Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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“Targeted Versus Universal Decolonization to Prevent ICU Infections”

Supplementary Material

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Statistical Analysis

Most methods for data analysis, including the proportional hazards or "Cox" regression models often used for time-to-event outcomes, include an assumption of uncorrelated observations. That is, they assume that no pair of observations is any more or less similar than any other pair of observations. However, in cluster-randomized trials like the REDUCE MRSA trials, this assumption does not hold. In particular, two observation from the same hospital are likely more similar than two observations from different hospitals, and this is expressed statistically as correlation. It may help to imagine why this would be so: for example, MRSA may be more endemic in one hospital's catchment area, or perhaps one or more staff members may be colonized at another hospital. A third hospital may have an inspiring leader who generates a culture of greater levels of hygiene than is possible elsewhere.

In any event, the correlation within hospital must be accounted for in the data analysis: applying a proportional hazards model without doing so will lead, generally, to a smaller p-value than is appropriate. One convenient way of accounting for the correlation is by introducing a random effect for each hospital. This approach has the salutary effect of also accounting for the different number of patients at each hospital. The model used in the REDUCE MRSA trial can be represented as:

$$\lambda_{ij}(t) = \lambda_0(t)e^{X_{ij}\beta+\gamma_i}$$

where i indexes hospitals and j indexes individuals within hospital. X_{ij} is a covariate vector containing a period indicator (=0 for patients seen in the baseline period and 1 for intervention), arm indicators (a variable which equals 1 for hospitals in arm 2 and 0 for the other arms, and a similar one for arm 3) and the interactions, simply the product of the period indictor with each of the arm indicators. The main study question is addressed by the 2 degree or freedom test of the two interactions. This assesses the hypothesis that the arm 2 difference in periods and the arm 3 difference in periods are simultaneously equal to the arm 1 difference in periods. The γ_i term is the random effect, or "shared frailty" that is unique to each hospital i and applies to all patients at that hospital, thus accounting for the correlation among the patients there.

Table S1. ICU Population Characteristics by Arm (Full Version)

	Baseline 12 months N = 48,390 Admissions with ICU Stay			Intervention 18 months N = 74,256 Admissions with ICU Stay		
Variable	**Arm 1 %**	**Arm 2 %**	**Arm 3 %**	**Arm 1 %**	**Arm 2 %**	**Arm 3 %**
Admissions with ICU stay (N)	15,816	15,218	17,356	23,480	24,752	26,024
Attributable ICU Patient Days (N)	63,135	57,418	69,668	88,222	92,978	101,603
ICU Type [a]						
Medical	3	5	5	3	5	5
Surgical	1	2	6	1	2	6
Mixed Medical/Surgical	19	14	18	19	15	17
Hospital Stay in Days (Median (IQR))	7 (5-12)	7 (5-12)	8 (5-12)	7 (5-12)	7 (5-12)	7 (5-12)
ICU stay in Days (Median (IQR))	3 (2-5)	3 (2-5)	3 (2-5)	3 (1-5)	3 (2-5)	3 (2-5)
Age in Years (Median (IQR))	65 (52-77)	66 (53-77)	65 (51-77)	65 (52-77)	66 (53-77)	65 (52-77)
Female [b]	47.2	47.2	47.9	47.6	47.2	47.5
Race						
White	74.1	77.9	69.2	74.1	76.5	68.3
Black	17.0	11.0	9.5	16.5	12.1	9.1
Hispanic	4.2	8.4	17.8	4.5	8.5	18.8
Asian	1.9	0.9	0.8	1.9	0.9	0.6
Other	1.7	0.8	1.5	1.9	0.9	1.8
Unknown	1.2	1.1	1.2	1.1	1.0	1.4
Insurance						
Medicare	57.4	61.1	57.3	57.9	61.6	57.4
Commercial	25.0	21.9	23.8	23.2	19.7	22.5
Medicaid	7.9	8.2	8.0	8.2	8.2	8.3
Self Pay	5.6	6.1	5.9	6.7	7.2	6.5
Free Care	2.3	1.8	3.4	2.1	2.0	3.2
Other	1.8	0.8	1.4	1.8	1.2	1.9
Unknown	0.1	0.1	0.2	0.1	0.0	0.2
Comorbidities						
COPD	32.2	30.7	28.4	30.8	30.2	27.3
Diabetes	31.3	33.0	30.7	31.8	32.7	31.5
Congestive heart failure	25.2	27.0	23.4	24.1	25.4	22.6
Renal failure	20.0	20.4	19.0	20.3	22.2	19.7
Myocardial infarction	18.1	19.7	16.9	17.1	17.9	15.9
Cerebrovascular disease	14.7	12.5	13.9	14.7	12.5	14.4
Peripheral vascular disease	11.8	11.7	10.7	10.9	11.0	10.1

Cancer	10.4	10.8	14.1	9.9	10.8	13.0
Hemiplegia/paraplegia	3.7	3.5	4.2	4.4	4.1	4.8
Liver failure	3.4	4.4	3.9	4.0	4.1	4.2
Peptic ulcer disease	2.8	3.7	3.1	3.0	3.5	2.9
Rheumatologic disease	2.8	2.9	2.8	2.8	2.9	3.1
Dementia	2.5	2.6	2.7	2.2	2.8	2.7
AIDS	0.6	0.5	0.5	0.6	0.5	0.4
History of MRSA [c]	10.2	11.5	10.6	9.7	11.1	3.9 [d]
Culture/screen from prior admission	7.3	8.7	7.3	7.1	8.3	2.7
Culture from current admission	2.9	2.8	3.3	2.5	2.8	1.2
Screen from current admission	0.02	0.00	0.02	0.00	0.01	N/A
Surgery During Admission	40.5	38.6	47.5	38.7	37.7	46.2

[a] Differences between baseline and intervention periods reflects small number of adult ICUs that opened or closed during the trial.

[b] Missing for 8 patients

[c] History of MRSA is defined using all available screening and clinical cultures, and HCA MRSA history flags within the year prior to admission until day 2 of the ICU stay. Subcategories are mutually exclusive and prioritized in the following order: 1) positive MRSA clinical culture or screen from prior admission, 2) positive MRSA clinical culture from current admission (up until 2 days of the ICU stay), and 3) MRSA identified solely by screening culture up until day 2 of the ICU stay.

[d] History of MRSA from the Arm 3 intervention is not comparable to the other arms because ICU screening was stopped in this arm and active decolonization was occurring for all patients. As the intervention progressed, patients being readmitted may have been less likely to be identified as MRSA-positive. Patients with a prior ICU admission would be less likely to be screened for MRSA and less likely to acquire MRSA due to universal decolonization. In this trial, 47% of patients with a history of MRSA had a previous admission in the past year.

Table S2. Adverse Events Associated with Chlorhexidine Decolonization [a]

Severity [b]	Frequency	Symptom	Body Location	Definitely Related	Drug Discontinued
Mild	7	erythema (6), pruritis (1)	localized (4), diffuse (3)	4	7
Moderate	0	N/A	N/A	N/A	N/A
Severe	0	N/A	N/A	N/A	N/A

[a] Based upon instruction to report any possible or probable events associated with any decolonization product. No reports of adverse events were received for mupirocin.

[b] Definitions are as follows: 1) mild: any criteria less than moderate, b) moderate: any moderate erythema, scaling or blistering that involves >30% body surface area, c) severe: any severe erythema, scaling or blistering that involves >30% body surface area

Table S3. Bloodstream Pathogens by Study Arm in Baseline and Intervention Periods per 1,000 Attributable ICU Days [a]

	Bloodstream Infections per 1,000 Attributable ICU Days					
Pathogen (Ordered by Frequency)	**Arm1**		**Arm 2**		**Arm 3**	
	Baseline	**Intervention**	**Baseline**	**Intervention**	**Baseline**	**Intervention**
Total Events (N)	**265**	**360**	**273**	**341**	**412**	**356**
***Staphylococcus aureus* (N)**	77	128	70	106	80	92
Methicillin-Resistant (MRSA)	0.46	0.49	0.47	0.56	0.58	0.38
Methicillin-Susceptible (MSSA)	0.77	0.97	0.75	0.59	0.61	0.54
Total	**1.23**	**1.46**	**1.23**	**1.15**	**1.19**	**0.92**
Coagulase-Negative *Staphylococcus*[b] (N)	48	54	43	42	116 [c]	36
Total	**0.77**	**0.62**	**0.75**	**0.46**	**1.72**	**0.36**
***Candida* (N)**	38	49	56	63	59	62
Candida albicans	0.37	0.21	0.51	0.31	0.44	0.26
Candida glabrata	0.11	0.21	0.26	0.20	0.22	0.22
Candida parapsilosis	0.06	0.11	0.07	0.08	0.09	0.05
Candida tropicalis	0.05	0.02	0.11	0.05	0.12	0.04
Candida krusei	0.00	0.00	0.04	0.03	0.00	0.02
Candida lusitaniae	0.00	0.00	0.00	0.01	0.00	0.01
Candida sp.(unspeciated)	0.02	0.01	0.00	0.00	0.00	0.02
Total	**0.61**	**0.56**	**0.98**	**0.68**	**0.87**	**0.62**
***Enterococcus* (N)**	33	42	37	45	44	50
Enterococcus faecalis	0.32	0.22	0.37	0.30	0.36	0.30
Enterococcus faecium	0.18	0.25	0.21	0.14	0.24	0.15
Enterococcus sp.	0.03	0.01	0.07	0.04	0.06	0.05
Total	**0.53**	**0.48**	**0.65**	**0.49**	**0.65**	**0.50**
***Klebsiella* (N)**	16	15	12	17	24	25
Klebsiella pneumoniae	0.24	0.13	0.21	0.17	0.27	0.25
Klebsiella oxytoca	0.02	0.05	0.00	0.01	0.09	0.00
Total	**0.26**	**0.17**	**0.21**	**0.18**	**0.36**	**0.25**
***Escherichia coli* (N)**	10	22	11	15	15	22
Total	**0.16**	**0.25**	**0.19**	**0.16**	**0.22**	**0.22**
***Enterobacter* (N)**	5	12	8	13	20	19
Enterobacter cloacae	0.02	0.09	0.12	0.11	0.22	0.12
Enterobacter aerogenes	0.06	0.03	0.02	0.01	0.06	0.07
Enterobacter agglomerans	0.00	0.01	0.00	0.00	0.00	0.00
Enterobacter sp.	0.00	0.00	0.00	0.02	0.01	0.00

Total	**0.08**	**0.14**	**0.14**	**0.14**	**0.30**	**0.19**
***Pseudomonas* (N)**	5	14	8	13	11	14
Pseudomonas aeruginosa	0.08	0.15	0.14	0.14	0.16	0.13
Pseudomonas sp.	0.00	0.01	0.00	0.00	0.00	0.01
Total	**0.08**	**0.16**	**0.14**	**0.14**	**0.16**	**0.14**
***Streptococcus* (N)**	6	3	8	9	11	5
Streptococcus viridans grp [b]	0.03	0.00	0.11	0.03	0.06	0.01
Streptococcus, Group B	0.03	0.02	0.04	0.03	0.03	0.02
Streptococcus pneumoniae	0.02	0.00	0.00	0.02	0.03	0.00
Streptococcus, Group A	0.00	0.00	0.00	0.00	0.03	0.00
Streptococcus, Group C	0.02	0.00	0.00	0.00	0.00	0.01
Streptococcus anginosis grp	0.00	0.01	0.00	0.00	0.00	0.01
Streptococcus, Group F	0.00	0.00	0.00	0.01	0.00	0.00
Streptococcus, Group G	0.00	0.00	0.00	0.00	0.01	0.00
Total	**0.10**	**0.03**	**0.14**	**0.10**	**0.16**	**0.05**
***Acinetobacter* (N)**	9	7	5	2	10	3
Acinetobacter baumannii	0.11	0.06	0.09	0.02	0.13	0.03
Acinetobacter lwoffii	0.03	0.00	0.00	0.00	0.01	0.00
Total	**0.14**	**0.08**	**0.09**	**0.02**	**0.15**	**0.03**
***Serratia* (N)**	2	2	5	3	10	5
Serratia marcescens	0.03	0.01	0.09	0.03	0.12	0.04
Serratia sp.	0.00	0.01	0.00	0.00	0.03	0.01
Total	**0.03**	**0.02**	**0.09**	**0.03**	**0.15**	**0.05**
***Bacteroides* (N)**	5	4	4	4	3	7
Bacteroides fragilis	0.03	0.05	0.02	0.02	0.03	0.03
Bacteroides, other sp.	0.05	0.00	0.05	0.02	0.01	0.04
Total	**0.08**	**0.05**	**0.07**	**0.04**	**0.04**	**0.07**
***Proteus mirabilis* (N)**	3	1	3	2	2	4
Total	**0.05**	**0.01**	**0.03**	**0.02**	**0.03**	**0.04**
***Stenotrophomonas maltophilia* (N)**	1	4	0	1	2	4
Total	**0.02**	**0.05**	**0.00**	**0.01**	**0.03**	**0.04**
***Clostridium* (N)**	1	1	1	1	2	4
Total	**0.02**	**0.01**	**0.02**	**0.01**	**0.03**	**0.04**
***Citrobacter* (N)**	1	1	0	1	0	1
Citrobacter freundii	0.02	0.01	0.00	0.00	0.00	0.01
Citrobacter koseri	0.00	0.00	0.00	0.01	0.00	0.00
Total	**0.02**	**0.01**	**0.00**	**0.01**	**0.00**	**0.01**
***Morganella morganii* (N)**	0	0	0	2	1	1
Total	**0.00**	**0.00**	**0.00**	**0.02**	**0.01**	**0.01**

***Achromobacter sp.* (N)**	0	1	0	0	1	1
Total	**0.00**	**0.01**	**0.00**	**0.00**	**0.01**	**0.01**
***Providencia stuartii* (N)**	2	0	0	1	0	0
Total	**0.03**	**0.00**	**0.00**	**0.01**	**0.00**	**0.00**
***Alcaligenes xylosoxidans* (N)**	2	0	0	0	0	0
Total	**0.03**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
***Pantoea agglomerans* (N)**	0	0	1	0	1	0
Total	**0.00**	**0.00**	**0.02**	**0.00**	**0.01**	**0.00**
Other (N)	1	0	1	1	0	1
Total	**0.02**	**0.00**	**0.02**	**0.01**	**0.00**	**0.01**
GRAND TOTAL	**4.25**	**4.11**	**4.78**	**3.69**	**6.11**	**3.56**

[a] Totals may not be the exact sum of components due to rounding.

[b] Bloodstream infection based upon CDC criteria for skin commensals (requires two cultures within two calendar days)

[c] 83 of the baseline events in Arm 3 occurred in the three facilities with bone marrow transplant units and solid organ transplant programs. In the baseline period, the risk of coagulase-negative staphylococcal bloodstream infection (2 cultures required by CDC criteria) in these three hospitals was 0.01 compared to 0.003 in Arm 1, 0.003 in Arm 2, and 0.004 in all other Arm 3 hospital.