

Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is “None”, please specify “None” as your response. “Not applicable” is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** The Trustees of the University of Pennsylvania
2. **Reporting Period (start and end date of grant award period):** 06/01/2009-05/31/2013
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Robert Speakman
4. **Grant Contact Person’s Telephone Number:** 215-898-7293
5. **Grant SAP Number:** 4100047865
6. **Project Number and Title of Research Project:** Epidemiology and Prevention of MRSA Transmission in the Community
7. **Start and End Date of Research Project:** 06/01/2009-05/31/2013
8. **Name of Principal Investigator for the Research Project:** Ebbing Lautenbach
9. **Research Project Expenses.**

9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

\$ \$5,543,076.30

9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	Institution	% of Effort on Project	Cost
Barrows,Emily S	Research Staff	University of Pennsylvania	100% Yr2-3	\$33,611.40
Bell,Sade Marie	PT Temp Staff	University of Pennsylvania	4% Yr2	\$3,850.47
Bilker,Warren B.	Co- Investigator	University of Pennsylvania	5% Yr1-3;10% Yr4	\$53,189.52
Bramble,Manuel Alfred	PT Temp Staff	University of Pennsylvania	4% Yr1	\$4,223.45
Calderone,Mary	PT Temp Staff	University of Pennsylvania	.07% Yr1	\$78.98
Chen,Niel L.	Research Staff	University of Pennsylvania	14% Yr4	\$28,161.00
Clarke,Thomas	Research Staff	University of Pennsylvania	100%	\$125,001.73
Clark,Sarah E.	PT Temp Staff	University of Pennsylvania	11% Yr3-4	\$23,775.03
Codrington,Lenora	PT Temp Staff	University of Pennsylvania	10.58% Yr2	\$3620.10
Davis,Kimberly	PT Temp Staff	University of Pennsylvania	27% Yr1	\$28,524.03
Davis,Wydia	PT Temp Staff	University of Pennsylvania	9.62% Yr2	\$3,291.00
Decker,Christopher	PT Temp Staff	University of Pennsylvania	7% Yr1-2	\$14,558.91
Doto,Aoife	Research Post Doc	University of Pennsylvania	100% Yr1	\$41,343.39
Edelstein,Martha A	PT Temp Staff	University of Pennsylvania	15% Yr3-4	\$31,362.13
Edelstein,Paul H	Co- Investigator	University of Pennsylvania	5%	\$52,783.75
Edwards,Rebecca T	PT Temp Staff	University of Pennsylvania	.2% Yr4	\$230.00
Ettela,Abora	PT Temp Staff	University of Pennsylvania	7.03% Yr4	\$1,604.91
Fishman,Neil	Co- Investigator	University of Pennsylvania	2.5%	\$25,521.73
Garrigan,Charles	Research Staff	University of Pennsylvania	13% Yr3	\$5,108.34
Gavin,Laurence J	Co- Investigator	University of Pennsylvania	10% Yr1-3; 5% Yr4	\$91,911.35
Han,Jennifer H	Research Post Doc	University of Pennsylvania	50% Yr3-4	\$72,678.57

Hollander,Judd E.	Co- Investigator	University of Pennsylvania	10% Yr1-3; 5% Yr4	\$91,893.69
Hu,Baofeng	Research Staff	University of Pennsylvania	74% Yr1; 100% Yr2-4	\$253,037.96
Jacob,Jack S	PT Temp Staff	University of Pennsylvania	1.7% Yr1	\$1768.91
Johnson,Kristen N	PT Temp Staff	University of Pennsylvania	3.8% Yr3-4	\$8,068.23
Kuncio,Danica	PT Temp Staff	University of Pennsylvania	19.23% Yr2-3	\$6,582.00
Lautenbach,Ebbing	Principal Investigator	University of Pennsylvania	17% Yr1; 19% Yr2; 18% Yr3; 30% Yr4	\$181,476.23
Lee,Jane J	PT Temp Staff	University of Pennsylvania	1.51% Yr2	\$293.72
Le,Ngoc-Le N	PT Temp Staff	University of Pennsylvania	3.8% Yr2-3	\$6,425.68
Lewis,Darren Andre	PT Temp Staff	University of Pennsylvania	.3% Yr1	\$403.15
Lijek,Rebeccah S.	Res. Lab Assist (Grad student)	University of Pennsylvania	100%	\$53,515.9
Linkin,Darren R.	Co- Investigator	University of Pennsylvania	2.5%	\$16,181.14
Li,Robert J.	Research Staff	University of Pennsylvania	100% Yr2; 90% Yr3; 89% Yr4	\$126,647.78
Lombo-Luque,Santiago	PT Temp Staff	University of Pennsylvania	4% Yr2	\$4,212.48
Margolis,David J	Co- Investigator	University of Pennsylvania	2.5%	\$26,482.57
Markes,Jhanelle	PT Temp Staff	University of Pennsylvania	20.67% Yr3	\$7,075.65
Mehta,Vijay	PT Temp Staff	University of Pennsylvania	23.46% Yr3	\$8,030.04
Metlay,Joshua P.	Co- Investigator	University of Pennsylvania	7% Yr1; 8% Yr2-4	\$108,250.41
Muhammad,Jibril	Research Staff	University of Pennsylvania	50% Yr4	\$31,789.88
Nachamkin,Irving	Co- Investigator	University of Pennsylvania	5% Yr1-2; 3% Yr3; 5% Yr4,	\$44,860.67
Ndicu,John W	Research Staff	University of Pennsylvania	100% Yr3; 68% Yr4	\$66,260.82
Nguyen,Valerie	PT Temp Staff	University of Pennsylvania	3.6% Yr3	\$3,762.16

Olson,Amy J	PT Temp Staff	University of Pennsylvania	.59% Yr3	\$213.92
Pitts,Julie A	ED Research Staff	University of Pennsylvania	48% Yr3; 12% Yr4	\$22,878.22
Robey,Jennifer	ED Research Staff	University of Pennsylvania	15% Yr2	\$17,442.60
Shchepetov,Mikhail	ED Research Staff	University of Pennsylvania	50% Yr1-2; 100% Yr3-4	\$184,481.89
Smith,Gary	Co- Investigator	University of Pennsylvania	5% Yr1; 2.5%; Yr2; 5% Yr3; 3% Yr4	\$29,834.85
Smith,Robyn	Research Staff	University of Pennsylvania	100% Yr3-4	\$63,277.86
Spitkovskaya,Marina	Research Staff	University of Pennsylvania	3.73% Yr3	\$1,275.26
Storey,Ashley	PT Temp Staff	University of Pennsylvania	19.23% Yr3	\$6,582.00
Strittmatter,Emily Rose	PT Temp Staff	University of Pennsylvania	23.56% Yr4	\$9,858.29
Tolomeo,Pam Capocci	Project Manager	University of Pennsylvania	53% Yr1; 40% Yr2; 65% Yr3; 54% Yr4	\$211,818.49
Torres,Keyshla	Research Staff	University of Pennsylvania	100% Yr3-4	\$73,567.02
Vazquez,Jamila	PT Temp Staff	University of Pennsylvania	1.44% Yr4	\$452.51
Walters,Michelle	PT Temp Staff	University of Pennsylvania	4.2% Yr3	\$4,388.00
Weiser,Jeffrey Neal	Co- Investigator	University of Pennsylvania	15%	\$125,723.21
Wheeler,Mary Katherine	Research Staff	University of Pennsylvania	5% Yr1;13% Yr2	\$13,684.47
Williams,Gloria A	Res. Lab Assist (Grad student)	University of Pennsylvania	50% Yr1	\$4,800
Wise,Jacqueleen	Research Staff	University of Pennsylvania	100% Yr1; 92% Yr 2; 75% Yr3	\$105,608.8
Brouwer, Heather N.	Program Manager	The Children's Hospital of Philadelphia	2.4% Yr1	\$2,203.50
Coffin, Susan E.	Co-Investigator	The Children's Hospital of	2.5% Yr2; 0.83% Yr3; 11.25% Yr4	\$23,541.70

		Philadelphia		
Douglas, Emily W.	Nursing Student	The Children's Hospital of Philadelphia	85.02% Yr2	\$9,328.50
Feemster, Kristen A.	Co-Investigator	The Children's Hospital of Philadelphia	23.33% Yr2; 24% Yr3; 6.6% Yr4	\$55,033.15
Gerber, Jeffrey S.	Co-Investigator	The Children's Hospital of Philadelphia	58.29% Yr1; 35% Yr2; 10.30% Yr3; 20% Yr4	\$86,221.63
Greene, Reesa J.	Research Tech	The Children's Hospital of Philadelphia	14.30% Yr1; 15.60% Yr2	\$1,200.00
Irace, Christina R.	Research Tech	The Children's Hospital of Philadelphia	2.4% Yr4	\$2,312.05
Kittick, Marlana	Program Coordinator	The Children's Hospital of Philadelphia	5.27% Yr1	\$2,677.50
Leckerman, Kateri	Clinical Research Associate	The Children's Hospital of Philadelphia	20.8% Yr3; 35% Yr4	\$25,524.52
Mistry, Rakesh	Co-Investigator	The Children's Hospital of Philadelphia	10% Yr1; 10% Yr2; 10% Yr3;	\$67,810.39

		Philadelphia	10% Yr4;	
Ndicu, Grace N.	Research Tech	The Children's Hospital of Philadelphia	66.54% Yr1; 100% Yr2; 100% Yr3; 100% Yr4	\$119,177.79
Robertshaw, Jennifer	Research Tech	The Children's Hospital of Philadelphia	15% Yr3	\$1,296.00
Ross, Rachael	Research Associate	The Children's Hospital of Philadelphia	6.10% Yr3	\$2,613.50
Vendetti, Neika D.	Research Assistant	The Children's Hospital of Philadelphia	39.20% Yr4	\$20,169.69
Zaoutis, Theoklis	PI	The Children's Hospital of Philadelphia	5% Yr1; 15% Yr2; 10% Yr3; 10% Yr4	\$58,108.28
Royer	Principal Investigator	Lincoln University	15%	54,522

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	Institution	% of Effort on Project
None			

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes _____ No _____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes _____ No _____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert “not funded” in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
MRSA Prevention in Long Term Care	<input type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____)	Aug, 2013	\$877,000	Pending review

	<input checked="" type="checkbox"/> Nonfederal source (specify: _____ PCORI _____)			
Identifying Patterns of Host Responses for Patients with Pneumococcal Pneumonia	<input checked="" type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _____)	June, 2013	\$275,000	Pending review
Combination Biomarker Algorithms to Optimize Antibiotic Use in Long Term Care	<input checked="" type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _____)	June, 2013	\$2,517,000	Pending Review
MRSA Prevention in Acute and Long Term Care Settings	<input type="checkbox"/> NIH <input checked="" type="checkbox"/> Other federal (specify: _AHRQ_ _____) <input type="checkbox"/> Nonfederal source (specify: _____)	Feb, 2013	\$1,963,000	Not funded
Pets and Environmental Transmission of Staphylococci” (Meghan Davis K22 training grant)	<input checked="" type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _____)	Nov, 2012	\$500,000	Not funded
Antibacterial Resistance Leadership Group	<input checked="" type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _____)	June, 2012	\$18,750	\$18,750
Development of an Antibiotic Stewardship Bundle to Improve Antibiotic Prescribing	<input type="checkbox"/> NIH <input checked="" type="checkbox"/> Other federal (specify: _CDC_ _____) <input type="checkbox"/> Nonfederal source (specify: _____)	May, 2012	\$100,000	\$100,000

	_____)			
Carbapenem-Resistant Klebsiella pneumoniae in Long-Term Acute Care Hospitals (Jennifer Han K01 training grant)	X NIH <input type="checkbox"/> Other federal (specify: _CDC_ _____) <input type="checkbox"/> Nonfederal source (specify: _____)	June, 2010	\$700,000	\$700,000
The Role of Pet Animals in Household Transmission of MRSA	X NIH <input type="checkbox"/> Other federal (specify: _CDC_ _____) <input type="checkbox"/> Nonfederal source (specify: _____)	June, 2010	\$1,926,000	Not funded

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes ___X___ No _____

If yes, please describe your plans:

Based on the work being performed as part of our grant, we have sought additional extramural funding to pursue several lines of research as noted above. Past extramural grant applications submitted during the grant period have been described in prior progress reports. There are several grants that have been submitted or will be submitted shortly that seek to extend the work conducted as part of our grant. During the past year, we submitted an R01 application to NIAID entitled "MRSA Prevention in Acute and Long Term Care". Although well reviewed, the grant was not funded. A resubmission is being planned once additional pilot data are available from our ongoing analyses of data from the CURE grant. An R01-equivalent grant entitled "MRSA Prevention in Long Term Care" is being submitted to PCORI on August 15, 2013. This grant, for which Dr. Lautenbach is serving as Principal Investigator seeks to examine the impact of active surveillance strategies on MRSA acquisition and infection in the long term care setting. As noted previously, Dr. Meghan Davis has been working on an additional component to our CURE grant which assesses MRSA colonization among pets in enrolled households. In addition to serving as the foundation for Dr. Davis' PhD dissertation, this work is building considerably upon the framework of our ongoing work. Dr. Davis also sought additional funding based on work conducted in the CURE grant. She submitted a K22 career development grant to NIAID focused on elucidating the transmission of MRSA by pets and the environment in households. This grant was not funded but Dr. Davis is pursuing other funding mechanisms for this work. Finally, Dr. Lautenbach is collaborating with Dr. Elizabeth Grice from the Department of Dermatology at Penn for a grant application in October 2013. Dr. Grice has expertise in the study of the skin microbiome and thus serves as an outstanding collaborator for Dr. Lautenbach. The planned

grant will focus on investigating the role of the skin microbiome on treatment outcome following MRSA skin/soft tissue infection as well as the role of the microbiome in predicting prolonged MRSA colonization. Finally, the CURE grant was instrumental in supporting the early career development of Dr. Jennifer Han. With the experience she gained working on the CURE grant, Dr. Han submitted a successful K01 Career Development Award from NIAID. This award has facilitated Dr. Han’s successful transition to faculty in the Division of Infectious Diseases at Penn where she will continue her research work focused on antimicrobial resistance in post-acute care settings.

12. Future of Research Project. What are the future plans for this research project?

There have already been 19 scientific manuscripts published or in press that have arisen from the CURE grant funding. While some of the manuscripts resulted from the prior work of the grant, many others were the results of related scientific work undertaken by trainees supported in part by the CURE grant. As such, the track for our CURE grant is already considerable. As noted in Section 20B below, we have a large number of analyses that remain underway as part of the primary work on the CURE grant. We anticipate that there will continue to be manuscripts emerging from this ongoing work over the next year. In addition, as noted above, we have submitted numerous grants to extend the work of the CURE grant and explore related areas of inquiry. Some of these grants have been funded. Those not funded will be considered for resubmission for funding. Perhaps the most exciting aspect of future projects is the work being undertaken by individuals who trained on the CURE grant. In particular, Drs. Jennifer Han and Kristen Feemster were both supported by the CURE grant and have now successfully received their own career development awards to pursue their independent lines of research related to the focus of the CURE grant. Dr. Davis has submitted a career development award and will continue to pursue independent funding as she establishes herself as an independent investigator. Even as the funding for the CURE grant is completed, there are many individuals, both senior and junior, who have benefited enormously from the CURE grant support and who continue to successfully pursue investigative careers focused on the core mission of our CURE grant.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes No

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male	2	0	2	0
Female	7	0	1	4

Unknown	0	0	0	0
Total	9	0	3	4

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic	1	0	0	1
Non-Hispanic	8	0	3	3
Unknown	0	0	0	0
Total	9	0	3	4

	Undergraduate	Masters	Pre-doc	Post-doc
White	1	0	0	2
Black	8	0	3	1
Asian	0	0	0	1
Other	0	0	0	0
Unknown	0	0	0	0
Total	9	0	3	4

14. Recruitment of Out-of-State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes _____ No _____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes _____ No _____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

The CURE grant has been instrumental in developing and consolidating the research efforts focused on antimicrobial resistance at Penn. As noted on the annual progress report, a retreat was held in the first year of this grant 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. This new center is tentatively entitled the “Center for Healthcare

Epidemiology and Antimicrobial Resistance Research and Policy (HARRP)". The mission and goals of the Center are described later in this final report. Even while the new center awaits final approval, the greatly enhanced research infrastructure built by the CURE grant has shown great promise. For example, our group successfully competed to be a site of the CDC's Prevention Epicenter network. One of only five such sites in the US, the Penn site focuses on improving antibiotic use and elucidation of the epidemiology of multidrug-resistant organisms. A clear strength of the Penn application was seen to be the close collaborative infrastructure, particularly between adult medicine and pediatrics, as exemplified by the CURE grant.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes _____ No X _____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes _____ No X _____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes _____ No X _____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations

at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (β) should not print as boxes (\square) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

OVERVIEW OF SPECIFIC AIMS, OBJECTIVES, AND HYPOTHESES

Staphylococcus aureus is one of the most common causes of bacterial infection. Methicillin-resistant *S. aureus* (MRSA) infections have increased markedly over the past 20 years and are associated with significant excess morbidity, mortality, and cost. Although historically limited to healthcare settings (i.e., healthcare-associated MRSA, or HA-MRSA), MRSA infection rates in the community (i.e., community-associated MRSA, or CA-MRSA) have risen substantially in recent years. Distinguishing CA-MRSA and HA-MRSA has become increasingly problematic and clinically irrelevant as these strains are now found in both healthcare and community settings. A more straightforward and clinically relevant nomenclature identifies MRSA by the setting in which infection is recognized; hospital onset (HO-MRSA) or community onset (CO-MRSA).

Patients with a CO-MRSA infection—most commonly a skin or soft tissue infection (SSTI)—typically improve with antibiotic therapy and/or incision and drainage. However, these patients and their household contacts often develop repeated episodes of CO-MRSA infection. Efforts to interrupt these infection cycles have been unsuccessful due to an incomplete understanding of the causal factors responsible for prolonged colonization, transmission and infection by CO-MRSA. Colonization is a key step linking transmission and infection because the longer a patient remains colonized with MRSA, the greater the likelihood of both developing a new MRSA infection and transmitting the pathogen to others. Thus, interventions to reduce the duration of the colonization state may have substantial impact on subsequent rates of infection.

New strategies for preventing MRSA transmission require an improved understanding of the longitudinal dynamics of colonization and infection among adults and children within households. Such data will then permit the identification and testing of possible intervention strategies, specifically decolonization, designed to curb transmission and subsequent infection. As with all infectious diseases, the process of transmission requires consideration of the classic triad of host, pathogen and environmental factors. Pathogen factors include not only intrinsic characteristics of the MRSA organisms but also the presence of co-colonizing pathogens that may influence the dynamics of MRSA carriage and transmission. Specifically, *Streptococcus pneumoniae* has been shown in recent studies to compete with *S. aureus* for colonization in the nasopharynx of humans and animals. Further, the observation of colonization interference between *S. pneumoniae* and *S. aureus* in immunocompetent but not immunocompromised individuals suggests a role for the host immune response in mediating *S. aureus* colonization levels. Thus, defining cross-reactive immunological determinants of *S. aureus* colonization status may lead to the development of novel prophylactic and therapeutic methods of controlling MRSA colonization. Similarly, a better understanding of host and environmental factors that modify patterns of MRSA transmission, colonization and infection may help identify additional targets for pharmacological or behavioral interventions.

The overall goal of this project is to elucidate the epidemiology of MRSA transmission in the community and test an intervention to prevent MRSA transmission in this setting. To achieve this goal, **our project will include 3 components, comprised of 8 primary aims:**

- Component 1:** the goal of Component 1 is to identify host, microbiological, and environmental risk factors for prolonged CO-MRSA colonization, CO-MRSA transmission and clinical CO-MRSA infection among patients with CO-MRSA SSTIs and their household contacts. This component includes the following specific aims:
- Specific Aim 1:** to identify risk factors for prolonged CO-MRSA colonization in subjects with a CO-MRSA SSTI.
 - Specific Aim 2:** to identify risk factors for new CO-MRSA clinical infection in CO-MRSA colonized subjects with a prior CO-MRSA SSTI.
 - Specific Aim 3:** to identify risk factors for new CO-MRSA clinical infection among CO-MRSA colonized household members of a patient with a prior CO-MRSA SSTI.
 - Specific Aim 4:** To identify factors that modify the inverse relationship between colonization with *S. pneumoniae* and prolonged colonization with MRSA among patients with SSTIs and their household contacts.
 - Specific Aim 5:** To use stochastic agent-based modeling methods to quantify secondary spread of CO-MRSA in households (i.e., estimate the basic reproduction number).

Component 2: The goal of Component 2 is to evaluate the impact of decolonization on MRSA infections in the household. This component includes the following specific aim:

- Specific Aim 6:** To determine if a decolonization protocol administered to index cases with CO-MRSA SSTI and their household contacts reduces the incidence of subsequent index case reinfection and household MRSA infections.

Component 3: The goal of this component of the study is to identify immunological and bacteriological determinants of MRSA colonization with respect to pneumococcal

colonization status among patients with MRSA and their household contacts. This component includes the following specific aims:

Specific Aim 7: To identify bacteriological determinants of MRSA colonization with respect to pneumococcal colonization status

Specific Aim 8: To identify the specific immune response induced by *S. pneumoniae* that shapes MRSA colonization patterns

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.

COMPONENT 1

Specific Aim 1. to identify risk factors for prolonged CO-MRSA colonization in subjects with a CO-MRSA SSTI

To provide as complete a summary of the work conducted below, we have organized the report as a scientific manuscript. Indeed, the report below represents the final manuscript resulting from this aim.

Risk Factors for Prolonged Duration of Colonization with Methicillin-Resistant *Staphylococcus aureus* in Community-Dwelling Adults and Children

INTRODUCTION

Staphylococcus aureus is one of the most common causes of infection in both the community and healthcare setting [1-3]. Until recently, infection with methicillin resistant *S. aureus* (MRSA) has been almost exclusively restricted to hospitalized and chronically ill patients [4]. However, in the past decade, MRSA infections have been increasingly reported in the community [5, 6]. The proportions of community-onset *S. aureus* infections that are methicillin resistant has been noted to be over 60% in adults [7-9] and over 75% in children [10-12] in many regions of the country.

The prevalence of colonization with MRSA in the community has been reported to be between 0.2 and 7.4% [6, 13, 14], but rates as high as 67% have been reported in household members of patients with recent MRSA infection [15, 16]. Household interactions likely influence the duration of colonization with MRSA as this is where individuals in the population spend the greatest amount of time in an average day [17]. Therefore, failure to identify and interrupt

colonization within the household may serve as a barrier to preventing persistent colonization or repeated infections [9, 18, 19].

Several studies have examined the duration of colonization with MRSA, with estimates ranging from two to forty months [20-25]. However, the risk factors for prolonged duration of colonization with MRSA in the community are unknown. Therefore, we sought to identify risk factors for prolonged colonization with MRSA in ambulatory patients presenting with an acute skin and soft tissue infection (SSTI) due to MRSA.

METHODS

Study Design and Study Subjects

We conducted a prospective cohort study to identify risk factors for prolonged duration of colonization with MRSA between January 1, 2010 and December 31, 2012 at five academic medical centers: Hospital 1, a 782-bed urban adult acute care hospital; Hospital 2, a 500-bed urban adult acute care hospital; Hospital 3, a 300-bed urban adult community hospital; Hospital 4, a 469-bed urban children's hospital; and Hospital 5, a 551-bed rural adult and pediatric hospital. Adults and children presenting to the Emergency Departments and primary care settings at any of the five study sites with an acute SSTI for which a sample was sent for microbiologic culture were approached for entry into the study. Additionally, hospitalized patients were approached if an acute SSTI was identified and a swab was sent for microbiologic culture within the first 48 hours of hospitalization. Eligible subjects were those whose culture subsequently revealed MRSA. To be enrolled, a study subject (i.e. index case) and all members of his/her household were required to agree to participate. All eligible households agreeing to participate were included in the study and each index case and household was enrolled only once. Informed consent was obtained from all adult index cases and household members; subjects 7-17 years of age provided assent; parents provided consent for children younger than seven. This study was approved by the Institutional Review Boards of all participating institutions.

Longitudinal Follow-up and Data collection

Index cases and all household members were asked to perform self-sampling for MRSA from three anatomic sites (nares, axillae, groin) every two weeks for six months from enrollment to assess for colonization with MRSA. Self-collection of swabs has proven highly sensitive compared to swabs collected by research staff [26]. Multiple anatomic sites were chosen for sampling in order to maximize the sensitivity of detection of colonization with MRSA [27, 28]. The ESwab™ System (Copan Diagnostics Inc, Murrieta, CA) was used for all sample collections. Subjects obtained specimens by placing a swab in the nares; the same swab was used for both nares. The subject then placed a second swab in both axillae followed by the groin. If a skin lesion (e.g., eczema, wound) was present, that site was also sampled with a third swab. The swab specimens were then mailed to the study laboratory. At the first visit to the household to enroll subjects, research staff demonstrated the method for sampling each anatomic site. For children unable to self-collect specimens, parents/guardians were instructed to perform the sampling. Only the households whose index cases returned at least two consecutive weeks of samples were included in the analysis.

The following data elements were collected on index cases and household members through the initial home visit interview and review of medical records: demographic data; medical history, including comorbidities and medications; number of people in the household; and, for index cases only, antibiotic use during the year prior to diagnosis of SSTI (past use), the 14 days following SSTI diagnosis (treatment), the period after treatment through end of follow-up (later use). Antibiotic use in the 14 days prior to SSTI diagnosis was not included as this was assumed to be empiric treatment for the presenting infection.

Laboratory Testing

Swab samples were plated to BBL ChromAgar MRSA (BD, Sparks, MD) and processed according to manufacturer's instructions [29]. Testing for *in vitro* susceptibility of *S. aureus* to oxacillin, penicillin, erythromycin, clindamycin, levofloxacin, chloramphenicol, gentamicin, trimethoprim-sulfamethoxazole, rifampin and vancomycin was performed using the Vitek 2 automated identification and susceptibility testing system with Advanced Expert System (AES) (bioMerieux, Inc.) and interpreted according to established criteria [30]. Isolates that were erythromycin-resistant but clindamycin-susceptible were routinely tested for inducible macrolide-lincosamide-streptogramin resistance by the disk diffusion method (D-test) [30].

Data Analysis

Subjects were presumed to be colonized with MRSA at date of enrollment. Termination of colonization was defined as two consecutive sampling periods with no MRSA positive swabs. The termination date was then considered to be the midpoint between the date of the last positive swab and the date of the first negative sampling period. Median duration of colonization was determined using a Kaplan Meier estimate. The presence of colonization in at least one household member was treated as a time-varying covariate. Bivariable analyses were performed to evaluate risk factors for prolonged duration of colonization in the index case, as determined by survival analysis. Cox proportional hazards regression models were used to determine the association between risk factors and prolonged duration of colonization with MRSA in the index case. Variables were included in the regression model if they were associated with time to resolution of colonization with MRSA on bivariable analysis ($p\text{-value} \leq 0.20$) [31]. Variables were maintained in the final model if they remained significantly associated with the outcome using backward deletion. Age younger than 18 and presence of at least one household member colonized with MRSA were identified *a priori* as potential risk factors and so were maintained in the model. A hazard ratio (HR) and 95% confidence interval (CI) were calculated to evaluate the strength of any association.

For all calculations, a 2-tailed P value <0.05 was considered to be significant. Statistical calculations were performed using commercially available software (SAS 9.3, SAS Institute Inc., Cary, North Carolina, USA)

RESULTS

A total of 350 households provided informed consent. Of these enrolled households, 273 (78%) index cases returned at least two samples (permitting a calculation of duration of colonization) and were included in the analysis. These 273 households included 273 index cases and 887 household members, for a total of 1160 subjects. Median duration of follow up for index cases

and household members was 181 days (interquartile range [IQR], 110-199) and 176 days (IQR, 107-195), respectively. Of the potential 14 sampling episodes per subject, index cases returned at least one swab for a median of 11 episodes (IQR 6-13) while household members returned at least one swab for a median of 9 episodes (IQR 5-13).

The median age of index cases was 21.8 years (IQR, 4.2-46.5) with 127 (46.5%) under the age of 18. Of the 273 index cases, 167 (61.2%) were female. The median age of household members was 22 (IQR 8.9-36.5). Of the 887 household members, 376 (42.4%) were younger than 18 and 497 (56.0%) were female. Sixty-four index cases reported a history of previous MRSA infection; however, 70 of the 273 index cases did not provide a response to this question.

Two-hundred forty (87.9%) index cases received antibiotic treatment for the MRSA SSTI, most commonly with trimethoprim-sulfamethoxazole (116 subjects, 42.5%) and clindamycin (115, 42.1%). Additionally, approximately 20% of subjects received a prescription for an intervention to attempt to eradicate colonization in the 14 days after SSTI diagnosis: 54 (19.8%) were prescribed topical nasal mupirocin while 55 (20.1%) were given bleach baths, body wipes or chlorhexidine. Complete antibiotic susceptibility data were available for 204 (85%) of the subjects who received antibiotic treatment; of these, 191 (93.6%) received an antibiotic to which the organism was susceptible.

Figure 1 shows the Kaplan Meier survival curve of colonization with MRSA over time. The median duration of colonization with MRSA was 36 days (95% confidence interval (CI), 32-42). Of the 273 index cases, 53 (19.4%) remained colonized with MRSA at the end of the study period.

In bivariable analyses (Table 1), subjects with prolonged duration of colonization with MRSA were more likely to be younger than 18 (unadjusted hazard ratio (HR), 1.44; 95% CI, 1.10-1.88; $P=0.007$), to be classified as non-white race (HR, 1.53; 95% CI 1.16-2.02; $P=0.003$) and to have had at least one household member colonized with MRSA (HR, 1.59; 95% CI, 1.19-2.13; $P=0.002$). In contrast, previous diagnosis of malignancy was associated with shorter duration of colonization with MRSA (HR, 0.43; 95%, 0.23-0.81; CI $P=0.010$). Table 2 shows the unadjusted associations between duration of colonization with MRSA and use of specific antibiotics in three discrete time periods. Treatment of the MRSA SSTI with clindamycin in the 14 days after diagnosis was associated with prolonged duration of colonization with MRSA (HR, 1.69; 95% CI, 1.29-2.22; $P<0.001$). Receipt of mupirocin or chlorhexidine/bleach baths or wipes after SSTI diagnosis had no association with the duration of colonization with MRSA (HR, 0.88; 95% CI, 0.62-1.25; $P=0.470$; and HR, 0.76; 95% CI, 0.54-1.07; $P=0.114$, respectively).

In multivariable analysis using a Cox proportional hazards model, presence of colonization with MRSA in at least one household member was a significant risk factor for prolonged duration of colonization in the index case (adjusted HR, 1.57; 95% CI, 1.17-2.11); $P=0.003$) (Table 3). Non-white race (HR, 1.44; 95% CI, 1.09-1.90; $P=0.011$) and treatment of the MRSA SSTI with clindamycin in the 14 days after SSTI diagnosis (HR, 1.50; 95% CI, 1.13- 1.99; $P=0.006$) were also associated with prolonged duration of colonization. Age less than 18 years old was not significantly associated with duration of colonization with MRSA (HR, 1.21; 95% CI, 0.91-1.60; $P=0.191$).

DISCUSSION

This multi-center prospective cohort study was the first to longitudinally examine the dynamics of MRSA colonization within the household in adults and children presenting with typical MRSA infections. Median duration of colonization with MRSA after diagnosis of SSTI was 36 days. Risk factors associated with prolonged duration of colonization with MRSA included presence of at least one household member colonized with MRSA, non-white race and treatment with clindamycin. Household size, age, and use of mupirocin were not associated with duration of colonization.

The median duration of colonization with MRSA in this study is shorter than the duration reported in prior studies [20-23]. However, most prior studies calculated duration of colonization using colonization status at hospital readmission [20, 21, 23], rather than via systematic, longitudinal sampling, which precludes the accurate measurement of duration of colonization. Two studies have followed subjects longitudinally to determine MRSA colonization. Eveillard and colleagues [22] followed healthcare workers colonized with MRSA, determining MRSA colonization status every three weeks until termination of colonization or for six months and found a median duration of MRSA colonization of 83 days. Also, Lucet et al. [24] followed subjects colonized with MRSA who were discharged from the hospital to home health care and checked for MRSA colonization every three months and found a median duration of colonization of 282 days. Although these studies used similar methods to determine duration of colonization with MRSA, the settings and study populations were significantly different from those in our study. Finally, a study conducted by Larsson and colleagues [25] in Sweden, where MRSA infections are publicly reported and serial sampling for MRSA colonization is performed until clearance, revealed that median duration of colonization with MRSA was 179 days; however, there was substantial variability and 43% of subjects were colonized for less than 2 months. Finally, it must be noted that, in our study, 19.4% of subjects remained colonized at the end of sampling, demonstrating that, for a considerable subset of patients, MRSA colonization was prolonged.

Not surprisingly, presence of colonization with MRSA in at least one household member was associated with prolonged duration of colonization in the index case. Household members likely play a role in transmission and maintenance of colonization through close personal contact and sharing of household objects, including personal hygiene items. Prior studies have shown that increased “colonization pressure” (defined as the proportion of patients colonized in a given time period) in hospital units increased the rate of MRSA transmission among hospitalized patients [32-35]. More recently, Fritz et al. [15] and Rodriguez et al. [36] showed that this was also true in the households of pediatric patients, while Larsson et al. [25] demonstrated similar findings in adults in Sweden. Our study confirms this association in subjects of all ages in the United States. Colonization with MRSA leads to subsequent infection in up to 38% of subjects [37-45]. Furthermore, it has been noted that up to two-thirds of household contacts of subjects with MRSA SSTI are subsequently colonized with MRSA [15, 16]. Disruption of colonization in household members may play a critical role in decreasing the burden associated with MRSA SSTI, as shown by Fritz and colleagues in households of pediatric patients [46]. Further studies are needed to determine if decolonization of household members decreases the rate of colonization with MRSA and subsequent infection in adults as well as children.

Although a previous study showed that treatment of SSTI with antibiotics was associated with shorter duration of colonization with MRSA [25], the role of specific antibiotics was not elucidated. Our study showed that treatment with clindamycin was associated with prolonged duration of colonization; the reason for which is unclear. The vast majority of subjects who received antibiotics as part of the treatment for the SSTI received antibiotics to which the MRSA isolate was susceptible. However, seven of the 13 subjects who received inappropriate therapy were prescribed clindamycin. Nevertheless, excluding these subjects from the analysis did not substantively alter the results (data not shown). Clindamycin's bacteriostatic mechanism of action may contribute to its inability to effectively eradicate colonization. Furthermore, clindamycin has been shown to induce the expression of genes encoding "colonization factors" in *Clostridium difficile* [47]; although this has not been shown in MRSA, it is possible that a similar mechanism may exist. Future studies should examine the role of clindamycin in colonization with MRSA.

African-American race has been identified as a risk factor for colonization and infection with MRSA in prior studies of children [48, 49]. However, after adjustment for insurance status, likely a surrogate for socioeconomic status, the association did not remain. Our study found that non-white race was also associated with prolonged duration of colonization with MRSA in adults and children. Although we did not collect data on insurance status, this confounder is likely present as was seen in previous studies.

Interestingly, household size was not associated with prolonged duration of colonization with MRSA. It appears that the more important factor is presence of a household member who is colonized with MRSA rather than the "crowding" factor. Although younger age was found to be a risk factor for MRSA transmission to household members by Mollema and colleagues [16], we did not find that it is a risk factor for prolonged duration of colonization with MRSA.

This study has several potential limitations. The full duration of colonization with MRSA in the index cases could not be precisely determined since the actual onset of colonization was unknown. Although onset was designated as the date of clinical presentation with the SSTI, the onset was almost certainly earlier than this date. However, previous studies report a short time (i.e., median 1-2 weeks) between new colonization with MRSA and subsequent MRSA infection [50-52], so we suspect that our findings are close to the true duration of colonization. Additionally, index cases may have been misclassified in terms of termination of colonization. However, defining termination of colonization as all samples negative for two consecutive sampling periods decreased the possibility that we were missing true termination of colonization. Selection bias might have also occurred. Seventy-seven households did not provide at least two samples and so were excluded from the analysis. However, the only significant difference between the included and excluded subjects regarding demographic factors and antibiotic use was in the proportion of white subjects (40.3% of included subjects vs. 15.8% of excluded subjects, $P < 0.001$). Recall bias is also an important limitation, as a large amount of the data was obtained from the subjects. This most likely affected the ascertainment of prior antibiotic use and use of decolonization methods (i.e. mupirocin, chlorhexidine); this bias is likely non-differential given that all the index cases were unaware of their ongoing colonization status. Furthermore, medical records were reviewed, when possible, to confirm and expand data collection. Similarly, potential interviewer bias was minimized by using a structured data

abstraction form utilized by interviewers who were unaware of the subject's colonization status. Finally, rates and patterns of antibiotic resistance may vary across regions and this variation may reflect differences in the distribution of risk factors. Nevertheless, this study was conducted at multiple sites comprised of a geographically, racially, and ethnically diverse population of both adults and children, which should improve the generalizability of these findings.

In conclusion, we found that household member MRSA colonization, non-white race and treatment with clindamycin were risk factors for prolonged duration of MRSA colonization in patients presenting with acute MRSA infection. Future studies should examine the impact of prolonged duration of colonization on development of MRSA reinfection as well as the potential role of total household decolonization efforts in adults and children. In addition, the association between clindamycin and prolonged duration of colonization with MRSA should be elucidated.

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Figure 1. Kaplan-Meier Curve of Duration of Colonization with MRSA

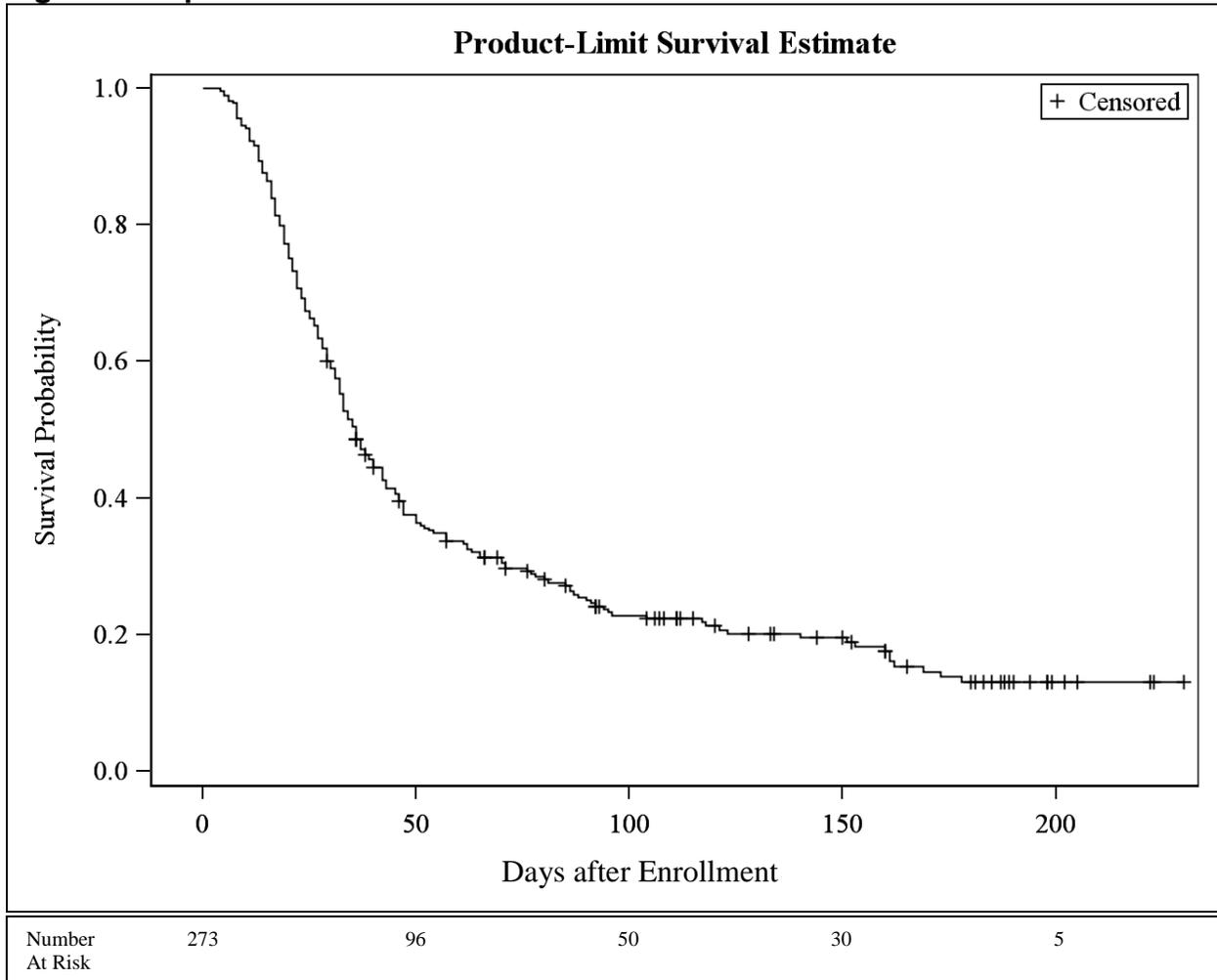


Table 1. Unadjusted Hazard Ratios for the Duration of Colonization with MRSA by Baseline Characteristics

Characteristic	Total (%)	HR (95% CI)	<i>P</i> -value
Mean age	26.8 (23.3)		
Age <18	127 (46.5)	1.44 (1.10, 1.88)	0.007
Female sex	167 (61.2)	1.23 (0.94, 1.62)	0.135
White Race	110 (40.3)	1.00 (reference)	reference
Non-white race	163 (59.7)	1.53 (1.16, 2.02)	0.003
Black/African-American	131 (49)		
Hispanic or Puerto Rican	3 (1.1)		
American Indian or Alaska Native	3 (1.1)		
Asian	2 (0.7)		
Mixed race	5 (1.8)		
Other	13 (4.8)		
Declined response	6 (2.2)		
Site of enrollment			
Hospital 1	78 (28.6)	1.00 (reference)	reference
Hospital 2	34 (12.5)	0.95 (0.60, 1.49)	0.824
Hospital 3	8 (2.9)	0.72 (0.31, 1.66)	0.442
Hospital 4	110 (40.3)	1.32 (0.96, 1.83)	0.090
Hospital 5	43 (15.8)	0.72 (0.47, 1.10)	0.124
Medical setting			
Emergency Dept.	185 (67.8)	1.00 (reference)	reference
Primary Care	71 (26.0)	0.89 (0.66, 1.20)	0.441
Inpatient	17 (6.2)	0.93 (0.54, 1.61)	0.798
Co-morbidities			
Hepatic dysfunction	13 (4.8)	1.01 (0.55, 1.85)	0.983
Renal dysfunction	6 (2.2)	0.47 (0.15, 1.47)	0.195
Diabetes mellitus	28 (10.3)	0.65 (0.41, 1.04)	0.071
Malignancy	18 (6.6)	0.43 (0.23, 0.81)	0.010
Organ transplant	4 (1.5)	0.45 (0.11, 1.81)	0.260
Intranasal steroid use	13 (4.8)	0.73 (0.37, 1.42)	0.350
Household size			
Single-person	26 (9.5)	1.00 (reference)	reference
Two-person	37 (13.6)	0.73 (0.40, 1.34)	0.312
Three-person	45 (16.5)	1.12 (0.65, 1.94)	0.677
Four-person	61 (22.3)	1.26 (0.75, 2.11)	0.382
Five-person	43 (15.8)	0.98 (0.56, 1.70)	0.939
>5-person	61 (22.3)	1.38 (0.82, 2.31)	0.224
Proportion of household members <18 years old (each 10% increase)		1.05 (1.00, 1.09)	0.053
At least 1 household member		1.59 (1.19, 2.13)	0.002

positive for colonization with
MRSA^a

HR: Hazard ratio, CI: 95% confidence interval, SD: standard deviation

^a Treated as time-varying covariate

Table 2. Unadjusted Hazard Ratios for the Duration of Colonization with MRSA by Antibiotic Use

Characteristic	Total (%)	HR (95% CI)	<i>P</i> -value
Past use	45 (16.5)		
Amoxicillin	14 (5.1)	0.96 (0.53, 1.71)	0.877
Amoxicillin-clavulanate	8 (2.9)	0.45 (0.17, 1.22)	0.118
Azithromycin	7 (2.6)	0.46 (0.17, 1.23)	0.123
Clindamycin	10 (3.7)	1.04 (0.53, 2.03)	0.911
Trimethoprim-Sulfamethoxazole	11 (4.0)	0.81 (0.40, 1.64)	0.559
Mupirocin	4 (1.5)	0.38 (0.09, 1.53)	0.172
Chlorhexidine	2 (0.7)	0.33 (0.47, 2.35)	0.269
Treatment period	240 (87.9)		
Amoxicillin-clavulanate	12 (4.4)	0.68 (0.34, 1.39)	0.292
Cephalexin	16 (5.9)	1.08 (0.60, 1.93)	0.801
Clindamycin	115 (42.1)	1.69 (1.29, 2.22)	<0.001
Doxycycline	15 (5.5)	0.79 (0.44, 1.42)	0.429
Trimethoprim-Sulfamethoxazole	116 (42.5)	0.93 (0.71, 1.21)	0.575
Mupirocin	54 (19.8)	0.88 (0.62, 1.25)	0.470
Bleach bath/Chlorhexidine	55 (20.1)	0.75 (0.54, 1.07)	0.114
Later use	52 (19.1)		
Clindamycin	14 (5.1)	0.93 (0.34, 2.51)	0.881
Doxycycline	7 (2.6)	0.47 (0.07, 3.37)	0.454
Trimethoprim-Sulfamethoxazole	20 (7.3)	0.78 (0.32, 1.90)	0.585
Mupirocin	9 (3.3)	0.29 (0.07, 1.18)	0.084
Chlorhexidine	7 (2.6)	0.17 (0.02, 1.24)	0.081

Footnote:

HR: Hazard ratio, CI: 95% confidence interval

Past use: the year prior to study enrollment, not including the fourteen days prior to SSTI diagnosis

Treatment period: 14 days following diagnosis of MRSA SSTI

Later use: from 15 days following diagnosis of MRSA SSTI until end of follow-up

Table 3. Multivariable Cox Proportional Hazards Regression Model of Risk Factors Associated with Duration of Colonization with MRSA

Variable	HR (95% CI)	<i>P</i> -value
Age < 18	1.21 (0.91, 1.60)	0.191
Non-white race	1.44 (1.09, 1.90)	0.011
Treatment with clindamycin	1.50 (1.13, 1.99)	0.006
At least 1 household member positive for Colonization with MRSA	1.57 (1.17, 2.11)	0.003

Footnote:

HR: Hazard ratio, CI: 95% confidence interval

COMPONENT 1 (continued)

Specific Aim 1 (secondary aim): to identify risk factors for recurrent MRSA colonization in subjects with a CO-MRSA SSTI.

While not included in the original specific aims, it became clear as the study progressed, that many subjects manifested recurrent colonization. As such, the investigators pursued an additional study to address the incidence of recurrent colonization and risk factors for recurrent colonization. To provide as complete a summary of the work conducted below, we have organized the report as a scientific manuscript. Indeed, the report below represents the final manuscript resulting from this aim.

Risk Factors Associated with Recurrent Colonization with Methicillin-Resistant *Staphylococcus aureus*

Introduction

Staphylococcus aureus is the most common cause of purulent skin and soft tissue infections (SSTI) in the United States [1, 2]. The proportion of *S. aureus* SSTI that are methicillin-resistant has increased considerably, with some studies revealing proportions of up to 60% in adults [3-5] and as high as 75% in children [6-8].

The prevalence of colonization with MRSA in the community has been reported to be between 0.2 and 7.4% [9-11]. The pattern of colonization with *S. aureus* varies among individuals; intermittent carriage has been reported in up to 60% of healthy subjects [12-14]. Colonization with MRSA often precedes infection [15, 16]. Previous studies have shown that colonization leads to subsequent infection in up to 38% of subjects [16-20] and recurrent infections with MRSA are common, with recurrence rates of 12-28% over four months [21-23]. No studies to date have examined the risk factors associated with recurrent colonization with MRSA. This knowledge is critical in order to effectively interrupt the colonization-infection cycle.

Colonization rates as high as 67% have been reported among household members of patients with MRSA SSTI [24, 25]. It is likely that high rates of colonization within the household may serve as a barrier to preventing persistent or recurrent colonization and repeated infections [5, 26, 27]. Therefore, the goal of this study was to identify the rate of and risk factors for recurrent colonization with MRSA after clearance through systematic sampling for MRSA colonization among patients presenting with a MRSA SSTI and their household members.

Methods

Study Design and Study Subjects

We conducted a prospective cohort study to identify risk factors for recurrent colonization with MRSA from January 1, 2010 through December 31, 2012 at five academic medical centers: Hospital 1 is a 782-bed urban adult acute care hospital; Hospital 2 is a 500-bed urban adult acute care hospital; Hospital 3 is a 300-bed urban adult community hospital; Hospital 4 is a 469-bed urban children's hospital; and Hospital 5 is a 551-bed rural adult and pediatric hospital. Adults and children presenting to the Emergency Departments and primary care settings at any of the five study sites with an acute SSTI for which a sample was sent for microbiologic culture were

approached for entry into the study. Additionally, hospitalized patients were approached if an acute SSTI was identified and a swab was sent for microbiologic culture within the first 48 hours of hospitalization. Eligible subjects were those whose culture subsequently grew MRSA. In order to be enrolled, a study subject (i.e. index case) and all members of his/her household were required to agree to participate. All eligible households agreeing to participate were included in the study and each index case and household was enrolled only once. Informed consent was obtained from all adult index cases and household members; subjects 7-17 years of age provided assent; parents provided consent for children younger than seven. This study was approved by the Institutional Review Boards of all participating institutions.

Longitudinal Follow-up and Data collection

Index cases and all household members were asked to perform self-sampling for MRSA from three anatomic sites (nares, axillae, groin) every two weeks for six months from enrollment to assess for colonization with MRSA. Self-collection of swabs has proven highly sensitive compared to swabs collected by research staff [28]. Multiple anatomic sites were chosen for sampling in order to maximize the sensitivity of detection of colonization with MRSA [29, 30]. The ESwab™ System (Copan Diagnostics Inc, Murrieta, CA) was used for all sample collections. Subjects obtained specimens by placing a swab in the nares; the same swab was used for both nares. The subject then placed a second swab in both axillae followed by the groin. If a skin lesion (e.g., eczema, wound) was present, that site was also sampled with a third swab. The swab specimens were then mailed to the study laboratory. At the first visit to the household to enroll subjects, research staff demonstrated the method for sampling each anatomic site. For children unable to self-collect specimens, parents/guardians were instructed to perform the sampling. Subjects collected and returned samples every two weeks for six months. Only the households whose index cases returned at least two consecutive weeks of samples, allowing for determination of termination of colonization, were included in the analysis.

The following data elements were collected on index cases and household members through the initial home visit interview and review of medical records: demographic data; medical history, including comorbidities and medications; information on the SSTI; number of people in the household; and, for index cases only, antibiotic use during the year prior to diagnosis of SSTI (past use), the 14 days following SSTI diagnosis (treatment), the period after treatment through end of follow-up (later use). Antibiotic use in the 14 days prior to diagnosis of SSTI was not included as this was assumed to be empiric treatment for the presenting infection. After the initial home visit, study personnel contacted the index case every four weeks to reinforce the sample collection schedule. During these telephone interviews, information about changes in the household size was recorded.

Laboratory Testing

Swab samples were plated to BBL ChromAgar MRSA (BD, Sparks, MD) and processed according to manufacturer's instructions [31]. Testing for *in vitro* susceptibility of *S. aureus* to oxacillin, penicillin, erythromycin, clindamycin, levofloxacin, chloramphenicol, gentamicin, trimethoprim-sulfamethoxazole, rifampin and vancomycin was performed using the Vitek 2 automated identification and susceptibility testing system with Advanced Expert System (AES) (bioMerieux, Inc.) and interpreted according to established criteria [32]. Isolates that were

erythromycin-resistant but clindamycin-susceptible were routinely tested for inducible macrolide-lincosamide-streptogramin resistance by the disk diffusion method (D-test) [32].

Data Analysis

Subjects were presumed to be colonized with MRSA at date of enrollment. Termination of colonization was defined as two consecutive sampling periods with no MRSA positive swabs. The termination date was then considered to be the midpoint between the date of the last positive swab and the date of the first negative sampling period. Recurrent colonization was defined as any positive swab after termination of colonization and recurrent colonization date was considered to be the midpoint between the last negative swab date and the subsequent positive swab date. Subjects with recurrent MRSA colonization were compared to subjects without recurrent MRSA colonization based on baseline demographic variables and antibiotic use in the 14 days after diagnosis of SSTI. Presence of colonization among household members and antibiotic and steroid use was determined in three distinct periods as we believed timing of exposure may be important: 1) the first 14 days after diagnosis of SSTI in the index case; 2) day 15 through termination of colonization in the index case; and 3) termination of colonization to recurrence of colonization in the index case. Differences between the groups were measured using Pearson's χ^2 or Fisher's exact test for categorical variables and student's t-test for continuous variables. Bivariable analyses were performed to evaluate for risk factors for recurrent colonization. Multivariable analyses using logistic regression were then performed; variables were included in the regression model if they were associated with recurrent MRSA colonization on bivariable analysis (p value ≤ 0.20) [33]. Variables were maintained in the final model if they remained significantly associated with the outcome using backward deletion. An odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the strength of any association.

For all calculations, a 2-tailed P value <0.05 was considered to be significant. All statistical calculations were performed using commercially available software (SAS 9.3, SAS Institute Inc., Cary, North Carolina, USA)

Results

During the study period, a total of 350 households provided informed consent. Of these enrolled households, 273 (78%) returned at least two samples (thus permitting a calculation of termination of colonization) and were included in the analysis. The median age of index cases was 18.3 (interquartile range [IQR], 3.6-42.7) and 138 (62.7%) were female. Among the 273 index cases, 220 (80.6%) were determined to have termination of MRSA colonization during the study period. These 220 subjects comprised the principal study cohort. Subsequently, 94 (42.7%) index cases had swabs positive for MRSA, indicating recurrent colonization. The median time to recurrence of colonization with MRSA after termination was 53 days (IQR, 35-87).

There were a total of 744 household members. The median age of household members was 21.2 years (IQR, 8.9-36.5) and 417 (56.1%) were female. Median duration of follow up for index cases and household members was 185 days (IQR, 127.5-200) and 180.5 days (IQR, 114-197), respectively. Of the potential 14 sampling episodes per subject, index cases returned at least one

swab for a median of 11 episodes (IQR, 7-13) while household members also returned at least one swab for a median of 11 episodes (IQR, 6-13).

There were no significant differences in demographic characteristics between the index cases who had recurrent colonization with MRSA and those who did not (Table 1). The only statistically significant difference between the two groups was the presence of MRSA colonization in at least one household member from 15 days after enrollment to termination of colonization, which was seen more commonly in the subjects who had recurrent colonization (33.0% vs. 19.8%; $P=0.027$).

In regard to antibiotic use after diagnosis of SSTI, those subjects who developed recurrent MRSA infection were more likely to have been prescribed trimethoprim-sulfamethoxazole (50.0% vs. 35.7%; $P=0.034$) and less likely to have been treated with clindamycin (36.2% vs. 51.6%; $P=0.023$) than those who did not develop recurrent MRSA colonization (Table 2). Additionally, subjects with recurrent MRSA colonization appeared to have received amoxicillin-clavulanate and cephalexin more often than those who did not, although these differences were not statistically significant (6.4% vs. 1.6%; $P=0.08$ and 8.5% vs. 3.2% $P=0.08$, respectively). There was no difference in receipt of topical mupirocin or bleach baths/chlorhexidine between the two groups.

In multivariable analyses (Table 3), index cases with recurrent MRSA colonization were more likely to have had a household member with MRSA colonization in the time period from 15 days after enrollment to termination of colonization (odds ratio (OR), 2.18; 95% confidence interval (CI) 1.15-4.10; $P=0.016$). Higher proportions of household members under the age of 18 (OR, 1.01; 95% CI, 1.00-1.02; $P=0.049$) and treatment of the MRSA SSTI with cephalexin (OR, 3.67; 95% CI, 1.02-13.22; $P=0.047$) were also associated with recurrent colonization in the index cases. Conversely, treatment of SSTI with clindamycin was associated with a decreased probability of recurrence of MRSA colonization (OR, 0.52; 95% CI, 0.30-0.92; $P=0.024$).

Discussion

This is the first study, to our knowledge, to identify risk factors for recurrent colonization with MRSA. Systematic longitudinal sampling for colonization with MRSA allowed an accurate determination of termination of colonization and subsequent recurrence of colonization. We identified several risk factors for recurrent colonization with MRSA, including being exposed to a household member who is colonized with MRSA during the period before clearance of colonization, living with persons under the age of 18 and receipt of cephalexin as treatment for MRSA SSTI. Conversely, treatment with clindamycin was associated with a lower risk of recurrence of colonization with MRSA.

Colonization with MRSA among household members was more common in those index cases with recurrent colonization across all time periods, but only reached statistical significance in the period prior to termination of colonization. Previous studies have demonstrated that the presence of colonization with MRSA among household members results in prolonged duration of colonization with MRSA in index cases [34, 35]. Therefore, it is not surprising that presence of colonization in at least one household member is a risk factor for recurrence of colonization in

the index case. It is interesting that the time period in which this exposure was most significant, day 15 after enrollment through termination of colonization, is not the risk period one would expect (i.e. after termination of colonization). However, this may suggest that early decolonization of household members could prevent recurrence of colonization with MRSA in those presenting with MRSA SSTI. Fritz and colleagues showed that decolonization of household members may play a critical role in decreasing the burden associated with MRSA SSTI among pediatric patients [36]. Further studies are needed to determine if decolonization of household members decreases the rate of colonization with MRSA and subsequent infection in adults as well as children.

Our study demonstrated that increased number of household members under the age of 18 is a risk factor for recurrence of colonization with MRSA in index cases. Young age has also been identified as a risk factor for prolonged duration of colonization with MRSA [35] as well as for transmission of MRSA within households [25, 26, 37], presumably due to the former. Although it has been postulated that the association between young age and MRSA colonization and transmission is due to crowding in households with many children, our study did not find that larger household size was a risk factor for recurrent colonization with MRSA. An alternative explanation could be poor hygiene in children as compared to adults or increased sharing of personal hygiene objects among children. On the other hand, Lucet et al. [38] found that older age was associated with prolonged MRSA carriage, transmission and acquisition of MRSA in a home healthcare environment; therefore, the association between age and the natural history of colonization with MRSA in the community is not fully clear and should be studied further.

It is not an unexpected finding that recurrence of colonization is associated with receipt of cephalexin during the 14 days following MRSA SSTI given that MRSA is resistant to cephalexin. However, nearly all (7 of 8) of the subjects with recurrent colonization who received cephalexin during the treatment time period were also prescribed an antibiotic to which the organism was ultimately demonstrated to be susceptible. This was also true for the subjects without recurrent colonization with MRSA (3 of 4). However, we were not able to ascertain accurate timing of antibiotics and so it is unclear whether subjects received cephalexin empirically until culture results were available (usually 24-48 hours later) or if they received a MRSA-active agent along with cephalexin. A possible explanation may be that subjects received cephalexin in addition to antibiotics targeted at MRSA because they appeared more ill and so required broader coverage (i.e. for streptococci) and this may be an important confounder.

Receipt of clindamycin was associated with a decreased risk of recurrent colonization with MRSA in our study. Clindamycin has been used as a component of MRSA decolonization bundles due to its activity against MRSA with eradication rates of up to 90% [39, 40]. Several other agents have also been studied as part of combination antibiotic treatment for MRSA colonization eradication, including doxycycline [40, 41] and trimethoprim sulfamethoxazole [40]. These antibiotics were not associated with decreased risk of recurrence in our study, however. Additionally, all of the decolonization strategies also included topical treatments and so the specific role of antibiotics remains unclear. Interestingly, receipt of agents used for decolonization (i.e. topical mupirocin, bleach baths, chlorhexidine) were not associated with decreased risk of recurrent colonization in the current study. However, compliance with these measures was not determined and prescription of these drugs may have been given to patients

with a perceived higher risk of recurrence. The combination of doxycycline and rifampin in addition to mupirocin and chlorhexidine has been investigated in a randomized controlled trial [41], but no such trials have been conducted with clindamycin and may be useful in elucidating its role in preventing recurrent colonization with MRSA.

This study has several potential limitations. Index cases may have been misclassified in terms of termination of colonization. However, defining termination of colonization as all samples negative for two consecutive sampling periods decreased the possibility that we were missing true termination of colonization. Selection bias might have also occurred. Seventy-seven households did not provide at least two samples and so were excluded. However, the only significant difference between the included and excluded subjects regarding demographic factors and antibiotic use was in the proportion of White subjects (40.3% of included subjects vs. 15.8%, $P < 0.001$). Recall bias is also an important limitation, as a significant amount of the data was obtained from the subjects. This most likely affected the ascertainment of prior antibiotic use and use of decolonization methods, such as mupirocin or chlorhexidine; this bias is likely non-differential, however, given that index cases were unaware of their colonization status. Furthermore, medical records were reviewed, when possible, to confirm and expand data collection. Similarly, potential interviewer bias was minimized by using a structured data abstraction form utilized by interviewers who were unaware of the subject's colonization status. Finally, rates and patterns of antibiotic resistance may vary across regions and this variation may reflect differences in the distribution of risk factors. Nevertheless, this study was conducted at multiple sites comprised of a geographically, racially, and ethnically diverse population of both adults and children, which should improve the generalizability of these findings.

In conclusion, we found that 42.7% of subjects who initially lost colonization with MRSA later recurred, with a median time to recurrence of 53 days. Household member MRSA colonization in the time period from 15 days after SSTI diagnosis to termination of colonization, increased number of household members under the age of 18 and receipt of cephalexin during the 14 days following SSTI diagnosis were risk factors for recurrent colonization with MRSA in patients presenting with acute MRSA SSTI. Conversely, receipt of clindamycin in the 14 days following MRSA SSTI diagnosis was associated with a decreased risk of recurrent colonization with MRSA. Future studies should examine the impact of recurrent colonization on development of MRSA reinfection as well as the potential role of total household decolonization efforts in adults and children. In addition, the role of clindamycin in the treatment of MRSA SSTI or as a component of decolonization bundles should be further studied.

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Table 1. Baseline Characteristics of Subjects With and Without Recurrent Colonization with MRSA

Characteristic	Recurrent MRSA colonization (N=94)	No Recurrent MRSA Colonization (N=126)	P-value
Mean age (SD)	25.5 (22.5)	24.9 (23.0)	0.868
Age <7	26 (27.7)	47 (37.3)	0.133
Age 7-17	18 (19.2)	18 (14.3)	0.335
Age ≥18	50 (53.2)	61 (48.4)	0.483
Proportion of household members <18			0.066
Female sex	58 (61.7)	80 (63.5)	0.786
White race	35 (37.2)	45 (35.7)	0.817
Site of enrollment			0.274
Hospital 1	24 (25.5)	38 (30.2)	
Hospital 2	14 (14.9)	13 (10.3)	
Hospital 3	4 (4.3)	2 (1.6)	
Hospital 4	35 (37.2)	58 (46.0)	
Hospital 5	17 (18.1)	15 (11.9)	
Medical setting			0.817
Emergency Dept.	63 (67.0)	84 (66.7)	
Primary Care	24 (25.5)	35 (27.8)	
Inpatient	7 (7.5)	7 (5.6)	
Co-morbidities			
Hepatic dysfunction	4 (4.3)	7 (5.6)	0.761
Renal dysfunction	1 (1.1)	2 (1.6)	1.00
Diabetes mellitus	6 (6.4)	13 (10.3)	0.296
Malignancy	2 (2.1)	8 (6.3)	0.194
Organ transplant	2 (2.1)	0 (0.0)	0.183
Presenting SSTI			
Drainage/Discharge^a	48 (55.8)	69 (61.1)	0.456
Abscess^a	81 (91.0)	112 (93.3)	0.532
Incision and drainage performed^a	57 (65.5)	79 (67.0)	0.830
Household size			0.611
Single-person	8 (8.5)	12 (9.5)	
Two-person	10 (10.6)	13 (10.3)	
Three-person	16 (17.0)	21 (16.7)	
Four-person	19 (20.2)	34 (27.0)	
Five-person	13 (13.8)	21 (16.7)	
>5-person	28 (29.8)	25 (19.8)	
Colonization in at least			

one household member			
Total Study Period	54 (57.5)	65 (51.6)	0.388
First 14 days	19 (20.2)	17 (13.5)	0.183
Day 15 through	31 (33.0)	25 (19.8)	0.027
termination of colonization			
Termination of colonization to recurrence	51 (54.3)	60 (47.6)	0.330

SD: standard deviation

^aPercentages calculated using data available

Table 2. Antibiotic and Immunosuppressant Use after Diagnosis of SSTI in Subjects With and Without Recurrent Colonization with MRSA

Antibiotic	Recurrent MRSA Colonization (N=94)	No Recurrent MRSA Colonization (N=126)	<i>P</i> -value
First 14 days			
<i>Antibiotics</i>			
Amoxicillin-clavulanate	6 (6.4)	2 (1.6)	0.076
Cephalexin	8 (8.5)	4 (3.2)	0.085
Clindamycin	34 (36.2)	65 (51.6)	0.023
Doxycycline	4 (4.3)	8 (6.4)	0.499
Trimethoprim-Sulfamethoxazole	47 (50.0)	45 (35.7)	0.034
Mupirocin	18 (19.2)	21 (16.7)	0.633
Bleach bath/Chlorhexidine	16 (17.0)	23 (18.3)	0.813
<i>Steroids</i>			
Prednisone	6 (6.4)	2 (1.6)	0.076
Intranasal steroids	2 (2.1)	7 (5.6)	0.307
Day 15 through termination of colonization			
<i>Antibiotics</i>			
Clindamycin	6 (6.4)	6 (4.8)	0.600
Doxycycline	3 (3.2)	3 (2.4)	0.702
Trimethoprim-Sulfamethoxazole	5 (5.3)	7 (5.6)	0.939
Mupirocin	7 (7.5)	9 (7.1)	0.932
Bleach bath/Chlorhexidine	16 (17.0)	23 (18.3)	0.813
<i>Steroids</i>			
Prednisone	4 (4.3)	2 (1.6)	0.406
Intranasal steroids	2 (2.1)	7 (5.6)	0.307
Termination of colonization to recurrence			
<i>Antibiotics</i>			
Azithromycin	3 (3.2)	0 (0)	0.077
Clindamycin	5 (5.3)	6 (4.8)	0.851
Doxycycline	1 (1.1)	3 (2.4)	0.638
Trimethoprim-	11 (11.7)	9 (7.1)	0.245

Sulfamethoxazole			
Mupirocin	7 (7.5)	9 (7.1)	0.932
Bleach bath/Chlorhexidine	16 (17.0)	22 (17.5)	0.932
Steroids			
Prednisone	2 (4.3)	4 (1.6)	1.00
Intranasal steroids	2 (2.1)	7 (5.6)	0.307

Table 3. Logistic Regression Model of Risk Factors Associated with Recurrent Colonization with MRSA

Variable	OR (95% CI)	P-value
At least one household member positive from 15 days after enrollment to termination of colonization	2.18 (1.15, 4.10)	0.016
Proportion of household members under the age of 18	1.01 (1.00, 1.02)	0.049
Treatment with cephalexin	3.67 (1.02, 13.22)	0.047
Treatment with clindamycin	0.52 (0.30, 0.92)	0.024

OR: Odds ratio; CI: confidence interval

COMPONENT 1 (continued)

Specific Aim 2: to identify risk factors for new CO-MRSA clinical infection in CO-MRSA colonized subjects with a prior CO-MRSA SSTI.

All data necessary to complete this aim have been collected and cleaned. Data analysis is currently underway but not yet complete. It is anticipated that this aim will be completed by May 1, 2014.

Specific Aim 3: to identify risk factors for new CO-MRSA clinical infection among CO-MRSA colonized household members of a patient with a prior CO-MRSA SSTI.

All data necessary to complete this aim have been collected and cleaned. Data analysis is currently underway but not yet complete. It is anticipated that this aim will be completed by July 1, 2014.

Specific Aim 4: To identify factors that modify the inverse relationship between colonization with *S. pneumoniae* and prolonged colonization with MRSA among patients with SSTIs and their household contacts.

All data necessary to complete this aim have been collected and cleaned. Data analysis is currently underway but not yet complete. It is anticipated that this aim will be completed by July 1, 2014.

Specific Aim 5: To use stochastic agent-based modeling methods to quantify secondary spread of CO-MRSA in households (i.e., estimate the basic reproduction number).

All data necessary to complete this aim have been collected and cleaned. Data analysis is currently underway but not yet complete. It is anticipated that this aim will be completed by July 1, 2014.

COMPONENT 2

Specific Aim 6: To determine if a decolonization protocol administered to index cases with CO-MRSA SSTI and their household contacts reduces the incidence of subsequent index case reinfection and household MRSA infections.

A total of 223 households were enrolled in the RCT, accounting for 981 total study subjects (including index cases and household members). Compared to the originally anticipated sample size projections, the number of households enrolled represents approximately 60% of the target while the number of study subjects represents approximately 81% of the target sample size. However, given our very conservative sample size estimates we believe we continue to have adequate power to achieve the study aims. As noted in prior progress reports, the primary reason for the lower than anticipated sample size was a delay in initiating enrollment into the RCT.

This was primarily due to unanticipated requirements from the Food and Drug Administration (FDA) mandating a formal Investigational New Drug (IND) application for our RCT intervention. Despite earlier assurances that no such IND application would be necessary (since all components of our decolonization intervention are already FDA-approved therapies) the FDA requirement for an IND application was entirely unanticipated. Based on the FDA review, there were several modifications to the protocol. First, because of FDA concerns regarding the safety of mupirocin ointment in children less than 6 months of age, we excluded the enrollment of households with children less than 6 months of age. Second, all household members less than 12 years of age who are enrolled in the decolonization arms (both “supervised” and “unsupervised”) were required to receive an in-person medical evaluation, including medical history and physical examination, by a trained clinician, within two days of the completion of the decolonization regimen. Finally, also in response to the FDA guidance, we changed slightly our approach for dispensing the mupirocin. We initially stated we would use 0.5mL tubes to dispense mupirocin. In discussing this further with our Investigational Drug Service, we identified a more efficient approach. We decided to use a metered dose device that dispenses exactly 0.5mL per stroke. Given the requirements set forth by the FDA as part of the IND application, our enrollment into the RCT was delayed considerably. Enrollment began on February 1, 2012. Despite this marked delay in initiating enrollment, recruitment of households progressed at an excellent rate thereafter. However, we could not make up all the time lost from the initial delays. Nevertheless, for reasons noted above, we believe we continue to have adequate power to achieve the study aims.

Among the 223 households enrolled, there were 15 one-person households, 34 two-person households, 36 three-person households, 49 households with four household members, 33 households with five household members, 23 households with six household members, and 33 households with greater than six household members. Among the participating study sites, 93 households were enrolled at the University of Pennsylvania Health System (UPHS), 107 households were enrolled at the Children’s Hospital of Philadelphia (CHOP), and 23 households were enrolled at Hershey Medical Center (HMC).

Data analysis on this aim is ongoing and expected to be completed by April 1, 2014. At that point, drafting of a scientific manuscript will commence which will be completed by May 1,

COMPONENT 3

Specific Aim 7: To identify bacteriological determinants of MRSA colonization with respect to pneumococcal colonization status

Specific Aim 8: To identify the specific immune response induced by *S. pneumoniae* that shapes MRSA colonization patterns

Work addressing specific aims 7 and 8 are described below and in the manuscript attached (Lijek et al, PNAS 2012;21:13823-8).

Protection from the acquisition of *Staphylococcus aureus* nasal carriage by cross-reactive antibody to a pneumococcal dehydrogenase

The Gram-positive bacterial pathogen *Staphylococcus aureus* is responsible for significant morbidity, mortality, and excess healthcare costs worldwide. The management of *S. aureus* disease has become increasingly difficult because of the rising prevalence of methicillin-resistant *S. aureus* (MRSA), which can account for 60% of *S. aureus* infections in hospital and community settings (1, 2). Given the limited treatment options for MRSA infection, novel preventative approaches are needed to protect against *S. aureus* infection and transmission. A predominant risk factor for *S. aureus* infection and transmission is asymptomatic colonization of the anterior nares (3). Eighty percent of *S. aureus* invasive infections in humans are caused by the host's colonizing strain (4). However, the specific host and bacterial determinants of *S. aureus* nasal carriage are not well understood (5). In children, significantly reduced *S. aureus* colonization rates have been associated with carriage of another member of the upper respiratory tract flora, *Streptococcus pneumoniae* (6–14). These large and geographically diverse cohorts have demonstrated reproducibly that colonization with *S. pneumoniae* reduces the risk of *S. aureus* carriage by approximately half. This interference phenomenon has been reported for both vaccine and nonvaccine serotypes of *S. pneumoniae* (13). Moreover, pneumococcal vaccination, which reduces *S. pneumoniae* carriage, has been associated with an increased incidence of *S. aureus*-induced otitis media in children (15).

The etiology of this interference phenomenon between *S. pneumoniae* and *S. aureus* colonization is unknown. Although in vitro studies have demonstrated that hydrogen peroxide secreted by *S. pneumoniae* is bactericidal to *S. aureus* in coculture (16–18), neither hydrogen peroxide secretion by *S. pneumoniae* nor hydrogen peroxide sensitivity of *S. aureus* is predictive of cocolonization patterns in vivo (19–21). Moreover, any direct competitive effect in vivo is unlikely, because *S. aureus* is found primarily in the anterior nares (5), whereas *S. pneumoniae* colonizes the nasopharynx (22). Instead, we and others (21) have hypothesized that an immunological mechanism may be involved, because the antagonistic effect of pneumococcal colonization on *S. aureus* carriage is observed in HIV-negative but not immunocompromised HIV-positive individuals within the same cohort (8, 9, 23). To date, the only study that has addressed the role of the immune system measured antibody titers to 17 predetermined pneumococcal proteins and found no correlation with *S. aureus* carriage in 57 infants (24). Therefore, a comprehensive examination of this hypothesis without preselection of candidate antigens has not yet been performed.

Here we investigate whether the host immune response to *S. pneumoniae* carriage can influence *S. aureus* colonization in vivo. We demonstrate that antibodies elicited during pneumococcal colonization in a mouse model cross-react with *S. aureus*, leading to a reduction in *S. aureus* nasal colonization. We identify the staphylococcal target of cross-reactive antibody and the homologous immunogen in *S. pneumoniae* and confirm that these antigens are necessary and sufficient to limit the acquisition of *S. aureus* nasal colonization in vivo.

MATERIALS AND METHODS

Bacterial Strains and Mutants.

S. pneumoniae was grown in tryptic soy (TS) broth at 37 °C in a nonshaking water bath. TIGR4 (a serotype 4 clinical isolate and genome-sequenced strain) and P1121 (a serotype 23F clinical isolate) were used because they colonize the murine nasopharynx efficiently (28). A TIGR4 mutant lacking *sp_1119* was constructed using overlap extension PCR (see *SI Materials and Methods* for details). *S. aureus* was grown in TS or brain-heart infusion broth at 37 °C with shaking (strains and sources are identified in *SI Materials and Methods*). An unmarked, in-frame deletion mutant of *rocA*, which encodes P5CDH, was constructed in strain 502A using pKOR1-*rocA* and was complemented using pCL55 (see *SI Materials and Methods* for details).

Mouse Model of Nasopharyngeal Colonization and Challenge.

The murine model of pneumococcal nasopharyngeal colonization has been described previously (28) and is described in full in *SI Materials and Methods*. Mice received an intranasal dose of 10^7 cfu of *S. pneumoniae* at weeks 0 and 2 and were challenged at week 7, at which time no pneumococci remained in the nasopharynx (28). Control animals were subjected to the same protocol but were mock-colonized with PBS. Intranasal challenge of *S. aureus* consisted of 10^8 cfu. Colonization densities from nasal lavages were quantified on BBL CHROMagar Staph aureus (BD Diagnostics) 24 h postchallenge.

Identification of Candidate Antigens.

The targets of cross-reactive pneumococcal antibody were identified by Western blot analysis and mass spectrometry. See *SI Materials and Methods* for further details.

Measurement of Serum Antibody Binding.

Binding of total serum IgG to whole bacteria was detected by flow cytometry using a FITC-conjugated anti-mouse IgG secondary antibody. Antigen-specific serum IgG titers were quantified by ELISA. Both methods are detailed in *SI Materials and Methods*.

Recombinant Antigen Purification and Generation of Specific Antisera.

The coding sequences for each of the four candidate antigens were amplified from the appropriate chromosomal DNA using primers listed in *SI Materials and Methods*. Amplicons were ligated into pET29b (Novagen) for expression of recombinant antigens in *E. coli* BL21(DE3) and purification under native conditions. As appropriate, his-tags were removed by a thrombin cleavage capture system (Novagen) and dialysis. Polyclonal rabbit sera to each purified recombinant antigen were prepared commercially.

Immunization with Purified Antigens.

As previously described (38), mice were immunized intranasally with 4 µg of recombinant protein and 1 µg cholera toxin as adjuvant (List Biological Laboratories) per 20-µL dose. Control mice received adjuvant alone. Three immunizations were given at weekly intervals, followed by intranasal *S. aureus* challenge at week 5, as described above.

Statistical Analysis.

Colonization density was expressed as the \log_{10} cfu/mL and analyzed for statistical significance using the Mann–Whitney U test. Paired t tests were used to compare pre- vs. posttreatment groups, and linear regressions were used to assess correlations. All other comparisons were made using the unpaired t test, as appropriate. A P value of less than 0.05 was considered significant. Statistical analyses were performed using Prism 4 (GraphPad).

RESULTS

To recapitulate the observed interference between *S. pneumoniae* and *S. aureus* colonization, we developed a mouse model of *S. aureus* nasal colonization using strain 502A, a clinical isolate known for superior nasal colonization in humans (25). Unlike previously described models of *S. aureus* nasal carriage, which are highly variable, nasal colonization by 502A is established reproducibly in naive C57BL/6 mice with higher and less variable densities than seen with other strains. 502A colonization was achieved with a dose of 10^5 cfu, but levels were highest and most reproducible at day 1 postinoculation with a dose of 10^8 cfu. For all further experiments, we chose to use these latter conditions, which reproducibly model the first step in colonization—nasal acquisition—but do not model the long-term human carrier state. Therefore, our studies with this model focus on the initial establishment of *S. aureus* nasal colonization rather than on persistent carriage. Under these conditions, the levels of *S. aureus* detected in our model are comparable to those recovered from experimentally colonized humans (26).

We next combined our 502A acquisition model with an established murine model of pneumococcal nasopharyngeal colonization that has colonization dynamics and immune responses similar to those observed in humans, including a robust antibody response to a diversity of pneumococcal antigens (27, 28). After colonizing mice with *S. pneumoniae* and allowing 5 wk for complete pneumococcal clearance, we challenged mice intranasally with *S. aureus* 502A. Compared with mock-colonized (PBS) controls, mice previously colonized with *S. pneumoniae* TIGR4 had significantly reduced levels of *S. aureus* 502A carriage, similar to observations made in children. The protective effect of prior pneumococcal colonization was not dependent on pneumococcal strain or serotype, because similar reductions in 502A colonization were seen following prior colonization with *S. pneumoniae* P1121.

Because the effect of prior pneumococcal colonization was observed at a time when pneumococci no longer can be detected in the nasopharynx, we hypothesized that the reduction in *S. aureus* levels might be caused by the presence of anti-pneumococcal antibody. To test this hypothesis, we repeated the dual-species colonization experiment in antibody-deficient μ MT mice and found no significant difference in 502A colonization levels between mice colonized previously with *S. pneumoniae* and mock colonized controls. These data suggest that antibody is necessary for the protective effect of pneumococcal colonization on *S. aureus* colonization.

Pneumococcal Colonization Elicits Antibody That Cross-React with *S. aureus*.

We next investigated whether the antibody response elicited by pneumococcal colonization was capable of recognizing *S. aureus*. Mice colonized with *S. pneumoniae* developed significantly increased levels of IgG that bound to the surface of live *S. aureus*, compared with levels in precolonization sera ($P = 0.043$ for five mice). In Western blots of staphylococcal whole-cell lysates, sera from mice postcolonization with *S. pneumoniae* cross-reacted with a single

prominent band of about 55 kD, *Right* two panels, arrow). In contrast, blots using sera after mock colonization with PBS resembled background levels of sera before colonization. After further separation by 2D gel electrophoresis and Western blot, the staphylococcal target of antibody induced by pneumococcal colonization was isolated for mass spectrometric analysis. Only two proteins, dihydrolipoamide dehydrogenase (DLDH, [YP_499592](#)) and 1-pyrroline-5-carboxylate dehydrogenase (P5CDH, [YP_501325](#)), were present at this position in equal abundance as determined by empirical protein-abundance index scores. For each staphylococcal protein, one closely homologous protein was identified in the *S. pneumoniae* TIGR4 genome by tBLASTn. The homologous loci in the TIGR4 genome are *sp_1161* (E value = $1e^{-56}$) and *sp_1119* (E value = $6e^{-68}$), respectively, and both encode putative but uncharacterized dehydrogenases which we refer to hereafter as “SP_1161” and “SP_1119.”

Candidate Antigen Is SP_1119 in *S. pneumoniae* and Its *S. aureus* Homolog, P5CDH.

Each candidate antigen was cloned, recombinantly expressed, purified, and used to generate specific antisera. IgG to P5CDH and DLDH bound to the surface of live *S. aureus*, indicating that these proteins are antibody accessible. In contrast, incubation of *S. pneumoniae* TIGR4 with antisera specific to the pneumococcal proteins did not result in surface IgG binding. However, elimination of the antiopsonic capsular polysaccharide in TIGR4*cps* facilitated surface binding by anti-SP_1119 and anti-SP_1161 IgG, suggesting that these antigens are surface associated but masked by capsule.

We investigated whether antibodies raised against each candidate protein could cross-react with the heterologous species. When *S. aureus* was incubated with antisera to the pneumococcal proteins, we observed cross-reactive binding with anti-SP_1119 but not with anti-SP_1161 IgG. Similarly, antisera to the staphylococcal homolog of SP_1119, P5CDH, bound to the surface of unencapsulated *S. pneumoniae*, but antisera to DLDH did not. Together, these data suggest that antisera to the homologous pair P5CDH and SP_1119, but not to DLDH and SP_1161, cross-react with the surface of the heterologous species.

For SP_1119 to induce cross-reactive antibody *in vivo*, it must be immunogenic during pneumococcal colonization. We investigated whether pneumococcal colonization in mice elicited antibodies to SP_1119 by Western blot and ELISA. By Western blot we observed an increase in antibody binding to both SP_1119 and P5CDH in sera of mice after pneumococcal colonization as compared with sera from mice before pneumococcal colonization. No increase in binding was observed in mock-colonized animals. Similarly, by ELISA, mice colonized with TIGR4 had significantly elevated IgG titers to SP_1119, whereas mock-colonized control mice did not. There was a significant intraindividual correlation between elevated IgG tiers to SP_1119 and P5CDH, indicating that animals with a robust response to SP_1119 mounted commensurate responses to P5CDH.

Because the clinical negative association between pneumococcal and *S. aureus* colonization appears to be independent of *S. aureus* strain, we reasoned that any target of cross-reactive antibody must be well conserved. In all publically available whole *S. aureus* genomes ($n > 12$), the amino acid sequence for P5CDH is at least 98% identical. We confirmed this widespread conservation by Western blot using a selection of methicillin-sensitive and methicillin-resistant *S. aureus* strains including the epidemic clinical isolate USA300. P5CDH was detected in all the

strains tested but not in the unmarked, in-frame P5CDH deletion mutant (502ArocA), which was used as a negative control. Similarly, SP_1119 is broadly conserved across pneumococci with at least 99% amino acid identity in all the publically available whole *S. pneumoniae* genomes ($n > 35$).

SP_1119 and P5CDH Are Necessary to Reduce *S. aureus* Carriage in a Mouse Model.

We deleted the locus *sp_1119* from *S. pneumoniae* TIGR4 to assess whether SP_1119 is necessary for the protective effect of pneumococcal colonization on subsequent *S. aureus* carriage. Although mice previously colonized with wild-type TIGR4 had significantly reduced levels of 502A carriage, mice previously colonized with TIGR4*sp_1119* did not differ from mock (PBS)-colonized controls in 502A colonization density. Colonization with both the wild-type and mutant resulted in significant increases in antibody titers to whole pneumococci compared with PBS controls, indicating that the lack of protection against 502A was not caused by an overall deficiency in the antibody response to the mutant. We confirmed by ELISA that animals colonized with TIGR4*sp_1119* did not mount antibodies to SP_1119, and animals colonized with wild-type TIGR4 had significantly higher anti-SP_1119 titers than those seen in PBS-inoculated controls. Following colonization with TIGR4*sp_1119*, cross-reactive titers to P5CDH were not significantly higher than those in PBS-inoculated controls and no longer correlated with intraindividual titers to SP_1119 (open symbols). The requirement of SP_1119 for cross-reactivity was supported by flow cytometry using a TIGR4*sp_1119cps* double mutant, demonstrating that deletion of SP_1119 abrogates binding by P5CDH antisera. Similarly, the protective effect of previous colonization with wild-type *S. pneumoniae* TIGR4 was lost when animals were challenged with 502ArocA, which lacks P5CDH. These results provide evidence that cross-protection against *S. aureus* by *S. pneumoniae* requires SP_1119 as an immunogen and P5CDH as a target.

Intranasal Immunization with SP_1119 or P5CDH Is Sufficient to Reduce *S. aureus* Colonization Levels.

Because SP_1119 and P5CDH were necessary for the protective effect of pneumococcal colonization on the acquisition of *S. aureus* carriage, we investigated whether immunization with these antigens alone was sufficient to recapitulate this effect. Mice were immunized intranasally with either adjuvant alone or in combination with purified recombinant SP_1119, P5CDH, or DLDH as a control protein. Mice immunized with SP_1119 had significantly lower levels of 502A colonization than those seen in controls administered adjuvant alone). Immunization with P5CDH resulted in a similar reduction in 502A colonization, but immunization with the control protein DLDH did not. As predicted, P5CDH or SP_1119 had no protective effect after challenge with 502ArocA, which lacks P5CDH. Complementation of the *rocA* deletion (using strain 502ArocA::pCL55-rocA⁺) restored expression of P5CDH and the protective effect of prior immunization with SP_1119 and P5CDH. Together, these data suggest that SP_1119 and P5CDH are necessary for the pneumococcal effect on *S. aureus* nasal carriage and are sufficient as mucosal immunogens to inhibit the acquisition of *S. aureus* 502A nasal carriage.

DISCUSSION

The concept of interspecies immune-mediated cross-reactivity is as old as vaccinology itself. Indeed, the first vaccine was based on Jenner's observation of immune-mediated cross-reactivity

between cowpox and smallpox. This seminal discovery was made by first identifying a naturally protected subset of the population. In that vein, we sought to investigate a subset of the population—healthy children colonized with *S. pneumoniae*—that was observed to be at reduced risk for *S. aureus* nasal carriage. This interspecies interference is one of the few epidemiological examples of protection against *S. aureus* acquisition, especially because exposure to *S. aureus* is not protective against future *S. aureus* carriage or infection in humans. Interspecies cross-reactive antibody is an important factor in natural immunity to other bacterial pathogens of the upper respiratory tract. For example, cross-reactivity between the capsular polysaccharides of certain enteric commensal *Escherichia coli* and *Haemophilus influenzae* type b has been implicated in the development of age-related natural immunity against this pathogen (29). Our study establishes that antibodies elicited in response to a specific protein during pneumococcal colonization cross-react with and inhibit *S. aureus* in vivo and thereby demonstrates the use of interspecies cross-reactivity to identify protective antigens.

Our findings implicate the antibody response to a homologous pair of putative dehydrogenases, P5CDH and SP_1119, in mediating cross-protection against *S. aureus*. SP_1119 elicits antibody to which the pneumococcus is resistant, whereas P5CDH may have limited immunogenicity during *S. aureus* colonization but still can be targeted by preexisting cross-reactive antibody. In humans, experimental colonization with *S. aureus* does not elicit antibody to P5CDH (30), although some antibody can be detected after invasive infection (31), indicating P5CDH is expressed in vivo. In addition to the identification of SP_1119 by *in silico* analysis, three lines of experimental evidence support the specific role of SP_1119 in inducing cross-protection: (i) antisera raised to SP_1119 cross-reacts with the surface of *S. aureus* in vitro; (ii) loss of SP_1119 in *S. pneumoniae* abolishes the protective effect of prior pneumococcal carriage on *S. aureus* colonization; and (iii) immunization with purified SP_1119 inhibits the establishment of *S. aureus* nasal carriage. The fact that SP_1119, like other protein antigens of *S. pneumoniae*, can be hidden from antibody by the antiopsonic capsular polysaccharide may explain the directional negative effect of pneumococcal colonization on *S. aureus* colonization and not vice versa. Preliminary data suggest that SP_1119 is immunogenic during childhood colonization with *S. pneumoniae*, and future studies will address whether these elevated antibody titers in childhood correlate with a reduced risk of nasal carriage of *S. aureus*.

SP_1119 shares extensive overall homology with P5CDH as well as a functional classification in the aldehyde dehydrogenase superfamily (32). Both proteins are highly conserved and can be detected on the bacterial surface, adding to the growing list of anchorless surface-exposed enzymes in Gram-positive bacteria (33). We predict that cross-reactivity between these two proteins is mediated by a region(s) of conformational similarity on a surface-exposed domain(s), given the lack of an identical stretch of amino acids indicative of a common linear epitope. Further investigation will be needed to define the precise region(s) responsible for inducing cross-reactivity. It would be beneficial for future studies to identify the minimal epitope(s) required for protection to minimize any undesired impact on other members of the flora or cross-reactivity with human proteins. The biological function of the proteins SP_1119 and P5CDH has not been characterized in the context of *S. pneumoniae* or *S. aureus*, respectively, and our data indicate that these proteins are not essential during in vitro growth or murine colonization. Whether these proteins affect fitness during human nasal carriage remains to be tested. However, there appears to be selective pressure for these proteins to be maintained in vivo, given

their extensive conservation among genome-sequenced strains. This conservation could account for the strain-independent interference between these two species observed in children (20). Our study required a small animal model of *S. pneumoniae* and *S. aureus* nasal colonization to evaluate our hypothesis in vivo. However, models of *S. aureus* carriage have been limited by a lack of *S. aureus* strains capable of establishing reproducible colonization. *S. aureus* 502A was used throughout the 1960s to colonize adults with furunculosis and healthy newborns deliberately to prevent acquisition of other, more virulent *S. aureus* strains during nosocomial outbreaks (25). We reasoned that 502A might be more proficient than other *S. aureus* strains at establishing colonization in mice, as appeared to be the case in humans. Indeed, the reproducibility of *S. aureus* 502A nasal acquisition in mice at day 1 postinoculation enabled the current study of *S. aureus* colonization and may be a useful tool for studying other host and bacterial determinants of the acquisition of *S. aureus* nasal carriage. Because the protective effects of our antigens were observed during the establishment of carriage, we did not test them in other animal models where disease is created artificially by circumventing the carrier state. For many bacterial pathogens of the upper respiratory tract, antibody functions to prevent the natural acquisition of carriage (34). In humans, pneumococcal conjugate vaccine is known to induce antigen-specific serum IgG, which is transported by transcytosis across epithelial barriers where it can be detected on the mucosa and is correlated with protection from the acquisition of colonization (35). However, the role of antibody in protection against *S. aureus* has been questioned, because *S. aureus* expresses protein A (Spa) which binds Ig nonspecifically. A Spa mutant often is used in vitro, especially whenever secondary antibody-detection methods are used. It has been assumed that the effect(s) of antibody in vivo would be negated similarly by Spa, but antibody-mediated protection has been demonstrated against nasal colonization with Spa-sufficient strains (31, 36). Passive i.p. immunization with a monoclonal antibody against clumping factor B resulted in reduced nasal carriage of *S. aureus* in mice (36), indicating that systemic antibody can protect against *S. aureus* colonization regardless of Spa. Our study provides another example of antibody-dependent inhibition of nasal carriage of a Spa-sufficient strain, suggesting that the immune-evasive effect ascribed to Spa may be of limited importance during colonization.

Much of the public health benefit of vaccines that target mucosal pathogens of the upper respiratory tract—including *S. pneumoniae*, *Neisseria meningitidis*, and *H. influenzae* type b—is the result of herd protection based on the inhibition of carriage in children and thus reduced transmission to unvaccinated members of the population (37). Clinical studies have demonstrated repeatedly that even modest (e.g., 50%) reductions in pathogen carriage following vaccination significantly reduce the risk of transmission, so that full protection ($\geq 90\%$) from invasive disease is afforded to both vaccinated and unvaccinated individuals (37). Indeed, it has been calculated that pneumococcal conjugate vaccine prevented many more cases of invasive pneumococcal disease in unvaccinated individuals than in vaccinated children (37). These findings illustrate how nonsterilizing decreases in pathogen colonization can have vast ramifications on disease incidence and population-wide protection. In our mouse model, we observed a relative reduction in *S. aureus* carriage and hypothesize that, if similar reductions in carriage were observed in humans, significant morbidity and mortality caused by *S. aureus* invasive disease could be prevented by herd immunity. Moreover, the success of our current pediatric conjugate vaccines reveals the importance of childhood colonization as a reservoir for bacterial pathogens within the population and thus the importance of designing immunizations

that inhibit carriage in children. We posit that a successful vaccine against *S. aureus* may benefit from the inclusion of antigens directed at reducing the acquisition of nasal carriage, such as SP_1119 and P5CDH. Future studies will be needed to address whether these antigens can protect against *S. aureus* in humans.

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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.**

Overall progress for these goals is described in turn, below.

- 1) **to foster multi-disciplinary and cross-institutional collaborations and develop the infrastructure for a Center of Excellence focused on antimicrobial drug resistance research.**

The CURE grant has been instrumental in developing and consolidating the research efforts focused on antimicrobial resistance at Penn. As noted on the annual progress report, a retreat was held in the first year of this grant 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.

This new center is tentatively entitled the “Center for Healthcare Epidemiology and Antimicrobial Resistance Research and Policy (HARRP)”. The mission of the Center is to promote the conduct of research focusing on healthcare epidemiology (e.g., infection prevention, healthcare-acquired infections) as well as the emergence, diagnosis, treatment, and prevention of antimicrobial drug resistance, with a specific emphasis on bacterial pathogens. Investigations will span from community-acquired to healthcare-acquired pathogens and include methods in clinical and molecular epidemiologic research, population sciences, outcomes research, and health policy research. Primary goals of the Center are to: 1) establish a national and international identity for the University of Pennsylvania in the area of healthcare epidemiology and antimicrobial drug resistance research and policy; 2) facilitate collaborations across departments, centers, institutes, and schools; 3) provide a forum for Penn faculty to meet, promote, and discuss new and ongoing research initiatives; 4) facilitate submission of new research grants and career development grants focused on antimicrobial resistance and healthcare epidemiology; 5) facilitate the rapid assembly of investigative teams and supporting materials to respond to research opportunities; 6) train junior investigators in careers focused on healthcare epidemiology and antimicrobial drug resistance; 7) recruit and retain faculty with research programs focused on healthcare epidemiology and antimicrobial resistance; 8) facilitate access to data resources (e.g., clinical and administrative databases, microbiological repositories) at local, regional, and national levels; and 9) promote use and facilitate access to research tools (e.g., clinical microbiology, molecular epidemiology, biostatistical support) in the areas of antimicrobial drug resistance and healthcare epidemiology. The launch of this center has been delayed by the arrival of a new Dean of the School of Medicine at Penn, although there remains great enthusiasm for the establishment of this center. The launch was also delayed in part due to the selection of Dr. Lautenbach (PI of the CURE grant and proposed founding Director of the new Center) as the new Chief of the Division of Infectious Diseases at Penn. At this point, it is anticipated that this new Center will be launched formally within the next year.

Even without the new center being formally established, the greatly enhanced research infrastructure built by the CURE grant has shown great promise. For example, our group successfully competed to be a site of the CDC’s Prevention Epicenter network. One of only five such sites in the US, the Penn site focuses on improving antibiotic use and elucidation of the epidemiology of multidrug-resistant organisms. A clear strength of the Penn application was seen to be the close collaborative infrastructure, particularly between adult medicine and pediatrics, as exemplified by the CURE grant.

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.

The overall goal of our grant was to train at least four undergraduate and four graduate under-represented minority students (cumulative). We are pleased to note that over the course of this grant, we have far exceeded our goals in providing training opportunities to under-represented minority (URM) students. Given the primary emphasis of this grant was on training Under-Represented Minority (URM) undergraduate and graduate students, the majority of students training on this grant were students from URM backgrounds. However, we also had two

outstanding non-URM students who trained with us as part of this grant. Overall, we have trained 16 students as part of this grant, 14 of which were from URM backgrounds, and two who were non-URM.

In the first year of the grant, Manuel Bramble, an African-American undergraduate student at the University of Pennsylvania, participated in the Summer Undergraduate Minority Research (SUMR) program, a national program for URM undergraduate students. SUMR provides rising sophomores, juniors and seniors with an opportunity to conduct health evaluation sciences on a topic of their choice, under the guidance of Penn faculty. In addition to formal didactic instruction, Mr. Bramble worked on various aspects of the study including drafting and revising informed consent forms, drafting data collection forms and study questionnaires, and drafting of protocol summaries IRB correspondence. The second student trained during the first summer was Gloria Williams, an African-American undergraduate student at the University of the Sciences in Philadelphia. She was participating in the Summer Undergraduate Internship Program (SUIP) for students interested in biomedical related research careers. In addition to the regular meetings of this program, Ms. Williams participated in the laboratory based research component of the project in the Weiser group.

In the second year of the grant, Ehimare Akhabue, an African-American medical student at Penn also worked on the project assisting in finalization of consent forms and data collection and interview forms. To gain more experience in epidemiologic research, he also headed up two projects, both of which resulted in scientific manuscripts (see publication list). For his work, Mr. Akhabue received the Moskowitz Award for medical student research. During this same year, we had four additional students working on the grant. Santiago Lombo-Luque 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.

In the third year of the grant, we had three URM students working on various projects. Jhanelle Markes, a student from Lincoln University, worked on various aspects of the grant including identification of eligible subjects, household recruitment, and data ascertainment. Ashley Storey, also from Lincoln University, worked primarily in the clinical microbiology laboratory under the supervision of Dr. Irving Nachamkin. She learned such laboratory techniques as bacterial identification, susceptibility testing, and pulsed field gel electrophoresis. Finally, Michelle Walters, an African-American student from Swarthmore College, worked in the laboratory of Dr. Weiser.

In the final year of the grant, we had three additional URM students gaining clinical research experience. John Ebrahim, an African-American medical student at the University of Pennsylvania, worked on various aspects of the RCT component of the grant. In addition to this work, he also pursued a project under the mentorship of Dr. Lautenbach, focused on *Clostridium difficile* infections in the hospital setting. Robyn Smith, an African-American student from Stanford University worked on the grant, primarily taking charge of data cleaning activities. Indeed, her work was so outstanding that she was ultimately hired as a research assistant for the

grant to facilitate completion of analytic datasets. Valerie Cluzet, MD, a Hispanic Infectious Diseases fellow and student in the Master of Science in Clinical Epidemiology (MSCE) training program at Penn, has also worked substantively on this project. She has been intimately involved in the data analysis ongoing for several manuscripts and has been invaluable in helping with interpretation of the data. Finally, Kristen Feemster, and African-American post-doctoral fellow at Penn, has worked on this grant throughout the study period, particularly focusing her work on *Streptococcus pneumoniae*. Dr. Feemster was recently appointed as an Assistant Professor of Pediatrics at CHOP/Penn to continue her investigative work focusing on community colonization with *S. pneumoniae*. Based in large part on her training on our grant, Dr. Feemster was also successful in securing a five-year career development grant from the Agency for Healthcare Research and Quality.

While the primary focus of this training component of this grant was on URM students, we were also fortunate to have two outstanding non-URM students working on this grant. Jennifer Han, MD, MSCE, an Asian post-doctoral fellow at Penn, focused her work on an area closely related to the primary scientific focus of the CURE grant. Based on ongoing work as part of the CURE grant, we became aware of the emerging issue of reduced vancomycin susceptibility among *Staphylococcus aureus* isolates. Dr. Han, supported in part by the CURE grant, spearheaded a number of studies focusing on the epidemiology and impact of reduced vancomycin susceptibility among *S. aureus* isolates. In addition to her work on the CURE grant, Dr. Han has taken the lead in completing several other studies focusing on the epidemiology and impact of antimicrobial resistance. The CURE grant support was instrumental in facilitating Dr. Han's early career development, as exemplified by her success in receiving a K23 Career Development Award from NIAID. She has recently joined the Penn faculty in the Division of Infectious Diseases. Finally, Meghan Davis, DVM, PhD is a post-doctoral fellow who worked closely on the CURE grant, focusing on the epidemiology of MRSA colonization in household pet animals and the impact of such colonization on human MRSA disease. Dr. Davis, facilitated greatly by her work on the CURE grant, has also submitted a career development award to continue this line of research.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

Yes
 No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

Yes
 No

If “Yes” to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both “No.”)

18(C) How many hospital and health care professionals were involved in the research project?

 0 Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

Cohort study

 405 Number of households originally targeted to be included in the study

 349 Number of households enrolled in the study

1,215 Number of subjects originally targeted to be included in the study

1,462 Number of subjects enrolled in the study

RCT

 405 Number of households originally targeted to be included in the study

 223 Number of households enrolled in the study

1,215 Number of subjects originally targeted to be included in the study

 981 Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

A total of 349 households were enrolled in the cohort study, accounting for 1,462 total study subjects (including index cases and household members). Among these 349 households, there were 34 one-person households, 45 two-person households, 66 three-person households, 72 households with four household members, 48 households with five household members, 38 households with six household members, and 46 households with greater than six household members. Among the participating study sites, 157 households were enrolled at the University of Pennsylvania Health System (UPHS), 146 households were enrolled at the Children’s Hospital of Philadelphia (CHOP), and 46 households were enrolled at Hershey Medical Center (HMC).

A total of 223 households were enrolled in the RCT, accounting for 981 total study subjects (including index cases and household members). Among these 223 households, there were 15 one-person households, 34 two-person households, 36 three-person households, 49 households with four household members, 33 households with five household members, 23 households with six household members, and 33 households with greater than six household members. Among the participating study sites, 93 households were enrolled at the University of Pennsylvania Health System (UPHS), 107 households were enrolled at the Children’s Hospital of Philadelphia (CHOP), and 23 households were enrolled at Hershey Medical Center (HMC).

Cohort study

Gender:

629 Males
833 Females
0 Unknown

Ethnicity:

126 Latinos or Hispanics
1253 Not Latinos or Hispanics
83 Unknown

Race:

9 American Indian or Alaska Native
13 Asian
869 Blacks or African American
0 Native Hawaiian or Other Pacific Islander
464 White
0 Other, specify: _____
107 Unknown

RCT

Gender:

434 Males
547 Females
0 Unknown

Ethnicity:

89 Latinos or Hispanics
884 Not Latinos or Hispanics
8 Unknown

Race:

4 American Indian or Alaska Native
6 Asian
619 Blacks or African American

3 Native Hawaiian or Other Pacific Islander
305 White
 0 Other, specify: _____
 44 Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

The research was conducted in the follow counties in Pennsylvania: Philadelphia, Delaware, Montgomery, Chester, Bucks, Dauphin

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
 Yes
 X No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
 Yes
 X No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

- Project 01 – Smith – Three cases of isolated
- Project 01 – Smith – Investigation of NEB1 deletions
- Project 03 – Zhang – Molecular profiling of aromatase
- Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Publications/Presentations

Manuscripts resulting directly from the CURE grant as well as work conducted by students as part of their training on the CURE grant are listed below. All publications acknowledge the support of the CURE grant funding.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. The impact of household transmission on duration of outpatient colonization with methicillin-resistant <i>Staphylococcus aureus</i> .	Lautenbach E, Tolomeo P, Nachamkin I, Hu B, Zaoutis TE	Epidemiology and Infection	May, 2010	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
2. “Equal” contributions and credit: an emerging trend in the characterization of authorship.	Akhabue E, Lautenbach E.	Annals of Epidemiology	Nov, 2010	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
3. Potential role of pet animals in household transmission of methicillin-resistant	Bramble M, Morris D, Tolomeo P, Lautenbach E.	Vector-Borne and Zoonotic Diseases	June, 2011	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published

Staphylococcus aureus: a narrative review.				
4. Cefepime Resistant Pseudomonas Aeruginosa.	Akhabue E, Synnestvedt M, Weiner MG, Bilker WB, Lautenbach E.	Emerging Infectious Diseases	Jun, 2011	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
5. Reduced vancomycin susceptibility and staphylococcal cassette chromosome <i>mec</i> (SCC <i>mec</i>) type distribution in methicillin-resistant <i>Staphylococcus aureus</i> bacteremia.	Han JH, Edelstein PH, Lautenbach E.	Journal of Antimicrobial Chemotherapy	Oct, 2012	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
6. Risk of invasive pneumococcal disease varies by neighbourhood characteristics: implications of prevention policies.	Feemster KA, Li Y, Localio AR, Shults J, Edelstein P, Lautenbach E, Smith T, Metlay JP.	Epidemiology and Infection	Aug, 2013	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
7. Derivation and validation of clinical prediction rules for reduced vancomycin susceptibility in <i>Staphylococcus aureus</i> bacteremia.	Han JH, Bilker WB, Edelstein PH, Mascitti KB, Lautenbach E	Epidemiology and Infection	Jan, 2013	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
8. Protection from acquisition of <i>Staphylococcus aureus</i> nasal carriage by cross-reactive	Lijek, RS, Luque SL, Parker D, Bae T, Weiser JN.	Proceedings of the National Academy of Sciences USA	Aug, 2012	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published

antibody to a pneumococcal dehydrogenase.				
9. Risk factors for infection or colonization with CTX-M extended-spectrum β -lactamase (ESBL)-positive <i>Escherichia coli</i> .	Han JH, Kasahara K, Edelstein PH, Bilker WB, Lautenbach E.	<u>Antimicrobial Agents and Chemotherapy</u>	Nov, 2012	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
10. Household transmission of methicillin-resistant <i>Staphylococcus aureus</i> and other staphylococci.	Davis MF, Iverson SA, Baron P, Vasse A, Silbergeld EK, Lautenbach E, Morris DO.	Lancet Infectious Diseases	Sep, 2012	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
11. Risk factors for efflux pump overexpression in fluoroquinolone-resistant <i>Escherichia coli</i> .	Han JH, Nachamkin I, Tolomeo P, Lautenbach E.	Journal of Infectious Diseases	Nov, 2012	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
12. Co-infection subverts mucosal immunity in the upper respiratory tract.	Lijek, RS, Weiser JN.	Current Opinion in Immunology	Aug, 2012	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
13. Risk factors for gastrointestinal tract colonization with extended-spectrum beta-lactamase (ESBL)-producing <i>Escherichia coli</i> and <i>Klebsiella</i> species in	Han JH, Nachmakin I, Zaoutis TE, Coffin SE, Linkin DR, Fishman NO, Weiner MG, Hu B, Tolomeo P, Lautenbach E.	Infection Control and Hospital Epidemiology	Dec, 2012	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published

hospitalized patients.				
14. Defining relatedness in studies of transmission of antimicrobial-resistant organisms: variability in definitions across studies and impact of different approaches on study conclusions.	Greenblatt RM, Han JH, Nachamkin I, Tolomeo P, Lautenbach E.	Infection Control and Hospital Epidemiology	Jan, 2013	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
15. The effect of staphylococcal cassette chromosome <i>mec</i> (SCC <i>mec</i>) type and clinical outcomes in methicillin-resistant <i>Staphylococcus aureus</i> bacteremia.	Han JH, Edelstein PH, Bilker WB, Lautenbach E.	Journal of Infection	Jan, 2013	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
16. Yield of methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) on moist swabs versus dry swabs.	Codrington L, Kuncio D, Han JH, Nachamkin I, Tolomeo P, Hu B, Lautenbach E.	American Journal of Infection Control	May, 2013	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
17. Temporal changes in resistance mechanisms in colonizing <i>Escherichia coli</i> isolates with reduced susceptibility to fluoroquinolones.	Han JH, Nachamkin I, Tolomeo P, Mao X, Bilker WB, Lautenbach E.	Diagnostic Microbiology and Infectious Diseases	Aug, 2013	<input type="checkbox"/> Submitted <input checked="" type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published
18. Impact of antibiotic	Han JH, Nachamkin I,	Infection Control and	Oct, 2013	<input type="checkbox"/> Submitted <input checked="" type="checkbox"/> Accepted

use during hospitalization on the development of gastrointestinal colonization with <i>Escherichia coli</i> with reduced fluoroquinolone susceptibility.	Tolomeo P, Bilker WB, Mao X, Fishman NO, Lautenbach E	Hospital Epidemiology		X Published
19. Risk factors for development of gastrointestinal colonization with fluoroquinolone-resistant <i>Escherichia coli</i> in residents of long-term care facilities.	Han JH, Maslow J, Han X, Xie SX, Tolomeo P, Santana E, Carson L, Lautenbach E.	Journal of Infectious Diseases	Jan, 2014	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes ___X___ No _____

If yes, please describe your plans:

As noted above, there have already been numerous manuscripts resulting directly from the CURE grant as well as work conducted by students as part of their training on the CURE grant. All publications acknowledge the support of the CURE grant funding. Also, as described in section 17, there are numerous data analyses currently ongoing which will result in a number of scientific manuscripts being submitted over the next year. These manuscripts will address various specific aims of the grant including: 1) identification of risk factors for prolonged CO-MRSA colonization in subjects with a CO-MRSA SSTI; 2) characterization of risk factors for new CO-MRSA clinical infection in CO-MRSA colonized subjects with a prior CO-MRSA SSTI; 3) identification of risk factors for new CO-MRSA clinical infection among CO-MRSA colonized household members of a patient with a prior CO-MRSA SSTI; 4) describing factors that modify the inverse relationship between colonization with *S. pneumoniae* and prolonged colonization with MRSA among patients with SSTIs and their household contacts; 5) quantifying secondary spread of CO-MRSA in households; and 6) evaluating, in an RCT, the impact of decolonization on MRSA infections in the household. In addition to these manuscripts focusing

on one of the primary aims of the grant, it is anticipated that numerous other manuscripts will emerge addressing other topics of interest within the study.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project.

Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert “None”; do not use “Not applicable.” Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

Since many of the primary manuscripts from this study have not yet been published, the full impact of this work has yet to be realized. However, novel approach of studying of cases and their household contacts over time has provided a unique opportunity to elucidate the longitudinal transmission dynamics of CO-MRSA. The inclusion of both adults and children significantly strengthens the generalizability of the results of this study. The study’s findings will provide crucial information regarding potential modifiable targets for intervention to limit the spread of CO-MRSA. The investigation of the immunological and clinical impact of pneumococcal colonization on CO-MRSA transmission and infection will provide an important opportunity to explore novel approaches to understanding and controlling CO-MRSA. In addition, decolonization strategies shown to be effective in our study could then be disseminated more broadly to effectively curb CO-MRSA transmission in the general population. Finally, understanding the interplay between the host immune system and *S. aureus* colonization patterns reveals novel opportunities for control and prevention of *S. aureus* infection. By investigating the immunological relationship between pneumococcal and MRSA colonization we are identifying the molecular determinant(s) that contribute to an individual’s ability to prevent *S. aureus* colonization. Ultimately, this work will lead to the identification of bacteriological and immunological factors necessary to design a *S. aureus* vaccine capable of preventing colonization by this pathogen. Considering the significant morbidity and mortality associated with MRSA infection, reducing MRSA carriage rates in the population will be a significant public health achievement

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment.

Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert “None”; do not use “Not applicable.” Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

We identified a novel target of protective antibody against the major pathogen *S. aureus*. Moreover, we showed protection from colonization – the first step in *S. aureus* infection. The target protein, P5CDH, and its homolog in *Streptococcus pneumoniae* (SP_1119) are putative vaccine candidates to protect against *S. aureus* infection.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes X No _____

- a. Title of Invention: MRSA Vaccine And Use Thereof
- b. Name of Inventor(s): RS Lijek and JN Weiser
- c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

Candidate immunogens to prevent S. aureus infection.

- d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes X No _____

If yes, indicate date patent was filed: 6/6/2011

- e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes _____ No X

If yes, indicate number of patent, title and date issued:

Patent number:

Title of patent:

Date issued:

- f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes _____ No X

If yes, how many licenses were granted? _____

- g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes ___ No X

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes X No _____

If yes, please describe your plans:

If ongoing studies are successfully, we hope to license the vaccine targets to a commercial entity that is able to advance pre-clinical and clinical development.

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

Please see the 2-page biosketches from all key investigators on the pages that follow.

EBBING LAUTENBACH, MD, MPH, MSCE - BIOSKETCH

NAME Ebbing Lautenbach, MD, MPH, MSCE	POSITION TITLE Professor of Medicine and Epidemiology Chief, Division of Infectious Diseases
eRA COMMONS USER NAME Ebbing	

EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Calvin College	BS	1989	Chemistry and Psychology
Columbia University College of Physicians &	MD	1993	Medicine
Columbia University School of Public Health	MPH	1993	General Public Health
University of Pennsylvania School of Medicine	MSCE	2001	Clinical Epidemiology

Positions and Honors

Positions and Employment

1993-1996	Intern and Resident in Medicine, Hospital of the University of Pennsylvania
1996-1997	Assistant Director, Telemetry Service, Division of Cardiology, Albert Einstein Medical Center
1997-1999	Fellow in Infectious Diseases, Hospital of the University of Pennsylvania
1999-2001	Instructor of Medicine, University of Pennsylvania School of Medicine
1999-2002	Hospital Epidemiologist, Penn Presbyterian Medical Center, University of Pennsylvania
2000-2001	Faculty-Fellow, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania
2001-2007	Assistant Professor of Medicine and Epidemiology, University of Pennsylvania
2001-2012	Associate Hospital Epidemiologist, Hospital of the University of Pennsylvania
2001-2012	Co-Director, Antimicrobial Management Program, Hospital of the University of Pennsylvania
2001-present	Senior Scholar, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania
2003-present	Fellow, Institute on Aging, University of Pennsylvania School of Medicine
2003-present	Senior Fellow, Leonard Davis Institute for Health Economics, University of Pennsylvania
2007-2008	Deputy Director, Graduate Training Programs in Epidemiology, University of Pennsylvania
2007-2012	Associate Professor of Medicine and Epidemiology, University of Pennsylvania
2008-present	Senior Fellow, Center for Public Health Initiatives, University of Pennsylvania
2008-present	Associate Director, Clinical Epidemiology Unit (Educational Programs), Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania
2012-present	Director of Research, Department of Healthcare Epidemiology and Infection Prevention, Hospital of the University of Pennsylvania
2012-present	Professor of Medicine and Epidemiology, University of Pennsylvania
2012-present	Chief, Division of Infectious Diseases. University of Pennsylvania

Honors

1998	Robert Austrian Award for Outstanding Infectious Diseases Fellow, Penn
2002-2012	Editorial Board, <u>Clinical Microbiology Reviews</u>

2003-2007 Editorial Board, Infection Control and Hospital Epidemiology
 2003 Young Investigator Award of the American Society for Microbiology
 2004 Infectious Diseases Faculty Teaching Award, Penn
 2005-present Associate Editor, Pharmacoepidemiology and Drug Safety
 2006 Fellow, Infectious Diseases Society of America (IDSA)
 2006-2010 Editorial Board, Antimicrobial Agents and Chemotherapy
 2007-present Associate Editor, Infection Control and Hospital Epidemiology
 2007 Investigator Award, Society for Healthcare Epidemiology of America (SHEA)
 2007-present Associate Editor, Annals of Internal Medicine
 2008 Fellow, American College of Physicians (ACP)
 2009-present Editorial Board, Microbial Drug Resistance
 2009 Member, American Society for Clinical Investigation (ASCI)
 2011 Fellow, Society for Healthcare Epidemiology of America (SHEA)
 2011 Excellence in Epidemiology Teaching Award, Penn

Selected Peer-Reviewed Publications (from over 150, excluding abstracts)

Lautenbach E, Fishman NO, Bilker WB, Castiglioni A, Metlay JP, Edelstein PH, Strom BL.

Risk factors for fluoroquinolone resistance in nosocomial *Escherichia coli* and *Klebsiella pneumoniae* infections. Arch Intern Med 2002;162:2469-77

Lautenbach E, Larosa LA, Kasbekar N, Peng HP, Maniglia RJ, Fishman NO.: Fluoroquinolone utilization in the emergency departments of academic medical centers: Prevalence of, and risk factors for, inappropriate use. Arch Intern Med 2003;163:601-5

Hyle EP, Lipworth AD, Zaoutis T, Nachamkin I, Bilker WB, **Lautenbach E.**: Risk factors for increasing multi-drug resistance among extended spectrum β -lactamase-producing *Escherichia coli* and *Klebsiella* species. Clin Infect Dis 2005;40:1317-24

Lautenbach E, Metlay JP, Bilker WB, Edelstein PH, Fishman NO. Association between fluoroquinolone resistance and mortality in *Escherichia coli* and *Klebsiella pneumoniae* infections: The role of inadequate empirical antimicrobial therapy. Clin Infect Dis 2005;41:923-9

Hyle EP, Lipworth AD, Zaoutis TE, Nachamkin I, Bilker WB, **Lautenbach E.**: Impact of inadequate initial antibiotic therapy on mortality in infections due to extended spectrum β -lactamase-producing Enterobacteriaceae. Arch Intern Med 2005;165:1375-80.

Lautenbach E, Fishman NO, Metlay JP, Mao X, Bilker WB, Tolomeo P, Nachamkin I. Phenotypic and genotypic characterization of fecal *Escherichia coli* isolates with decreased susceptibility to fluoroquinolones: Results from a large hospital-based surveillance initiative. J Infect Dis 2006;194:79-85.

Gasink LB, Blumberg EA, Localio AR, Desai SS, Israni AK, **Lautenbach E.** Hepatitis C virus seropositivity and survival in heart transplant recipients. JAMA 2006;296:1843-50

Albrecht S, Fishman NO, Kitchen J, Nachamkin I, Bilker W, Hoegg C, Samel C, **Lautenbach E.** Re-emergence of gram-negative healthcare-associated bloodstream infections. Arch Intern Med 2006;166:1289-94.

Lautenbach E, Tolomeo P, Mao X, Fishman NO, Metlay JP, Bilker WB, Nachamkin I. Duration of outpatient fecal colonization due to *Escherichia coli* isolates with decreased susceptibility to fluoroquinolones. Antimicrob Agents Chemother 2006;50:3939-43

Lautenbach E, Tolomeo P, Black N, Maslow JN. Risk factors for fecal colonization with multiple distinct strains of *Escherichia coli* among long-term care facility residents. Infect Control Hosp Epidemiol 2009;30:491-3. PMID: 2666107

JOSHUA P. METLAY, MD, PHD - BIOSKETCH

NAME Metlay, Joshua Paul		POSITION TITLE Professor of Medicine and Epidemiology	
eRACOMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.</i>)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Yale University, New Haven, CT	B.A.	05/84	Biology
Rockefeller University, New York, NY	Ph.D.	06/90	Immunology
Cornell University, New York, NY	M.D.	05/91	Medicine
Harvard School of Public Health, Boston, MA	M.Sc.	06/97	Health Policy/Management

Positions and Honors

Positions and Employment

1991-95	Intern, Resident and Chief Resident in Medicine, Univ Pittsburgh Medical Center
1995-97	Clinical and Research Fellow in Medicine, Massachusetts General Hospital,
1997-06	Assistant Professor of Medicine and Epidemiology, University of Pennsylvania
1997-2013	Senior Scholar, Center for Clinical Epidemiology and Biostatistics, Penn
1997-2009	Staff Physician, Veterans Affairs Medical Center, Philadelphia, PA
1997-2013	Senior Fellow, Leonard Davis Institute of Health Economics, Penn
2006-2010	Associate Professor of Medicine and Epidemiology (Tenure), Penn
2006-2010	Program Leader, Doris Duke Clinical Research Fellowship, Penn
2006-2013	Co-Director, Robert Wood Johnson Foundation Clinical Scholars Program, Penn
2009-2013	Chief, Section of Hospital Medicine, University of Penn School of Medicine
2009-2013	Director, Center for Healthcare Improvement and Patient Safety, Penn
2010-2013	Professor of Medicine, Emergency Medicine and Epidemiology, Penn
2013-	Chief, Division of General Medicine, Massachusetts General Hospital

Honors

1982	Phi Beta Kappa, Yale University
1989	Alpha Omega Alpha, Cornell University Medical College
1995	National Associates Award for Outstanding Research, Society of Gen Intern Med
1999	Robert Wood Johnson Foundation Generalist Physician Faculty Scholar
2003	Robert Austrian Faculty Research Award. Department of Medicine, Penn
2005	Penn Pearls Teaching Award, University of Pennsylvania School of Medicine
2008	Christian and Mary Lindback Foundation Award for Distinguished Teaching
2009	Samuel Martin Health Evaluation Sciences Research Award, Penn
2010	Mid-Career Research and Mentorship Award, Society of General Intern Med
2011	Arthur Asbury Outstanding Faculty Mentor Award, University of Pennsylvania

Selected Peer-reviewed Publications (out of 130)

1. Metlay JP, Fine MJ, Schulz R, Marrie TJ, Coley CM, Kapoor WN, Singer DE. Measuring symptomatic and functional recovery in patients with community-acquired pneumonia. *J Gen Intern Med.* 1997;12:423-430.
2. Metlay JP, Stafford RS, Singer DE. National trends in the use of antibiotics by primary care physicians for adult patients with cough. *Arch Intern Med.* 1998;158:1813-1818.
3. Metlay JP, Hofmann J, Cetron MS, Fine MJ, Farley MM, Whitney C, Breiman RF. "Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia." *Clin Infect Dis.* 2000;30:520-528.
4. Metlay JP, Shea JA, Crossette LB, Asch DA. "Tensions in antibiotic prescribing: Pitting social concerns against the interests of individual patients." *J Gen Intern Med.* 2002;17:87-94.
5. Metlay JP, Fine MJ. "Testing strategies in the initial management of patients with community-acquired pneumonia." *Annals Intern Med.* 2003;138:109-118.
6. Metlay JP, Branas CB, Fishman NO. Small area variation in hospital reported rates of pneumococcal susceptibility to penicillin. *Emerging Infectious Diseases.* 2004 10:54-59.
7. Metlay JP, Fishman NO, Joffe M, Edelstein PH. Impact of pediatric vaccination with pneumococcal conjugate vaccine on risk of bacteremic pneumococcal pneumonia in adults. *Vaccine.* 2006;24:468-475.
8. Metlay JP, Camargo CA, MacKenzie T, McCulloch C, Maselli J, Levin SK, Kersey A, Gonzales R. Cluster-randomized trial to improve antibiotic use for adults with acute respiratory infections treated in emergency departments. *Annals of Emergency Medicine.* 2007;50:221-230.
9. Shah SS, Downes KJ, Elliott MR, Bell LM, McGowan KL, Metlay JP. How long does it take to "rule-out" bacteremia in children with central venous catheters? *Pediatrics.* 2008;121:135-141.
10. Pines JM, Localio AR, Hollander JE, Baxt WG, Lee H, Phillips C, Metlay JP. The impact of ED crowding measures on time to antibiotics for patients with community-acquired pneumonia. *Annals of Emergency Medicine.* 2007;50:510-516.
11. Berjohn CM, Fishman NO, Joffe MM, Edelstein PH, Metlay JP. Treatment and outcomes for patients with bacteremic pneumococcal pneumonia. *Medicine;* 2008;87(3):160-166.
12. Metlay JP, Lautenbach E, Li Y, Shults J, Edelstein PH: The changing role of exposure to children as a risk factor for bacteremic pneumococcal disease in the post conjugate vaccine era. *Archives of Internal Medicine.* 2010;170:725-731. NIHMS 15969
13. Soneji S, Metlay J. Mortality reductions for older adults differ by race/ethnicity and gender since the introduction of adult and pediatric pneumococcal vaccines. *Public Health Reports.* 2011;126:259-269. PMID: PMC3056039
14. Feemster KA, Li Y, Localio AR, Shults J, Edelstein P, Lautenbach E, Smith T, Metlay JP: Risk of invasive pneumococcal disease varies by neighborhood characteristics: Implications for prevention policies. *Epidemiology and Infection* Epub ahead of print Oct, 2012. PMID: PMC Journal-In Process.
15. Gonzales R, Anderer T, McCulloch CE, Maselli JH, Bloom FJ, Graf TR, Stahl M, Yefko M, Molecavage J, Metlay JP: A cluster-randomized trial of decision support strategies for reducing antibiotic use for acute bronchitis. *JAMA Internal Medicine.* 173:267-273, 2013.PMID:PMC3582762

JEFF WEISER, MD - BIOSKETCH

NAME Jeffrey N. Weiser M.D.		POSITION TITLE	
eRA COMMONS USER NAME: JWEISER		Professor of Microbiology and Pediatrics	
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE (<i>if applicable</i>)	MM/YY	FIELD OF STUDY
Stanford University, Stanford, CA	B.S.	06/79	Biology
Harvard University, Boston, MA	M.D.	06/84	Medicine
Oxford University, Oxford, UK	Post-doc	10/89	Lab of E.R. Moxon
Rockefeller University, New York, NY	Post-doc	06/92	Lab of E.C. Gotschlich

Positions and Honors

1984-87	Intern and Resident in Pediatrics, Univ Washington School of Medicine,
1987-89	Fellow, Institute of Molecular Medicine, Oxford University, Oxford, U.K.
1992-2000	Assistant Professor of Pediatrics and Microbiology, Univ. of Pennsylvania,
2000-2005	Associate Professor of Microbiology and Pediatrics, Univ. of Pennsylvania
2005-	Professor of Microbiology and Pediatrics, Univ. of Pennsylvania

Awards and Other Professional Activities:

1991	National Foundation for Infectious Disease Burroughs Welcome Fund Young Investigator
1991-97	Lucille P. Markey Scholar in Biomedical Science
1996-03	DARPA Advisory Panel on Pathogen Countermeasures
2001-04	Member, Bacteriology and Mycology II Study Section
2000-	Fellow, Infectious Disease Society of America
2002-12	Editor, Infection and Immunity
2005-	Fellow, American Academy of Microbiology
2006-10	Associate Editor, PLoS Pathogens
2007-08	Faculty 1000, Biology
2007-10	Associate Editor, Journal of Clinical Investigation
2011-14	Member, Host-Interaction with Bacterial Pathogens NIH Study Section
2012	Division Lecturer, American Society for Microbiology

Peer-Reviewed Publications (selected from >124 total publications)

1. McCool, T, TR Cate, G Moy, and JN Weiser. The immune response to pneumococcal proteins during experimental human carriage. **J Experimental Medicine**. 195:359-365. 2002. PMID: 11828011
2. King, SJ, KR Hippe, and JN Weiser. Deglycosylation of human glycoconjugates by the sequential activities of exoglycosidases expressed by *Streptococcus pneumoniae*. **Molecular Microbiology**. 59:961-74. 2006. PMID: 16420364

3. Ratner, AJ, KR Hippe, JL Aguilar, MH Bender, AL Nelson, and JN Weiser. Epithelial cells are sensitive detectors of bacterial pore-forming toxins. **J Biol Chemistry**. 281:12994-12998. 2006. PMID: 16520379
4. Nelson, AL, AM Roche, JM Gould, K Chim, AJ Ratner, and JN Weiser. Pneumococcal capsule enhances colonization by limiting mucus-mediated clearance. **Infection and Immunity**. 75:83-90. 2007. PMID: 17088346
5. Zola TA, Lysenko ES, Weiser JN. Mucosal Clearance of Capsule-Expressing Bacteria Requires Both TLR and Nucleotide-Binding Oligomerization Domain 1 Signaling. **J Immunol**. 2008, 181:7909-7916. PMID: 19017981
6. Davis KM, Akinbi HT, Standish AJ, Weiser JN. Resistance to mucosal lysozyme compensates for the fitness deficit of peptidoglycan modifications by *Streptococcus pneumoniae*. **PLoS Pathogens**. 2008. 12:e1000241. PMID: 19079576
7. Beisswenger, C, ES Lysenko, and JN Weiser. Early bacterial colonization induces TLR-dependent TGF- β signaling in epithelium. **Infect Immun**. 77:2212-20. 2009. PMID: 19255194
8. Zhang Z, Clarke TB, Weiser JN. Cellular effectors mediating Th17-dependent clearance of pneumococcal colonization in mice. **J Clinical Investigation**. 2009, 119:1899-909. PMID: 19509469
9. Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. **Nature Medicine**. 2010, 16:228-31. PMID: 20081863
10. Dalia AB, Standish AJ, Weiser JN. Three surface exoglycosidases from *Streptococcus pneumoniae*, NanA, BgaA, and StrH, promote resistance to opsonophagocytic killing by human neutrophils. **Infect Immun**. 2010, 78:2108-16. PMID: 20160017
11. Lysenko ES, Lijek RS, Brown SP, Weiser JN. Within-host competition drives selection for the capsule virulence determinant of *Streptococcus pneumoniae*. **Current Biol**. 2010, 20:1222-6. PMID: 20619820
12. Clarke TB, Francella N, Huegel A, Weiser JN. Invasive bacterial pathogens exploit TLR-mediated downregulation of tight junction components to facilitate translocation across the epithelium. **Cell Host Microbe**. 2011, 9:404-14. PMID: 21575911
13. Nakamura S, Davis KM, Weiser JN. Synergistic stimulation of type I interferons during influenza virus coinfection promotes *Streptococcus pneumoniae* colonization in mice. **J Clinical Investigation**. 2011,121:3666-76. PMID: 21841315
14. Dalia, AB and JN Weiser. Minimization of bacterial size allows for complement evasion and is subverted by the agglutinating effect of antibody. **Cell Host & Microbe** 10:486-96. 2011. PMID: 22100164
15. Lijek, RS, SL Luque, D Parker, T Bae, and JN Weiser. Protection from acquisition of *Staphylococcus aureus* nasal carriage by cross-reactive antibody to a pneumococcal dehydrogenase. **Proceedings of the National Academy of Sciences USA**. 109:13823-8. 2012. PMID: 22869727

KATHLEEN JULIAN, MD - BIOSKETCH

NAME Julian, Kathleen	POSITION TITLE Associate Professor
eRA COMMONS USER NAME (credential, e.g., agency login)	Division of Infectious Diseases Penn State MS Hershey Medical Center

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Yale University, New Haven, CT	BA	1989-1993	Biochemistry
Medical College of Virginia, Richmond, VA	MD	1993-1997	Medicine
Rhode Island Hospital/Brown Univ., Providence, RI	Residency	1997-2000	Internal Medicine
Penn State Milton S. Hershey Medical Ctr., Hershey, PA	Fellowship	2002-2005	Infectious Diseases

Positions and Honors

Work/Research Experience

1997-2000 Internal Medicine House Officer, Rhode Island Hospital/Brown University
Sep/Oct -1999 Guest Researcher, Centers for Disease Control, Hospital Infections Program
2000-2002 Epidemic Intelligence Service Officer, CDC, Division of Vector-Borne Infectious Diseases, Arbovirus Diseases Branch
2002-2005 Infectious Diseases Fellow, Penn State Milton S. Hershey Medical Center
2005-2012 Assistant Professor of Medicine, Division of Infectious Diseases, Penn State Hershey Medical Center
2012-current Associate Professor of Medicine, Division of Infectious Diseases, Penn State Hershey Medical Center

Honors/Awards

1993 *Cum laude*, Yale University
1995-1997 Aesculapian Scholarship, Medical College of Virginia
1995 Alpha Omega Alpha, Medical College of Virginia
1996 Sidney Barham Scholarship, Medical College of Virginia
2001 EIS conference poster prize, Atlanta, GA

B. Selected peer-reviewed publications (in chronological order).

Julian KG, Eidson M, Kipp AM, Weiss E, Petersen LR, Miller JR, Hinten SR, Marfin AA. Early season crow mortality as a sentinel for West Nile virus disease in humans, northeastern United States. *Vector Borne Zoonotic Diseases* 2002; 2:145-55.

Julian KG, Mullins JA, Olin A, Peters H, Nix WA, Oberste MS, Lovchik JC, Bergmann A, Brechner RJ, Myers RA, Marfin AA, Campbell GL. Aseptic meningitis epidemic during a West Nile virus avian epizootic. *Emerging Infectious Diseases* 2003; 9:1082-8.

Whitener CW, Park SY, Browne FA, Parent LJ, Julian KG, Bozdogan B, Appelbaum PC, Chaitram J, Weigel LM, Jernigan J, Tenover FC, Fridkin SK. Vancomycin-resistant

Staphylococcus aureus in the absence of vancomycin exposure. *Clinical Infectious Diseases* 2004; 38:1049-55.

M'ikanatha NM, Welliver DP, Rohn DD, Julian KG, Lautenbach E. Use of the Web by state and territorial health departments to promote reporting of infectious disease. *JAMA* 2004;291:1069-70.

Julian KG, de Flesco L, Clarke LE, Parent LJ. *Actinomyces viscosus* endocarditis requiring aortic valve replacement. *Journal of Infection* 2005; 50:359-362.

Clarke LE, Julian KG, Clarke JT, Ioffreda MD. Reactive angioendotheliomatosis in association with a well-differentiated angiosarcoma. *American Journal of Dermatopathology* 2005; 27:422-7.

M'ikanatha NM, Julian KG, Kunselman AR, Aber RC, Rankin JT, Lautenbach E. Patients' request for and emergency physicians' prescription of antimicrobial prophylaxis for anthrax during the 2001 bioterrorism-related outbreak. *BMC Public Health* 2005; 5:2.

Julian KG, Brumbach AM, Chicora MK, Houlihan C, Riddle AM, Umberger T, Whitener CJ. First year of mandatory reporting of healthcare-associated infections, Pennsylvania. *Infection Control and Hospital Epidemiology* 2006; 27:926-930.

M'ikanatha NM, Rohn DD, McAdams T, Welliver D, Julian KG. Use of the Worldwide Web to Enhance Infectious Disease Surveillance. In: M'ikanatha, NM, Lynfield R, Van Beneden CA, De Valk H, editors. *Infectious Disease Surveillance*. London: Blackwell; 2007.

M'ikanatha NM, Julian KG, Lynfield R, Van Beneden C, De Valk H. Infectious Disease Surveillance: A Cornerstone for Prevention and Control. In: M'ikanatha, NM, Lynfield R, Van Beneden CA, De Valk H, editors. *Infectious Disease Surveillance*. London: Blackwell; 2007.

M'ikanatha NM, Imunya SG, Fisman DN, Julian KG. Sharps injuries and perceived risk of bloodborne pathogens among healthcare workers in rural Kenya. *Infection Control and Hospital Epidemiology* 2007; 28:761-3.

Julian K, Kosowska-Shick K, Whitener C, Roos M, Labischinski H, Rubio A, Parent L, Ednie L, Koeth L, Bogdanovich T, Appelbaum PC. Characterization of a daptomycin-nonsusceptible vancomycin-intermediate *Staphylococcus aureus* strain in a patient with endocarditis. *Antimicrobial Agents and Chemotherapy* 2007; 51:3445-8.

Julian KG, Subramanian K, Brumbach A, Whitener CJ. Attitudes of healthcare workers and patients toward individualized hand hygiene reminders. *Infection Control and Hospital Epidemiology* 2008; 29:781-2.

Kishel JJ, Maguire M, Pankratz L, Julian K. Implementing an electronically based, nurse-driven pneumococcal vaccination protocol for inpatients. *American Journal of Health-system Pharmacy: AJHP* 2009 Jul 15;66(14):1304-8.

Kwak EJ, Julian K. Human papillomavirus infection in solid organ transplant recipients. *American Journal of Transplantation* 2009; 9: S151-S160.

Kosowska-Shick K, Julian KG, McGhee PL, Appelbaum PC, Whitener CW. Molecular and epidemiologic characteristics of linezolid-resistant coagulase-negative staphylococci at a tertiary care hospital. *Diagnostic Microbiology and Infectious Disease* 2010;68:34-9.

Boltz MM, Hollenbeak CS, Julian KG, Ortenzi G, Dillon PW. Hospital costs associated with surgical site infections in general and vascular surgery patients. *Surgery* 2011;150(5):934-42.

Peterson AE, Davis MF, Julian KG, Awantang G, Greene WH, Price LB, Waters A, Doppalapudi A, Krain LJ, Nelson K, Silbergeld EK, Whitener CJ. Molecular and phenotypic characteristics of healthcare- and community-associated methicillin-resistant *Staphylococcus aureus* at a rural hospital. *PLoS One*. 2012;7(6):e38354. Epub 2012 Jun 15.

DAVID ROYER, PhD

Education

Lehigh University, Bethlehem, PA

1980 Ph.D. in Biology

- Thesis: The Effects of a Sewage Treatment Effluent on the Benthic Macrofauna of a Salt Marsh Estuary

1977 M.S. in Biology

- Thesis: The Effects of Suspended Sediment on the Respiration and Survival of Grass Shrimp of the Genus *Palaemonetes*

DeSales University, Center Valley, PA

1970 B.S. in Biology

Professional Career Summary

Lincoln University, PA

1998-Present **Professor of Biology**

2000-2011 **Chair, Department of Biology**

1988-1998 **Associate Professor of Biology**

1981-1988 **Assistant Professor of Biology**

Courses Taught: General Biology I and II, General Ecology, Microbial Ecology, Environmental Science, Conservation Biology, Invertebrate Zoology, Genetics, First Year Experience, University Seminar I, Research, Senior Seminar, Religion and Science

Research Interests: Role of bacterioplankton in aquatic nutrient cycles; benthic ecology, biology of opportunistic species, bacterial indicators of sewage pollution, ecology and physiology of stressed communities

Research Support

May, 2011 – Faculty Development Grant to investigate what our Biology and Environmental Science graduates of the past five years are doing and to determine the fate of students who changed from the Biology major after their freshman or sophomore years. Expected completion date: 12/31/12.

May, 2010 – Faculty Development Grant to prepare a premed manual for our students. The manual was completed, reviewed by Dr. Singh at Hershey Medical School, and distributed to our premed students.

June, 2009 – Co-Investigator on a Pennsylvania Department of Health funded grant that was awarded to the University of Pennsylvania titled “Epidemiology and Prevention of MRSA Transmission in the Community”.

September, 2007 – Principal Investigator on a NSF Grant (Undergraduate Research and Mentoring in Biology). Four year grant to support undergraduate research by Lincoln students in the field of estuarine research in collaboration with the College of Earth, Ocean and Environment at the University of Delaware.

September, 2003 – *Cycling of DOC and DON by Novel Heterotrophic and Photoheterotrophic Bacteria in the Ocean*. A three-year grant funded by the Department of Energy. A collaboration with Dr. David Kirchman at the University of Delaware College of Marine Studies.

September, 2003 – Principal Investigator on a MSEIP Grant to develop the environmental science program at Lincoln. The University of Maryland Eastern Shore is the principal recipient, and Lincoln is a participating institution. This grant supports student research, acquisition of equipment and supplies, and course development.

April, 2003 – Program Director for a grant from EPA, Region III Office to conduct a summer environmental science program for high school students.

September, 2000 - *Hydrolysis and Uptake of Organic Matter by Major Bacterial Groups in a Coastal Ocean*. A three-year grant funded by the Department of Energy. The work was done as a collaboration with Dr. David Kirchman at the Univ of Delaware College of Marine Studies

September, 1997 - *Bacterial Degradation of Organic Matter at the Molecular level: Chitinases as Tracers for Carbon Export from Coastal Oceans*. A three-year grant funded by the Department of Energy. The work was done as a collaboration with Dr. David Kirchman at the University of Delaware College of Marine Studies.

Summer, 1997: I became the director for Project ExCITE (described above). This program was funded through October of 1998.

Spring, 1997 - I served as the codirector for Project ExCITE, a NASA funded program that is supporting a community service project at two local middle schools. One school worked on promoting public awareness regarding Lyme Disease, and the other school worked on restoring natural grasslands in a serpentine barrens system. A third school in California was also part of this grant; they worked on restoring a tidal wetland area.

1995 – I participated in the preparation of the Project ExCITE proposal for submission to NASA. This proposal was funded, and I worked with Jerry Isaac (Principal Investigator) on the implementation involving two middle schools – one in Oxford and one in California as part of this grant.

1984-1992 – Support from the Minority Biomedical Research Support Program of the National Institutes of Health (MBRS). A study of the use of the bacterium, *Clostridium perfringens*, as an indicator of sewage pollution in marine waters. \$200,000 for eight years. Support for one student the first year and two students for each of the other years.

Publications

Royer, D. 1998. "Project ExCITE: Using Technology to Stimulate Student Interest in Careers in Science". In *Technology-Enriched Education at Historically Black Colleges and Universities*. Executive Leadership Foundation.

Honors and Awards

2013 – Teacher of the Year Award – awarded at the Annual Faculty Appreciation Day

2010 – Teacher of the Year Award – awarded at The First Annual Faculty Appreciation Day

1993 – Lindback Teaching Award

IRVING NACHAMKIN, DrPH, MPH - BIOSKETCH

NAME Irving Nachamkin	POSITION TITLE PROFESSOR, PATHOLOGY & LABORATORY MEDICINE
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EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of Bridgeport, Bridgeport, CT	BSc	6/75	Medical Lab Science
University of North Carolina, Chapel Hill, NC	MPH	6/78	Public Health Laboratory Practice
University of North Carolina, Chapel Hill, NC	DrPH	6/80	Microbiology, Public Health Laboratory Practice
Virginia Commonwealth University, MCV Hospitals, Richmond, VA		6/82	Fellow in Clinical Microbiology

Positions and Honors

1982-88	Assistant Professor, Pathology and Laboratory Medicine, Penn
1982-	Associate Director, Clinical Microbiology Laboratory, Penn
1988-05	Associate Professor, Pathology and Laboratory Medicine
2000	Fellow, American Academy of Microbiology
2000	Fellow, Infectious Diseases Society of America
2002-10	Voting Member, Microbiology Devices Panel, FDA (2010-pres, Consultant)
2002-12	Editor-in-Chief, Clinical Microbiology Reviews (ISI Impact Factor 16.129)
2003	Fellow, College of Physicians and Surgeons of Philadelphia
2004-pres	Co-Director, Pathology Residency Training Program
2005-pres	Professor, Pathology and Laboratory Medicine
2009-11	Interim Vice-Chair and Director, Division of Laboratory Medicine, Department of Pathology and Laboratory Medicine
2011-pres	Director, Division of Laboratory Medicine

Selected Publications (from 140 peer-reviewed papers)

- Codrington, L, Kuncio D, Han, J, **Nachamkin I**, Tolomeo P, Hu B, Lautenbach E. Yield of methicillin-resistant Staphylococcus aureus on moist swabs versus dry swabs. Am J Infect Control 41: 469-70, 2013.
- Han, JH, **Nachamkin, I.**, Mao, X., Tolomeo, P., Bilker, W, Fishman, N., Lautenbach, E. Impact of Antibiotic Use During Hospitalization on the Development of Gastrointestinal Colonization with Escherichia coli with Reduced Fluoroquinolone Susceptibility. Infect Cont Hosp Epidemiol, 2013 (in press)

- Han, JH, **Nachamkin, I.**, Zaoutis TE, Coffin SE, Linkin DR, Fishman, NO, Weiner MG, Hu, B., Tolomeo, P., Lautenbach, E. Risk factors for gastrointestinal colonization with ESBL producing *E. coli* and *Klebsiella* species in hospitalized patients. Infect Cont Hosp Epidemiol 33: 1242-5, 2012. PMID: 23143363
- Han JH, **Nachamkin I.**, Zaoutis TE, Coffin SE, Linkin DR, Fishman NO, Weiner MG, Hu B, Tolomeo P, Lautenbach E. Risk Factors for Efflux Pump Overexpression in Fluoroquinolone-Resistant *Escherichia coli*. J Infect Dis 2012;206:1597-603. PMID: 3475638
- Mikanatha NM, Dettinger LA, Perry A, Rogers P, Reynolds SM, **Nachamkin I.** Culturing stool specimens for *Campylobacter* spp., Pennsylvania, USA. Emerg Infect Dis 18:484-7, 2012.
- Lee, I., Zaoutis, TE, Fishman, NO, Morales, KH, **Nachamkin, I.**, Lautenbach, E.: Risk Factors for Fluconazole Resistance among Patients with *Candida glabrata* Bloodstream Infections. Am J Infect Cont 38:456-60, 2010
- Lautenbach, E., Tolomeo, P., **Nachamkin, I.**, Hu, B., Zaoutis, T.E.: The Impact of Household Transmission on Duration of Outpatient Colonization with Methicillin-Resistant *Staphylococcus aureus*. Epidemiol Infect 138: 683-5, 2010.
- Lee, I., Morales, K.H., Zaoutis, T.E., Fishman, N.O., **Nachamkin, I.**, Lautenbach, E.: Clinical and Economic Outcomes of Decreased Fluconazole Susceptibility in Patients with *Candida glabrata* Bloodstream Infections. Am J Infect Control 38: 740-745, 2010.
- Lautenbach, E., Metlay, J.P., Mai, X., Han, X., Fishman, N.O., Bilker, W.B., Tolomeo, P., Wheeler, M., **Nachamkin, I.**: The prevalence of fluoroquinolone resistance mechanisms in colonizing *E. coli* isolates from hospitalized patients. Clin. Infect Dis. 51:280-5, 2010
- McGettigan, S.E., Hu, B., Andreacchio, K., **Nachamkin, I.**, Edelstein, P.H.: Prevalence of CTX-M β -lactamases in Philadelphia. J Clin Microbiol 47: 2970-4, 2009.
- Lautenbach, E., **Nachamkin, I.**, Hu, B., Fishman, N.O., Tolomeo, P., Prasad, P., Bilker, W.B., Zaoutis, T.E.: Surveillance Cultures for Detection of Methicillin-Resistant *Staphylococcus aureus*: Diagnostic Yield of Anatomic Sites and Comparison of Provider- and Patient-Collected Samples. Infect. Cont. Hosp. Epidemiol. 30: 380-382, 2009.
- Lee, I., Fishman, N.O., Zaoutis, T.E., Morales, K., Weiner, M.G., Synnestvedt, M., **Nachamkin, I.**, Lautenbach, E.: Risk Factors for Fluconazole-Resistant *Candida glabrata* Bloodstream Infections. Arch Intern Med. 169: 379-383, 2009. PMID: PMC2890272
- Lautenbach, E., Metlay, J.P., Weiner, M.G., Bilker, W.B., Tolomeo, P., Mao, X., **Nachamkin, I.**, Fishman, N.O.: Gastrointestinal Tract Colonization with Fluoroquinolone-Resistant *Escherichia coli* in Hospitalized Patients: Changes in Risk Factors for Resistance over Time. Infect Cont Hosp Epidemiol 30: 18-24, 2009. PMID: PMC2883613
- Lautenbach, E., Tolomeo, P., Mao, X., Fishman, N.O., Metlay, J.P., Bilker, W.D., **Nachamkin, I.**: Duration of Outpatient Fecal Colonization due to *Escherichia coli* with Decreased Susceptibility to Fluoroquinolones: Longitudinal Study of Patients Recently Discharged from the Hospital. Antimicrob Agents Chemother 50: 3939-43, 2006.
- Lautenbach, E, Fishman, N.O., Metlay, J.P., Mao, X., Bilker, W.B., Tolomeo, P., **Nachamkin, I.**: Phenotypic and genotypic characterization of fecal *Escherichia coli* isolates with decreased susceptibility to fluoroquinolones: results from a large hospital-based surveillance initiative. J Infect Dis 194: 79-85, 2006

PAUL EDELSTEIN, MD - BIOSKETCH

NAME Edelstein, Paul H.		POSITION TITLE Professor of Pathology and Laboratory Medicine, Director of Clinical Microbiology Hospital Univ Penn	
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
San Jose State University, San Jose, Calif.	None	1969	Chemistry
UCLA Medical School	M.D.	1973	Medicine

Positions and Honors

Positions and Employment

1973-1976 Internship, Residency in Internal Medicine, VA Medical Center/UCLA
 1976-1978 Fellowship in Infectious Diseases, VAMC/UCLA, Los Angeles
 1977 Chief resident in Internal Medicine, VAMC/UCLA
 1978-1980 Associate Investigator, Wadsworth VA Medical Center
 1978-1983 Assistant Professor of Medicine, UCLA
 1980-1982 Research Associate, Wadsworth VA Medical Center
 1983-1986 Associate Professor of Medicine, UCLA
 1986-1994 Associate Professor of Pathology and Laboratory Medicine, Penn
 1987- Secondary appointment in the Department of Medicine, Penn
 1994- Professor of Pathology and Laboratory Medicine, University of Pennsylvania

Other Experience

1983-1984 Director, Medical Intensive Care Unit, Wadsworth VA Medical Center
 1978-1986 Director of Legionnaires' Disease Laboratory, Wadsworth VA Medical Center
 1986- Director of Clinical Microbiology Laboratory, Hospital of the Univ Penn
 9/95-6/96 Visiting Scholar, Department of Microbiology and Immunology, Stanford
 University School of Medicine (Laboratory of Stanley Falkow)
 1983 Organizing committee of the 1983 International Conference on Legionella.
 1991 Organizing committee of the 1992 International Conference on Legionella.
 1991-1994 American Board of Medical Microbiology Part I examination committee.
 1993-1994 Chair organizing committee Medical Microbiology Interdisciplinary Commission
 symposium on pneumonia, Prague 7/94
 2000-2005 Organizing committee of the 2005 International Conference on Legionella
 2005-2009 Scientific committee of the 2009 International Conference on Legionella
 2011- Scientific committee of the 2013 International Conference on Legionella

Professional Certifications and Memberships

1976, 1978 American Board of Internal Medicine in Internal Medicine (76), Infectious
 Diseases (78)

1985	Diplomat of American Board of Medical Microbiology in Public Health and Medical Microbiology
1977-2000	Member, American College of Physicians
1976-	Member, American Society for Microbiology
1984-2001	Member, American Thoracic Society
1979-1994	Member, American Federation for Clinical Research
1981-1984	Member, Infectious Diseases Society of America
1984-	Fellow, Infectious Diseases Society of America
1998-	Member, British Society for Antimicrobial Chemotherapy

Honors

1967-1969	National Science Foundation Fellowship in Physical Chemistry Research
1969	Elected member of Phi Kappa Phi, National Scientific Fraternity
2002	Fellow, American Academy of Microbiology

Selected Peer-reviewed Publications (selected from 140 peer reviewed publications)

1. Edelstein PH, Edelstein MAC, Higa F, Falkow S. Discovery of virulence genes of *Legionella pneumophila* by using signature tagged mutagenesis in a guinea pig pneumonia model. *Proc Nat Acad Sci USA* 96:8190-8195, 1999.
2. Edelstein PH, Shinzato T, Doyle E, Edelstein MAC. In vitro activity of gemifloxacin (SB-265805, LB20304a) against *Legionella pneumophila*, its pharmacokinetics in guinea pigs, and use to treat guinea pigs with *L. pneumophila* pneumonia. *Antimicrob. Agents Chemother.* 45: 2204-2209, 2001.
3. Lautenbach E, Fishman NO, Bilker WB, Castiglioni A, Metlay J, Edelstein PH, Strom BL. Risk factors for fluoroquinolone resistance in nosocomial *Escherichia coli* and *Klebsiella pneumoniae* infections. *Arch Intern Med* 2002;162:2469-2477.
4. Metlay JP, Fishman NO, Joffe M, Edelstein PH. Impact of pediatric vaccination with pneumococcal conjugate vaccine on the risk of bacteremic pneumococcal pneumonia in adults. *Vaccine* 2006;24: 468-475.
5. Kasahara K, Baltus AJ, Lee SH, Edelstein MA, Edelstein PH. Prevalence of Group B streptococcus in Philadelphia and the specificity of penicillin resistance screening methods. *J Clin Microbiol* 2010;48:1648-9.
6. Metlay JP, Lautenbach E, Li Y, Shults J, Edelstein PH. Exposure to children as a risk factor for bacteremic pneumococcal disease: changes in the post-conjugate vaccine era. *Arch Intern Med* 2010;170:725-31.
7. Adams KN, Takai K, Connolly LE, Wiedenhof H, Winglee K, Humbert O, Edelstein PH, Cosma CL, Ramakrishnan L. Drug tolerance in replicating mycobacteria mediated by a macrophage-induced efflux mechanism. *Cell* 2011;145:39-53.
8. Mascitti KB, Edelstein PH, Fishman NO, Morales KH, Baltus AJ, Lautenbach E: Prior vancomycin use is a risk factor for reduced vancomycin susceptibility in methicillin-susceptible but not methicillin-resistant *Staphylococcus aureus* bacteremia. *Infect Control Hosp Epidemiol* 2012;33:160-166.
9. Han JH, Mascitti KB, Edelstein PH, Bilker WB, Lautenbach E: Effect of reduced vancomycin susceptibility on clinical and economic outcomes in *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother* 2012;56:5164-5170.

WARREN BILKER, PHD - BIOSKETCH

NAME Warren Bilker	POSITION TITLE Professor of Biostatistics
eRA COMMONS USER NAME (credential, e.g., agency login) wbilker	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Temple University	B.A.	1976-1981	Mathematics
Temple University	M.S.	1981-1984	Statistics
Johns Hopkins University	Ph.D.	1984-1992	Biostatistics

Positions and Honors**Positions and Employment**

- 1982-83 Adjunct Lecturer, Department of Statistics, Temple University
1991-92 Instructor, Department of Health Policy and Management, Johns Hopkins University
1992-93 Lecturer, Department of Medicine, University of Pennsylvania, School of Medicine
1993-95 Research Assistant Professor of Biostatistics in Medicine, Department of Medicine, University of Pennsylvania School of Medicine
1995-2002 Assistant Professor of Biostatistics, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine
2002-2007 Associate Professor of Biostatistics, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine
2007 Professor of Biostatistics, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine.

Other Experience and Professional Memberships

- 1998-1999 Associate Editor, Journal of General Internal Medicine
1998- Associate Editor, Pharmacoepidemiology and Drug Safety
2001 (June) Member, Special Emphasis Panel for National Institute of Dental & Craniofacial Research
2001 – 2011 Member/Chair, Special Emphasis Panel for NIMH (16 Panels)
2003-2006 Member, Transplant DSMB for NIAID
2003-2008 Member DSMB, “Advancing Caregiver Training Project”, PI: Laura Gitlin, Thomas Jefferson University
2004- Member DSMB, “Social Anxiety Treatment Study”, PI: Michael Liebowitz, Columbia University
2006-2009 Member, NIHM Standing Review Committee: Interventions Committee for Schizophrenia Spectrum Disorders, Personality Disorders, and Disorders of Late Life
2008-2012 Member of FDA Advisory Committees (4): Dermatologic and Ophthalmic

Panel (12/2008), Pharmacologic Drugs Panel (4/2009), Joint Anesthetic and Life Support Drugs and Safety & Drug Safety and Risk Management Panels (10/2010), Arthritis Panel (3/2012)

Honors

2008

Dean's Award for Excellence in Basic Science Teaching, University of Pennsylvania, School of Medicine

Selected Peer-reviewed Publications (Selected from 264 peer-reviewed publications)

Lautenbach E, Metlay JP, Weiner MG, Bilker WB, Tolomeo P, Mao X, Nachamkin I, Fishman NO. Gastrointestinal tract colonization with fluoroquinolone-resistant *escherichia coli* in hospitalized patients: changes over time in risk factors for resistance. *Infection Control and Hospital Epidemiology* 2009; **30**(1):18-24.

Lautenbach E, Synnestvedt M, Weiner MG, Bilker WB, Vo L, Schein J, Kim M. Imipenem resistance in *pseudomonas aeruginosa*: emergence, epidemiology, and impact on clinical and economic outcomes. *Infection Control and Hospital Epidemiology* 2010; **31**(1):47-53.

Lautenbach E, Metlay JP, Mao X, Han X, Fishman NO, Bilker WB, Tolomeo P, Wheeler M, Nachamkin I. The prevalence of fluoroquinolone resistance mechanisms in colonizing *escherichia coli* isolates recovered from hospitalized patients. *Clinical Infectious Diseases* 2010; **51**(3):280-285.

Rattanaumpawan P, Tolomeo P, Bilker WB, Fishman NO, Lautenbach E. Risk factors for fluoroquinolone resistance in gram-negative bacilli causing healthcare-acquired urinary tract infections. *Journal of Hospital Infection* 2010; **76**(4):324-327.

Akhabue E, Synnestvedt M, Weiner MG, Bilker WB, Lautenbach E. Cefepime-resistant *pseudomonas aeruginosa*. *Emerging Infectious Diseases* 2011; **17**(6):1037-1043.

Rattanaumpawan P, Tolomeo P, Bilker WB, Fishman NO, Lautenbach E. A clinical prediction rule for fluoroquinolone resistance in healthcare-acquired gram-negative urinary tract infection. *Infection Control and Hospital Epidemiology* 2011; **32**(11):1124-1126.

Lautenbach E, Han J, Santana E, Tolomeo P, Bilker WB, Maslow J. Colonization with extended-spectrum beta-lactamase (ESBL)-producing *escherichia coli* and *klebsiella* species in long-term care facility residents. *Infection Control and Hospital Epidemiology* 2012; **33**:302-4.

Han J, Kashara K, Edelstein PH, Bilker WB, Lautenbach E. Risk factors for infection or colonization with CTX-M extended-spectrum b-lactamase (ESBL)-positive *escherichia coli*. *Antimicrobial Agents and Chemotherapy* 2012; **56**(11):5575-80

Han J, Nachamkin I, Tolomeo P, Mao X, Bilker WB, Lautenbach E. Risk factors for efflux pump overexpression in fluoroquinolone-resistant *escherichia coli*. *Journal of Infectious Diseases* 2012; **206**(10):1597-603

Han J, Mascitti KB, Edelstein PH, Bilker WB, Lautenbach E. Effect of reduced vancomycin susceptibility on clinical and economic outcomes in *staphylococcus aureus* bacteremia. *Antimicrobial Agents and Chemotherapy* 2012; **56**(10):5164-70

Lautenbach E, Han J, Santana E, Tolomeo P, Bilker WB, Maslow J. Colonization with extended-spectrum beta-lactamase (ESBL)-producing *escherichia coli* and *klebsiella* species in long-term care facility residents. *Infection Control and Hospital Epidemiology* 2012; **33**(3):302-4

Han J, Bilker W, Edelstein PH, Mascitti K, Lautenbach E. Derivation and validation of clinical prediction rules for reduced vancomycin susceptibility in *Staphylococcus aureus* bacteraemia. *Epidemiology and Infection* 2013; **141**(1):165-73

JUDD HOLLANDER, MD - BIOSKETCH

NAME Hollander, Judd Eric		POSITION TITLE Professor of Emergency Medicine	
eRA COMMONS USER NAME (credential, e.g., agency login) juddinpa		Clinical Research Director, Department of Emergency Medicine	
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	BS	1982	Psychology
New York University School of Med, NY, NY	MD	1986	Medicine
Barnes Hospital, Wash Univ. St. Louis, MO	Residency	1989	Internal Medicine
Jacobi Hospital, Albert Einstein, Bronx, NY	Residency	1992	Emergency Medicine

Positions and Honors

1992-1997 Assistant Professor of Clinical Emergency Medicine and Medicine, Departments of Emergency Medicine and Medicine, SUNY Stony Brook Health Sciences; Stony Brook, NY
 1997-2001; Associate Professor, Emergency Medicine, University of Pennsylvania, Phila., PA;
 2001-present Professor, Emergency Medicine, University of Pennsylvania, Philadelphia, PA

Honors:

1980 - Phi Beta Kappa, SUNY Albany, Albany, NY;
 1981- Psi Chi Honor Society, Summa Cum Laude, University of Pennsylvania, Phila, PA
 1984 – Alpha Omega Alpha, New York University School of Medicine, NY, NY
 1989 – Diplomate, American Board of Internal Medicine
 1994 – Diplomate, American Board of Emergency Medicine
 1999-2002; Chair, Scientific Review Committee of the Emergency Medicine Foundation
 2006-2009 Board of Directors for Society of Academic Emergency Medicine
 2007-2008, President, SAEM
 2001 - ACEP Outstanding Contribution in Research Award
 2003 - Academic Excellence Award (SAEM)

Selected Peer-reviewed Publications (selected from a total of more than 400)

- Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW, Leaming JM, Gavin LJ, Pacella CB, Hollander JE. Safety of CT angiography for rapid “rule-out” of acute coronary syndrome. *N Engl J Med.*, 2012;366:1393-1403.
- Ryan RJ, Lindsell CJ, Hollander JE, O'Neill B, Jackson R, Schrieber D, Christenson R, Gibler WB. A multicenter randomized controlled trial comparing central laboratory and point of care cardiac marker testing strategies: The Disposition Impacted by Serial Point of Care Markers in Acute Coronary Syndromes (DISPO-ACS) Trial. *Ann Emerg Med.*, 2009;53:321-328.
- Chang AM, Walsh KM, Shofer FS, McCusker CM, Litt HI, Hollander JE. Relationship between cocaine use and coronary artery disease in patients with symptoms consistent

- with an acute coronary syndrome. *Acad Emerg Med.*, 2011;18:1-9.
4. Hess EP, Agarwal D, Chandra S, Murad MH, Erwin PJ, Hollander JE, Montori VM, Stiell IG. Accuracy of the TIMI risk score in emergency department patients with potential acute coronary syndromes: a systematic review and meta-analysis. *Can Med Assoc J.* 2010;182(10):1039-44.
 5. Hollander JE, Chang AM, Shofer FS, Collin MJ, Walsh KM, McCusker CM, Baxt WG, Litt HI. One year outcomes following coronary computerized tomographic angiography for evaluation of emergency department patients with potential acute coronary syndrome. *Acad Emerg Med.*, 2009;16:693-698.
 6. Singer AJ, Birkhahn RH, Guss D, Chandra A, Miller CD, Tiffany B, Levy B, Dunne R, Bastani A, Thode HC, Hr., Hollander JE. Rapid emergency department heart failure outpatients trial (REDHOT-II): a randomized controlled trial of the effect of serial B-type natriuretic peptide testing on patient management. *Circ Heart Failure*, 2009;2:287-293.
 7. Hollander JE, Chang AM, Shofer FS, McCusker CM, Baxt WG, Litt HI. Coronary computerized tomographic angiography for rapid discharge of low risk chest patients with potential acute coronary syndromes. *Ann Emerg Med.*, 2009;53:295-304.
 8. Hess E, Thiruganasambandamoorthy V, Wells G, Erwin P, Jaffe AS, Hollander JE, Montori VM, Stiell I. Diagnostic accuracy of clinical prediction rules to exclude acute coronary syndrome in the emergency department setting: a systematic review. *Can J Emerg Med.*, 2008;10(4):373-82.
 9. Chang AM, Mumma B, Sease KL, Robey JL, Shofer FS, Hollander JE. Gender bias in cardiovascular testing persists after adjustment for presenting characteristics and cardiac risk. *Acad Emerg Med.*, 2007;14:599-606.
 10. Hollander JE, Sites FD, Pollack CV Jr., Shofer FS. Lack of utility of telemetry monitoring for identification of cardiac death and life threatening ventricular dysrhythmias in low risk patients with chest pain. *Ann Emerg Med.* 2004;43:71-76.
 11. Hollander JE, Sease KL, Sparano DM, Sites FD, Shofer FS, Baxt WG. Effects of neural network feedback to physicians on admit/discharge decision for emergency department patients with chest pain. *Ann Emerg Med.* 2004;44:199-205.
 12. Weber JE, Shofer FS, Larkin GL, Kalaria AS, Hollander JE. Validation of a brief observation period for patients with cocaine associated chest pain. *N Engl J Med* 2003; 348:510-517.
 13. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AHB, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA, for the BNP Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161-167.
 14. Baumann BM, Perrone J, Hornig SE, Shofer FS, Hollander JE. Randomized controlled double blind placebo controlled trial of diazepam, nitroglycerin or both for treatment of patients with potential cocaine associated acute coronary syndromes. *Acad Emerg Med*, 2000;7:878-885.

JENNIFER HAN, MD, MSCE - BIOSKETCH

NAME Han, Jennifer	POSITION TITLE Instructor of Medicine
eRA COMMONS USER NAME JENHAN	

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Northwestern University, Evanston, IL	B.A.	06/00	Biology
Northwestern U. School of Medicine, Chicago, IL	M.D.	05/04	Medicine
University of Pennsylvania, Philadelphia, PA	M.S.C.E	05/12	Clinical Epidemiology

Positions and Honors**Positions and Employment**

2004-2005 Intern, Internal Medicine, New York Presbyterian/Columbia
2005-2007 Resident, Internal Medicine, New York Presbyterian/Columbia
2007-2008 Attending Physician, Section of Hospitalist Medicine, University of Chicago Hospital
2008-2010 Infectious Diseases Clinical Fellow, University of Pennsylvania
2010-2013 Post-Doctoral Research Fellow, University of Pennsylvania
2013- Instructor of Medicine, University of Pennsylvania
2013- Faculty Fellow, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania

Honors

2000 *Summa cum laude*, Northwestern University
2001 International Public Health Fellowship Award, Northwestern University
2001 Phi Beta Kappa, Northwestern University
2003 Alpha Omega Alpha, Northwestern University School of Medicine
2012 Jonathan Freeman Scholarship, Society for Healthcare Epidemiology of America (SHEA) Education and Research Foundation
2012 Finalist, SHEA EPI Project: Advancing Young Investigators in Healthcare Epidemiology Research
2012 National Institutes of Health (NIH) Loan Repayment Program Award
2013 Robert Austrian Outstanding Fellow Award, University of Pennsylvania

Other Experience and Professional Memberships

2002-2003 Honors Program in Medical Education Admissions Committee, Northwestern University Medical School
2007-present American College of Physicians (ACP)
2008-present Infectious Diseases Society of America (IDSA)
2010-2012 Pharmacy and Therapeutics Committee, Philadelphia VA Medical Center

2011-present Society for Healthcare Epidemiology of America (SHEA)
2011-present Peer reviewer, *Emerging Infectious Diseases*
2011-present Peer reviewer, *Clinical Infectious Diseases*
2011-present Peer reviewer, *The Lancet Infectious Diseases*
2011-present Top peer reviewer, *Pharmacoepidemiology and Drug Safety*
2011-present Antibiotic Stewardship Committee, Philadelphia Veterans Affairs Medical Center
2011-present Member, Infection Control Committee, Hosp of the University of Pennsylvania
2011-present Member, Antibiotic Stewardship Subcommittee, Hosp of the Univ of Penn
2011-present Peer reviewer, *The Journal of the American Medical Association (JAMA)*
2012-present Top peer reviewer, *Annals of Internal Medicine*
2012-present American Society for Microbiology (ASM)

C. Peer-Reviewed Publications

Lautenbach E, **Han JH**, Santana E, Tolomeo P, Bilker WB, Maslow J. Colonization with extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* species in long-term care facility residents. *Infect Control Hosp Epidemiol* 2012; 33:302-4. PMID: PMC3492935.

Han JH, Nachamkin I, Zaoutis TE, Coffin SE, Linkin DR, Fishman NO, Weiner MG, Hu B, Tolomeo P, Lautenbach E. Risk factors for gastrointestinal tract colonization with extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* species in hospitalized patients. *Infect Control Hosp Epidemiol* 2012; 33:1242-5. PMID: in process.

Han JH, Kasahara K, Edelstein PH, Bilker WB, Lautenbach E. Risk factors for infection or colonization with CTX-M extended-spectrum β -lactamase (ESBL)-positive *Escherichia coli*. *Antimicrob Agents Chemother* 2012; 56:5575-80. PMID: PMC3486585.

Han JH, Crane HM, Bellamy SL, Frank I, Cardillo S, Bisson GP, on behalf of the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS). HIV infection and glycemic response to newly initiated diabetic medical therapy. *AIDS* 2012; 26:2087-95. PMID: in process.

Han JH, Edelstein PH, Lautenbach E. Reduced vancomycin susceptibility and staphylococcal cassette chromosome *mec* (SCC*mec*) type distribution in methicillin-resistant *Staphylococcus aureus* bacteremia. *J Antimicrob Chemother* 2012; 67:2346-9. PMID: PMC3444231.

Han JH, Mascitti KB, Edelstein PH, Bilker WB, Lautenbach E. Effect of reduced vancomycin susceptibility on clinical and economic outcomes in *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother* 2012; 56:5164-70. PMID: PMC3457402.

Han JH, Nachamkin I, Tolomeo P, Bilker WB, Lautenbach E. Risk factors for efflux pump overexpression in fluoroquinolone-resistant *Escherichia coli*. *J Infect Dis* 2012; 206:1597-603. PMID: PMC3475638.

Han JH, Bilker WB, Edelstein PH, Mascitti KB, Lautenbach E. Derivation and validation of clinical prediction rules for reduced vancomycin susceptibility in *Staphylococcus aureus* bacteremia. *Epidemiol Infect* 2013; 141:165-73. PMID: PMC3518568.

Han JH, Edelstein PH, Bilker WB, Lautenbach E. The effect of staphylococcal cassette chromosome *mec* (SCC*mec*) type and clinical outcomes in methicillin-resistant *Staphylococcus aureus* bacteremia. *J Infection* 2013; 66:41-7. PMID: PMC3518704.

Han JH, Nachamkin I, Tolomeo P, Mao X, Bilker WB, Lautenbach E. Temporal changes in resistance mechanisms in colonizing *Escherichia coli* isolates with reduced susceptibility to fluoroquinolones. *Diagn Microbiol Infect Dis*, *in press*. PMID: in process.

KRISTEN FEEMSTER, MD, MPH, MS

NAME Kristen Allysn Feemster	POSITION TITLE Assistant Professor of Pediatrics (CE Track)
eRA COMMONS USER NAME (credential, e.g., agency login) krisfeem krisfeem	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/Y Y	FIELD OF STUDY
Yale University, New Haven, CT	B.S.	1995	Environmental Biology
Columbia University College of Physicians and Surgeons	M.D.	2002	Medicine
Columbia University Mailman School of Public Health	M.P.H	2001	Population and Family Health
The Children's Hospital of Philadelphia Pediatric Residency Program	N.A.	2005	Pediatrics
Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Phila., PA	M.S.	2008	Health Policy Research
The Children's Hospital of Philadelphia Fellowship Program in Infectious Diseases	N.A.	2010	Pediatric Infectious Diseases

Positions and HonorsPositions and Employment:

2005-08 Assistant Attending Physician, The Children's Hospital of Philadelphia
Departments of General Pediatrics and Emergency Medicine / Urgent Care, Philadelphia, PA
2005-08 Program Scholar, The Robert Wood Johnson Clinical Scholars Program, Penn
2005- Senior Fellow, Leonard Davis Institute of Health Economics at Penn
2010- Attending Physician, Division of Infectious Diseases, CHOP
2010- Assistant Professor, Department of Pediatrics, Penn
2010- Physician Scientist, Vaccine Education Center, CHOP
2011- Commissioner, Advisory Commission on Childhood Vaccines, Health Resources and Services Administration, Rockville, MD

Honors:

2000-01 Macy Scholarship Program- Fellowship for Public Health Study, New York, NY
2002 Fellowship for Malaria Clinical & Research Training Program, Mali, West Africa
2002 Watson Prize for Excellence in Pediatrics, Columbia University, New York, NY
2005 Philadelphia Pediatric Society Award for Commitment to Community Pediatrics
2005 Nancy Elizabeth Barnhart Award for Dedication to Children in the Community
2006 Eisenberg Scholar Research Award- University of Pennsylvania
2008 Finalist- Young Investigators Award, Society for Adolescent Medicine
2010 Fellows' Travel Grant, Infectious Diseases Society of America 2010 Annual Mtg

Selected Peer-reviewed Publications

1. **Feemster KA**, Winters SE, Fiks A, Kinsman S, Kahn, JA. Pediatricians' intention to recommend Human Papillomavirus (HPV) vaccines to 11- to 12-year-old girls post-licensing. *Journal of Adolescent Health*. 2008;43(4) 408-11. PMID: 18809140.
2. **Feemster KA**, Spain CV, Eberhard M, Pati S, Watson B. Identifying infants at increased risk for late initiation of immunizations: maternal and provider characteristics. *Public Health Reports*. 2009; 124(1):42-53.
3. Pati S, **Feemster KA**, Mohamad Z, Fiks A, Grundmeier R, Cnaan A. Maternal Health Literacy and Late Initiation of Immunizations among an Inner-city Birth Cohort. *Maternal and Child Health Journal*. 2011 Apr.; 15(3):386-94.
4. **Feemster KA**, Prasad P, Smith MJ, Feudtner C, Caplan A, Offit P, Coffin S. Employee Designation and Health Care Worker Support of an Influenza Vaccine Mandate at a Large Pediatric Tertiary Care Hospital. *Vaccine*. 2011; 29(9):1762-69.
5. Grimberg A, **Feemster KA**, Pati S, Ramos M, Grundmeier R, Cucchiara AJ, Stallings VA, "Medically Underserved Girls Receive Less Evaluation for Short Stature," *Pediatrics*, 2011; 127: 696–702.
6. Hughes CC, Jones AL, **Feemster KA**, Fiks A. "HPV vaccine decision making in pediatric primary care: a semi-structured interview study", *BMC Pediatrics*, 2011, 11:74.
7. **Feemster KA**, Li Y, Grundmeier R, Localio AR, Metlay JP. Validation of a Pediatric Primary Care Network in a US Metropolitan Region as a Community-Based Infectious Disease Surveillance System. *International Perspectives on Infectious Diseases*. 2011:219859. Epub 2011 Dec 7.
8. **Feemster KA**, Leckerman K, Middleton M, Zerr DM, Elward A, Newland J, Asti L, Guth E, Selvarangan R, Coffin S. Use of administrative data for the identification of laboratory-confirmed influenza infection: the validity of influenza-specific ICD-9 codes. *Journal of the Pediatric Infectious Diseases Society*. 2012;doi: 1093/jpids/pis052.
9. Mayne S, Karavite D, Grundmeier RW, Localio R, **Feemster K**, DeBartolo E, Hughes CC, Fiks AG, "The Implementation and Acceptability of an HPV Vaccination Decision Support System Directed at Both Clinicians and Families." AMIA Annu Symp Proc. 2012; 2012:616-624. PMID: 23304334
10. **Feemster KA**, Li Y, Localio AR, Shults J, Edelstein P, Lautenback E, Smith TE, Metlay JP. Risk of invasive pneumococcal disease varies by neighbourhood characteristics: implications for prevention policies. *Epidemiology and Infection*, 2013 Aug;141(8):1679-89. PMID: 23114061
11. Fiks AG, Grundmeier RW, Mayne S, Song L, **Feemster K**, Karavite D, Hughes CC, Massey J, Keren R, Bell LM, Wasserman R, Localio AR. Effectiveness of Decision Support for Families, Clinicians, or Both on HPV Vaccine Receipt, *Pediatrics*, 2013 Jun;131(6):1114-24. PMID:23650297

DARREN R. LINKIN, MD, MSCE - BIOSKETCH

NAME Darren R. Linkin, MD, MSCE	POSITION TITLE Assistant Professor C-E		
eRA COMMONS USER NAME LINKIN			
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.</i>)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Wesleyan University	BA	1993	
University of Chicago, Pritzker School of Medicine	MD	1997	
University of Pennsylvania	MSCE	2006	Clinical Epidemiology

Positions and Honors**Positions and Employment**

1997-2000	Internship/Residency in Internal Medicine, Hospital of Univ of Pennsylvania
2000-2003	Fellowship in Infectious Diseases, Hospital of the Univ of Pennsylvania
2001-2004	Staff Privileges in Internal Medicine, Pennsylvania Hospital, Penn
2003-2004	Postdoctoral Fellowship in Medicine, Hospital of the University of Pennsylvania
2003-2007	Faculty-Fellow, Center for Clinical Epidemiology and Biostatistics, Penn
2003-present	Infectious Diseases Attending Physician, Philadelphia VA Medical Center
2003-present	Hospital Epidemiologist, Philadelphia VA Medical Center
2004-2007	Instructor in Medicine, Department of Medicine, Univ Pennsylvania,
2004-present	Infectious Diseases Attending Physician, Hosp of the University of Pennsylvania
2007-2009	Assistant Professor of Epidemiology in Biostatistics and Epidemiology, Penn
2007-2010	Senior Scholar, Center for Clinical Epidemiology and Biostatistics, Penn
2007-present	Assistant Professor of Medicine at the Hospital of the University of Pennsylvania and the Veteran's Administration Medical Center, Penn
2012-present	Infectious Diseases Attending Physician, Penn Presbyterian Medical Center
2012-present	Associate Scholar, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Perelman School of Medicine

Other Experience and Professional Memberships

2001-present	Infectious Diseases Society of America, Member
2003-present	Society for Healthcare Epidemiology of America, Member, Education Committee 2006-2010; Member, Research Committee 2013-2014
2007-present	Infectious Diseases Expert Physician Panel, Veterans Health Administration National MRSA Education Program, Member
2008-present	FDA, Drug Safety and Risk Management Advisory Committee, Consultant
2009-present	Center for Occupational Safety and Infection Control, Veterans Health Administration, Study Section and Organization, Member
2011	VHA "Career Development Award" Study Section, Member
2012	Veteran Health Administration (VHA) Health Services Research & Development

(HSR&D) Collaborative Research to Enhance and Advance Transformation and Excellence (CREATE) Initiative Study Section, Member

Honors

2003-2009 National Institutes of Health Loan Repayment Program
2012 Outstanding Teaching Award, Infectious Diseases Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania

C. Selected peer-reviewed publications (selected from 30 peer-reviewed publications)

1. Cohen AE, Lautenbach E, Morales KH, Linkin DR (2006). Fluoroquinolone-resistant *Escherichia coli* in the long-term care setting Am J Med 119(11): 958-63
2. Hyle EP, Gasink LB, Linkin DR, Bilker WB, Lautenbach E (2007). Use of different thresholds of prior antimicrobial use in defining exposure: impact on the association between antimicrobial use and antimicrobial resistance J Infect 55(5): 414-418
3. Linkin DR, Fishman NO, Landis JR, Barton TD, Gluckman S, Kostman J, Metlay JP (2007). Effect of communication errors during calls to an antimicrobial stewardship program Infect Control Hosp Epidemiol 28(12): 1374-1381 PMID: PMC3653314
4. Anthony KB, Fishman NO, Linkin DR, Gasink LB, Edelstein PH, Lautenbach E (2008). Clinical and microbiological outcomes of serious multidrug-resistant gram-negative organisms treated with tigecycline Clin Infect Dis 46(4): 567-570
5. Cerceo E, Lautenbach E, Linkin D, Bilker WB, Lee I (2009). Role of matching in case-control studies of antimicrobial resistance Infect Control Hosp Epidemiol 30(5): 479-83 PMID: PMC2767121
6. Haynes K, Linkin DR, Fishman NO, Bilker WB, Strom BL, Pifer EA, Hennessy S (2011). Effectiveness of an information technology intervention to improve prophylactic antibacterial use in the postoperative period J Am Med Inform Assoc 18(2): 164-8
7. Han JH, Nachamkin I, Zaoutis TE, Coffin SE, Linkin DR, Fishman NO, Tolomeo P, Lautenbach E (2012). Risk Factors for Gastrointestinal Tract Colonization with Extended-Spectrum Beta-Lactamase (ESBL)-Producing *Escherichia coli* and *Klebsiella* Species in Hospitalized Patients Infect Control Hosp Epidemiol 33(12): 1242-5
8. Han JH, Bilker WB, Nachamkin I, Zaoutis TE, Coffin SE, Linkin DR, Hu B, Tolomeo P, Fishman NO, Lautenbach E (2013). The Effect of a Hospital-Wide Urine Culture Screening Intervention on the Incidence of Extended-Spectrum Beta-Lactamase (ESBL)-Producing *Escherichia coli* and *Klebsiella* Species Infect Control Hosp Epidemiol

SUSAN COFFIN, MD, MPH - BIOSKETCH

NAME Susan E. Coffin, MD, MPH	POSITION TITLE Associate Professor C-E
eRA COMMONS USER NAME	
POSITION TITLE Associate Professor C-E	

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Williams College	B.A.	1983	History
University of Vermont College of Medicine	M.D.	1987	
Johns Hopkins School of Hygiene and Public Health	M.P.H.	1991	Epidemiology

B. Positions and Honors.

Positions and Employment

1987-1990	Intern and Resident in Pediatrics, Johns Hopkins Hospital, Baltimore, MD
1991-1992	Chief Resident, Johns Hopkins Hospital, Baltimore, MD
1992-1997	Fellowship, Infectious Diseases, The Children's Hospital of Philadelphia
1995-present	Member, The Joseph Stokes Research Institute, CHOP
1998-2004	Assistant Professor of Pediatrics, Univ Pennsylvania School of Medicine
2002-present	Associate Scholar, Center for Clinical Epidemiology and Biostatistics, Penn
2003-present	Hospital Epidemiologist and Medical Director, Department of Infection Prevention and Control, The Children's Hospital of Philadelphia
2004-2007	Assistant Professor of Pediatrics at the Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine
2004-present	Faculty Member, Graduate Program in Public Health Studies, Penn
2006-2011	Member, Center for Education and Research on Therapeutics, Penn
2007-2010	Associate Director, Center for Pediatric Clinical Effectiveness, CHOP
2007-present	Associate Professor of Pediatrics at Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine

Other Experience and Professional Memberships

1987-present	American Academy of Pediatrics
1992-present	Pediatric Infectious Diseases Society, Member, Nominations Committee: 200
1992-present	Infectious Diseases Society of America
2002-present	Society for Pediatric Research
2005-present	State of Pennsylvania, Member of Governor's Advisory Health Board
2006-present	State of Pennsylvania DOH, Member, Healthcare Infections Advisory Commi
2006-present	Association for Professionals in Infection Control and Epidemiology
2006-2008	National Quality Forum, Member of Technical Advisory Panel for Pediatrics, Voluntary Consensus Standards for the Reporting of Healthcare-associated In

- 2007-present National Institutes of Allergy, Immunology, and Infectious Diseases, National Institutes of Health, Member, Contract Review Panels
- 2009-present U.S. News and World Reports, Best Children's Hospitals Survey, Member, Infection Control Working Group: 2009-2010; Leader, Infection Control Working Group: 2010-present
- 2009-present Special Emphasis Panel, CDC, Member of Review Committees: 2009 - present

Honors

- 1987 Alpha Omega Alpha
- 1991 Delta Omega Alpha
- 2011 Alfred Stengel Health System Champion Award; University of Pennsylvania School of Medicine and University of Pennsylvania Health System
- 2012 Distinguished Academic Achievement Award; University of Vermont College of Medicine
- 2013 F1000 Infectious Diseases Faculty Member of the Year

Selected peer-reviewed publications (selected from 84 peer-reviewed publications)

1. Coffin, S.E., Klompas, M., Classen, D., et al. (2008). Strategies to prevent ventilator-associated pneumonia in acute care hospitals. Infect Cont Hosp Epidemiol 29: S31-40
2. Gerber, J.S., Coffin, S.E., Smathers, S.A., Zaoutis, T.E. (2009). Trends in the incidence of methicillin-resistant Staphylococcus aureus infection in children's hospitals in the United States. Clin Infect Dis 49: 65-71
3. Wilkes, J.J., Leckerman, K.H., Coffin, S.E., Keren, R., Metjian, T.A., Hodinka, R.L., Zaoutis, T.E. (2009). Use of antibiotics in children hospitalized with community-acquired, laboratory-confirmed influenza. J Pediatr 154: 447-449 PMID: 19874761
4. Nolan, S.M., Gerber, J.S., Zaoutis, T., Prasad, P., Rettig, S.L., Gross, K., McGowan, K.L., Reilly, A.F., Coffin, S.E. (2009). Outbreak of vancomycin-resistant Enterococcus colonization among pediatric oncology patients. Infect Cont Hosp Epidem 30:338-345
5. Marlowe, L., Mistry, R.D., Coffin, S.E., Leckerman, K.H., McGowan, K.L., Dai, D., Bell, L.M., Zaoutis, T.E. (2010). Blood culture contamination rates after skin antisepsis with chlorhexidine gluconate versus povidone-iodine in a pediatric emergency department Infect Cont Hosp Epidemiol 31: 171-176
6. Leckerman, K.H., Sherman, E.R., Zaoutis, T.E., Coffin, S.E. (2010). Risk factors for healthcare-associated influenza in hospitalized children Infect Cont Hosp Epidemiol 31: 421-424 PMID: 20184439
7. Feemster, K.A., Prasad, P., Smith, M.J., Feudtner, C., Caplan, A., Offit, P.A., Coffin, S.E. (2011). Employee designation and health care worker support of an influenza vaccine mandate at a large pediatric tertiary care hospital Vaccine 29(9): 1762-1769
8. Kronman, M.P., Zaoutis, T.E., Haynes, K., Feng, R., Coffin, S.E. (2012). Antibiotic exposure and IBD development among children: a population-based cohort study Pediatr 130: e794-803
9. Kim, J., Shaklee, J.F., Smathers, S., Prasad, P., Zoltanski, J., Nerandzic, M., Asti, L., Coffin, S.E., Toltzis, P., Zaoutis, T.E. (2012). Risk factors and outcomes associated with severe Clostridium difficile infection in children. Pediatr Infect Dis J 31: 134-138
10. Milstone, A.M., Elward, A., Song, X., Zerr, D.M., Orscheln, R., Speck, K., Obeng, D., Reich, N.G., Coffin, S.E., Perl, T. (2013). Daily chlorhexidine bathing to reduce bacteremia in critically ill children: a multi center, cluster-randomized, two-period crossover trial Lancet : 1099-1106

DAVID MARGOLIS, MD, PHD - BIOSKETCH

NAME David J. Margolis, MD PhD	POSITION TITLE Professor		
eRA COMMONS USER NAME DAVID__MARGOLIS			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Wesleyan University	B.A.	1981	Biology
University of Chicago-Pritzker	M.D.	1985	Medicine
University of Pennsylvania	M.S.C.E.	1998	Epidemiology
University of Pennsylvania	Ph.D.	2000	Epidemiology

Positions and Honors**Professional Positions and Employment:**

- 2004-present Director, Division of Dermatoepidemiology, Department of Dermatology, University of Pennsylvania School of Medicine
- 2008-present Chair, Conflict of Interest Standing Committee, Provost Office, University of Pennsylvania.
- 2008-present Professor of Dermatology, University of Pennsylvania School of Medicine
- 2008-present Professor of Epidemiology, Univ of Pennsylvania School of Medicine
- 2011-present Founding Director, Center for DermatoEpidemiology and Translation, Univ. of Pennsylvania School of Medicine

Honors and Awards:

- Hohenberg Lectureship (1999).
- Saul Weingard Award for Outstanding PhD Dissertation (2000).
- Excellence in Teaching in Epidemiology Award (2004)
- Dean's Award for Excellence in Basic Science Teaching (2005)
- American Dermatology Association (2010)
- Samuel Martin Health Evaluation Sciences Research Award (2012)

Selected Peer-reviewed Publications (15 out of more than 200):

- Margolis DJ, Taylor LA, Hoffstad O, Berlin JA. Diabetic Neuropathic Foot Ulcer The Association Of Wound Size, Wound Duration, and Wound Grade On Healing. *Diabetes Care* 25:1835-1839, 2002. PMID: 12351487
- Margolis DJ, Gelfand JM, Hoffstad O, Berlin JA. Surrogate Endpoints For The Treatment Of Diabetic Neuropathic Foot Ulcers. *Diabetes Care* 26:1696-1700, 2003. PMID: 12766096
- Margolis DJ, Taylor LA, Hoffstad O, Berlin JA. Diabetic Neuropathic Foot Ulcers: Predicting Who Will Not Heal. *American Journal of Medicine* 115:627-631, 2003. PMID: 14656615
- Margolis DJ, Hofstad O, Taylor L, Berlin JA. Diabetic neuropathic foot ulcers and amputation. *Wound Repair and Regeneration*, 13:230-236, 2005. PMID: 15953040
- Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. The risk of myocardial infarction in patients with psoriasis. *Journal of the American Medical Association* 296:1735-1741, 2006. PMID: 17032986

- Margolis DJ, Hoffstad O, Feldman H. The association between renal failure and foot ulcer or lower extremity amputation in those patients with diabetes. *Diabetes Care*, 31: 1331-1336, 2008. PMID: PMC2453658;
- Kurd SK, Hoffstad OJ, Bilker WB, Margolis DJ. Evaluation of the use of prognostic information for the care of individuals with venous leg ulcer or diabetic neuropathic foot ulcers. *Wound Repair and Regeneration*, 17: 318-325, 2009. PMID: PMC2724840;
- Margolis DJ, Morris LM, Papadopoulos M, Weinberg L, Filip JC, Lang SA, Vaikunth SS, Crombleholme TM. Phase I study of H5.020CMV.PDGF- β to treat venous leg ulcer disease. *Molecular Therapy* 17: 1822-1829, 2009. NIHMSID: NIHMS182297; PMID: 19638959 PMC2835007
- Margolis DJ, Hoffstad O, Thom S, Bilker W, Maldonado AR, Cohen RM, Aronow BJ, Crombleholme T. The differential effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with respect to foot ulcer and limb amputation in those with diabetes. *Wound Repair and Regeneration*, 18: 445-451 2010; PMID: 20840518.
- Thom SR, Milovanova TN, Yang M, Bhopale VM, Sorokina EM, Uzun G, Malay DS, Troiano MA, Hardy KR, Lambert DS, Logue CJ, Margolis DJ. Vasculogenic stem cell mobilization and wound recruitment in diabetic patients: increased cell number and intracellular regulatory protein content associated with hyperbaric oxygen therapy. *Wound Repair and Regeneration* 19(2): 149-61, 2011; PMID: 21362081.
- Margolis DJ, Hoffstad O, Nafash J, Leonard C, Freeman C, Hennessy S, Weibe D. Location, location, location: Geographic clustering of lower extremity amputation among Medicare beneficiaries with diabetes. *Diabetes Care*, 34: 2363-7, 2011; PMID21933906 PMC3673572
- Margolis DJ, Fanelli M, Kupperman E, Papadopoulos M, Metlay JP, Xie SX, DiRienzo J, Edelstein PH. Association of pharyngitis with oral antibiotic use for the treatment of acne: A cross-sectional and prospective cohort study. *Archives of Dermatology*, 148:326-332, 2012. PMID: PMC3673016
- Margolis DJ, Apter AJ, Gupta J, Hoffstad O, Papadopoulos M, Campbell LE, Sandilands A, McLean WHI, Rebbeck TR, Mitra N, The persistence of atopic dermatitis and Filaggrin mutations in a US longitudinal cohort. *Journal of Allergy and Clinical Immunology*. 130(4), 912-17, 2012. PMID 22951058 PMC3462287
- Margolis DJ, Gupta J, Thom SR, Townsend RR, Kanetsky PA, Hoffstad O, Papadopoulos M, Fscher M, Schelling JR, Mitra N. Diabetes, lower extremity amputation, loss of protective sensation, and neuronal nitric oxide synthase associated protein in the Chronic Renal Insufficiency Cohort Study. *Wound Repair Regen*, 21: 17-24, 2013 PMID 3667959
- Margolis DJ, Apter AJ, Mitra N, Gupta J, Hoffstad O, Papadopoulos M, Rebbeck T, MacCallum S, Campbell LE, Sandilands A, McLean WHI. Reliability and validity of genotyping filaggrin *null* mutations. *J Dermatologic Science*, 36(7)1961-6 2013 PMID 23274172
- Garrett J P-D, Apter AJ, Hoffstad O, Spergel JM, Margolis DJ. Asthma and frequency of wheeze: Risk factors for the persistence of atopic dermatitis in children. *Annals of Allergy, Asthma & Immunology*, 110(3):146-9 2013. PMID 23548521

NEIL FISHMAN, MD - BIOSKETCH

NAME: Neil O. Fishman, MD	POSITION TITLE		
eRA COMMONS USER NAME NEIL.FISHMAN	Associate Professor of Medicine		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Haverford College	B.A.	1979	Biology (cum laude)
Temple University	M.D.	1983	Medicine
University of Pennsylvania	PDF	1988-92	Infectious Diseases

Positions and Honors**Positions and Employment**

1983-84 Intern in Medicine, Temple University Hospital, Philadelphia, PA
1984-86 Resident in Medicine, Temple University Hospital, Philadelphia, PA
1986-88 Assistant Professor of Medicine, Department of Medicine, Temple University
1988-92 Clinical and Research Fellow in Infectious Diseases, University of Pennsylvania
1992-93 Instructor of Medicine, Department of Medicine, University of Pennsylvania
1993-03 Assistant Professor of Medicine, Department of Medicine, Univ of Pennsylvania
2003- Associate Professor of Medicine, Department of Medicine, Univ of Pennsylvania

Other Experience and Professional Memberships

1992- Director, Antimicrobial Stewardship Program, Hosp of the Univ of Pennsylvania
2001- Director, Healthcare Epidemiology and Infection Prevention and Control, Penn
2005-2006 President, Division L, American Society for Microbiology
2007-2010 Chair, Antimicrobial Resistance Working Group, Infect Diseases Soc of America
2008-2009 Vice President, Society for Healthcare Epidemiology of America
2009-2010 President Elect, Society for Healthcare Epidemiology of America
2010-2011 President, Society for Healthcare Epidemiology of America
2011-2012 Immediate Past President, Society for Healthcare Epidemiology of America

Honors

1982 Alpha Omega Alpha
1989 National Research Science Award in Virology and Infectious Diseases
1995 The Donald B. Martin Department of Medicine Teaching Service Award
1995 The Maurice F. Attie Department of Medicine Faculty Teaching Award
1995 The Infectious Diseases Society of America Abbott Achievement Award
1999 The Alfred Stengel Health System Champion Award, Penn
2009 The Association for Prudent Use of Antibiotics Leadership Award

Selected peer-reviewed publications

1. Gross R, Morgan AS, Kinky DE, Weiner M, Gibson GA, Fishman NO. Impact of a hospital-based antimicrobial management program on clinical and economical outcomes. *Clin Infect Dis* 2001;33:289.

2. Cosgrove SE, Fishman NO, Talbot TR, et al. (2005) Strategies for the use of a limited influenza vaccine supply. *JAMA* 293:229-32.
3. Albrecht SJ, Fishman NO, Kitchen J, Nachamkin I, Bilker WB, Hoegg C, et al. (2006) Reemergence of gram-negative healthcare-associated bloodstream infections. *Arch Intern Med* 116:1289-94.
4. Han Z, Lautenbach E, Fishman N, Nachamkin I. (2007) Evaluation of mannitol salt agar, CHROMagar *S. aureus* and CHROMagar MRSA for detection of methicillin-resistant *S. aureus* from nasal swab specimens. *J Med Microbiol* 56:43-6.
5. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, IDSA, SHEA. (2007) Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 44:159-77.
6. LaRosa LA, Fishman NO, Lautenbach E, Koppel RJ, Morales KH, Linkin DR. (2007) Evaluation of antimicrobial therapy orders circumventing an antimicrobial stewardship program: investigating the strategy of "stealth dosing". *Infect Control Hosp Epidemiol* 28:551-6.
7. Linkin DR, Fishman NO, Landis JR, Barton TD, et al. (2007) Effect of communication errors during calls to an antimicrobial stewardship program. *Infect Control Hosp Epidemiol* 28:1374-81.
8. Connor DM, Binkley S, Fishman NO, Gasink LB, Linkin D, Lautenbach E. (2007) Impact of automatic stop orders to discontinue vancomycin therapy on vancomycin use in an antimicrobial stewardship program. *Infect Control Hosp Epidemiol* 28:1408-10.
9. Anthony KB, Fishman NO, Linkin DR, Gasink LB, Edelstein PH, Lautenbach E. (2008) Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. *Clin Infect Dis* 46:567-70.
10. Gasink LB, Singer K, Fishman NO, Holmes WC, Weiner MG, Bilker WB, Lautenbach E. (2008) Contact isolation for infection control in hospitalized patients: is patient satisfaction affected? *Infect Control Hosp Epidemiol* 29:275-8.
11. Lautenbach E, Metlay JP, Weiner MG, Bilker WB, Tolomeo P, Mao X, Nachamkin I, Fishman NO. (2009) Gastrointestinal tract colonization with fluoroquinolone-resistant *Escherichia coli* in hospitalized patients: changes over time in risk factors for resistance. *Infect Control Hosp Epidemiol* 30:18-24.
12. Lautenbach E, Nachamkin I, Hu B, Fishman NO, Tolomeo P, Prasad P, Bilker WB, Zaoutis TE. (2009) Surveillance cultures for detection of methicillin-resistant *Staphylococcus aureus*: Diagnostic yield of anatomic sites and comparison of provider- and patient-collected samples. *Infect Control Hosp Epidemiol*;30:380-2.
13. Lautenbach E, Metlay JP, Mao X, Han X, Fishman NO, Bilker WB, Tolomeo P, Wheeler M, Nachamkin I. (2010) The prevalence of fluoroquinolone resistance in colonizing *Escherichia coli* isolates recovered from hospitalized patients. *Clin Infect Dis* 51:280-5.
14. Mascitti KB, Edelstein PH, Fishman NO, Morales KH, Baltus AJ, Lautenbach E. (2012) Prior vancomycin use is a risk factor for reduced vancomycin susceptibility in methicillin-susceptible but not methicillin-resistant *Staphylococcus aureus* bacteremia. *Infect Control Hosp Epidemiol* 33:160

GARY SMITH, DPhil - BIOSKETCH

NAME Gary Smith (garysmith48)		POSITION TITLE Professor of Population Biology & Epidemiology	
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Oxford University (UK)	BA (Hons)	1970	Zoology
Cambridge University (UK)	BA (Hons)	1972	Education
University of York (UK)	D. Phil.	1978	Ecology

Positions and Honors.

Positions and Employment

1978-81 Wooldridge Fellowship, Dept of Pure & Applied Biology, Imperial College, London
 1981-83 Research Associate, Dept of Pure & Applied Biology, Imperial College, London
 1986-92 Assistant Professor of Population Biology & Epidemiology, School of Vet Med, Penn
 1992-96 Associate Professor of Population Biology & Epidemiology, School of Vet Med, Penn
 1992- Associate Scholar in the Center for Clinical Epidemiology and Biostatistics, Penn
 1995- Professor of Population Biology & Epidemiology, School of Vet Med, Penn
 1998- Secondary Appointment in the Department of Biostatistics and Epidemiology, Penn

Other Experience and Professional Memberships

1988-1990 Chief of the Section of Animal Health Economics, School of Vet Med, Penn
 1991-1998 Editorial Board of *Parasitology Today*
 1992 FAO Expert Committee on “*Implementation of disease models in developing countries*”
 1993- Chief of the Section of Epidemiology and Public health, School of Vet Med, Penn
 1994-1998 Director of the Center for Infectious Disease and Food Safety, Penn
 1995-1997 Specialist Editor, *International Journal for Parasitology*
 1999 European Commission: Risk Assessment Exercise on Geographical BSE-Risk
 2001 President of the New Jersey Society for Parasitology
 2001- Director, Epidemic Disease GIS Research Unit, University of Pennsylvania
 2002 Organizing Committee: National Veterinary Conference - “*Agenda for Action: Veterinary Medicine’s role in Biodefense and Maintenance of Public Health*”. Washington DC, 2002.
 2003 Blue Ribband Panel on “Agroterrorism”, Office of Science and Technology Policy, Department of Homeland Security, White House Conference Center, Washington, DC.

Selected peer-reviewed publications (most recent first)

Dolente B.A., Beech J., Lindborg S., **Smith G** (2005) Evaluation of risk factors for development of catheter-associated jugular thrombophlebitis in horses: 50 cases (1993-1998). *Journal of the American Veterinary Medical Association* 227:1134-1141

Massung R F, Courtney JW, Baker SL, **Smith G** & Dryden RL. (2005) *Anaplasma phagocytophilum* in White-tailed Deer. *Emerging Infectious Diseases* 11:1604-1606.

Maslow JN, Brar I, **Smith G**, Newman GW, Mehta R, Thornton C, Didier P. (2003) Latent infection as a source of disseminated disease caused by organisms of the *Mycobacterium avium complex* in simian immunodeficiency virus-infected rhesus macaques. *Journal of Infectious Diseases*. 187(11):1748-55, Jun 1.

Courtney J. W., Dryden R. L., Montgomery J., Schneider B. S., **Smith G**. & Massung R. F. (2003) Molecular Characterization of *Anaplasma phagocytophilum* and *Borrelia burgdorferi* in *Ixodes scapularis* Ticks from Pennsylvania. *Journal of Clinical Microbiology*. 41: 1569-1573

Cornell S.J., Isham V. S., **Smith G**. & Grenfell B. T. (2003) Spatial transmission, drug resistance and the spread of rare gene. *Proceedings of the National Academy of Sciences of the USA*. 100: 7401-7405.

Orsini, JA., Haddock, M., Stine, L., Sullivan, EK., Rabuffo, TS., **Smith G**. (2003) Odds of moderate or severe gastric ulceration in racehorses receiving antiulcer medications. *Journal of the American Veterinary Medical Association*. 223:336-339.

Bebak-Williams J., McAllister P. E., **Smith G**., Boston R. (2002) The effect of fish density and number of infectious fish on the survival of rainbow trout fry during epidemics of infectious pancreatic necrosis. *Journal of Fish Diseases* 25: 715-726.

Donaldson M.T., LaMonte B. H., Morresey P., **Smith G**. & Beech J. (2002) The effects of treatment with pergolide or cyproheptadine on corticotropin, insulin and glucose concentrations in horses with pituitary pars intermedia dysfunction (equine Cushings disease). *Journal of Veterinary Internal Medicine* 16: 742-746.

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THEOKLIS ZAOUTIS, MD, MSCE - BIOSKETCH

NAME Theoklis E Zaoutis, MD, MSCE	POSITION TITLE Professor of Pediatrics and Epidemiology		
eRA COMMONS USER NAME ZAOUTIS			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
State University of New York at Stonybrook	BS	1985	Biology
Hahnemann University	MCM	1987	Clinical Microbiology
Jefferson Medical College, Thomas Jefferson Univ	MD	1996	Medicine
University of Pennsylvania School of Medicine	MSCE	2005	Clinical Epidemiology

Positions and Honors.

Positions and Employment

1987-1989 Research Assistant/Microbiologist, The Rockefeller University, New York
 1987-1992 Senior Clinical Scientist, Clinical Research and Development, Wyeth-Ayerst, Radnor, PA
 1996-2000 Resident/Chief Resident in Pediatrics, A.I. duPont Hospital for Children/Jefferson Medical College
 2000-2003 Fellow, Pediatric Infectious Diseases, Children's Hosp of Philadelphia (CHOP)
 2003-2009 Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine
 2003-present Attending Physician, Division of Infectious Diseases, CHOP
 2003-2011 Director, Antimicrobial Stewardship Program, CHOP
 2004-2010 Director, Pediatric Infectious Diseases Training Program, CHOP
 2005-2009 Assistant Professor of Epidemiology, University of Pennsylvania, Penn
 2005-present Senior Scholar, Center for Clinical Epidemiology and Biostatistics, Penn
 2007-present Associate Director, Center for Pediatric Clinical Effectiveness, CHOP
 2009-present Associate Professor of Pediatrics and Epidemiology, UPENN School of Medicine
 2013-present Professor of Pediatrics and Epidemiology, UPENN School of Medicine
 2013-present Thomas Frederick McNair Scott Endowed Chair in Pediatrics, CHOP

Editorial Positions:

2006-12 Associate Editor, Pharmacoepidemiology and Drug Safety
 2006- Editorial Board Member, Current Fungal Infection Reports
 2008- Editorial Board Member, Pediatric Infectious Diseases Journal
 2011- Editor-in-Chief, The Journal of the Pediatric Infectious Diseases Society

Honors

1995 Alpha Omega Alpha
 1999 Herman Rosenblum, M.D. Award for Clinical Excellence, Outstanding Senior Resident, A.I. duPont Hospital for Children
 1999 Resident Teaching Award, A.I. duPont Hospital for Children
 2001 Fellow Teacher of the Year Award, The Children's Hospital of Philadelphia
 2001 Jonathan Freeman Scholarship, CDC/SHEA

2003-2007	Faculty Honor Roll, The Children's Hospital of Philadelphia
2006	Astellas Young Investigator Award
2007	Elected Member, Society of Pediatric Research
2009	Society for Healthcare Epidemiology of America Pediatric Investigator Award

C. Selected peer-reviewed publications (in chronological order).

1. Keren R, Zaoutis TE, Bridges CB, Herrera G, Watson B, Wheeler A, Licht DJ, Luan XQ, Coffin SE. (2005). Neurologic and Neuromuscular Diseases as Risk Factors for Respiratory Failure in Children Hospitalized with Influenza Infection. JAMA 294(17): 2188-94.
2. Zaoutis TE, Argon J, Chu J, Berlin JB, Feudtner, C. (2005). The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the US: A propensity analysis. Clinical Infectious Diseases 41:1232-9.
3. Zaoutis TE, Toltzis P, Chu J, Abrams T, Dul M, Kim J, McGowan KL, Coffin SE. (2006). Clinical and molecular epidemiology of community-acquired methicillin-resistant Staphylococcus aureus infections among children with risk factors for health-care associated infection: 2001-2003. Pediatr Infect Dis J 25(4):343-48.
4. Conway PH, Cnaan A, Zaoutis TE, Henry B, Grundmeier RW, Keren R. (2007). Recurrent urinary tract infections in children: Risk Factors and association with prophylactic antimicrobials. JAMA. 298(2):179-86.
5. Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T: Epidemiology of Clostridium Difficile Associated Disease Among Inpatients at Children's Hospitals, 2001-2006. Pediatrics 122 (6): 1266-70, December 2008.
6. Zaoutis T, Localio AR, Leckerman KH, Saddlemire S, Bertoch D, Keren R: Prolonged intravenous versus early conversion to oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics 123; 636-642, February 2009.
7. Lautenbach E, Nachamkin I, Hu B, Fishman NO, Tolomeo P, Prasad P, Bilker W, Zaoutis TE: Surveillance cultures for detection of methicillin-resistant Staphylococcus aureus: Diagnostic Yield of Anatomic Sites and Comparison of Provider-and Patient Collected Samples. Infect Control and Hosp Epidemiology 30(4): 380-2, April 2009.
8. Toltzis P, Kim J, Dul M, Zotlanski J, Smathers S, Zaoutis T: Presence of the Epidemic North American Pulse Field Type 1 Clostridium Difficile Strain in Hospitalized Children. J Pediatr 154(4): 607-8, April 2009.
9. Gerber JS, Coffin SE, Smathers SA, Zaoutis TE: Trends in the incidence of methicillin-resistant Staphylococcus aureus infection in children's hospitals in the United States. Clin Infect Dis 49(1): 65-71, July 2009.
10. Marlowe L, Mistry R, Coffin S, Leckerman KH, McGowan KL, Dai D, Bell LM, Zaoutis T: Blood culture contamination rates after skin antisepsis with chlorhexidine versus povidone-iodine in a pediatric emergency department. Infect Control Hosp Epidemiol 2010 31:171-6,
11. Gerber JS, Prasad PA, Localio R, Xiao R, Fiks AG, Grundmeier RW, Bell LM, Wasserman RC, Rubin DM, Keren R, Zaoutis TE. Racial Differences in antibiotic prescribing by primary care pediatricians. Pediatrics 2013;131(4):677-84
12. Gerber JS, Prasad PA, Fiks AG, Localio Arm Grundmeier RW, Bell LM, Wasserman RC, Keren R, Zaoutis TE. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. JAMA 309(22):2345-52, June 2013.