The Perfidious Effect of Topical Placebo: Calibration of Staphylococcus aureus Ventilator-Associated Pneumonia Incidence within Selective Digestive Decontamination Studies versus the Broader Evidence Base

James C. Hurley
Rural Health Academic Centre, Melbourne Medical School, University of Melbourne, Ballarat Health Services, and Infection Control Commissions, St John of God Hospital and Ballarat Health Services, Ballarat, Victoria, Australia

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 10 systematic reviews. S. aureus as a proportion of VAP isolates (S. aureus IP) among component groups was calibrated versus that among 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% confidence interval [CI], 19 to 25) for 37 observational groups versus 32% (24 to 41) and 20% (15 to 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, in 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 pernicious; it could contribute to the higher VAP incidence and inflate the apparent "effectiveness" of SDD. The SDD evidence base requires reappraisal.

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 oropharynx (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 than a benchmark of VAP incidence proportion (VAP-IP) derived from observational studies and also versus control groups of studies of other strategies of VAP prevention using antimicrobial 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 10 percentage points of the VAP incidence benchmark (17). Finally, the explanation for the profound difference in VAP incidence seen between intervention and control groups of SDD studies is unclear. Specifically, an antipseudomonal 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 nonconcurrent 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 (nonintervention) 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 achieve observer blinding through the use of topical placebo.

MATERIALS AND METHODS

Overview. This is a group-level analysis of the S. aureus isolate proportion (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, 15).
The objectives here are as follows: (i) to derive a benchmark of *S. aureus* IP from groups from the observational studies, (ii) 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, (iii) using generalized estimating equation (GEE) methods, to calibrate the impact of membership of control groups receiving versus not receiving topical placebo within the SDD studies versus other group-level factors as explanatory variables for 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 and (iv) 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 intensive care unit (ICU) patients included in 1 of 10 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. (16) were applied to achieve harmonization across data sources from all 10 reviews. Studies published prior to 1984 were also excluded since those study types do not appear in the review of Liberati et al. (16).

Component group designations. The component groups were classified into the following categories.

1. Baseline group was a group from observational (i.e., observational) studies of VAP incidence as listed in two systematic reviews (5, 6).
2. The control and intervention groups from studies of various antibiotic trials 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 routine (control) of subglottic secretion drainage (22), passive (control) versus active (intervention) humidification (23, 24), systemic intervention versus control (24, 25) or open (control) versus closed (intervention) methods of tracheal suction (25).
3. The control and intervention groups from studies of various methods of VAP prevention using topically applied oral care regimen including the use of antibiotics (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. (16).

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, *P. aeruginosa* IP, and likewise *P. aeruginosa* IP are the proportions of *S. aureus* IP and *P. aeruginosa* IP in each group. These calculations allow 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 log 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 [logit*IP*] = log(N/D) - log(N) and its variance is [1/D + 1/R] - 1/R (28). Using these precalculated logit and log variances, group-specific 95% confidence intervals, summary logit, and associated summary 95% confidence intervals (CIs) were generated using the "meta2" command in the software program STATA (release 12.1, Stata Corp., College Station, TX, USA) (28–31). 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 intervals 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 squared, which are measures of within- and between-group variances, respectively (30).

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

GEE modeling. Comparisons of the *S. aureus* IP for intervention and control groups was more problematic, since 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, generalized estimating equation (GEE) methods were used (32) to accommodate any intraclass correlation using the "geeglm" command in STATA (release 12.1, 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, the type of intervention under study, the use or nonuse of topical placebo in the AS or SDD studies; admission to a trauma ICU; study publication originating with a member state of the European Union as of 2010 or Switzerland or Norway, year of publication centered at 1995, number of patients per group of >75 versus <75, groups for which <50% of patients received >24 h of IV, 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 249 studies sourced from the 10 systematic reviews (5, 6, 10, 21–27), either *S. aureus* IP or *P. aeruginosa* IP data were available for 96 studies, and both were available for 91 studies. There were 37 observational studies (see Table S1 in the supplemental material), 27 studies of five antibiotic trials of VAP prevention (see Table S2), 10 studies of topical antibiotic methods (see Table S3), and 22 studies of SDD (see Table S4) (Table 1). Seven studies had either a second control group or a second intervention group. One study was a subgroup 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 1990s.

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 (see Tables S3 and S4 in the supplemental material). The mode of VAP diagnosis was based on bronchoscopic sampling for all studies, 65 studies were published from a member country of the European Union (EU), and 20 studies were undertaken in trauma ICUs. 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 [df] = 1). One SDD study was unique in that all control group patients routinely received 4 days of cefotaxime intravenously.

The mean VAP-IP derived from the observational studies was 33% (95% CI, 20 to 27) (Table 1). The mean VAP-IP derived from the control groups of SDD studies that did or did not receive
<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Observational studies</th>
<th>Topical amoxicillin used</th>
<th>Topical placebo not used</th>
<th>SDD</th>
<th>Topical placebo not used</th>
<th>Topical placebo used</th>
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<td>No. of studies</td>
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<td>Table S2 (21:23)</td>
<td>Table S3 (26:27)</td>
<td>Table S4 (11:19)</td>
<td>Table S5 (10)</td>
<td></td>
</tr>
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<td>Total</td>
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<td>25</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>12</td>
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<tr>
<td>With origin in an EU country</td>
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<td>16</td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>11</td>
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<tr>
<td>With bronchoscope sampling</td>
<td>14</td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>In the ICU*</td>
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<td>1</td>
<td>2</td>
<td>3</td>
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<td>No. of control groups for which &lt;90% of patients received &gt;23 h of MV</td>
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<td>3</td>
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<table>
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<th>SDD</th>
<th>Topical placebo not used</th>
<th>Topical placebo used</th>
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<td>180 (155–204)</td>
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<td>No. of VAP episodes per group, median (IQR)</td>
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<td>22 (11–46)</td>
<td>21 (12–21)</td>
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<tr>
<td>VAP incidence per 100 patients, mean (95% CI (%))</td>
<td>35.2 (32.9–37.6)</td>
<td>31.4 (30.6–32.2)</td>
<td>32.5 (31.6–33.3)</td>
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<td>8.1–17.3 (25.8)</td>
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<tr>
<td>No. of patients per ICU setting, mean (95% CI (%))</td>
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<td>31.4 (30.6–32.2)</td>
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<tr>
<td>Intervention</td>
<td>16.3–27.3 (36.9)</td>
<td>7.2–17.3 (25.8)</td>
<td>8.1–17.3 (25.8)</td>
<td>10.3–17.3 (25.8)</td>
<td>10.3–17.3 (25.8)</td>
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</tbody>
</table>

* Abbreviations: ICU, intensive care unit; MV, mechanical ventilation; EU, European Union; NA, not applicable
* Bronchoscopy versusotracheal sampling for VAP diagnosis
* VAP incidence derived from observational studies

Other studies cited: Moulton et al. 2009, 26% (using only studies from European centers); 22% (using studies only from non-European centers) and 26% using only studies from trauma ICUs.
* As derived in Fig. 3. * As derived in Fig. 5. * As derived in Fig. 7.
* As derived in Fig. 5.
* As derived in Figs. 3 and 4.
* As derived in Fig. 5.
* As derived in Fig. 5.
* As derived in Fig. 3.
* In no. of groups

Topical placebo is 39 (95% CI, 23 to 44) or 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 SDD groups (4 of 39) and observational studies (10 of 37; chi square = 6.877; df = 2; P = 0.032) (see Table S1 to S4 in the supplemental material). 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; standard error [SE], 0.08; 95% confidence interval [CI], 0.13) (Fig. 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 subgroups of observational studies as identified within Table 1 were all within four percentage points of the S. aureus IP benchmark (Table 1).

The distribution profiles of S. aureus IP for all component groups are shown in the caterpillar plots (Fig. 1 to 4). Caterpillar plots which display the P. aeruginosa IP distributions among the
Benchmark groups

Non-antibiotic studies

![Diagram showing benchmark groups and non-antibiotic studies](image)

**FIG 1.** Caterpillar plots 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%, 50%, 70%, 50%, 60%, 70%, and 80% are −2.4, −1.4, −0.53, −0.41, 0.0, 0.04, 0.085, and 1.4, respectively. "Tr" adjacent to an author name indicates studies in trauma ICUs. Studies are listed in Table S1 in the supplemental material. Note that the x-axis is a log scale.

![Diagram showing non-antibiotic studies](image)

**FIG 2.** Caterpillar plots of the group-specific (small diamonds) and summary (large open diamond) S. aureus IP and 95% CI (control) and intervention (top) groups of studies of VAP prevention using nonantibiotic methods. For comparison, the summary S. aureus IP (vertical line) derived from the benchmark groups from Fig. 1 are shown. "Tr" adjacent to an author name indicates studies in trauma ICUs. Studies are listed in Table S2 in the supplemental material. Note that the x-axis is a log scale.

Various observational and component groups are in the supplemental material (see S3 to 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 (Fig. 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 (see S5 to S8).

The mean S. aureus IP derived from the control groups that did versus did not receive topical placebo is higher (3.3 [95% CI, 2.4 to 4.1] versus 2.0 [95% CI, 1.3 to 2.6] (Table 1). The S. aureus IP for 14 of the 17 intervention groups of SDD studies exceeded 229%, versus only 11 of the 30 other intervention groups (Fig. 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 2). Members of other types of component group, mode of diagnosis, origin in an EU country, year of publication, group size, and having fewer than 90% of patients in the group receiving ≥24 h 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 and nontrauma ICUs.

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 and modeling the 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 (GEE coefficient, −0.71; 95% confidence interval, −0.89 to −0.52; P < 0.001), whereas membership of either control (−0.61; −0.47 to −0.42; P = 0.06) or intervention (−0.14; −0.13 to −0.05; P = 0.009) group of an SDD study in which topical placebo was being used were not significantly influential.
DISCUSSION

The use of placebo to achieve concealment of group allocation minimizes observer bias in controlled trials and is generally accepted as a high-quality study design. This is particularly important for study endpoints 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 more than 100 studies in which placebo was compared against no treatment 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 endpoint 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 among 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 placebo within studies of SDD versus other control groups in this evidence base. These discrepancies in S. aureus IP would likely contribute to the profound and paradoxical discrepancies among VAP incidences within the SDD evidence base (Table 1), as noted previously (17), which as yet remain unexplained.

The higher S. aureus IP among 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 antiseptics were the intervention agent (Fig. 3 and 4). There are three observations here which implicate a profound, pernicious, 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...
TABLE 2 Logit S aureus IP, GEE models

<table>
<thead>
<tr>
<th>Factor</th>
<th>Component group</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>P value</th>
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<tr>
<td>studies (reference group)</td>
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*Abbreviations: GEE, generalized estimating equation; ICU, intensive care unit; MV, mechanical ventilation; VAP, ventilator-associated pneumonia.

**Interpretation:** For each variable, the reference group consists of the observational study (benchmark) groups, and the coefficient equals the difference in logit (log-odds) equal to one dose relative to one proportion of 28% (a large odds ratio of 1.28 relative to a proportion of 22.1%). and the other coefficients represent the difference in logit that grows positively for the factor versus the reference group.

- Repeat the analysis with exclusion of one SDD study for which all control-group patients routinely received 4 days of colistin instead of an increase in the coefficient to 0.49 (0.38 to 0.60); P = 0.02

**Diagnosis of VAP using bronchoscopic versus tracheal-based sampling:**

- Alternative testing for VAP included BAL and tracheal aspirate for tracheal-based sampling.

**Originating with a member state of the European Union (EU):**


- Per year, with year at publication corrected to 1993.

- Groups for which 96% of patients received ≥44 h of MV.

- Groups for which <30% of patients received ≥44 h of MV.

The 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 (see Fig. S7 in the supplemental material) (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 antiseptic agents was without significant effect on S. aureus IP.

This analysis was specifically limited to studies identified in 10 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 as questions within an entire evidence base. The largest trial of selective decontamination (20) was unable to be included here since it was not included in the relevant systematic review and any case did not report VAP incidence, S. aureus IP, or P. aeruginosa IP data but reported colonization only as a secondary endpoint. This study (20) is of note in that the cluster randomized crossover 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 because this allowed 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), U.S. (23.7%) (7), Canadian (20.3%) (37), and literature-derived (20.4%) (3) multicenter 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 (RR) or odds ratio (OR) in VAP incidence with SDD is 0.28 (OR) (0.20 to 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 antiseptics (RR, 0.44; 0.45 to 0.56) (26), tooth brushing (RR, 0.75; 0.50 to 1.11) (27), closed tracheal suction (RR, 0.88: 0.70 to 1.21) (25), and mechanical ventilation (OR, 0.38: 0.28 to
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0.53) (24), passive humidification (RR, 0.85; 0.62 to 1.16) (23), subglottic secretion drainage (RR, 0.55; 0.46 to 0.66) (22), and various types of stress ulcer prophylaxis (OR, 0.62; 0.36 to 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 2) (18) and consistently so across all the studies and yet also be profoundly unevenly distributed, predominating in the groups of 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 a VAP incidence of <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 inapparent outbreaks occurred within these studies (39). Genotypic studies of ICU bacterial isolates reveal that inapparent cross-colonization and infection with S. aureus occur even in nonoutbreak 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. First, in the intervention group, SDD directly affects colonization pressure with Gram-positive bacteria such as S. aureus (12–13). 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 control 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 and also studies of antiseptics, needs to be considered.

Conclusion. The use of topical placebo paste within studies of SDD is associated with higher S. aureus-associated VAP and a higher VAP incidence. The SDD evidence base requires reappraisal to consider the potential for this pernicious effect of topical placebo to accentuate the contextual effect of SDD and inflate its apparent "effectiveness." 3

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