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Estimating the herd effects of anti-microbial-based decontamination (ABD) interventions on intensive care unit (ICU) acquired bloodstream infections: a deductive meta-analysis

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ABSTRACT

Objective To estimate the herd effects of anti-microbial-based decontamination (ABD) interventions on bloodstream infections (BSIs) among groups of intensive care unit (ICU) patients in relation to group mean length of stay (LOS). To deduce which of three competing hypotheses of ABD effect mediation best accounts for the observed effects.

Design Arms-based meta-regression of ICU-acquired BSI incidence against group mean LOS for control and interventions arms of ABD and non-ABD controlled trials each versus that in arms of observational studies.

Exposures Within controlled trials of ABD, intervention, concurrent control (CC) and non-concurrent (NCC) groups are directly, indirectly and non-exposed, respectively.

Main outcomes and measures BSI incidence, both overall and for BSI subtypes.

Results In the arms-based meta-regression, the predicted BSI incidence per 100 patients in the ABD intervention arms increased from 4.6 (95% CI 3.8 to 5.5) at mean LOS 7 days to 13.0 (10.4–16.0) at mean LOS 20 days (n=60 arms) and CC arms 8.5 (6.7–11.0) increasing to 19.3 (14.8–24.8; n=52). These increases were double those in the observational (7.2; 6.1–8.5 increasing to 12.9; 10.4–16.7; n=99) and NCC arms and non-ABD arms. These results triangulate with the notional effect size observed in contrast-based meta-analyses.

Conclusions The increased tempo of BSI acquisition, both overall and for various BSI subtypes, within intervention and CC groups of ABD randomised concurrent controlled trials versus other groups implicate rebound and spillover, respectively. Mechanisms other than colonisation resistance mediate ABD effects.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The main strength of this analysis is that the indirect (herd) effects from using anti-microbial-based decontamination (ABD) to concurrent control group patients within the intensive care unit (ICU) context are estimated using literature derived data. These effects, being potentially harmful, might otherwise be difficult or even unethical to study.
⇒ The analysis here enables a basis for testing the validity of literature derived summary ABD effects sizes and, as a proof of concept, a comparison of three competing hypotheses for how ABD interventions mediate the effects observed in randomised concurrent controlled trials.
⇒ The data is traceable to the 201 individual publications with triangulation of summary findings derived using alternate arms-based versus contrast-based realignments of the data.
⇒ Heterogeneity of the populations, interventions and publication dates is discussed as both a strength and a limitation in the generalisability of the results.
⇒ There is uncertain generalisability of these findings to study populations outside of published studies and also outside of ICUs in Northern Europe and North America.

INTRODUCTION

Intensive care unit (ICU) patients are at high risk of acquiring bloodstream infections (BSIs).[1 2] Anti-microbial-based decontamination (ABD) interventions, using either topical antiseptics[3 4] or topical antibiotics,[5–8] appear to be highly effective at preventing ICU-acquired infections within randomised concurrent controlled trials (RCCTs) as summarised using contrast-based meta-analyses.

Paradoxically, despite this apparent prevention effect, the incidence of BSI is higher within RCCTs of ABD interventions versus controlled trials where the control and intervention groups are non-concurrent and also large observational cohorts.[8 9] Moreover, interventions other than ABD (non-ABD interventions) are relatively ineffective and yet have event rates in the expected range.[10–16]

There are three competing hypotheses to explain the effect of ABD interventions on the risk of acquiring infections in ICU patients to account for these paradoxical observations (figure 1). The original model

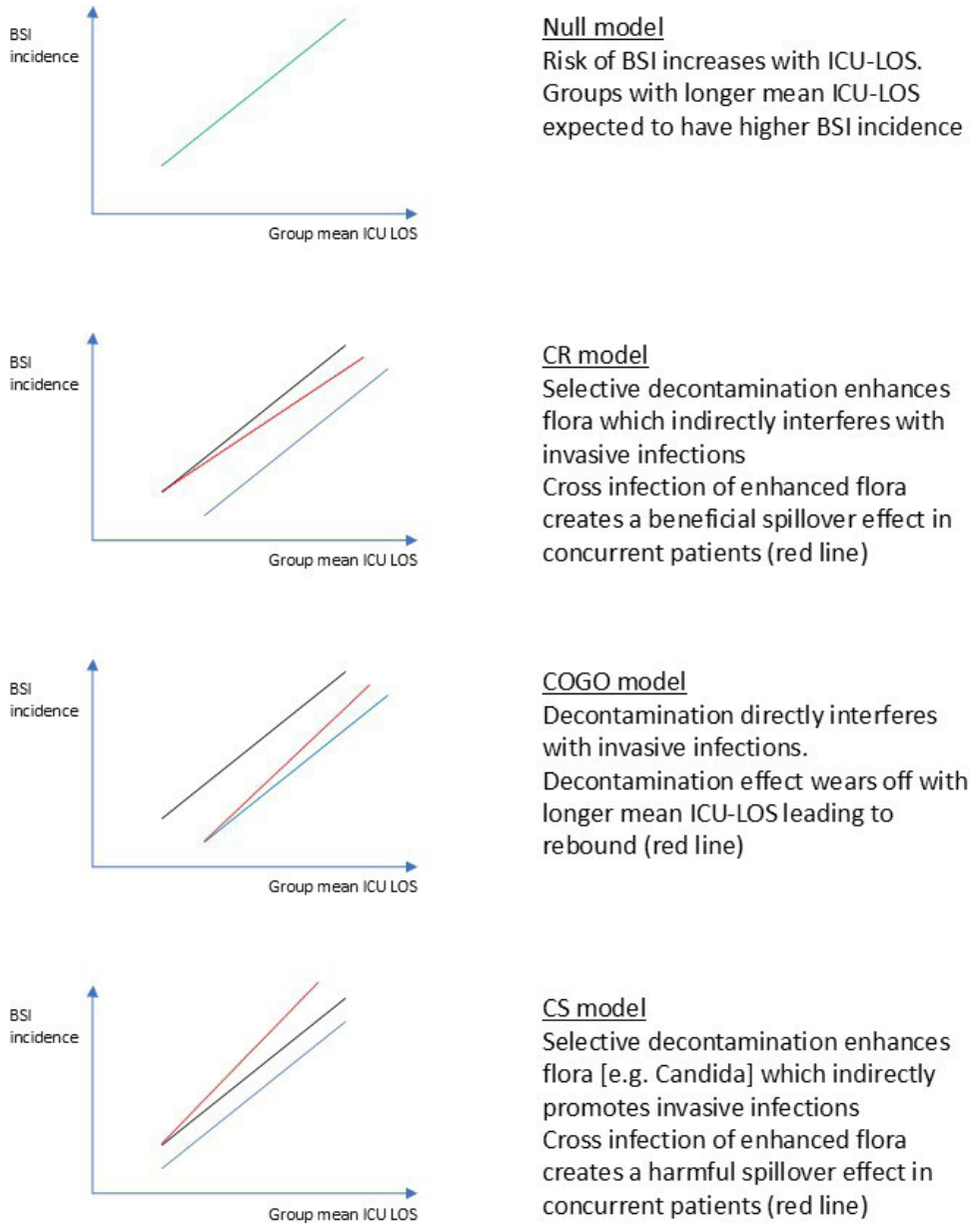

Figure 1 Three competing hypotheses and a null model of the tempo of increase in bloodstream infection (BSI) incidence in relation to group mean intensive care unit-length of stay (ICU-LOS) observed for control (black line) versus intervention (blue line) groups of randomised concurrent controlled trials (RCCTs) of topical antibiotics as infection prevention in ICU patients. The null model (green line) represents the tempo of increase among observational groups without any specific study intervention. The postulated mediation of anti-microbial-based decontamination (ABD)-based intervention in the colonisation resistance (CR) and colonisation susceptibility (CS) models are characterised by spillover of microbiome components to concurrent control groups and, in the control of gut overgrowth (COGO) model, by rebound of microbiome components in the intervention groups. These effects are expected to be manifested as deviations in the tempo of increase in BSI incidence in either the control or intervention arms (red lines). These deviations cannot be appreciated in a contrast-based meta-analysis and can only be appreciated by reference to the tempo in the null model. These deviations are not expected to manifest in RCCTs of non-ABD interventions, which do not impact the microbiome, and are relatively ineffective. Deviations in relation to spillover are not expected to manifest in the NCC groups of NCC-controlled trials of ABD interventions as being non-concurrent and are not exposed to spillover.

(colonisation resistance (CR)) postulates that topical anti-microbials selectively decontaminate the intestinal microbiome to enhance flora that might inhibit invasive pathogenic microbes from the gut. This enhanced flora was predicted to spillover to provide an indirect (herd) effect that would confer benefit to concurrent patients in the ICU.[17]

The control of gut overgrowth (COGO) model postulates that topical antibiotics directly inhibit the invasive pathogenic microbes in the gut.[18 19] This inhibition

would degrade over time with rebound of the pathogenic microbes on withdrawal of the topical anti-microbials.[20 21]

The colonisation susceptibility (CS) model postulates that topical anti-microbials enhance the emergence of flora (such as Candida) which are known to promote invasive pathogenic microbes from the gut. This enhanced flora would be transmissible to provide an indirect (herd) effect that would confer harm to concurrent patients in the ICU.[22] This harm among the concurrent control groups would spuriously create the appearance of a beneficial effect of ABD intervention.

Estimating herd effects from any intervention on BSI in the ICU population requires three considerations. First, any herd effects to concurrent control groups within RCCTs of infection prevention interventions cannot be appraised from contrast-based estimates of the prevention effect size.[23] For example, an arms-based reanalysis of the results of a cholera vaccination RCCT was required to demonstrate herd immunity from this intervention.[24]

Second, given the daily hazard for BSIs peaks after day 21 of ICU admission,[1] ICU length of stay (LOS) is a potential effect modifier.[25]

Third, ABD interventions have complex effects on the patient and ICU microbiome. Any spillover to concurrent non-recipients within the ICU may vary for various BSI types.[26 27]

The objectives here are first to recapitulate estimates of the apparent effectiveness of ABD and non-ABD interventions using a conventional contrast-based meta-analysis. Second is to estimate herd effects through comparing the tempo of increase in BSI incidence in relation to varying group mean LOS within arms exposed directly or indirectly to ABD interventions versus those not exposed using an arms-based meta-regression analysis.[28] The third objective is to triangulate the apparent effect estimates of ABD interventions from the arms-based versus contrast-based approaches, as was done for an analysis of mortality.[29] The overarching objective is to compare the three competing hypotheses as possible mechanisms to deduce which might best explain the observed controlled trial data.[30]

MATERIALS AND METHODS

Study selection and decant of groups

This is a deductive meta-analysis that uses controlled trial data from systematic reviews, and other sources, of ABD and non-ABD interventions to prevent infections in ICU patients. The literature search (online supplemental figure 1), as described previously,[29] is opportunistic. Cochrane reviews and other systematic reviews were used as the primary source of studies, with additional studies being found by snowball sampling using the 'Related articles' function within Google Scholar. All primary studies were published between 1987 and 2023.

The inclusion criteria were ICU patient cohorts for which the BSI counts and either the mean or median LOS or duration of mechanical ventilation (MV) were reported. Where possible, data were extracted for each identifiable subcohort representing different observation eras. Paediatric cohorts were included, but cohorts with patient selection based on having risk factors for Candida BSI were excluded.[31]

The studies were classified into three broad categories: ABD interventions, either antiseptic-based or antibiotic-based; studies of interventions other than ABD (non-ABD); and a third category, studies without an intervention under study. The third category serves as the benchmark category in the arms-based meta-regression of BSI incidence.[32–35]

Non-ABD interventions include approaches to control upper gastrointestinal tract or airway colonisation through stress ulcer prevention, feeding and various approaches to airway management.[10–16]

Antiseptic-based ABD[3 4] includes the use of agents such as chlorhexidine, povidone-iodine and iseganin. All antiseptic exposures were included regardless of whether the site of application was to the oropharynx, by toothbrushing or by body washing. Antibiotic-based ABD[5–7 36 37] includes variously formulated topical antibiotic prophylaxis applied to the oropharynx or stomach and may also include protocolised parenteral antibiotic prophylaxis as an additional component.

Metrics of interest

The BSI counts, both overall and for various subtypes, were extracted and used to derive proportions using the number of patients as the denominator for each study group. The independent variable in the regression models was the mean (or median) LOS or, if this was not available, the mean (or median) duration of MV. The LOS data were log transformed for analysis after truncating any LOS <5 days to 5 days and truncating any LOS>25 days to 25 days.

Meta-analysis: contrast-based

The contrast-based analysis of controlled trial data, whether including either concurrent (CC) or non-concurrent (NCC) control groups, used mixed-effect methods of meta-analysis with the 'meta' and 'meta meregress' commands in Stata 18 (Stata Corp., College Station, TX, USA).[38] According to these multilevel meta-analyses, the study was a random effect, whereas the intervention categories were fixed effects. The study-specific and overall summary BSI prevention effect sizes and associated 95% CIs were calculated for each intervention category and subcategory of CC and NCC-designed controlled trials.

Meta-analysis: arms-based

The arms-based analysis uses data from controlled trials that have either or both of control or intervention arms together with data from observational studies serving as an incidence benchmark, as outlined in figure 1. Arms-based meta-analysis is commonly used where the assumption of independence between observations in the control and

intervention groups is untenable, as is typically the case in the meta-analysis of diagnostic tests.[28 39]

Meta-regression

Contrast-based meta-regression of controlled trial effect sizes versus group mean LOS using the 'meta meregress' command modelled the relationship between the prevention effect size and the group mean LOS.

Arms-based meta-regression was performed to model the logit-transformed BSI incidence proportion versus the group mean LOS. Post-model predictions of BSI incidence were obtained using the 'Stata' command 'nlcom' to obtain non-linear combinations of the BSI incidence estimators corresponding to mean LOS day 7 and day 20. The post-model predictions of the direct effect were non-linear combinations of the summary mean BSI incidence in the ABD intervention arms minus the benchmark. The indirect effect was a non-linear combination of the summary mean BSI incidence in the CC control arms minus the benchmark. The notional effect size is the summary mean BSI incidence in the intervention arms minus the summary mean BSI incidence in the CC control arms. This is equivalent to the sum of the direct and indirect effects (online supplemental figure 2).

Threats to validity

Risk of bias assessments were not done here although these are available in the Cochrane reviews for the controlled trials sourced there. Here, the spillover risk, which is not considered to be estimated, was considered a greater threat to effect size validity.

The risk of publication bias was addressed by a sensitivity test that reclassified the controlled trials that were non-ABD, which were generally negative, to the ABD category and repeating the meta-regression to test the robustness of the findings.

Data availability

All data analysed are provided in the supplemental material, where the data are traceable to the 201 studies by citation number.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Characteristics of the studies

Of the 201 controlled trials and non-interventional studies identified, most were published between 1990 and 2010 (online supplemental tables 1-4). Twenty controlled trials had more than one type of intervention group, and 23 controlled trials had either more than one or no control group. Most observational study groups had >150 patients per group versus <150 patients in the interventional study groups. Most studies were from either North American or Northern European ICUs (table 1).

There were 21 broad types of interventions among non-ABD RCCTs and 28 different topical antiseptic, oral care or topical antibiotic interventions among the ABD controlled trials. The mean LOS appeared to be constant over 35 years of publication (online supplemental figure 3), but the LOS was longer among the category of ABD-CC group. The mean LOS was not available for 16 studies.

Bloodstream infection (BSI) prevention effect sizes (contrast-based)

Non-ABD interventions had no effect on overall BSI incidence (table 1, online supplemental figure 4). The significant summary prevention effects against BSI for both the antiseptic and antibiotic subcategories of ABD interventions were less apparent for NCC-controlled trials (online supplemental figure 5) than for CC controlled trials (online supplemental figures 6,7; table 1). The ABD effect size attenuated with increasing group mean LOS for studies with CC controls but not for studies with NCC controls (figure 2).

Meta-regression of bloodstream infection (BSI) incidence versus mean length of stay (LOS) (arms-based)

An increase in the incidence of BSIs versus the group mean LOS was generally apparent both for the overall incidence of BSIs (figure 3a) for candidemia (figure 3b) and for other BSI subtypes (figures 4 and 5; online supplemental figures 8-14; table 2). Among ABD RCCTs, the increase in overall BSI incidence among CC arms (8.5; 6.7–11.0; mean LOS 7 days increasing to 19.3; 14.8–24.8; mean LOS 20 days; n=52) and that in ABD intervention arms (4.6; 3.8–5.5 increasing to 13.0; 10.4–16.0; n=60) were double the increase in observational arms (7.2; 6.1–8.5 increasing to 12.9; 10.4–16.7; n=99) and the increase in NCC and arms of non-ABD studies (5.9; 4.5–7.6 increasing to 10.5; 7.9–13.7; n=41) (table 2).

The tempo of acquisition of BSI, estimated as the slope of the meta-regression models (table 3), was significantly greater than benchmark among ABD intervention groups for *Candida*, *Pseudomonas*, *S. aureus* and *Enterococcus* BSI and among ABD control groups for *Candida* and *Pseudomonas*.

Predicted bloodstream infection (BSI) incidences (arms-based)

The predicted overall BSI incidence among the ABD intervention groups was 2.6 percentage points lower than the benchmark for groups with a 7 days mean LOS (table 2) versus 6.4 percentage points greater than the benchmark for the group with a 20-day mean LOS. The predicted overall BSI incidences for non-ABD arms and NCC and intervention arms of ABD studies at 7- and 20-day group mean LOS were all within 2.5 percentage points of the benchmark (figure 3a; table 2).

The predicted incidences of *Pseudomonas*, *Candida* and *S. aureus* BSIs among the ABD intervention groups were less than the benchmark by as much as 0.2 percentage points at 7 days mean LOS and were greater

Table 1 Characteristics of the studies

	Observational	Non-ABD	Anti-microbial-based decontamination (ABD)	
			(NCC)	(CC)
Study characteristics				
Listing	Online supplemental table 1	Online supplemental table 2	Online supplemental table 3	Online supplemental table 4
Number of studies*	86	21	43	52
Studies from systematic reviews	16	10	6	43
Study publication year (range)	1987–2023	1987–2023	2000–2023	1974–2023
Study origins				
North America	29	5	2	11
Northern Europe	35	10	17	29
Types of groups (N)*				
Observational	98	NA	NA	NA
NCC	NA	0	26	NA
CC	NA	21	NA	52
Intervention	NA	20	54	60
Group characteristics				
Group mean LOS† ‡ (mean, 95% CI)	11; 9.9–12.2	13.6; 11.1–16.1	11.7; 9.5–13.8	14.3; 12.7–16.0
Group mean LOS missing	9	0	3	4
Numbers of patients per study group; median (IQR)§	459 150–2527	108 60–282	130 72–347	114 42–397
Overall BSI prevention summary ES (contrast-based) (OR; 95% CI; n)	NA	1.04;¶ 0.88–1.22 (19) (online supplemental figure 4)	0.72;** 0.62–0.83 (28) (online supplemental figure 5)	0.63;†† 0.53–0.75 (52) (online supplemental figures 6,7)

*Note, several studies had more than one control and/or intervention group. Hence, the number of groups does not equal the number of studies.
†Test of equality in mean LOS between categories, p =0.002; one-way analysis of variance
‡LOS for antiseptic (CC) 8.3 (5.0–11.5) versus antibiotic (CC) 14.5 (12.8–16.2); p <0.01
§The data are presented as the median and interquartile range (IQR).
¶Heterogeneity test I^2 = 0.0%; H^2 = 1.0
**The overall BSI prevention summary effect for studies of antiseptics with an NCC design was 0.75, 0.62–0.92 (n = 6; online supplemental figure 5), and that for studies of antibiotics with an NCC design was 0.69, 0.56–0.84 (n = 22; online supplemental figure 5). Heterogeneity test I^2 = 77.5%; H^2 = 3.64
††The overall BSI prevention summary effect for studies of antiseptics with a CC design was 0.54, 0.39–0.73 (n = 11; online supplemental figure 6), and that for studies of antibiotics with a CC design was 0.65, 0.54–0.80 (n = 41; online supplemental figure 7). Heterogeneity test I^2 = 28.1%; H^2 = 1.39
NA – not available; ABD, antimicrobial-based decontamination; BSI, bloodstream infection; CC, concurrent control; ES, effectsize; LOS, length of stay; NCC, non-concurrent control.

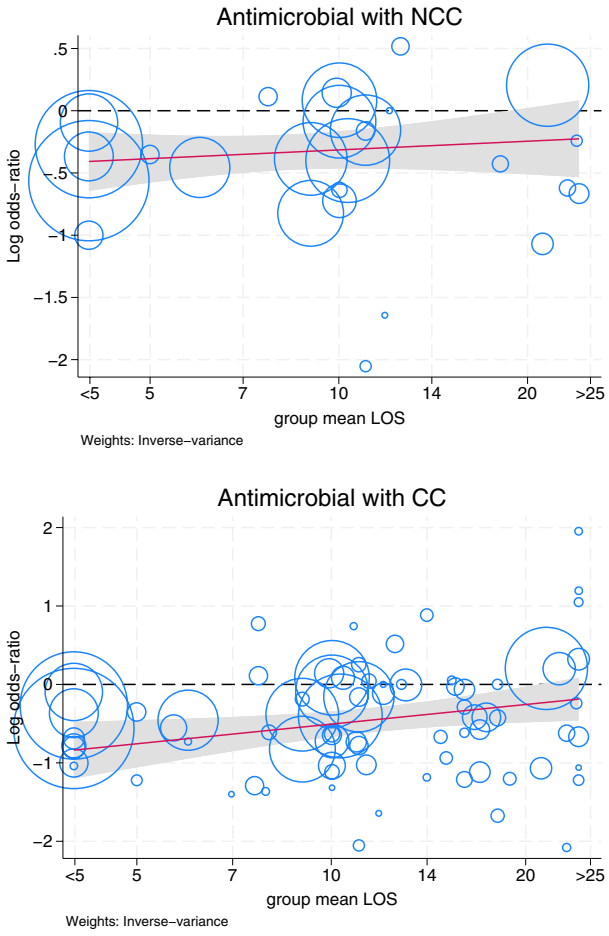

Figure 2 Meta-regression (and 95% confidence limits) of bloodstream infection prevention effect size for antimicrobial-based decontamination infection prevention interventions with non-concurrent control (NCC) (top) and concurrent control (CC) (bottom) vs group mean LOS (length of stay). The slope of the meta regression lines for NCC (+0.10; −0.16 to +0.36) and CC (+0.36; +0.06 to +0.67) versus the line of no effect are shown (dotted horizontal line). Symbol size weighted by the inverse variance.

than the benchmark by up to 1.2 percentage points at 20 days mean LOS (figures 3–5; table 2). Among the ABD CC control groups, the predicted incidences of *Pseudomonas*, *Candida* and *S. aureus* BSIs were above the benchmark by up to 3.8 percentage points at 20-day group mean LOS.

The predicted incidences of coagulase negative *Staphylococci* (CNS) and *Enterococcus* BSIs for the ABD intervention and CC control groups were mostly above the benchmark by as much as 0.5 percentage points for at 7-day group mean LOS and above by between 1 and 4 percentage points at 20-day group mean LOS (figure 5).

Of note, none of the incidences for ABD intervention groups at 20-day group mean LOS were below benchmark (table 2).

Triangulation

The notional effect size derived from an arms-based analysis, being equivalent to the sum of the direct and indirect effects, for ABD interventions (OR 0.5; 0.33–0.67) corresponding to 7-day group mean LOS attenuating to 0.64 (0.39–0.9) at 20-day group mean LOS, respectively (table 2), were comparable to the summary effect sizes derived from the contrast-based meta-analyses (OR 0.65; 0.54–0.80; table 1).

The indirect, direct and notional effect sizes of ABD interventions for Candidemia and other BSI subtypes are given in online supplemental table 5. The indirect effects of ABD interventions indicate increases in both *Pseudomonas* BSI (OR 3.0; 1.05–4.9) and Candidemia (OR 4.6; 1.6–7.7) at 20 -day group mean LOS among CC arms, whereas the corresponding notional effects seemingly indicate strong apparent prevention effects (OR 0.51, 0.16–0.87, and OR 0.41, 0.12–0.17, respectively).

DISCUSSION

Meta-analyses of BSI incidence data from ABD intervention RCCTs versus group mean LOS from 201 studies were performed to address three objectives. An overarching finding is that the results of arms-based versus contrast-based meta-analyses lead to contrary inferences. The arms-based meta-regression enables a deductive meta-analysis.

First, using contrast-based methods, the BSI prevention effect size estimates derived here (table 1) recapitulate estimates for ABD using either topical chlorhexidine (OR 0.74; 0.37–1.50, n=5[36]) or topical antibiotics (OR 0.68; 0.57–0.81; n=32[7]) and other estimates from various sources in the literature (online supplemental table 6).[27 40] These effect size estimates, all derived using contrast-based methods, equate to strong effects of ABD interventions versus various types of BSI within RCCTs but are unable to differentiate whether the mechanism of mediation is CR, COGO or CS.

Second, with arms-based methods, which use observational studies as the benchmark and are not limited to controlled trials with CC control arms, indirect effects originating either as spillover or rebound from ABD interventions can be estimated. The increase in the incidence of BSI between 7- and 20-day group mean LOS among the ABD intervention and more so CC arms was higher versus the increase in the observational studies (table 3). With arms-based methods, the direct and indirect effects of ABD interventions can be estimated. These estimates infer strong indirect effects of ABD interventions on BSI incidence within RCCTs. These indirect effects equate to CC patients acquiring BSI at double the rate of NCC patients or patients within observational studies.

Third, triangulation can be achieved. The notional effect size with 7- and 20-day group mean LOS (table 2; online supplemental figure 3), which is the non-linear summation of direct and indirect effects derived from arms-based analyses, is nearly identical to the contrast-based

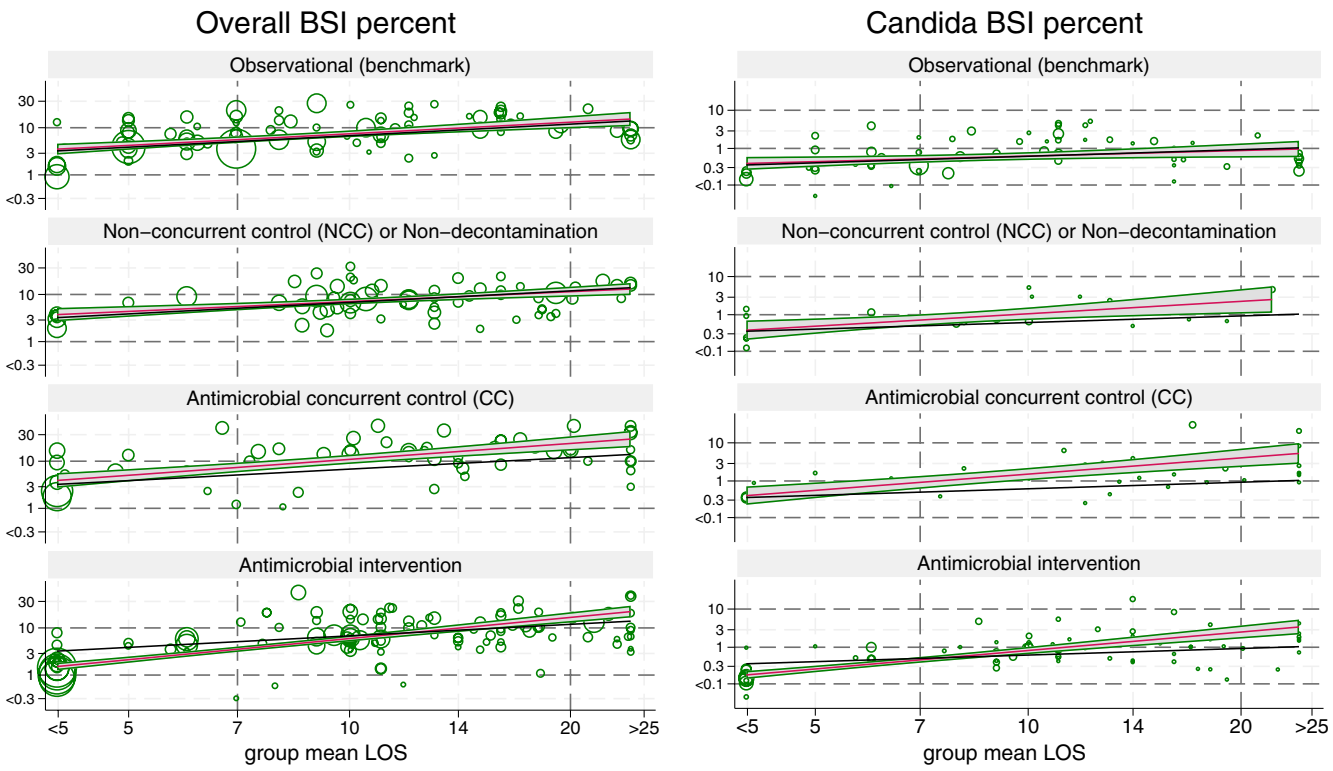

Figure 3 Meta-regression (95% CIs) of the overall (left) and *Candida* (right) bloodstream infection (BSI) incidence percentages (per 100 patients) for the (top to bottom) observational groups, non-ABD and NCC groups, CC groups, and intervention groups of ABD interventions versus group mean length of stay (LOS). In each panel, the meta-regression (red line) and 95% CI (green outline) derived from the BSI incidences in the groups in that panel are displayed together with a benchmark (black line) representing the meta-regression derived from the observational groups (top panel). These 95% CIs are derived by a linear regression using the inverse variance of BSI incidence to weight. The y-axis is a logit scale, and the x-axis is a logarithmic scale truncated at mean LOSs of 5 and 25 days. Note that the y-axis scales differ. Figures with citations of the individual studies are provided in online supplemental figures 8,11.

effect size estimates derived previously in the literature based on fewer studies (online supplemental table 6).

The findings here resemble the conflicting inferences derived from arms-based versus contrast-based meta-analyses as previously noted for the acquisition of ventilator-associated pneumonia (VAP) among 190 controlled trials of ABD and other interventions abstracted among the same source Cochrane reviews as used here.[41] Of note, there were only 22 studies common to both the current and previous analysis. The previous analysis used methods applicable to diagnostic test meta-analysis to enable spillover to be visualised.

In reconciling the contrary inferences derived from contrast- versus arms-based meta-analyses, it should be noted that any indirect (herd) effects are not observable without an arms-based analysis. Notably, the inferences from the results of contrast-based analyses and indeed from any individual RCCT rely on assumptions that indirect effects are either absent or negligible. These assumptions, which are critical to validity, can only be tested in an arms-based analysis (figure 1, online supplemental figure 1).

Accounting for spillover as a population effect of ABD requires a reappraisal of the magnitude of inapparent cross infection in the ICU. For example, increasing the use of carbapenem antibiotics within the ICU increases the risk of acquiring carbapenem-resistant Gram-negative bacteria as an indirect effect among patients who are not exposed to these antibiotics.[42] Additionally, patients acquire colonisation from contaminated surfaces within the hospital environment. For example, patient admission to previously occupied rooms doubles the risk of acquiring pathogenic organisms from the previous patient's flora.[43 44] Patients receiving topical antibiotics as ABD can serve as reservoirs for *Pseudomonas* and other Gram-negative bacteria within the ICU.[21] Estimating the size of spillover as an indirect effect from ABD interventions would be difficult. To demonstrate a 2-percentage point difference in any endpoint would require a CRT with >100 ICUs, each with 90 patients. However, beyond logistical considerations, such a CRT would be infeasible due to the complex ethical issues of studying an intervention for postulated population harm.[45]

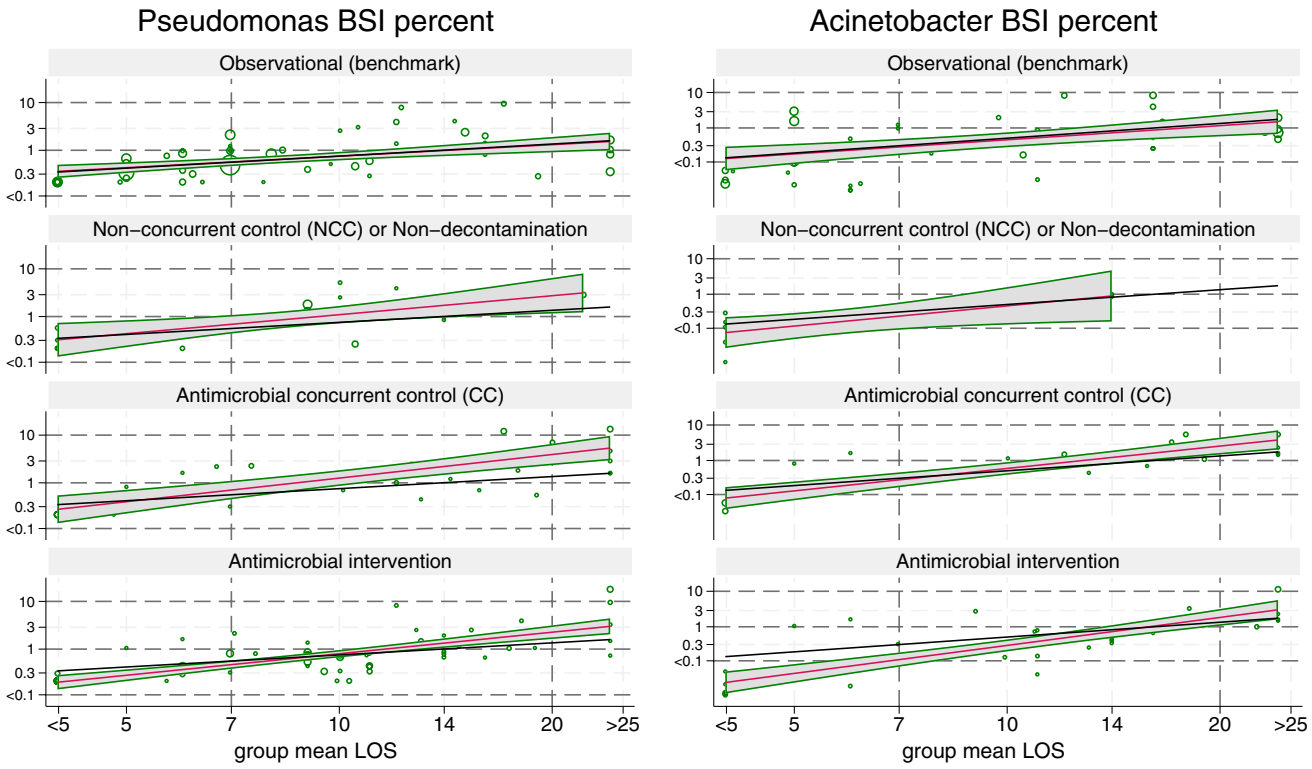

Figure 4 Meta-regression (95% confidence limits) of *Pseudomonas* (left) and *Acinetobacter* (right) bloodstream infection (BSI) incidence percentages (per 100 patients) for the (top to bottom) observational groups, non-ABD and NCC groups, CC groups, and intervention groups of ABD interventions versus group mean length of stay (LOS). In each panel, the meta-regression (red line) and 95% CI (green outline) derived from the BSI incidences in the groups in that panel are displayed together with a benchmark (black line) representing the meta-regression derived from the observational groups (top panel). These 95% CIs are derived by a linear regression using the inverse variance of BSI incidence to weight. The y-axis is a logit scale, and the x-axis is a logarithmic scale truncated at mean LOSs of 5 and 25 days. Figures with citations of the individual studies are provided in online supplemental figures 9,10.

Considering rebound as a population effect of ABD requires a reappraisal of the complex changes in patient and ICU microbiomes that accompany ABD use and more so on ABD cessation or ABD failure to act.[46–51]

The timing of ABD cessation in ICU patients varies. ABD cessation might accompany the cessation of MV, but in nonventilated patients, the timing of ABD cessation is variable[46] and may occur with patient refusal. Notably, protocol violations among controlled trials of topical antibiotics as ABD range between 10%[47] and 30%.[48 49] In a study of the use of topical antibiotics as ABD for infection prevention prior to colorectal surgery, 480 of 929 patients declined to participate due to the unpleasant taste of the topical antibiotics.[50]

Rebound infections resulting from discontinuation of topical antibiotics as ABD have been noted among patients after ICU discharge when the infection risk is increased by approximately 50%.[20] The risk of severe, and occasionally fatal, infection on premature withdrawal of topical antibiotics as ABD was noted in haematology units in the 1970s when this was used to prevent infections in association with neutropenia from cytotoxic chemotherapy.

Rebound may occur as a 'whole of ICU' phenomenon that is not limited to recipients of topical antibiotics as ABD and persists as an ecological effect for several months after withdrawal of topical antibiotics.[27] The extent to which rebound colonisation in patients who remain in the ICU after cessation of topical antibiotics contributes to an altered ICU microbiome remains unknown.

Failure of topical antibiotics used as ABD occurs in as many as 29% of patients and requires two times a week surveillance cultures for detection.[46] Patients with failure of topical antibiotics as ABD who then receive an intensified ABD regimen experience high rates of BSI with *Enterococcus* and CNS.[51]

The presumed mediation of ABD, whether by CR, COGO or CS, remains unclear.[17 19] Of note, the microbes responsible for mediating CR, and the optimal antibiotic regimen for their promotion, have never been identified.[17] The counterpart to CR is CS, where microbes selected through ABD failure, rebound and spillover might facilitate invasive bacterial infection.[22] Several preclinical studies implicate *Candida* spp. as strong facilitators of bacterial invasion.[52–55] In modelling studies based on published clinical data, the magnitude of

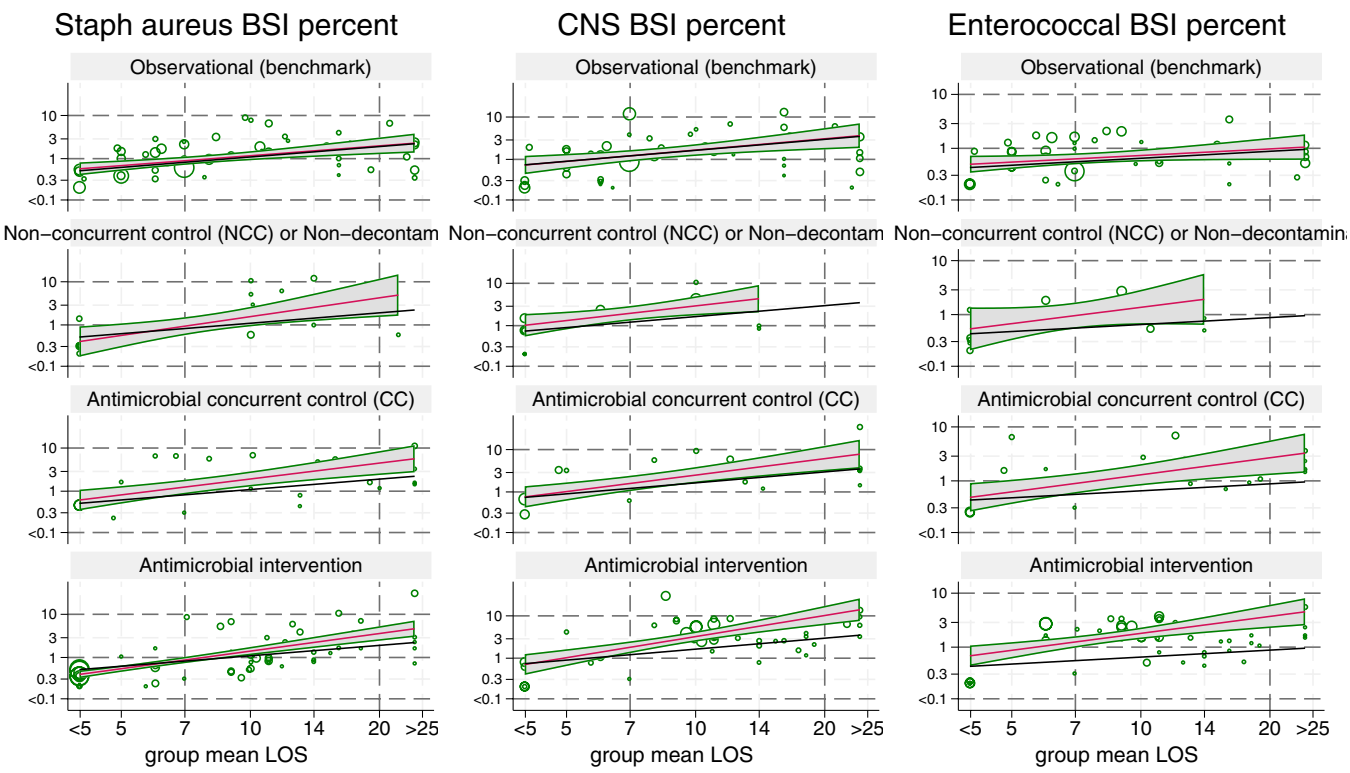

Figure 5 Meta-regression (95% confidence limits) of the *Staphylococcus aureus* (left), coagulase negative *Staphylococci* (CNS) (middle) and *Enterococcus* (right) bloodstream infection (BSI) incidence percentages (per 100 patients) for the CC (top to bottom) observational groups, non-ABD and NCC groups, CC groups and intervention groups of ABD interventions versus group mean length of stay (LOS). In each panel, the meta-regression (red line) and 95% CI (green outline) derived from the BSI incidences in the groups in that panel are displayed together with a benchmark (black line) representing the meta-regression derived from the observational groups (top panel). These 95% CIs are derived by a linear regression using the inverse variance of BSI incidence to weight. The y-axis is a logit scale, and the x-axis is a logarithmic scale truncated at mean LOSs of 5 and 25 days. Figures with citations of the individual studies are provided in online supplemental figures 12-14.

Candida colonisation as a cofactor towards *Acinetobacter*,[56] Pseudomonas,[56] *S. aureus*,[57] *Enterococcus* and CNS[58] BSI is similar to that of topical antibiotics used for prophylaxis but in the opposite direction. The facilitation of invasive bacterial infections by *Candida* colonisation is a process that has been described as 'microbial hitchhiking'.

Candida colonisation of ICU patients is associated with poor patient outcomes, including increased ICU mortality.[59] This association is disproportionate to the scarcity of invasive candida infections among this patient population. Randomised controlled trials evaluating antifungal prophylaxis among ICU patients are difficult to perform, and the results for any endpoint are few and inconclusive.[60 61]

Limitations

Many controlled trials were unable to be included due to missing BSI data. BSI incidences were generally not the primary endpoint. Those controlled trials that reported BSI may have been subject to biased reporting. There was no ability to obtain additional data from publications that, in many cases, were published several decades ago. The MV duration was used when LOS data were unavailable for a small number of studies.

The reporting of BSI counts may have been biased towards those controlled trials where a difference was apparent. However, the findings for ABD controlled trials were robust to the inclusion of a small number of generally negative non-ABD controlled trials as a sensitivity test.

These findings relate to population (herd) level effects rather than patient-level effects. Specifically, the timing of ABD cessation among the ABD intervention arms is variable. The mean LOS can be taken to represent the mean level of group exposure to specific ICU contexts and does not relate to patients with that LOS. However, spillover and rebound are population-level effects that are unmeasurable at the individual level.

There was considerable heterogeneity in the interventions, publication dates, populations, study quality and study designs among the controlled trials published over several decades included in the analysis. This heterogeneity is a threat to the validity of summary effect size estimates derived here as well as in the originating systematic reviews. However, given this heterogeneity and especially

Table 2 Predicted BSI incidences per 100 patients from arms-based meta-regression models versus length of stay‡

	Overall BSI (online supplemental figure 8)	*Pseudomonas* (online supplemental figure 9)	*Acinetobacter* (online supplemental figure 10)	*Candida* (online supplemental figure 11)	*Staphylococcus aureus* (online supplemental figure 12)	CNS (online supplemental figure 13)	*Enterococcus* (online supplemental figure 14)
Day 7							
Observational (benchmark)	7.2	0.7	0.3	0.7	1.3	1.4	0.8
95% CI	6.1–8.5	0.5–0.8	0.2–0.5	0.6–0.9	1.0–1.6	1.1–1.9	0.6–1.0
NCC or non-ABD	6.0	0.6	0.2	0.7	0.9	1.8	0.8
95% CI	4.6–7.7	0.4–0.9	0.1–0.6	0.5–1.1	0.6–1.4	1.1–3.0	0.5–1.3
ABD control	8.5*	0.9	0.5	1.4	1.8	2.7	1.3
(CC) 95% CI	6.7–11.0	0.6–1.5	0.2–1.1	0.9–2.1	1.1–2.9	1.6–4.2	0.8–2.2
ABD intervention	4.6*	0.5	0.1	0.6	0.9	1.9	1.1
95% CI	3.8–5.5	0.4–0.6	0.1–0.2	0.5–0.8	0.7–1.2	1.4–2.5	0.8–1.5
Day 20							
Observational (benchmark)	12.9	1.4	1.5	0.9	2.0	2.8	0.9
95% CI	10.2–16.2	1.0–1.9	0.9–2.6	0.6–1.3	1.3–2.9	1.9–4.3	0.6–1.4
NCC or non-ABD	10.5	1.7	0.9	1.8	2.8	3.5	1.7
95% CI	8.0–13.7	0.8–3.7	0.1–10.4	0.9–3.8	1.2–6.4	1.1–10.5	0.5–5.5
ABD control (CC)	19.3†	4.2	2.4	3.9	4.1	5.4	2.3
95% CI	14.8–24.8	2.4–7.0	1.1–5.3	2.3–6.5	2.3–7.2	3.0–9.5	1.2–4.7
ABD intervention	13.0†	2.1	1.6	2.1	3.2	6.9	3.1
95% CI	10.4–16.0	1.4–3.2	0.8–3.1	1.4–3.2	2.1–4.7	4.5–10.2	1.9–4.9

*The difference between incidences in the intervention and concurrent control groups on day seven equates to a prevention effect size of 0.5 (0.33–0.69) for ABD exposure.
†The difference between incidences in the intervention and concurrent control groups on day 20 equates to a prevention effect size of 0.64 (0.39–0.89) for ABD exposure.
‡The meta-regression models are presented in online supplemental figures 8-14.
ABD, anti-microbial-based decontamination; BSI, bloodstream infection; CC, concurrent control; CNS, coagulase negative *Staphylococci*; NCC, non-concurrent control.

Table 3 Meta-regression models of BSI incidence versus length of stay* †

	Intercept		Slope	
Factor‡	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
All BSI (figure 3a)				
Observational (benchmark)	−3.85	−4.57 to −3.1	0.65	0.34 to 0.96
NCC or non-ABD	−0.13	−1.37 to 1.11	−0.04	−0.55 to 0.48
ABD control (CC)	−0.02	−1.21 to 1.17	0.16	−0.34 to 0.65
ABD intervention	−1.19‡	−2.19 to −0.2	0.39	−0.03 to 0.82
Candida (figure 3b)				
Observational (benchmark)	−5.81	−6.76 to −4.9	0.39	−0.03 to 0.8
NCC or non-ABD	−1.35	−3.36 to 0.65	0.77	−0.17 to 1.7
ABD control (CC)	−1.58	−3.51 to 0.36	1.03* ‡	0.23 to 1.8
ABD intervention	−2.22 §	−3.67 to −0.77	0.98§	0.33 to 1.6
Pseudomonas (figure 4a)				
Observational (benchmark)	−6.84	−7.67 to −6.0	0.86	0.5 to 1.2
NCC or non-ABD	−0.9	−3.08 to 1.3	0.5	−0.48 to 1.5
ABD control (CC)	−1.51	−3.31 to 0.29	0.89* ‡	0.15 to 1.6
ABD intervention	−1.7‡	−3.09 to −0.3	0.74‡	0.13 to 1.4
Acinetobacter (figure 4b)				
Observational (benchmark)	−9.41	−10.96 to −7.9	1.68	1.03 to 2.3
NCC or non-ABD	−0.52	−4.66 to 3.6	0.29	−1.93 to 2.5
ABD control	−0.36	−3.46 to 2.7	0.35	−0.89 to 1.6
ABD intervention	−2.57	−5.2 to 0.05	0.97	−0.12 to 2.1
Staphylococcus aureus (figure 5a)				
Observational (benchmark)	−5.64	−6.65 to −4.6	0.58	0.13 to 1.0
NCC or non-ABD	−1.93	−4.14 to 0.28	0.95	−0.08 to 2.0
ABD control (CC)	−0.48	−2.5 to 1.5	0.44	−0.41 to 1.3
ABD intervention	−2.23§	−3.69 to −0.77	0.99§	0.34 to 1.6
Coagulase negative *Staphylococci* (CNS) (figure 5b)				
Observational (benchmark)	−5.93	−7.05 to −4.8	0.78	0.29 to 1.3
NCC or non-ABD	−0.4	−3.15 to 2.3	0.4	−0.98 to 1.8
ABD control (CC)	−0.09	−2.23 to 2.0	0.29	−0.61 to 1.2
ABD intervention	−0.85	−2.64 to 0.9	0.62	−0.15 to 1.4
Enterococcus (figure 5c)				
Observational (benchmark)	−5.55	−6.55 to −4.6	0.29	−0.16 to 0.8
NCC or non-ABD	−1.08	−3.5 to 1.3	0.65	−0.6 to 1.9
ABD control (CC)	−0.46	−2.4 to 1.5	0.48	−0.37 to 1.3
ABD intervention	−1.08	−2.72 to 0.55	0.78‡	0.05 to 1.5

*As a sensitivity test, groups from 21 non-ABD control trials were reclassified as ABD groups, and the meta-regression models were repeated. There was no appreciable change in the coefficients. For example, the slope coefficients for *Candida* and *Pseudomonas* became +0.90 (+0.14 to +1.65) and +0.81 (+0.10 to +1.52), respectively, in the sensitivity test.
†As another sensitivity test, the meta-regression was limited to those studies abstracted from systematic reviews, and the meta-regression models were repeated. There was no appreciable change in the coefficients, but the 95% CIs were wider.
‡Coefficients with a statistically significant increment from base line ($p<0.05$)
§Coefficients with a statistically significant increment from base line ($p<0.01$)
ABD, anti-microbial-based decontamination; BSI, bloodstream infection; CC, concurrent control; NCC, non-concurrent control.

the disparate nature of the interventions, it is surprising that divergence from the benchmark at 20 days group mean LOS is more apparent for the BSI incidence among the CC control than the ABD intervention arms.

This heterogeneity, which is possibly better reflected visually in plots derived from arms-based than contrast-based meta-analyses,[41] is possibly a strength towards realising spillover and rebound effects as being not confined to any specific topical ABD regimen or ICU study population.

Few controlled trials were published outside North America and Northern Europe. The patterns of infections among ICU patients differ around the world in relation to the bacterial causes of infection.[62 63] This may limit the geographical generalisability of the findings.

The relative merits of contrast-based versus arms-based meta-analyses are discussed elsewhere.[28] Notably, contrast-based methods require intervention and control group pairs, and this in turn requires greater assumptions regarding both the absence of indirect effects between the pairs and missing values.[28 64]

CONCLUSION

The tempo of acquisition of BSIs among CC control groups of ABD intervention RCCTs is increased versus that within other groups. This implicates rebound and spillover effects among the ABD RCCTs which are inapparent within individual RCCTs and conflate the appearance of ABD benefit. Rebound and spillover causing higher-than-expected BSI incidence would contribute to the higher-than-expected mortality within the CC arms of ABD RCCTs.[29] With these findings, the mediation of ABD effects observed in controlled trials are mediated by COGO and CS, whereas CR is untenable as a mechanism.

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