		18.6 ± 7.9	19.6 ± 8.8	19.9 ± 8.9
Mechanical ventilation (no (%)) +	*	1,751 (88.1)	1,790 (94.2)	1,888 (92.9)
Clinical outcome **		8		
Length of MV, days (median (IQR	))	6 (9)	7 (8)	6 (9)
Length of stay ICU, days (median	(IQR))	8 (11)	9 (9)	9 (10)
Length of stay hospital, days (me	dian (IQR)) ***	15 (23)	15 (22)	15 (21)
Resource use				
Study medication, DDD (total (me	ean))	0	7,609 (4.0)	8,068 (3.95)
Systemic antibiotics, DDD (total (	mean))	33,688 (5.9)	30,299 (6.2)	29,663 (5.2)
Microbiology (total (mean))	Rectal	0	0	7,247 (3.8)
	BAL	263 (1.3)	221 (1.3)	253 (1.3)
	Sputum	5,430 (3.7)	7,467 (4.3)	8,073 (4.4)
	Throat	431 (2.7)	6,277 (3.5)	7,176 (3.8)
	Blood	4,113 (3.7)	4,849 (4.1)	4,461 (4.1)

Table 2: Baseline characteristics, clinical outcomes and resource use of patients

SDD, Selective Decontamination of the Digestive tract; SOD, Selective Oropharyngeal Decontamination; SC, Standard Care; IQR, inter quartile range; DDD, defined daily

doses; MV, mechanical ventilation; ICU, Intensive Care Unit; BAL, Brancheoalveolar Lavage

P value <0.05 for: † SC vs SOD ; * SC vs SDD ; # SOD vs SDD

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

** Values differ from previously reported values as not all patients could be included in the present analysis

*** Duration in the hospital is the number of days in the hospital after ICU-discharge, for patients who were discharged from the ICU alive

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

		SC	SOD	SDD
		N=1990	N=1904	N=2045
Length of Stay	ICU	€29,553.45 (€28,152.40 - €30,954.49)	€28,684.46 (€27,412.05 - €29,956.87)	€29,069.78 (€27,636.40 - €30,503.16
	Hospital	€8,621.85 (€8,059.10 - €9,184.61)	€7,830.55 (€7,345.91 - €8,315.20)	€7,963.94 (€7,476.75 - €8,451.13)
	MV	€3,225.06 (€3,045.61 – €3,404.51)	€3,316.36 (€3,151.14 – €3,481.58)	€3,308.18 (€3,116.09 – €3,500.27)
	Total	€41,400.36 (€39,672.04 -€43,128.68)	€39,831.37 (€38,261.92 - €41,400.82)	€40,341.90 (€38,599.66 - €42,084.14
Study medication		-	€3.48 (€3.47 - €3.49)	€41.35 (€41.07 – €41.62)*
Systemic Antibiot	ics	€358.29 (€321.34 - €395.24)	€317.65 (€280.89-€354.42)	€439.14 (€406.69-€471.59)
Microbiology	Rectal swabs	-	-	€102.75 (€97.64 – €107.86)
	BAL	€6.44 (€5.42 – €7.46)	€4.70 (€3.92 – €5.49)	€4.77 (€4.01 – €5.53)
	Sputum	€114.83 (€106.87 – €122.79)	€135.85 (€127.99 – €143.71)	€117.57 (€110.78 – €124.36)
	Throat	€8.12 (€6.39 – €9.84)	€86.66 (€83.07 – €90.25)	€89.65 (€85.68 – €93.63)
	Blood	€52.61 (€48.74 – €56.49)	€53.72 (€49.64 – €57.79)	€45.45 (€41.87 – €49.04)
	Total	€182.15 (€170.60 – €193.69)	€280.93 (€267.00 – €294.87)	€360.73 (€343.69 – €377.76)
Total		€41,940.79	€40,433.42	€41,183.12
		(€40,183.93 – €43,697.66)	(€38,837.50 - €42,029.35)	(€39,408.39 - €42,957.85)

*Excluding cefotaxim. Cefotaxim use is included in total systemic antibiotic use.

SDD, Selective Decontamination of the Digestive tract; SOD, Selective Oropharyngeal Decontamination; SC, Standard Care; MV, mechanical ventilation; ICU, Intensive Care

Unit; BAL, Brancheoalveolar Lavage

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2	
3 4	
5 6 7	
7 8 9	
10 11	
12	
14 15	
13 14 15 16 17 18 19	
18 19 20	
20 21 22	
23 24	
25 26	
20 27 28 29	
30	
31 32 33	
34 35	
32 33 34 35 36 37 38	
39	
40 41 42	
42 43 44	
45 46	
47 48	
<u>4</u> 9	

	LYG*	Cost difference	ICER	-
SOD vs SC (95% CI)	+ 0.25 (-0.05 – 0.55)	-€1507.37 (-€3,186.45 – €171.72)	SOD dominates SC	-
SDD vs SC (95% CI)	+ 0.04 (-0.26 – 0.34)	-€757.67 (-€2,522.56 – €1,007.21)	SDD dominates SC	
SOD vs SDD (95% CI)	+ 0.21 (-0.09 – 0.51)	-€749.69 (-€2,439.35 – €939.97)	SOD dominates SDD	
Table 4: Outcomes of cc	ost-effectiveness comparisons across	groups		-
* Effects are discounted	l at 1.5% a year			
LYG, life years gained ;	; 95% CI, 95% confidence intervals	; SDD, Selective Decontamination of the Digestive	e tract; SOD, Selective Oropharyngeal	Decontamination; SC,
Standard Care; ICER, inc	cremental costs effectiveness ratio (c	costs/LYG)		
		costs/LYG)		

		SC	SOD	SDD	ICER analyses	ICER analyses	ICER analyses
					SC vs SOD	SC vs SDD	SDD vs SOD
Sensitivity analysis	BC	4.27	4.02	4.23	SC = dominated by	SC = dominated by	SDD = dominated b
discounting effects (Life	+1.5%	(3.96 – 4.57)	(3.72 – 4.32)	(3.94 – 4.53)	SOD	SDD	SOD
years lost)	+0%	6.07	5.62	5.97	SC = dominated by	SC = dominated by	SDD = dominated b
		(5.58 – 6.55)	(5.15 – 6.08)	(5.50 – 6.44)	SOD	SDD	SOD
	+3%	2.82	2.68	2.82	SC = dominated by	SC = dominated by	SDD = dominated b
		(2.63 – 3.01)	(2.49 – 2.87)	(2.63 – 3.00)	SOD	SDD	SOD
Sensitivity analysis	BC	€41,940.79	€40,433.42	€41,183.12	SC = dominated by	SC = dominated by	SDD = dominated b
mechanical ventilation*	+15%	(€40,183.93 -	(€38,837.50 -	(€39,408.39 –	SOD	SDD	SOD
		€43,697.66)	€42,029.35)	€42,957.85)			
	+ 0%	€38,715.73	€37,117.07	€37,874.94	SC = dominated by	SC = dominated by	SDD = dominated b
		(€37,112.32 –	(€35,659.90 -	(€36,270.73 –	SOD	SDD	SOD
		€40,319.14)	€38,574.24)	€39,479.15)			
	+30%	€45,165.85	€43,749.78	€44,491.30	SC = dominated by	SC = dominated by	SDD = dominated b
		(€43,251.01 -	(€42,010.47 -	(€42,542.03 –	SOD	SDD	SOD
		€47,080.69)	€45,489.09)	€46,440.57)			
Sensitivity analysis price		€41,940.79	€40,493.15	€42,720.23	SC = dominated by	ICER 21,590	SDD = dominated b
study regimen*#		(€40,183.93 -	(€38,996.62 -	(€40,943.82 -	SOD		SOD
		€43,697.66)	€42,189.67)	€44.496.65)			

Table 5: Sensitivity analysis

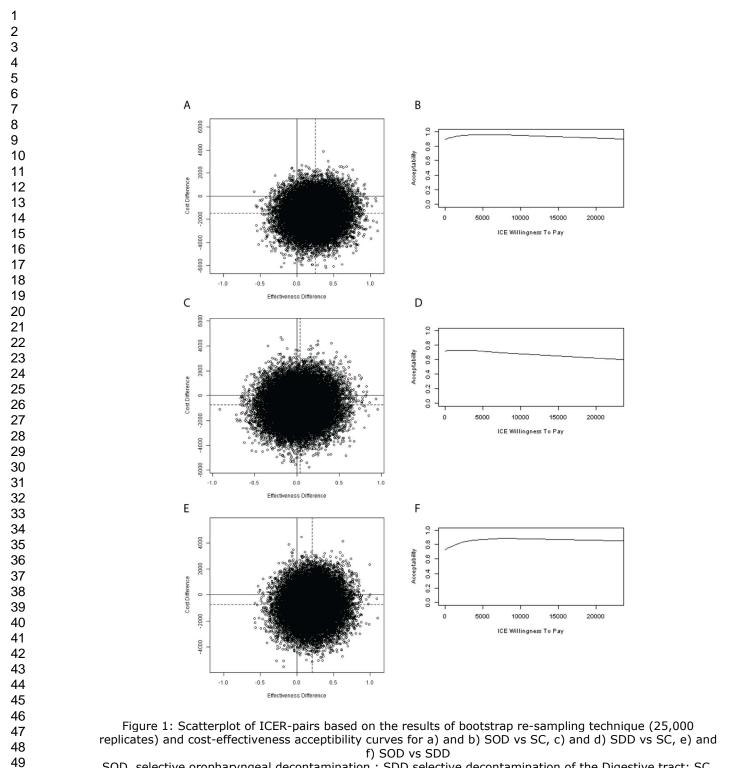
# Price SOD €40 and SDD €400 per day * Effects are discounted 1.5% a year

BC base case results ; SDD Selective Decontamination of the Digestive tract, SOD Selective Oropharyngeal Decontamination, SC Standard Care, ICER incremental costs

effectiveness ratio (costs/LYG)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

**BMJ Open** 



SOD, selective oropharyngeal decontamination ; SDD selective decontamination of the Digestive tract; SC, standard care 187x251mm (150 x 150 DPI)

1	
2	
2 3 4 5 6	
4	
5	
5	
6	
7	
8	
g	
10	
10	
11	
12	
13	
1/	
45	
15	
16	
17	
18	
19	
20	
20 21	
21	
22	
23	
2/	
7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 32 4 25 26 27 28 9 30 132 33 4 35 6 37 8 9	
25	
26	
27	
28	
20	
29	
30	
31	
32	
33	
24	
34	
35	
36	
37	
38	
30	
39	
40	
41	
42	
43	
43 44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
<u>^</u>	

	1	[
Study design	Item	Page
1	The research question is stated	5
2	The economic importance of the research question is stated	5
3	The viewpoint(s) of the analysis are clearly stated and justified	5
4	The rationale for choosing the alternative programmes or interventions compared is stated	5
5	The alternatives being compared are clearly described	5,6
6	The form of economic evaluation used is stated	6
7	The choice of form of economic evaluation is justified in relation to the questions addressed	6
Data		
collection		
8	The source(s) of effectiveness estimates used are stated	8
9	Details of the design and results of effectiveness study are	5
5	given (if based on a single study)	5
10	Details of the method of synthesis or meta-analysis of	Na
10	estimates are given (if based on an overview of a number	
	of effectiveness studies)	
11	The primary outcome measure(s) for the economic	6
	evaluation are clearly stated	
12	Methods to value health states and other benefits are	8
	stated	
13	Details of the subjects from whom valuations were	Na
	obtained are given	
14	Productivity changes (if included) are reported separately	Na
15	The relevance of productivity changes to the study question is discussed	Na
16	Quantities of resources are reported separately from their unit costs	17,19
17	Methods for the estimation of quantities and unit costs are described	6,7
18	Currency and price data are recorded	7
19	Details of currency of price adjustments for inflation or currency conversion are given	7
20	Details of any model used are given	Na
21	The choice of model used and the key parameters on which it is based are justified	Na
Analysis and		
interpretation		
of results		<u> </u>
22	Time horizon of costs and benefits is stated	6
23	The discount rate(s) is stated	7
24	The choice of rate(s) is justified	7
25	An explanation is given if costs or benefits are not discounted	7
26	Details of statistical tests and confidence intervals are given for stochastic data	8
27	The approach to sensitivity analysis is given	8
28	The choice of variables for sensitivity analysis is justified	8
29	The ranges over which the variables are varied are stated	8
30	Relevant alternatives are compared	Na

31	Incremental analysis is reported	9, 10
-	Major outcomes are presented in a disaggregated as well	21, 22
-	as aggregated form	, <b></b>
3	The answer to the study question is given	10
34	Conclusions follow from the data reported	11
5	Conclusions are accompanied by the appropriate caveats	12

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

2
2 3
4
5
6
7
0
0
9
10
11
12
13
14
15
16
17
18
10
2 3 4 5 6 7 8 9 10 11 2 3 4 15 6 7 8 9 10 11 2 3 4 5 6 7 8 9 10 11 2 3 4 5 6 7 8 9 10 11 2 3 4 5 6 7 8 9 10 11 2 2 2 2 2 2 2 2 2 2 2 2 2 2 3 3 1 2 3 3 4 5 6 7 8 9 10 10 10 10 10 10 10 10 10 10 10 10 10
∠∪ ⊃4
21
22
23
24
25
26
27
28
20
29
30
31
32
33
34
35
36
37
38
30
40
40
41
42
43
44
45
46
47
48
49
<del>5</del> 0
51
52
53
54
55
56
57
58
59

1

1	Selective Decontamination of the Digestive Tract and Selective Oropharyngeal Decontamination in
2	ICU patients: a cost-effectiveness analysis
3	
4	E.A.N. Oostdijk MD ^{1,2} , G.A. de Wit PhD ^{3,4} , M. Bakker MSc ¹ , A.M.G.A. de Smet MD PhD ⁵ , M.J.M.
5	Bonten ^{1,3} MD PhD on behalf of the Dutch SOD-SDD trialists group
6	
7	¹ Department of Medical Microbiology, ² Department of Intensive Care Medicine and ³ Julius Center for Health
8	Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The
9	Netherlands
10	⁴ Center for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM),
11	Antonie van Leeuwenhoeklaan 9, 3721 MA, Bilthoven, The Netherlands
12	⁵ Department of Critical Care, University of Groningen, University Medical Center Groningen, Hanzeplein 1,
13	9713 GZ, Groningen, The Netherlands
14	
15	Running title: Cost-effectiveness of selective decontamination
16	
17	This work was presented in part at the 25th Annual Congress of the European Society of Intensive
18	Care Medicine, Lisbon, Portugal, October 13-17, 2012.
10	Words: 3100
19	
20	Words: 3100
21	
22	The Dutch SOD-SDD trialists group include the following persons and sites:
23	Cor J. Kalkman, Hans (J.) C.A. Joore, Maurine A. Leverstein-van Hall, Hetty E.M Blok, University
24	Medical Center Utrecht, Utrecht; Jan A.J.W Kluytmans, Nardo J.M van der Meer, Amphia Hospital,
25	Breda; Ellen M. Mascini, Karin Kaasjager, Frank H.Bosch, Rijnstate Hospital, Arnhem; Robin F.J.Benus,

**BMJ Open** 

### **BMJ Open**

Tjip S. van der Werf, Jan P. Arends, University Medical Center, Groningen; Johannes G. van der
Hoeven, Peter Pickkers, Patrick D.J. Sturm, Andreas Voss, Radboud University, Nijmegen Medical
Center, Nijmegen; Alexandra T. Bernards, Ed J. Kuijper, Hubertus I.J Harinck, Leiden University
Medical Center, Leiden; Alexander .J.G.H. Bindels, Arjan R. Jansz, Catharina Hospital, Eindhoven;
Ronald M.J. Wesselink, Bartelt M de Jongh, St. Antonius Hospital, Nieuwegein; Paul J.W. Dennesen,
Gerard J. van Asselt, Medical Center Haaglanden, The Hague; Leonard F. te Velde, Ine H.M.E. Frenay,
Albert Schweitzer Hospital, Dordrecht; Mat van Iterson , Steven F.T. Thijsen, Diakonessen Hospital,
Utrecht; Georg H. Kluge, Slotervaart Hospital, Amsterdam; Jacob W. de Vries, Jan A. Kaan, Mesos
Medical Center, Utrecht — all in the Netherlands.
Corresponding author: E.A.N. Oostdijk
Mailing address: Department of Medical Microbiology, University Medical Center Utrecht, G04.614,
PO box 85500, 3508 GA Utrecht, The Netherlands.
Phone: +31 88 7555006. Fax +31 88 7555132; Email: E.A.N.Oostdijk@umcutrecht.nl
Keywords: SDD, SOD, Intensive Care, cost-effectiveness, economic evaluation
2

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

44	Article summary:
45	Article Focus
46	• Selective digestive tract decontamination (SDD) and selective oropharyngeal
47	decontamination (SOD) are prophylactic antibiotics used as infection prevention strategy in
48	Intensive Care Units (ICU)
49	• In a Dutch 13-center study, SDD and SOD were associated with relative risk reductions of
50	mortality at day 28 of 13% and 11%, respectively, as compared to standard care (i.e. no SDD
51	or SOD) and with lower incidence of ICU-acquired bacteremia and ICU-acquired colonization
52	of the respiratory tract with multi-resistant bacteria
53	• This paper describes the costs and effects of SDD and SOD from the healthcare perspective
54	in Dutch ICUs
55	Key Messages
56	Both SDD and SOD were cheaper and more beneficial as compared to standard care and
57	these findings were insensitive to changes in discount rates and extra costs for ventilation
58	days
59	• SOD, but not SDD, was still dominant (i.e. cheaper and more beneficial) over standard care
60	to current tenfold higher market-prices of the topical components (€40/day for SOD and
61	€400/day for SDD)
62	Strengths and Limitations.
63	• This is the first head-to-head comparison of the costs and benefits of SDD and SOD and the
64	first comparison of both interventions versus standard care using data from a multi-center
65	trial including 5,939 patients
66	Baseline differences were present between the three study groups
67	Only direct medical costs were included in the analysis and cost data were restricted to
68	health care settings
69	

70	ABSTRACT
71	Objective: To determine costs and effects of Selective digestive tract decontamination (SDD) and
72	selective oropharyngeal decontamination (SOD) as compared to standard care (i.e. no SDD/SOD (SC))
73	from a healthcare perspective in Dutch ICUs
74	Design: A post-hoc analysis of a previously performed cluster-randomized trial (NEJM 2009;360:20).
75	Setting: 13 Dutch ICUs
76	Participants: Patients with ICU-stay of >48 hours that received SDD (n=2,045), SOD (n=1,904) or SC
77	(n=1,990).
78	Interventions: SDD or SOD.
79	Primary and secondary outcome measures: Effects were based on hospital survival, expressed as
80	crude Life Years Gained (cLYG). The incremental cost effectiveness ratio (ICER) was calculated, with
81	corresponding cost acceptability curves. Sensitivity analyses were performed for discount-rates,
82	costs of SDD, SOD and mechanical ventilation.
83	<b>Results:</b> Total costs per patient were €41,941 for SC (95%Cl €40,184-€43,698), €40,433 for SOD
84	(95%CI €38,838-€42,029) and €41,183 for SOD (95%CI €39,408-€42,958). SOD and SDD resulted in
85	crude LYG of +0.04 and +0.25, respectively, as compared to SC, implying that both SDD and SOD are
86	dominant (i.e. cheaper and more beneficial) over SC. In cost-effectiveness acceptability curves
87	probabilities for cost-effectiveness, compared to standard care, ranged from 89% to 93% for SOD
88	and from 63% to 72% for SDD, for acceptable costs for 1 LYG ranging from €0 to €20,000. Sensitivity
89	analysis for mechanical ventilation and discount rates did not change interpretation. Yet, if costs of
90	the topical component of SDD and SOD would increase tenfold to €400/day and €40/day (maximum
91	values based upon free market prices in 2012), the estimated ICER as compared to SC for SDD would
92	be €21,590 per LYG. SOD would remain cost-saving.
93	Conclusions SDD and SOD were both effective and cost-saving in Dutch ICUs
94	
95	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

2
3
4
5
6
7
8
9
10
11
10
12
13
14
15
16
1/
18
19
20
21
22
23
$egin{array}{c} 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 1 \\ 1 \\ 1 \\ 2 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$
25
26
27
28
29
20
21
21
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
50 51 52
52
52 52
53 54 55 56
54 57
55
56
57
58
59
60

1

2

### 96 Introduction

97	Many patients in Intensive Care Units (ICU) are affected by nosocomial infections. ¹ These infections
98	are associated with increased mortality and morbidity, and considerable extra costs. ² Selective
99	oropharyngeal decontamination (SOD) and selective decontamination of the digestive tract (SDD)
100	are prophylactic antibiotic regimens, that consist of topical antibiotics applied to the oropharynx and
101	the intestinal tract to prevent colonization of gram-negative bacteria, Staphylococcus aureus and
102	yeasts. During SOD topical antibiotics are exclusively applied to the oropharynx throughout ICU-stay.
103	During SDD topical antibiotics are applied to the oropharynx but also to the intestinal tract
104	throughout ICU-stay, in combination with intravenous administration of cefotaxime during the first
105	four days in ICU, to pre-emptively treat infections with commensal respiratory tract bacteria. ³ SDD
106	has been a widely evaluated but highly controversial intervention in ICU. ⁴ Many, but not all, studies
107	reported statistically significant reductions in the incidence of Ventilator-Associated Pneumonia
108	(VAP), but only few were able to demonstrate outcome benefits such as reduced mortality and
109	length of ICU-stay. ⁵ In the absence of indisputably documented outcome benefits, the fear for
110	selection of antibiotic resistance has prevailed and SDD has not been recommended in most
111	infection prevention guidelines. ⁶⁻⁹ In a cluster-randomized study in 13 Dutch ICUs, SDD and SOD
112	were associated with relative risk reductions of mortality at day 28 of 13% and 11%, respectively, as
113	compared to standard care (i.e. no SDD or SOD). ³ Although SOD and SDD are currently widely used in
114	Dutch ICUs, the costs and effects of both regimens have not yet been determined. We, therefore,
115	conducted a cost-effectiveness analysis (CEA), comparing Standard Care, SOD and SDD using data
116	from the Dutch multi-center trial.
117	
118	Methods
119	Data collection
120	A post-hoc analysis was performed of the cluster randomized crossover trial comparing SOD and

121 SDD to standard care (SC). The trial was conducted in 13 Dutch ICUs and included 5,939 patients

### **BMJ Open**

~		
3		
4		
5		
6		
7		
8		
9		
1	0	
1		
1	1	
1		
1	2	
1	3	
1	Λ	
	4	
1	5	
1	6	
1	2	
1	7	
1	Q	
1	0	
1	3 4 5 6 7 8 9	
2	n	
~	5	
2	1	
2	2	
2	~	
۰,	· 🖌 👘	
2	4	
2 2 2 2	-	
2	5	
2	6	
2	2	
2	1	
2	8	
2	~	
2 2 2 2	9	
З	0	
2	ŭ	
3 3 3 3 3 3 3 3 3 3 3	1	
3	2	
2	~	
3	3	
3	4	
Š		
3	C	
3	6	
S	7	
S	1	
3	8	
3	0	
J	9	
4	0	
4		
4	2	
4	3	
4	4	
4	5	
4	6	
4	7	
4		
4	9	
5	υ	
5	1	
5		
0	2	
5	3	
5	л	
J	4	
5	5	
5		
5	7	
5	8	
2	0	
5	9	

(2,045 received SDD, 1,904 received SOD and 1,990 were treated according to SC). All centers were
assigned to all three regimens during periods of six months, however, the order of implementation
of SC, SOD and SDD was randomized per center.³

SOD and SDD have been described in detail elsewhere.³ In short, SOD consists of a paste applied to 125 126 the oropharynx, containing polymyxin E, tobramycin and amphotericin B (all in a 2% concentration, 127 applied every 6h). SDD consists, besides of the paste used in SOD, also of a 10 mL suspension of 100 128 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B that is applied via a nasogastric tube, 129 every 6h, and of cefotaxime (1000 mg, every 6h) applied intravenously during the first four days of 130 ICU-admission. The topical antibiotics of both regimens are applied until ICU-discharge. During the 131 trial there were no restrictions to systemic antibiotic use during SC and SOD. During SDD, the use of 132 antibiotics with anti-anaerobic activity was discouraged. This resulted in a marked increase of cephalosporin use and lower usage of penicillins, carbapenem and clindamycin.³ Surveillance 133 134 cultures of endotracheal aspirates, oropharynx and rectum were obtained on admission and twice 135 weekly during SDD. During SOD surveillance cultures of endotracheal aspirates and the oropharynx 136 were obtained on admission and twice weekly thereafter. During SC no surveillance cultures were 137 obtained. Clinical cultures were obtained on clinical suspicion of infection in all three periods.

138

139 Approach for economic evaluation

140 We performed a cost-effectiveness analysis (CEA) from a healthcare perspective, hence, only including direct medical costs.¹⁰⁻¹² The time horizon of the study was the period from ICU-admission 141 142 until hospital-discharge. Life Years Gained (LYG) was used as effectiveness measure. The outcome of 143 the CEA was the incremental cost effectiveness ratio (ICER), expressed as cost per life year gained (LYG). The informal Dutch threshold for cost-effectiveness is €20,000 per LYG.^{13 14} Data from all 144 145 individual patients were used for analyses. The CEA was performed post-hoc, however, using data 146 that were prospectively collected in Case Report Forms during the trial. Total direct medical costs of 147 the three regimens consisted of three main categories: Length of Stay (LOS), antibiotic use and

6

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

2	
3	
4 5	
6	
7	
8 9	
10	
11	
12 13	
14	
15	
16 17	
18	
12 13 14 15 16 17 18 19 20 21	
20 21	
22	
23	
22 23 24 25	
26 27	
27 28	
20 29	
30	
31 32	
33	
33 34	
35 36	
37	
38	
39 40	
41	
42 43	
44	
45	
46 47	
48	
49 50	
50 51	
52 53	
53 54	
55	
56	
57 58	
59	
60	

1

148	microbiology costs (table 1). LOS was based on the length of ICU-stay and the number of days on a
149	hospital ward after ICU-discharge. Costs for days in ICU and other hospital days were based upon the
150	Dutch guidelines for costing research in health economic studies. ¹¹ Days in ICU were categorized in
151	days with and without mechanical ventilation; days with mechanical ventilation were considered to
152	be 15% more expensive than ICU-days without mechanical ventilation. ¹⁵⁻¹⁷ Antibiotic use consisted
153	of the topical components of the SDD and SOD-regimen, hereafter referred to as study medication,
154	and of all systemic antibiotics used in ICU during all periods, including the four days cefotaxime
155	during SDD as part of the SDD-protocol. The price of study medication was €0.87 and €10.48 per day,
156	for SOD and SDD respectively. Costs of systemic antibiotics were based upon prices per Defined Daily
157	Dose (DDD) provided by the Dutch information project on medication and medical devices (Genees-
158	en hulpmiddelen Informatie Project (GIP)-database ¹⁸ ). For microbiology costs blood cultures,
159	broncheoalveolar lavages (BAL), sputum-, throat- and rectal cultures were considered. Rectal
160	cultures were only obtained during SDD as part of SDD-surveillance. Cultures obtained from the
161	other sites were either obtained as part of surveillance (throat- and sputum cultures during
162	SDD/SOD) or as part of daily clinical practice. Microbiological costs were obtained as the internal
163	tariffs applied within the University Medical Center Utrecht. These costs included costs for the
164	microbiological culture, order tariff and extra costs for species determination and susceptibility
165	resistance testing in case of relevant bacterial growth, irrespective of the species. The year 2009 was
166	taken as the reference year for all costs. Costs that were not available for 2009 were corrected for
167	inflation (with respect to 2009) based on the price index. ¹¹ An overview of all unit costs used in the
168	analysis is provided in table 1. LYG were discounted at 1.5% a year, following Dutch guidelines for
169	health economic evaluation. ¹⁹ Discounting of costs was not necessary, as all costs occurred within
170	the first year after inclusion. ²⁰
171	

172 Analysis

173 Life Years Gained (LYG) were determined by calculating Life Years Lost (LYL) of the patients who

Page 35 of 53

### **BMJ Open**

1	174	deceased in the hospital, using life tables for the Dutch population combined with age and sex, 21
-	175	with LYG defined as the difference in LYL between regimens. The ICER was defined as the
1	176	incremental difference between the mean cost of treatment regimens, divided by the incremental
-	177	difference in mean effect between treatment regimens. To estimate confidence limits for the ICER,
1	178	bootstrapping (25,000 repeats) was performed, as this does not depend on parametric assumptions
1	179	about the distribution of the data. ^{22 23} Results of the bootstrap procedure were plotted in a cost-
1	180	effectiveness plane that graphically represents the cost-difference and effect difference between
1	181	either SDD or SOD and SC, and for SDD versus SOD, for each of the bootstrap replications. Cost-
1	182	effectiveness acceptability curves (CEAC) were plotted to express the probability that treatment
1	183	regimens were cost-effective as compared to standard care, for a range of willingness to pay levels
1	184	for one life year gained ( $\lambda$ ). ²⁴ The curves display the proportion of bootstrapped ICER-pairs that are
-	185	cost-effective, meaning that they either fall within the south-east quadrant of the cost-effectiveness
-	186	plane or remain below the $\lambda$ threshold in the north-east and south-west quadrants of the plane.
-	187	Additionally, sensitivity analyses were performed: The discounted results (at 1.5% a year) were
-	188	compared to results without discounting and to a discount rate of 3% a year; costs for ICU-days with
-	189	mechanical ventilation were analyzed for 0% and 30% extra per ICU-day as compared to 15%
1	190	additional costs in basecase analysis; daily costs of study medication were analyzed with maximum
1	191	values based upon free market prices in 2012 (€40 for SOD and €400 for SDD). Mann-Whitney U test
1	192	was used to calculate P-values. P-value < 0.05 was considered to denote statistical significance and all
1	193	reported p-values are two-sided. All analyses were performed using Statistical Package for Social
1	194	Sciences version 20 (SPSS, Chicago, IL) version 17.0 and R version 2.14.2.
1	195	

196 Results

In this cluster-randomized trial 5,939 patients were included; 1,990 patients in the SC group, 1,904
received SOD and 2,045 received SDD. For this post-hoc analysis 19 patients were excluded (3
patients during SC, 3 during SOD and 13 during SDD). Twelve patients declined permission to use

1
3
2 3 4 5 6 7
5
6
7
1
8
9
10
11
12
13
14
15
16
17
7 8 9 10 11 12 13 14 5 6 7 8 9 10 11 23 22 23 24 25 27 8 9 31 23 34 56 7 23 33 34 56 7 23 24 25 26 27 8 9 30 31 23 34 56 77 8 9 30 31 32 33 34 56 77 8 9 30 31 32 33 34 35 36 37 37 37 37 37 37 37 37 37 37 37 37 37
19
20
21
22
23
24
25
26
20
20
20
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
49 50
50 51
51 52
-
53
54
55
55 56 57 58
57
58
59
60

200	clinical data. Seven additional patients were excluded because data on hospital discharge and/or
201	hospital mortality was missing, as reported previously. ³
202	Baseline characteristics differed among the three groups (table 2). Patients receiving SDD were on
203	average 62.4 ( $\pm$ 15.8) years old, compared to 61.4 ( $\pm$ 16.3) and 61.4 ( $\pm$ 16.2) years for patients
204	receiving SOD and SC, respectively. Patients receiving SC had a lower mean APACHE II score (18.6)
205	than those receiving SOD (19.6) and SDD (19.9), and were less likely to be on mechanical ventilation
206	(88.1% for SC vs. 94.2% and 92.9% for SOD and SDD, respectively).
207	Mean LOS in ICU and in hospital and mean duration of mechanical ventilation did not differ
208	significantly between SC, SOD and SDD. These data differ somewhat from original LOS data reported
209	previously 3 , which included only data of patients who were alive at day 28.
210	In all, 7,609 daily doses of study medication were used in the SOD group and 8,068 during SDD, with
211	average numbers of 4.0 doses/day for SOD patients and 3.95 for SDD patients. The average number
212	of DDD of systemic antibiotics during ICU-stay was lowest during SDD with absolute numbers of
213	33,688 DDDs during SC, 30,299 during SOD and 29,663 during SDD.
214	
215	Cost analysis
216	Average total costs per patient were €41,941 for SC (95%CI €40,184-€43,698), €40,433 for SOD
217	(95%Cl €38,838-€42,029) and €41,183 for SDD (95%Cl €39,408-€42,958) (Table 3). LOS accounted for
218	approximately 98% of total costs, and these costs were highest for patients during SC. Mean costs
219	per patient for study medication were €3.48 and €41.35 during SOD and SDD, respectively. Mean
220	costs of systemic antibiotics per patient were €358.29 (95%CI €321.34 - €395.24) during SC, €317.65
221	(95%Cl €280.89 - €354.42) during SOD and €439.14 (95%Cl €406.69 - €471.59) during SDD (P<0.01
222	for SDD vs SC and SOD). Mean costs for microbiology cultures were highest for SDD (€ 371.72), as
223	compared to SOD (€287.27) and SC (€220.05) (P<0.01 for SDD vs SC and SOD) .
224	Hospital mortality was 31.8%, 30.7% and 32.3% during SC, SOD and SDD respectively. The difference
225	in hospital mortality for SDD, as compared to reported mortality previously, ³ (32.3% vs 32.6%)

Page 37 of 53

### **BMJ Open**

226	results from inclusion of outcome data from the twelve patients that declined permission to use
227	clinical (not mortality) data in the main analysis. Estimated life years lost were, on average, 6.07
228	years for SC patients, 5.62 years for SOD patients and 5.97 years for SDD patients. Effects were
229	discounted with 1.5% a year resulting in life years gained (LYG) of +0.25 years for SOD and +0.04
230	years for SDD as compared to SC (table 4). SOD resulted in +0.21 LYG when compared to SDD. In the
231	cost-effectiveness plane, point estimates of the differences in costs and effects indicated that both
232	SOD and SDD were beneficial and cheaper (i.e. south-east quadrant) over SC. As depicted in figure 1,
233	SOD and SDD were dominant (i.e. southeast quadrant of plane) in 77.5% and 40.1% of the bootstrap
234	estimates respectively. When comparing SOD vs SDD, SOD dominates SDD in 60.2% of the bootstrap
235	replicates. If only cost aspects were taken into account (i.e. combining the south-east and south-
236	west quadrants), 89.3% and 72.4% of the bootstrap replicates were cheaper than SC during SOD and
237	SDD, respectively. In addition, bootstrap results were graphically displayed in cost-effectiveness
238	acceptability curves showing the probability that a treatment is cost-effective in comparison with
239	another treatment, given a certain threshold value for the willingness to pay for one life year gained.
240	These probabilities varied for values ranging from €0 to €20,000, between 89% and 93% for SOD and
241	between 63% and 72% for SDD (figure 1). For SOD vs SDD, these probabilities varied from 73% to
242	87%.
243	In the cost-analysis, €69.59 per one DDD of cefotaxime was used as reference price ¹⁸ and average
244	costs of systemic antibiotics were highest during SDD. ³ The price of 1 DDD cefotaxime should be
245	€39.37 and €19.07 to balance costs for systemic antibiotics between SDD and SC and SDD and SOD
246	respectively.
247	Sensitivity analyses on mechanical ventilation costs and discount rates did not change the
248	interpretation of results (table 5, figure 1). Yet, daily costs of €10 and €400 for study medication in
249	SOD and SDD resulted in an ICER of €21,590 per LYG for SDD vs SC whereas SOD remained dominant
250	over SC. For all situations, SOD was more effective and cheaper than SDD (table 4 and 5). To stay

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

### **BMJ Open**

below the Dutch threshold of €20,000 per life year gained, the maximum daily price for the topical
SDD-components should be €375.

**Discussion** 

255 This post-hoc analysis of a large cluster-randomized trial performed in 13 Dutch ICUs including 5,920

256 patients revealed that both SOD and SDD are cost-saving and more effective as compared to

257 standard care. These findings were insensitive to changes in discount rates and extra costs for

258 ventilation days. Furthermore, for SOD, but not for SDD, these findings were insensitive to current

259 (higher) market-prices of the topical components. The probabilities that SOD and SDD are cost-

260 effective for a willingness to pay threshold of €20,000 per life year gained as compared to standard

261 care, were 93% and 63%, respectively.

This is the first head-to-head comparison of the costs and benefits of SDD and SOD and the first
comparison of both interventions versus standard care. Strengths of the present study include the
large study size and the completeness of data collection.

265 Limitations of the study are the baseline differences between the three study periods. Patients

266 receiving standard care were younger, had lower APACHE II scores and were less likely to receive

267 mechanical ventilation and, therefore, seemed to have a better prognosis. In the original trial

268 random effects logistic regression modelling was applied to adjust for these differences.³ Here we

269 have used crude data, without any adjustments for baseline differences. Our analysis points at

270 superiority of SOD and SDD when compared to standard care, despite the somewhat more

271 favourable prognosis at the time of ICU-admission of patients receiving standard care. Our findings

272 on the cost-effectiveness of both interventions are, therefore, conservative estimates. Furthermore,

273 patients receiving SOD were, on average, one year younger than those receiving SDD, which may

274 have affected the difference in life years lost between both interventions. Other limitations are the

275 restriction of cost data to the health care setting and the absence of antibiotic and microbiology cost

276 data after ICU-discharge, which could not be obtained retrospectively. Finally, this trial was

### **BMJ Open**

2		
3	277	performed in ICU-settings with low endemicity of antibiotic resistance, which may limit
4	270	
5 6	278	generalizability to other settings.
7 8	279	The main contributor to the total costs was length of stay, which was composed of stay in ICU and
9 10	280	hospital after ICU-discharge. The other costs, microbiology and antibiotics, were highest for SDD,
11 12	281	which had been reported previously. ²⁵ Some, relatively small single-centre studies, also determined
13 14	282	the effects of SDD on costs of days in ICU or in the hospital. In a German study SOD with cefotaxime
15 16 17	283	prophylaxis resulted in lower average costs for antibiotic therapy and for days on ventilation than
18 19	284	during standard care. ²⁶ In a French study of trauma patients both daily ICU-costs as well as mean
20 21	285	antibiotic costs, including SDD treatment, were lower during SDD compared to standard care. ²⁷ In a
22 23	286	Spanish study mean costs of systemic antibiotics were lower and less diagnostic procedures for
24 25	287	infections were performed during SDD, compared to standard care, which resulted in a 21%
26 27 28	288	reduction of total costs per survivor in the SDD-treated group. ²⁸ Yet, in none of these studies a
29 30	289	formal cost-effectiveness analysis was performed.
31 32	290	VAP incidences were not determined in the Dutch SDD-SOD trial ³ because of the perceived
33 34	291	difficulties in uniformly diagnosing VAP in 13 ICUs. Yet, both SDD and SOD have been associated with
35 36	292	reduced incidences of VAP, as compared to standard care. ^{5 29} In addition to SDD and SOD there are
37 38 20	293	other preventive measures that have been associated with reductions in the incidence of VAP, such
39 40 41	294	as the use of silver-coated endotracheal tubes and continuous subglottic suctioning. In a large multi-
42 43	295	centre randomized controlled trial silver-coated endotracheal tubes were associated with a relative
44 45	296	risk reduction of the incidence of VAP of 35.9%, without discernible beneficial effects on patient
46 47	297	outcome. ³⁰ In a cost-effectiveness analysis of this trial the use of silver-coated tubes, although 45-
48 49	298	fold more expensive than normal tubes (\$90 vs \$2 per tube), yielded savings of \$12,840 per episode
50 51 52	299	of VAP prevented. ³¹ Continuous subglottic suctioning (CSS) was, in a recent meta-analysis of 13
53 54	300	randomized trials, associated with a 45% reduction in the incidence of VAP (RR 0.55 (95%CI 0.46-
55 56	301	0.66), but also without discernible beneficial effects on patient outcome (RR 1.01 (95%CI 0.85-
57 58 59	302	1.20). ³² The intervention appeared cost saving in two studies, saving \$4,992 and €1,176 per episode

2	
3	
4	
5	
6	
7	
8	
9	
9 10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
14 15 16 17 18 19 20 21 22 23 24 25	
22	
23	
24	
25	
25 26	
26 27	
27 28 29 30	
29	
30	
31	
22	
32	
33	
34	
35	
36	
37 38	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55 56	
50 57	
57 58	
20	
59	
60	

1

303	of VAP prevented. ^{33 34} However, these analyses were based on extrapolated costs per episode of
304	VAP, rather than on the true costs generated during the trials. Other widely recommended measures
305	to prevent VAP, such as the semi-recumbent patient position and different bundle approaches have
306	not been associated with documented improvements in patient outcome and have not been
307	evaluated with formal cost-effectiveness analyses.
308	In conclusion, both SOD and SDD appeared more beneficial and cost saving as compared to standard
309	care and even if the costs of both measures would increase tenfold SOD will remain cost-saving and
310	the incremental cost effectiveness ratio of SDD will be around the Dutch threshold for cost-
311	effectiveness of €20,000 per life year gained. The higher price for medication follows from the higher
312	costs for amphotericine B, which could be alleviated by replacing amphotericine B by nystatin, which
313	has also good antifungal activity in topical application. ³⁵ With 1,180 ICU-beds in a country of 16.6
314	million inhabitants (year 2010), extrapolation of our findings suggests that nationwide
315	implementation of SOD or SDD in ICUs, as occurred after the trial, has saved, per year, 18-36 million
316	euros.
317	The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome ³ , lower
318	antibiotic resistance prevalence in the ICUs, ³⁶ lower incidence of ICU-acquired bacteremia and ICU-
319	acquired colonization of the respiratory tract with multi-resistant bacteria, ³⁷ effective eradication of
320	intestinal carriage with cephalosporin-resistant Enterobacteriaceae, ³⁸ and low rates of resistance
321	development to colistin ³⁹ . Importantly, these beneficial effects were obtained in ICUs with low levels
322	
	of antibiotic resistance, reflected by incidence rates of bloodstream infections caused by methicillin-
323	of antibiotic resistance, reflected by incidence rates of bloodstream infections caused by methicillin- resistant <i>S. aureus</i> , vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of
323	resistant S. aureus, vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of
323 324	resistant <i>S. aureus</i> , vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of <0.1, <0.1 and 0.5 per 1,000 patient at risk, respectively. ³⁷ Whether these benefits can be realized in
323 324 325	resistant <i>S. aureus</i> , vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of <0.1, <0.1 and 0.5 per 1,000 patient at risk, respectively. ³⁷ Whether these benefits can be realized in ICUs with different bacterial ecology remains to be determined, ⁴⁰ but given the potential gains

1 2 3 4	329	Acknowledgment
5 6 7	330	Contributors: AMdS and MJMB conceived the study. EO, AdW and MJMB designed the study. The
8 9	331	SDD-SOD trialist group and AMdS collected the trial data. EO, AdW, MB and MJM analyzed and
10 11	332	interpreted the data. EO, MB and MJMB drafted the manuscript and AdW, AMdS and The SDD-SOD
12 13 14	333	trialist group critically revised the manuscript for important intellectual content. All the authors had
15 16	334	full access to the data and approved the final manuscript. EO is the guarantor.
17 18 19	335	Ethical approval: Ethical approval for the trial was granted by the institutional review board at each
20 21	336	participating hospital, as published previously (NEJM 2009;360:20). The requirement for informed
22 23 24	337	consent was waived.
25	338	
26 27 28	339	Data sharing: statistical code is available from the corresponding author
29 30	340	
31 32	341	Obtained funding: no financial support was provided
33 34 35	342	
36 37 38		
39 40		
41		
42 43		
44 45		
46		
47 48		
49		
50 51		
52		
53		
54 55		
56		
57 58		
59		
60		14

1 2		
2	343	References
4		
5	344	1. Vincent JL. Nosocomial infections in adult intensive-care units. <i>Lancet</i> 2003;361(9374):2068-77.
6	345	2. Bearman GM, Munro C, Sessler CN, Wenzel RP. Infection control and the prevention of
7	346	nosocomial infections in the intensive care unit. <i>Semin Respir Crit Care Med</i> 2006;27(3):310-
8	347	24.
9	348	3. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, et al.
10	349	Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med
11	350	2009;360(1):20-31.
12	351	4. Wunderink RG. Welkommen to our world. Emergence of antibiotic resistance with selective
13	352	decontamination of the digestive tract. Am J Respir Crit Care Med 2010;181(5):426-7.
14	353	5. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce
15 16	354	respiratory tract infections and mortality in adults receiving intensive care. Cochrane
17	355	Database Syst Rev 2009(4):CD000022.
18	356	6. American Thoracic Society. Guidelines for the management of adults with hospital-acquired,
19	357	ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med
20	358	2005;171(4):388-416.
21	359	7. Dodek P, Keenan S, Cook D, Heyland D, Jacka M, Hand L, et al. Evidence-based clinical practice
22	360	guideline for the prevention of ventilator-associated pneumonia. Ann Intern Med
23	361	2004;141(4):305-13.
24	362	8. Healthcare Infection Control Practices Advisory Committee, Centers for Disease Control and
25	363	Prevention (U.S.). Guidelines for preventing health-care-associated pneumonia, 2003
26	364	recommendations of the CDC and the Healthcare Infection Control Practices Advisory
27	365	Committee. Respir Care 2004;49(8):926-39.
28	366	9. Torres A, Carlet J. Ventilator-associated pneumonia. European Task Force on ventilator-associated
29	367	pneumonia. <i>Eur Respir J</i> 2001;17(5):1034-45.
30	368	10. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic
31	369	evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press, 2005.
32 33	370	11. Hakkaart-Van Roijen L, Tan SS, Bouwmans CA. Handleiding voor kostenonderzoek. Methoden en
33 34	371	standaard kostprijzen voor economische evaluaties in de gezondheidszorg., 2011.
35	372	12. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct,
36	373	analysis, and reporting. Bmj 2011;342:d1548.
37	374	13. Boersma C, Carides GW, Atthobari J, Voors AA, Postma MJ. An economic assessment of losartan-
38	375	based versus atenoiol-based therapy in patients with hypertension and left-ventricular
39	376	hypertrophy: results from the Losartan Intervention For Endpoint reduction (LIFE) study
40	377	adapted to The Netherlands. <i>Clin Ther</i> 2007;29(5):963-71.
41	378	14. Simoens S. Health economic assessment: a methodological primer. <i>Int J Environ Res Public Health</i>
42	379	2009;6(12):2950-66.
43	380	15. Al Maiwenn MJ, Hakkaart L, Tan SS, Bakker J. Cost-consequence analysis of remifentanil-based
44	381	analgo-sedation vs. conventional analgesia and sedation for patients on mechanical
45	382	ventilation in the Netherlands. <i>Crit Care</i> 2010;14(6):R195.
46	383	16. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the
47	384	contribution of mechanical ventilation. <i>Crit Care Med</i> 2005;33(6):1266-71.
48	385	17. Tan SS, Hakkaart-van Roijen L, Al MJ, Bouwmans CA, Hoogendoorn ME, Spronk PE, et al. A
49 50		
50 51	386 387	microcosting study of intensive care unit stay in the Netherlands. J Intensive Care Med
52		2008;23(4):250-7.
53	388	18. The Dutch Drug Information System of the Health Care Insurance Board.
54	389	http://www.gipdatabank.nl/.
55	390	19. Gravelle H, Smith D. Discounting for health effects in cost-benefit and cost-effectiveness analysis.
56	391	Health Econ 2001;10(7):587-99.
57	392	20. De Wit GA, Tariq, L., Van Gils, P.F. and Panneman, M.J.M. Handleiding voor economisch
58	393	evaluatieonderzoek bij gezondheidsbevordering: Over Euro en Effect, 2010.
59		
60		15

# **BMJ Open**

2		
3	394	21. Centraal Bureau Voor de Statistiek. Levensverwachting; geslacht en leeftijd, 2012.
4	395	22. Obenchain RL. Resampling and multiplicity in cost-effectiveness inference. J Biopharm Stat
5	396	1999;9(4):563-82.
6	397	23. O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: an
7	398	introduction to statistical issues and methods. Stat Methods Med Res 2002;11(6):455-68.
8 9	399	24. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curvesfacts, fallacies and
9 10	400	frequently asked questions. <i>Health Econ</i> 2004;13(5):405-15.
11	401	25. van der Voort PH, van Roon EN, Kampinga GA, Boerma EC, Gerritsen RT, Egbers PH, et al. A
12	402	before-after study of multi-resistance and cost of selective decontamination of the digestive
13	403	tract. Infection 2004;32(5):271-7.
14	404	26. Abele-Horn M, Dauber A, Bauernfeind A, Russwurm W, Seyfarth-Metzger I, Gleich P, et al.
15	405	Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal
16	406	decontamination (SOD). Intensive Care Med 1997;23(2):187-95.
17	407	27. Langlois-Karaga A, Bues-Charbit M, Davignon A, Albanese J, Durbec O, Martin C, et al. Selective
18	408	digestive decontamination in multiple trauma patients: cost and efficacy. Pharm World Sci
19	409	1995;17(1):12-6.
20	410	28. Sanchez Garcia M, Cambronero Galache JA, Lopez Diaz J, Cerda Cerda E, Rubio Blasco J, Gomez
21	411	Aguinaga MA, et al. Effectiveness and cost of selective decontamination of the digestive
22	412	tract in critically ill intubated patients. A randomized, double-blind, placebo-controlled,
23 24	413	multicenter trial. Am J Respir Crit Care Med 1998;158(3):908-16.
24 25	414	29. Bergmans DC, Bonten MJ, Gaillard CA, Paling JC, van der Geest S, van Tiel FH, et al. Prevention of
26	415	ventilator-associated pneumonia by oral decontamination: a prospective, randomized,
27	416	double-blind, placebo-controlled study. Am J Respir Crit Care Med 2001;164(3):382-8.
28	417	30. Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, et al. Silver-coated
29	418	endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT
30	419	randomized trial. <i>Jama</i> 2008;300(7):805-13.
31	420	31. Shorr AF, Zilberberg MD, Kollef M. Cost-effectiveness analysis of a silver-coated endotracheal
32	421	tube to reduce the incidence of ventilator-associated pneumonia. Infect Control Hosp
33	422	Epidemiol 2009;30(8):759-63.
34	423	32. Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion
35	424	drainage for the prevention of ventilator-associated pneumonia: a systematic review and
36	425	meta-analysis. Crit Care Med 2011;39(8):1985-91.
37	426	33. Hallais C, Merle V, Guitard PG, Moreau A, Josset V, Thillard D, et al. Is continuous subglottic
38 39	427	suctioning cost-effective for the prevention of ventilator-associated pneumonia? Infect
39 40	428	Control Hosp Epidemiol 2011;32(2):131-5.
41	429	34. Shorr AF, O'Malley PG. Continuous subglottic suctioning for the prevention of ventilator-
42	430	associated pneumonia: potential economic implications. Chest 2001;119(1):228-35.
43	431	35. Normand S, Francois B, Darde ML, Bouteille B, Bonnivard M, Preux PM, et al. Oral nystatin
44	432	prophylaxis of Candida spp. colonization in ventilated critically ill patients. Intensive Care
45	433	Med 2005;31(11):1508-13.
46	434	36. Oostdijk EA, de Smet AM, Blok HE, Thieme Groen ES, van Asselt GJ, Benus RF, et al. Ecological
47	435	effects of selective decontamination on resistant gram-negative bacterial colonization. Am J
48	436	Respir Crit Care Med 2010;181(5):452-7.
49	437	37. de Smet AM, Kluytmans JA, Blok HE, Mascini EM, Benus RF, Bernards AT, et al. Selective digestive
50	438	tract decontamination and selective oropharyngeal decontamination and antibiotic
51	439	resistance in patients in intensive-care units: an open-label, clustered group-randomised,
52 53	440	crossover study. Lancet Infect Dis 2011;11(5):372-80.
53 54	441	38. Oostdijk EA, de Smet AM, Kesecioglu J, Bonten MJ. Decontamination of cephalosporin-resistant
55	442	Enterobacteriaceae during selective digestive tract decontamination in intensive care units. J
56	443	Antimicrob Chemother 2012;67(9):2250-3.
57	-	
58		
59		
60		16

40. Walden AP, Bonten MJ, Wise MP. Should selective digestive decontamination be used in critically

resistance in gram-negative bacteria during prophylactic topical colistin use in intensive care

39. Oostdijk EA, Smits L, de Smet AM, Leverstein-van Hall MA, Kesecioglu J, Bonten MJ. Colistin

41. Ioannidis JP, Garber AM. Individualized cost-effectiveness analysis. PLoS Med

units. Intensive Care Med 2012.

ill patients? Bmj 2012;345:e6697.

2011;8(7):e1001058.

42. Internal Revenue Service.

2
2
3
4
5
5
6
7
Q
0
9
10
11
11
12
13
11
14
15
16
17
40
١Ŋ
19
20
20
$\begin{array}{c} 2\\ 3\\ 4\\ 5\\ 6\\ 7\\ 8\\ 9\\ 10\\ 11\\ 2\\ 3\\ 4\\ 15\\ 16\\ 17\\ 18\\ 9\\ 01\\ 22\\ 23\\ 24\\ 25\\ 26\\ 7\\ 8\\ 9\\ 01\\ 32\\ 33\\ 4\\ 35\\ 6\\ 7\\ 8\\ 9\\ 01\\ 12\\ 33\\ 4\\ 5\\ 6\\ 7\\ 8\\ 9\\ 01\\ 12\\ 3\\ 34\\ 5\\ 6\\ 7\\ 8\\ 9\\ 01\\ 12\\ 3\\ 34\\ 5\\ 6\\ 7\\ 8\\ 9\\ 01\\ 12\\ 3\\ 34\\ 5\\ 6\\ 7\\ 8\\ 9\\ 01\\ 12\\ 3\\ 34\\ 5\\ 6\\ 7\\ 8\\ 9\\ 01\\ 12\\ 22\\ 22\\ 22\\ 22\\ 22\\ 22\\ 22\\ 22\\ 2$
22
23
24
24
25
26
27
21
28
29
20
30
31
32
33
33
34
35
36
50
37
38
30
33
40
41
42
42 43
43
43 44
45
46
40
47 48
48
49
50
51
50 51 52
50
53
54
54 55 56
56
50
57
58

59 60

1

444

445

446

447

448

449

450

451

452 453 454 BMJ Open: first published as 10.1136/bmjopen-2012-002529 on 5 March 2013. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

Category		Prices per unit
Length of Stay	Day in ICU	€2,183 ¹¹
	Day in hospital ward	€505 ¹¹
	Mechanical ventilation, additional costs	€327.45 ¹⁵⁻¹⁷
Topical antibiotics	Cost of SOD per day	€0.87 ³⁴²
	Cost of SDD per day	€10.48 ³⁴²
Microbiology	Blood culture	€11.89 per culture + €12.90 order rate
	Throat culture	€7.78 per culture + €12.90 order rate *
	Sputum culture	€7.78 per culture + €12.90 order rate *
	Bronchoalveolar lavage	€7.78 per sample + €12.90 order rate *
	Rectum culture	€7.78 per sample + €12.90 order rate *
	Species determination	Extra €13.00 per isolate + €18.52 *
	Resistance profile determination	8.96 per isolate
Antibiotics		According to GIP database ¹⁸

Table 1: Costs used per unit

SOD, selective oropharyngeal decontamination ; SDD selective decontamination of the Digestive tract; SC,

- standard care
- * UMCU costs

$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		19
00	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	19

		SC	SOD	SDD
		N=1,987	N=1,901	N=2,032
Baseline characteristics				
Age, years (mean (SD)) *#		61.4 ± 16.2	61.4 ± 16.3	62.4 ± 15.8
Male sex (no (%))		1219 (61.3)	1211 (63.7)	1242 (63.7)
Apache II score (mean (SD)) **		18.6 ± 7.9	19.6 ± 8.8	19.9 ± 8.9
Mechanical ventilation (no (%)) +*		1,751 (88.1)	1,790 (94.2)	1,888 (92.9)
Clinical outcome **		8		
Length of MV, days (median (IQR	))	6 (9)	7 (8)	6 (9)
Length of stay ICU, days (median (IQR))		8 (11)	9 (9)	9 (10)
Length of stay hospital, days (median (IQR)) ***		15 (23)	15 (22)	15 (21)
Resource use				
Study medication, DDD (total (me	ean))	0	7,609 (4.0)	8,068 (3.95)
Systemic antibiotics, DDD (total (	mean))	33,688 (5.9)	30,299 (6.2)	29,663 (5.2)
Microbiology (total (mean))	Rectal	0	0	7,247 (3.8)
	BAL	263 (1.3)	221 (1.3)	253 (1.3)
	Sputum	5,430 (3.7)	7,467 (4.3)	8,073 (4.4)
	Throat	431 (2.7)	6,277 (3.5)	7,176 (3.8)
	Blood	4,113 (3.7)	4,849 (4.1)	4,461 (4.1)

Table 2: Baseline characteristics, clinical outcomes and resource use of patients

SDD, Selective Decontamination of the Digestive tract; SOD, Selective Oropharyngeal Decontamination; SC, Standard Care; IQR, inter quartile range; DDD, defined daily

doses; MV, mechanical ventilation; ICU, Intensive Care Unit; BAL, Brancheoalveolar Lavage

P value <0.05 for: + SC vs SOD ; * SC vs SDD ; # SOD vs SDD

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

** Values differ from previously reported values as not all patients could be included in the present analysis

.s as not all patients could be included in the preser. .eer of days in the hospital after ICU-discharge, for patients who w *** Duration in the hospital is the number of days in the hospital after ICU-discharge, for patients who were discharged from the ICU alive

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

⊿0

		SC	SOD	SDD
		N=1990	N=1904	N=2045
Length of Stay	ICU	€29,553.45 (€28,152.40 - €30,954.49)	€28,684.46 (€27,412.05 - €29,956.87)	€29,069.78 (€27,636.40
	Hospital	€8,621.85 (€8,059.10 - €9,184.61)	€7,830.55 (€7,345.91 - €8,315.20)	€7,963.94 (€7,476.75 - €
	MV	€3,225.06 (€3,045.61 – €3,404.51)	€3,316.36 (€3,151.14 – €3,481.58)	€3,308.18 (€3,116.09 – €
	Total	€41,400.36 (€39,672.04 -€43,128.68)	€39,831.37 (€38,261.92 - €41,400.82)	€40,341.90 (€38,599.66
Study medication	I	- 0	€3.48 (€3.47 - €3.49)	€41.35 (€41.07 – €41.62
Systemic Antibiot	ics	€358.29 (€321.34 - €395.24)	€317.65 (€280.89-€354.42)	€439.14 (€406.69-€471.
Microbiology	Rectal swabs		-	€102.75 (€97.64 – €107.
	BAL	€6.44 (€5.42 – €7.46)	€4.70 (€3.92 – €5.49)	€4.77 (€4.01 – €5.53)
	Sputum	€114.83 (€106.87 – €122.79)	€135.85 (€127.99 – €143.71)	€117.57 (€110.78 – €124
	Throat	€8.12 (€6.39 – €9.84)	€86.66 (€83.07 – €90.25)	€89.65 (€85.68 – €93.63
	Blood	€52.61 (€48.74 – €56.49)	€53.72 (€49.64 – €57.79)	€45.45 (€41.87 – €49.04
	Total	€182.15 (€170.60 – €193.69)	€280.93 (€267.00 – €294.87)	€360.73 (€343.69 – €37
Total		€41,940.79	€40,433.42	€41,183.12
		(€40,183.93 – €43,697.66)	(€38,837.50 - €42,029.35)	(€39,408.39 - €42,957.8

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1	
2	
3 4 5 6 7 8 9 10	
4 5	
6	
7	
8	
9 10	
11	
12	
13	
12 13 14 15 16 17 18 19	
15 16	
17	
18	
19	
20 21	
21 22 23	
23	
23 24 25	
25 26	
26 27	
28	
28 29 30	
30	
31	
32 33	
34	
35	
31 32 33 34 35 36 37 38	
37	
39	
40	
41	
42	
43 44	
44 45	
46	
47	
48 ⊿q	

	LYG*	Cost difference	ICER	
SOD vs SC (95% CI)	+ 0.25 (-0.05 – 0.55)	-€1507.37 (-€3,186.45 – €171.72)	SOD dominates SC	_
SDD vs SC (95% CI)	+ 0.04 (-0.26 – 0.34)	-€757.67 (-€2,522.56 – €1,007.21)	SDD dominates SC	
SOD vs SDD (95% CI)	+ 0.21 (-0.09 - 0.51)	-€749.69 (-€2,439.35 – €939.97)	SOD dominates SDD	
Table 4: Outcomes of co	ost-effectiveness comparisons across	s groups		_
* Effects are discounted	at 1.5% a year			
LYG, life years gained ;	; 95% CI, 95% confidence intervals	; SDD, Selective Decontamination of the Digestive	tract; SOD, Selective Oropharyngeal	Decontamination; SC,
Standard Care; ICER, inc	cremental costs effectiveness ratio (	costs/LYG)		
Standard Care; ICER, inc	cremental costs effectiveness ratio (o	costs/LYG)		
Standard Care; ICER, inc	cremental costs effectiveness ratio (o	costs/LYG)		
Standard Care; ICER, inc	cremental costs effectiveness ratio (o	costs/LYG)		
Standard Care; ICER, inc	cremental costs effectiveness ratio (o	costs/LYG)		

Page 51 of 53

		SC	SOD	SDD	ICER analyses	ICER analyses	ICER analyses
					SC vs SOD	SC vs SDD	SDD vs SOD
Sensitivity analysis	BC	4.27	4.02	4.23	SC = dominated by	SC = dominated by	SDD = dominated b
discounting effects (Life	+1.5%	(3.96 – 4.57)	(3.72 – 4.32)	(3.94 – 4.53)	SOD	SDD	SOD
years lost)	+0%	6.07	5.62	5.97	SC = dominated by	SC = dominated by	SDD = dominated b
		(5.58 – 6.55)	(5.15 – 6.08)	(5.50 – 6.44)	SOD	SDD	SOD
	+3%	2.82	2.68	2.82	SC = dominated by	SC = dominated by	SDD = dominated b
		(2.63 – 3.01)	(2.49 – 2.87)	(2.63 – 3.00)	SOD	SDD	SOD
Sensitivity analysis	BC	€41,940.79	€40,433.42	€41,183.12	SC = dominated by	SC = dominated by	SDD = dominated b
mechanical ventilation*	+15%	(€40,183.93 -	(€38,837.50 –	(€39,408.39 –	SOD	SDD	SOD
		€43,697.66)	€42,029.35)	€42,957.85)			
	+ 0%	€38,715.73	€37,117.07	€37,874.94	SC = dominated by	SC = dominated by	SDD = dominated b
		(€37,112.32 –	(€35,659.90 -	(€36,270.73 -	SOD	SDD	SOD
		€40,319.14)	€38,574.24)	€39,479.15)			
	+30%	€45,165.85	€43,749.78	€44,491.30	SC = dominated by	SC = dominated by	SDD = dominated b
		(€43,251.01 -	(€42,010.47 –	(€42,542.03 –	SOD	SDD	SOD
		€47,080.69)	€45,489.09)	€46,440.57)			
Sensitivity analysis price	1	€41,940.79	€40,493.15	€42,720.23	SC = dominated by	ICER 21,590	SDD = dominated b
study regimen*#		(€40,183.93 -	(€38,996.62 –	(€40,943.82 –	SOD		SOD
		€43,697.66)	€42,189.67)	€44.496.65)			

Table 5: Sensitivity analysis

# Price SOD €40 and SDD €400 per day * Effects are discounted 1.5% a year

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

..mination of the Digestive tract, SOD Selective Orv, BC base case results ; SDD Selective Decontamination of the Digestive tract, SOD Selective Oropharyngeal Decontamination, SC Standard Care, ICER incremental costs

effectiveness ratio (costs/LYG)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

