Supplemental Appendix:

Methods:

Cultures methods:

Swabs were inoculated onto 5% sheep blood agar plates with and without colistin/nalidixic acid. Plates were incubated at 35 degrees C and inspected at 18-24 hours, then were held at room temperature and reinspected at 48 hours. Suspect colonies were tested for production of catalase (using hydrogen peroxide; if positive, *Staphylococcus*) and coagulase and/or protein A (using the Staphaurex assay [Remel]; if positive, presumptive SA). Catalase-positive, Staphaurex-negative colonies that resembled SA underwent a tube coagulase test (if positive, presumptive SA). Susceptibility testing of presumptive SA isolates was done using the Vitek 2 instrument (bioMerieux).

Sample size and power calculation:

We estimated power for a range of possible treatment effects for this outpatient intervention. With 56 participants per group, power was 0.98 if SA eradication was assumed to be 62.5% in the decolonization bundle group (i.e., 37.5% with post-treatment SA carriage) and 25% in the control group (i.e., 75% with post-treatment SA carriage), with type 1 error = 0.05 (2-sided). If SA eradication was assumed to be 50% in the decolonization bundle group, power was 0.79. For reference, Kalmeijer et al. found in a decolonization trial that among inpatients with pre-treatment nasal SA carriage, 16.5% of mupirocin recipients and 78.2% of placebo recipients had post-treatment nasal SA carriage.17 We anticipated screening 400 participants to identify 112 SA-colonized participants who were eligible for randomization.

Results:

Safety

No participants experienced a SAE during the study. By contrast, 45% of decolonization bundle group members and 21% of control group members reported an ADE. Most ADEs were mild; none was life threatening (Supplemental Tables 4a and 4b). By drug, the most common ADEs and their prevalence (proportion [% of participants]) were: for nasal mupirocin, mild burning (2/57 [3.5%]); for CHG soap, mild dryness (5/57 [8.8%]); and for CHG mouthwash, mild unpleasant taste (4/57 [9.5%]) and moderate dryness (4/57 [9.5%]). No safety concerns were identified at the interim data safety monitoring review or subsequently.

**Supplemental Table 1. Number of reported missed doses for treatment arm participants who had completed drug diary information for chlorhexidine gluconate (CHG) mouthwash, CHG soap, and mupirocin ointment.**.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Treatment Component** | |  | **Number of Reported Missed Doses\*** | | | | | | | | | | | | | | |
| **0** | | **1** | | **2** | **3** | | **4** | | **5** | | **7** | | **9** | | |
| **Mupirocin (n=52)** | 35 (67.3%) | | | 7 (13.5%) | | 3 (5.8%) | | 3 (5.8%) | | 2 (3.8%) | | 0 (0.0%) | | 1 (1.9%) | | 1 (1.9%) | |
| **CHG soap\*\* (n=52)** | 43 (82.7%) | | | 5 (9.6%) | 2 (3.8%) | | | 1 (1.9%) | | 1 (1.9%) | | 0 (0.0%) | | - | | - |
| **CHG mouthwash\*\*\* (n=41)** | 29 (70.7%) | | | 5 (12.2%) | | 3 (7.3%) | | 2 (4.9%) | | 0 (0.0%) | | 0 (0.0%) | | 1 (2.4%) | | 1 (2.4%) | |

Note: \*No one reported missing 6, 8, or 10 doses of any treatment and these have been excluded from the table. \*\*CHG soap is only applied once a day for 5 days and the mupirocin nasal ointment and CHG mouthwash are applied twice daily for 5 days. \*\*\*Mouthwash information only included for those enrolled after mouthwash added to treatment bundle.

**Supplemental Table 2. *Staphylococcus aureus* (SA) culture results at baseline and post-treatment by site of culture and treatment group for evaluable participants (n = 110).**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Site** | **Group** | **Both positive** | **Both negative** | **Baseline positive,**  **post-treatment**  **negative** | **Baseline negative, post-treatment positive** |
| **Nares** | **Bundle** | 5/57 (8.8 %) | 6/57 (10.5 %) | 46/57 (80.7 %) | 0/57 (0.0 %) |
| **Control** | 37/53 (69.8 %) | 8/53 (15.1 %) | 7/53 (13.2 %) | 1/53 (1.9 %) |
| **Throat** | **Bundle** | 7/57 (12.3 %) | 39/57 (68.4 %) | 9/57 (15.8 %) | 2/57 (3.5 %) |
| **Control** | 6/53 (11.3 %) | 27/53 (50.9 %) | 13/53 (24.5 %) | 7/53 (13.2 %) |
| **Perianal** | **Bundle** | 0/57 (0.0 %) | 48/57 (84.2 %) | 7/57 (12.3 %) | 2/57 (3.5 %) |
| **Control** | 5/53 (9.4 %) | 41/53 (77.4 %) | 5/53 (9.4 %) | 2/53 (3.8 %) |
| **Axilla** | **Bundle** | 2/57 (3.5 %) | 51/57 (89.5 %) | 3/57 (5.3 %) | 1/57 (1.8 %) |
| **Control** | 4/53 (7.5 %) | 44/53 (83.0 %) | 3/53 (5.7 %) | 2/53 (3.8 %) |

Mouthwash was added to the bundle after the first 35 SA carriers were randomized.

.**Supplemental Table 3. Study participants with *Staphylococcus aureus* (SA) carriage following treatment, showing subgroup comparisons for whether participants received mouthwash with the decolonization bundle or not.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Participants with SA,**  **proportion (%)** | |  |  | |
| **Site(s)** | **Mouthwash use in bundle** | **Decolonization**  **bundle group** | **Control group** | **Absolute difference**  **[95% CI]** | | **p-value for inter-action** |
| Any site | Overall | 16/57 (28.1%) | 40/53 (75.5%) | -47.4% [-62.9, -29.6] |  | |
|  | No-mouthwash period | 3/15 (20.0%) | 12/15 (80.0%) | -60.0% [-84.6, -22.9] | 0.72 | |
|  | Mouthwash period | 13/42 (31.0%) | 28/38 (73.7%) | -42.7% [-61.3, -21.3] |  | |
| Throat | Overall | 9/57 (15.8%) | 13/53 (24.5%) | -8.7% [-27.1, 10.2] |  | |
|  | No-mouthwash period | 3/15 (20.0%) | 3/15 (20.0%) | 0.0% [-37.4, 37.4] | 0.85 | |
|  | Mouthwash period | 6/42 (14.3%) | 10/38 (26.3%) | -12.0% [-33.2, 10.2] |  | |

In this table we are comparing if the proportions are different overall in the two study groups overall, and by study period, before and after mouthwash added to bundle.

Mouthwash was added to the bundle after the first 35 SA carriers were randomized. The interaction between the change in treatment protocol and treatment group was not significant for all sites. **Supplemental Table 4a. Participant reported adverse drug events (ADEs) and strength of ADE by component for decolonization bundle group.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Strength of Effect** | | |
| **Component and ADE** | **Mild** | **Moderate** | **Severe** |
| |  |  |  |  | | --- | --- | --- | --- | |  | | | | | **Mupirocin nasal ointment (N = 57)** | | | | | **Burning** | 2 (3.5 %) | 0 (0.0 %) | 0 (0.0 %) | | **Itching** | 1 (1.8 %) | 0 (0.0 %) | 0 (0.0 %) | | **Redness** | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | | **Dryness** | 1 (1.8 %) | 0 (0.0 %) | 0 (0.0 %) | | **Tenderness** | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | | **Other** | 5 (8.8 %) | 1 (1.8 %) | 1 (1.8 %) | |  |  |  |  | | **CHG soap (N = 57)** | | | | | **Burning** | 1 (1.8 %) | 0 (0.0 %) | 1 (1.8 %) | | **Itching** | 2 (3.5 %) | 1 (1.8 %) | 2 (3.5 %) | | **Redness** | 2 (3.5 %) | 0 (0.0 %) | 1 (1.8 %) | | **Dryness** | 5 (8.8 %) | 1 (1.8 %) | 1 (1.8 %) | | **Tenderness** | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | | **Other** | 1 (1.8 %) | 1 (1.8 %) | 0 (0.0 %) | |  | | | | | **CHG mouthwash (N = 42)** | | | | | **Burning** | 1 (2.4 %) | 2 (4.8 %) | 0 (0.0 %) | | **Dryness** | 1 (2.4 %) | 4 (9.5 %) | 0 (0.0 %) | | **Unpleasant Taste** | 4 (9.5 %) | 3 (7.1 %) | 1 (2.4 %) | | **Discolored Teeth** | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | | **Tenderness** | 1 (2.4 %) | 1 (2.4 %) | 0 (0.0 %) | | **Other** | 1 (2.4 %) | 3 (7.1 %) | 0 (0.0 %) |   **Note: CHG, chlorhexidine gluconate** | | | |

**Supplemental Table 4b. Participant reported adverse drug events (ADEs) and strength of ADE** **for control group**, **using** **antiseptic soap (N=53).**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Strength of Effect** | | |
| **ADE** | **Mild** | **Moderate** | **Severe** |
| **Burning** | 3 (5.7%) | 1 (1.9%) | 0 (0.0%) |
| **Itching** | 3 (5.7%) | 0 (0.0%) | 0 (0.0%) |
| **Redness** | 2 (3.8%) | 0 (0.0%) | 0 (0.0%) |
| **Dryness** | 3 (5.7%) | 2 (3.8%) | 0 (0.0%) |
| **Tenderness** | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Other** | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

**Supplemental Table 5. Distribution by body site of *Staphylococcus* *aureus* genotypes from the baseline cultures of pre-operative patients, according to pulsed-field gel electrophoresis.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Site** | **Hospital-Acquired** | | **Community-Acquired** | | **Other** | |
| **MSSA** | **MRSA** | **MSSA** | **MRSA** | **MSSA** | **MRSA** |
| **Nares** | 16 | 2 | 3 | 3 | 79 | 6 |
| **Throat** | 6 | 1 | 1 | 3 | 24 | 3 |
| **Perianal** | 1 | 0 | 1 | 2 | 15 | 0 |
| **Axilla** | 2 | 0 | 1 | 0 | 7 | 3 |

Pre-operative counts of hospital-acquired (USA type 100/200), community-acquired (USA type 300/400) MSSA (methicillin sensitive *Staphylococcus aureus*), or MRSA (methicillin resistant *Staphylococcus aureus*), and Other (other USA types or unclassified types).