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The perfidious effect of topical placebo: A calibration of *Staphylococcus aureus* Ventilator Associated Pneumonia incidence within Selective Digestive Decontamination (SDD) studies versus the broader evidence base.

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Abstract:

Among various methods for preventing ventilator associated pneumonia (VAP), the evidence base for selective digestive decontamination (SDD) appears most compelling. However, the extent of *Staphylococcus aureus* emergence with SDD use remains uncertain. Groups from 37 observational studies and component (control and intervention) groups from 58 studies of SDD and other methods of VAP prevention were sourced exclusively from ten systematic reviews. *S aureus* as a proportion of VAP isolates (*S aureus*-IP) among component groups was calibrated versus observational groups (the benchmark). The influence of topical placebo used for blinding purposes and other group level factors was estimated using generalized estimating equation methods (GEE). The mean *S aureus*-IP is 22% (95% CI; 19 – 25) for 37 observational groups versus 32% (24 – 41) and 20% (15 – 25) for 22 control groups from the SDD evidence base which did versus did not receive topical placebo, respectively. In GEE models including all 148 observational and component groups, membership of a control ($p = 0.03$) or intervention ($p < 0.001$) group of an SDD study that used topical placebo was associated with higher *S aureus*-IP whereas by contrast membership of these groups was without effect on *Pseudomonas aeruginosa*. Topical placebo is implicated as a vehicle for selective cross infection with *S aureus* within the specific context of the SDD evidence base. This effect of topical placebo is perfidious; it could contribute to the higher VAP incidence and inflate the apparent 'effectiveness' of SDD. The SDD evidence base requires re-appraisal.

Key words: Ventilator associated pneumonia; contextual analysis; Antibiotic prophylaxis, Study design, Intensive care, Mechanical ventilation, Cross infection, Nosocomial infection, Outbreaks; *Staphylococcus aureus*.

Introduction

Approximately 20% of patients receiving prolonged mechanical ventilation (MV) develop ventilator-associated pneumonia (VAP) and *Staphylococcus aureus* and *Pseudomonas aeruginosa* each account for approximately 20% of VAP isolates [1-8]. Selective Digestive Decontamination (SDD), an extensively studied method for VAP prevention [9, 10], achieves decreased colonization with aerobic gram negative bacilli at the oro-pharynx [11] through the use of topical antibiotic paste. However, SDD may increase colonization with gram positive bacteria [12, 13] including Staphylococci [14, 15].

The SDD evidence base is unusual in four respects. The mean VAP incidence in the concurrent control groups of SDD studies is more than 10 percentage points higher and the dispersion is greater versus a benchmark of VAP incidence proportion (VAP-IP) derived from observational studies and also versus control groups of studies of other methods of VAP prevention using non-antibiotic methods [16]. Strikingly, the disparity versus this benchmark is even greater for control groups from SDD studies rated as higher in study quality as a consequence of observer blinding achieved by the use of topical placebo [17]. Paradoxically, the VAP incidence of the intervention groups within the SDD evidence base is more homogeneous and the mean is within less than 10 percentage points of the VAP incidence benchmark [17]. Finally, the explanation for the profound difference in VAP incidence seen between intervention versus control groups of SDD studies is unclear. Specifically, an anti-pseudomonal activity of SDD is not evident within the listings of VAP isolates within the SDD studies despite polymyxin and tobramycin being common SDD constituents [18].

That SDD could influence the VAP incidence in the control groups of studies with a concurrent design through cross colonization was postulated in the original 1984 SDD

study [19] and others [20] which as a consequence were intentionally non-concurrent in design [19, 20]. However, this postulated contextual effect remains untested due to the methodological and analytical challenges which cannot be adequately addressed within the confines of the typical single center concurrent group study design.

The objective of this analysis is to derive benchmarks of *S aureus* and *Pseudomonas aeruginosa* each as a proportion of VAP isolates and also VAP incidence from observational (non-intervention) studies of VAP with which to enable a calibration of these proportions among component groups of studies of SDD and other methods of VAP prevention within the broader evidence base. Of particular interest are the control groups from studies of SDD which either did or did not achieved observer blinding through the use of topical placebo.

Materials and methods,

Overview.

This is a group level analysis of *S. aureus* –IP among the component groups of studies as included in published systematic reviews of observational studies of VAP incidence and systematic reviews of studies of various VAP prevention methods [5, 6, 10, 21-27]. The objectives here are (1) to derive a benchmark of *S. aureus* –IP from groups from the observational studies, (2) using random effect methods to achieve summations, and also using caterpillar plots to achieve a visual display, to compare the dispersion of *S. aureus* –IP among the various component groups from their respective benchmarks, (3) using generalized estimating equation (GEE) methods, to calibrate the impact of membership of a control groups receiving versus not receiving topical placebo within the SDD studies versus other group level factors as explanatory variables toward the differences in group specific *S. aureus* –IP. Other group level factors include membership of the various component groups of studies within the broad evidence base of methods of VAP prevention, (4) to compare the dispersion of VAP-IP and *P aeruginosa*-IP each from similarly derived benchmarks among the component groups of studies within the same evidence base.

Study selection

The inclusion criteria for this analysis was a study of ICU patients included in one of ten systematic reviews for which VAP-IP, and either *S. aureus* –IP or *P aeruginosa*-IP data were available [5, 6, 10, 21-27]. The reason for obtaining studies from among those included in previously published systematic reviews was to obtain studies constituent within an entire evidence base. Exclusion criteria as specified by Liberati et al [10] were applied to achieve harmonization across studies sourced from all ten reviews. Studies

published prior to 1984 were also excluded as those study types do not appear in the review of Liberati et al [10].

Component group designations

The component groups were classified into the following categories;

- Benchmark groups being groups from observational (i.e. non-interventional) studies of VAP incidence as listed in two systematic reviews [5, 6].
- The control and intervention groups from studies of various non-antibiotic methods of VAP prevention were sourced from one of five systematic reviews [21-25]. These methods were two types of stress ulcer prophylaxis [21], the use (intervention) versus non-use (control) of sub-glottic secretion drainage [22], passive (control) versus active (intervention) humidification [23], kinetic (intervention) versus conventional (control) bed therapy [24], and open (control) versus closed (intervention) methods of tracheal suction [25].
- The control and intervention groups from studies of various methods of VAP prevention using topically applied oral care regimens including the use of anti-septics [26] and also tooth-brushing [27] were sourced from two systematic reviews [26, 27].
- The control and intervention groups from studies of VAP prevention using an SDD regimen were sourced from the systematic review by Liberati *et al*. [10]
- For these last two categories, the studies were further stratified into studies for which the control group received versus did not receive topical applications of placebo.

Data extraction

The primary outcome is the *S. aureus*-IP. *S. aureus*-IP and likewise *P aeruginosa*-IP are the proportion of *S. aureus* and *P aeruginosa*, respectively among the VAP isolates

for each group. These calculations allows for patients with multiple isolates. The VAP-IP, is the incidence proportion of ventilator associated pneumonia per 100 patients. All data, including whether the mode of VAP diagnosis required bronchoscopic sampling versus tracheal sampling, and the proportion of admissions to the ICU that were for trauma, were abstracted directly from the original publication. The designation of trauma ICU here was determined by whether >50% of patients in the study were admitted for trauma.

Statistical analysis

The *S. aureus*-IP data were logit transformed for analysis as follows; with the number of VAP isolates as the denominator (D), the number of *S. aureus* isolates as the numerator (N), and R being the *S. aureus*-IP proportion (N/D), the logit(*S. aureus*-IP) is log(N/(D-N)) and its variance is 1/(D*R*(1-R)) [28]. Using these pre-calculated logits and logit variances, group specific 95% confidence intervals, summary logits and the associated summary 95% CI's were generated using the 'metan' command in STATA (release 12.0, STATA Corp., College Station, TX, USA) [29-31]. On the logit scale the 95% confidence intervals for a proportion are symmetrical and remain within the interval of 0 to 100%.

For each category of component group the logit mean *S. aureus* –IP and associated 95% confidence interval were calculated. These were then back-transformed to the percentage scale. The mean *S. aureus* –IP of the groups from the observational studies is the benchmark. To create a caterpillar plot, for each category of component group the studies were ranked in order of increasing *S. aureus*-IP. Random effects methods were used to derive standard errors (SE) and tau^2, which are measures of within and between group variances, respectively [30].

P aeruginosa-IP and VAP-IP data were likewise logit transformed for analysis and generation of caterpillar plots.

Generalized estimating equation methods (GEE) modelling

Comparisons of the *S. aureus* –IP for intervention and control groups was more problematic as the independence of the data is not a tenable assumption given the potential transmission of patient colonization within multiple groups derived from the same study. Hence, GEE methods were used [32] to accommodate any intra-cluster correlation using the 'xtgee' command in STATA (release 12.0, STATA Corp., College Station, TX, USA). In this analysis, the predictor variables were the component group membership being either membership of a group from an observational study; a control group or; an intervention group; type of intervention under study; the use or non-use of topical placebo within the AS or SDD studies; admission to a trauma ICU; study publication originating from a member state of the European Union as at 2010 or Switzerland or Norway, year of publication centred at 1995, number of patients per group > 75 versus <75, groups for which <90% of patients received >24 hours of MV and, whether the mode of diagnosis of VAP required bronchoscopic sampling [33]. The GEE analysis was undertaken with an exchangeable covariance structure applied and as a sensitivity test, an independence structure was applied.

Results.

Of the 149 studies sourced from the ten systematic reviews [5, 6, 10, 21-27], either *S. aureus*-IP or *P aeruginosa*-IP data was available for 96 studies and both were available for 91 studies. There were 37 observational studies (supplementary file Table S1), 27 studies of five non-antibiotic methods of VAP prevention (supplementary file Table S2), 10 studies of topical anti-septic methods (supplementary file Table S3) and 22 studies of SDD (supplementary file Table S4) (Table 1). Seven studies either had a second control group or a second intervention group. One study was a sub-group analysis of trauma patients from a larger study. Two studies each had two control groups which either did or did not receive topical placebo. Most studies were published in the 1990's.

In those studies that used a topical placebo, this was typically applied four times daily with the duration of application being for as many days as for the intervention agent (supplementary file Table S3 & S4). The mode of VAP diagnosis was based on bronchoscopic sampling for 36 studies, 65 studies were published from a member country of the European Union (EU) and 20 studies were undertaken in trauma ICU's. These proportions were similar for the SDD studies versus the other studies except that 21 of 22 SDD studies were published from EU countries versus 45 of the remaining 74 studies ($p = 0.006$; Chi-square, degrees of freedom =1). One SDD study was unique in that all control group patients routinely received four days of cefotaxime intravenously.

The mean VAP-IP derived from the observational studies is 23% (95% CI 20 to 27) (Table 1). The mean VAP-IP derived from the control groups of SDD studies that did versus did not receive topical placebo, is 39 (95% CI 23 to 44) versus 32% (95% CI 29 to 51), respectively. The VAP incidence more commonly exceeded 30% among control groups of SDD studies (13 of 24) versus control groups of studies of other methods of VAP prevention (8 of 39) and observational studies (10 of 37; chi-square = 6.877, d.f. =2;

p = 0.032) (Fig S1-S4). Strikingly, among the SDD studies in which topical placebo was used the difference between the mean VAP-IP in the control groups and the VAP-IP benchmark was 13 percentage points whereas the difference between the mean VAP-IP in the intervention groups and the VAP-IP benchmark was only 3 percentage points.

S aureus-IP

The mean *S aureus*-IP derived from observational studies (the *S aureus*-IP benchmark) is 22% (95% CI 19 to 25; SE 0.08, tau^2 0·13) (Figure 1). The 95% prediction interval in association with the *S aureus*-IP benchmark is 12 to 37. Replicate derivations of the mean *S aureus*-IP using various sub-groups of observational studies as identified within Table 1 were all within four percentage points of the *S aureus*-IP benchmark (Table 1).

The distribution profile of *S aureus*-IP for all component groups are shown in the caterpillar plots (Fig 1-4). Caterpillar plots which display the *P aeruginosa*-IP distributions among the various observational and component groups are in the supplementary data file (Fig S5-S8). Among the studies of SDD, there is a rightward shift in the distributions of *S aureus*-IP among the control groups that received topical placebo (Figure 3) and also the SDD intervention groups (Fig 4) in comparison to the *S aureus*-IP benchmark. No such shift was apparent within the *P aeruginosa*-IP caterpillar plots (Fig S5-S8).

The mean *S aureus*-IP derived from the control groups that did versus did not receive topical placebo is higher (33; 95% CI 24 to 41 versus 20; 95% CI 15 to 26; Table 1). The *S aureus*-IP's for 14 of the 17 intervention groups of SDD studies exceeded 22% versus only 11 of the 30 other intervention groups (Figures 2 and 4).

GEE models

The following were significant positive predictors of *S aureus*-IP; membership of an SDD intervention group from either type of SDD study; membership of a control group of an SDD study that had used topical placebo and, being in a trauma ICU (table 3). Memberships of other types of component group, mode of diagnosis, origin from an EU country, year of publication, group size and having fewer than 90% of patients in the group receiving > 24 hours of MV were not significantly predictive. The coefficients for trauma in the GEE model equate to a difference of ~6 percentage points in *S aureus*-IP between groups from trauma versus non-trauma ICU's.

Repeating the GEE model with the following variations to the base model did not change the overall findings; use of a GEE model with independence structure rather than an exchangeable structure, modelling proportion of trauma admissions as a continuous rather than categorical variable (data not shown). Repeating the analysis using logistic regression also did not change the overall findings (data not shown).

In a similar GEE analysis of *P aeruginosa*-IP (data not shown), membership of a trauma ICU was a significant negative influence (coeffficient -0.61; -0.89 - -0.32; $p<0.001$) whereas membership of either a control (-0.01; -0.47 - +0.44; $p=0.96$) or intervention group (-0.147; -0.81 - +0.47; $p=0.60$) of an SDD study in which topical placebo was being used were not significantly influential.

Discussion.

The use of placebos to achieve concealment of group allocation minimizes observer bias in controlled trials and is a generally accepted marker of higher quality in study design. This is particularly important for study end points which lack diagnostic criteria that are objective and unambiguous, such as VAP [33]. The effects of placebo interventions are difficult to study but recent systematic reviews of over 100 studies in which placebo use was compared against no treatments have revealed that these effects are less influential than previously thought [34, 35]. However, a crucial assumption is that the placebo has no context specific effect on the study end point of interest. This assumption has been tested here through a calibration of *S aureus*-IP in the various component groups of interest against an external benchmark together with similar calibrations of *P aeruginosa*-IP and VAP-IP.

The analyses here have revealed discrepancies in *S aureus*-IP as well as VAP-IP but not *P aeruginosa*-IP amongst the control groups of the broader evidence base of various VAP prevention methods relevant to this patient group in comparison to external benchmarks derived from observational studies. The *S aureus*-IP and VAP-IP are higher for control groups that received topical placebos within studies of SDD versus other control groups in this evidence base. These discrepancies in *S aureus*-IP would likely contribute toward the profound and paradoxical discrepancies among the VAP incidence within the SDD evidence base (Table 1) as noted previously [17] which as yet remain unexplained.

The higher *S aureus*-IP amongst the intervention groups of studies of SDD likely reflects the increase in staphylococcal colonization associated with its use whereas there was no such increase where topical anti-septics were the intervention agent (Figures 3 &

4). There are three observations here which implicate a profound, perfidious and context specific effect of topical placebo on *S aureus*-IP within the SDD evidence base.

As a group level predictor of *S aureus*-IP, apart from membership of an SDD intervention group, membership of a control group of an SDD study that used topical placebo paste was the strongest group level predictor in the GEE model.

Second, the effect was specific for *S aureus*-IP in that there was no effect of topical placebo on *Pseudomonas aeruginosa* as a proportion of VAP isolates (*P aeruginosa*-IP) within the control groups of the SDD evidence base (figure S7 & [18]). Indeed, the magnitude of the insignificant negative influence of SDD on *P aeruginosa*-IP within SDD intervention groups was less than the magnitude of the significant positive influence of topical placebo on *S aureus*-IP in the control groups receiving topical placebo within the studies of SDD.

Finally, the use of topical placebo within studies of topical anti-septic agents was without significant effect on *S aureus*-IP.

This analysis was specifically limited to studies identified in ten published systematic reviews and to the use of those studies exclusively. A new literature search was not undertaken. This narrowed focus allows scrutiny of component groups constituent within an entire evidence base. The largest trial of selective decontamination [20] was unable to be included here as it was not included in the relevant systematic review and in any case did not report VAP incidence, *S aureus*-IP or *P aeruginosa*-IP data but only reported colonization as a secondary end point. This study [20] is of note in that the cluster randomized cross over trial design used was in an attempt to minimize the influence of cross colonization between the component groups. Interestingly, this study [20] itself experienced complex ecological effects [36].

An important consideration here is whether the independence of observations within each ICU is a tenable assumption; this is unlikely given the transmissibility of colonization within this ICU patient group. GEE, a computationally intensive method, was used as this allows a population averaged summation under less restrictive assumptions regarding the underlying population distributions and data independence [32]. Another strength of this analysis is that the *S aureus*-IP benchmark derived here (22%), as with the *P aeruginosa*-IP benchmark derived previously [18], is stable to derivation from variously sourced observational groups (Table 2). Moreover, the *S aureus*-IP benchmark is within 2 percentage points of that reported in large French (20·4%) [8], US (23·7%) [7], Canadian (20·3%) [37], and literature derived (20·4%) [3] multi-center databases.

There are several limitations of this analysis. Only 91 of the 149 studies in the evidence base had *S aureus*-IP data available. However, the apparent reduction in VAP-IP seen among the SDD studies as included here is similar to that seen in the systematic reviews from which these studies had been sourced [5, 6, 10, 21-27]. The relative risk reduction (Risk ratio; RR or odds ratio; OR) in VAP incidence with SDD is 0.28 (0.20-0.38) among the studies overall [10] which is broadly similar to the differences in mean VAP incidence among the studies summarized here (Table 1). Likewise the reduction in VAP incidence seen with oral anti-septics (RR 0.61; 0.45-0.82) [26], tooth brushing (RR 0.77; 03.50-1.21) [27], closed tracheal suction (RR 0.88; 0.70-1.12) [25], kinetic bed therapy (OR 0.38; 0.28-0.53) [24], passive humidification (RR 0.85; 0.62-1.16) [23], sub-glottic secretion drainage (RR 0.55; 0.46-0.66) [22], and various types of stress ulcer prophylaxis (OR 0.62; 0.36-1.07) [21] as seen in the systematic reviews from which these studies had been sourced are broadly similar to the differences in mean VAP incidence among the studies summarized here (Table 1).

This analysis is observational and is conducted at a group level rather than a patient level. It was not possible to study the impact of unmeasured and unknown patient level risk factors for *S aureus*-IP. However, it is unlikely that such unidentified patient level risk factors would be able to account for the discrepancies noted here. Such a putative patient level risk factor would need to be a stronger risk factor for *S aureus*-IP than for example trauma (Table 3, [38]) and consistently so across all the studies and yet also be profoundly unevenly distributed, predominating in the groups of the SDD studies that had used topical placebo versus other groups within the broader evidence base examined here.

The possible influence of unpublished studies remains to be considered. However, previous testing for possible publication bias among the entire SDD evidence base indicated that >400 studies with control groups with VAP incidence <47% would need to have been unpublished or to have been otherwise 'missing' to be able to normalize the negatively skewed distribution in VAP incidences among the control groups of the SDD studies [16, 17].

It is likely that in-apparent outbreaks occurred within these studies [39]. Genotyping studies of ICU bacterial isolates reveal inapparent cross colonization and infection with *S. aureus* occurs even in non-outbreak settings and patients receiving mechanical ventilation are at higher risk [40-42]. Indeed others have reported that the discontinuation of SDD was useful in the control of an ICU outbreak of methicillin-resistant *S aureus* [15].

The mechanism for the profound effect of topical placebo on *S aureus*-IP identified here can be postulated as follows. Firstly, in the intervention group, SDD directly affects colonization pressure with gram positive bacteria such as *S. aureus* [12-15]. This increase in *S. aureus* colonization is reflected in the higher *S. aureus*-IP among SDD intervention groups. This increase in colonization pressure increases the risk for cross-infection in an ICU [40-41]. Second, the application of placebo paste in the control groups, and also the

SDD paste in the intervention groups, each typically four times daily in these studies, could have been vehicles for inapparent cross colonization and infection both to and from the patients in each study leading to a contextual effect of placebo within studies of SDD. Finally, the influence of lack of observer blinding contributing to the higher VAP incidence among those studies not using topical placebo, both among the studies of SDD as also studies of anti-septics, needs to be considered.

Conclusion

The use of topical placebo paste within studies of SDD is associated with higher *S. aureus*- associated VAP and higher VAP incidence. The SDD evidence base requires re-appraisal to consider the potential for this perfidious effect of topical placebo to accentuate the contextual effect of SDD and inflate its apparent 'effectiveness'.

Abbreviations;

GEE, Generalized estimating equations; ICU, Intensive Care Unit; MV, Mechanical Ventilation ; *S aureus*-IP, *Staphylococcus aureus* isolate proportion; *P aeruginosa*-IP *Pseudomonas aeruginosa* isolate proportion; SDD, Selective Digestive Decontamination; VAP, Ventilator associated pneumonia; VAP-IP, Ventilator associated pneumonia isolate proportion;

Competing interests

The author declares that he has no competing interests.

Author contributions

As sole author, JH produced the design of the study, performed the statistical analysis and wrote the manuscript. JH read and approved the final manuscript. I acknowledge the helpful comments of an anonymous referee who suggested the analysis leading to figure 4.

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Figure legends.

Figure 1. Caterpillar plot of the group specific (small diamonds) *S aureus*-IP and 95 % CI of observational (benchmark) groups together with the summary *S aureus*-IP (vertical line), 95 % CI (large open diamond) and 95 % prediction interval (horizontal line). The logit values equivalent to percentage values of 3%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, and 80% are -3.5, -2.9, -2.2, -1.4, -0.85, -0.41, 0.0, 0.41, 0.85, and 1.4 respectively. 'Tr' adjacent to author name indicates studies in trauma ICU's. Studies are listed in Table S1. Note that the x axis is a logit scale.

Figure 2. Caterpillar plots of the group specific (small diamonds) and summary (large open diamond, broken vertical line) *S aureus*-IP and 95 % CI of control (bottom) and intervention (top) groups of studies of VAP prevention using non-antibiotic methods. For comparison, the summary *S aureus*-IP (vertical line) derived from the benchmark groups from figure 1 are shown. 'Tr' adjacent to author name indicates studies in trauma ICU's. Studies are listed in Table S2. Note that the x axis is a logit scale.

Figure 3. Caterpillar plots of the group specific (small diamonds) and summary (large open diamond, broken vertical line) *S aureus*-IP and 95 % CI of control groups of studies of VAP prevention using anti-septic (AS) methods and SDD for which the control groups did not or did receive topical placebo. For comparison, the summary *S aureus*-IP (vertical line) derived from the benchmark groups from figure 1 are shown. 'Tr' adjacent to author name indicates studies in trauma ICU's. "CC', 'SC' and 'NC' adjacent to author name indicate untreated concurrent, saline control treated and non-concurrent control groups from the same study, respectively. One control group (Ferrer* [S82]) routinely received 4 days iv cefotaxime. Studies are listed in Tables S3 and S4. Note that the x axis is a logit scale.

Figure 4. Caterpillar plots of the group specific (small diamonds) and summary (large open diamond, broken vertical line) *S aureus*-IP and 95 % CI of intervention groups of studies of VAP prevention using anti-septic (AS) methods and SDD for which the control groups did not or did receive topical placebo. For comparison, the summary *S aureus*-IP (vertical line) derived from the benchmark groups from figure 1 are shown. 'Tr' adjacent to author name indicates studies in trauma ICU's. Studies are listed in Tables S3 and S4. Note that the x axis is a logit scale.

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542 **Table 1. Characteristics of studies** [a]

	Observational studies	Groups of interventional studies of VAP prevention				
		Non-antibiotic	Topical antiseptic		SDD	
			Topical placebo not used	Topical placebo used	Topical placebo not used	Topical placebo used
Study characteristics						
Sources [ref]	Table S1 [5, 6]	Table S2 [21-25]	Table S3 [26, 27]		Table S4 [10]	
Number of studies	37	27	4	7	10	12
Study origin from an EU country [b]	20	16	3	5	10	11
Bronchoscopic sampling [c]	14	11	2	2	3	4
Trauma ICU's [d]	5	4	1	1	4	5
Numbers of control groups for which <90% of patients received >24 hours of MV	4	3	0	1	1	0
Study publication year (range)	1989-2007	1989-2010	2000-2012	2005-2009	1989-2007	1992-2001

543

544

545 **Table 1. Characteristics of studies (continued)**

546

	Observational studies	Groups of interventional studies of VAP prevention				
		Non-antibiotic	Topical antiseptic		SDD	
			Topical placebo not used	Topical placebo used	Topical placebo not used	Topical placebo used
Group characteristics						
Numbers of patients per study group; median (IQR) [e]	270 (175 – 514)	80 (50 – 184)	52 31-146	114 52-347	49 (41 – 88)	48 (31 – 75)
Numbers of VAP isolates per group; median (IQR) [e]	69 (41 – 101)	22 (14 – 46)	21 18-24	20 12-74	25 (18 – 32)	28 (13 – 36)
VAP incidence per 100 patients; mean; 95% CI (number of groups)						
Cohort	23%; 20–27%(37) [f]	NA	NA	NA	NA	NA
Control	NA	19%; 16-24% (27) [g]	29%; 13-52% (4) [h]	19% 14-25% (7) [h]	32%; 23-44% (12) [h]	39%; 29 - 51%(12) [h]
Intervention	NA	16%; 13-21% (22) [g]	25%; 7 - 18 (2) [i]	11%; 8-14% (8) [i]	13% 9-17% (8) [i]	20% 15 - 26% (9) [i]

547

548

549 **Table 1. Characteristics of studies (continued)**

550

	Observational studies	Groups of interventional studies of VAP prevention				
		Non-antibiotic	Topical antiseptic		SDD	
			Topical placebo not used	Topical placebo used	Topical placebo not used	Topical placebo used
VAP microbiology per 100 isolates; mean; 95% CI (number of groups)						
• *Staphylococcus aureus*						
Cohort	22%; 19–25% (36) [j, k]	NA	NA	NA	NA	NA
Control	NA	24%; 22-27% (26) [l]	28%; 17-43% (4) [m]	19% 12-29% (7) [m]	20%; 15-25% (12) [m]	32%; 24 – 41%(10) [m]
Intervention	NA	23%; 19-27% (21) [l]	18%; 7 - 38 (2) [n]	17%; 9-30% (8) [n]	37% 24-53% (8) [n]	44% 32 – 57% (9) [n]
• *Pseudomonas aeruginosa*						
Cohort	23%; 20–26% (36) [o]	NA	NA	NA	NA	NA
Control	NA	21%; 17-27% (26) [p]	19%; 9-34% (3) [q]	14% 7-25% (6) [q]	17%; 13-23% (11) [q]	23%; 17 - 30%(10) [q]
Intervention	NA	27%; 20-35% (22) [p]	23%; 11 - 43 (2) [r]	17%; 9-30% (7) [r]	20% 11-33% (7) [r]	17% 10 - 27% (7) [r]

551

Footnotes to table 1

a. Abbreviations; ICU, Intensive care unit; MV; EU, European Union; Mechanical ventilation; NA not applicable

b. Originating from a member state of the EU as at 2010 or Switzerland or Norway

c. Bronchoscopic versus tracheal sampling for VAP diagnosis.

d. Trauma ICU defined as an ICU with >50% of patient admissions for trauma

e. Data is median and inter-quartile range (IQR)

f. As derived in Figure S1

g. As derived in Figure S2

h. As derived in Figure S3

i. As derived in Figure S4

j. As derived in Figure 1

k. The mean S aureus-IP as separately derived using the following types of observational groups was as follows; 22% (using only studies cited in Safdar et al, 2005[5]); 22% (using only studies cited in Melsen et al, 2009 [6]); 22% (using only studies cited from European centers); 22% (using studies only cited in from Non-European centers); 26% (using only studies from Trauma ICU's).

l. As derived in Figure 2

m. As derived in Figure 3

n. As derived in Figure 4

o. As derived in Figure S5

p. As derived in Figure S6

q. As derived in Figure S7

r. As derived in Figure S8

578 **Table 2: Logit *S aureus*-IP; GEE models** [a]
579

Factor	Component group	Coefficient [b]	95% CI	p
Groups from observational studies (reference group)		-1·42	-1·77 to -1·08	<0·001
Non-antibiotic studies	control	+0·07	-0·21 to +0·36	0·61
Non-antibiotic studies	intervention	+0·06	-0·27 to +0·39	0·70
AS studies; placebo not used	control	+0·09	-0·68 to +0·86	0·83
AS studies; placebo not used	intervention	-0·08	-1·25 to +1·09	0·68
AS studies; placebo used	control	+0·12	-0·43 to +0·66	0·67
AS studies; placebo used	intervention	-0·01	-0·58 to +0·57	0·99
SDD studies; placebo not used	control	-0·21	-0·64 to +0·22	0·34
SDD studies; placebo not used	intervention	+0·61	+0·09 to +1·13	0·02
SDD studies; placebo used [c]	control	+0·45	+0·03 to +0·86	0·03
SDD studies; placebo used	intervention	+0·88	+0·42 to +1·33	<0·001
Mode of diagnosis [d]		+0·12	-0·10 to +0·35	0·28
Trauma ICU [e]		+0·33	+0·09 to +0·58	0·008
EU origin [f]		+0·03	-0·20 to +0·27	0·78
Year of study publication [g]		-0·004	-0·02 to +0·02	0·72
Group size [h]		+0·05	-0·23 to +0·32	0·74
<90% MV [i]		+0·02	-0·31 to +0·35	0·90

580 Footnotes

581 a. Abbreviations; GEE; generalized estimating equations; ICU, Intensive care unit; MV;
582 Mechanical ventilation

583 b. Interpretation. For each model the reference group is the observational study (benchmark)
584 groups and this coefficient equals the difference in logits from 0 (a logit equal to 0 equates
585 to a proportion of 50%; a logit equal to -1.26 equates to a proportion of 22.1%) and the
586 other coefficients represent the difference in logits for groups positive for that factor versus
587 the reference group.

588 c. Repeating the analysis with omission of one SDD study for which all control group
589 patients routinely received four days of cefotaxime resulted in an increase in this
590 coefficient to 0.49; 0.08 – 0.91, p=0.02.

591 d. Diagnosis of VAP using bronchoscopic versus tracheal based sampling

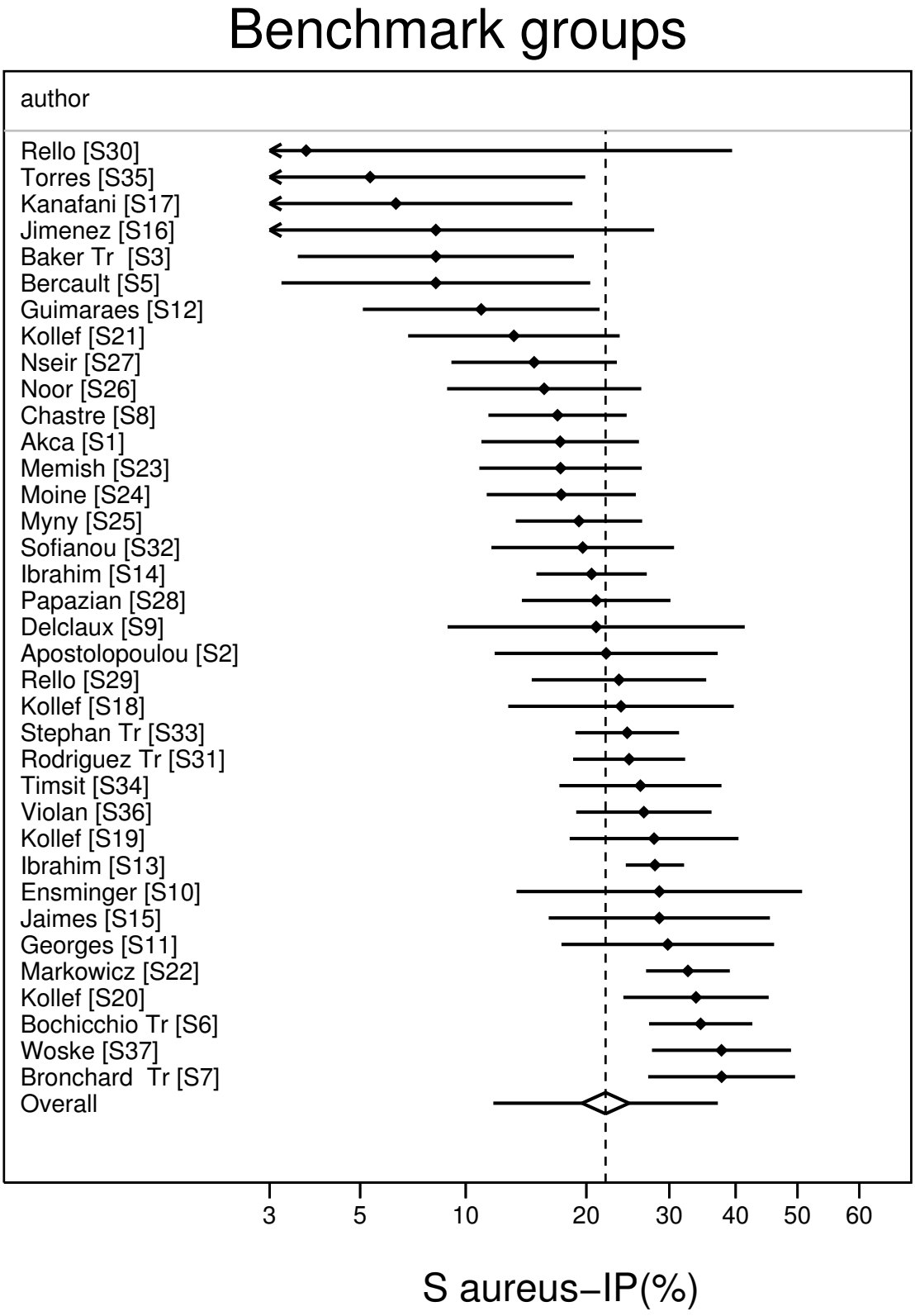
592 e. Trauma ICU arbitrarily defined as an ICU for which >50% of admissions were for trauma

593 f. Originating from a member state of the European Union as at 2010 or Switzerland
594 or Norway

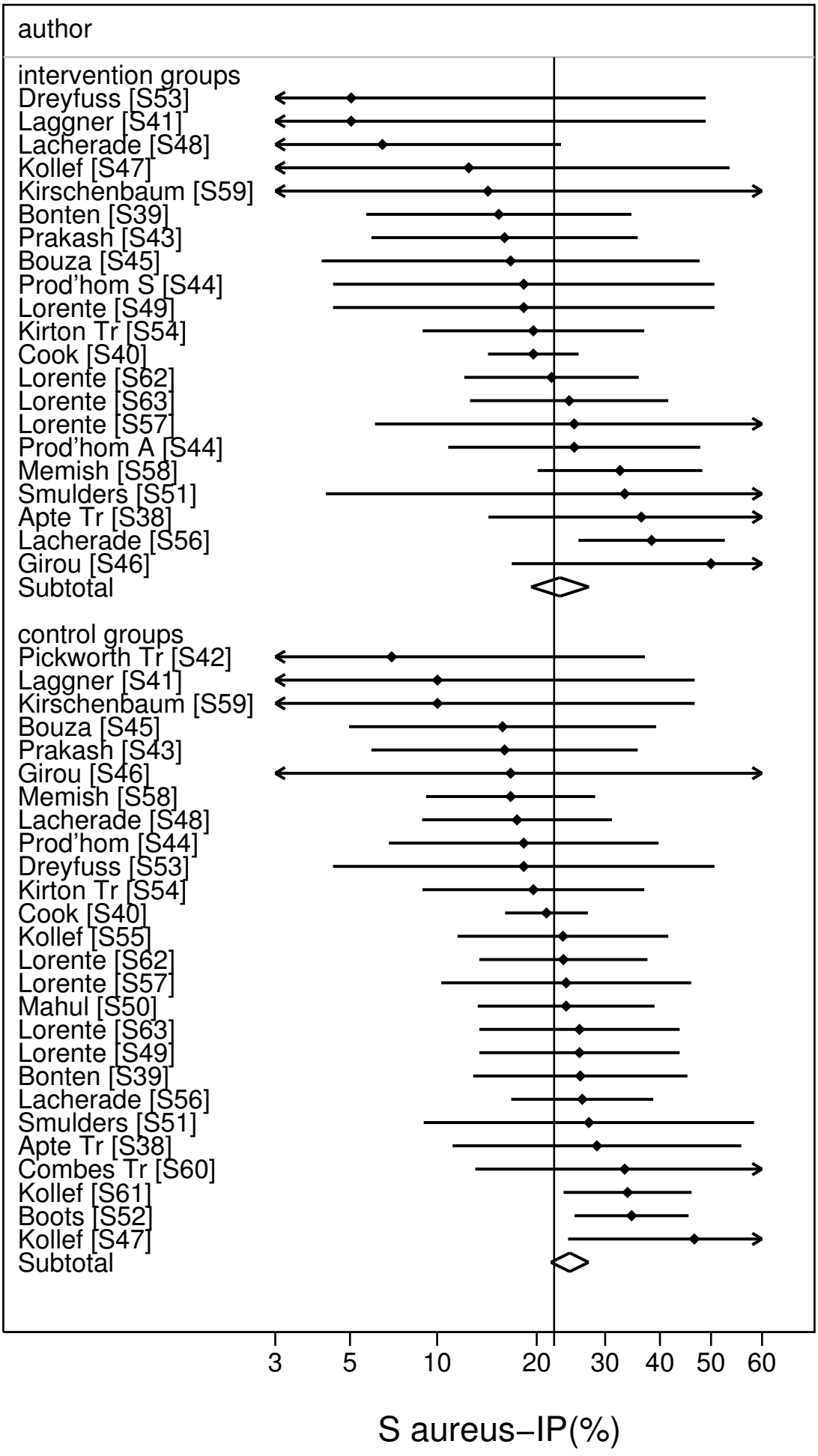
595 g. Per year, with year of publication centred at 1995

596 h. Categorical with number of patients per group > 75 versus <75.

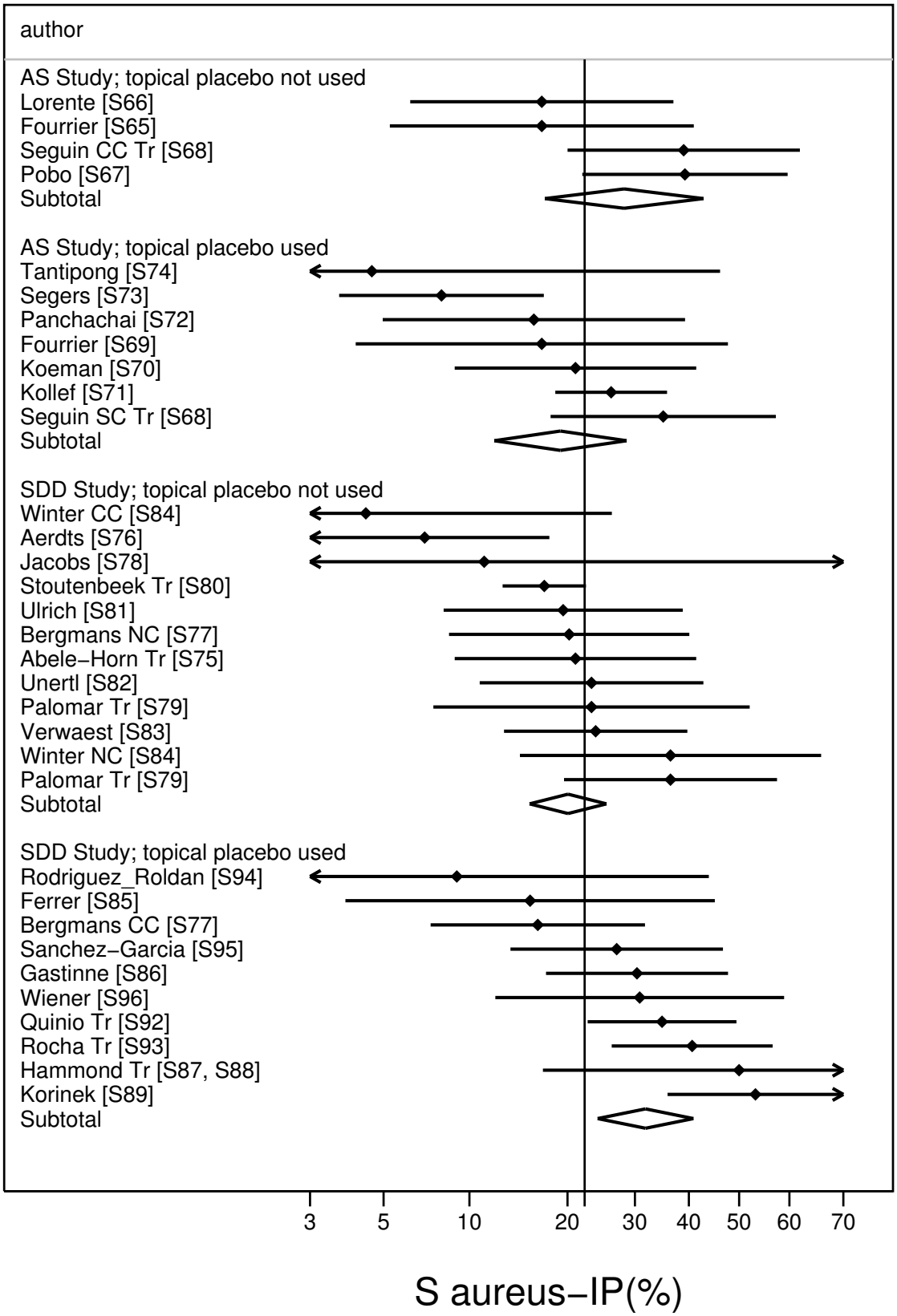
597 i. Groups for which <90% of patients received >24 hours of MV



Non–antibiotic studies



Control groups of AS and SDD studies



Intervention groups of AS and SDD studies