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Letter to the Editor

Split-surface randomization as a pragmatic design for early-phase environmental disinfection trials

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Introduction

Environmental disinfection trials in acute care patient rooms are limited by substantial heterogeneity in environmental contamination. Prior studies have shown marked variability in bioburden across rooms and across surfaces within the same unit, even when sampling is performed contemporaneously, with baseline differences often spanning orders of magnitude.[1–6] Much of this variability reflects differences in patient-level microbial shedding, which is influenced by clinical and behavioral factors including infection status, diarrhea, incontinence, mobility, and activities of daily living. As a result, environmental contamination is often driven by highly variable patient contributions. This heterogeneity complicates both trial design and interpretation, as intervention effects may be obscured by between-room differences rather than reflecting true disinfectant efficacy. These challenges are particularly relevant for early-phase studies translating laboratory-based findings into clinical environments.

One approach to address environmental heterogeneity is to randomize at the room level and enroll a sufficiently large number of rooms to overcome baseline variability. However, power calculations based on observed inter-room differences in environmental bioburden indicate that thousands of rooms may be required to detect modest reductions. In practice, this translates to large, multicenter trials with substantial financial and operational burden. Such studies are rarely feasible for disinfectants that have demonstrated efficacy only under controlled laboratory conditions, creating a gap between bench-based evidence and pragmatic evaluation in real-world clinical settings.

Pre–post sampling designs are commonly used to improve feasibility in environmental disinfection studies, but these approaches introduce important methodological limitations. Baseline sampling typically requires wiping or swabbing of surfaces, which itself functions as a mechanical cleaning event and can reduce recoverable bioburden in subsequent sampling. This phenomenon, a repeated-sampling effect, may lead to an apparent reduction in contamination that is independent of the disinfectant intervention. As a result, pre–post designs can overestimate disinfectant efficacy, particularly when evaluating interventions expected to produce modest effects in complex clinical environments.[2,7–9]

To address these limitations, we propose split-surface randomization as a pragmatic design for early-phase environmental disinfection trials. In this approach, comparable surfaces within the same patient room are divided (e.g., left–right) and randomized to intervention or control conditions, allowing each room to serve as its control. For example, surfaces such as bedrails divided left–right, randomly assigned intervention disinfectant or standard cleaning, and paired environmental samples compare contamination within the same room. By reallocating environmental heterogeneity from between-room to within-room variance, this design reduces the influence of baseline differences that otherwise drive sample size requirements. We developed and implemented this approach in recent real-world disinfection studies. In one randomized clinical trial, enrollment of 50 patient rooms yielded approximately 600 environmental samples, allowing detection of a significant reduction in contamination despite substantial between-room variability.[3] In a separate randomized study, baseline equivalence between split surfaces was established across 122 fomites (phase 1), followed by evaluation of disinfectant efficacy across 196 fomites and 392 paired samples (phase 2), again enabling detection of a clear efficacy signal.[10] Across studies, baseline bioburden between split surfaces was highly comparable prior to intervention; no statistically significant differences between split surfaces were detected at baseline, supporting the validity and efficiency of within-room comparisons.

Split-surface randomization offers several practical advantages for early-phase environmental disinfection studies. By enabling within-room comparisons, this approach increases statistical power without requiring enrollment of large numbers of rooms, thereby reducing cost and logistical burden. It also minimizes confounding from patient-level, room-level, and temporal factors that are difficult to control in clinical environments. Importantly, this design can be implemented within single-center studies without disrupting environmental services workflows and without withholding cleaning or disinfection from any patient care area, making it both operationally feasible and ethically acceptable.

Failure to account for environmental heterogeneity and sampling-related artifacts may contribute to inconsistent findings in disinfection studies. Interventions producing modest but meaningful reductions in contamination may be misclassified as ineffective when evaluated using underpowered room-level designs, while repeated-sampling effects may exaggerate apparent efficacy in uncontrolled pre–post studies. By enabling efficient within-room comparisons, split-surface randomization provides a more

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reliable means to detect true intervention effects under real-world conditions.

Despite these advantages, split-surface randomization has important limitations. Because only a portion of a patient room receives the intervention, this design is not suited to evaluating patient-level clinical outcomes, such as healthcare-associated infection incidence. Certain interventions, particularly those with substantial aerosolization, surface carryover, or whole-room effects, may introduce cross-surface contamination that could attenuate observed differences. Left–right (or door-side vs non–door-side) surfaces may also differ in contact frequency due to patient or caregiver handedness and room workflow patterns; although randomization helps balance these effects, residual asymmetry may persist. Finally, because split-surface designs generate paired, nonindependent observations, appropriate paired or mixed-effects methods are required to avoid biased inference. For these reasons, split-surface randomization should be viewed as a complementary approach for early-phase studies rather than a replacement for whole-room trials.

We propose that split-surface randomization be used as an initial, real-world trial design to evaluate environmental disinfectant efficacy prior to undertaking large, room-level randomized controlled trials. By allowing efficient detection of environmental efficacy signals under routine clinical conditions, this approach can inform go/no-go decisions and guide selection of interventions worthy of further evaluation. Once efficacy has been demonstrated using split-surface designs, subsequent whole-room randomized trials can be appropriately powered and structured to assess clinical outcomes, cost-effectiveness, and implementation at scale. Aligning trial design with study phase may help bridge the persistent gap between laboratory-based disinfectant testing and rigorous evaluation in patient care environments.

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