Structural equation modelling the 'control of gut overgrowth' in the prevention of ICU acquired Gram-negative infection.

James C Hurley (jamesh@bhs.org.au)

Research

Keywords: Bacteremia, Acinetobacter, Pseudomonas, Antibiotic prophylaxis, Study design, Intensive care, Mechanical ventilation, Selective Digestive Decontamination, Polymyxin generalized structural equation model

Posted Date: January 27th, 2020

DOI: https://doi.org/10.21203/rs.2.21941/v1

Abstract

Background: Conceptually, the 'control of gut overgrowth' (COGO), including 'abnormal Gram-negative bacilli' (AGNB), is key to the mediation of infection prevention by Selective Digestive Decontamination (SDD). However, the relative importance of the SDD components; topical (TAP), enteral (EAP) and protocolized parenteral antibiotic prophylaxis (PPAP), versus other methods of infection prevention and versus other contextual exposures cannot be resolved within individual studies.

Methods: Generalized structural equation models (GSEM) based on COGO concepts were confronted with data derived from >200 infection prevention studies reporting incidences of overall, Pseudomonas and Acinetobacter bacteremia as well as ventilator associated pneumonia (VAP) data including the following group level exposures; TAP, EAP and PPAP use versus antiseptic versus non-decontamination mode of infection prevention; proportion receiving mechanical ventilation (MV); trauma ICU; mean length of ICU stay and concurrency versus non-concurrency of TAP study control groups.

Results: In GSEM modelling of Pseudomonas and Acinetobacter gut overgrowth (GO) as latent variables, anti-septic interventions had the strongest negative effect against Pseudomonas GO but no intervention was significantly negative against Acinetobacter GO. Strikingly, PPAP and concurrency each have positive effects in the model, EAP is neutral and Acinetobacter bacteremia incidences are high within TAP studies, moreso with PPAP exposure. Paradoxically, TAP (moreso with PPAP) appears to provide the strongest summary prevention effects against bacteremia and VAP overall.

Conclusions: GSEM modelling of published data provides novel insights into the COGO concept and the complex and profoundly paradoxical relationships between various interventions, concurrency and other exposures in relation to infection with AGNB.

Introduction

Of three broad categories of infection prevention in the ICU patient group, Selective oral decontamination / selective digestive decontamination (SOD/SDD) shows superior apparent benefit toward overall infection prevention within the ICU context versus anti-septic based and non-decontamination-based prevention methods [1–9].

The control of gut overgrowth (COGO) is one mechanism to explain how SOD/SDD regimens might prevent ICU acquired infection. SOD/SDD antibiotics such as topical polymyxin and aminoglycosides target 'abnormal Gram-negative bacilli' (AGNB) including Pseudomonas and Acinetobacter bacteria whereas anti-septic and non-decontamination-based prevention methods do not [10].

After > 200 studies among patients requiring prolonged mechanical ventilation (MV) or ICU stay, the exact mechanism for how each method prevents ICU acquired infection, the basis for the apparent superiority of SDD/SOD and even the optimal locus for decontamination, the gut or elsewhere, remains unclear [11]. Specifically, the relative importance of the SDD components; topical (TAP), enteral (EAP) and protocolized parenteral antibiotic prophylaxis (PPAP; as with EAP not contained within SOD regimens) versus other methods of infection prevention, and versus other contextual exposures such as length of stay and being in a trauma ICU context remain unclear. Moreover, concurrency, being the concurrent mixing of study and control patients within the ICU, as typically occurs

with random allocation of patient exposures, is believed to influence the results of SOD/SDD studies versus studies without concurrency (i.e. concurrent versus Non-concurrent control; CC versus NCC) [10, 12].

The objectives here are threefold. Firstly, to recapitulate the evidence for overall ventilator associated pneumonia (VAP) and bacteraemia prevention among the three broad categories of infection prevention for which Pseudomonas and Acinetobacter infection data is available. Second, to develop and confront models based on COGO concepts using Pseudomonas and Acinetobacter infection data from these studies as well as studies without an intervention using GSEM modelling. Thirdly, to compare the relative impacts of the various group level exposures and interventions within the optimal GSEM model.

Materials And Methods

Being an analysis of published work, ethics committee review of this study was not required.

Study Selection And Decant Of Groups

The literature search and study decant used here (Fig S1; see Electronic Supplementary Material for additional ESM tables, ESM figures, and ESM references) is in six steps is described in full in the ESM and as described previously [13].

Of note, studies undertaken in the context of an ICU outbreak [14–16] were excluded. Due to the absence of eligible studies of TAP undertaken in Asia and Central and South America, together with the significant worldwide variation in Acinetobacter associated VAP [17], studies from these regions were excluded from this analysis. A snowballing search strategy [18] using the ‘Related articles’ function within Google Scholar was undertaken for additional studies not identified within systematic reviews.

All eligible studies were then collated, and any duplicate studies were removed and streamed into groups of patients from studies with or without an infection prevention interventions. Those studies without an intervention provide the observational groups.

The component groups were decanted from each study as either observational, control or intervention groups. Within studies of TAP any group receiving TAP in any formulation was regarded as an intervention group and all other groups were regarded as a control group regardless of other interventions. The control groups from studies of TAP were stratified into NCC and CC groups.

Outcomes Of Interest

The incidences of overall, Pseudomonas and Acinetobacter VAP as well as the incidences of overall, Pseudomonas and Acinetobacter bacteremia were extracted. These were each expressed as a proportion using the number of patients with prolonged (> 24 hours) stay in the ICU as the denominator. Pseudomonas and Acinetobacter gut overgrowth are latent variables which are defined within the GSEM models (see below).

Exposures Of Interest

The following were also extracted where available; the proportion of each group receiving MV, the proportion of admissions for trauma, and the mean length of ICU stay (LOS). An anti-septic exposure included agents such as

chlorhexidine, povidone-iodine and iseganan. These were included whether the application was to the oropharynx, by tooth-brushing or by bodywash.

TAP is defined here as the application of topical antibiotic (TA) prophylaxis to the oropharynx without regard to the specific TA constituents nor to concomitant EAP, being the enteral applications of TA, or PPAP. Note that SOD generally consists of only TAP whereas SDD typically involves TAP together with both EAP and PPAP. A control group of an SDD/SOD study was classified as a CC control if the group was concurrent within the same ICU at the same time as the intervention group receiving TAP.

Visual Benchmarking

Scatter plots of the overall and Pseudomonas and Acinetobacter VAP and bacteremia incidence data were generated to facilitate a visual survey. A benchmark for each was generated from the groups of the observational studies using the 'metan' command as described in the ESM. The caterpillar plots illustrating the derivation of each bacteremia benchmark is shown in the supplementary material.

Structural Equation Modelling

Seven GSEM models were developed using Pseudomonas and Acinetobacter gut overgrowth (GO) as the central latent variables. Group exposure or not to the following binary factors served as indicator variables toward these two latent variables; non-decontamination based prevention methods, anti-septic based prevention methods, TAP based prevention methods, membership of a CC control group within a TAP intervention study, whether the majority of the group were trauma patients, whether more than 90% of patients of the group received more than 24 hours of MV, and whether the mean (or median) length of ICU stay for the group was seven days or more.

The VAP and bacteremia count data for each of Pseudomonas and Acinetobacter using the number of observed patients as the denominator served as the measurement component for the latent variables using a logit link function in each GSEM. In each model, the observations were clustered by a study identifier in order to generate a robust variance covariance matrix of the parameters of the coefficient estimates. The various exogenous variables were entered into each model without any preselection step and the model with the lowest Akaike's information criterion (AIC) score was selected as having parsimony and optimal fit using the 'GSEM' command in Stata [19].

Availability Of Data And Materials

All data generated or analysed during this study are included in this published article and its supplementary information files (see ESM).

Results

Characteristics of the studies

Of the 214 studies identified by the search, 130 were sourced from 23 systematic reviews. Others were found during previous searches or by snowball sampling [18] (Fig S1) Most studies were published between 1990 and 2010 and most had a mean ICU-LOS exceeding seven days. A minority originated from either North American or trauma ICU's. Twenty-one studies had either no control group or more than one control or intervention group. The majority of groups from studies of infection prevention interventions had less than 150 patients per group versus more than 150 patients in the observational studies.

Among the various types of TAP regimen, either topical polymyxin or a topical aminoglycoside or both was contained in every regimen except two. PPAP, being a cephalosporin in every case except two, was used within eight control and 29 intervention groups of TAP studies. Among TAP intervention groups, 23 used TAP alone (i.e SOD) and 29 used TAP, EAP and PPAP in combination (i.e SDD).

Overall Infection Prevention Effect

The summary effect sizes for the three categories of interventions against overall bacteremia and also against overall VAP incidence are presented as forest plots (Fig. S1-S2. The TAP based interventions provided greater apparent protection against VAP versus the two other intervention categories (Table 1). Of note, the TAP studies which did (i.e. SDD) versus did not (i.e. SOD) include PPAP within the intervention demonstrated greater protection against both overall bacteremia and overall VAP (Table 1).

GSEM Modelling

Seven GSEM models of the relationship between various group level exposures on Pseudomonas and Acinetobacter GO as latent variables were evaluated for fit and parsimony (see Table 2; Fig S8 – S14). The optimal model (model 6) is shown (Fig. 1). In developing the GSEM model, exposure to PPAP and non-decontamination interventions on Pseudomonas and Acinetobacter GO were both associated with weak coefficients and these pathways were dropped from model 2 onwards. EAP was not a significant factor and its introduction failed to improve the model fit (model 7, Fig S14).

A mean length LOS ≥ 7 days was strongly correlated with both Pseudomonas GO (+ 0.97; 0.53 to 1.45) and Acinetobacter GO (+ 0.98; 0.41 to 1.54). Exposure to anti-septic interventions was associated with a stronger negative coefficient (-0.93; -1.46 to -0.46) than was exposure to TAP (-0.57; -0.91 to -0.29) towards Pseudomonas GO but neither was significant towards Acinetobacter GO. Membership of a control group concurrent to a TAP intervention group was associated with a significant positive coefficient (+ 0.56; 0.08 to 1.10) towards Pseudomonas GO. PPAP use was a strong positive correlate of Pseudomonas bacteremia (+ 0.95; 0.27 to 1.61).

Vap And Bacteremia Count Data

The Pseudomonas and Acinetobacter VAP and bacteremia infection data is presented as percentages (Fig. 2) and as tallied counts (Tables 3 & 4). There were a small number of very large studies with either a mean LOS < 7 days, less than 90% of patients receiving prolonged MV or without VAP data. Hence, the tallied counts limited to studies with mean length of stay ≥ 7 days is also shown (Tables 3 & 4).

Whether as percentages or counts, the incidences of infection were generally higher among the control and intervention groups of TAP studies with respect to both Pseudomonas and Acinetobacter with one exception (Fig. 2). The Pseudomonas VAP among TAP intervention groups were mostly below the Pseudomonas VAP benchmark as was the Pseudomonas VAP tally among groups with LOS < 7 days excluded (p = 0.05; Table 3)

Of note, among the TAP intervention groups, the Acinetobacter bacteremia tally among groups also exposed to PPAP (12/6609; 0.18%) was higher versus the tally among those exposed to TAP alone (3/6681; 0.04%; p = 0.02, Fisher's exact test). Likewise for Pseudomonas bacteremia among the TAP intervention groups after excluding those groups with LOS < 7 days (Table 4), there was a marginally higher count among groups also exposed to

PPAP (53/5908; 0.9%) versus the tally among those exposed to TAP alone (41/6623; 0.62%; p = 0.07, Fisher's exact test).

Discussion

Generally accepted risk factors towards the acquisition of AGNB in the ICU include LOS > 7 days, exposure to invasive devices such as MV, and exposure to antibiotics together with acquisition by cross infection within the ICU environment [10]. The COGO concepts are used as a framework in which to evaluate these risk factors versus other group level exposures within a GSEM model. This framework enables the component groups of studies of the various infection prevention methods to be considered as a natural experiment with various group wide exposures among a large number of ICU populations in the literature. This enables a novel perspective on the COGO concept that would not be possible within any one study or systematic review examined in isolation [20].

The data used here to confront the COGO model is drawn mostly from studies located in systematic reviews. In this regard, the summary effect sizes here for each of the three broad categories of TAP, anti-septic and non-decontamination methods, against both overall VAP and against overall bacteremia are similar to prior published estimates [1–10]. TAP (moreso when in combination with PPAP [21]) appears to be have the strongest prevention effect as previously noted.

In confronting the COGO model with the Pseudomonas and Acinetobacter infection data, the COGO model is robust with several factors remaining consistent over the evolution through seven versions of the GSEM. There are several expected observations. Length of stay and admission to a trauma ICU are strong positive factors and non-decontamination interventions appear not to mediate significant effects on either Pseudomonas GO or Acinetobacter GO. TAP exposure is associated with a negative coefficient towards Pseudomonas GO, albeit weaker than that associated with anti-septic interventions. This association with TAP exposure is consistent with the generally lower Pseudomonas VAP among the intervention groups of these studies.

On the other hand, the various components of the SOD/SDD regimens, TAP, EAP and PPAP have mixed effects. Neither TAP nor EAP have negative coefficient towards Acinetobacter GO. This is surprising as in nearly all instances these contain polymyxin and or an aminoglycoside. PPAP is associated with a strong positive correlation with Pseudomonas bacteremia.

Finally, patient groups exposed to the full SDD regimen (i.e. TAP, EAP and PPAP) have Pseudomonas and Acinetobacter bacteremia incidences that are either higher or else not lower than patient groups receiving TAP alone. This is possibly not paradoxical as antibiotics used for PPAP typically lack activity against Pseudomonas and Acinetobacter and the cumulative days of exposure to antibiotics without activity against Pseudomonas is a risk factor for acquiring P aeruginosa and Acinetobacter in the ICU [22–24]. Moreover, concomitant systemic antibiotic therapy (CSAT) fails to prevent the acquisition of respiratory tract colonization with Gram negative bacteria [25] and more than triples the risk of subsequent infection among ICU patients receiving an enteral decolonization regimen with gentamicin against KPC-producing Klebsiella pneumonia [26] and CRE producing Acinetobacter [27].

The exact relationship between gut colonization, PPAP use and subsequent bacteremia remains controversial amid conflicting reports that this may or may not be important for some Gram negative bacteremias versus others [28–31]. In studying the relative prevention effects of SDD versus SOD each versus standard care in the prevention

of gram-negative bacteremias (i.e. not limited to Pseudomonas bacteremia), the majority of bacteremias occur after 4 days in the ICU (the typical duration of PPAP) and indeed the daily risk peaks after day 30 [11, 30]. Moreover, among patients receiving SDD or SOD, Pseudomonas accounts for one third of GN bacteremia episodes with most episodes not preceded by enteral colonization.

Defining the separate effects of EAP, TAP and PPAP is difficult as these are variably confounded with each other as constituent of different SDD regimens in different studies. Also, the duration of application of the regimens varied among the studies. In this regard, a non-significant increase in hospital acquired infections post discharge from the ICU as great as 50% was noted in a small SDD sub-study [32].

Limitations.

There are four key limitations to this analysis, the first being that this analysis is a group level modelling of two latent variables, Pseudomonas GO and Acinetobacter GO, within the COGO construct. These latent variables and the coefficients derived in the GSEM are indicative and intended for internal reference only. They have no counterpart at the level of any one patient or study and cannot be directly measured. There was no ability nor purpose to adjust for the underlying patient level risk. There was considerable heterogeneity in the interventions, populations, and study designs among the studies here as the inclusion criteria for the various studies have been intentionally broadly specified. In this regard, a strength of the analysis is that the heterogeneity among the studies here generally resembles that expected among ICU populations to which these interventions might be targeted.

The second limitation is that the analysis is inherently observational. Only a limited number of key group level factors were entered into the GSEM models. Moreover, the GSEM modelling is deliberately simplistic with exposures entered as only binary variables and no use of interaction terms. In reality, the relationships between expoures and outcomes will likely be complex and expoure interactions could have great importance.

Thirdly, the analysis is likely underpowered to examine the Acinetobacter infection data, being such a rare end point.

Fourthly, only those studies for which Pseudomonas and Acinetobacter infection data were available were able to be included in this analysis. However, the effect of the interventions on overall VAP and bacteremia incidences (Figure S2-S7) resembles that in the broader literature.

Finally, it should be noted that the various interventions among the studies here targeted a range of sites which may or may not have included the oropharynx and gastrointestinal tract. In this regard, it is surprising that the TAP and EAP interventions, which most directly targeted the oropharynx and gastrointestinal tract had weaker effects than did anti-septic interventions several of which, such as chlorhexidine body washes, target other sites.

Can the paradoxical findings of the GSEM model be reconciled with the apparent summary effects of TAP versus overall VAP and bacteremia? TAP exposure and control group concurrency have associations with Pseudomonas GO that are similar in size but contrary in direction. In this regard, the incidence of overall VAP and bacteremia among the concurrent control groups within studies of SDD/SOD are as much as ten percentage points higher than control groups within studies of equivalent ICU populations. This higher VAP incidence can partly be accounted for by incidences of VAP with Acinetobacter [33], Pseudomonas [34] and Staphlococcus aureus [35] being each 3 to 5 percentage points higher among CC (but not NCC) control groups and each up to 2 percentage points higher for intervention groups.

Likewise, the higher bacteremia incidence can partly be accounted for incidences of bacteremia with specific bacteria being each 1 to 4 percentage points higher among CC (but not NCC) control groups and up to 3 percentage points higher for intervention groups for Acinetobacter (Fig. 2), Pseudomonas (Fig. 2) [36], Staphlococcus aureus [37], Enterococci [38] and coagulase negative Staphlococci [39].

In each case, the increased incidence within control groups of CC design studies of topical antibiotics remains apparent in meta-regression models adjusting for other recognized associations. The influence of topical placebo use, concurrent colonization with Candida and other influences is yet to be considered in this process [40–42].

Conclusion

TAP based decontamination regimens appear superior versus other methods at reducing incidences of overall VAP and bacteremia infections among ICU patients. GSEM modelling of Pseudomonas and Acinetobacter GO as latent variables demonstrates complex relationships with group level exposures which would not be apparent in any study examined in isolation nor within a summary effect of randomized studies. Paradoxically, Acinetobacter bacteremia incidences are unusually high among studies of TAP. Moreover, in TAP exposed groups, the additional exposure to PPAP is associated with higher Acinetobacter bacteremia incidences and PPAP is a strongly positive factor towards Pseudomonas bacteremia in the GSEM model.

Abbreviations

AGNB = abnormal Gram-negative bacilli

COGO = control of gut overgrowth

EAP = enteral antibiotic prophylaxis

GO = gut overgrowth

GSEM = Generalized structural equation models

ICU = Intensive Care Unit;

MV = Mechanical Ventilation;

NCC = non-concurrent control;

CC = concurrent control;

SOD/SDD = Selective Digestive Decontamination / Selective Digestive Decontamination;

TAP = topical antibiotic prophylaxis

Declarations

- Ethics approval and consent to participate:

Being an analysis of published work, ethics committee review of this study was not required.

- Consent for publication:

Not applicable

- Availability of data and material:

The datasets analysed during the current study are provided in the online appendix

- Competing interests:

The author declares that he has no competing interests.

- Funding:

This research has been supported by the Australian Government Department of Health and Ageing through the Rural Clinical Training and Support (RCTS) program.

- Authors' 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 and is the guarantor of the paper.

References

1. 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 (Review). Cochrane Database Syst Rev 2009; (4):CD000022.
2. Pileggi C, Bianco A, Flotta D, Nobile CG, Pavia M: Prevention of ventilator-associated pneumonia, mortality and all intensive care unit acquired infections by topically applied antimicrobial or antiseptic agents: a meta-analysis of randomized controlled trials in intensive care units. Crit Care. 2011;15: R155.
3. Silvestri L, Van Saene HK, Casarin A, Berlot G, Gullo A: Impact of selective decontamination of the digestive tract on carriage and infection due to Gram-negative and Gram-positive bacteria: a systematic review of randomised controlled trials. Anaesthesia Intensive Care. 2008;36(3):324-38.
4. Hurley JC: Prophylaxis with enteral antibiotics in ventilated patients: Selective decontamination or selective cross-infection? Antimicrob Agents Chemother. 1995;39:941–947.
5. Silvestri L, Van Saene HK, Milanese M, Gregori D, Gullo A: Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients. Systematic review of randomized, controlled trials. J Hosp Infect. 2007;65(3):187-203.
6. Silvestri L, Weir WI, Gregori D, Taylor N, Zandstra DF, van Saene JJ, van Saene HK. Impact of Oral Chlorhexidine on Bloodstream Infection in Critically Ill Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Cardiothoracic Vasc Anesthesia. 2017;31(6):2236-44.
7. Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI: Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. Lancet Infect Dis. 2011;11:845-854.
8. Klompas M, Speck K, Howell MD, Greene LR, Berenholtz SM. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis.

JAMA Intern Med. 2014;174(5):751-61.

9. Alhazzani W, Smith O, Muscedere J, Medd J, Cook D: Toothbrushing for Critically Ill Mechanically Ventilated Patients: A Systematic Review and Meta-Analysis of Randomized Trials Evaluating Ventilator-Associated Pneumonia. Crit Care Med. 2013;41:646-655
10. Silvestri L, Miguel A, van Saene HK. Selective decontamination of the digestive tract: the mechanism of action is control of gut overgrowth. Intensive Care Med. 2012;38(11):1738-50.
11. Frencken JF, Wittekamp BH, Plantinga NL, Spitoni C, van de Groep K, Cremer OL, Bonten MJ. Associations Between Enteral Colonization With Gram-Negative Bacteria and Intensive Care Unit–Acquired Infections and Colonization of the Respiratory Tract. *Clin Infect Dis.* 2017;66(4):497-503.
12. Hurley JC: Profound effect of study design factors on ventilator-associated pneumonia incidence of prevention studies: benchmarking the literature experience. J Antimicrob Chemother. 2008;61:1154–1161.
13. Hurley JC. Is selective decontamination (SDD/SOD) safe in the ICU context? J Antimicrob Chemother. 2019;74(5):1167-72.
14. Agusti C, Pujol M, Argerich MJ, Ayats J, Badia M, Dominguez MA, Corbella X, Ariza J: Short-term effect of the application of selective decontamination of the digestive tract on different body site reservoir ICU patients colonized by multi-resistant *Acinetobacter baumannii*. J Antimicrob Chemother. 2002;49(1):205-8.
15. Halaby T, al Naiemi N, Kluytmans J, van der Palen J, Vandenbroucke-Grauls CM: Emergence of colistin resistance in *Enterobacteriaceae* after the introduction of selective digestive tract decontamination in an intensive care unit. Antimicrob Agents Chemother. 2013;57:3224-3229.
16. Lübbert C, Faucheux S, Becker-Rux D, et al. Rapid emergence of secondary resistance to gentamicin and colistin following selective digestive decontamination in patients with KPC-2-producing *Klebsiella pneumoniae*: a single-centre experience. Int J Antimicrob Agents. 2013;42(6):565-70.
17. Hurley JC. World-wide variation in incidence of *Acinetobacter* associated ventilator associated pneumonia: a meta-regression. BMC Infect Dis. 2016;16(1):577.
18. Goodman LA. Snowball sampling. Ann Math Statistics. 1961:148-70.
19. Stata corporation (2109): Stata structural equation modelling reference manual, in Stata 16 documentation. College Station, TX, USA. https://www.stata.com/bookstore/structural-equation-modeling-reference-manual/. Accessed 06 January 2020.
20. Hurley JC: How the Cluster randomized trial 'works'. Clin Infect Dis. 2020;70:341–346.
21. Oostdijk EAN, Kesecioglu J, Schultz MJ, et al. Notice of Retraction and Replacement: Oostdijk et al. Effects of Decontamination of the Oropharynx and Intestinal Tract on Antibiotic Resistance in ICUs: A Randomized Clinical Trial. JAMA. 2014;312(14):1429-1437. JAMA 2017
22. Venier AG, Leroyer C, Slekovec C, Talon D, Bertrand X, Parer S, Alfandari S, Guerin JM, Megarbane B, Lawrence C, Clair B. Risk factors for *Pseudomonas aeruginosa* acquisition in intensive care units: a prospective multicentre study. *J Hosp Infect*. 2014;88(2):103-8.
23. Hoang S, Georget A, Asselineau J, Venier AG, Leroyer C, Rogues AM, Thiébaut R. Risk factors for colonization and infection by *Pseudomonas aeruginosa* in patients hospitalized in intensive care units in France. PloS one. 2018;13(3):e0193300.
24. Medina J, Formento C, Pontet J, Curbelo A, Bazet C, Gerez J, Larrañaga E. Prospective study of risk factors for ventilator-associated pneumonia caused by *Acinetobacter* J Crit Care. 2007;22(1):18-26.

25. Jongerden IP, Speelberg B, Satizábal CL, Buiting AG, Leverstein-van Hall MA, Kesecioglu J, Bonten MJ. The role of systemic antibiotics in acquiring respiratory tract colonization with gram-negative bacteria in intensive care patients: a nested cohort study. *Crit care Med*. 2015;43(4):774-80.
26. Tascini C, Sbrana F, Flammini S, Tagliaferri E, Arena F, Leonildi A, Ciullo I, Amadori F, Di Paolo A, Ripoli A, Lewis R. Oral gentamicin gut decontamination for prevention of KPC-producing Klebsiella pneumoniae infections: relevance of concomitant systemic antibiotic therapy. Antimicrob Agents Chemother. 2014;58(4):1972-6.
27. Munoz-Price LS, Rosa R, Castro JG, Laowansiri P, Latibeaudiere R, Namias N, Tarima S. Evaluating the impact of antibiotic exposures as time-dependent variables on the acquisition of carbapenem-resistant *Acinetobacter baumannii. Crit care Med*. 20152016;44(10):e949-56.
28. Boukadida J, De Montalembert M, Gaillard JL, Gobin J, Grimont F, Girault D, Véron M, Berche P. Outbreak of gut colonization by *Pseudomonas aeruginosa* in immunocompromised children undergoing total digestive decontamination: analysis by pulsed-field electrophoresis. J Clin Microbiol. 1991;29(9):2068-71.
29. Corbella X, Pujol M, Ayats J, Sendra M, Ardanuy C, Dominguez MA, Liñares J, Ariza J, Gudiol F. Relevance of digestive tract colonization in the epidemiology of nosocomial infections due to multiresistant *Acinetobacter baumannii. Clin Infect Dis*. 1996;23(2):329-34.
30. Oostdijk EA, de Smet AM, Kesecioglu J, Bonten MJ. The role of intestinal colonization with gram-negative bacteria as a source for intensive care unit-acquired bacteremia. Crit Care. M 2011;39(5):961-6.
31. Timsit JF, Garrait V, Misset B, Goldstein FW, Renaud B, Carlet J. The digestive tract is a major site for *Acinetobacter baumannii* colonization in intensive care unit patients. *J Infect Dis*. 1993;168(5):1336-7.
32. de Smet AM, Hopmans TE, Minderhoud AL, Blok HE, Gossink-Franssen A, Bernards AT, Bonten MJ. Decontamination of the digestive tract and oropharynx: hospital acquired infections after discharge from the intensive care unit. Intensive Care Med. 2009;35(9):1609.
33. Hurley JC. Paradoxical *Acinetobacter* associated Ventilator associated pneumonia incidences within prevention studies using respiratory tract applications of topical polymyxin: benchmarking the evidence base. J Hosp Infect. 2018; 100:105-113.
34. Hurley JC. Incidences of Pseudomonas aeruginosa-associated ventilator-associated pneumonia within studies of respiratory tract applications of polymyxin: testing the Stoutenbeek concurrency postulates. Antimicrob Agents Chemother. 2018;62(8):e00291-18.
35. Hurley J. Unusually high incidences of *Staphylococcus aureus* infection within studies of ventilator associated pneumonia prevention using topical antibiotics: benchmarking the evidence base. Microorganisms. 2018;6(1):2.
36. Hurley JC: Unusually high incidences of Pseudomonas bacteremias within topical polymyxin based decolonization studies of mechanically ventilated patients: benchmarking the literature. Open Forum Infect Dis. 2018:5(11); ofy256
37. Hurley JC. Concordance of Endotoxemia With Gram-Negative Bacteremia: A Meta-analysis Using Receiver Operating Characteristic Curves. Arch Pathol & Lab Med. 2000;124(8):1157-64.
38. Hurley JC. Studies of selective digestive decontamination as a natural experiment to evaluate topical antibiotic prophylaxis and cephalosporin use as population-level risk factors for enterococcal bacteraemia among ICU patients. J Antimicrob Chemother. 2019;74(10):3087-94.
39. Hurley JC. Incidence of coagulase-negative staphylococcal bacteremia among ICU patients: decontamination studies as a natural experiment. *Eur J Clin Micro Infect Dis*. 2019. doi:10.1007/s10096-019-03763-0

40. Hurley JC: ICU-acquired candidemia within selective digestive decontamination studies: a meta-analysis. Intensive Care Med. 2015;41(11):1877-85.
41. Hurley JC: Ventilator-associated pneumonia prevention methods using topical antibiotics: herd protection or herd peril? Chest. 2014;146(4):890-8.
42. Hurley JC. The perfidious effect of topical placebo: calibration of Staphylococcus aureus ventilator-associated pneumonia incidence within selective digestive decontamination studies versus the broader evidence base. Antimicrob Agents Chemother. 2013;57(9):4524-31.

Tables

Table 1. Characteristics of studies [a]

	Observational studies	Infection prevention studies		
	(no intervention)	Non-decontamination	Anti-septic	TAP ± PPAP/EAP
Study characteristics				
Sources	Table S1	Table S2	Table S3	Table S4
Number of studies	111	45	13	48
Origin from systematic review [b]	46	38	7	38
North American ICU's [c]	32	10	6	3
LOS > 7 days	88	37	9	37
MV for >48 hours for <90% [d]	21	1	5	11
Trauma ICUs [e]	22	8	2	14
PPAP use in control group [f]	0	0	1	8
Study publication year (range)	1987-2014	1987-2017	2000-2018	1984-2018
Group characteristics				
Numbers of patients per control group; (median; IQR) [g]	279 135-707	75 61-161	96 36-217	86 31-128
Prevention effect size; (odds ratio; 95% CI; number of studies)				
VAP	NA	0.73; 0.66-0.80 (45) (see Fig S2)	0.89; 0.72-1.11 (10) (see Fig S3)	0.38; 0.33-0.44 (37) (see Fig S4)

Bacteremia	NA	0.99; 0.71-1.39 (6) (see Fig S5)	0.72; 0.66-0.79 (10) (see Fig S6)	0.69; 0.62-0.76 (33) (see Fig S7)

Footnotes to table 1

1. Note, several studies had more than one control and or intervention group. Hence the number of groups does not equal the number of studies
2. Studies that were sourced from 16 systematic reviews (references in web-only supplementary)
3. Study originating from an ICU in Canada of the United States of America
4. Studies for which less than 90% of patients were reported to receive > 48 hours of MV
5. Trauma ICU arbitrarily defined as an ICU with more than 50% of admissions for trauma.
6. Use of PPAP for control group patients
7. Data is median and inter-quartile range (IQR)
8. VAP prevention effect size for studies not including versus including PPAP in the antibiotic intervention was 0.44; 0.36 – 0.55 (n = 13) and 0.34; 0.28 – 0.41 (n = 24), respectively (see Fig S4).
9. Bacteremia prevention effect size for studies not including versus including PPAP in the antibiotic intervention was 0.77; 0.68 – 0.88 (n = 10) and 0.57; 0.48 – 0.67 (n = 22), respectively (see Fig S7).

Table 2: Development of GSEM model [a]

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 7	Model 6	.
	Fig S8	Fig S9	Fig S10 Fig S8	Fig S11	Fig S12	Fig S12	Fig S13	95%CI 95% CI(955
Factor [b-j]								
b_Ps_n								
Pseudomonas GO	1	1	1	1	1	1	1	(constrained)
ppap			1.11**	0.97**	0.97**	1.00**	0.95**	0.27 to 1.61
_cons	-5.18***	-5.19***	-5.38***	-6.00***	-6.00***	-6.05***	-6.05***	-6.6 to -5.4
b_Ac_n								
Acinetobacter GO	1	1	1	1	1	1	1	(constrained)
ppap			0.6	0.46	0.48	0.44	0.47	-0.51 to 4639
_cons	-6.74***	-6.74***	-6.83***	-7.38***	-7.44***	-7.47***	-7.47***	-8.0 to -7.0
v_Ps_n								
Pseudomonas GO	0.67***	0.67***	0.71***	0.80***	0.80***	0.81***	0.81***	0.51 to 1.09
mvp90	0.55*	0.54*	0.49*	0.43	0.43	0.48*	0.49*	0.03 to 0.92
non_D	-0.37*	-0.58***	-0.61***	-0.60***	-0.60***	-0.54***	-0.54***	-0.79 to -0.31
_cons	-3.63***	-3.63***	-3.56***	-4.17***	-4.17***	-4.24***	-4.25***	-4.7 to -3.7
v_Ac_n								
Acinetobacter GO	0.73***	0.73***	0.74***	0.83***	0.83***	0.83***	0.83***	+0.66 to 1.01
mvp90	0.79*	0.79*	0.73	0.71	0.69	0.71	0.7	-0.12 to 1.55
non_D	-0.35	-0.31	-0.33	-0.27	-0.21	-0.17	-0.17	-0.56 to 0.23
_cons	-5.13***	-5.13***	-5.06***	-5.79***	-5.85***	-5.88***	-5.87***	-6.8 to -4.9
Pseudomonas								

GO								
TAP	-0.65**	-0.65**	-0.67***	-0.68***	-0.68***	-0.47*	-0.57***	-0.91 to -0.29
a_S	-1.34***	-1.33***	-1.20***	-1.01***	-1.00***	-0.94***	-0.93***	-1.46 to -0.46
eap					_	-0.21		
ppap	0.27	0.27			_			
non_D	-0.33				_	_	_	
los7				1.03***	1.03***	0.96***	0.97***	0.53 to 1.45
trauma50					0.04	0.03	0.02	-0.33 to 0.36
CC					_	0.56**	0.56**	0.08 to 1.10

Table 2: Development of GSEM model (continued) [a]

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 7	Model 6 .	
	Fig S8	Fig S9	Fig S10 Fig S8	Fig S11	Fig S12	Fig S12	Fig S13	95%CI 95% CI(955
Factor [b-j]								
Acinetobacter GO								
TAP	-0.25	-0.25	-0.27	-0.27	-0.5	-0.58	-0.43	-1.04 to 0.15
a_S	-1.26*	-1.27*	-1.21*	-1.04*	-0.85	-0.8	-0.82	-1.83 to 0.19
eap						0.25		
ppap	0.1	0.1						
non_D	0.06							
los7				1.15***	1.01***	0.99***	0.98***	0.41 to 1.54
trauma50					1.09***	1.04***	1.04***	0.47 to 1.62
CC						0.42	0.42	-0.22 to 1.22
Error terms								
var(e.Ps_GO)	1.32*	1.32*	1.17**	0.76**	0.76**	0.71**	0.72**	0.36 to 1.47
var(e.Ac_GO)	2.66***	2.66***	2.56***	1.92***	1.62***	1.60***	1.60***	1.01 to 2.48
Model fit [k]								
AIC	3345.94	3344.15	3329.29	3274.57	3261.55	3259.1	3255.53	
N	22	20	20	22	24	28	26	
Groups (n)	334	334	334	334	334	334	334	

Clusters (n)	213	213	213	213	213	213	213

Footnotes

1. Legend: * p<0.05; ** p<0.01; *** p<0.001
2. v_ps_n is the count of *Pseudomonas* VAP; v_ac_n is the count of *Acinetobacter* VAP; b_ps_n is the count of *Pseudomonas* bacteremia and b_ac_n is the count of *Acinetobacter* bacteremia
3. PPAP is the group wide use of protocolized parenteral antibiotic prophylaxis; tap is topical antibiotic prophylaxis; eap is enteral antibiotic prophylaxis
4. Acinetobacter GO is the Acinteobacter gut overgrowth latent variable
5. Pseudomonas GO is the Pseudomonas gut overgrowth latent variable
6. MVP90 is use of mechanical ventilation by more than 90% of the group
7. LOS7 is a mean or median length of ICU stay for the group of 7 days or greater
8. Trauma ICU arbitrarily defined as an ICU for which >50% of admissions were for trauma
9. CC is concurrency of control groups with an intervention group receiving TAP
10. Less than 90% of the group receiving prolonged mechanical ventilation.
11. Model fit; AIC is Akaike's information criteria. This indicates model fit taking into account the statistical goodness of fit and the number of parameters in the model. Lower values of AIC indicate a better model fit. N is the number of parameters in the model.

Table 3: VAP count data [a]

	Observational studies	Infection prevention studies		
	(no intervention)	Non-dec	Anti-septic	TAP ±PPAP
Excluding groups with LOS<7 days				
Acinetobacter				
CC or observational groups	586/37026 [b, c] 1.6% (67)	30/2620 [b] 1.1% (25)	4/780 [b] 0.5% (5)	67/1521 [b] 4.4% (25)
Intervention groups		34/2429 [c] 1.4% (24)	8/786 [c] 1.0% (5)	41/1721 [c] 2.4% (26)
Pseudomonas				
CC or observational groups	2217/60131 [d, e] 3.7% (81)	200/4288 [d] 4.7% (38)	27/914 [d] 3.0% (8)	179/2161 [d] 8.3% (34)
Intervention groups		167/4169 [e] 4.0% (37)	24/1027 [e] 2.3% (8)	106/3193 [e] 3.3% (37)

Footnotes to table 3

1. Non-dec = Non-decontamination studies; TAP = Topical antibiotic prophylaxis; PPAP = Protocolized parenteral antibiotic prophylaxis.
2. The counts of *Acinetobacter* VAP among the three categories of control groups and the category of observation groups among studies after excluding those with length of stay <7 days differed significantly ($p < 0.001$; Fisher's exact test)
3. The counts of *Acinetobacter* VAP among the three categories of intervention groups and the category of observation groups among studies after excluding those with length of stay <7 days differed significantly ($p = 0.038$; Fisher's exact test)
4. The counts of *Pseudomonas* VAP among the three categories of control groups and the category of observation groups among studies after excluding those with length of stay <7 days differed significantly ($p < 0.001$; Fisher's exact test)
5. The counts of *Pseudomonas* VAP among the three categories of intervention groups and the category of observation groups among studies after excluding those with length of stay <7 days was differed marginally ($p = 0.05$; Fisher's exact test)

Table 4: Bacteremia count data [a]

	Observational studies	Infection prevention studies		
	(no intervention)	Non-dec	Anti-septic	TAP ±PPAP
All groups				
Acinetobacter				
CC or observational groups	203/189338 0.11% (20)	1/553 0.18% (2)	17/39162 0.04% (8)	15/1860 0.8% (13)
Intervention groups		1/526 0.19% (2)	7/57009 0.01% (8)	15/13290 [b] 0.11% (18)
Pseudomonas				
CC or observational groups	567/192203 0.30% (27)	2/553 0.36% (2)	23/39162 0.06% (8)	63/5280 1.2% (16)
Intervention groups		3/526 0.57% (2)	52/59117 0.09% (9)	139/23543 0.59% (25)
Excluding groups with LOS<7 days				
Acinetobacter				
CC or observational groups	37/12913 [c, d] 0.29% (11)	0/200 [c] 0% (1)	0/308 [c] 0% (3)	14/904 [c] 1.5% (11)
Intervention groups		1/199 [d] 0.5% (1)	1/305 [d] 0.33% (3)	11/1256 [d] 0.88% (14)
Pseudomonas				
CC or observational groups	111/14453 [e, f] 0.77% (16)	0/200 [e] 0% (1)	0/308 [e] 0.0% (3)	63/5249 [e] 1.2% (15)
Intervention groups		2/199 [f]	17/2413 [f]	94/12531 [f,

		1.0% (1)	0.7% (4)	g
				0.75% (22)

Footnotes to table 4

1. Non-dec = Non-decontamination studies; TAP = Topical antibiotic prophylaxis; PPAP = Protocolized parenteral antibiotic prophylaxis.
2. Among intervention groups of TAP based prevention studies, the count of *Acinetobacter* bacteremias was 12/6609 (0.18%; 13 studies) versus 3/6681 (0.04%; 4 studies) for those using versus not including PPAP in the intervention (p = 0.02, Fisher's exact test)
3. The counts of *Acinetobacter* bacteremias among the three categories of control groups and the category of observation groups among studies after excluding those with length of stay <7 days differed significantly (p < 0.001; Fisher's exact test)
4. The counts of *Acinetobacter* bacteremias among the three categories of intervention groups and the category of observation groups among studies after excluding those with length of stay <7 days differed significantly (p = 0.012; Fisher's exact test)
5. The counts of *Pseudomonas* bacteremias among the three categories of control groups and the category of observation groups among studies after excluding those with length of stay <7 days differed significantly (p = 0.010; Fisher's exact test)
6. The counts of *Pseudomonas* bacteremias among the three categories of intervention groups and the category of observation groups among studies after excluding those with length of stay <7 days was not significantly different (p = 0.90; Fisher's exact test)
7. Among intervention groups of TAP based prevention studies excluding those with a LOS less than 7 days, the count of *Pseudomonas* bacteremias was 53/5908 (0.9%; 16 studies) versus 41/6623 (0.62%; 6 studies) for those using versus not including PPAP in the intervention (p = 0.07, Fisher's exact test)

Figures

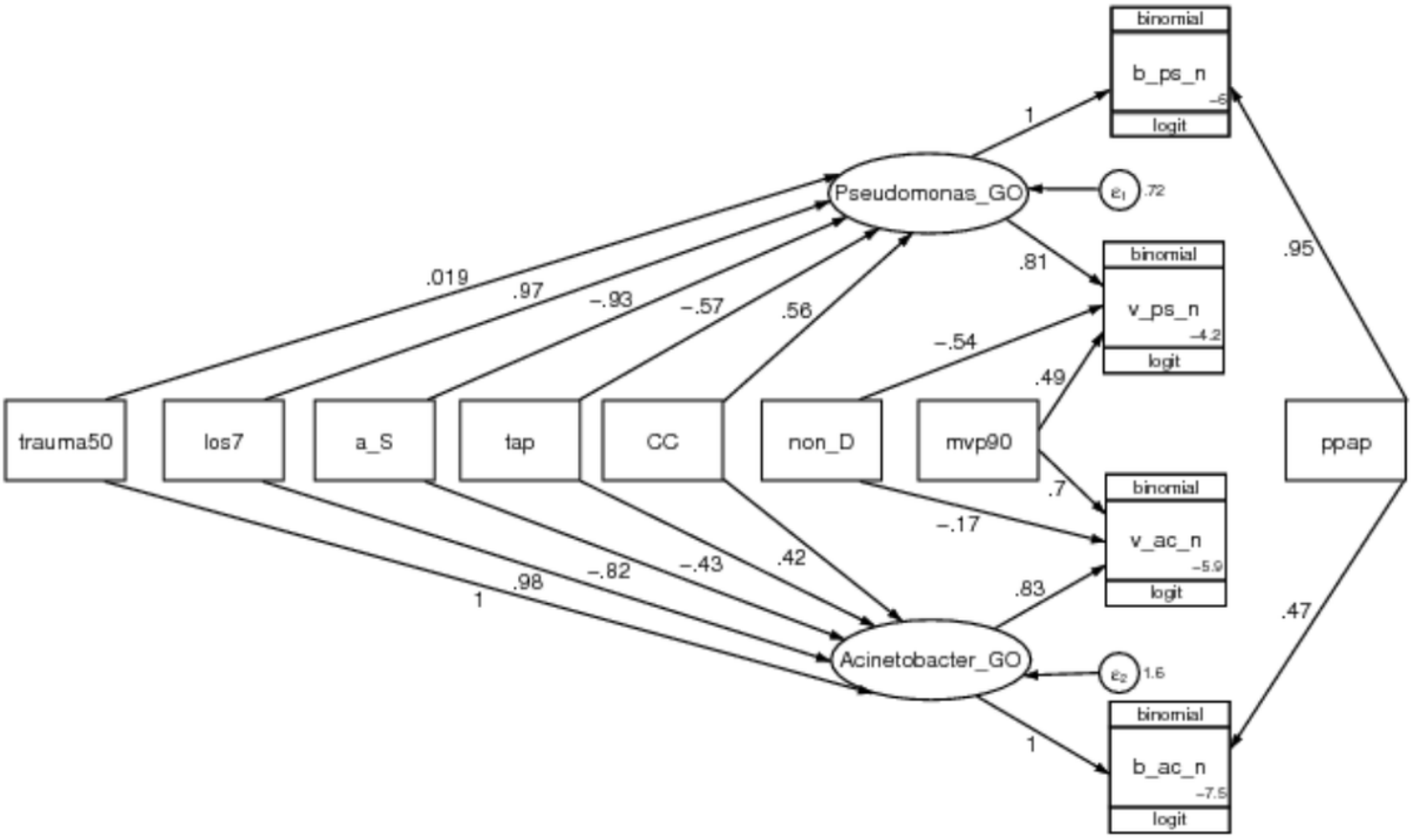

Figure 1

GSEM of the COGO model in relation to Pseudomonas and Acinetobacter infection data. Pseudomonas GO and Acinetobacter GO (ovals) are latent variables representing Pseudomonas and Acinetobacter gut overgrowth (GO), respectively. The variables in rectangles are binary predictor variables representing the group level exposure to the following; trauma ICU setting (trauma50), mean or median length of ICU stay ≥ 7 days (los7), exposure to a topical anti-septic based prevention method (a_S), exposure to a TAP based prevention method (tap), concurrency of a control group with a TAP intervention group (CC), exposure to a non-decontamination based prevention method (non-D), greater than 90% use of mechanical ventialtion (mvp90) or exposure to PPAP (ppap). The circles contain error terms. The three part boxes represent the binomial data for Pseudomonas and Acinetobacter VAP (v_ps_n, v_ac_n) and bacteremia (b_ps_n, b_ac_n) counts with the number of patients as the denominator which is logit transformed using the logit link function in the generalized model. Note that EAP use is linked to PPAP use and that EAP use when seperately entered into model 7 (ESM Fig S14) was non-significant.

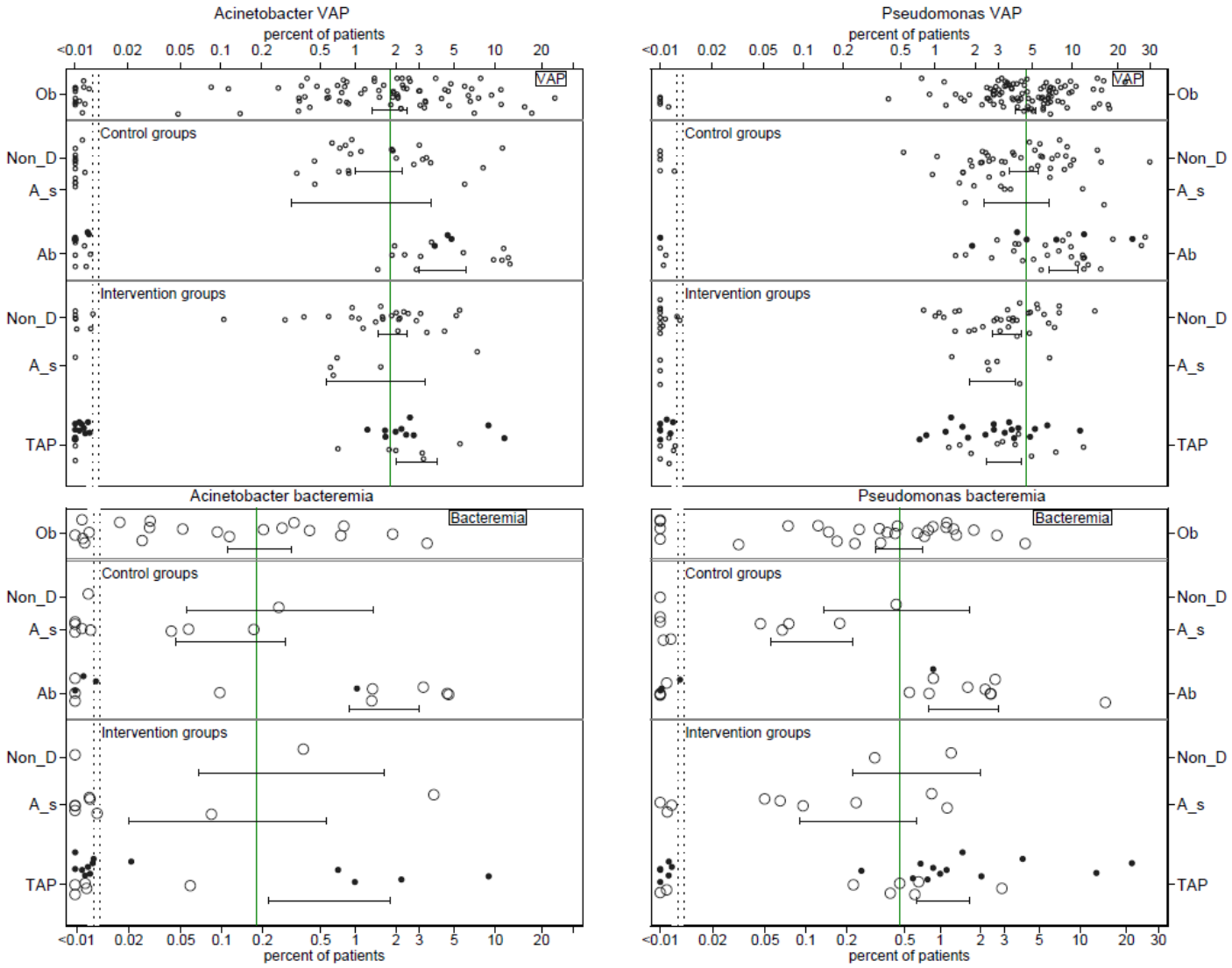

Figure 2

Scatter plots of Pseudomonas (right) and Acinetobacter (left) VAP (top) and bacteremia (bottom) incidence proportions for the component groups from all studies versus benchmarks derived from observational (Ob) groups. The control and intervention groups are stratified by studies of either non-decontamination (Non-D) methods, anti-septic (A_s) or TAP based methods. The summary mean and summary 95% confidence limits are displayed for each category. The derivation of these confidence intervals by random effects methods is displayed in the ESM for the bacteremia data. Note that the x axis is a logit scale. Groups exposed to PPAP within TAP studies are indicated as solid symbols versus not exposed (open symbols).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- onlinesupplDec2019.pdf