

Pennsylvania Department of Health Final Performance Summary Report Non-Formula Grants

Overview of the Health Research Project Performance Review Process and Criteria

An applicant that receives a health research grant under Tobacco Settlement Act / Act 77 of 2001, Chapter 9, is subject to a performance review by the Department of Health upon completion of the research project. The performance review is based on requirements specified by Act 77 and criteria developed by the Department in consultation with the Health Research Advisory Committee.

As part of the performance review process, each research project contained in a grant is reviewed by at least three experts who are physicians, scientists or researchers. Reviewers are from the same or similar discipline as the research grant/project under review and are not from Pennsylvania. Reviewers use the applicant's proposed research plan (strategic plan), the annual progress reports, interim review reports, corrective action plan, and final progress report to conduct the review. A grant that receives an unfavorable performance review by the Department may be subject to a reduction in funding or become ineligible for health research funding in the future. The overall grant evaluation rating is based on the ratings for the individual research projects contained in the grant.

This performance review report contains the outcome of the review for the grant as a whole (outstanding, favorable, or unfavorable), strengths and weaknesses of each research project, as well as recommendations for future improvement.

The following criteria were applied to information submitted by research grant recipients:

- **Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?**
 - Did the project meet the stated objectives?
 - Consider these questions about the data and empirical results: Were the data developed sufficiently to answer the research questions posed? Were the data developed in line with the original research protocol?
 - If changes were made to the research protocol, was an explanation given, and, if so, is it reasonable?
 - Consider (only for clinical research grants) the extent of laboratory and clinical activities initiated and completed and the number of subjects relative to the target goal.
 - Were sufficient data and information provided to indicate or support the fact that the project met its objectives or made acceptable progress?
 - Were the data and information provided applicable to the project objectives listed in the strategic plan?

- **Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?**
 - Consider any changes in risk factors, services provided, incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of impact and effectiveness of the research being conducted.
 - Consider any major discoveries, new drugs and new approaches for prevention, diagnosis and treatment, which are attributable to the completed research project.
 - What are the future plans for this research project?

- **Criterion 3 - Did the project leverage additional funds or were grant applications submitted?**
 - If leveraging of funds were expected, did these materialize?
 - Are the researchers planning to apply for additional funding in the future to continue or expand the research?

- **Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted / filed?**
 - If any of the above listed were expected, did these materialize?
 - Are the researchers planning to submit articles to peer-reviewed publications, file for any licenses or patents or begin any commercial development opportunities in the future?
 - Consider the number/quality of each and what was proposed in the original application.

- **Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?**
 - If any improvements in infrastructure were expected, were they made?
 - Were any new investigators added or were any researchers brought into the institution to help carry out this research?
 - Were funds used to pay for research performed by pre- or post-doctoral students?

- **Criterion 6 - Did the project lead to collaboration with research partners outside the institution, or new involvement with the community?**
 - Are the researchers planning to begin any collaborations as a result of the research?
 - For clinical research only: consider the number of hospitals and health care professionals involved and the extent of penetration of the studies throughout the region or the Commonwealth.

Overall Evaluation Rating

An overall evaluation rating is assigned to each research project. The rating reflects the overall progress the project attained in meeting the stated goals and objectives. The rating is based on a scale of 1–3, with 1 being the highest. An average rating is obtained from all the reviews (minimum of 3) of each project and is the basis for the determination of the final overall rating for each project as follows:

1.00 – 1.33 = *Outstanding*

1.34 – 2.66 = *Favorable*

2.67 – 3.00 = *Unfavorable*

The grant level rating is an average rating from all projects as above. The numerical rating appears in parentheses for the grant and each project in the ***Overall Grant Performance Review Rating*** section of the report.

Overall Grant Performance Review Rating

Grant Rating: Favorable (1.57)

Project Rating:

Project	Title	Average Score
08864	Center of Excellence in Prevention and Control of Antibiotic Resistant Bacterial Infections	Favorable (1.57)

Project Number: 08864
Project Title: Center of Excellence in Prevention and Control of
Antibiotic Resistant Bacterial Infections
Investigator: Lee H. Harrison, MD

Section A. Project Evaluation Criteria

Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?

STRENGTHS AND WEAKNESSES

Reviewer 1:

Aim 1. *Develop, validate, and employ novel molecular detection methods of asymptomatic C. difficile carriage and assess an intervention to control this source of C. difficile disease.*

Asymptomatic carriers were identified as the sources of 29% of symptomatic hospital C. difficile infections. Having a positive VRE screen was a risk factor (OR 3.7). Persistent room contamination was common, with the patient call bell the most frequently contaminated site. A paper describing these findings was published (PMID 23881150).

These studies have provided some useful information. However, the central finding essentially corroborates studies performed by Curtis Donskey in Cleveland (PMID 17879913, PMID 22561724, PMID 23954113).

A C. difficile PCR assay was developed: the assay requires 1.5 hrs for extraction (47 min machine time + 45 min tech time) and 3.5 hrs to perform (2.8 hr machine time + 45 min tech time).

The amount of time required to process specimens and perform the homebrew assay is quite inferior to currently available commercial assays (PMID 23090736).

The use of selective broth improved assay sensitivity to 1 CFU.

However, selective broth culture has a detrimental impact on turnaround time in comparison to assays performed directly on clinical specimens. The trade-off is probably not worthwhile, as patients with clinical disease tend to have high organism burdens and can generally be detected by direct PCR. The authors erroneously state that PCR sensitivity was only 77.3% in the "only published study to use anaerobic toxigenic culture on all specimens as the gold standard." However, Tenover et al. showed higher sensitivity (94%) of a PCR assay compared to toxigenic culture in PMID 20702676.

The intervention was not performed because of a decline in prevalence. This aim was replaced with a food survey finding a low prevalence of *C. difficile* in retail meat.

The replacement aim adds little to studies by Scott Weese and Glenn Songer on the prevalence of *C. difficile* in retail foods (PMID 17552108, PMID 19525267, PMID 19402980).

A pilot evaluation of whole genome sequencing for *C. difficile* epidemiology compared this method to multilocus variable-number tandem-repeat analysis (MLVA).

Wilcox has found the two methods to yield comparable results (PMID 24108611).

The investigators' finding of toxigenic *C. difficile* in 6.6% of 108 healthy adults is consistent with prior estimates. A larger sample size will be needed to have confidence in the results. The investigators report that they lacked sufficient personnel to complete a planned QA project to identify and isolate *C. difficile* carriers.

Aim 2. Understand characteristics of and risk factors for infection with community-associated MRSA strains that have recently been introduced into the hospital and employ rapid, PCR-based diagnosis of MRSA infection and colonization, to optimize antimicrobial therapy, reduce use of broad spectrum antimicrobials for treatment of S. aureus infections, and reduce transmission of MRSA.

The investigators found that 10% of 86 MRSA-colonized subjects developed MRSA infection in 6 mos.

This is comparable to findings by others-- 8.5% in 3 mos. (PMID 23290578).

The USA300 strain is associated with HIV/AIDS and shorter length of stay (possibly due to community acquisition). A manuscript describing this work is in preparation.

Popovich has published extensively on USA300 in patients with HIV/AIDS (PMID 20192731, PMID 22354926, PMID 23325428).

An RT-PCR assay for MRSA was abandoned because of "unexpected" incongruent results. False-positive and false-negative molecular MRSA assay results are well described-- "empty cassettes" and SCCmec variants are the principal causes (e.g., PMID 15131143, PMID 18945832). The researchers did not adequately investigate the causes of their false-positive/-negative results or consider alternative assays to the BD GeneOhm StaphSR (e.g., Verigene). A multiplex PCR assay was compared with chromogenic agar. A sizeable proportion (17%) of subjects had to be excluded because they were not assessed for contact precautions, suggesting a systematic infection control problem at the institution. Only 44 subjects were studied, which is quite inadequate. Molecular testing was about one day (26.2 h) faster, which is hardly surprising).

High quality studies to compare clinical outcomes of molecular vs. conventional MRSA screening methods are needed; unfortunately this was not provided here. Any impact on clinical

outcomes (transmission, infection, cost effectiveness) could not be assessed with such a small sample size.

S. aureus isolates with a hetero-vancomycin-intermediate (hVISA) resistance phenotype were analyzed; mostly *mprF* (lysylphosphatidylglycerol synthase) mutations were identified. This is already established (PMID 12726988).

Some differentially expressed genes were identified, but their significance is not known. The VISA phenotype has been shown to result from multiple mutation events (PMID 17517606, PMID 23539745).

The investigators conclude that a simple marker for VISA is not feasible. This is already known (PMID 24018261, PMID 24092658).

Aim 3. Develop a new, multilocus variable number tandem repeat analysis-based molecular subtyping tool for tracking MDR A. baumannii transmission, validate improved methods for detecting MDR A. baumannii colonization, and assess an intervention to control the spread of this organism in intensive care units.

Two multilocus variable-number tandem-repeat analysis (MLVA) methods have been reported in the literature. The authors built upon these and published their findings in the Journal of Clinical Microbiology (PMID 21918019). The investigators found MLVA to be more discriminatory than PFGE in identifying epidemiologically distinct clusters. Performance of the assay requires a single PCR reaction and capillary electrophoresis. For *A. baumannii* screening they obtained 89% sensitivity by combining sponge screening of the upper arm and thigh.

This is a useful approach to identify colonized patients at risk for invasive disease (PMID 20980559), which exhibits improved sensitivity compared to other approaches. The investigators observed a decline in colonization over a 3 yr period.

Although correlation does not necessarily imply causation, it is likely that the combined approach positively impacted the prevalence of *A. baumannii*. Others have demonstrated similar success during *A. baumannii* outbreaks using a combination of screening, environmental decontamination, etc. (PMID 11060073, PMID 19199531).

The investigators studied the mechanism of colistin resistance in *A. baumannii* and found it to be associated with the PmrAB two-component regulatory system and lipid A modification. This is well established (PMID 19528270, PMID 21576434, PMID 21646482).

The investigators did not explore strategies to prevent colistin resistance from emerging in *A. baumannii*. Given the nearly universal presence of heteroresistance (PMID 16940086), emergent resistance is not surprising. Combination therapy should be explored (PMID 22441575).

Aim 4. Employ infectious diseases modeling to leverage the findings from specific aims 1-3 and to understand the morbidity, mortality, and economic impact of the strategies we develop.

The modelling aim was not completed because the principal investigator of this section left the university.

Periodic MRSA surveillance was found to be cost effective using either PCR or culture. This is already known (PMID 23991635).

Preoperative MRSA screening and decolonization were also found to be cost-effective. Again, this is already known (PMID 23991635).

C. difficile screening was found to be cost-effective. The economic burden associated with *C. difficile*-associated disease was high (\$13-16K), in fact somewhat higher than what has been calculated in other studies \$3,791-6,959 (PMID 18197759; PMID 17265392; PMID 17926270; PMID 18643746).

This is an original and potentially important analysis that will have important implications if confirmed.

The cost-effectiveness of *A. baumannii* screening depends on the prevalence.

This is good to document but not particularly surprising.

Aim 5. Establish a research training program for racial minorities that are underrepresented in biomedical and clinical research and health services research.

A Summer Internship Program was established with participation by 12 trainees. Of the trainees, 1 became a research tech, 3 enrolled in master's programs, 1 enrolled in a neuroscience Ph.D. program, 2 are in medical school and 1 is applying to medical school.

This appears to have been a successful URM training program.

Reviewer 2:

Specific Aim 1 (*C. difficile*). *Develop, validate, and employ novel molecular detection of asymptomatic C. difficile carriage and assess an intervention to control this source of C. difficile disease;* [Specific Aim 1 revision requests approved April 30, 2012, to discontinue original sub-aim 4, authorize proteomic and genomic *C. difficile* analyses, study the role of food in infection, and expand a quality assurance project to additional skilled nursing centers.]

Overall, the investigators met stated objectives for this specific aim. Rating is: Outstanding, and this aim, including the findings is a major strength of this grant.

The work from this aim resulted in 5 original research publications, two of which were published in a high impact infectious diseases journal (Clinical infectious diseases), in addition to several oral presentations and conference proceedings. The study objectives were clear, and appropriate to answer the posed research question, and the grant strategic plan. The data obtained were in line with the original research proposal. One modification was submitted and approved. The modification was reasonable, as the project would have been under power for analysis as the

number of CDI was significantly decreasing, and the hospital changed testing methods during the study.

Specific Aim 2. MRSA. Understand characteristics of and risk factors for infection with community-associated MRSA strains that have recently been introduced into the hospital and employ rapid, PCR-based diagnosis of MRSA infection and colonization, to optimize antimicrobial therapy, reduce use of broad spectrum antimicrobials for treatment of S. aureus infections, and reduce transmission of MRSA; [Revision requests approved February 4, 2011, to discontinue Aim 2 as originally stated and authorize related molecular characterization studies on MRSA isolates and whole genome sequencing on heteroresistant vancomycin-intermediate S. aureus (hVISA) isolates. Additional revision request approved April 30, 2012, to expand the project to conduct molecular epidemiologic analysis of MRSA infections in lung transplantation patients]

Overall, the investigators met the stated objectives (including the modifications) for this specific aim. Rating is outstanding, due to the significance and impact of this work at the project sites at time of submission (2009). The findings before the necessary and unexpected modifications (problems with RT-PCR accurately identifying MRSA/MSSA, a patient safety concern) and the new directions taken were commendable.

The work from this aim resulted in 2 original research publications in addition to several oral presentations and conference proceedings. The publications (economic impact of screening hemodialysis and orthopedic surgical candidates contributed to the literature in the area of research). The study objectives were clear, and appropriate to answer the posed research question, and the grant's strategic plan. The data obtained in this study was in line with the original research proposal and accepted modifications. The investigators analyzed data from 863 subjects, which was quite impressive. Two modifications were submitted and approved. The modifications were reasonable and commendable. The findings (discordance of MRSA/MSSA results from RT-PCR) were impressive beyond the appropriate modification to further characterize MRSA predictors.

Specific Aim 3. A. baumannii. Develop a new, multilocus variable number tandem repeat analysis-based molecular subtyping tool for tracking MDR A. baumannii transmission, validate improved methods for detecting MDR A. baumannii colonization, and assess an intervention to control the spread of this organism in intensive care units; [Specific Aim 3 revision and expansion request approved June 6, 2011, to authorize genomic and proteomic analysis of colistin-resistant A. baumannii. An additional revision request was approved April 30, 2012, to expand the project to measure the effectiveness of bleach used in environmental cleaning for A. baumannii-positive.]

Overall, the investigators met the stated objectives (including the modifications) for this specific aim. The rating is outstanding, due to the impressive findings and contributions to the scientific community. Major strengths include the automated MLVA typing protocol of A. baumannii (and additional MDRO molecular identification), in addition to describing the active surveillance program for detecting A. baumannii at Mercy Hospital. This could be considered a best practice and a roadmap for hospitals with similar needs. The data obtained in this study was in line with

the original research proposal and accepted modifications. The modifications were reasonable and necessary (expansion of genomic and proteomic analysis when investigators observed a trend of colistin-resistant isolates. The work from this aim resulted in 6 original research publications in addition to several oral presentations and conference proceedings.

Specific Aim 4. Modeling. Employ infectious diseases modeling to leverage the findings from specific aims 1-3 and to understand the morbidity, mortality, and economic impact of the strategies we develop; and [Specific Aim 4 revision request approved April 30, 2012, to expand the project to determine the value of antibiotic-resistant bacteria surveillance from the perspective of a large health system.]

Overall, the investigators met the stated objectives (including the modifications) were met for this specific aim. This was an important and necessary component of this grant proposal. The publications resultant from this aim were apparent in several original research publications mentioned in aims (1-3 above). The data obtained in this study was in line with the original research proposal and accepted modifications. The modifications were reasonable and necessary. Since this work was important to the work conducted in Aims 1, 2 and 3, I consider this more of a supportive aim, and not a stand-alone aim. The work did meet its stated objectives with few, if any, unanticipated weaknesses; and the project is likely to have some beneficial impact. Therefore, it will receive a rating of outstanding.

Specific Aim 5. Training for minorities. Establish a research-training program for racial minorities that are underrepresented in biomedical, health services, and clinical research.

Overall, this was a necessary and critically important component of this grant. There were some concerns, such as the lower numbers of students enrolled in comparison to the original targeted, and the limited number of minorities. It is very difficult to assess these types of programs, as there are a lot of variables that are out of the investigators control. The students that were placed in labs/studies under qualified investigators seem to be pursuing a career in biomedical and health sciences. The investigators report that: "For the summer 2010 program, 271 students submitted the basic application, and 161 completed their applications with all required documentation. For the summer 2011 program, 299 students submitted basic applications, while 178 completed the full application. In 2012, the final summer of the project, 311 submitted basic applications and a record 242 completed their applications." Recruitment seemed appropriate, as leaders have over 25 years of experience in this area. This should be documented by the investigators as a "lessons learned" and what they feel future similar grants can do to improve these numbers.

This work was a critically important component to this grant. Most of the stated objectives for this aim were met with few, if any, unanticipated weaknesses; and the project is likely to have some beneficial impact. Therefore, it will receive a rating of outstanding.

Reviewer 3:

The five broad aims outlined in this project were all at least favorably met. The results generated from Aims 1, 3, and 5 are particularly notable for their quality and thoroughness:

Aim 1 has provided valuable information regarding many facets of *C. difficile* (CD) colonization and infection: the prevalence and epidemiologic characteristics of CD (route of transmission and acquisition, co-colonization with VRE) at a hospital, prevalence of CD at a skilled nursing facility, an evaluation of environmental CD contamination at said hospital. A thorough genetic study of CD isolates provided valuable information regarding genetic relatedness of CD from asymptomatic, colonized individuals and individuals with hospital-acquired CD infections. The development of a real-time PCR assay for rapid CD identification was a notable addition to the set of tools for combatting CD infection. A surveillance and control program was justifiably cancelled due to low prevalence of CD in the home institution. Replacement sub-aims including (1) an analysis of CD contamination in food products, (2) identification of single nucleotide polymorphisms (SNP) in CD, (3) identification of asymptomatic CD colonization in healthy adults were well-conceived and well-executed, although on samples limited by the late initiation of the projects. This reviewer encourages the investigators to perhaps further expand these three replacement aims, as well as consider initiation of a 4th replacement aim regarding the identification of CD carriers at a skilled nursing facility. Overall, this aim was very successful in meeting its objectives.

Aim 3 was notable for the successful development of a multilocus variable number tandem repeat analysis (MLVA) assay for molecular typing of *A. baumannii*. The publication resulting from the analysis of data from the development of their MLVA3 will place an important cap on this project. The surveillance and control program was also notably successful, as investigators successfully identify best practices for identifying *A. baumannii* infections, and implemented a control program that demonstrably reduced the proportion of positive screens at their institution. An additional sub-aim, initiated later in the grant period, included genomic and proteomic analysis of *A. baumannii*. Promising preliminary results have been developed and this reviewer encourages extension of this study.

The minority training program of Aim 5 was a clear success. Enrollees in the summer research and post-baccalaureate programs clearly benefitted from the exposure, as demonstrated by the described laboratory experience provided, exposure to biomedical research, and outcomes of the program, including poster presentations, publications, and talks given.

Aim 2 did not completely meet the original stated objectives. Sub-Aim 1 was a well-conducted epidemiologic prospective cohort study, the purpose of which was to identify factors predictive of community-acquired MRSA (CA-MRSA) relative to healthcare-associated MRSA (HCA-MRSA). The investigators noted that black race, male gender, HIV/AIDS, higher age, and shorter stay during index hospitalization were positively associated with CA-MRSA. Based on these results, the investigators suggest possible additional factors perhaps surrogated by the factors they identified. A longitudinal component of this study evaluated factors associated with the risk of infection from these colonizations. It was noted that there was no significant difference in the rate of infection between CA- and HCA-MRSA. The investigators are encouraged to continue the process to publication of these results. Sub-Aim 2 was not met due to incongruent real time PCR results in two of the three proposed study groups – those with gram-positive cocci/SA bacteremia and those with gram-positive cocci/SA infections. The cancellation of the study in these groups, although unfortunate, was justifiable and proper. The study of the resulting group – those undergoing nasal swabbing for MRSA – was well-

conducted. The investigators did a good job of integrating a hospital-wide automated pushed MRSA isolation order, and were able to show that use of RT-PCR coupled with the pushed isolation order significantly decreased the time from a nasal swab to a MRSA alert. Publication of this result is forthcoming. In a first replacement sub-aim, the investigators examined the reasons for incongruent RT-PCR results and found mischaracterization of the *mecA* gene. Additional literature on RT-PCR errors precluded the publication of these results. A second sub-aim sought to investigate the genetic mechanism of vancomycin and daptomycin resistance. This study produced only preliminary results; investigators suggest that additional study is needed to further understand the complexity of this resistance.

Aim 4 was implemented as a series of epidemiologic and economic models to evaluate morbidity, mortality, and costs of the three infections study in this program as well as the cost-effectiveness of surveillance and control programs. Five models were created, analyzed, and data published therefrom. A notable characteristic of these models is that several parameters necessary for running model simulations were culled from the research in the other program aims. Other parameters were identified through comprehensive literature searches or stochastically simulated. These studies generally show that screening for infections (MRSA, CD, *A. baumannii*) is a cost-effective strategy. The results of these studies would benefit greatly from some practical context. Most of the studies present the results of sensitivity analyses in which the parameters of the simulations (infection rates, etc.) are varied and the effects of this variation on incremental cost-effectiveness noted. Without context, these results appear academic, (e.g.) when screening for MRSA appears cost-effective up to a certain prevalence, it is helpful to know what prevalence values are plausible in general, in which settings, and the plausibility of prevalence values above the cost-effectiveness threshold. The studies of MRSA and *A. baumannii* appear to be location specific – hemodialysis patients and orthopedic surgery patients for MRSA and ICU patients for *A. baumannii*. Is there any rationale for these settings? The *C. difficile* cost-effectiveness paper is for hospital admissions, which is more in line with the goals of the program at large. Each cost-effectiveness analysis compares a surveillance/control program against doing nothing. Are there other alternatives? In one of the papers, the authors note that decolonization with mupirocin may advance resistance to mupirocin in MRSA. This reviewer agrees and wonders if (1) the impact of such a stimulus could/should be included in the analysis and (2) if other stimuli were not considered as well.

In summary, the program was largely quite successful in meeting its stated goals. Sub-aims that failed or became impractical were generally replaced with strong studies that furthered the agenda of the program. It is strongly encouraged that unpublished results be moved to publication as soon as feasible.

Reviewer 4:

Strengths: The investigators did an outstanding job of carrying out the proposed studies from their original proposal. When difficulties were encountered they adjusted by designing new but relevant studies to replace the original plan. They also provided a clear rationale for their change in plans.

The studies relating to *C. difficile* infections were nicely designed and have achieved meaningful outcomes. The studies will have a direct impact on patient management and our approach to *C. difficile* colonization.

The PCR assay may prove especially useful for the detection of carriers given its improved sensitivity.

The investigation of *C. difficile* contamination of food while interesting would be more relevant if an association with carriers in the community were found.

The investigators successfully enrolled their target populations in the different phases of the study.

An outstanding job was done regarding the training of students and other researchers.

Weaknesses: In general, the MRSA studies were disappointing. They duplicated studies that have for the most part already been published. Much of the data on VISA and hVISA strains is published.

The comment regarding the investigator's failure to contribute to the report for Aim 4 is a limitation. The description of the studies however suggests that the modeling aim was productive.

Reviewer 5:

Aim 1.1 Determine the prevalence of asymptomatic toxigenic C. difficile carriage and environmental contamination among non-isolated patients at an academic tertiary care hospital and at a community long-term care facility.

Aim 1.2 Determine the genetic relatedness of C. difficile isolates from asymptomatic colonized patients with C. difficile isolates from the environment and from CDAD patients.

Results were published in Clin Infect Dis 2013. During 117 days of screening VRE surveillance cultures for *C. diff*, 417 isolates were obtained from 384 pts. 58.9% of pts were detected using screening cultures only. 5 pts with room sites positive for *C. diff* had isolates highly related to screening isolates. The most frequently contaminated room site was the patient call bell. The strength of this study is the identification of carriers identified by screening cultures that could serve as sources of transmission.

Aim 1.1b Prevalence of *C. diff* carriage and environmental contamination at a skilled nursing facility. Manuscript in preparation for ICHE. 78 residents (target 210) were enrolled. Four samplings over one year showed 5.2% to 7.8% rate of colonization. One persistently colonized patient had one positive environmental culture. The investigators conclude that the facility had low rates of colonization. It is not clear how generalizable these findings are, based on geographic and policy variation among long term care facilities. Also, less than half of the residents participated in the study and it could be that the residents who were more capable of personal hygiene were the ones who consented, so there is the potential for bias. While this is

not an optimal sample or study, it does provide some data on C diff in long term care, of which little information exists.

Aim 1.1 add on. Extent of hospital environmental contamination with C diff. Thirteen rooms were sampled and 4 were positive for C diff (30.8%). Environmental isolates matched clinical isolates in 2/4 instances. This is not really novel information and the data were presented at SHEA but not published. It is being used to improve quality of room disinfection (apparently with bleach dilution) at UPMC, although how it is being used it not specific here.

Aim 1.3 Develop/validate RT PCR assay for C diff carriage using peri-rectal swabs. A modified tcdB PCR assay was developed and found to be 100% sensitive and 85.9% specific. This exceeds some currently existing assays and it is not clear why a patent is not applied for. In the validation phase, the investigators found that selective broth amplification increases the sensitivity of the PCR assay significantly. In a small sample of known C diff pts (n=10), sensitivity of the assay was 100% compared to toxigenic culture. These findings are important and suggest there may be a more sensitive rapid assay to detect C diff. This is a major strength of the work.

Aim 1.4 Implement enhanced surveillance/control of C diff using active surveillance. This aim was replaced by Aims 1.4a-4c due to the lower rates of C diff at the hospital and the change in C diff assay. These are very reasonable reasons to change the Aim.

Aim 1.4a Identify prevalence of C diff in the food supply. 102 ground meat products from the Pittsburgh area were sampled; 2 samples were positive for toxigenic C diff. A particular brand was selected for focused sampling and 10% to 67% of 34 samples were positive. A link with clinical isolates was not found. This work was published in Applied Environmental Microbiology 2012. There have been previous studies looking at C diff in retail meat and these results were confirmatory.

Aim 1.4b Genomic studies to identify discriminatory SNPs in ribotype 027 C diff isolates. SNP typing correlated well with a current standard, MLV typing and in some cases SNP was more discriminatory. These findings may be helpful in future studies of C diff that require molecular typing.

Aim 1.4c Identification of asymptomatic C diff colonization in healthy adults. 6.6% of the 106 subject samples were colonized and this is confirmatory of previous studies.

Aim 1.4d Identify and isolate C diff carriers at 2 Kane Regional (long term care) centers. This study was not initiated due to lack of personnel and time. There is not an explanation of the shortfall here, and a better explanation may be that the colonization rate was low in the Center studied and this study may have not been fruitful.

Aim 2.1 Incidence and risk factors of MRSA in patients colonized with HA MRSA and CA MRSA in the hospital. Colonization with USA300 CA MRSA was associated with black race, male gender, HIV/AIDS, younger age, and shorter LOS. There was not a higher rate of infection compared to HA MRSA. With the exception of the association with shorter LOS, similar risk

factors have been found in other studies at least in the community setting. The study suggests the importance of preventing colonization with CA and HA MRSA

Aim 2.2 Evaluate RT PCR for MRSA to decrease time for initiation of appropriate isolation precautions. The investigators found a number of test results incongruent between RT PCR and clinical cultures and use of the assay was discontinued. The use of an automated MRSA Push Order decreased mean time to MRSA alert/precautions by 25 hours. The finding of incongruence in the commercial assay was important and the use appropriately discontinued. The automated Push Order may be useful to other institutions in improving timeliness of Contact Precautions. This is a strength of the work.

Aim 2.2a Lack of the *mecA* gene in several MRSA strains and presence of *mecA* gene in an MSSA strain were found to be an explanation of the incongruent RT PCR results. Other groups have published similar findings and the investigators will not pursue publication of this work.

Aim 2.2b Mechanism of heteroresistance in hVISA isolates. Fifteen strains from 4 patients with persistent MRSA bacteremia were selected for analysis. 5 strains were found to be hVISA and these also had reduced susceptibility to daptomycin. Genotypic and phenotypic studies showed that cell wall changes, previously the explanation for reduced vanco susceptibility, did not account for hVISA expression. Rather, there were genetic changes suggesting complex regulatory changes. These findings will be useful for further studies of new mechanisms of resistance in hVISA. This is a major strength of the work.

Aim 3.1 Develop and validate a MLVA assay for typing *Acinetobacter baumannii*. 54 MDR A. *baumannii* were collected and molecular epidemiology described (JCM 2011). MLVA3 was developed and can be performed as a single multiplex PCR reaction. It is not clear why no patent was applied for.

Aim 3.2 Active surveillance for MDR A. *baumannii* and effectiveness. The most sensitive sampling method was upper arm and thigh with sponge (JCM 2011). Interventions included automatic isolation precautions order, chlorhexidine baths, terminal cleaning with bleach. Published in ICHE 2012.

Aim 3 additional. Genomic and proteomic analysis colistin-R A. *baumannii*. Three sets of colistin-S and colistin-R strains were analyzed. Addition of a phosphoethanolamine moiety to lipAA and mutations in *pmrCAB* appears to account for some resistance changes. Published in AAC 2013.

Aim 4.1-3 Mortality, morbidity, economic burden simulation of C diff, MRSA, MDR A. *baumannii*. MRSA surveillance judged to be cost-effective. This may be a moot point now that a multicenter RCT shows universal chlorhexidine baths and mupirocin decolonization to be superior for control of MRSA in the ICU compared to active surveillance screening. Preoperative screening and decolonization of MRSA may be cost-effective in orthopedic surgery patients. C diff screening with isolation precautions may be cost effective (depending on prevalence). C diff is costly to the healthcare system and society. A. *baumannii* screening of ICU pts may be cost-effective. Six publications resulted from these studies. The PI for this study has left for another institution and at this point is no longer communicating. While some of these

findings have been shown previously and appear evident, the economic models may be useful in convincing administrators of investment in control programs.

Aim 5. Minority training program. Thirteen URM students completed a summer training program with a resulting research project/presentation. 11/12 URM students completed a post-bacc program and those completing the program had a research project/presentation. This is a considerable strength of the work, due to the glaring need in our field.

Reviewer 6:

This 4-year (6/1/2009 – 5/31/ 2013) research project entitled “Center of Excellence in Prevention and Control of Antibiotic Resistant Bacterial Infections” was led by Lee H. Harrison, M.D., and received a total of \$4,724,321 from the Pennsylvania Department of Health. The primary goal of the Center of Excellence in Prevention and Control of Antibiotic-Resistant Bacterial Infections is to employ novel strategies to reduce the morbidity and mortality caused by 3 bacterial pathogens that have recently emerged as major threats to vulnerable patients in the health care setting: *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), and multidrug-resistant (MDR) *Acinetobacter baumannii*. In summary, the project that was performed mostly met the stated objectives. The data were developed sufficiently to answer the majority of the research questions posed. The data developed were in line with the original research protocol except for several planned and unplanned changes. For the changes made to the research protocol, there were good and reasonable explanations given. The extent of laboratory and clinical activities initiated and completed and the number of subjects are relative to the target goal. In general, the data and publications provided were applicable to the project objectives listed in the strategic plan.

Regarding each specific aim:

Specific Aim #1 was to *develop, validate, and employ novel molecular detection methods of asymptomatic C. difficile carriage and assess an intervention to control this source of C. difficile disease*. The investigators were very productive and met their performance measures. The data below pertain to both sub-Aims 1 and 2 which are interdependent aims both conducted in the same prospective study from July – November 2009 and published in Clinical Infectious Diseases (Curry SR et al. *Clin Infect Dis*. 2013;57:1094-102). In addition, they have submitted a few grants to NIH and NSF. Collaborations with Kane Regional Centers went well. The development of a home-brew kit was not successful.

Specific Aim #2: *Understand characteristics of and risk factors for infection with community-associated MRSA strains that have recently been introduced into the hospital and employ rapid, PCR-based diagnosis of MRSA infection and colonization, to optimize antimicrobial therapy, reduce use of broad spectrum antimicrobials for treatment of S. aureus infections, and reduce transmission of MRSA*. The investigators met many of the performance measures. Validation of the BD GeneOhm assay was not cost-effective.

Specific Aim #3: *Develop a new, multilocus variable number tandem repeat analysis-based molecular subtyping tool for tracking MDR A. baumannii transmission, validate improved methods for detecting MDR A. baumannii colonization, and assess an intervention to control the*

spread of this organism in intensive care units. The investigators met major performance measures.

Specific Aim #4: *Employ infectious diseases modeling to leverage the findings from specific Aims 1-3 and to understand the morbidity, mortality, and economic impact of the strategies develop.* The investigators met several performance measures and several publications were produced. Completion of this section of the report has been complicated by the fact that the PI for this specific aim left the University of Pittsburgh shortly after the end of the funding period. He has not provided input into this report since leaving the university. The clinical relevance of this modeling was hard to determine.

Specific Aim #5. *Establish a research training program for racial minorities that are underrepresented in biomedical and clinical research and health services research.* The investigators met some of their performance measures. A total of twelve trainee spots have been filled. The minority training portion of the project, a seven-week summer research training program and a post-baccalaureate program, were both designed to expose underrepresented and disadvantaged students to biomedical research in infectious diseases, specifically, MRSA, *C. difficile*, and *A. baumannii*. It was highly successful in not only attracting talented trainees, but also in advancing their careers.

Reviewer 7:

The primary goal of the research project was to reduce the morbidity and mortality caused by bacterial pathogens in the healthcare setting: *Clostridium difficile*, MRSA, and multi drug-resistant *Acinetobacter baumannii*. These are very important pathogens and the project was an ambitious one; however, the stated objectives were met and exceeded. For the *C. difficile* project the prevalence of asymptomatic *C. difficile* carriage and environmental contamination were determined; the genetic relatedness of different *C. difficile* isolates were determined; a real time PCR assay for rapid identification of *C. difficile* carriage was developed; the original sub-aim was replaced with sub-Aims 4a-4c. Studies on the contamination of food by *C. difficile*, identification of single nucleotide polymorphisms in ribotype 27 strains, and identification of asymptomatic carriage of *C. difficile* were carried out. In specific Aim 2 risk studies of colonization with healthcare-associated and community-associated MRSA were carried out. Replacement sub-Aim 2b focused on vancomycin-intermediate and decreased daptomycin susceptibility strains. In specific Aim 3 a multilocus variable number tandem repeat analysis was developed for molecular typing of *A. baumannii* in sub-aim1. In sub-Aim 2 a surveillance program for MDR *A. baumannii* colonized patients was implemented. Specific Aim4 involved infectious disease modelling of specific Aims 1-3. Specific Aim 5 was to establish a training program for underrepresented minorities in biomedical, clinical, and health services research.

Overall, large amounts of data were developed sufficient to answer the questions posed. Appropriate justifications were provided when alternate aims were substituted for aims in the original proposal where the original aim became non-viable.

Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the original proposal and the dollars budgeted?

STRENGTHS AND WEAKNESSES

Reviewer 1:

This project has focused on three important bacterial pathogens. The principal benefits of the project are the creation of a method for molecular subtyping of *Acinetobacter baumannii*, the institution of a successful infection control program for *A. baumannii*, the analysis of nosocomial *C. difficile* transmission from asymptomatic carriers, the demonstration that *C. difficile* screening can be cost-effective, and the provision of a training experience for underrepresented minorities. These are solid accomplishments, but not transformative ones. I assess the beneficial impact to be relatively modest in consideration of the number of dollars awarded. The impact of the project could have been greater if the aims and methods had been more innovative; many of the results were simply corroborative of other published work, and some of the studies were insufficiently powered to be conclusive. Nevertheless, the work has been well done and makes a solid contribution to the literature.

Reviewer 2:

Overall, the significance and justification of this work has been reviewed in detail during the peer review process of the original application and again at the interim report. I agree with these findings. Regarding the major discoveries, and future plans for this research, my comments are as follows.

Aims 1 and 2 are major strengths of this grant, as they provide strong molecular and economical considerations regarding the active surveillance and infection control of patients infected or asymptomatically colonized with *C. difficile*, and *A. baumannii*. Rapid detection and initiation of isolation may result in reductions in incidence of disease and death. This is extremely important information for the scientific community interested in infection control and prevention. This research will serve as the foundation work for future research. Specific Aim 2 evaluated molecular epidemiology and predictors for MRSA colonization and infection. This work is also important, but during the 4-year funding period similar research has been conducted and published by other researchers around the country/globe. This may not have been preventable, nor is this the fault of poor planning or research by these investigators. Their findings are still an important contribution to science. Aim 4 (economic considerations) could be a major strength for sites/centers that have similar patient populations, and similar health care structure and resources. Aim 5 (training minorities) seems to have significantly impacted the lives of a number of students who appear to be headed for careers in biomedical and health sciences.

Reviewer 3:

Aim 1 has provided a more thorough understanding of the epidemiology of *C. difficile*, including prevalence in a hospital setting, a skilled nursing facility, and among asymptomatic adults, information on the route of acquisition and transmission, co-incidence with VRE, and molecular typing. Environmental and food contamination rates were established and preliminary

information on characteristic SNPs were identified. A notable new diagnostic tool, the real-time PCR for *C. difficile*, was developed.

Aim 2 identified correlates of CA-MRSA colonization (relative to HCA-MRSA) and determined that the risk of infection secondary to colonization did not significantly differ between CA- and HCA-MRSA. The combination of RT-PCR with automated pushed isolation orders for MRSA was found to substantially decrease the time between nasal swab and isolation orders, which may have a large impact on hospital transmission of MRSA.

A molecular typing method for *A. baumannii* (MLVA3) in Aim 3 was developed and shown to be superior to current technology for typing *A. baumannii*. A pilot surveillance and control program targeting *A. baumannii* was successful in reducing the proportion of positive screens and can serve as a model for other facilities.

Financial costs associated with the three pathogens were explored in Aim 4, as well as potential best practices for monitoring and control of infections in several settings.

The minority training program directly impacted 24 undergraduate and pre-doc students, and, if continued in any capacity, will be a positive influence in steering talented minority students toward careers in biomedical science.

Reviewer 4:

Strengths: The studies on *C. difficile* will have an impact on our approach to carriers of the organism and environmental cleaning. This will be of use in the health care setting. The studies illustrate the importance of asymptomatic carriage in this setting.

The studies on acinetobacter are important contributions to the field. Despite their increasing importance, integration of epidemiologic data with whole genome sequencing to date has been limited. Using isolates from geographically dispersed hospitals, the investigators determined that MLVA is sufficiently discriminatory to serve as a useful tool for hospital epidemiologic studies.

Surveillance for acinetobacter was carried out and was associated with a reduction in the number of positives. Given the low numbers it is unclear whether the screening is necessary and whether the additional interventions described in the report were primarily responsible for the reduction in colonization.

Although the data on WGS is still preliminary, it should provide useful data regarding the pathogenetic and antimicrobial resistant determinants of these strains.

Weaknesses: Overall the MRSA aims were limited in their overall contribution to the field. The study of CO- vs. HCA-MRSA confirmed earlier findings and added a limited amount of new information.

Reviewer 5:

The incongruence of the MRSA RT PCR and culture results in the commercial assay is significant. While reported by others recently, the findings by this group suggest it may be more common than expected. This is useful information for institutions using the assay for active surveillance screening.

The finding of hVISA isolates with perhaps a new mechanism of reduced susceptibility to vancomycin and daptomycin is important and may lead to advances in drug discovery once the mechanism is more fully elucidated. This aspect is a major strength of the work

The MRSA Push Order is a clinical decision support tool that may assist other hospitals in expediting appropriate contact precautions for MRSA.

SNP and whole genome sequencing may be more useful tools for typing of C diff than current standards. This can be useful in outbreak investigations.

The MLVA assay for *A. baumannii* typing can be useful for preventing transmission in institutions with *A. baumannii* outbreaks.

The investigators plan further work on the hVISA/MRSA project and additional work on C diff, MRSA, *A. baumannii*.

Reviewer 6:

A stable infrastructure has been established with direct outcomes of 12 publications and 24 trainees. The strategies raised and proved in the studies need to be extended to reach more broad, long-term benefits.

No new drugs or devices were developed through the project. As more and more diagnostic companies are becoming involved in developing and producing rapid and accurate detection devices, it was smart for the investigators to decide not to develop “home-brew” molecular assays to detect several nosocomial pathogens. However, it was not cost-effective to spend time and efforts to develop home-brew C diff kit and to validate the BD GeneOhm assay and apply it for invention studies (it is still a long turnaround time). In contrast, the investigators should have spent efforts to seek and develop new assays for assessing infections. One example is the functional and quantitative assay for *C. difficile* toxins.

Reviewer 7:

The project has resulted in a significant increase in knowledge. There have been many presentations at multiple conferences. Thirteen peer reviewed publications in prestigious journals are listed. This knowledge is being applied in improved methods of prevention, diagnosis and treatment of *C. difficile*, MRSA, and MDR *A. baumannii*. It is likely that further publications will emanate from this research and research initiated under this award.

Criterion 3 - Did the project leverage additional funds or were additional project applications submitted?

STRENGTHS AND WEAKNESSES

Reviewer 1:

To date the investigators report only \$99,355 from other sources. Other grants were not funded or the review is pending, although an *Acinetobacter* grant by Doi received a score in the 11th percentile (just missing the funding payline).

Reviewer 2:

Page 6 of the final report describes the six submitted federal grant proposals that have been packaged, submitted and funded during this 5-year period. While it is difficult to assess the full sustainability of this project from only a 4-year review, the progress made towards sustainability of the research from specific Aim 1 and 3 is most promising.

Specific Aim 1 (*C. difficile*). Three different federal grants (NIH-K08, NSF and NIH-R01) have been submitted from this aim. None have been funded to date, but they are under various stages of review and are noted to be under review or resubmission.

Specific Aim 2 (MRSA). One grant was funded from AHRQ for \$99,355. This was submitted in October 2011. No other grants have been submitted/funded for the MRSA work.

Specific Aim 3 (*A. baumannii*). Two federal grants have been submitted from this aim. One (NIH) is in the 11th percentile and the status is pending, the other is an R01 that was submitted in October of 2013, the outcome should be known at this point and this should be updated in the final report.

Specific Aim 4 (economic modeling). No grant submissions.

Specific Aim 5 (minority training). While no grants have been submitted to further this program, the students that received training look to have promising careers in science and medicine.

Reviewer 3:

Affiliated investigators have applied for over \$6.6M worth of funding through the NIH, AHRQ, NSF, and other sources. An AHRQ grant of \$100,000 was funded, and NIH grant of \$1.8M received a fundable score, and two grants totaling \$3.9M are currently in review. These applications appear to extend the research conducted in the current project, and include projects investigating optimal detection of MRSA carriage, colistin resistance in *A. baumannii*, and further studies on asymptomatic carriage, transmission, and the control and prevention of *C. difficile* infections. The researchers have also indicated that additional applications for funding are being developed.

Reviewer 4:

Some additional funding relevant to the CURE grant has been obtained. Additional proposals have been submitted or are currently being planned or resubmitted. Although not specified as to the nature of future applications, the investigators state that future applications are planned.

Reviewer 5:

Five grants, including 1 NIH grant, were submitted as a result of this work. One AHRQ grant has been funded.

The researchers do plan to apply for additional grants. It would be helpful to describe what specific avenues will be explored with regards to grants that will study these resistant organisms.

Reviewer 6:

The investigators have successfully used the data generated from this project to file several research grants applications from major grant agents including NIH, NSF and AHRQ. One of the applications has been funded by AHRQ. One NIH application has reached a fundable score (11%). The researchers are planning to apply for additional funding in the future to continue/expand the research.

Reviewer 7:

Several major grant proposals to the National Institutes of Health were developed from work under this proposal. At the time of submission of the report no award had been received although one proposal was scored in the eleventh percentile. One minor award of \$99,000 was received.

Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents or commercial development opportunities? Were any of these submitted/filed?

STRENGTHS AND WEAKNESSES

Reviewer 1:

The project supported 13 original research articles in Clinical Infectious Diseases, Journal of Clinical Microbiology, European Journal of Clinical Microbiology and Infectious Diseases, Applied and Environmental Microbiology, Clinical Microbiology and Infection, Infection Control and Hospital Epidemiology, and Antimicrobial Agents and Chemotherapy. This is reasonable productivity but not impressive for a budget of nearly \$5 million.

Reviewer 2:

Specific Aim 1 (*C. difficile*). The work from this aim resulted in 5 original research publications, two of which were published in a high impact infectious diseases journal (Clinical Infectious Diseases), in addition to several oral presentations and conference proceedings. No patents were identified.

Specific Aim 2. (MRSA). The work from this aim resulted in 2 original research publications in addition to several oral presentations and conference proceedings. No patents were identified.

Specific Aim 3. (*A. baumannii*). The work from this aim resulted in 6 original research publications in addition to several oral presentations and conference proceedings. No patents were identified.

Specific Aim 4. (Economic Modeling) The publications resultant from this aim were apparent in several original research publications mentioned in aims (1-3 above). The data obtained in this study was in line with the original research proposal and accepted modifications. The modifications were reasonable and necessary. No patents were identified.

Specific Aim 5. (Training for minorities) Not applicable.

Reviewer 3:

Currently, thirteen peer-reviewed publications have resulted from the research, the most notable of which include reports MLVA genotyping in asymptomatic *C. difficile* carriers, surveillance of *C. difficile* via rectal swab and real-time PCR, sponge-screening for *A. baumannii*, the molecular epidemiology of carbapenem-non-sensitive *A. baumannii*, and vancomycin against colistin-resistant *A. baumannii*. The six publications from the economic modeling projects, although notable, are weaker. None of the clinical/epidemiologic studies of MRSA were published. Several papers are forthcoming according to the investigators, and publication of these results will substantially improve the volume of literature arising from this project. Publication of results from the MRSA studies should be a focus of the investigators, as this is a notable hole in production.

Reviewer 4:

There were an appropriate number of publications in respected journals. Additional manuscripts are either planned or have been submitted. No patent applications resulted from this proposal.

Reviewer 5:

There are 13 peer-reviewed publications from this work, most in respected journals in our field, and they are quality publications. They plan to submit further work on hVISA. No patents were applied for.

Reviewer 6:

While no licenses, patents or commercial developments were produced, the investigators did produce 13 peer-reviewed publications. Several manuscripts are being prepared. I suggest that several review articles be prepared and published to “advertise” the findings of the project. Most of the strategic studies included important findings and are useful in future practice.

Reviewer 7:

Thirteen peer-reviewed publications resulted from this work with more submissions likely. The publications were of high quality as judged by the impact factors and perceived prestige of the journals in which they were published.

Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?

STRENGTHS AND WEAKNESSES

Reviewer 1:

The project enhanced the quality and capacity for research at the grantee's institution to some extent. The investigators' findings were used to inform infection control practices for *C. difficile* and *A. baumannii* at their institution(s), and the molecular subtyping method can be used for subsequent studies. In addition, the summer internship provided training experiences for underrepresented minorities, several of whom are now pursuing graduate or medical training.

Reviewer 2:

Overall, the University of Pittsburgh had a strong existing research program. No improvements were expected to be made, beyond the approximately \$205,000 of equipment (freezer, centrifuge, and RT-PCR and molecular biology equipment) which has been purchased to perform the studies proposed. This study funded (full or in part) 57 persons including students/trainees (n=26), research IV/research assistants assistant professors, associate professors, professors, bioinformatics specialists, administrators, research coordinators, program directors.

Reviewer 3:

The capacity for research was greatly improved by the project. All of the equipment purchased with grant funds, and in particular the tools for genetic and proteomic analysis and the real-time PCR system, will be key components of future research into *C. difficile*, MRSA, and *A. baumannii* colonization and infection. Funds from this grant fed the minority training program introduced or further exposed 24 undergraduates and 24 pre-doc students of minority status to biomedical science.

Reviewer 4:

Funds were used to support trainees, students and research associates and faculty. No out-of-state investigators were recruited during the study. Equipment that will improve the overall infrastructure for this type of research was obtained.

Reviewer 5:

The laboratory infrastructure was improved by acquiring the equipment listed. New collaborations with investigators were established, and with other institutions, including the relationship with the long term care center.

Reviewer 6:

The investigators set up a center of excellence as a great infrastructure for the development and validation of methodology and strategy for prevention and intervention of diseases and outbreaks caused by these antibiotic resistant bacteria. The quality and capacity for research of infectious disease (internal medicine) and clinical microbiology sections have been significantly enhanced in the areas of bacterial genomics, proteomics, and infectious disease modeling. The purchase of equipment increased laboratory infrastructure. A significant improvement in practice in Kane

Glen Hazel was noted. The project has created the University of Pittsburgh Intramural Research Training Award (UPIRTA) program and recruited and trained 12 post baccalaureate minority trainees.

Reviewer 7:

The project made major contributions to the research infrastructure of the institutions represented. Multiple personnel were involved and compensated at least in part from the project. New investigators were brought along. New research areas were developed in omics approaches. New equipment was purchased to improve the infrastructure.

Criterion 6 - Did the project lead to collaboration with research partners outside of the institution, or new involvement with the community?

STRENGTHS AND WEAKNESSES

Reviewer 1:

One of the publications (PMID 21918019) involved a multicenter collaboration studying the molecular epidemiology of carbapenem-nonsusceptible *A. baumannii* in the U.S., and another (PMID 23422916) involved collaborators at the University of Maryland. A *C. difficile* colonization study was performed at Allegheny County skilled nursing facility. Otherwise, the contributors to publications were within the institution.

Reviewer 2:

The research has resulted in collaborations between local and state level health care professionals, in addition to academic and non-academic institutions. This includes Carnegie Mellon as well as a variety of health care minority groups. In addition, collaboration with Kane Regional Centers (residential and skilled nursing facilities throughout Allegheny County) that have not previously been involved in research (from what is ascertained in this report) is an additional strength. Research training/outreach of students from local Pennsylvania universities (University of Pittsburgh, Cheyney University, Lehigh University, and Lincoln University) in addition to students from Tuskegee and Florida Atlantic Universities is a strength. It is unclear if these students were Pennsylvania natives.

Reviewer 3:

The collaboration with John J. Kane Regional Center- Glen Hazel, Division of Nursing Care Facilities in Allegheny County was notable. This collaboration resulted in the successful fulfillment of a study sub-aim – estimation of cross-sectional *C. difficile* prevalence at a skilled nursing facility and the identification of asymptomatic carriers. An identification and isolation program for *C. difficile* carriers went unimplemented due to lack of time and personnel. A continued collaboration with this facility would be a fruitful relationship.

Reviewer 4:

A collaboration with a skilled nursing facility occurred.

Reviewer 5:

New involvement with the community included collaboration with the long-term care facilities.

Clinical research involved UPMC and Kane long term care facility. Approximately 10 hospital/health care professionals were involved.

Reviewer 6:

The project has been focused on researched within the University and community hospitals and clinics. John J. Kane Regional Center- Glen Hazel, Division of Nursing Care Facilities in Allegheny County, was collaborated for (1) *Specific Aim 1: Control of C. difficile* through identification of asymptomatic carriers and (2) *Sub-Aim 1b: Determining cross-sectional prevalence of asymptomatic colonization*. The number of hospitals and health care professionals involved and the extent of penetration of the studies throughout the region or the commonwealth, however, was limited. The investigators should extend the scopes and levels of their training project not limiting in post baccalaureate minority trainees.

Reviewer 7:

Researchers at nursing care facilities were involved in the studies.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

1. Future proposals should provide specific justification for the novel aspects of each aim that will advance the field.
2. Unsuccessful aims should be sufficiently investigated to provide an explanation for the lack of success.

Reviewer 2:

None.

Reviewer 3:

Continue to seek publication of any unpublished results, particularly for the MRSA studies which are currently represented only by the economic analyses in the literature.

Reviewer 4:

1. Overall the studies outlined in the MRSA section were limited in scope and in their novelty.
2. Further studies characterizing the utility of screening for acinetobacter would be useful.

Reviewer 5:

1. One sub-aim was not initiated due to lack of time and personnel. However, this was likely to be a low yield study due to the low prevalence of *C. difficile* in the long-term care facility. As the investigators have no doubt concluded, *C. difficile* studies, at least in this particular facility's long term population are not likely to be fruitful. It is not clear how generalizable

this is, however. It may be useful to look at other centers and also to look at antibiotic use patterns to correlate with *C. difficile* prevalence.

2. Several original aims were changed or substituted and there was good rationale for this. With regard to the *C. difficile* studies, there is a lot of work now regarding changes in the colonic microbiome that may be very important with regard to preventing *C. difficile* colonization and/or disease. While looking at detection of carriers and prevention of transmission is important, ultimately the most successful interventions may include manipulation of the microbiome. The investigators may want to consider working in this area, especially since there is expertise in anaerobic cultures.
3. It appears there may be 2 opportunities for patents (RT PCR for *C. difficile* carriage, MDR *A. baumannii* screen) and this could potentially provide funding for future studies.
4. The work appears to be centered at UPMC except for the Kane long-term care study. Could larger sample sizes and more generalizable results be found by including other area hospitals?
5. Regarding the minority training program, the summer program and post-baccalaureate program are admirable. Can longer term experiences, leading to grants and potential faculty positions be incorporated?

Reviewer 6:

1. Extend the training opportunities by not limiting to post baccalaureate minority trainees.
2. Enhance collaborations to more tertiary medical centers and community medical centers.
3. Spend efforts to explore the clinical applications of the modeling results.

Reviewer 7:

None.

Generic Recommendations for the University of Pittsburgh

Reviewer 6:

Enhance exposure of the Center to all departments of the institutes and support the investigators to collaborate with other institutes inside and outside of the U.S. to extend these findings.

ADDITIONAL COMMENTS

Reviewer 1:

Although some of the stated objectives were met, and some components of the project are likely to have a beneficial impact, enthusiasm for this project is tempered by the fact that too many of the objectives were simply confirmatory of other published work. Moreover, discordant results from an MRSA RT-PCR assay that prevented one aim from being accomplished represent a missed opportunity, as this problem was not sufficiently investigated to determine the cause of

the discordance. The *C. difficile* intervention and modelling aims were not completed, and other aims were not addressed conclusively due to underpowered studies.

Reviewer 2:

Conclusions: Throughout the project, all major strengths were identified with few, if any, weaknesses; all projects met all or most of the stated objectives; and all of the projects are likely to have some beneficial impact.

I did not identify any weaknesses that require improvements.

Reviewer 4:

- For the most part the investigators carried out the studies that were outlined in the proposal.
- Most aims resulted in publications in respected journals in a timely manner.
- An outstanding job was done with the recruitment of under-represented minorities and their training.
- The investigators integrated new technologies into their studies, defining the advantages and disadvantages of these approaches.

Reviewer 6:

- A strong and solid center was established.
- Trainees were limited to post-baccalaureate minority trainees.
- Outside collaborations were limited.