# Integrating Personal and Household Environmental Hygiene Measures to Prevent Methicillin-Resistant *Staphylococcus aureus*

**Principal Investigator: Stephanie A. Fritz, MD, MSCI**

**Version Number: 1.0**

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## STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (1997)
- AHRQ Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

## SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:*
Signed: Date:

*Name: Stephanie A. Fritz*
*Title: Principal Investigator*

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event/Adverse Experience |
| AHRQ | Agency for Healthcare Research and Quality |
| CA-MRSA | Community-Associated Methicillin-Resistant *Staphylococcus aureus* |
| CDC | Centers for Disease Control and Prevention |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CLSI | Clinical Laboratory Standards Institute |
| DSMP | Data and Safety Monitoring Plan |
| ED | Emergency Department |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HA-MRSA | Healthcare-Associated Methicillin-Resistant *Staphylococcus aureus* |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IDSA | Infectious Diseases Society of America |
| IEC | Independent or Institutional Ethics Committee |
| IRB | Institutional Review Board |
| JAMA | Journal of the American Medical Association |
| MRSA | Methicillin-Resistant *Staphylococcus aureus* |
| MSSA | Methicillin-Susceptible *Staphylococcus aureus* |
| N | Number (typically refers to subjects) |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| OHRP | Office for Human Research Protections |
| PAWS | Pediatric Acute Wound Service |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| QC | Quality Control |
| REDCap | Research Electronic Data Capture |
| repPCR | repetitive-sequence polymerase chain reaction |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SCCmec | *Staphylococcal* cassette chromosome *mec* |

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|---|---|
| SLCH | St. Louis Children's Hospital |
| SSTI | Skin and Soft Tissue Infection |
| TSB/TSA | Trypticase Soy Broth/Trypticase Soy Agar |
| US | United States |
| WU | Washington University - St. Louis, MO |
| WUCA | Washington University Clinical Associates |
| WU PAARC | Washington University Pediatric & Adolescent Ambulatory Research Consortium |

# PROTOCOL SUMMARY

| | |
|---|---|
| **Title:** | Integrating Personal and Household Environmental Hygiene Measures to Prevent Methicillin-Resistant *Staphylococcus aureus* |
| **Phase:** | IV |
| **Population:** | 207 index patients (the pediatric patient presenting with a community-onset *Staphylococcus aureus* infection who is screened for study participation) aged birth to 21 years with documented *S. aureus* infections and their household members (an individual who sleeps in the home ≥4 nights per week). |
| **Study Duration:** | October 2015 through October 2020 (anticipated) |
| **Subject Participation Duration:** | Approximately 9 months |
| **Description of Agent or Intervention:** | Following a 5-day Baseline Personal Decolonization performed by all household participants, households will be allocated 1:1:1 to one of three treatment groups. The assigned intervention will be performed for 3 months, and participants will be followed for an additional 6 months to track primary and secondary outcomes. The interventions are:<br><br>Group 1: Periodic Personal Decolonization: All household participants will perform chlorhexidine body washes (as described above) twice weekly for 3 months and apply mupirocin ointment to the anterior nares twice daily for five consecutive days each month for 3 months (Figures 2 and 3). Sufficient study materials for each assigned participant will be provided. A member of the study team will contact each household (via the family's preferred method: phone call, text message, or e-mail) several days prior to their designated period for monthly mupirocin application.<br><br>Group 2: Household Environmental Hygiene: In addition to their usual cleaning, households assigned to Group 2 will be asked to perform targeted household hygiene focusing on sources known to harbor *S. aureus* and serve as reservoirs for transmission. Specific recommendations include:<br><br>• Launder all bed linens once a week. |

- Replace each kitchen and bathroom hand towel with a clean towel each day. Alternatively, rather than cloth towels, disposable paper towels (provided by the study team) may be used in the kitchen and bathroom.
- Replace the kitchen sponge with a new sponge (provided by the study team) once a week.
- Wipe the following surfaces with Clorox Disinfecting Wipes (provided by the study team) once a week, using 1 wipe per surface:
    - TV remote controls, telephones, computer keyboards and mouse
    - Bathrooms: Countertop, sink, and sink faucet handles; light switch; bathtub and faucet handles; toilet handle and seat
    - Kitchen: Refrigerator and freezer door handles; microwave door handle and key pad; oven door handle; sink and sink faucet handle; table top; counter tops

At the enrollment visit, cleaning procedures will be demonstrated by study personnel, and printed instructions will be provided. Throughout the 3-month intervention period, to enhance adherence to the protocol, a member of the study team will contact each household weekly to remind them to perform targeted cleaning with the Clorox Disinfecting Wipes and to replace the kitchen sponge.

Group 3: Integrated Approach of Personal and Household Environmental Hygiene: Participants in households randomized to Group 3 will perform the Periodic Personal Decolonization described for Group 1, plus the Household Environmental Hygiene described for Group 2.

**Objectives:** To determine whether periodic personal decolonization performed by all household members (following baseline decolonization), weekly household environmental hygiene (following baseline decolonization) or a combination of the two for 3 months, results in a decreased incidence of *S. aureus* colonization and SSTI, both during and after the intervention period.

**Description of Study Design:** This is a pragmatic comparative effectiveness trial evaluating several decolonization strategies in patients with *S. aureus* infection, their

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| | household contacts, and household environmental surfaces. |
| **Estimated Time to Complete Enrollment:** | Forty-eight (48) months |

## Figure 1. Schematic of Study Design

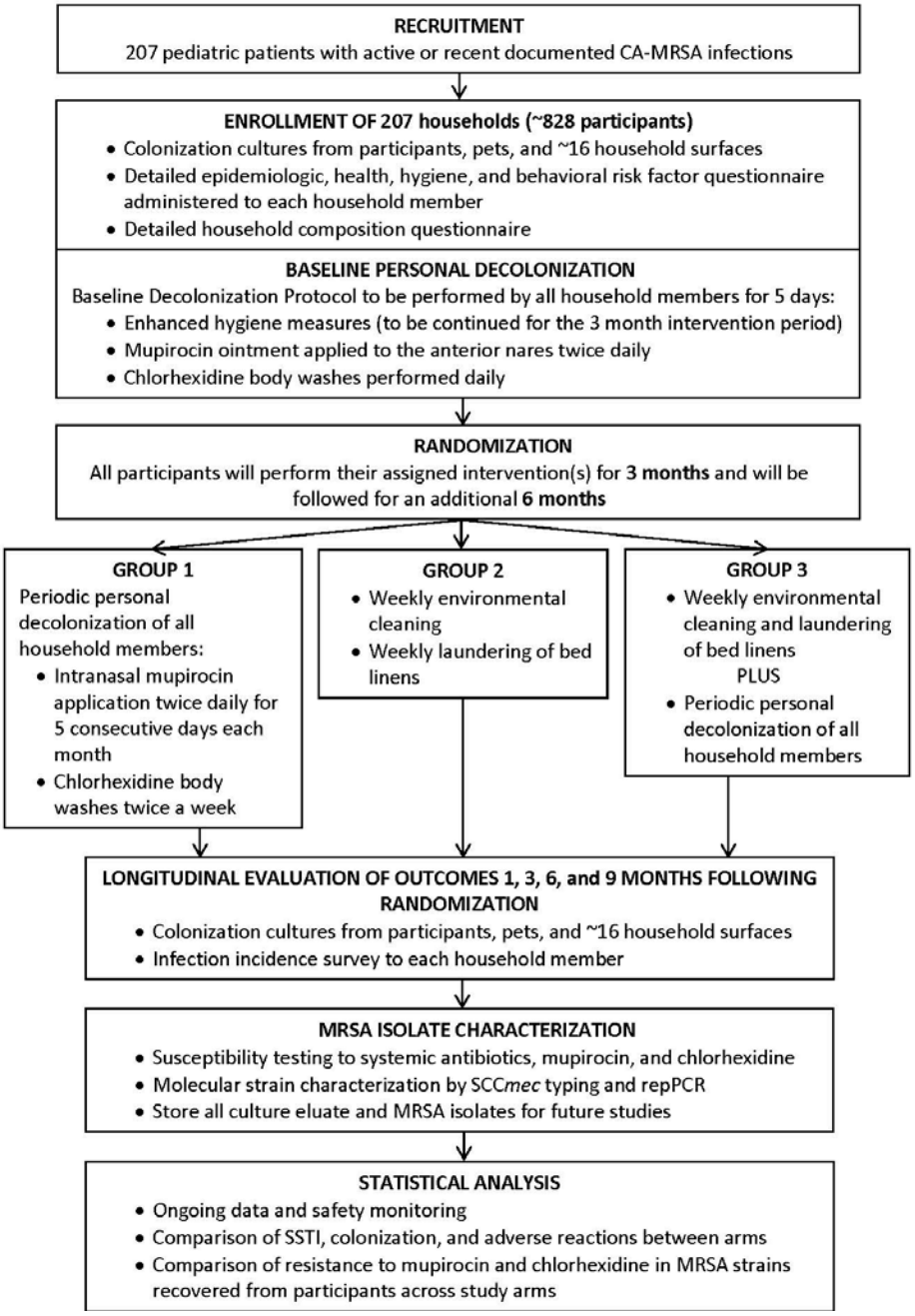


**Figure 1.** Schematic of Study Design

# 1 KEY ROLES

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# 2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 Background Information

**Description of the Proposed Clinical Trial.** This study is a pragmatic comparative effectiveness trial evaluating several decolonization strategies in patients with *Staphylococcus aureus* infection, their household contacts, and household environmental surfaces. The central hypothesis of this proposal is that an integrated approach of periodic personal and household environmental hygiene will reduce *S. aureus* transmission in households and subsequently decrease the incidence of skin and soft tissue infections (SSTI). Patients with active or recent *S. aureus* SSTI will be recruited from St. Louis Children's Hospital and community pediatric practices affiliated with our practice-based research network. All participants (index patients and their household contacts) will perform a baseline *S. aureus* decolonization protocol for 5 days consisting of enhanced hygiene measures, application of mupirocin antibiotic ointment to the anterior nares twice daily, and daily body washes with chlorhexidine antiseptic. Following the 5-day baseline decolonization regimen, households will be randomized to one of three intervention groups: 1) Periodic personal decolonization performed by all household members, to include chlorhexidine body washes twice weekly for 3 months and application of intranasal mupirocin for 5 consecutive days each month for 3 months; 2) Household environmental hygiene, including targeted cleaning of household surfaces and laundering of bed linens, weekly for 3 months; and 3) Integrated periodic personal decolonization and household environmental hygiene for 3 months. Households will be followed prospectively (1-, 3-, 6-, and 9-months following randomization) to measure the prevalence of *S. aureus* colonization in the participants, household environmental surfaces, and pet dogs and cats and to document the incidence of recurrent SSTI. Molecular strain typing will be performed on all recovered *S. aureus* isolates to illuminate transmission dynamics and the effects of the decolonization measures on genetic epidemiology. Resistance to the prescribed topical antimicrobials will be assessed at baseline and longitudinal samplings.

**Summary of Relevant Studies.** The *Staphylococcus aureus* epidemic poses a significant health and economic burden. The community has become an important and expanding reservoir for the spread of virulent Staphylococcus aureus strains into hospitals, likely increasing the severity of nosocomial *S. aureus* infections. Efforts are needed to lessen the spread of *S. aureus* in the community and decrease the burden of *S. aureus* infections. Households are significant reservoirs for *S. aureus* transmission and important targets for *S. aureus* eradication. Our prior study demonstrated that a one-time decolonization regimen performed by all household members reduced (but did not eliminate) the incidence of skin and soft tissue

infection (SSTI) in index patients and household contacts. Given the widespread dissemination of *S. aureus* and risk for ongoing exposure, a periodic approach to personal decolonization may provide sustained protection against *S. aureus* reacquisition. Additionally, environmental surfaces in households of patients with *S. aureus* infection are frequently and persistently contaminated with *S. aureus*. These surfaces serve as vectors for the acquisition and spread of *S. aureus* among household members. Thus, decontamination of household surfaces may limit the acquisition and spread of *S. aureus*.

**Burden of *S. aureus*:** In its 2013 "Threat Report," the Centers for Disease Control and Prevention classified methicillin-resistant *S. aureus (*MRSA*)* as having a threat level of "serious" [46]. In the U.S., annual deaths due to *S. aureus* infections exceed deaths due to influenza, viral hepatitis, and HIV/AIDS combined [47]. The tremendous burden posed by CA-*S. aureus* in the U.S. is evidenced by its annual incidence of 2 million infections, resulting in an estimated $16 billion in costs to third-party payers and society [48]. Over the past decade, the incidence of invasive CA-*S. aureus* infections has risen substantially, with a case-fatality rate of 6% [39,49-51]. The most common manifestation of CA-*S. aureus* infection is skin and soft tissue infection (SSTI). Although many SSTIs are superficial, they carry significant morbidity, including pain and subsequent scarring caused by drainage procedures, and time lost from school and work by patients and their families. Severe SSTI ranks among the top 10 reasons for pediatric hospital admissions [52]. Importantly, up to 70% of patients with CA-*S. aureus* SSTI will experience recurrences, even after successful initial treatment [6,8,53-55], provoking frustration for both patients and clinicians. These recurrent infections also necessitate repeated courses of antibiotic therapy, further driving the pressure for development of antibiotic resistance [12,56].

**Determinants of *S. aureus* infection:** *S. aureus* colonizes the anterior nares, throat, and skin, including the axilla, inguinal area, perineum, and rectum [4,57-64]. *S. aureus* carriage is a risk factor for the development of subsequent infections [2,57,65-69], and colonized individuals are also important sources for transmission [25]. Behavioral and environmental factors also play an important role in the transmission and pathogenesis of CA-*S. aureus* infection [17,71,72]. CA-*S. aureus* infections have been associated with use of contaminated fomites (e.g., shared personal hygiene items), poor hygiene, and close contact with infected individuals [17,73,74]. Prior SSTI is also a risk factor for developing subsequent SSTI [2,75]. CA-*S. aureus* disproportionately affects children, African Americans, and individuals of lower socioeconomic status [1-3,29,47,50,76-80]. Importantly, the epidemiology of *S. aureus* infections differs between children and adults [50,81]; as many preventive studies have focused mainly on adults, investigating optimal strategies to prevent *S. aureus* infections in children is of high priority.

**CA-*S. aureus* transmission:** Investigations of the evolution and spread of contemporary CA-*S. aureus* strains have determined that households serve as major reservoirs of CA-*S. aureus* persistence and transmission, even more so than other institutional environments [12,25]. *S. aureus* colonization and infections cluster among individuals within households [5,64,82-96]. Transmission of *S. aureus* between pets and humans has been described, although the

directionality is unclear [97-103]. Environmental surfaces serve as reservoirs for *S. aureus* transmission, and *S. aureus* strains persist within the household environment for prolonged periods of time, posing risk for the development of recurrent infections [17,32,75,90-92,96,104-108]. In healthcare settings and schools, enhanced cleaning of heavily used fomites and contaminated surfaces has resulted in reduced environmental contamination and decreased incidence of infection [107-110]. Yet, even in these settings, challenges persist [110]. To date, there are no controlled studies evaluating the effect of household hygiene on interrupting *S. aureus* household transmission or preventing *S. aureus* infections. These data are essential to inform clinical guidelines to reduce the burden of *S. aureus* disease [111-113].

**Prevention of CA-*S. aureus* infections:** There is no available vaccine against *S. aureus*. Thus, other preventive measures, including decolonization (i.e., "the use of antimicrobial or antiseptic agents to suppress or eliminate *S. aureus* carriage" [111]), have been used in an effort to prevent staphylococcal infections. Decolonization therapies include nasal mupirocin (a topical antibiotic with activity against *S. aureus*) and bathing with chlorhexidine (a topical antiseptic). While application of these therapies for a discrete period is effective in *S. aureus* eradication, maintenance of eradication diminishes over time [6,8,114-120]. Decolonization measures traditionally employed in hospitals to combat S. *aureus* have been extrapolated to CA-*S. aureus* patients in community settings [18,111,113]. However, the paucity of data available to guide the prevention of recurrent *S. aureus* SSTI in community settings has engendered inconsistency in treatment and decolonization practices [111,113]. Several studies performed by our group and others in community settings have demonstrated that brief applications of topical antimicrobials effectively eradicate *S. aureus* carriage, yet patients continue to suffer a high burden of subsequent SSTI [6,8,72,119]. These findings may reflect ongoing exposure to other sources of *S. aureus*, including other individuals and environmental reservoirs, and suggest that a periodic approach to decolonization may provide more effective, sustained protection. Of note, a recent trial of twice-weekly bleach baths performed for 3 months did not result in a statistically significant reduction of medically-attended SSTI [63]. As not all patients with recurrent SSTI seek medical attention [4], the effectiveness of this intervention may have been underestimated. Additionally, this trial did not utilize mupirocin, and thus, did not address intranasal staphylococcal carriage.

An important consideration for *S. aureus* decolonization is the emergence of staphylococcal strains resistant to topical antimicrobial agents. The genes conferring resistance to mupirocin (most commonly *mupA*) and chlorhexidine (most commonly *qacA/B*) are carried on plasmids that can also harbor genes conferring resistance to other systemic antibiotics [121-128]. Indiscriminate use of topical antimicrobials has been associated with increased prevalence of *S. aureus* strains resistant to these agents, which predicts failure of *S. aureus* decolonization efforts [9,121,124,128-134]. In patients undergoing peritoneal dialysis, repeated topical prophylaxis with mupirocin was associated with subsequent carriage of mupirocin-resistant *S. aureus* strains [135,136]. However, targeted use of mupirocin in immunocompetent patients was effective in preventing recurrent SSTI and did not result in development of widespread resistance over time [137]. Currently, the prevalence of mupirocin and chlorhexidine resistance is low in our community [9]. However, topical antimicrobials are being utilized with increasing frequency for *S. aureus*

eradication to prevent recurrent SSTI, preoperative eradication to prevent postsurgical infections, and routine bathing of hospitalized patients [120,121,138]. Thus, it is imperative to understand the epidemiology of mupirocin and chlorhexidine resistance, and to monitor the emergence of these resistant strains in healthcare and community settings.

**Importance of the Study.** The proposed trial takes an integrated approach to eradicating carriage and interrupting transmission of contemporary CA-*S. aureus*. To date, the majority of *S. aureus* eradication studies have evaluated protocols employing brief applications of topical antimicrobials. The few trials which have employed a prolonged decolonization approach have employed only intranasal colonization or antimicrobial body washes not a comprehensive approach aimed at the many anatomic sites which may harbor *S. aureus*. In addition, the household environment as a key reservoir for *S. aureus* is a recent revelation, and at present, the effect of enhanced, targeted household hygiene on reducing *S. aureus* transmission, infection, and colonization has not been evaluated. In this pragmatic comparative effectiveness trial, we will take an integrated approach to *S. aureus* eradication, evaluating both periodic personal decolonization and household hygiene to prevent *S. aureus* infection and transmission. We will monitor for selection of *S. aureus* strains resistant to mupirocin and chlorhexidine when these topical antimicrobials are used repeatedly over time. In addition, the biological repositories established in this study will support future innovative investigations of how eradication efforts influence the human and environmental microbiota.

## 2.2 Rationale

**Study Population.** We will recruit 207 index patients aged birth to 21 years with documented CA-*S. aureus* infections and their household members. Patients will be recruited from the St. Louis Children's Hospital ED, inpatient units, Pediatric Acute Wound Service (PAWS), and the *S. aureus* clinic, a subspecialty outpatient clinic devoted to the care of patients with CA-*S. aureus* infections. Patients will also be referred from community pediatric practices affiliated with the Washington University Pediatric and Adolescent Ambulatory Research Consortium (WU PAARC), a practice-based research network in metropolitan St. Louis and through electronic reports of applicable diagnostic codes from WUCA (Washington University Clinical Associates) practices. Recruitment from SLCH and WUCA/WU PAARC-affiliated practices provides a diverse geographic and sociodemographic study population. Additionally, prior participants from our household transmission dynamics study will be contacted; those interested and eligible will be enrolled.

The study team will recruit 207 households (~828 total participants) on a continuous basis over 48 months. Trial enrollment and randomization will take place in the homes of the study participants. Written informed consent will be obtained from all adult participants. A parent or legal guardian will provide consent for all minors. We will obtain written assent from minors of a developmentally appropriate age (typically ≥13 years).

**Study Arms.** Group 1: Periodic Personal Decolonization: All household participants will perform chlorhexidine body washes twice weekly for 3 months and apply mupirocin ointment to the anterior nares twice daily for five consecutive days each month for 3 months (**Figure 2**). Sufficient study materials for each assigned participant will be provided. A member of the study team will contact each household (via the family's preferred method: phone call, text message, or e-mail) several days prior to their designated period for monthly mupirocin application.

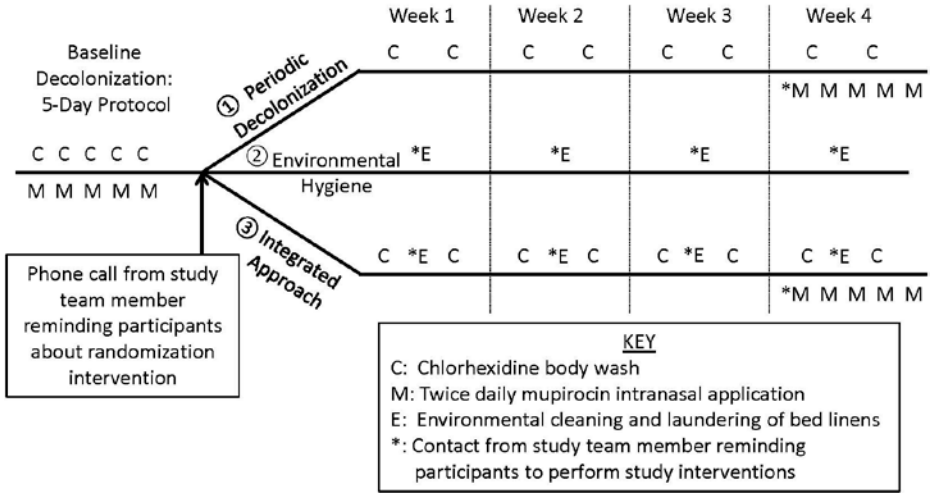



**Figure 2.** Timeline of baseline decolonization and interventions. The first month of the intervention is depicted and will be repeated for two additional months.

Group 2: Household Environmental Hygiene: In addition to their usual cleaning, households assigned to Group 2 will be asked to perform targeted household hygiene (**Figure 2**) focusing on sources known to harbor *S. aureus* and serve as reservoirs for transmission. Specific recommendations include:

- Launder all bed linens once a week.
- Replace each kitchen and bathroom hand towel with a clean towel each day. Alternatively, rather than cloth towels, disposable paper towels (provided by the study team) may be used in the kitchen and bathroom.
- Replace the kitchen sponge with a new sponge (provided by the study team) once a week.
- Wipe the following surfaces with Clorox Disinfecting Wipes (provided by the study team) once a week, using 1 wipe per surface:
    - TV remote controls, telephones, computer keyboards and mouse
    - Bathrooms: Countertop, sink, and sink faucet handles; light switch; bathtub and faucet handles; toilet handle and seat
    - Kitchen: Refrigerator and freezer door handles; microwave door handle and key pad; oven door handle; sink and sink faucet handle; table top; counter tops

At the enrollment visit, cleaning procedures will be demonstrated by study personnel, and printed instructions will be provided. Throughout the 3-month intervention period, to enhance adherence to the protocol, a member of the study team will contact each household weekly to remind them to perform targeted cleaning with the Clorox Disinfecting Wipes and to replace the kitchen sponge.

Group 3: Integrated Approach of Personal and Household Environmental Hygiene: Participants in households randomized to Group 3 will perform the Periodic Personal Decolonization described for Group 1, plus the Household Environmental Hygiene described for Group 2 (**Figure 2**).

**Hypothesis.** There are two primary scientific hypotheses for this study.

1. An integrated approach of periodic personal and household environmental hygiene will result in a lower incidence of SSTI at the household level 3 months following randomization compared to periodic personal decolonization or household environmental hygiene alone.

2. An integrated approach of periodic personal and household environmental hygiene will reduce *S. aureus* colonization in participants and household environmental surfaces and *S. aureus* transmission within households. Following baseline decolonization for 5 days performed by all participants, periodic decolonization with mupirocin and chlorhexidine over 3 months (Groups 1 and 3) will not result in a significant increase in the prevalence of resistance to these agents among *S. aureus* strains recovered at longitudinal samplings compared to baseline decolonization alone (Group 2).

## 2.3 Potential Risks

### 2.3.1 Potential Risks

Participants may experience one or more of the risks indicated below during this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study. Some questions the researchers ask might be uncomfortable. Obtaining swabs from the nostrils, underarms, and groin area might be uncomfortable. Dry skin may result from the use of chlorhexidine baths. The mupirocin ointment may cause diarrhea and/or irritation such as itching, burning, or stinging. Chlorhexidine baths may cause a mild rash, skin irritation, or sensitivity.

All of these problems will go away if use of the mupirocin or chlorhexidine products is stopped.

Chlorhexidine is for topical use only and should be applied from the neck down, avoiding the face. When using chlorhexidine, keep it out of mucus membranes. If contact with these areas does occur, rinse with cold water immediately. Do not routinely apply to open wounds. Avoid applying to genitals. Chlorhexidine is not readily absorbed through the skin. However, children under 2 months of age will not be assigned to use chlorhexidine. Women currently breastfeeding should avoid washing their breasts with chlorhexidine to ensure it is not ingested by their child.

There is a risk of loss of confidentiality but the study team will use best efforts to keep the information collected for this study secure.

### 2.3.2 Known Potential Benefits

This project may decrease the incidence of *S. aureus* infections, and thus reduce healthcare utilization for *S. aureus* treatment, potentially preventing additional spread of virulent *S. aureus* strains. The project findings may lead to therapeutic and/or preventive advances that will benefit a large number of patients and have a positive impact on healthcare utilization and expenditures.

# 3 OBJECTIVES

## 3.1 Study Objectives

The overall objective is to identify best strategies for curtailing the incidence of CA-*S. aureus* infections, thus reducing healthcare utilization for CA-*S. aureus* treatment, potentially preventing additional migration of virulent CA-*S. aureus* strains into hospitals. Non-immunocompromised pediatric subjects and their household contacts will be enrolled into an open-label, randomized, pragmatic, comparative effectiveness trial. Households will be randomized to periodic personal decolonization, environmental hygiene, or an integrated approach to help interrupt the spread of CA-*S. aureus* and prevent CA-*S. aureus* infections.

*Primary null hypotheses:*

1. The incidence of SSTI at the household level 3 months after randomization will not differ between the three decolonization strategies (integrated, periodic personal, and environmental hygiene).

*Primary objective:*

1. To determine whether periodic personal decolonization performed by all household members (following baseline decolonization), weekly household environmental hygiene (following baseline decolonization), or a combination of the two for 3 months, results in a decreased incidence of *S. aureus* colonization and SSTI, both during and after the intervention period.

## 3.2 Study Outcome Measures

### 3.2.1 Primary Outcome Measures

Incidence of SSTI at the household level (i.e., occurring in any household member) 3 months after randomization.

### 3.2.2 Secondary Outcome Measures

1. Baseline and longitudinal prevalence of *S. aureus* colonization in index patients, household contacts, pet dogs and cats, and household surfaces, and the molecular characterization (i.e., strain type) and relatedness of these recovered strains.
2. SSTI incidence at the household level 1, 6, and 9 months following randomization and at the individual level 1, 3, 6, and 9 months following randomization.
3. Development of a confirmed *S. aureus* infection over 9 months at the household and individual level.

4. *S. aureus* transmission within households over 9 months as determined by molecular strain typing.
5. Safety, tolerability, and adherence to study interventions.
6. Mupirocin and chlorhexidine resistance in *S. aureus* strains recovered at serial samplings.

# 4 STUDY DESIGN

**Study Description.** This is a phase IV open label, randomized, pragmatic, comparative effectiveness trial.

**Study Population.** Non-immunocompromised patients aged birth to 21 years with a culture confirmed *S. aureus* infection within the last two months will be eligible.

**Baseline Decolonization.** All household participants will complete a 5-day baseline decolonization regimen (prior to randomization into the intervention arms) as this is considered standard-of-care for decolonization. Participants will apply mupirocin ointment to the anterior nares twice daily for five consecutive days and perform daily body washes with chlorhexidine gluconate (Hibiclens) in the bath or shower for five consecutive days.

**Study Groups and Treatment Arms.**

1. Group 1: Periodic Personal Decolonization: All household participants will perform chlorhexidine body washes twice weekly for 3 months and apply mupirocin ointment to the anterior nares twice daily for five consecutive days each month for 3 months. Sufficient study materials for each assigned participant will be provided. A member of the study team will contact each household (via the family's preferred method: phone call or e-mail) several days prior to their designated period for monthly mupirocin application.
2. Group 2: Household Environmental Hygiene: In addition to their usual cleaning, households assigned to Group 2 will be asked to perform targeted household hygiene focusing on sources known to harbor *S. aureus* and serve as reservoirs for transmission. Specific recommendations include:
    - Launder all bed linens once a week.
    - Replace each kitchen and bathroom hand towel with a clean towel each day. Alternatively, rather than cloth towels, disposable paper towels (provided by the study team) may be used in the kitchen and bathroom.
    - Replace the kitchen sponge with a new sponge (provided by the study team) once a week.
    - Wipe the following surfaces with Clorox Disinfecting Wipes (provided by the study team) once a week, using 1 wipe per surface:
        - TV remote controls, telephones, computer keyboards and mouse
        - Bathrooms: Countertop, sink, and sink faucet handles; light switch; bathtub and faucet handles; toilet handle and seat
        - Kitchen: Refrigerator and freezer door handles; microwave door handle and key pad; oven door handle; sink and sink faucet handle; table top; counter tops

At the enrollment visit, cleaning procedures will be demonstrated by study personnel, and printed instructions will be provided. Throughout the 3-month intervention period, to enhance adherence to the protocol, a member of the study team will contact each household weekly to remind them to perform targeted cleaning with the Clorox Disinfecting Wipes and to replace the kitchen sponge.

3. Group 3: Integrated Approach of Personal and Household Environmental Hygiene: Participants in households randomized to Group 3 will perform the Periodic Personal Decolonization described for Group 1, plus the Household Environmental Hygiene described for Group 2.

A total of 207 households (~828 subjects) will be enrolled, with 69 households in each of the three groups. The projected time to complete study enrollment is approximately 72 months.

**Subject Participation.** The total duration of subject participation will be approximately 9 months. The active treatment period is 3 months. Subjects will be evaluated at 5 study visits:

1. the baseline visit (enrollment)
2. 1 month follow up visit
3. 3 month follow up visit (end of intervention visit)
4. 6 month follow up visit
5. 9 month follow up visit

Subjects who fail to show for scheduled visits will be contacted by telephone or email (per consent) and, if necessary, by mail to request that a follow-up visit be rescheduled. The research team will inquire about the reason for the missed visit and will work with the subject to facilitate a follow-up visit.

**Study Drugs.**

Please refer to drug insert information.

**Data Collection.** At study enrollment, detailed questionnaires will be administered to identify risk factors for CA-*S. aureus* colonization, infection, and transmission. Specifically, for each participant, we will collect data regarding past medical history, prior *S. aureus* infections, occupation, daycare or school location, activities, frequency and modes of bathing (showers vs. bath), washing of clothing (frequency and water temperature used), and sharing of personal hygiene and other household items (and which household members share specific items). To identify household factors contributing to CA-*S. aureus* transmission, a household questionnaire will be administered (one per household) and will ascertain current cleaning practices (frequency, surfaces cleaned, products used), layout of the home (number of rooms, square footage), and presence of appliances (e.g., clothes washer and dryer). In addition, detailed

information about the number, type, and health of pets in the home, and pet behaviors (e.g., where they sleep) will be obtained.

Longitudinal study visits will be conducted in the participants' homes 1, 3, 6, and 9 months following randomization. At these visits, a questionnaire will be administered to each participant to document interval SSTI and any changes of occupation, daycare or school location, activities, frequency and modes of bathing (showers vs. bath), washing of clothing (frequency and water temperature used), and sharing of personal hygiene and other household items (and which household members share specific items). If a participant sought medical care for any infection, records from the hospital and/or provider's office will be obtained for verification. The household questionnaire will also be administered at each follow-up visit to capture any changes to cleaning frequency, etc.

**Specimen Collection, Processing, and Culture Methods.** Culture swab samples (BD ESwab; Becton Dickinson) will be obtained from each household member at the enrollment visit and at each follow-up visit. Three swabs will be used for each participant, to separately culture the anterior nares, axillae, and inguinal folds. At each study visit, standardized collection methods [7] will be used to collect environmental cultures: sterile swabs (BD ESwab) and environmental sampling plates (Baird-Parker agar contact plate, Hardy Diagnostics) will be used to sample ~21 household surfaces with frequent skin contact that will be targeted with the environmental cleaning intervention (the exact number will vary per household depending on the surfaces and objects present in the home). Items to be cultured include the bathroom sink/faucet handles, toilet handle/seat, bathtub, refrigerator and freezer door handle, microwave door handle and keypad, oven door handle, kitchen table, counter tops, kitchen sink/sink faucet handles, bed linens, primary television remote control, main telephone, and computer keyboard and mouse. Pet dogs or cats will also be cultured (nasal/oral and dorsal fur) at each study visit.

Laboratory technicians will be blinded to participant randomization assignment. All culture swabs will be incubated overnight in tryptic soy broth (TSB) with 6.5% NaCl at 35°C. A sample of the broth will be plated to trypticase soy agar with 5% sheep blood (blood agar plate [BBL]; Becton Dickinson) and incubated for 24-48 hours. *S. aureus* identification and antibiotic susceptibility testing will be performed by established procedures [1,139,140]. All isolates will be stored in TSB with glycerol at -80°C. For future microbiota studies, the eluate from the culture swabs will be frozen at -80°C immediately after the study visit.

***S. aureus* Strain Characterization and Detection of Mupirocin and Chlorhexidine Resistance.** Prior study data projects that we will amass ~5200 *S.aureus* isolates over the study period. To determine relatedness of isolates colonizing or infecting individuals in the same household, and those colonizing household pets and environmental surfaces, all recovered *S. aureus* isolates will be analyzed by genetic typing. Multiplex PCR will also be performed for staphylococcal cassette chromosome *mec* (SCC*mec*) characterization of all recovered *S. aureus* isolates using established methods [141]. All *S. aureus* isolates will be interrogated for chlorhexidine resistance via PCR to detect *qacA/B* [9,123] and for mupirocin resistance by disk

diffusion; isolates phenotypically resistant to mupirocin will be genotyped using PCR to detect *mupA* [121,142].

**Interim Analyses.** Interim analysis is discussed in Section 10.3. Safety monitoring and reviews and interim analyses for the study as a whole will be conducted by a Data and Safety Monitoring Plan (DSMP).

**Safety Oversight.** Safety oversight will be provided by via safety monitoring plan. The monitors will meet a minimum of twice per year and will review interim and cumulative data for evidence of study-related adverse events and for quality, completeness, and timeliness.

## 4.1 Substudies (if applicable)

Not applicable at the present time.

# 5 STUDY ENROLLMENT AND WITHDRAWAL

Projected enrollment is 207 households (~828 subjects). The total of 207 households includes a 10% attrition rate among enrollees, a rate derived from our previous household study.

## 5.1 Subject Inclusion Criteria

1) Inclusion Criteria**:** Patients with confirmed (i.e., culture-positive) active or recent (within the past 2 months) *S. aureus* cutaneous infections who reside within 90 miles of SLCH will be screened. When possible, infecting isolates will be obtained for analysis; at minimum, antibiotic susceptibility reports will be obtained. There are no restrictions for household contacts. Only participants providing written, informed consent, or for whom consent is provided by a parent or legal guardian, will be included.

## 5.2 Subject Exclusion Criteria

Subjects meeting any of the following criteria at baseline will not be eligible:

1) Exclusion Criteria: As the focus of this study is community-onset infections, we will exclude patients with nosocomial infections (i.e., >48 hours after hospitalization) and those with traditional risk factors for HA-*S. aureus* (e.g., immunodeficiency, indwelling catheter or percutaneous medical device, undergoing dialysis, presenting with a surgical site infection, or residing in a long-term care facility within the past year). Patients who are unable to give consent or for whom consent is not obtained, those refusing home Environmental cultures by the study team, and patients without a permanent home (e.g., living in a shelter or group home) will be excluded.

### 5.2.1 Randomization Procedures

Following Baseline Personal Decolonization performed by all household participants, households will be allocated 1:1:1 to one of the three treatment groups. Randomization assignments will be generated by the statistician with REDCap (Research Electronic Data Capture, a secure, web-based database application, http://www.biostat.wustl.edu/redcap). The assigned intervention will be performed for 3 months, and participants will be followed for an additional 6 months to track primary and secondary outcomes

### 5.2.2 Masking Procedures

Laboratory technicians will be blinded to participant randomization assignment. Research team members will be blinded to laboratory results to prevent bias during sampling.

### 5.2.3 Reasons for Withdrawal

A study subject will be discontinued from participation in the study if:

- Any clinical adverse event (AE), intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- If the safety of the study team personnel is in danger while at the home of a participant

Subjects are free to withdraw from participating in the study at any time upon request. The investigators may also withdraw a subject at any time for safety, behavioral, or administrative reasons.

### 5.2.4 Handling of Withdrawals

Participants will be instructed to call us immediately and discontinue the protocol if they experience skin or nasal burning, pain, rash, or other adverse effects. Participants who discontinue measures early will not be withdrawn from the study, and we will record the number of applications of each component of the protocol completed by the participant. Participants will be free to withdraw from study participation at any time, and the participants or their physicians may choose to stop the decolonization measures at any time.

### 5.2.5 Termination of Study

The study may be terminated early for the following reasons:

- Safety concerns due to an excessive rate or number of serious adverse events
- Study closure resulting from DSMP recommendation
- Lack of efficacy of a treatment arm
- At the discretion of the PI

# 6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

Mupirocin 2% ointment
See package insert

Chlorhexidine 4% (Hibiclens)
See package insert

## 6.1 Assessment of Subject Compliance with Study Intervention/Investigational Product

All participants will be asked to complete a “Memory Aid” (tailored for each study group) to record their completion of the assigned personal and/or environmental hygiene measures; the Memory Aids will be collected by the study team at the 1- and 3-month longitudinal study visits.

## 6.2 Concomitant Medications/Treatments

Concomitant medications will be recorded at baseline and all subsequent study visits. Concomitant medications and treatments are permitted unless it is medication that is contraindicated for administration with study medications.

# 7 STUDY SCHEDULE

## 7.1 Screening/Recruitment

**Screening.** Potential participants with active or recent *S. aureus* SSTI will be recruited from St. Louis Children's Hospital and community pediatric practices affiliated with WU PAARC, a practice-based research network in metropolitan St. Louis. Additionally, prior participants from our household transmission dynamics study will be contacted; those interested and eligible will be enrolled. Informed consent will be collected prior to any study procedures being conducted.

## 7.2 Enrollment/Study visits

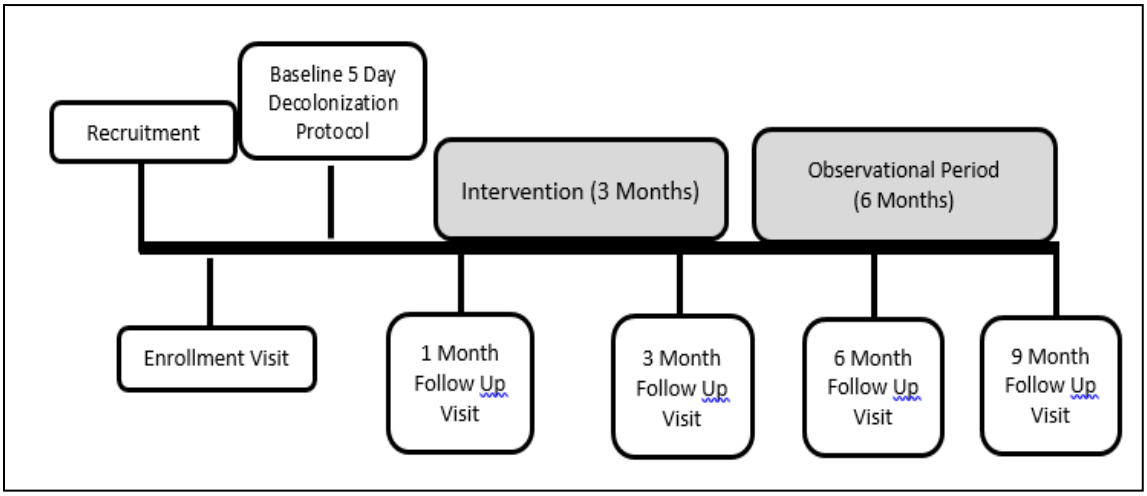
At the enrollment visit, conducted in the study participant's home, each household member will be consented for this study. A detailed questionnaire covering health history, hygiene, and activities to help identify potential risk factors for *S. aureus* will be conducted. A separate survey about the household (e.g., number of bedrooms and bathrooms, frequency of cleaning the kitchen and bathrooms, presence of pets, etc.) will also be completed. Swabs from the consented participants, indoor pet dogs and/or cats, and specific environmental surfaces will also be collected. Information regarding which treatment group the household was randomized to will be given to the participants as well as all supplies needed to complete the intervention. All study supplies and instructions will be provided at no cost to the research participants.

All follow-up study visits will occur as stated in schedule of events (**Figure 3**).

Randomization will occur at the enrollment visit and participants will begin the baseline decolonization protocol on the following day.

**Memory Aid Diary.** Participants will be given a Memory Aid diary at the enrollment visit and 1 month follow-up visit to record the completion of the assigned intervention measures. Memory Aids will be collected by the study team at the 1-month follow-up visit and 3-month follow-up visit.

Figure 3. Schedule of Events



# 8 STUDY PROCEDURES/EVALUATION

## 8.1 Definitions

**Informed consent.** Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Written informed consent will be obtained for all participating subjects.

**Index patient.** The pediatric patient presenting with a CA-*S. aureus* infection who is screened for study participation.

**Household member.** An individual who sleeps in the home ≥4 nights per week.

**Participant.** Index patients and their household members consenting to study participation.

**Colonization.** Carriage of *S. aureus* as determined by a positive culture from the nares, axillae, or inguinal folds.

**Infection.** Symptomatic manifestation of disease (e.g., skin abscess, boil, or cellulitis, necrotizing pneumonia, musculoskeletal or bloodstream infection).

**Transmission.** Colonization of an individual over the longitudinal period with a new strain type (i.e., not previously carried by that individual) that is identical to a strain type colonizing a household contact, environmental surface, or pet at a prior sampling.

**Concomitant Medications.** Concomitant medications will be recorded and any changes to concomitant medications will be recorded at all subsequent study visits.

**Initial Wound Culture.** A culture of the enrollment wound (the wound which qualified the patient for the present study) will be obtained when possible. Culture reports will be obtained for all index patients (the pediatric patient presenting with a CA-*S. aureus* infection who is screened for study participation).

**Randomization.** Each household consented will be randomized to one of the three treatment protocols using the deterministic minimization method (see Section 5).

**Intervention Supplies.** All households will be given study intervention supplies along with verbal and written information concerning proper application/use.

**Memory Aid.** All participants will be asked to complete a "Memory Aid" (tailored for each study group) to record their completion of the assigned personal and/or environmental hygiene measures; this will be collected by the study team at the 1-month and 3-month longitudinal study visits.

## 8.2 Laboratory Evaluations

### 8.2.1 Laboratory Evaluations

**Microbiological Studies.** Culture swab samples (BD ESwab; Becton Dickinson) will be obtained from each household member at the enrollment visit and at each follow-up visit. Three swabs will be used for each participant, to separately culture the anterior nares, axillae, and inguinal folds. At each study visit, standardized collection methods [7] will be used to collect environmental cultures: sterile swabs (BD ESwab) and environmental sampling plates (Baird-Parker agar contact plate, Hardy Diagnostics) will be used to sample ~21 household surfaces with frequent skin contact that will be targeted with the environmental cleaning intervention (the exact number will vary per household depending on the surfaces and objects present in the home). Items to be cultured include the bathroom sink/faucet handles, toilet handle/seat, bathtub, refrigerator and freezer door handle, microwave door handle and keypad, oven door handle, kitchen table, counter tops, kitchen sink/sink faucet handles, bed linens, primary television remote control, main telephone, sofa, and computer keyboard and mouse. Pet dogs or cats will also be cultured (nasal/oral and dorsal fur) at each study visit. Laboratory technicians will be blinded to participant randomization assignment. All culture swabs will be incubated overnight in tryptic soy broth (TSB) with 6.5% NaCl at 35°C. A sample of the broth will be plated to trypticase soy agar with 5% sheep blood (blood agar plate [BBL]; Becton Dickinson) and incubated for 24-48 hours. *S. aureus* identification and antibiotic susceptibility testing will be performed by established procedures [1,139,140]. Any unusual isolates or isolates collected from pets will be identified by matrix-assisted laser desorption/ionization (MALDI). All isolates will be stored in TSB with glycerol at -80°C. For future microbiota studies, the eluate from the culture swabs will be frozen at -80°C immediately after the study visit.

For more information on specific laboratory procedures, refer to the Laboratory Protocols binder.

### 8.2.2 Special Assays or Procedures

Not applicable.

### 8.2.3 Specimen Preparation, Handling, and Shipping.

Clinical isolates of bacteria obtained from skin cultures will be handled and stored on-site in accordance with local lab policy.

# 9 ASSESSMENT OF SAFETY

## 9.1 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

### 9.1.1 Adverse Events

Adverse events (AEs) will be classified, recorded, and reported in compliance with federal regulations (45 CFR 46.103(b)(5)) and policies and procedures of the Washington University School of Medicine Human Research Protection Office (HRPO) and the IRB. An adverse event (AE) is defined as any unfavorable or undesirable effect (sign, symptom, laboratory abnormality, or condition), regardless of causal relationship to study procedures or participation that occurs in a subject while enrolled in this clinical trial. Any medical condition that is present at the time that the subject is screened should be considered as baseline and not reported as an AE. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care.

All AEs including local and systemic reactions meeting the criteria for “serious adverse events” will be captured on the case report form. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship (related or unrelated) to study product assessed only by those with the training and authority to make a diagnosis, which would include MD, PA, or Nurse Practitioner, and time of resolution or stabilization of the event. All AEs occurring while on study will be documented. All AEs will be followed to adequate resolution or stabilization.

**Solicitation and Collection of Adverse Events.** The PI will monitor adverse events on a continuous basis and is responsible for providing the DSMP members with new safety information relevant to the study. Adverse events will be collected over the entire period that subject is enrolled in the study or, in the case of a serious adverse event associated with study drug, until resolution of the outcome of that event.

Occurrences of adverse events will be collected at all 4 follow-up study visits. Adverse events will be captured by open ended questions to address whether other events not specifically solicited might have occurred and these also will be captured from the Memory Aid diary.

### 9.1.2 Serious Adverse Events

As required by the WU HRPO, the PI will report the following serious adverse events to the WU HRPO using methods specified by the WU HRPO: deaths will be reported immediately, life-threatening events will be reported within 7 calendar days, and all other serious adverse events will be reported within 15 calendar days.

## 9.2 Reporting Procedures

### 9.2.1 Serious Adverse Events

The PI will monitor adverse events on a continuous basis and is responsible for providing the DSMP members with new safety information relevant to the study as required by the WU HRPO, the PI will report the following serious adverse events to the WU HRPO using methods specified by the WU HRPO: deaths will be reported immediately, life-threatening events will be reported within 7 calendar days, and all other serious adverse events will be reported within 15 calendar days.

### 9.2.2 Reporting of Pregnancy

Women who become pregnant while enrolled will be followed per the schedule of events, for the duration of the protocol.

## 9.3 Halting Rules

No formal halting rules are pre-specified.

## 9.4 Safety Oversight

The DSMP members will review interim and cumulative data for evidence of study-related adverse events and for quality, completeness, and timeliness. The DSMP members will assess compliance with study goals for patient recruitment and retention, protocol adherence, and factors external to the study that may impact patient safety or the ethics of the study. Ad hoc meetings may occur at the request of the DSMP members or the WU HRPO. A safety and interim analysis report will be generated by the monitors twice annually. As required by the WU HRPO, the PI will report the following serious adverse events to the WU HRPO using methods specified by the WU HRPO: deaths will be reported immediately, life-threatening events will be reported within 7 calendar days, and all other serious adverse events will be reported within 15

calendar days. The PI will monitor adverse events on a continuous basis and is responsible for providing the DSMP members with new safety information relevant to the study.

# 10 STATISTICAL CONSIDERATIONS

This trial will assess three decolonization strategies for the treatment of CA-*S. aureus*. Primary analyses will be comparisons across the three randomization groups for occurrence of SSTI at the household level at 3 months. Since Group 3 is of chief interest, the primary analysis will compare SSTI incidence in Group 3 to SSTI incidence in Groups 1 and 2 combined. As a secondary analysis, we will perform a chi-squared test across all 3 groups, and if significant, we will analyze the pairwise differences between the 3 groups as well. Since all analyses are pre-specified, no adjustment for multiple comparisons is necessary. We will also perform the analyses at the household level for all time points to investigate potential time trends using repeated measures generalized estimating equation (GEE) models, adjusting for potential clinical and demographic covariates.

Similarly, as secondary analyses, we will also use GEE models on the individual participant level, accounting for clustering of individuals within households and repeated measurements at 1, 3, 6, and 9 months to assess differences in colonization status, SSTI incidence, confirmed *S. aureus* infection, and transmission over 9 months between the randomization arms, adjusting for pertinent covariates. Adherence to study interventions will be described and compared between the 3 groups using GEE models, with appropriate link functions (e.g., log for number of chlorhexidine baths, applications of mupirocin ointment, or performance of environmental hygiene measures). Reported adverse reactions will also be characterized and compared between the 3 treatment groups. Additionally, we will evaluate mupirocin and chlorhexidine resistance in *S. aureus* isolates collected at baseline as predictors of decolonization failure (i.e., presence of colonization at 1 month). We will also compare the prevalence of mupirocin and chlorhexidine resistance in strains recovered at longitudinal samplings between Groups 1 and 3 combined (those performing baseline and periodic personal decolonization) and Group 2 (those performing only baseline personal decolonization).

## 10.1 Study Hypotheses

The primary null hypothesis is: The three decolonization strategies (integrated, periodic personal, and environmental hygiene) will result in the same incidence of SSTI at the household level 3 months after randomization.

## 10.2 Sample Size Considerations

**Primary Endpoint.** The primary efficacy endpoint is occurrence of SSTI at the household level (i.e., in any household member) 3 months after randomization.

**Study Populations**

1. *The evaluable population* for an analysis comprises all subjects for whom the endpoint is determined.
2. *The intent-to treat (ITT) population* comprises all randomized subjects.

**Power Calculations**.

The primary outcome is incidence of SSTI at the household level (i.e., occurring in any household member) 3 months after randomization. The expected rate of SSTI in households randomized to Groups 1 and 2 is 40% based on our prior study [6]. We expect the integrated personal and environmental approach (Group 3) will result in a 50% relative reduction, resulting in a household-level SSTI incidence of 20%. A sample of 189 households (63 per group; calculated using SAS 9.3) will have 80% power at $\alpha$=0.05 to detect this difference. A total of 207 households (~828 subjects) are planned to be randomized with 69 households in each of the three groups.

The three groups are:

1. Periodic Personal Decolonization
2. Household Environmental Hygiene
3. Integrated Approach of Personal and Household Environmental Hygiene

The planned total of 207 households includes a 10% attrition from trial enrollment to the 3-month follow-up visit, a rate based on our prior household studies.

## 10.3 Planned Interim Analyses

**Interim Analyses.** Annual reports will be generated according to the Data Safety and Monitoring Plan. These reports include information on any adverse events, updates on patient retention and recruitment, outcomes, and protocol violations. Additionally, progress reports for AHRQ are submitted annually.

## 10.4 Final Analysis Plan

**Primary Analysis Plan.** The primary outcome, occurrence of SSTI at the household level (i.e., in any household member) 3 months after randomization, will be determined for the 3 intervention groups: 1) Periodic personal decolonization, 2) Household environmental hygiene,

and 3) Integrated periodic personal decolonization and household environmental hygiene. A time point of 3 months was selected for the primary outcome as this is a reasonable interval for individuals to reacquire the organism and for a subsequent infection to develop. The analysis will be performed on the intention-to-treat population. At the household level, each household will be considered a unit of analysis and we will use a chi-square test to compare the incidence of SSTI between the 3 groups at 3 months. Since Group 3 is of chief interest, the primary analysis will compare SSTI incidence in Group 3 to SSTI incidence in Groups 1 and 2 combined. We will also perform the analyses at the household level for all time points to investigate potential time trends using repeated measures generalized estimating equation (GEE) models, adjusting for potential clinical and demographic covariates.

**Secondary Analysis Plans.** As a secondary analysis, we will perform a chi-squared test across all 3 groups, and if significant, we will analyze the pairwise differences between the 3 groups as well. Since all analyses are pre-specified, no adjustment for multiple comparisons is necessary Similarly, as secondary analyses, we will also use GEE models on the individual participant level, accounting for clustering of individuals within households and repeated measurements at 1, 3, 6, and 9 months to assess differences in colonization status, SSTI incidence, confirmed *S. aureus* infection, and transmission over 9 months between the randomization arms, adjusting for pertinent covariates. Adherence to study interventions will be described and compared between the 3 groups using GEE models, with appropriate link functions (e.g., log for number of chlorhexidine baths, applications of mupirocin ointment, or performance of environmental hygiene measures). Reported adverse reactions will also be characterized and compared between the 3 treatment groups. Additionally, we will evaluate mupirocin and chlorhexidine resistance in *S. aureus* isolates collected at baseline as predictors of decolonization failure (i.e., presence of colonization at 1 month). We will also compare the prevalence of mupirocin and chlorhexidine resistance in strains recovered at longitudinal samplings between Groups 1 and 3 combined (those performing baseline and periodic personal decolonization) and Group 2 (those performing only baseline personal decolonization).

# 11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Appropriate medical and research records will be kept for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

# 12 QUALITY CONTROL AND QUALITY ASSURANCE

All data collected via interview questionnaires, intervention treatment adherence, serious adverse events, wound assessment, laboratory results, and clinical lab reports will be entered into the REDCap database by research team members. Research members will be assigned to one of two data groups so all data can be entered two independent times. Once all data is entered for a family, both copies on the database will be merged and reconciled by a research team member (not on either of the data teams). This double data entry process is utilized to avoid entry mistakes or mistypes.

For more detailed information, refer to the Data Entry Protocol, Micro Data Entry Protocol, Good Data Practices powerpoint, and Laboratory QC protocols.

# 13 ETHICS/PROTECTION OF HUMAN SUBJECTS

## 13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46, 21CFR Parts 50 and 56, and/or the ICH E6; 62 Federal Regulations 25691 (1997).

## 13.2 Institutional Review Board

This study must provide the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate independent ethics committee (IEC) or IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States and in other countries, only institutions holding a current US Federal-wide Assurance issued by OHRP may participate. Refer to: http://www.hhs.gov/ohrp/assurances/.

## 13.3 Informed Consent Process

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject (or parent, legal guardian, or person with power of attorney for subjects who cannot consent for themselves, such as those below the legal age). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A signed copy of the consent form will be given to the subject, parent, or legal guardian, which will be documented on the consent checklist.

### 13.3.1 Informed Consent/Assent Process

Informed consent will be obtained from one parent or legal guardian for subjects under 18 years of age. Minors who are 0-6 years old are considered not old enough to provide verbal or written assent. Minors 6-12 years old will have the purpose of the study, the procedures to be followed, and the risks and benefits of participation explained to them in terms that are age appropriate and then asked if it is OK to continue. After getting an age-appropriate description of the study

and its procedures, minors 13-17 years old will sign the consent document to assent to the study above where their parent/guardian signs to consent to the study. A signed copy of the consent form will be given to the subject, parent, or legal guardian, which will be documented on the consent checklist.

## 13.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain subject confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NIAID, the OHRP, or the pharmaceutical supporters or the supporters' designees.

## 13.5 Study Discontinuation

The study may be discontinued at any time by the PI, who holds primary responsibility for this decision, based on recommendations from the WU IRB, AHRQ, the FDA, DSMP, or other government agencies as part of their duties to ensure that research subjects are protected.

## 13.6 Future Use of Stored Specimens

Clinical isolates of *S. aureus* and other bacteria isolated from cultures will be stored in the PI's laboratory space. These will be coded and delinked to personal identifying information.

# 14 DATA HANDLING AND RECORD KEEPING

## 14.1 Data Management Responsibilities

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data reported in the interview form should be consistent with the source documents or the discrepancies should be documented. Data collection is the responsibility of the clinical trial staff under the supervision of the PI. During the study, the investigator must maintain complete and accurate documentation for the study.

Hard copy records will be transferred from homes to Washington University in a locked briefcase. The records will be stored in a locked filing cabinet in a locked office. Participant data will be collected, entered, and stored electronically. All data will be protected with a secure computer network and password access. Specifically, The Division of Biostatistics Informatics Core will be used as a central location for data processing and management. Washington University belongs to a consortium of institutional partners that work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Division of Biostatistics Informatics Core. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are securely housed in an on-site limited access data center managed by the Division of Biostatistics at Washington University. All web-based information transmission is encrypted. REDCap was developed specifically around HIPAA Security guidelines and is implemented and maintained according to Washington University guidelines. REDCap currently supports > 170 academic/non-profit consortium partners on six continents and 13,000 research end-users (www.project-redcap.org).

## 14.2 Data Capture Methods

Data will be collected prospectively and entered into a REDCap database built by the study team.

## 14.3 Types of Data

Data for the study will be entered directly into the REDCap data entry system. Data for this study will include all information gathered via the interview questionnaires, intervention treatment adherence, serious adverse events, and wound assessment.

## 14.4 Study Records Retention

All research records, including signed consent forms, must be kept in their original form or a certified scanned electronic form for at least seven years beyond close of the study. Additional retention requirements may be required under State and Federal laws, the Covered Organization's policies or at the request of the study sponsor. Protected Health Information must be stored in accordance with HIPAA and the Covered Organization's HIPAA policies

## 14.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be sent to the IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

# 15 PUBLICATION POLICY

Following completion of the study, results of the research are planned for publication in a scientific journal. The policy of the International Committee on Medical Journal Editors (ICMJE) member journals, which that have adopted a trials-registration policy as a condition for publication, will be adhered to. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov sponsored by the National Library of Medicine. It is the responsibility of the study team to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject enrollment.

The Principal Investigator will formulate plans, organize data and prepare manuscript(s) for publication as appropriate. Authorship decisions will be made by the Principal Investigator with guidance from published guidelines from Cohen JJ and Siegel EK, Academic Medical Centers and Medical Research: The Challenges Ahead. JAMA.2005; 294: 1367-1372.

Published guidelines will also be followed regarding the disclosure of relationships with government funding agencies such as the NIH and the CDC, foundations like the Grant Health Care foundation and corporate sponsors of related research.

# 16 LITERATURE REFERENCES

**REFERENCES**

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# MUPIROCIN OINTMENT USP, 2%

For Dermatologic Use

℞ only

Rev. F 3/2005
70033021

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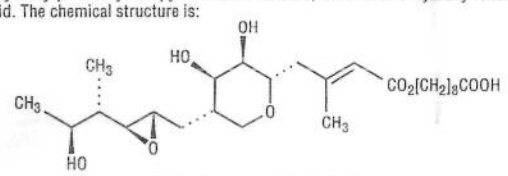
## DESCRIPTION

Each gram of Mupirocin Ointment 2% contains 20 mg mupirocin in a bland water miscible ointment base (polyethylene glycol ointment, N.F.) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The chemical name is (*E*)-(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β- methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. The chemical structure is:




$C_{26}H_{44}O_9$ M.W. 500.63

## CLINICAL PHARMACOLOGY

Application of $^{14}C$-labeled mupirocin ointment to the lower arm of normal male subjects followed by occlusion for 24 hours showed no measurable systemic absorption (< 1.1 nanogram mupirocin per milliliter of whole blood). Measurable radioactivity was present in the stratum corneum of these subjects 72 hours after application.

Following intravenous or oral administration, mupirocin is rapidly metabolized. The principal metabolite, monic acid, is eliminated by renal excretion, and demonstrates no antibacterial activity. In a study conducted in seven healthy adult male subjects, the elimination half-life after intravenous administration of mupirocin was 20 to 40 minutes for mupirocin and 30 to 80 minutes for monic acid. The pharmacokinetics of mupirocin has not been studied in individuals with renal insufficiency.

### Microbiology

Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. It is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also active against certain gram-negative bacteria. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin demonstrates no *in vitro* cross-resistance with other classes of antimicrobial agents.

Resistance occurs rarely. However, when mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC > 1024 mcg/mL) has been reported in some strains of *S. aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical administration. However, the minimum bactericidal concentration (MBC) against relevant pathogens is generally eight-fold to thirty-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (> 97%), and the effect of wound secretions on the MICs of mupirocin has not been determined. Mupirocin has been shown to be active against most strains of *Staphylococcus aureus* and *Streptococcus pyogenes*, both *in vitro* and in clinical studies. (See **INDICATIONS AND USAGE**.) The following *in vitro* data are available, BUT THEIR CLINICAL SIGNIFICANCE IS UNKNOWN. Mupirocin is active against most strains of *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*.

## INDICATIONS AND USAGE

Mupirocin ointment 2% is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus* and *Streptococcus pyogenes*.

## CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components.

## WARNINGS

Mupirocin ointment is not for ophthalmic use.

## PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with use of mupirocin ointment 2%, treatment should be discontinued and appropriate alternative therapy for the infection instituted.

As with other antibacterial products prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

Mupirocin ointment is not formulated for use on mucosal surfaces. Intranasal use has been associated with isolated reports of stinging and drying. A paraffin-based formulation – *Bactroban® Nasal (mupirocin calcium ointment) – is available for intranasal use.

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol-based ointments, mupirocin ointment should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

### Information for Patients

Use this medication only as directed by your health provider. It is for external use only. Avoid contact with the eyes. The medication should be stopped and your health care practitioner contacted if irritation, severe itching, or rash occurs.

If impetigo has not improved in 3 to 5 days, contact your health care practitioner.

### Drug Interactions

The effect of the concurrent application of mupirocin ointment and other drug products has not been studied.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of mupirocin have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium *in vitro* and *in vivo* did not indicate a potential for genotoxicity: rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Reproduction studies were performed in male and female rats with mupirocin administered subcutaneously at doses up to 14 times a human topical dose (approximately 60 mg mupirocin per day) on a mg/m$^2$ basis and revealed no evidence of impaired fertility and reproductive performance from mupirocin.

### Pregnancy

Teratogenic Effects

*Pregnancy category B*

Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 22 and 43 times, respectively, the human topical dose (approximately 60 mg mupirocin per day) on a mg/m$^2$ basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mupirocin ointment is administered to a nursing woman.

### Pediatric Use

The safety and effectiveness of mupirocin ointment have been established in the age range of 2 months to 16 years. Use of mupirocin ointment in these age groups is supported by evidence from adequate and well-controlled studies of mupirocin ointment in impetigo in pediatric patients studied as a part of the pivotal clinical trials (see **CLINICAL STUDIES**).

## ADVERSE REACTIONS

The following local adverse reactions have been reported in connection with the use of mupirocin ointment: burning, stinging, or pain in 1.5% of patients; itching in 1% of patients; rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudate in less than 1% of patients.

## DOSAGE AND ADMINISTRATION

A small amount of mupirocin ointment should be applied to the affected area three times daily. The area treated may be covered with a gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be reevaluated.

## CLINICAL STUDIES

The efficacy of topical mupirocin ointment in impetigo was tested in two studies. In the first, patients with impetigo were randomized to receive either mupirocin ointment or vehicle placebo t.i.d. for 8 to 12 days. Clinical efficacy rates at end of therapy in the evaluable populations (adults and pediatric patients included) were 71% for mupirocin ointment (n = 49) and 35% for vehicle placebo (n = 51). Pathogen eradication rates in the evaluable populations were 94% for mupirocin ointment and 62% for vehicle placebo. There were no side effects reported in the group receiving mupirocin ointment.

In the second study, patients with impetigo were randomized to receive either mupirocin ointment t.i.d. or 30 to 40 mg/kg oral erythromycin ethylsuccinate per day (this was an unblinded study) for 8 days. There was a follow-up visit 1 week after treatment ended. Clinical efficacy rates at the follow-up visit in the evaluable populations (adults and pediatric patients included) were 93% for mupirocin ointment (n = 29) and 78.5% for erythromycin (n = 28). Pathogen eradication rates in the evaluable patient populations were 100% for both test groups. There were no side effects reported in the mupirocin ointment group.

### Pediatrics

There were 91 pediatric patients aged 2 months to 15 years in the first study described above. Clinical efficacy rates at end of therapy in the evaluable populations were 78% for mupirocin ointment (n = 42) and 36% for vehicle placebo (n = 49). In the second study described above, all patients were pediatric except two adults in the group receiving mupirocin ointment. The age range of the pediatric patients was 7 months to 13 years. The clinical efficacy rate for mupirocin ointment (n = 27) was 96%, and for the erythromycin it was unchanged (78.5%).

## HOW SUPPLIED

Mupirocin Ointment USP, 2% is supplied in 22 gram tubes.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

* Bactroban® Nasal is a registered trademark of SmithKline Beecham Pharmaceuticals.

Manufactured In Croatia By:
**PLIVA HRVATSKA d.o.o**
Zagreb, Croatia

Manufactured For:
**TEVA PHARMACEUTICALS USA**
Sellersville, PA 18960

Rev. F 3/2005

PRODUCT INFORMATION

# Hibiclens Package Insert 1 OF 3

## HIBICLENS® Antiseptic/Antimicrobial Skin Cleanser (4% chlorhexidine gluconate)

### DESCRIPTION

HIBICLENS is an antiseptic antimicrobial skin cleanser possessing bactericidal activities. HIBICLENS contains 4% w/v chlorhexidine gluconate, with inactive ingredients: Fragrance, isopropyl alcohol 4%, purified water, Red 40, and other ingredients, in a mild, sudsing base adjusted to pH 5.0-6.5 for optimal activity and stability as well as compatibility with the normal pH of the skin.

### ACTION

HIBICLENS is bactericidal on contact. It has antiseptic activity and a persistent antimicrobial effect with rapid bactericidal activity against a wide range of microorganisms, including gram-positive bacteria and gram-negative bacteria such as *Pseudomonas aeruginosa*. The effectiveness of HIBICLENS is not significantly reduced by the presence of organic matter, such as blood.[1]

In a study[2] simulating surgical use, the immediate bactericidal effect of HIBICLENS after a single six-minute scrub resulted in a 99.9% reduction in resident bacterial flora, with a reduction of 99.98% after the eleventh scrub.

Reductions on surgically gloved hands were maintained over the six-hour test period. HIBICLENS displays persistent antimicrobial action. In one study[2], 93% of a radiolabeled formulation of HIBICLENS remained present on uncovered skin after five hours. HIBICLENS helps prevent skin infection thereby reducing the risk of cross-infection.

### INDICATIONS

HIBICLENS is indicated for use as a surgical hand scrub, as a health-care personnel handwash, as a patient pre-operative skin preparation, and as a skin wound cleanser and general skin cleaner.

### SAFETY

The extensive use of chlorhexidine gluconate for over 20 years outside the United States has produced no evidence of absorption of the compound through intact skin. The potential for producing skin reactions is extremely low.

### WARNINGS

**For external use only. Keep out of eyes, ears and mouth. Hibiclens should not be used as a preoperative skin preparation of the face or head. Misuse of hibiclens has been reported to cause serious and permanent eye injury when it has been permitted to enter and remain in the eye during surgical procedures. If Hibiclens should contact these areas, rinse out promptly and thoroughly with water.**

Avoid contact with meninges. HIBICLENS should not be used by persons who have a sensitivity to it or its components. Chlorhexidine gluconate has been reported to cause deafness when instilled in the middle ear through perforated eardrums. Irritation, sensitization, and generalized allergic reactions have been reported with chlorhexidine-containing products, especially in the genital areas. If adverse reactions occur, discontinue use immediately and if severe, contact a physician. Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.



## PRODUCT INFORMATION

# Hibiclens Package Insert 2 OF 3

### WARNINGS *(cont.)*

**Accidental ingestion:** Chlorhexidine gluconate taken orally is poorly absorbed. Treat with gastric lavage using milk, egg white, gelatin or mild soap. Employ supportive measures as appropriate. Avoid excessive heat (above 104°F).

### DIRECTIONS FOR USE

- **Skin Wound and General Skin Cleansing**
  Wounds which involve more than the superficial layers of the skin should not be routinely treated with HIBICLENS. To use, thoroughly rinse the area to be cleansed with water. Apply the minimum amount of HIBICLENS necessary to cover the skin or wound area and wash gently. Rinse again thoroughly.
- **Preoperative Skin Preparation**
  Apply HIBICLENS liberally to surgical site and swab for at least two minutes. Dry with a sterile towel. Repeat procedure for an additional two minutes and dry with a sterile towel.

### HEALTH-CARE PERSONNEL USE

- **Surgical Hand Scrub**
  **Directions for use of HIBICLENS Antiseptic/Antimicrobial Skin Cleanser:** Wet hands and forearms with water. Scrub for 3 minutes with about 5 mL of HIBICLENS and a wet brush, paying particular attention to the nails, cuticles, and interdigital spaces. A separate nail cleaner may be used. Rinse thoroughly. Wash for an additional 3 minutes with 5 mL of HIBICLENS and rinse under running water. Dry thoroughly.
- **Personnel Hand Wash**
  Wet hands with warm water. (Avoid using very cold or very hot water.) Dispense about 5 mL of HIBICLENS into cupped hands. Wash for 15 seconds. (Do not use excessive pressure to produce additional lather.) Rinse thoroughly with warm water. Dry thoroughly.

### IMPORTANT LAUNDERING ADVICE FOR HOSPITAL STAFF AND OTHER USERS OF ANTISEPTIC PATIENT SKIN PREPARATIONS CONTAINING CHLORHEXIDINE GLUCONATE

Chlorhexidine gluconate is a unique agent that closely fits the definition of an ideal antimicrobial agent, having (among others) one of the most important characteristics of persistent activity. This persistence is due to chlorhexidine gluconate binding to the protein of the skin and, thus, being available for residual activity over a relatively long period of time.

Chlorhexidine gluconate, however, binds not only to protein of the skin, but also to many fabrics, particularly cotton. Thus, special laundering procedures should be considered when such products contact these fabrics. As a result of such contact, chlorhexidine gluconate may become adsorbed onto the fabric and not be removed by washing.

If sufficient available chlorine is present during the washing procedure, a fast brown stain may develop due to a chemical reaction between chlorhexidine gluconate and chlorine.

### SUGGESTED LAUNDERING PROCEDURES TO LIMIT STAINING

1. **Not Aging.** Avoid allowing the product to age (set) on unwashed linens.
2. **Flushing and Washing.** A flush operation as the initial step in the wash process is helpful in the laundering of linen exposed to chlorhexidine gluconate. Such flushing is also important in the laundering of linen which contains organic materials such as blood or pus. For best results, warm water flushes (90°-100°F) are recommended. After a number of initial flushings followed by a washing with a low alkaline/non-chlorine detergent, most articles which come in contact with chlorhexidine gluconate should have an acceptable level of whiteness. If a rewash process using bleach is necessary to achieve a greater degree of whiteness, the bleach used should be non-chlorine bleach.

## PRODUCT INFORMATION

# Hibiclens Package Insert 3 OF 3

### SUGGESTED LAUNDERING PROCEDURES TO LIMIT STAINING *(cont.)*

3. **Not Using Chlorine Bleach.** Modern laundering methods often make the use of chlorine bleach unnecessary. It is worthwhile trying to wash without chlorine to ascertain if the resulting degree of whiteness is acceptable. Omission of chlorine from the laundering process can extend the useful life of cotton articles since oxidizing bleaches such as chlorine may cause some damage to cellulose even when used in low concentration.
4. **Changing to a Peroxide-Type Bleach, Such as Sodium Perborate, Sodium Percarbonate or Hydrogen Peroxide.** This should eliminate the reaction that could occur with the use of chlorine bleaches. If a chlorine bleach must be used, a concentration of less than 7 ppm available chlorine (1/10 the normal bleach level) is suggested to minimize possible staining.

### A NOTE ON LAUNDERING OF PERSONAL CLOTHING

The laundering procedures set forth above using low alkaline, non-chlorinated laundry detergents are also applicable to laundering of uniforms and lab coats. Commercially available laundry detergents that do not contain chlorine include Borax, Borateem, Dreft, Oxydol, and Ivory Snow. These products, however, will not remove stains previously set into the fabric.

### RECLAMATION OF STAINED LINENS

For those linens which previously have been stained due to the chemical reaction between chlorhexidine gluconate and chlorine, the following laundering procedure may be helpful in reducing the visible stain:

Operation Water Temperature Time Supplies
Level (Min) 100 lb__
Break Low 180°F 20 1.5 lb oxalic acid
Flush High Cold 1 _____
Emulsify Low 160°F 5 18 oz emulsifier
Flush High Cold 1 _____
Bleach Low 180°F 20 2 lb alkali builder and 1 lb organic bleach
Rinse High Cold 1 _____
Antichlor High Cold 2 4 oz antichlor
Rinse High Cold 1 _____
Rinse High Cold 1 _____
Sour Low Cold 4 2 oz rust removing sour

### HOW SUPPLIED

- *For general hand washing locations*: pocket-size, 15 mL foil packettes; plastic disposable bottles of 4 oz and 8 oz with dispenser caps; and 16 oz filled globes.
- *For surgical scrub areas*: plastic disposable bottles of 32 oz and 1 gal. The 32-oz bottle is designed for a special foot-operated wall dispenser. A hand-operated wall dispenser is available for the 16-oz globe. Hand pumps are available for 16 oz, 32 oz, and 1 gal sizes. Store at controlled room temperature 20-25°C (68-77°F) [see USP].
- *Liquid*: NDC 0234-057504, 0234-057508, 0234-057516, 0234-057532, & 0234-057591).

### REFERENCES


[1] Lowbury, EJL and Lilly, HA: The effect of blood on disinfection of surgeons' hands, Brit. J. Surg. 61:19-21 (Jan.) 1974

[2] Peterson AF, Rosenberg A, Alatary SD: Comparative evaluation of surgical scrub preparations, Obstet, 146:63- 65 (Jan.) 1978

NDC 0234-0575-04

# HIBICLENS®

**(Chlorhexidine Gluconate solution 4.0% w/v)**

**Antiseptic/Antimicrobial Skin Cleanser**

HIBICLENS® prevents skin infections thereby reducing the risk of cross-infection. HIBICLENS® has antiseptic activity and a persistent antimicrobial effect with rapid bactericidal activity against a wide range of microorganisms.

MÖLNLYCKE® HEALTH CARE

**4 Fl. oz. (118 mL)**

Distributed by Mölnlycke Health Care US, LLC
Norcross, GA 30092

## Drug Facts

### Active ingredient Purpose

Chlorhexidine gluconate solution 4.0% w/v ..... Antiseptic

### Uses

- antimicrobial skin cleanser helps reduce bacteria that potentially can cause disease
- for skin wound and general skin cleansing
- surgical hand scrub
- healthcare personnel handwash

### Warnings

**For external use only**

**Do not use**

- if you are allergic to chlorhexidine gluconate or any other ingredients in this preparation
- as a patient preoperative skin preparation of the head or face
- in contact with the meninges
- in the genital area
- on wounds that involve more than the superficial layers of skin

## Drug Facts (continued)

**When using this product**

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures, or may cause deafness when instilled in the middle ear through perforated eardrums.
- if contact occurs in any of these areas, rinse with cold water right away

**Stop use and ask a doctor if**

irritation, sensitization, or allergic reaction occurs and lasts for 72 hours. These may be signs of a serious condition.

**Keep out of reach of children.** If swallowed, get medical help or contact a Poison Control Center right away.

### Directions

- use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns.
- *skin wound and general skin cleansing.* Thoroughly rinse the area to be cleansed with water. Apply the minimum amount of the product necessary to cover the skin or wound area and wash gently. Rinse thoroughly.

## Drug Facts (continued)

- *surgical hand scrub.* Wet hands and forearms with water. Scrub for 3 minutes with about 5mL of the product with a brush. Rinse thoroughly under running water. Repeat. Dry thoroughly.
- *healthcare personnel handwash.* Wet hands with water. Dispense about 5mL of the product into cupped hands and wash in a vigorous manner for 15 seconds. Rinse and dry thoroughly.

### Other information

- store between 20-25°C (68-77°F)
- avoid excessive heat above 40°C (104°F)

### Inactive ingredients

fragrance, gluconolactone, isopropyl alcohol 4% w/v, lauramine oxide, poloxamer 237, purified water and red 40

### Questions? 1-800-843-8497

26000-09-MHC

Lot number and expiration date printed on bottom of container.

Laundering/Cleaning Instructions. Chlorhexidine gluconate skin cleansers will cause stains if used with chlorine releasing products. Rinse out plenty and use only non-chlorine detergents. See website for more details. www.hibiclens.com

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