

University of Pennsylvania

Annual Progress Report: 2008 Nonformula Grant

Reporting Period

July 1, 2010 – June 30, 2011

Nonformula Grant Overview

The University of Pennsylvania received \$5,531,053 in nonformula funds for the grant award period June 1, 2009 through May 31, 2013. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Epidemiology and Prevention of MRSA Transmission in the Community - The purpose of this study is to understand the reasons for recent dramatic increases in infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) in the community. Through a broad collaboration with partners in Eastern and Central Pennsylvania, we will study why patients with MRSA infections frequently have recurrent infections despite appropriate treatment. We will also study how often and why household members of such patients develop new MRSA infections. We will determine how often MRSA spreads between household members and how long individuals harbor MRSA over time. We will also test whether treatment to eliminate MRSA colonization prevents MRSA infections in the household. Finally, we will establish a program to develop a pipeline of new scientists and clinicians among underrepresented minorities in the Commonwealth.

Anticipated Duration of Project

6/1/2009 - 5/31/2013

Project Overview

This study will elucidate the longitudinal dynamics of MRSA colonization and infection and test an intervention to prevent MRSA transmission. To achieve this objective, we propose three scientific objectives:

- 1) to identify host, microbiological and environmental risk factors for prolonged MRSA colonization, MRSA transmission, and MRSA infection among patients with MRSA skin or soft tissue infections (SSTIs) and their household contacts and to use stochastic agent-based modeling methods to quantify secondary spread of CO-MRSA in households
- 2) to evaluate the impact of a decolonization intervention on MRSA infections in the household.
- 3) to identify immunological mechanisms underlying the ability of *S. pneumoniae* colonization to inhibit MRSA colonization, transmission and infection.

In conjunction with these scientific goals, we also propose two educational and organizational objectives:

- 1) to foster multi-disciplinary and cross-institutional collaborations and develop the infrastructure for a Center of Excellence focused on antimicrobial drug resistance research.
- 2) to enhance opportunities for basic and clinical research training for undergraduate and graduate students, particularly from underrepresented minorities, to increase the pipeline of future scientists.

To achieve the study aims, we propose a multicenter prospective cohort study of outpatients with newly diagnosed MRSA SSTIs. The source population for this study will be all adults and children receiving care in the emergency departments (EDs) and outpatient practices of the Hospital of the University of Pennsylvania (HUP), Penn Presbyterian Medical Center (PPMC), the Children's Hospital of Philadelphia (CHOP), and Hershey Medical Center (HMC). These subjects and their household members will undergo regular sampling for MRSA colonization over time. Subsequently, we will conduct a randomized controlled trial to assess the impact of two decolonization interventions on MRSA infections in the household. The proposed novel approach to sampling of cases and their household contacts over time represents a unique opportunity to elucidate the longitudinal transmission dynamics of MRSA in the community. The inclusion of adults and children from a geographically, racially, and ethnically diverse population will greatly strengthen the generalizability of the results and maximize the public health impact for all Pennsylvanians.

Principal Investigator

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Other Participating Researchers

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Rakesh D. Mistry, MD, MS, Susan Coffin, MD, MPH, Theoklis Zaoutis, MD, MSCE - employed by Children's Hospital of Philadelphia
Kathleen Julian, MD, Lawrence E. Kass, MD - employed by Penn State Hershey Medical Center
David F. Royer, PhD - employed by Lincoln University
Jonathan Finkelstein, MD - employed by Harvard University
Barry N. Kreiswirth, PhD - employed by New York University
Loren G. Miller, MD, MPH - employed by UCLA Medical Center

Expected Research Outcomes and Benefits

Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) among both adults and children in the community have increased markedly in recent years. These infections are associated with significant morbidity, mortality and cost. Our study will identify why patients with skin and soft tissue infections due to MRSA often have subsequent MRSA infections despite appropriate treatment for the initial infection. Identifying why these subsequent MRSA infections occur will help identify strategies to prevent these infections. We will identify how often, and why, household members of patients with MRSA infections also develop new MRSA infections. Identifying such factors will be critical in targeting approaches to prevent MRSA infections in household members as well. We will also investigate the impact of colonization with *Streptococcus pneumoniae* on MRSA infection. In particular, by elucidating the immunological mechanism underlying the ability of *S. pneumoniae* to inhibit MRSA colonization, we hope to identify immunological targets for future vaccine strategies. While our primary focus will be on MRSA infections, we will also study MRSA colonization (i.e., when an individual harbors the MRSA organism but is not infected). This is important because individuals are typically colonized before they are infected. Thus, preventing colonization will help to prevent infection. We will also identify how MRSA spreads in the household and investigate ways to prevent spread. Indeed, a major focus of our study will be to specifically test two decolonization interventions to prevent MRSA infections in households. This will provide critical evidence to support interventions to halt the further spread and impact of MRSA in the community which can be broadly applied across the commonwealth of Pennsylvania and beyond. In addition to research outcomes, this proposal contains a significant focus on teaching and education in order to produce a durable result for years to come. We will reach out to undergraduate and graduate students at Lincoln University to provide valuable opportunities and role models for aspiring under-represented minority students.

Summary of Research Completed

This report addresses progress on our grant during the period July 1, 2010 – June 30, 2011. The milestones listed in our original timeline for this time period (7/1/10-6/30/11) were: 1) Enroll cumulative total of 270 households into cohort study by end of period; 2) start recruitment into RCT on 1/1/11; 3) enroll 50 households into RCT by end of period; 4) expression of proteins and generation of antibody; 5) train at least two undergraduate and two graduate under-represented minority students (cumulative); 6) hold second Scientific Advisory Committee meeting.

1) Enroll cumulative total of 270 households into cohort study by end of period

This milestone has been achieved. A total of 274 households have been enrolled into the cohort study as of June 30, 2011. Among these 274 total households, there are 32 one-person households, 31 two-person households, 58 three-person households, 54 households with four household members, 37 households with five household members, 28 households with six household members, and 36 households with greater than six household members. Among the participating study sites, 131 households have been enrolled at Penn, 116 households have been enrolled at the Children's Hospital of Philadelphia (CHOP), and 38 households have been

enrolled at Hershey Medical Center. Across all households, a total of 1,148 individual subjects have been enrolled into the study.

Our ability to meet this milestone has been most rewarding in light of the delays in household enrollment noted at the last progress report (June 30, 2010). At that time, only 27 of the 50 households projected in last year's milestone had been enrolled. Furthermore, during our presentation for the interim performance review process on December 16, 2010, we noted that only 102 households had been enrolled to that point. Noting the clear delays in enrollment, we presented a comprehensive plan at that time to achieve our milestones. These included expanding participating study sites to all outpatient settings rather than limiting enrollment to emergency departments. Furthermore, refinements in our use of the hospital information systems approaches allowed us to more fully capture all eligible subjects in an accurate and efficient way. At that time, we presented an ambitious plan designed to increase enrollment to achieve the milestones. The impact of these approaches has been tremendous. It is notable that 102 households were enrolled between January and December 2010, while 172 household have been enrolled in the first 6 months of 2011. With this significant increase in enrollment, we are now back on track with enrollment into the cohort study.

2) Start recruitment into RCT on 1/1/11

As described above, our many efforts to ramp up enrollment in the cohort study have been extremely successful. However, this has necessarily resulted in a delay in initiation of the RCT. Now that 270 households have been enrolled in the cohort study, our RCT can begin. Indeed, the RCT will be commencing August 1, 2011.

3) Enroll 50 households into RCT by end of period

No patients have yet been enrolled in this phase of the study.

4) Expression of proteins and generation of antibody

The laboratory based research project has made substantial progress. Two full-time members of Dr. Weiser's lab have identified specific antigens from *Streptococcus pneumoniae* that generate a cross-reactive antibody response to *Staphylococcus aureus* following model murine colonization. These two pneumococcal antigens and the corresponding homologs from *S. aureus* have been cloned, expressed and used to raise antibody to confirm this cross-reactivity. In addition, we have developed a mouse model of *S. aureus* colonization. Using this model, we have shown that prior pneumococcal colonization is protective against subsequent challenge with *S. aureus*. An under-represented minority (URM) summer student constructed a mutant in one of the pneumococcal genes and used this mutant to show that this gene is necessary for this cross-protection in vivo. Purified antigens are currently being used to test whether these antigens are not only necessary but also sufficient to induce this mucosal protection in mice. If successful these antigens could be vaccine candidates to protect against both MRSA and MSSA. A provisional patent based on these genes/proteins and this idea has been submitted by the Center for Technology Transfer at Penn. To further support the project, sera from individuals in other parts of the study will be used to determine whether antibody titers to these candidates correlate with MRSA and MSSA carriage in humans.

5) Train at least two undergraduate and two graduate under-represented minority (URM) students (cumulative)

During the summer of 2010, we had 4 URM students working on the grant. Santiago Lomboluque was a Hispanic student from Swarthmore College working in the Weiser lab. Lenora Codrington and Wydia Davis, both African-American students from Lincoln University, and Sade Bell, a SUMR student from Emory University, all worked on various components of the study including subject enrollment, recruitment of households, follow up of study subjects, microbiological evaluations, and data entry. Ms. Codrington led an independent project evaluating the potential impact dry versus wet swabs on yield of MRSA. A scientific manuscript from this work is currently being prepared for submission for publication. Including the students from the summer of 2010, we have now trained 7 total URM students (cumulative).

6) Hold second Scientific Advisory Committee meeting.

The second Scientific Advisory Committee meeting was designed to be held during the early phase of the RCT. Since the RCT initiation has been delayed slightly, the Scientific Advisory committee is now scheduled for Fall of 2011.

Other activities

New Grant application/new collaboration

Based in part on the review led by Manuel Bramble, an URM student who worked on the project during 2009, we submitted an NIH R01 application to investigate the impact of MRSA-colonized pet animals in MRSA household transmission. Although this grant was not funded, we established a new collaboration with Meghan Davis, a veterinarian and PhD epidemiology candidate at Johns Hopkins University. We are currently working with Dr. Davis to add on a component to our ongoing grant which will further assess MRSA colonization among pets in enrolled households. In addition to serving as the foundation for Dr. Davis' PhD dissertation, this work will build considerably upon the framework of our ongoing work.

Center for Antimicrobial Resistance Research

On 9/25/09, a retreat was held to lay the groundwork for the creation of a new center focused on antimicrobial drug resistance research. The proposal and business plan for this center have been finalized by Drs Lautenbach and Zaoutis who will serve as Director and Associate Director of the Center, respectively.