Title: Individualized vs. Household MRSA Decolonization (HOME2DS)

NCT number: NCT01814371

PI: Stephanie A. Fritz, M.D, MSCI

Date: 04.11.13

PROTOCOL: HOME 2 Decolonization Study
Protocol #201301035 version #1
Single Site Study

PI: Stephanie A. Fritz, M.D, MSCI

Study Team Members: Patrick Hogan, MPH
Lauren Singh, MPH
Duha Al-Zubeidi, MD
Mary Boyle MSN, RN
Madeline Martin, BSN
John Lukas
Carol Patrick

OVERVIEW

Background and Rationale

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) causes significant morbidity and mortality in children. There is no available vaccine against *S. aureus*. Thus, other preventive measures, including topical antimicrobial therapies, have been used in an attempt to prevent staphylococcal infections. These therapies include mupirocin (a topical antibiotic with activity against MRSA) and chlorhexidine (a topical antiseptic which is available as a medicated liquid soap as well as impregnated in cloths for sponge baths). In addition to traditional interventions (e.g., mupirocin or chlorhexidine), bathing in dilute bleach water has also been prescribed to patients with recurrent CA-MRSA infections. For the present study, we will utilize a decolonization regimen of mupirocin, dilute bleach water baths, and hygiene education. Our objective is to assess the effectiveness of decolonization measures when performed by individuals with a history of skin and soft tissue infection (SSTI) in the prior year (individualized approach) compared to decolonization of all household members (household approach) in reducing the incidence of recurrent SSTI. We hypothesize an individualized decolonization approach will be equally as effective as decolonization of all household members to prevent SSTI. The information we learn from this study may help us develop inexpensive and readily available interventions to prevent *Staph* infections.

Objectives

1. Compare the effectiveness of decolonization of individuals with a history of skin and soft tissue infection (SSTI) in the prior year (individualized approach) to decolonization of all household members (household approach) in reducing the incidence of recurrent SSTI.
2. Test whether or not application of mupirocin to the anterior nares twice daily for 5 days will result in a higher prevalence of colonization with mupirocin-resistant strains at subsequent longitudinal samplings.
3. Determine the role of environmental contamination and household characteristics in household CA-MRSA transmission. We will quantify the baseline burden of household MRSA colonization by culturing twenty-one frequently handled household surfaces and objects.

Potential Contribution: Decolonization measures are costly and inconvenient. Therefore, targeting only household members at greatest risk for recurrent SSTI would decrease the burden and cost of performing these measures, and increase adherence to the protocol. Evaluating decolonization of all household members compared to decolonization of only those individuals experiencing SSTI in the prior 12 months, will inform prevention strategies for both specialists and primary care physicians. If we find that an individualized approach is not inferior

to a household approach to decolonization, we will design a study for dissemination and implementation of this practice, partnering with the practice-based research network, Washington University Pediatric and Adolescent Ambulatory Research Consortium (WU PAARC). If we determine that decolonization is successful in preventing SSTI, but observe an increasing incidence in mupirocin resistance over the study, we will evaluate the effectiveness of decolonization utilizing only topical solutions (e.g., dilute bleach or chlorhexidine) without application of intranasal mupirocin.

METHODS

Timeline: After randomization and distribution of study materials participants will have study visits every 3 months for 12 months to ascertain colonization status and development of subsequent SSTI.

Inclusion criteria: Households which participated in the “Community-Associated Methicillin-Resistant Staphylococcus aureus (CA-MRSA) Among Household Members and the Home Environment" study (HRPO 201104330). Only participants providing written, informed consent, or for whom consent is provided by a parent or legal guardian, will be included.

Exclusion Criteria: Households in which all members experienced SSTI during the 12-month natural history study will be ineligible to participate in the trial, to eliminate the bias that would be introduced if these families were randomized to the Individualized Approach arm. We will also not approach individuals who have declined contact for future studies on the HRPO 201104330 study consent form.

Procedures: The households participating in the "Community-Associated Methicillin-Resistant Staphylococcus aureus (CA-MRSA) Among Household Members and the Home Environment" (HRPO 201104330) study will be invited to enroll in this randomized trial upon completion of the 12-month follow-up period.

Randomization: Due to logistics and the use of objective outcome measures, this study will be performed as an open trial. Enrolled households will be allocated to one of two treatment groups (household vs. individualized decolonization) 1:1 randomization using the minimization method to assure balance in family size and composition (e.g., number of household members experiencing SSTI in the prior year). Minimization is a dynamic randomization algorithm that will help to ensure that treatment arms are balanced with respect to our predefined household factors as well as the number of households in each group. REDCap will be used to implement the minimization algorithm. Assignments will be generated by the REDCap program and revealed to the study coordinator immediately prior to the enrollment visit

Enrollment visit: Will take place in the participants' homes

- Time: 30-45 minutes
- The PI or research coordinator will provide standardized hygiene education curriculum regarding handling of lotions, soaps, hygiene items, and linens.
- Participants will be given instructions on how to perform the decolonization regimen (described below).
- The inside tip of the nose, armpits, and inguinal folds (groin) of each participant will be swabbed with a culture swab.
- The inside tip of the nose of dogs and cats will be swabbed with a culture swab
- Specified household surfaces will be swabbed with a culture swab (21 sites)

Decolonization regimen:

- Application of 2% mupirocin ointment (a “pea-sized” amount) to the anterior nares with a sterile cotton applicator twice daily for 5 days.
- Daily bathing (15-minute soaks) in dilute bleach water (¼ cup of 6-8.5% sodium hypochlorite [Clorox®, Clorox Company, Oakland, CA] per ¼ tub of water) for 5 days.

(participants <1 month of age will not be asked to complete the decolonization regimen)

- Participants will be given and asked to complete a "Memory Aid" to record their daily completion of the measures, ease or difficulty of completing the measures, occurrence of adverse reactions, development of new infections, and costs incurred completing the protocol.

Follow-up phone call: Each participant will be contacted by phone 7-10 days after the enrollment visit to confirm completion of the study protocol.

Follow-up visits: Will take place in the participants' homes

- Will occur 1, 3, 6, 9, and 12 months following the enrollment visit
- Time: 15-25 minutes for each visit

At the 1 month follow-up visit:

- Each participant will complete a brief survey inquiring whether they developed any infections during the interval since the prior visit
- The inside tip of the nose, armpits, and inguinal folds (groin) of each participant will be swabbed with a culture swab. There will also be a separate household survey administered inquiring about household cleaning.
- The inside tip of the nose of dogs and cats will be swabbed with a culture swab
- Specified household surfaces will be swabbed with a culture swab (21 sites)

At the 3, 6, 9, and 12 month follow up visits:

- Each participant will complete a brief survey inquiring whether they developed any infections during the interval since the prior visit
- The inside tip of the nose, armpits, and inguinal folds (groin) of each participant will be swabbed with a culture swab.
- The inside tip of the nose of dogs and cats will be swabbed with a culture swab
- Specified household surfaces will be swabbed with a culture swab (21 sites)

If at any visit during the study a participant informs us that they have had a *staph aureus* infection and sought medical care for that infection, we will obtain and verify as much information as possible about the infection, such as date, body site, if drainage surgery was required, if a culture was obtained, what the culture results were, and whether or not antibiotics were prescribed. To obtain this information we will check ClinDesk for hospital records or ask their primary care doctor to fax us any pertinent results. If the participant was seen at SLCH, the actual specimen will be collected from the microbiology laboratory and compared to other specimens we have obtained from the household and participant swabs within that family.

Presence of high-level mupirocin resistance will be assessed in all recovered MRSA strains using PCR to detect the *mupA* gene; isolates positive for the *mupA* gene (indicating genotypic

evidence for high-level mupirocin resistance) will be confirmed phenotypically by Etest (BioMerieux, St. Louis, MO).

INFORMED CONSENT

Potential participants will be identified among participants in the "Community-Associated Methicillin-Resistant Staphylococcus aureus (CA-MRSA) Among Household Members and the Home Environment Study" (HRPO 201104330). The PI or research coordinator will provide verbal information and a letter explaining the study at the 9 month follow-up visit of the observational study. After household members have discussed the study amongst themselves, enrollment will take place at the 12 month follow-up visit of the observational study.

The enrollment visit will take place in the home. After the study design and expectations have again been described to all household members, the PI and study coordinator will obtain written informed consent from each household member. Parents or legal guardians will provide written consent for all minor participants. Children of a developmentally appropriate age (typically 7 years or older) will also be asked to sign an assent document.

Two different consent forms will be used: one for the individual approach group and one for the household approach group. Participants who agree to be in the study will be given the consent form for the treatment group to which they were randomized. The reason for having two consent forms is to minimize the chance that household members in the "Individualized Approach" arm who have not experienced SSTI in the prior 12 months (and thus NOT assigned to use the decolonization measures) will use the decolonization measures provided to the "affected" household members (those with SSTI in the prior 12 months).

The study team will emphasize that study participation is voluntary and the fact that if some household members do not wish to participate in the study, this does not exclude the remainder of the household from participation.

PROCEDURES FOR MAINTAINING CONFIDENTIALITY

Privacy: The recruitment and consent process will take place in the participants' home, in a private, quiet area. At those times they may ask any questions that they may have about the study. Participants are given the opportunity to conduct their questionnaire and provide the colonization swabs in any location in their own home. Some children like to stay by their parents to feel safer during the swabs. Others don't want to be seen when it is occurring and ask to go into a different room. We let them and their guardians decide how they want to proceed. The intervention (bleach baths, mupirocin) will take place when we are not in the home, and will be at their own discretion as to how they complete it as a family. All information we collect is relevant to learning about the transmission of *S. aureus* in the household environment so that we can learn how to prevent *S. aureus* infections. All participants are informed during the consent process that they can choose to not answer any question they feel uncomfortable answering

De-identification of data: Patient data and specimens will be coded with a study number to link the data with the specimens.

Data Security: Hard copy records will be transferred from homes to Washington University in a locked brief case. 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. The device we will use to enter data over the secure server is the IPAD 2. The IPAD will be password protected and only study team members will have access. All data will also be entered to the secure REDCap server and not stored anywhere else on the IPAD.

ASSESSMENT OF RISKS AND BENEFITS

Risks:

Likely / Common:
None

Less Likely / Less Common:
Mild
•Some questions the researchers will ask might make participants feel uncomfortable.
•Obtaining swabs from the nostrils, underarms, and groin area might be uncomfortable for some people.
•Dry skin may result from the use of dilute bleach water baths.

Rare:
Mild
•The mupirocin ointment applied to the nose may cause irritation such as itching, burning, or stinging.
•Bleach baths may cause a mild rash.
•All of these problems will go away once the participant stops using the products.
•There is a chance that the confidentiality of your participation could be breached.

Protection against potential risks: Participants will have the right to refuse to answer any question for any reason throughout the study. The risk of discomfort from the nasal swabs will be minimized by moistening the swab prior to culturing and by sampling the anterior portion of the nares. Decolonization products will be applied topically which poses minimum risk. Participants will be instructed (orally and in writing) to contact the study team as well as their primary care providers or seek care from a local ED if they suspect they are experiencing adverse effects from their treatments. The primary care provider may prescribe an alternative treatment at any time during the study. In addition, participants will be closely followed by study personnel for the development of SSTI. Participant data will be protected with a secure computer network and password access. All hard-copy data will be protected in a locked office and locked file cabinet.

Benefits: Study participants may benefit from a decreased incidence of CA-MRSA disease, thereby eliminating the need for painful drainage procedures, potential hospitalization, and antibiotic administration. Even household members randomized to the “Individualized Decolonization Approach” group who are not assigned decolonization measures (because they

had not experienced SSTI during the 12-month natural history study) may benefit from the decolonization of household contacts as the burden of CA-MRSA in the household may decrease and subsequently reduce the risk of transmission. Participants will also receive education about the *Staph* germ. This project may decrease the incidence of CA-MRSA infections, and thus reduce healthcare utilization for CA-MRSA treatment, potentially preventing additional spread of virulent CA-MRSA 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.

Statistical Plan

Sample Size and Determination of Power: The expected rate of SSTI in individuals in the Household Approach group is 9% at 3 months based on one of our prior studies. An absolute difference of 10% is considered to be clinically equivalent and has been recommended for anti-infective trials; thus, 9% SSTI incidence in the Household Approach group and 19% SSTI incidence in the Individualized Approach group 3 months post-decolonization would be considered clinically equivalent. Considering the variance inflation factor due to clustering of participants within households (estimated to be 1.4 based on our prior studies), and considering 4 interim analysis for the primary outcome to be conducted under the Data Safety Monitoring Plan, a total sample of 344 participants (172 per group) or 86 total households (43 households per group) will have 80% power at alpha=0.05 to conclude that the SSTI incidence in the Individualized Decolonization Approach is not inferior to that of the Household Decolonization Approach with a non-inferiority margin of 10%. Sample size calculations were performed using PASS 11. "The Community-Associated Methicillin-Resistant Staphylococcus aureus (CA-MRSA) Among Household Members and the Home Environment" study (HRPO 201104330) will enroll 150 households (approximately 600 participants). Taking into consideration exclusion criteria, lost to follow-up and declining participation, we believe 25-35% of households will not enroll in the HOME 2 Decolonization Study, resulting in approximately 100 households enrolling in the trial. Anticipating 10% attrition from trial enrollment to the 3-month follow-up visit, we will have 90 households for analysis of the primary outcome SSTI at 3 months.

Analysis Plan: Descriptive statistics will be used to characterize the study population, the proportion of participants colonized and infected with MRSA over the course of the study, and the types and relatedness of colonizing and infecting strains recovered from participants.

The primary outcome, occurrence of SSTI 3 months after randomization, for all participants will be determined for the two groups: 1) Individualized Decolonization Approach and 2) Household Decolonization Approach. Three months was chosen as the time point for the primary outcome as this is a reasonable amount of time for individuals undergoing decolonization to reacquire the organism from other colonized household contacts and for a subsequent infection to develop. To test non-inferiority of the Individualized Approach versus the Household Approach, the difference in proportion of SSTI at 3 months and the 2-sided 95% confidence interval for the difference in proportions will be calculated. Non-inferiority will be defined as the upper limit of the 2-sided 95% confidence interval being less than 10% (our margin of non-inferiority). A 10% absolute difference is considered to be clinically equivalent and has been recommended for anti-infective trials. One thousand sample bootstrapping (household sampling with replacement) will be used to estimate the 95% confidence interval and account for clustering within households. The analysis will be performed on both the intention-to-treat population and the per-protocol population because the intention-to-treat analysis can be biased in non-inferiority trials. Secondarily, we will perform comparisons of SSTI recurrence among only participants who had an SSTI in the prior year.

We will also use longitudinal mixed effects logistic regression models using SAS PROC GLIMMIX to assess differences in colonization status, SSTI incidence, and confirmed MRSA infection over the entire course of the study (12 months) between the Household Approach group and the Individualized Approach group, adjusting for pertinent covariates accounting for clustering of individuals within households. Adherence to recommended hygiene practices and decolonization measures (application of mupirocin ointment twice daily for 5 days and daily bathing in dilute bleach water for 5 days) will be described and compared between the two groups using generalized linear mixed effects models, with appropriate link functions (e.g., log for number of days of bleach water baths or number of applications of mupirocin ointment). Adherence to decolonization measures will be compared only among individuals intended to receive the decolonization regimen (i.e., household members in the Individualized Approach group not assigned decolonization measures will not be included in the analysis). In addition, we will assess the level of adherence to each part of the intervention (hygiene practices, application of mupirocin ointment, bleach water baths) as risk factors for colonization and SSTI. All critical results will be validated with comparable generalized estimating equation (GEE) models. Reported adverse reactions will also be characterized and compared between the two treatment groups.

To test the relationship between environmental contamination at baseline and household characteristics with persistent colonization, we will use mixed effects logistic regression models with a random effect for household. Hypothesized risk factors include household surface contamination at baseline and household crowding. To test the relationship between environmental contamination at baseline with infection at follow-up time points, we will use longitudinal mixed effects logistic regression models. We will also incorporate CA-MRSA recovery from household environmental surfaces as a predictor of acquisition, infection, and colonization with the same strain.

Data and Safety Monitoring Plan

Study Monitoring: The proposed decolonization measures have been previously studied and pose minimal risk to study participants. Thus, a Data and Safety Monitoring Plan, rather than a formal Board, is appropriate. Monitors for this study include the PI (Stephanie A. Fritz, MD, MSCI), an independent monitor, Bernard Camins, MD, MSCR (Infectious Diseases specialist at Washington University), and the trial biostatistician, Professor J. Philip Miller. The PI will monitor adverse events on a continuous basis and is responsible for providing the monitors with new safety information relevant to the study. 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. The study monitors 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. After each data evaluation, the monitors will consider continuation, modification, or termination of the trial. Ad hoc meetings may occur at the request of the monitors or the WU HRPO.

Data to be reviewed:

1. Adverse Events
    a. Description of individual serious and non-serious adverse events
    b. Rates of serious and non-serious adverse events by study group, and overall
2. Patient Recruitment and Retention
    a. Eligibility and refusal rates for subjects
    b. Reasons for exclusion

    c. Baseline demographic characteristics of randomized participants and household characteristics to check adequacy of randomization (including gender, race/ethnicity, number of household members overall, and number of individuals per household experiencing SSTI during the natural history study)
    d. Attrition rates by study group (only available during the follow-up period)
3. Outcomes
    a. Incidence of SSTI (Primary outcome is SSTI incidence 3 months following decolonization)
    b. MRSA colonization status of study participants
4. Protocol Violations
    a. Descriptions of any protocol violations that occur

Stopping Criteria: Interim analysis for the primary outcome, incidence of SSTI 3 months following decolonization, will be conducted approximately every 6 months throughout the trial (~4 times). The trial will be terminated or modified upon interim data analysis if there is overwhelming evidence of the benefit of one treatment arm compared to the other arm of the study, defined as an absolute difference of 50% in the 3-month incidence of SSTI during the longitudinal study period between the Individualized Approach and Household Approach arms. The Lan-DeMets spending function approach will be used to examine our primary outcome when interim analyses are performed to allow for flexible interim monitoring while also preserving the type-I error of the study.

Reporting: 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.