The effects of Selective Decontamination

Marc Bonten, University Medical Center Utrecht, The Netherlands

What is SDD?

- Intravenous prophylaxis
- Oropharyngeal decontamination
- Gastric and intestinal decontamination
- Avoiding the use of anti-anaerobic antibiotics
- Surveillance cultures
- High level of hygiene

What is SOD?

- .
- Oropharyngeal decontamination
- .
- .

- Surveillance cultures
- High level of hygiene

Antibiotics in SDD/SOD

- Cefotaxim 4 dd 1 gr. i.v. during first 4 days of treatment.
- Oropharyngeal application 4 dd 0.5 gr. paste containing 2% polymyxin E, 2% tobramycin and 2% amphotericin B.
- Intragastric application 4 dd 10 ml of suspension containing 100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B (suppositoria in case of stoma).
- To be started (asap) in intubated patients with an expected duration of intubation of at least 48 hours.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Decontamination of the Digestive Tract and Oropharynx in ICU Patients

A.M.G.A. de Smet, M.D., J.A.J.W. Kluytmans, M.D., Ph.D., B.S. Cooper, Ph.D.,
Werf, M.D., Ph.D.,
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F. te Velde, M.D.,
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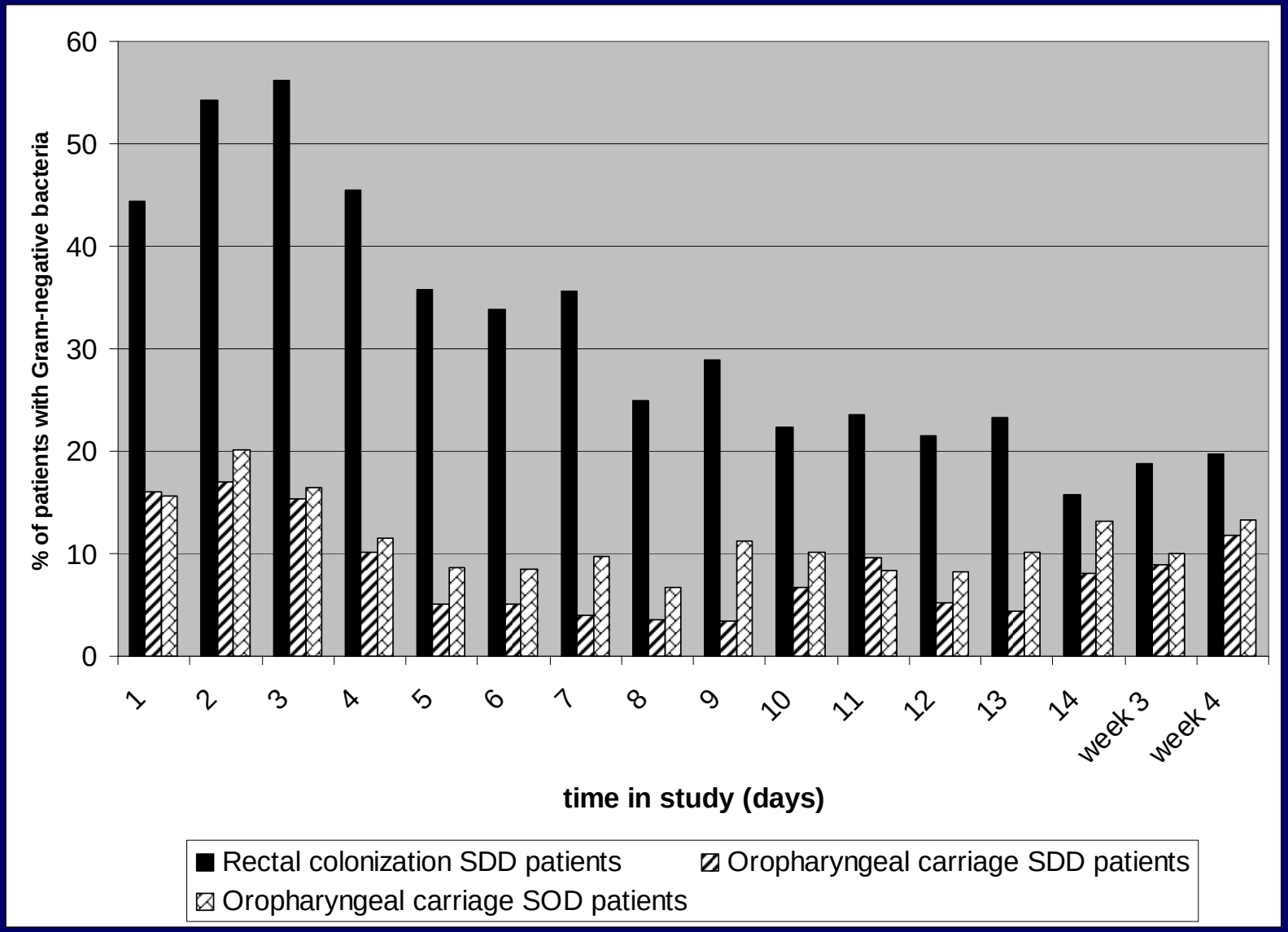
P. Arends, M.D.,
arinck, M.D., Ph.D.,
Blok, M.Sc.,
, M.D., Ph.D.,
and M.J.M. Bonten, M.D., Ph.D.

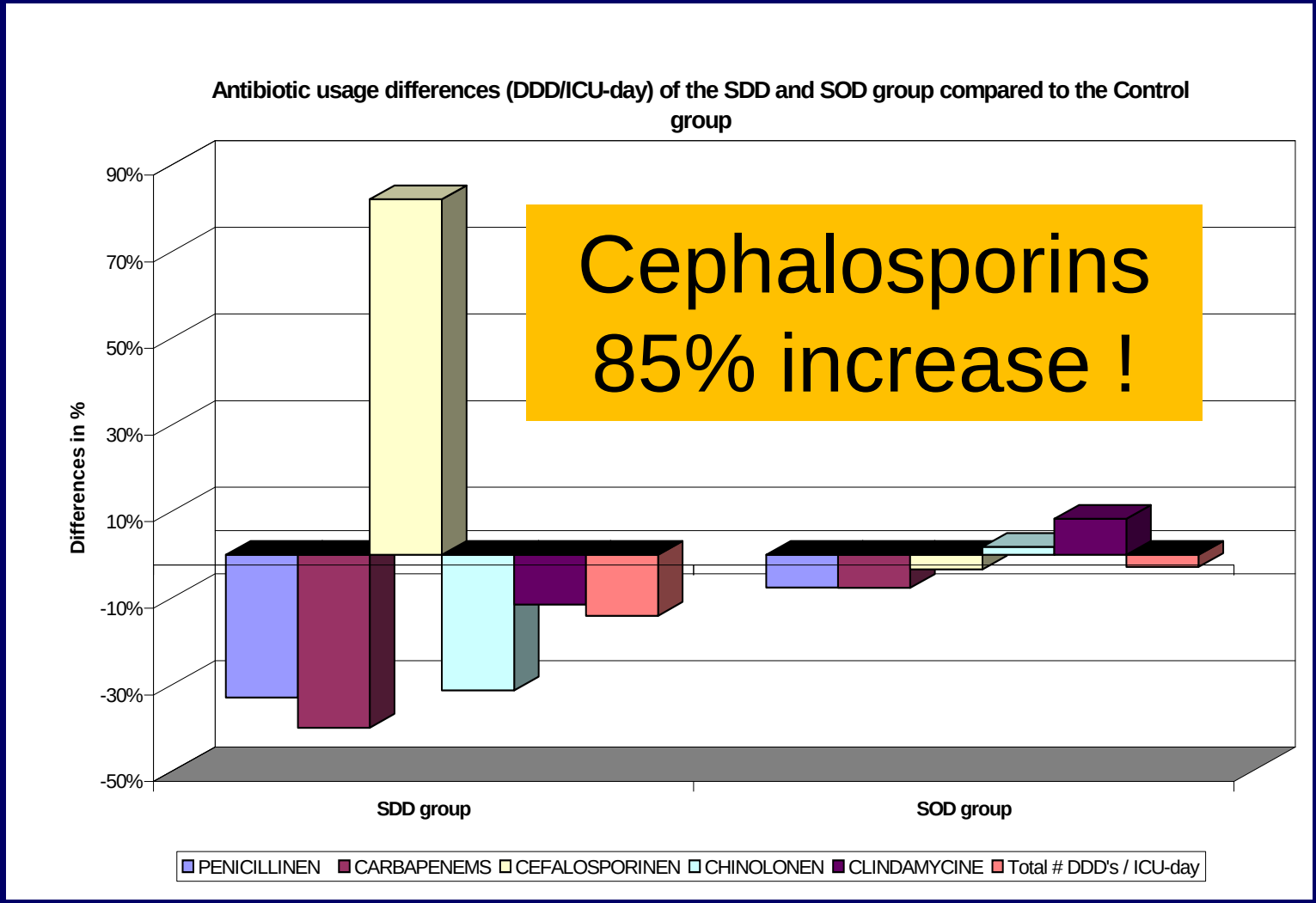
Resistance ecology in Dutch ICUs:

MRSA <1% of *S. aureus* infections
VRE <1% of enterococcal infections
ESBL <5% of Enterobacteriaceae infections
CRE 0%
C. diff infections: sporadic

Efficacy of decontamination



Effects on antbiotic use in ICU



Intensive Care Med (2003) 29:677–690
DOI 10.1007/s00134-003-1722-2

REVIEW

Hendrick K. E. van Saene
Andy
Grah
Derr

All great truths are iconoclastic:

In 2003:

No convincing evidence of survival benefit, or benefit on other relevant endpoints (LOS)

No data on cost-effectiveness

Contradictory results on effects on antibiotic resistance

Ma
Chr
Robert A. Weinstein

tract: to stimulate or stifle?

Would you use in an intervention if it

- Improves patient outcome (day-28 mortality)?
- Reduces ICU-acquired Gram-negative bacteremia?
- Reduces VAP?
- Reduces intravenous antibiotic use?
- Reduces ICU-acquired bacteremia caused by MDR?
- Reduces acquisition of MDR in the respiratory tract?
- Reduces carriage with ESBL-producing bacteria in the intestinal tract?
- Is cost-effective (costs <€20,000/life year gained)?
- Has it all?

Would you use in an intervention if it

- Improves patient outcome (day-28 mortality)?
- Reduces ICU-acquired Gram-negative bacteremia?
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- Is cost-effective (costs <€20,000/life year gained)?
- Has it all?

Clinical endpoints

Adjusted outcomes			
	Standard Care N=1990	SDD N=2045	SOD N=1904
M… da…			
IC…			
H…			
Du… in…			
Duration of ICU-stay	1	1.09 (0.99-1.21)	1.06 (0.94-1.19)
Duration of hospital stay	1	1.13 (1.01-1.25)	1.13 (0.96-1.32)

At day 28 SDD and SOD were associated with:

- Reduced mortality at day 28 of 13% and 11%
- Absolute mortality reductions of 3.5% and 2.9%
- Number needed to treat of 29 and 34

SDD and SOD tended to reduce:

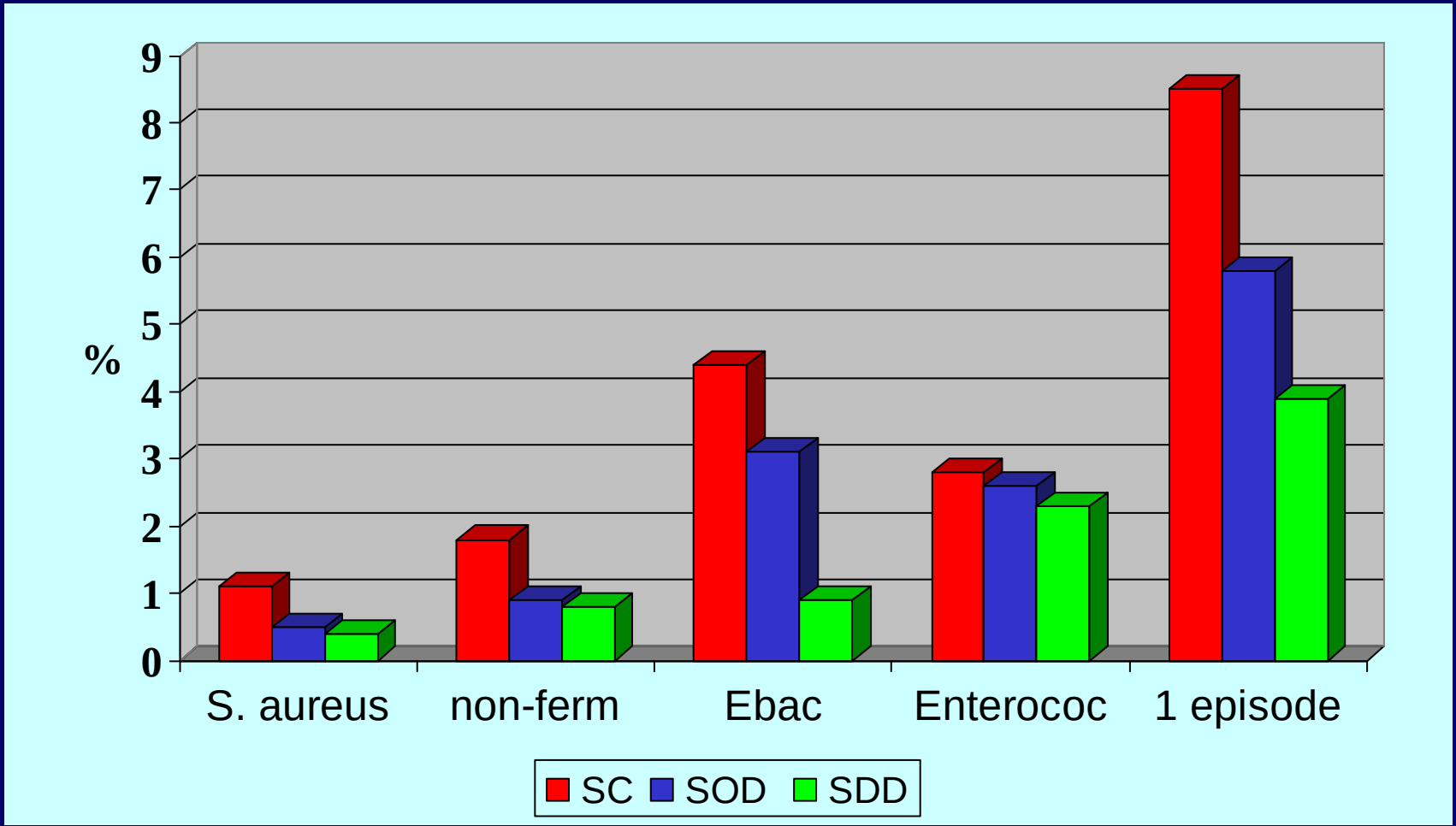
- Duration of ventilation
- Duration of ICU-stay
- Duration of hospital stay

Random effects logistic regression model with adjustment for age, gender, APACHE II score, ventilation, surgical/non-surgical and study center.

Would you use in an intervention if it

- Improves patient outcome (day-28 mortality)?
- Reduces ICU-acquired Gram-negative bacteremia?
- Reduces VAP?
- Reduces intravenous antibiotic use?
- Reduces ICU-acquired bacteremia caused by MDR?
- Reduces acquisition of MDR in the respiratory tract?
- Reduces carriage with ESBL-producing bacteria in the intestinal tract?
- Is cost-effective (costs <€20,000/life year gained)?
- Has it all?

Incidences of ICU-acquired bacteremia.



N ENGL J MED 360;1 NEJM.ORG JANUARY 1, 2009

The role of intestinal colonization with Gram-negative bacteria as a source for intensive care unit-acquired bacteremia*

Evelien A. N. Oostdijk, MD; Anne Marie G. A. de Smet, MD, PhD; Jozef Kesecioglu, MD, PhD; Marc J. M. Bonten, MD, PhD; on behalf of the Dutch SOD-SDD Trialists Group

Crit Care Med 2011 Vol. 39, No. 5

Table 1. Incidence densities and rate ratios of intensive care unit-acquired Gram-negative bacteria bacteremia during standard care, SOD_{total}, and SDD_{total}

Variable	Standard Care	SOD_{total}	SDD_{total}
No. of patients	1,945	2,166	2,667
Patient days	26,824	28,575	35,394
No. of gram-negative bacteria bacteremia	121	86	52
Percentage	6.2%	4.0%	1.9%
95% confidence interval	5.13–7.27	3.15–4.79	1.43–2.47
Median onset (interquartile range)	10 (11)	13 (15.25)	13 (14)
Incidence density	4.51	3.01	1.43
No. of patients with ≥1 rectal sample		259	2476
No. of patients with ≥1 episode of rectal colonization		219 (83%)	1134 (46%)
No. of "at-risk" patient days		3,163	34,011
No. of rectal colonization days		2,242 (71%)	8,961 (26%)
No. of no rectal colonization days		921 (29%)	25,049 (74%)

SOD_{total}, selective digestive tract decontamination cohorts 1 and 2; SDD_{total}, selective digestive tract decontamination cohorts 1 and 2.

Shown are numbers of patients and patient days with Gram-negative bacteria colonization during SOD cohort 2 and SDD_{total}. Data represent median onsets in days after ICU admission.

Eradication of the intestinal Gram-negative flora associated with lower incidence ICU-acquired Gram-negative bacteremia

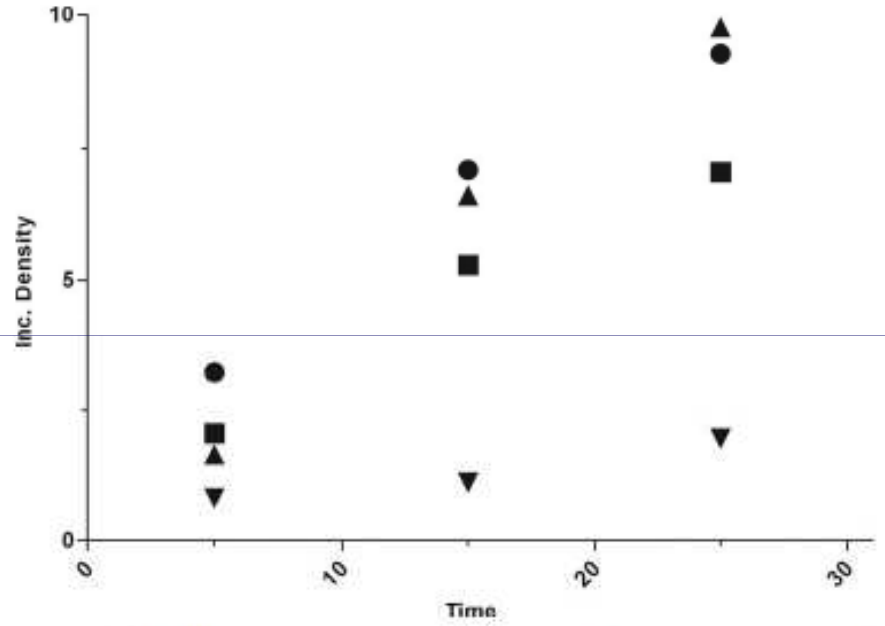


Figure 3. Incidence densities for intensive care unit-acquired Gram-negative bacteria bacteremia per 10 days. ●, standard care; ■, SOD_{total}; ▲, SDD_{total} colonized bacteremia; ▼, SDD_{total} noncolonized bacteremia. *SOD*, selective oropharyngeal decontamination; *SDD*, selective decontamination of the digestive tract. SOD_{total} is explained in the text. SOD_{total} consists of SOD-C1 and SOD-C2.

Would you use in an intervention if it

- Improves patient outcome (day-28 mortality)?
- Reduces ICU-acquired Gram-negative bacteremia?
- Reduces VAP?
- Reduces intravenous antibiotic use?
- Reduces ICU-acquired bacteremia caused by MDR?
- Reduces acquisition of MDR in the respiratory tract?
- Reduces carriage with ESBL-producing bacteria in the intestinal tract?
- Is cost-effective (costs <€20,000/life year gained)?
- Has it all?

Would you use in an intervention if it

- Improves patient outcome (day-28 mortality)?
- Reduces ICU-acquired Gram-negative bacteremia?
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- Reduces acquisition of MDR in the respiratory tract?
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- Is cost-effective (costs <€20,000/life year gained)?
- Has it all?

Systemic antibiotic use (totals in DDD)

	SDD group	SOD group	Standard care
Antibiotics	Total DDD use (Δ SDD vs Control)	Total DDD use (Δ SOD vs Control)	Total DDD use
Penicillins	9,767 (-27.8%)	12,805 (+5.3%)	13,523
Carbapenems	724 (-45.7%)	995 (-25.4%)	1,334
Cefalosporins	8,473 (+86.6%)	3,935 (-13.3%)	4,541
Quinolones	2,637 (-31.4%)	3,291 (-14,4%)	3,846
Clindamycins	473 (-11.6%)	553 (+3.4%)	535
Other antibiotics	7,589 (- 23.4%)	8,720 (-12.0%)	9,909
All Systemic antibiotics	29,663 (-12.0%)	30,299 (-10.1%)	33,688

N ENGL J MED 360;1 NEJM.ORG JANUARY 1, 2009

Would you use in an intervention if it

- Improves patient outcome (day-28 mortality)?
- Reduces ICU-acquired Gram-negative bacteremia?
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- Reduces ICU-acquired bacteremia caused by MDR?
- Reduces acquisition of MDR in the respiratory tract?
- Reduces carriage with ESBL-producing bacteria in the intestinal tract?
- Is cost-effective (costs <€20,000/life year gained)?
- Has it all?

Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study

Anne Marie G A de Smet, Jan A J W Kluytmans, Hetty E M Blok, Ellen M Mascini, Robin F J Benus, Alexandra T Bernards, Ed J Kuijper, Maurine A Leverstein-van Hall, Arjan R Jansz, Bartelt M de Jongh, Gerard J van Asselt, Ine H M E Frenay, Steven F T Thijsen, Simon N M Conijn, Jan A Kaan, Jan P Arends, Patrick D J Sturm, Martin C J Bootsma, Marc J M Bonten

www.thelancet.com/infection **Published online March 21, 2011**

Incidence of MDR bacteremia

	SC n=1989	SOD n=1904	SDD n-=2034
Frequency of obtaining blood cultures (per pt day)	0,11	0,13	0,11
HRMO ≤2 days in ICU	6	3	3
HRMO ≥3 days in ICU (%)	19 (1.7)	20 (1.4)	8 (1.0)

SDD vs SC: OR 0,41 (0,18-0,94); SDD vs SOD: OR 0,37 (0,16-0,85)

SC: Rate reduction: 59%; Absolute Risk Reduction 0,6%; NNT=170
SOD: Rate reduction: 63%; Absolute Risk Reduction 0,7%; NNT=145

Would you use in an intervention if it

- Improves patient outcome (day-28 mortality)?
- Reduces ICU-acquired Gram-negative bacteremia?
- Reduces VAP?
- Reduces intravenous antibiotic use?
- Reduces ICU-acquired bacteremia caused by MDR?
- Reduces acquisition of MDR in the respiratory tract?
- Reduces carriage with ESBL-producing bacteria in the intestinal tract?
- Is cost-effective (costs <€20,000/life year gained)?
- Has it all?

	SC	SOD	SDD
Acquired HRMO	128 (14.5)	88 (10.0)	74 (8.9)
Acinetobacter spp	14	3	7
Stenothrophomonas maltophilia	8	6	7
Pseudomonas aeruginosa	29	9	10
Other GNF-GNR	3	5	20
Enterobacter spp	18	19	9
Escherichia coli	23	9	4
Klebsiella spp	22	21	9
Citrobacter spp	4	3	0
Morganella spp	1	0	1
Proteus spp	2	0	2
Serratia marcescens	3	9	3
Streptococcus pneumoniae	1	2	0
Staphylococcus aureus	0	2	2

SDD versus SC: Odds ratio 0,58 (0,43-0,78)

Rate reduction: 38%; Absolute Risk Reduction 5,5%; NNT=18

SOD versus SC: Odds ratio 0,65 (0,49-0,87)

Rate reduction: 32%; Absolute Risk Reduction 4,6%; NNT=22

De Smet et al. LID 2011

Acquired Respiratory Tract Colonization

	SC N=881	SOD N=886	SDD N=828
Tobramycine resistance:			
•*Escherichia coli* and Klebsiella spp	31 (3.5)	19 (2.1)	9 (1.1)
•Other Enterobacteriaceae	25 (2.8)	41 (4.6)	15 (1.8)
•Acinetobacter spp and *S. maltophilia*	40 (4.5)	45 (5.1)	49 (5.9)
•Other GNF-GNR¶	18 (2.0)	20 (2.3)	49 (5.9)
•Any Gram-negative rods	104 (11.8)	112 (12.6)	115 (13.9)
Cefotaxime resistance:			
•*Escherichia coli* and Klebsiella spp	13 (1.5)	12 (1.4)	2 (0.2)
•Other Enterobacteriaceae	44 (5.0)	42 (4.7)	18 (2.2)
•With any Enterobacteriaceae	56 (6.4)	56 (6.3)	20 (2.4)
Colistine resistance:			
Proteus spp and Serratia spp	130 (14.8)	112 (12.6)	55 (6.6)

De Smet et al LID 2011

Ecological Effects of Selective Decontamination on Resistant Gram-negative Bacterial Colonization

Evelien A. N. Oostdijk[1], Anne Marie G. A. de Smet[2], Hetty E. M. Blok[1], Emily S. Thieme Groen[2], Gerard J. van Asselt[3], Robin F. J. Benus[4], Sandra A. T. Bernards[5], Ine H. M. E. Frénay[6], Arjan R. Jansz[7], Bartelt M. de Jongh[8], Jan A. Kaan[9], Maurine A. Leverstein-van Hall[1], Ellen M. Mascini[10], Wouter Pauw[11], Patrick D. J. Sturm[12], Steven F. T. Thijsen[13], Jan A. J. W. Kluytmans[14,15], and Marc J. M. Bonten[1,16]

Am J Respir Crit Care Med Vol 181. pp 452–457, 2010

TABLE 2. PROPORTIONS OF PATIENTS COLONIZED WITH ANTIBIOTIC-RESISTANT GRAM-NEGATIVE BACTERIA DURING MONTHLY POINT PREVALENCE SURVEYS PER PERIOD AND MONTHLY CHANGES DURING THE SPECIFIC PERIODS*

	Average Prevalence per Period [mean (95% CI)]			*Change in Prevalence during Period [β coefficient (P value)]*		
	Pre	Intervention	Post	Pre	Intervention	Post
Rectal samples						
Ceftazidime	6% (4.7–7.5%)	5% (3.9–6.7%)	15%† (12.4–17.0%)	−0.07 (0.038)	−0.05 (NS)	−0.04 (NS)
Tobramycin	9%† (7.7–11.2%)	7% (5.5–8.7%)	13%† (10.4–14.7%)	0.00 (NS)	−0.05 (NS)	−0.04 (NS)
Ciprofloxacin	12%† (9.7–13.5%)	7% (5.1–8.2%)	13%† (10.8–15.2%)	−0.01 (NS)	0.03 (NS)	−0.03 (NS)
Respiratory samples						
Ceftazidime	10%† (7.6–13.3%)	4% (2.6–4.6%)	10%† (7.4–13.0%)	0.00 (NS)	0.09 (0.039)	0.07 (NS)
Tobramycin	10%† (6.9–12.5%)	6% (4.5–6.9%)	12%† (8.8–14.6%)	0.17 (NS)	0.04 (NS)	−0.04 (NS)
Ciprofloxacin	14%† (10.4–17.0%)	5% (3.5–5.7%)	12%† (9.0–14.9%)	0.05 (NS)	0.02 (NS)	−0.02 (NS)

Definition of abbreviations: CI = confidence interval; Intervention = intervention period; Pre = preintervention period; Post = postintervention period; NS = not significant. The β coefficient is considered significant if the *P* value is less than 0.05.

* Adjusted for changes between centers.

† $P < 0.05$ as compared with the intervention period. Adjusted for changes between centers.

Conclusions: Colistin resistance

- During continuous topical use of colistin acquisition rates (per 1,000 patient days at risk) were
  - 1.2 -2.4 in rectal swabs during SDD
  - 0.7 -1.1 In respiratory samples during SDD, SOD and SC

Intensive Care Medicine, *in press*

Colistin resistance

- Not prevalent in the community
- Not located on plasmid/transposon -> no horizontal gene transfer
- IV-use appears to be a risk factor
  - Leading to *de novo* resistance
- Cross-transmission of resistant bacteria is possible
- Unknown:
  - Duration of carriage
  - Stability of resistance

Would you use in an intervention if it

- Improves patient outcome (day-28 mortality)?
- Reduces ICU-acquired Gram-negative bacteremia?
- Reduces VAP?
- Reduces intravenous antibiotic use?
- Reduces ICU-acquired bacteremia caused by MDR?
- Reduces acquisition of MDR in the respiratory tract?
- Reduces carriage with ESBL-producing bacteria in the intestinal tract? SDD does (*JAC 2012*)
- Is cost-effective (costs <€20,000/life year gained)?
- Has it all?

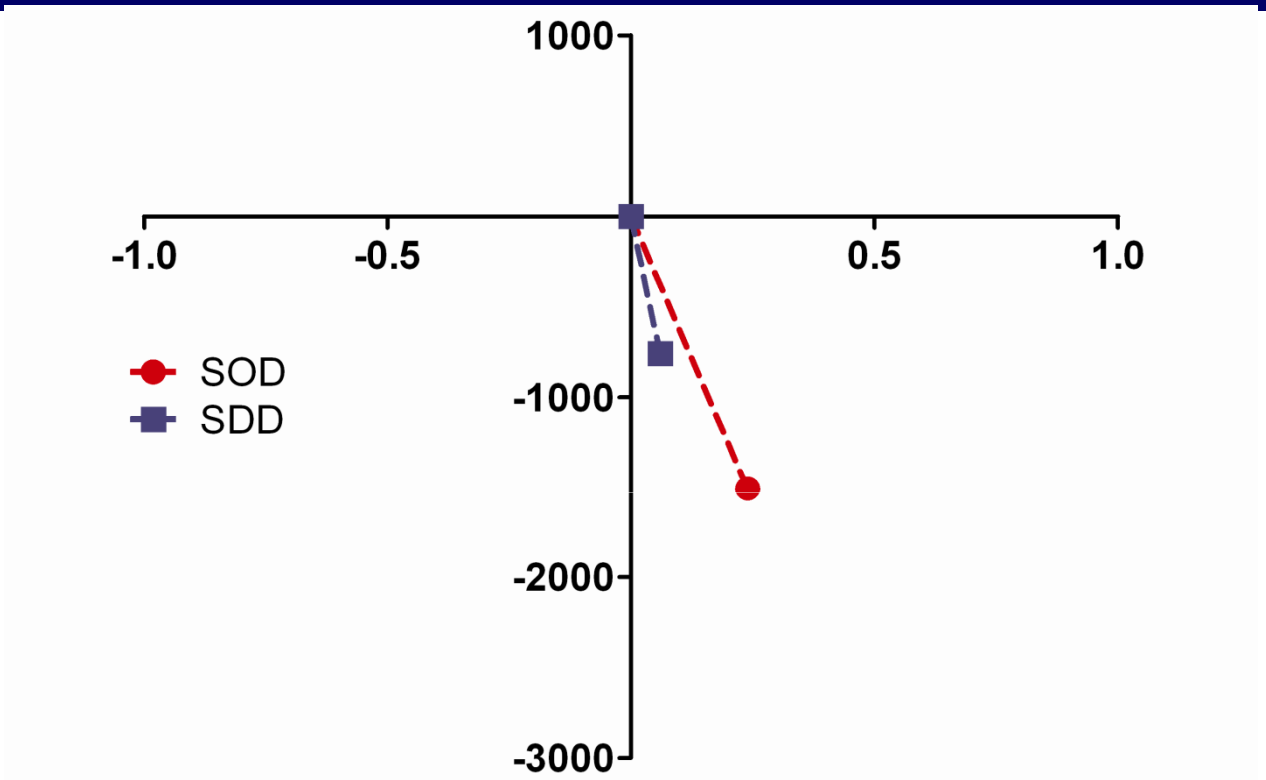
Patients and Methods: costs

Length of stay	**ICU stay** (+/- mechanical ventilation)	**Hospital stay**	
Antibiotics	**Study medication** **SDD or SOD** (topical application)	**Systemic antibiotics** (incl. cefotaxime during SDD) (per DDD)	
Microbiology	**Clinical cultures** **(blood, sputum, BAL, throat)** (per culture and extra costs for pos. cult.)		**Rectal surveillance (SDD)**

Results: mean costs per patient

	SC n = 1987	SOD n = 1901	SDD n = 2032
Length of stay	**€ 41,400**	**€ 39,831**	**€ 40,342**
Antibiotics	**€ 358**	**€ 318**	**€ 439**
Topical SDD/SOD	**€ 0**	**€ 3**	**€ 41**
Microbiology	**€ 182**	**€ 281**	**€ 361**
Total	**€ 41,941**	**€ 40,433**	**€ 41,183**

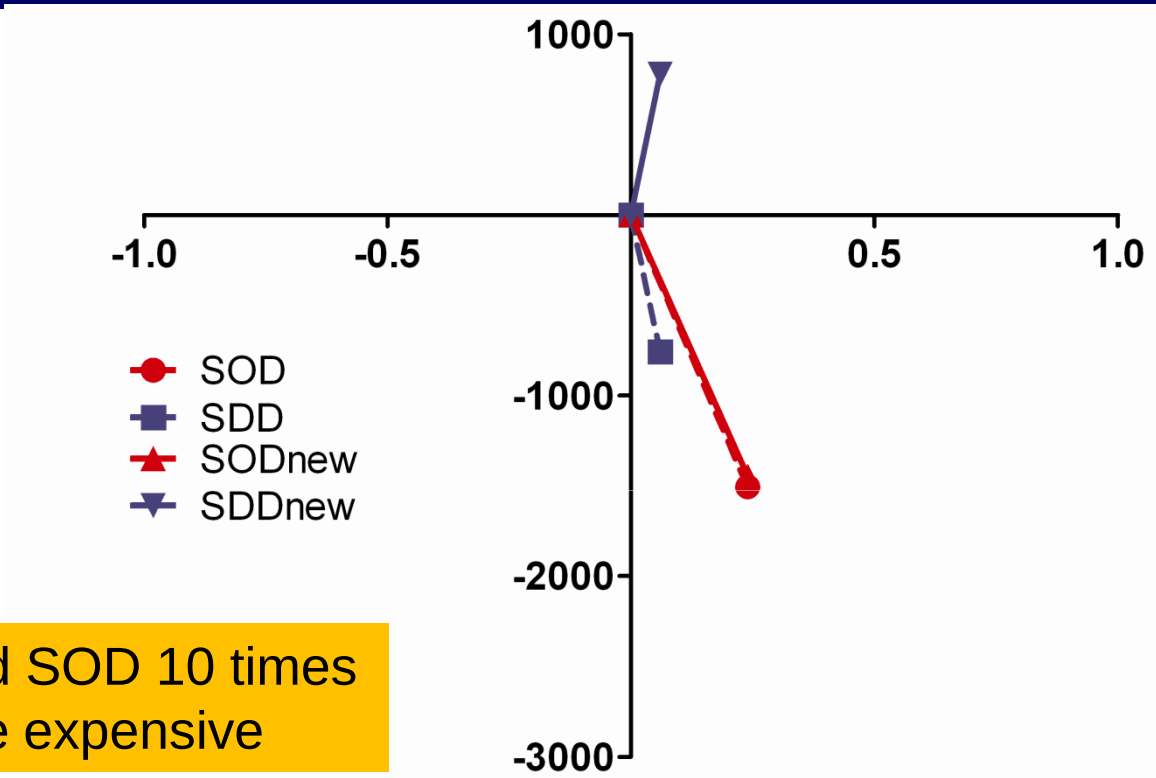
Incremental Cost Effectiveness Ratios (ICER) in a cost effectiveness plane



	LYG*	Costs	ICERs
SOD vs SC	**+ 0.24yr**	**-1,507**	**SC dominated by SOD**
SDD vs SC	**+ 0.07yr**	**-758**	**SC dominated by SDD**

** Life Years Gained*

Incremental Cost Effectiveness Ratios (ICER) in a cost effectiveness plane



SDD and SOD 10 times more expensive

	LYG*	Costs old	Costs new (€40 / €400)
SOD vs SC	**+ 0.24yr**	**-1,507**	**-1,448**
SDD vs SC	**+ 0.06yr**	**-758**	**+779 (ICER 12,633)**

** Life Years Gained*

Benefit on	SDD	SOD	CHX
Day-28 survival	+	+	?
Gram-negative ICU-acquired bacteremia	++	+	?
VAP	+	+	+
Intraveous antibiotic use	+	+	?
ICU-acquired (MDR) bacteremia	+	-	?
MDR acquisition in respiratory tract	++	+	?
Cost-saving	-	+	?
Cost-effecttive	+	++	?
Does fit to concept of prudent antibiotic use	-	+	++
Score	9	9	3

SDD in your – not greenish - country

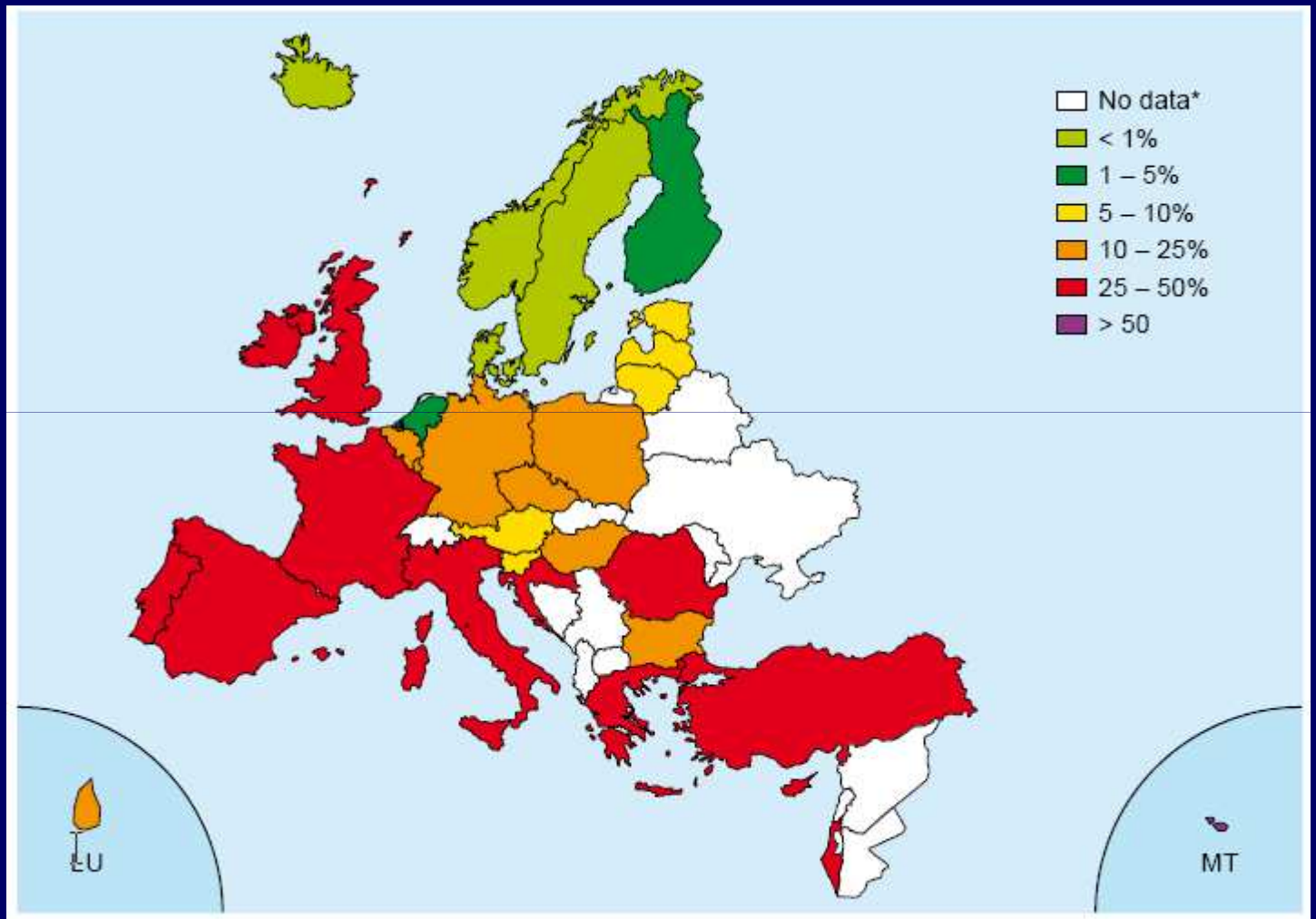


Figure 4.8. *Staphylococcus aureus*: proportion of invasive isolates resistant to oxacillin (MRSA) in 2007.
* These countries did not report any data or reported less than 10 isolates.

Benefit on	SDD	SOD	CHX
Day-28 survival	?	?	?
Gram-negative ICU-acquired bacteremia	?	?	?
VAP	+	+	?
Intraveous antibiotic use	?	?	?
ICU-acquired MDR bacteremia	?	?	?
MDR acquisition in respiratory tract	?	?	?
Cost-saving	?	?	?
Cost-effecttive	?	?	?
Does fit to concept of prudent antibiotic use	-	+	++
Score	1	2	2

FP7 – Theme 1 HEALTH

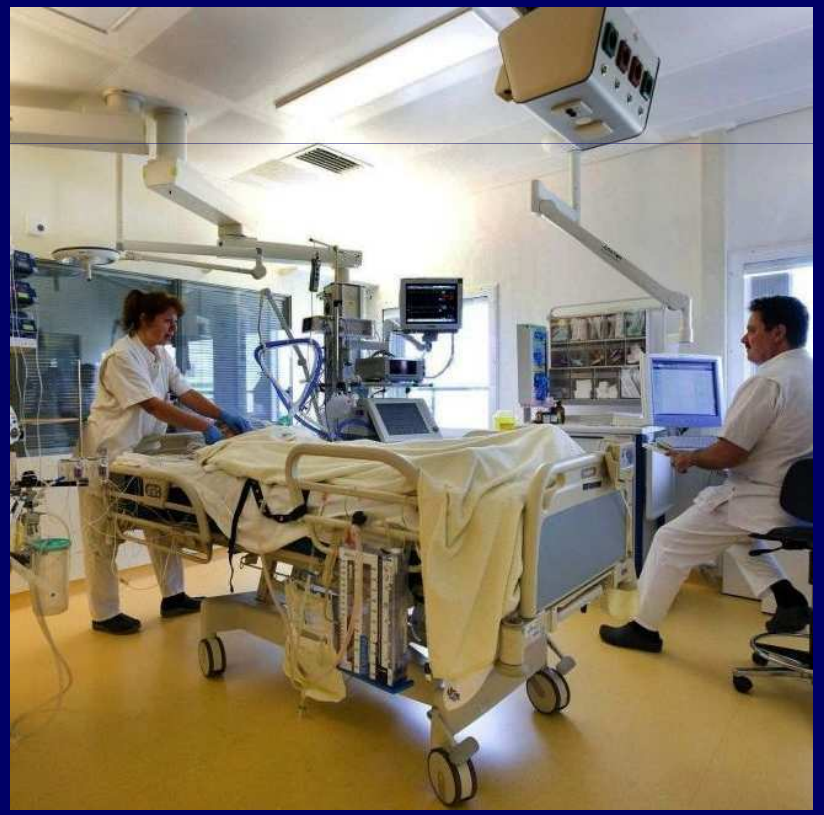
Resistance in **G**ram-**N**egative **O**rganisms: **S**tudying **I**ntervention **S**trategies

R-GNOSIS

COLLABORATIVE PROJECT – Large Scale Integrating Project

WP6 Decolonization strategies in Intensive Care

- **To determine the effectiveness of 3 decolonization regimens (SDD, SOD and oro-CHX) in ICU patients in reducing ICU-acquired MDR-GNB bacteraemia when compared to standard care.**



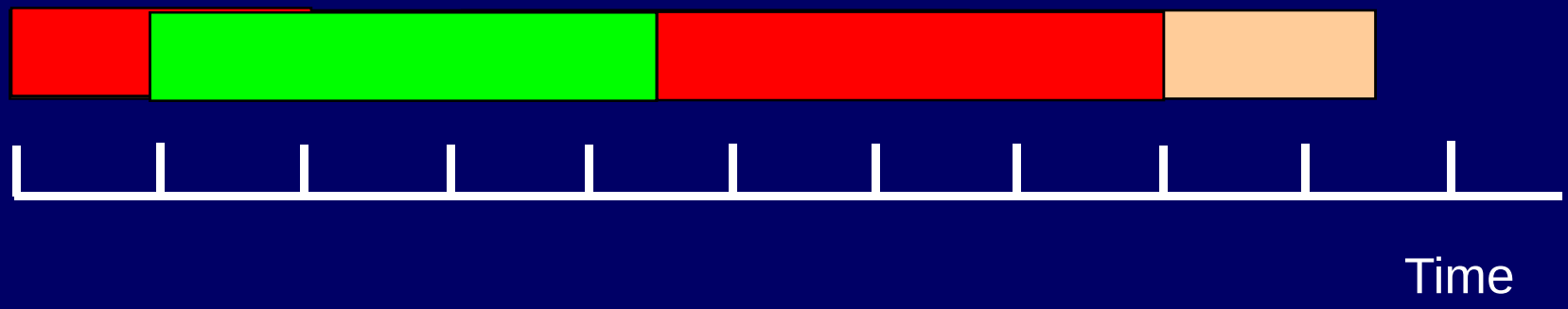
Lead:
Christian Brun-Buisson (Universite Paris XII – Val Marne)

Marc Bonten (UMC Utrecht)
mbonten@umcutrecht.nl

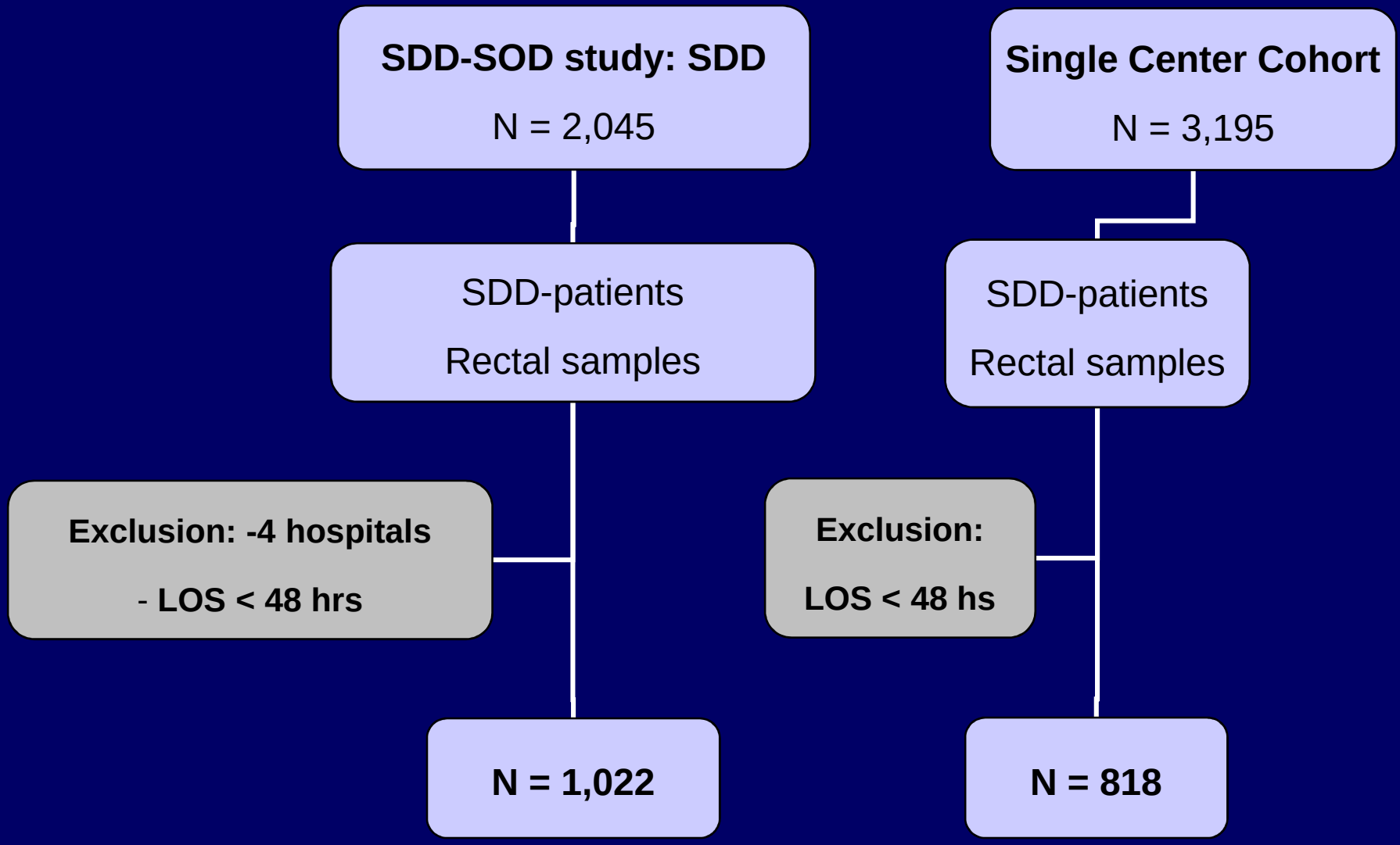
- Rectal colonization was determined for:
  - *Enterobacter spp*
  - Escherichia coli
  - *Klebsiella spp*
- Respiratory tract colonization was determined for:
  - *Enterobacter spp*
  - Escherichia coli
  - *Klebsiella spp*
  - *Acinetobacter spp*
  - *Pseudomonas spp*

Definitions of colistin resistance

- *At admission: within first 3 days*
- *Acquisition: after 3 days of ICU-stay*
  - *Conversion of colistin S to colistin R within same species*



Patient numbers: rectal carriage



Results: rectal colonization

	SDD-SOD study Rectal samples	Single Center Rectal samples
N patients	1,022	818
N cultures	4,740	4,158
Cultures/patientday	0.28	0.32
Culture positivity GNB	373 (36%)	443 (54%)

Results: rectal colonization

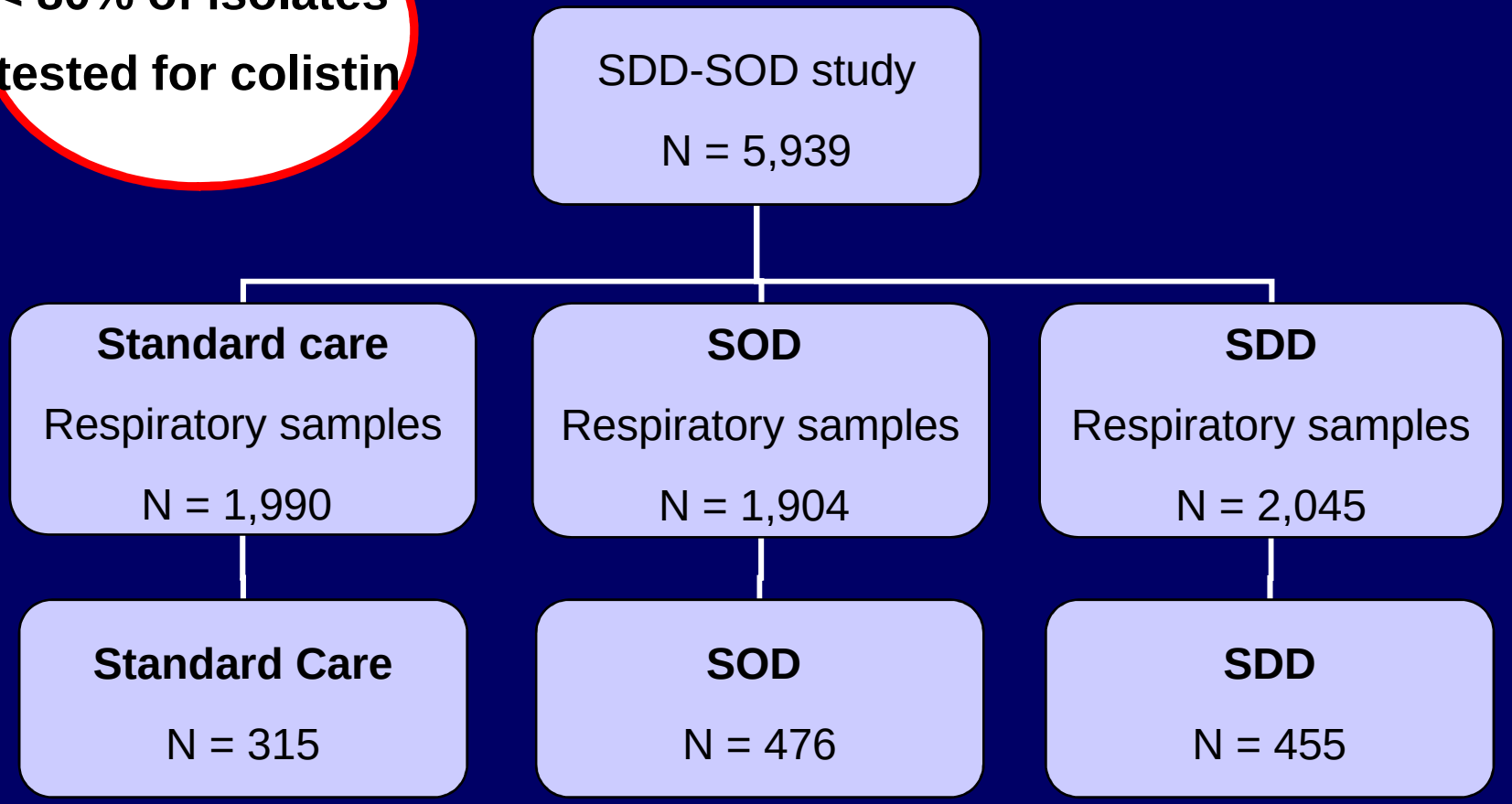
	SDD-SOD study Rectal samples	Single Center Rectal samples
N patients	1,022	818
Colistin R/I (95% CI)	55 (5.4%) (4.2% – 7.0%)	16 (2.0%) (1.2% –3.2%)
On admission	14 (1.4%)	1 (0.1%)
Acquired	41 (4.0%)	15 (1.8%)
Acquisition rate / 1,000 pat days (95% CI)	2.4 (1.5 – 4.2)	1.2 (0.7 – 2.0)

Results: rectal colonization

	SDD-SOD study Rectal samples	Single Center Rectal samples
N patients	1,022	818
Conversion COL S->R	17 (1.7%)	9 (1.1%)
Median Time Till Conversion	5 (2-71 ; IQR 3)	19 (6-50 ; IQR 30)
Conversion Rate / 1,000 patientdays	1.0	0.7

Data collection: Respiratory tract

< 80% of isolates tested for colistin



Results: respiratory tract

	Standard Care	SOD	SDD
N patients	315	476	455
N cultures	1,611	2,382	2,473
Cultures/patientday	0.25*	0.32	0.32
Culture positivity GNB	139 (44%)	155 (33%)	140 (31%)

Results: respiratory tract

	Standard Care	SOD	SDD
N patients	315	476	455
Colistin R/I	7 (2.2%)	10 (2.1%)	9 (2.0%)
On admission	2 (0.6%)	2 (0.4%)	4 (0.9%)
Acquired	5 (1.6%)	8 (1.7%)	5 (1.1%)
Acquisition rate / 1,000 pat days (95% CI)	0.8 (0.3 – 1.8)	1.1 (0.5 – 2.1)	0.7 (0.4 – 2.4)

Results: respiratory tract

	Standard Care	SOD	SDD
N patients	315	476	455
COL S-R	3 (1.0%)	4 (0.8%)	5 (1.1%)
Median TTC	19 (IQR 14-37)	8 (IQR 4-36)	12 (IQR 4-63)
Conversion Rate / 1,000 patientdays	0.5	0.5	0.7
Colonized CR / 1,000 col. pat.days	1.1*#	2.6	3.6