CURRICULUM VITAE

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Education

2014 – 2018	University of Maryland School of Medicine, Baltimore Graduate Program in Life Sciences Department of Epidemiology and Public Health Doctor of Philosophy
2007 – 2008	The George Washington University Milken Institute of Public Health Department of Epidemiology and Biostatistics Master of Public Health
1997 – 2001	Grinnell College Bachelor of Arts Political Science with a concentration in Russian and Eastern European Studies

Employment History

University of Maryland School of Medicine, Baltimore, MD
September 2014 to May 2018
Graduate Research Assistant

- Provided analytical support, including data analysis, to Dr. Wilbur Chen on cholera vaccine studies.
- Designed and developed database for the clinical research staff at the Center for Vaccine Development.
- Managed day-to-day operations of study looking at patient transmission of VRE. Responsibilities included, study logistics (ordering supplies, screening daily patient lists), collecting patient and healthcare worker samples, creation and review of data collection forms, data entry and cleaning.
- Provide analytical support to Dr. Anthony Harris for an AHRQ grant on risk adjustment of healthcare outcomes. Perform literature review, clean and validate data sets, perform

statistical analysis, write manuscripts, write statistical section for grants, and present work at conferences.

- Provide analytical support to Dr. Kerri Thom on NIH grants. Performed data analysis for study on healthcare worker hand hygiene, which was presented at the 2017 Society for Healthcare Epidemiology of America Annual Meeting. Ongoing data analysis for a study of *Acinetobacter baumannii* transmission in the ICU.
- Provide analytical support, including data analysis, to Dr. Mary-Claire Roghmann for her CDC grant. Created a clinical prediction rule for MRSA transmission in nursing home facilities.
- Dissertation Topic: Risk factors for transmission of multidrug-resistant organisms and acquisition of healthcare-associated infections

Social & Scientific Systems, Inc., Silver Spring, MD
January 2013 to August 2014
Health Research Analyst

- Support the Performance Evaluation Program of the AIDS Clinical Trials Group (ACTG).
- Developed data visuals and report tables to analyze of site and laboratory performance evaluation data using SAS, R and Excel.
- Designed, developed, and maintained the ACTG performance evaluation data management systems.
- Designed, developed, and maintained special website projects using Drupal for the ACTG Leadership Group.

The EMMES Corporation, Rockville, MD
February 2009 to January 2013
Data Manager/Protocol Monitor

- Responsible for the preparation of draft protocol, informed consent and Manual of Procedures.
- Coordinated with project team to determine data collection requirements based on the protocol, and to develop, test and modify software programs for electronic data capture.
- Created and implemented data validation processes for multiple methods of data collection using SAS.
- Responsible for the coordination and submission of regulatory reports, which included coordinating with colleagues create tables and figures, reviewing data tables for quality assurance, and writing the text of the reports.
- Served as a mentor to new staff.
- Served as an alternate on the EMMES IRB.

DC Department of Health, Bureau of Surveillance and Epidemiology, Washington, DC
July 2008 to February 2009
Research Assistant

- Assisted with development of a database for viral hepatitis surveillance (VHS).
- Responsible for data management, including data cleaning, de-duplication and entering lab reports.
- Trained staff members on VHS database and provided ongoing support.

The George Washington University, National HIV Behavioral Surveillance System, Washington, DC
January 2007 to December 2008
Research Assistant

- Conducted 30-60 minute interviews with research participants about HIV, sexual behavior and drug use.
- Administered OraQuick Rapid HIV test and conducted pre- and post-test HIV counseling with research participants.
- Assisted with new staff training on how to conduct the rapid oral HIV test and interviewer methods.

Publications

(Refereed Journals)

Harris AD, Sbarra AN, Leekha S, **Jackson SS**, Johnson JK, Pineles L, Thom KA. Electronically Available Comorbid Conditions for Risk Prediction of Healthcare-Associated Clostridium difficile Infection. Infect Control Hosp Epidemiol. 2018 Feb 5:1-5 [Epub ahead of print]

Sbarra AN, Harris AD, Johnson JK, Madger LS, O'Hara LM, **Jackson SS**, Thom KA. Guidance on Frequency and Location of Environmental Sampling for Acinetobacter baumannii. Infect Control Hosp Epidemiol. 2018 Jan 30:1-4 [Epub ahead of print]

Jackson SS, Leekha S, Magder L. et al. The effect of adding comorbidities to current Centers for Disease Control and Prevention central-line-associated bloodstream infection Risk-Adjustment Methodology. Infect Control Hosp Epidemiol. 2017; 38(9):1019-1024.

O'Hara LM, Masnick M, Leekha S, **Jackson SS**, et al. Indirect versus direct standardization methods for reporting healthcare-associated infections: An analysis of central line-associated bloodstream infections in Maryland. Infect Control Hosp Epidemiol. 2017;38(8):989-992.

Jackson SS, Leekha S, Magder L. et al. Electronically available comorbidities should be used in surgical site infection risk adjustment. Clin Infect Dis. 2017;65(5):803-810.

Thom KA, Rock C, **Jackson SS**, et al. Factors Leading to Transmission Risk of Acinetobacter baumannii. Crit Care Med. 2017; 45(7):e633-e639.

Jackson SS, Leekha S, Pineles L, Magder LS, Thom KA, Wang Y, Harris AD. Improving risk adjustment above current Centers for Disease Control and Prevention methodology using electronically available comorbid conditions. *Infect Control Hosp Epidemiol.* 2016 Oct;37(10):1173-8.

Jackson, SS, St. George DM, Loffredo CA, Amr S. Non-occupational exposure to agricultural work and risk of urinary bladder cancer among Egyptian women, *Archives of Environmental & Occupational Health*. Mar 30:1-7

Harris AD, **Jackson SS**, Robinson G, Pineles L, Leekha S, Thom KA, Wang Y, Doll M, Pettigrew MM, Johnson JK. Pseudomonas aeruginosa colonization in the intensive care unit: prevalence, risk factors, and clinical outcomes. *Infect Control Hosp Epidemiol*. 2016 Feb 1:1-5.

Jackson SS, Chen WH. Evidence for CVD 103-HgR as an effective single-dose oral cholera vaccine. *Future Microbiol*. 2015;10(8):1271-81

Nover, CH and **Jackson, SS**. Primary care-based educational interventions to decrease risk factors for metabolic syndrome for adults with serious mental illness: a systematic review. *Systematic Reviews*. 2013, 2:116.

(Oral Presentations)

Jackson SS, Leekha S, Magder LS, et al. Electronically available comorbidities should be used to improve current CDC SSI risk adjustment. Presented at Society for Healthcare Epidemiology of America Annual Meeting March 31, 2017 in the **Best Oral Abstract Session**

Jackson SS, Leekha S, Magder LS, et al. The effect of adding comorbidities to current CDC CLABSI risk adjustment methodology. Presented at Society for Healthcare Epidemiology of America Annual Meeting March 31, 2017 in the **Best Oral Abstract Session**

(Poster Presentations)

Jackson SS, Harris AD, Magder L et al. Bacterial burden and risk factors for transmission of vancomycin-resistant Enterococcus to healthcare workers. Presented at Society for Healthcare Epidemiology of America Annual Meeting April 20, 2018. **Top Poster Abstract Award**

Jackson SS, Leekha S, Magder L. et al. Electronically Available Comorbid Conditions Should Be Used to Improve Current CDC Surgical Site Infection Risk Adjustment Methodology. Presented at Academy Health Annual Meeting in New Orleans, LA June 26, 2017. **Featured on Poster Walk**

Jackson SS, Leekha S, Magder L. et al. The Effect of Adding Comorbidities to Current CDC Central Line-Associated Bloodstream Infection Risk Adjustment Methodology. Presented at Academy Health Annual Meeting in New Orleans, LA June 26, 2017

Jackson SS, Harris AD, Magder L. Validation methods to adjust for optimism in a risk prediction model. Presented at Society for Epidemiologic Research Annual Meeting Seattle, WA June 19, 2017.

Blanco N, **Jackson SS**, O'Hara L, Magder L, Stafford KA. The effect of age on immune system reconstitution among HIV infected patients: a cautionary tale on the importance of stratification. Presented at Society for Epidemiologic Research Annual Meeting June 19, 2017.

Woodard JA, **Jackson SS**, Thom KA, et al. Beyond entry and exit: infection prevention at the bedside. Presented at Society for Healthcare Epidemiology of America Annual Meeting March 31, 2017

O'Hara LM, Masnick M, Leekha S, **Jackson SS**, et al. Indirect vs. direct standardization methods for reporting healthcare-associated infections. Presented at Society for Healthcare Epidemiology of America Annual Meeting March 29, 2017

Jackson SS, Leekha S**,** Williams S, et al. Risk factors for surgical site infection following colorectal surgery. Presented at IDWeek October 27, 2016

Jackson SS, Leekha S, Pineles L, et al. Improving risk adjustment above current CDC methodology using electronically-available comorbid conditions. Presented at Society for Healthcare Epidemiology of America Annual Meeting May 18, 2016. **Top Poster Abstract Award**

Honors and Awards

2018	Awarded Best Oral Abstract for presentation on SSI risk adjustment at Society for Healthcare Epidemiology of America Annual Meeting (Portland, OR)
2017	Poster on SSI risk adjustment was selected for participation in the Academy Health Annual Meeting (New Orleans, LA)
2017	Awarded Best Oral Abstract for presentation on SSI risk adjustment at Society for Healthcare Epidemiology of America Annual Meeting (St. Louis, MO)
2017	Awarded Best Oral Abstract for presentation on CLABSI risk adjustment at Society for Healthcare Epidemiology of America Annual Meeting (St. Louis, MO)
2017	GSA Travel Award of $275 to attend Society for Healthcare Epidemiology of America Annual Meeting to give to two oral presentations University of Maryland, Baltimore
2017	GSA Research Award of $1,000 towards lab supplies for dissertation. University of Maryland, Baltimore

2016	Awarded Top Poster Abstract for poster presented at Society for Healthcare Epidemiology of America Annual Meeting (Atlanta, GA)
2010	Inducted into Delta Omega Honor Society
2009	Oral Presentation Finalist for Master's Thesis: Homelessness and Unstable Housing as Risk Factors for HIV George Washington University Research Day

Teaching Services

2017 — Teaching Assistant for PREV 621 – Principles of Biostatistics
- Graded weekly assignments

2016 — Teaching Assistant for PREV 749 – Infectious Disease Epidemiology
- Managed class website and materials
- Wrote and graded midterm and final exams
- Graded and provided written feedback on final papers

2016 – 2018 — Teaching Assistant for PREV 749 – Research Practicum II
- Provided feedback and graded student presentations and papers
- Assisted students with methods, study design, and data analysis

2016 – 2018 — Teaching Assistant for PREV 748 – Research Practicum I
- Created content and lectured on Data Management in SAS, Presenting Data – Tables and Graphs, Assessing Confounding, and Assessing Effect Measure Modification
- Assisted students with methods, study design, and data analysis
- Provided feedback and graded student presentations

2015 — Teaching Assistant for PREV 620 – Principles of Biostatistics
- Managed class website and materials
- Graded weekly assignments

2015 — Teaching Assistant for PREV 610 – Behavioral Foundations of Public Health
- Managed class website and materials
- Graded weekly assignments

Institutional Leadership and Service

2016 – 2017 — Served on Graduate Program in Life Sciences Awards Committee
- Reviewed for students and faculty nominations packets

2015 – 2018 — Founder of SAS/R Student Group
- Created a student group for those interested in gaining SAS and R skills
- Developed topics, created content, presented lectures, and found speakers for various SAS/R topics

2015 – 2018	Big Sister Student Mentor, Department of Epidemiology and Public Health, University of Maryland, Baltimore • Attended orientation week events • Assisted 1st year PhD student acclimate to the university
2015 – 2016	Student Recruitment Host, Department of Epidemiology and Public Health, University of Maryland, Baltimore • Hosted applicants to epidemiology department
2015 – 2016	Served as a peer reviewer for *Archives of Environmental & Occupational Health*.

Software Skills

Statistics and Surveys: SAS, SPSS, R, EpiInfo, WinPepi

Publishing, Web: Adobe Acrobat, Dreamweaver, Drupal, Reference Manager, RefWorks

Microsoft Office: Word, Excel, Access, PowerPoint, Outlook, Publisher

ABSTRACT

Dissertation Title: Risk factors for transmission of multidrug-resistant organisms and acquisition of healthcare-associated infections

Sarah S. Jackson, Doctor of Philosophy, 2018

Dissertation Directed By:

Anthony D. Harris MD, MPH
Professor
Department of Epidemiology and Public Health
and
Kerri A. Thom MD, MS
Associate Professor
Department of Epidemiology and Public Health

Background: Healthcare-associated infections (HAI) increase hospitalized patients' morbidity and mortality. In order to prevent the spread of HAI among patients in the healthcare setting, a better understanding of transmission dynamics and how patient-level factors influence acquisition is needed.

Objectives: To estimate the association between patients' bacterial burden of vancomycin-resistant *Enterococcus* (VRE) and transmission to others and to build risk adjustment models taking into account patient case-mix for a more accurate comparison of rates HAIs between hospitals.

Methods: Using a prospective cohort design, quantitative cultures (perianal, skin, and stool samples) were obtained from VRE-colonized ICU patients at the University of Maryland Medical Center. The association between patient bacterial burden and transmission to healthcare workers (HCW) gloves or gowns was estimated using generalized estimating equations. HCWs were observed during patient care to identify risk factors for transmission. Retrospective cohorts

of surgical and ICU patients in 28 US hospitals were assembled to build risk adjustment models using hospital discharge codes for surgical site infections and central line-associated bloodstream infections using mixed models.

Results: There were 71 transmission events among 479 HCW-patient interactions. VRE transmission was associated with VRE burden on the perianal swab (OR: 1.37 [95% CI 1.19, 1.57]); skin swabs (OR: 2.14 [95% CI: 1.51, 3.02)]; and in the stool (OR: 1.95 [95% CI: 1.39, 2.72]). Independent risk factors for transmission of VRE to HCWs in a multivariable model were touching the patients' skin (OR: 2.18 [95% CI: 1.15, 4.13]) and transferring the patient in/out of bed (OR: 2.66 [95% CI: 1.15, 6.43]). There were 573 (1.3%) surgical site infections among the 45,394 surgical patients and the risk adjustment model yielded a C-statistic was 0.73 (95% CI, 0.71–0.75). Of the 85,849 ICU patients, 162 (0.2%) developed a central line-associated bloodstream infection and the risk adjustment model yielded a C-statistic of 0.64 (95% CI, 0.60–0.69).

Conclusions: Our first study shows that ICU patients with higher bacterial burden are more likely to transfer VRE to HCWs. Our second study demonstrates the importance of including comorbidities in risk adjustment models. These findings have implications for infection control interventions and HAI rate comparisons.

Risk Factors for Transmission of Multidrug-Resistant Organisms and Acquisition of Healthcare-Associated Infections

by
Sarah S. Jackson

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
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Doctor of Philosophy
2018

DEDICATION

To Dan.

ACKNOWLEDGEMENTS

I would like to thank Drs. Anthony Harris and Kerri Thom for their mentorship. I am extremely grateful for the numerous opportunities and support they have given me throughout my studies. I am very grateful to Dr. Larry Magder for his statistical mentoring, Dr. Kristen Stafford for her methodological expertise, and Dr. J. Kristie Johnson for her microbiology assistance. I am thankful to all committee members for their time and effort, and support of my dissertation.

I would also like to highlight members of the faculty for their support and mentorship. Dr. Surbhi Leekha, especially, for her help on the second aim of this dissertation and allowing me to be a part of her Practicum class for so many years. To Dr. Sania Amr, for her excellent mentorship and believing in me so early on.

I am eternally grateful to the assistance and support of the entire Division of Genomic Epidemiology and Clinical Outcomes. Thank you to Natalia Blanco Herrera for her help with understanding the microbiology and laboratory techniques, and the much-needed coffee runs. Thank you to Lyndsay O'Hara for training me on data collection and for answering my innumerable questions. Thank you to Shirley Goodman and Alyssa Sbarra for helping with data collection in the ICU. Thank you to Nicole Karikari, Licheng Zhao, and Gwen Paszkiewicz for processing all the specimens. Thank you to Lisa Pineles, without whose help, neither aim of this dissertation would be possible.

Thank you to my fellow students who offered advice, moral support, and friendship: Rotana Alsaggaf, Annie Noone, Emily Stucke, Andrea Buchwald, Kara Moser, Shana Burrowes, Danielle Abraham, Elizabeth Humphries, and Anthony Herrera.

And finally, to my loving husband, Dan, and stepson, Quinn. Dan, thank you for your unconditional love and support, and for always believing in me. Quinn, thank you for always listening to my practice talks and asking insightful questions. Guys, I think we are done!

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACA	Patient Protection and Affordable Care Act
ASA	American Society of Anesthesiologists
CCI	Charlson comorbidity index
CDC	The Centers for Disease Control and Prevention
CDS	Chronic disease score
CHG	Chlorhexidine
CI	Confidence interval
CLABSI	Central line-associated bloodstream infection
CMS	Centers for Medicaid and Medicare Services
EI	Elixhauser index
HAC	Hospital-Acquired Condition Reduction Program
HAI	Healthcare-associated infection
HCW	Healthcare workers
ICD	*International Disease Classification*
ICU	Intensive care unit
IP	Infection preventionist
MDRO	Multidrug-resistant organism
MICU	Medical ICU
MRL	Microbiology Research Laboratory
NHSN	National Healthcare Safety Network
NNIS	National Nosocomial Infections Surveillance system
OR	Odds ratios
SICU	Surgical ICU
SIR	Standardized infection ratio
SSI	Surgical site infections
US	United States
UMMC	University of Maryland Medical Center
VRE	Vancomycin-resistant *Enterococcus*

CHAPTER I. INTRODUCTION AND SPECIFIC AIMS

Healthcare-associated infections (HAI) increase hospitalized patients' morbidity and mortality. Increasingly, many of the bacteria that cause HAI are resistant to antibiotics. In 2013, the Centers for Disease Control and Prevention (CDC) estimated that multidrug-resistant organisms (MDROs) were responsible for over two million patient infections and 23,000 deaths in the United States (US).[1] These MDROs increase the cost of care substantially compared to antibiotic susceptible organisms, making the prevention of these organisms a top public health priority.[1]

In order to prevent the spread of HAI among patients in the healthcare setting, a better understanding of transmission dynamics and how patient-level factors influence both acquisition and transmission is needed. As such, I explored the relationship between patients' microbial burden of vancomycin-resistant *Enterococcus* (VRE) and transmission to others (Aim 1). Using a prospective cohort design, we quantified the amount of bacterial colonization in intensive care unit (ICU) patients and estimated their transmission potential by testing the gowns and gloves of the healthcare workers (HCW) who cared for these patients. Few studies have investigated how much bacteria patients are colonized with is needed to transmit the bacteria to others.[2] Next, to accurately compare safety outcomes between hospitals, rates need to be adjusted for patient case-mix (Aim 2). We had the opportunity to build risk adjustment models and compare outcome rates between hospitals in a large, multicenter dataset of patients at risk of surgical site infection (SSI) and central line-associated bloodstream infection (CLABSI). These aims will advance two important areas under study in the field of hospital epidemiology.

A. Aim 1: To examine VRE transmission from the patient to healthcare worker in the ICU

Specific Aim 1a: ***To investigate the relationship between the bacterial burden of VRE a patient is colonized with and transmission to healthcare worker gloves and gowns.***

Hypothesis: Patients with higher bacterial burden of VRE will have a higher proportion of transmission than patients with lower bacterial burden.

Specific Aim 1b: ***To examine the risk factors for transmission of VRE to HCWs' gowns and gloves.***

Hypothesis: Type of HCW and patient contact will result in a greater proportion of transmission to HCWs' gloves and gowns.

B. Aim 2: To build risk adjustment models for SSI and CLABSI

Specific Aim 2a: ***To construct risk adjustment models to compare rates of surgical site infection (SSI) and central line-associated bloodstream infection (CLABSI) between hospitals.***

Hypothesis: Adjustment for comorbid conditions results changes in the comparisons of hospitals with respect to HAI rates

CHAPTER II. BACKGROUND

A. Aim 1: VRE transmission in the ICU

Epidemiology of Vancomycin-Resistant Enterococcus (VRE)

Enterococci are Gram positive bacteria that are a normal component of the bowel flora, but in hospitalized and ICU patients, can be the cause of serious infections including urinary tract and bloodstream infections. VRE is a strain of *Enterococcus* that has acquired resistance to the antibiotic vancomycin. Roughly 20,000 (or 30%) of the annual *Enterococcus* HAI in the US are vancomycin resistant and are responsible for 1,300 deaths each year.[1] The prevalence of VRE colonization in ICU patients has been estimated to be 7-17%.[3] The continued use of vancomycin and other antibiotics most likely maintains selective pressure for VRE in hospitals.[4] After *Staphylococcus aureus, enterococci* are the second most common cause of all HAI and the most common pathogen among CLABSIs and SSIs within certain procedure types.[5]

VRE colonization is associated with increased morbidity, length of hospitalization, hospital costs, and mortality. Patients colonized with VRE often have a hospital stay twice as long as patients not colonized with VRE.[6] One study found that VRE acquisition was associated with a 40% increase in post-ICU length of stay even after controlling pre-ICU length of stay and comorbidities.[7] These increases are associated with an average excess of $77,000 per patient attributable to VRE.[6] Vancomycin resistance is also a significant predictor of death from enterococcal bacteremia. A meta-analysis found that after controlling for severity of illness, those with VRE bacteremia are two and half times as likely to die in-hospital than those with vancomycin-susceptible enterococcal bacteremia.[8]

There are two predominant species of *Enterococcus: E. faecium* and *E. faecalis*. Of the isolates tested by the CDC's National Healthcare Safety Network (NHSN) for CLABSI, approximately 83% of *E. faecium* are resistant to vancomycin, while roughly 10% of *E. faecalis* are resistant.[5] This is a dramatic increase from the 0% of *E. faecium* resistant to vancomycin reported in 1980.[9] *E. faecium* is more common among those with invasive disease and incidence of *E. facecium* is rising. In 1999, 25% of enterococcal isolates recovered from patients in the ICU were resistant to vancomycin.[10] In 2007, VRE accounted for on third of all enterococcal isolates,[3] while in 2010, a total of 35.5% of enterococcal isolates were VRE.[11] The increasing incidence of resistance is concerning because treatment options are limited and due to the potential transfer of resistance genes to other, more virulent, organisms such as *S. aureus*.[10]

Asymptomatic colonization of the gastrointestinal tract with VRE is ten times more common than VRE infection.[11] Colonization can persist for months or years with a median time of 26 months[11] as is typical of other antibiotic-resistant bacteria. Colonization with a resistant strain is more likely to lead to infection than colonization with a susceptible strain.[11] Infection can develop when the immune defenses of colonized individuals are weakened due to immunosuppression from disease, advanced age, or surgery.[12] Roughly, 19% of patients colonized with VRE in the ICU will develop subsequent infection with VRE during the same hospitalization[12]

Risk factors for VRE colonization include prolonged hospital stay, immunosuppressant drugs like corticosteroids, severity of underlying disease, and comorbidities.[12] Several studies have found VRE colonization associated with the use of certain antibiotics prior to ICU admission, such as vancomycin, penicillin, imipenem, and

fluoroquinolones.[8,13] Being placed in an ICU room where the prior room occupant was colonized with VRE confers a 40% increased odds of VRE acquisition.[7]

Transmission of VRE

Understanding VRE transmission is paramount to preventing its spread and acquisition. VRE is believed to be spread between patients by two main routes: HCWs and the environment. HCWs' hands can serve as a major vector in patient-to-patient transmission.[11] HCWs may contaminate their gloved or ungloved hands when touching colonized patients and/or surfaces in the patients' environment. HCWs can then transfer VRE from their gloves or gown/clothes to other parts of the patient or patient's environment.

VRE colonizes the human gut, the highest concentration is seen in patient stool. Sethi et al found that those with higher VRE density in the stool were more likely to have skin and environmental contamination.[14] Patients with diarrhea are more likely to spread VRE to the environment than patients without diarrhea.[14,15] However, the transmission of VRE from patients' skin to HCWs is poorly understood as skin contamination remained the same between those with diarrhea and those without.[14] In a small study of 22 patients Duckro et al. found the antecubital fossa to be a highly efficient origin of transfer despite its distance from the patient's rectum, the putative reservoir of VRE.[2] Transmission from patients' antecubital fossa to HCWs occurred in all of the observed contacts and from the chest in roughly 60% of the contacts.[2] About 50% of transmission came from wrists, less than 40% from the inguinal area, and ~30% from ankles.[2]

Antibiotic administration can also play an important role in transmission as antibiotics promote the overgrowth of VRE in the intestinal tract through the inhibition of

intestinal anaerobic bacteria.[16] Vancomycin may exert selective pressure on gut bacteria that leads to the proliferation of VRE.[12] Patients exposed to antibiotics in the previous week and for longer periods of time had significantly higher VRE densities in their stools.[12] Yoon et al found that antibiotics prolonged the duration of VRE. Patients treated with Vancomycin had a 4-fold increase in the odds of prolonged duration of colonization compared to those not treated with antibiotics.[17] Donskey et al. found that the mean interval between the discontinuation of antibiotics and undetectable VRE in stool was 17.4 week.[16] However, some of these studies may have suffered from confounding by indication, where sicker patients may have been more likely to both have VRE colonization and a need for IV antianaerobic antibiotics than healthier patients who received a short course of oral antibiotics.[16] Regardless, others have shown that patients treated with 3rd and 4th generation cephalosporins and carbapenems were more likely to contaminate their environment than those on non-antianaerobic antibiotics,[15] which has important implications for transmission.

Patients colonized with VRE can spread VRE to their hospital environment. Environmental contamination has been shown to be as high as 60-70% in colonized patient rooms.[18] Transmission can occur when medical equipment is shared between patients (i.e. stethoscopes, ultrasound machines). If the room is not cleaned thoroughly between patients, VRE can spread to the next patient to occupy that room. VRE has been shown to survive heat, some disinfectants, and can live on fomites for days or months.[11,19] The most contaminated objects in the patient's room were determined to be those that were located near the patient and frequently touched by the HCW. These included the bedside shelves, bed rail, and stethoscopes.[20] Research has shown that less than 50%

of surfaces in patient rooms are cleaned properly during terminal cleaning. [19] While, the level of contamination of the environment is thought to be relatively low, usually less than 10 organisms/cm^2 , [19] one study found high transmission from the environment to HCWs with100% transmission from blood pressure cuff, 75% from hygiene products, 50% suction equipment, 45% bed rail, 30% bedding, less than 30% soap dispenser and bed table. [2]

Hospitals have adopted several strategies to reduce the spread of VRE and other bacteria from patient to HCW. These prevention efforts are divided into horizontal, covering a broad range of organisms, and vertical, or organism-specific, strategies. Horizontal strategies for prevention of VRE include infection control practices such as hand hygiene, environmental cleaning, and contact precautions. [3] The implementation of Contact Precautions can vary between facilities, but generally include the use of gloves and gowns during all patient care activities, the use of single patient rooms, and dedicated in-room medical equipment. [11] The duration of contact precautions can also vary from one year after last positive culture to indefinite once positive for VRE. [11] Vertical strategies include active surveillance to identify asymptomatically colonized patients. [3] Daily chlorhexidine gluconate (CHG) bathing has been shown to decrease the incidence of VRE acquisition and VRE bacteremia. The use of CHG was associated with a 2.5 $\log_{10}$ colony count reduction of VRE contamination on patient's skin, HCWs' hands, and environmental surfaces. [21] CHG bathing was also associated with a 60% reduction in VRE acquisition. [21] Despite the use of infection control protocols, VRE is endemic to many ICUs and its incidence is increasing. [12]

Gaps in the Literature

There have been four studies examining transmission of VRE from the patient or the patient's environment to HCWs (see Table 1). Two of these studies looked at transmission to HCWs' gloves only [2,22] and found a range of transmission rates of 11% to 62%. The other two observational studies found rates ranging from 8.5% to 13% for consolidated glove and gown transmission. [23,24] In both of these studies, transmission was higher to gloves (7.7% to 10%) than gowns (4.3% to 5%). [23,24] Three of the four studies were conducted in 1 ICU only and all four suffered from low sample size. The number of patient sampled range from 22-27 and the number of HCW observations ranged from 94-180. The current study samples 100 patients and records 500 HCW-patient observations, nearly 5 times the sample size of the previous studies.

Table 1. Studies of VRE transmission from patient to HCW

Study	Setting	Quantify VRE	Patient Sample Size	HCW Sample Size	Gloves	Gowns	Either
Morgan 2012[23]	6 ICUs	No	27	180	10%	5%	13%
Hayden 2008[22]	1 ICU	No	22	103	62%	--	--
Snyder 2008[24]	1 ICU	No	56	94	7.7%	4.3%	8.5%
Duckro 2005[2]	1 ICU	Yes	22	151	10.6%	--	--

Abbreviations: HCW, healthcare worker; VRE, vancomycin resistant *Enterococcus*

Only one of the above studies quantified the amount of VRE found on the patient, and did not look at the influence of bacterial count on transmission potential. [2] The findings from Duckro et al. implied that VRE density may not correlate with efficiency of transfer. [2] For instance, environmental surfaces were found to be less contaminated than body sites, but two of the four sites with greatest transmission efficacy were environmental sites. [2] Further, the antecubital fossa was much less heavily colonized than the inguinal area, but was implicated in more transmission. These findings suggest that the duration of contact and/or number of contacts may affect the likelihood of transfer

more than colony density. However, this study did not look at the association between colony counts and transmission in a linear fashion or examine whether a dose response curve could be constructed. Instead the researchers looked at 22 patients within one ICU and described 16 transfers. With an increased sample size, such as proposed for our study, we may be able to elucidate some of the unanswered questions from this study.

Innovation and Significance

Whether the bacterial load of VRE increases the risk of transmission is thus far unknown. While many studies have found that colonized patients can transmit MDROs, including VRE, to healthcare workers [22-24] there have been no published studies examining the relationship between the quantity of VRE that the patient is colonized with and transmission to HCW.[2] Previous studies of VRE in ICU have dichotomized colonization into presence or absence of the organism. Quantification allows us to determine the amount of bacterial load that leads to transmission. Further, this study will help us gain a better understanding of the risk factors that lead to transmission in the ICU. These results could have major implications for infection prevention practices, such as isolation and contact precautions of patients with high bacterial carriage. Other strategies could include enhanced environmental cleaning or the de-colonization of high burden carriers.

B. Aim 2. Risk Adjustment

Many hospital quality improvement systems have been enacted in an effort to stem the rise of HAI. In the 2015 fiscal year, the Patient Protection and Affordable Care Act established the Hospital-Acquired Condition Reduction Program to incentivize hospitals to reduce HAIs. Under this program hospitals are scored on several quality

measures, including for central line-associated bloodstream infections (CLABSIs) and surgical site infections (SSIs). Points are awarded to hospitals based on the average of the standardized infection ratios (SIR) for each of these measures. Risk adjusted SIRs are derived from NHSN. Beginning in fiscal year 2017, hospitals with a HAC reduction score above 6.57 will have 1% of their reimbursement withheld by the Centers for Medicaid and Medicare Services (CMS).[25] Therefore the risk adjustment methodology employed by NHSN for both SSIs and CLABSIs is of paramount importance.

Epidemiology of SSI

In acute care facilities, SSIs occur in 2-5% of patients undergoing surgery which roughly translates to 160,000 - 300,000 SSI in the US each year.[26] SSIs account for 31% of all HAIs in hospitalized patients making it the most common cause of HAI. SSIs are associated with a mortality rate of 3% and with an increased length of hospital stay averaging 7-11 additional days.[1] Postoperative infections increase healthcare costs with an estimated $3.5 billion to $10 billion in healthcare expenditures annually.[26] *S. aureus* is a commonly-isolated organism in SSI and accounts for 15-20% of inpatient SSI.[1] Other common organisms isolated from SSIs include gram-negative bacilli, coagulase-negative staphylococci, *Enterococcus* spp. (including VRE), and *Escherichia coli*.[27]

SSIs are classified as either superficial or complex by NHSN. Superficial SSI are infections in the skin or subcutaneous tissue of the incision. There are two types of complex SSI: deep incisional, which involve the fascia and/or muscle layers, and organ/space, an infection that involves any part of the body that was manipulated during surgery that is not the skin, fascia, or muscle layers.[28] Complex SSIs are much more

likely than superficial SSIs to require rehospitalization and/or reoperation, and contribute to increased patient morbidity. [26]

The likelihood of developing an SSI involves a complex relationship between intrinsic, patient related (preoperative) and extrinsic, procedure related (perioperative) factors. [26] Extrinsic factors can be further divided into patient preparation, operative characteristics, and operating room characteristics. Patient preparation includes treating pre-operative infections like urinary tract infections. Operative characteristics include performing preoperative hygiene (appropriate hand washing and glove and gown use), administering antimicrobial prophylaxis as indicated, minimizing the need for blood transfusion, adhering to standard principles of asepsis, and minimizing operative time as much as possible. Operating room characteristics include proper room ventilation, sterilization of surgical equipment, and disinfection of the environment. [26]

Patient risk factors can be further divided into those that are modifiable and non-modifiable. Non-modifiable risk factors for SSI include advanced age (perhaps due to increased likelihood of comorbidities or immunosenescence), a history of radiation (causing tissue damage), and a history of prior skin infection (may be a marker for immune function). Modifiable risk factors include glucose control, obesity, smoking, and immunosuppressive medications. [28] As such patients are encouraged to lose weight, stop smoking, and avoid immune suppressive medications prior to the procedure if possible. A systematic review of SSI risk factors found that BMI, smoking, wound class severity, diabetes status, increased comorbidity score, and increased surgery duration were consistently associated with an increased risk of SSI. [27] Comorbid conditions were consistently found to be associated with the development of SSI. In 13 adjusted analyses,

85% of the studies showed a statistically significant association between diabetes and SSI.[27] The number of comorbidities was associated with a 70% increase in the odds of SSI for each additional condition and the presence of at least comorbidity was associated with a six fold increased odds of SSI compared to no comorbid conditions in general surgery.[27]

Epidemiology of CLASBI

CDC NHSN defines CLABSI as a positive blood culture in a patient with a central line in the absence of another site of infection.[29] The development of CLABSI is associated with increased morbidity and mortality, with a reported mortality rate of 12-25%.[29] CLABSIs are also responsible for increased length of hospital stay and increased hospital costs. In 2009, the CDC reported a CLABSI rate of 1.14 infections per 1,000 central line-days, which translates to 23,000 CLABSI cases in the US.[29] This is a substantial decrease from the 2001 CLABSI rate of 3.64 CLABSIs per 1,000 central line-days or 43,000 CLABSI cases.[29] This decrease is due in part to CLABSI reduction efforts which include bundled intervention during central line insertion, enhanced maintenance, and prompt removal of lines when no longer needed.[29]

Patients admitted to the ICU are at increased risk of developing a CLABSI because of the frequency of catheter insertion and the frequency of access to it, the types of catheters used, and the length of time the catheter is in place.[30] The risk of infection increases with prolonged duration of catheterization, prolonged hospitalization before catheterization, microbial contamination of the skin at the insertion site, reduced nurse to patient ratio, and substandard care of the central line.[30]

Patient specific risk factors for developing a CLABSI are poorly understood. Female gender was been identified as a protective factor in some studies [30] though not in others. [31] The only variable consistently predictive of CLABSI is duration of central line use, which itself may be a proxy for severity of illness and/or comorbidities. [30,31]

Risk Adjustment

Risk adjustment is a method that statistically controls for the effect of patient risk factors on the outcome of interest. [32] In a multivariable model, the residual differences in outcome are then related to provider quality. [32] The CDC compares HAI rates between hospitals using risk adjusted SIRs. An SIR is the ratio of the observed number of HAI to the expected number of events at each hospital. The expected number events is estimated using logistic regression. An SIR above 1 indicates the hospital reported a greater number of SSIs than expected, while an SIR below 1 indicates the hospital reported a lower number of events than expected by the model. [28,33]

The performance of risk adjustment models is measured using discrimination and calibration. Discrimination is a measure of how well the model separates the diseased from the non-diseased. The C-statistic is a measure of discrimination, or the model's ability to discriminate between those with and without the outcome. The C-statistic is the chance that the model will assign a higher probability to patients with SSI than without. [34] Values for the C-statistic range from 0.50, a probability no different from chance, to 1.0, which is perfect prediction. A model has perfect discrimination if the predicted values for the diseased are always higher than the non-diseased. [35] However, it is not the probability that patients are correctly classified. The C-index measures how well the model can rank patients, but is not a function of the predicted probabilities. [35] For instance, the predicted

risk for a case may be 0.40 and 0.39 for a non-case. This model would have perfect discrimination because the model always assigns a higher value to being a case than a non-case, but the predicted risk difference may not be clinically or epidemiologically meaningful. [35]

Calibration, on the other hand is a measure of how well the predicted probabilities agree with the observed risk. A model is well calibrated when the predicted risk is equal to the proportion of that actually develops the disease. [35] There is a tradeoff between calibration and discrimination and usually a model cannot be perfectly calibrated and have a C of 1.0 at the same time. Calibration is often assessed with a calibration plot in which the predicted probabilities are plotted against the observed proportion of disease in deciles. A 45-degree line is added to the plot to visually inspect how well the model is calibrated. In a perfectly calibrated model the points would rest exactly on the 45-degree line, implying that the predicted risks are equal to the observed frequencies. [36,37] Calibration may be more important than discrimination when comparing hospital rates. If the model's calibration is worst among patients in the highest decile of risk, then hospitals with the sickest patients may be unduly labeled as poor performers. [38]

Risk adjustment models are often built in administrative data sets. These data are generally collected for billing or regulatory oversight that usually include demographics, procedures performed, and diagnoses made during hospitalization among other variables. [32] Administrative datasets are appealing because data are easy to obtain, usually available for patients across the US, allow for large samples size which can provide adequate statistical power for a host of healthcare outcomes, [32] and are sometimes able to provide population-based samples. [39] However, because the data were not collected for

risk adjustment specifically, some variables may be missing and not all patients may have data values. Further, these datasets are often subject to issues of bias such as selection bias (the target population may not be captured adequately) or confounding by indication.

On the other hand, clinical data from sources like a prospectively designed cohort study or a data registry will have near complete data on each patient and precise definitions that are standard across clinical centers. However, data collection is time consuming, expensive, and thus, can limit the number of centers willing to participate. [32] Because of this, the ability to sample across a broad distribution of hospitals (geographically, academic, size, etc) is reduced. [32]

Evolution of CDC's Risk Adjustment Models

One of the first attempts at risk adjustment was the National Nosocomial Infections Surveillance system (NNIS) risk index developed in 1991. Variables included in this model were an American Society of Anesthesiologists (ASA) score ≥3, wound class, and duration of surgery longer than the 75th percentile within the same procedure type. [40] In 1998 NNIS index added endoscopy to their risk stratification models for cholecystectomy, colon, appendectomy, and gastric surgery. [40] The c-statistics for this model are shown in Table 2. The C-statistics were 0.56 for colons, 0.61 for hips, 0.62 for hysterectomy, and 0.60 for knees. [41]

Table 2. National Nosocomial Infections Surveillance System (NNIS) risk index for all SSIs [41]

Procedure type	Variables in final model	C-Statistic
Colectomy	Wound class, CO/D vs. C/CC	0.56
	Duration, >75th percentile	
	ASA, ≥3 vs <3	
	Endscope use	
Hip arthroplasty	Wound class, CO/D vs. C/CC	0.61
	Duration, >75th percentile	
	ASA, ≥3 vs <3	
	Endscope use	
Hysterectomy	Wound class, CO/D vs. C/CC	0.62
	Duration, >75th percentile	
	ASA, ≥3 vs <3	
	Endscope use	
Knee arthroplasty	Wound class, CO/D vs. C/CC	0.60
	Duration, >75th percentile	
	ASA, ≥3 vs <3	
	Endscope use	

Abbreviations: ASA, American Society of Anesthesiologists; C, clean; CC, clean-contaminated; CO, contaminated; D, dirty; and SSIs, surgical site infections

In 2011, Mu et al. revised the risk adjustment models to take into account some patient case-mix risk factors to develop models for public reported SSI rates. [41] These models included a range of procedure-specific variables, but only a few comorbid conditions in select procedures. Table 3 presents the risk adjustment models for the Mu 2011 update. The candidate variables, final model, and C-statistic are present for colectomies, hip replacement, hysterectomies, and knee replacement procedures. The new models showed statistically significant performance improvement over the NNIS. [41]

Table 3. NHSN Risk Adjustment Models for Complex SSIs in Select Procedures for the Years 2012-2016 [41]

Procedure type	Candidate variables	Variables in final model	C-Statistic
Colectomy	Gender, age, emergency, trauma, general anesthesia, ASA score, wound class, duration, medical school affiliation, number of beds, endoscope, outpatient	Age, ≤75 vs. >75 ASA, >2 vs. ≤2 Duration10 Endoscope, No vs. Yes Medical school, No vs. Yes Bed size, >200 vs. ≤200 Wound class, CO/D vs. C/CC	0.61
Hip arthroplasty	Gender, age, emergency, trauma, general anesthesia, ASA score, wound class, duration, medical school affiliation, number of beds, endoscope, outpatient, type of surgery (total primary, partial primary, partial revision, total revision)	Age10 Anesthesia, Yes vs. No ASA, 3 vs. 1/2 ASA 4/5 vs. 1/2 Duration10 Type of surgery (see list) Medical school, Yes vs. No Bed size, >200 vs. ≤200 Trauma, Yes vs. No	0.67
Hysterectomy	Gender, age, emergency, trauma, general anesthesia, ASA score, wound class, duration, medical school affiliation, number of beds, endoscope, outpatient	Age10 ASA (1, 2, 3/4/5) Duration10 Bed size, ≤500 vs. >500	0.64
Knee arthroplasty	Gender, age, emergency, trauma, general anesthesia, ASA score, wound class, duration, medical school affiliation, number of beds, endoscope, outpatient, type of surgery (revision, primary)	Age, ≤58 vs. >58 ASA, (1/2, 3, 4/5) Duration10 Gender, Male vs Female Revision vs. Primary Medical school, Yes vs No Bed size, >200 vs. ≤200 Trauma, Yes vs. No	0.65

Abbreviations: ASA, American Society of Anesthesiologists; C, clean; CC, clean-contaminated; CO, contaminated; D, dirty; NHSN, National Healthcare and Safety Network; and SSIs, surgical site infections

In 2017, NHSN revised its SSI risk adjustment models again. [33] These new models include comorbidities such as diabetes and/or obesity for many of the procedure types. However, discrimination statistics have not been published for these models nor have validation been conducted in external datasets so the performance of these models is unknown.

Because risk factors for CLABSIs have not been well characterized the CDC has stratified CLABSI rates by ICU type within each facility. However, included in the 2017 CDC update was a new model for CLABSI. CDC's risk adjustment model now includes academic affiliation and hospital size (as measured by number of beds) in addition to ICU type. [42] The performance of the risk adjustment model for CLABSIs has not be tested nor validated externally.

Methodological Issues with the Existing Models

The variables in the NHSN risk adjustment models for both SSI and CLABSI suffer from several methodological issues. First, the NHSN surveillance is a voluntary system and only a selection of US hospitals participate. Therefore, the Mu analysis may suffer from selection bias such that risk factors for SSIs may be different had other hospitals been included. Second, the variables selected in each model are variables of convenience, i.e. variables that easily and readily collected by the NHSN system. Many comorbid conditions were not included by the NHSN surveillance and were therefore excluded from their models.

Many of the procedure-specific models for SSI and the new 2017 CDC model include medical school affiliation and hospital size. [42] These variables are unlikely causally related to the development of SSI or CLABSI, but instead were selected as proxy variables for patient case-mix. However, while medical school affiliation may represent a case-mix of patients who have more comorbid conditions and higher severity of illness that merits risk adjustment, it may also represent more inexperienced providers. Provider experience should not be adjusted for if the intent is to use those adjusted rates for quality of care comparisons. Similarly, facility hospital size is likely associated with

several patient case-mix and care delivery factors making the direction of influence on SSI or CLABSI difficult to predict.

Many of the SSI-specific variables included in the CDC's risk adjustment models are similarly problematic. These include wound class, ASA score, duration of surgery, and laparoscopic approach.

Surgical wound is classified into four categories: clean, clean/contaminated, contaminated, and dirty. Risk adjustment models often include wound class because different classes confer differing levels of risk. The risk of SSI ranges from 2% to greater than 30% depending on wound class. [43] However, with a few exceptions, most non-trauma surgeries within the same procedure type have the same wound classification, i.e. most knee replacement surgeries have a wound class clean and most colectomies have a wound class of clean contaminated. [41,43] Therefore, the utility of this variable in predicting risk within the same procedure type may be limited.

ASA score, or the American Society of Anesthesiologists physical status classification system is another variable commonly used in risk adjustment models. In practice, it is used to assess patient health status before surgery. It has undergone modification since its introduction in 1961, but is now a part of the standard preoperative assessment of surgical patients around the world. [44] The score ranges from 1 to 6, with increasing score representing increasing severity of illness. Patients designated an ASA score of 6 are generally not used in procedures for risk adjustment as it represents patients declared brain dead. [44]

ASA was not originally designed to identify surgical risk, though some clinical studies have found that the classification does correlate to morbidity and mortality

attributable to surgery and may be useful in predicting patient outcomes. However, other studies have shown no correlation between ASA score and outcomes.[45] It was designed to be a measure of patient case-mix and to allow hospitals to compare mortality rates.[46] Further inconsistencies among anesthesiologists assigning the scores have been found. Aronson found a lack of inter-rater reliability between anesthesia providers in assigning ASA scores to hypothetical patients.[45] Another study conducted in Australia found fair agreement (k=0.40) between anesthesiologists.[46] Though, not one case in either study was scored with perfect unanimity. Another study that found moderate [k=0.61] inter-rater reliability between anesthesiologists scoring in real patients within a Canadian hospital.[47] These results may indicate that there is more consistency between scoring when real patient scenarios are used or that the previous studies suffered from small sample size. On the other hand, Sankar et al's study was conducted within one hospital where the scoring may have been done by the same group of surgeons, thus the inter-rater reliability between hospitals may be much lower.[47] There are financial incentives to provide care to patients with an ASA score of III or higher and Nie has found that this had led to an increase in the number of patients being assigned a higher score.[47,48]

However, ASA has been shown to be predictive of postoperative mortality. One study found both Charlson Comorbidity Index (CCI), a comorbidity score, and ASA to be predictive of mortality though the CCI (C=0.865) better than ASA (C=0.833).[49] One study found ASA alone was predictive of 30 day postoperative mortality (C=0.889) and 30 day morbidity (C=0.722) but that other risk factors had greater predictive ability for the same measures (C=0.958 for mortality and C=0.769 morbidity) and that the addition of ASA to these models did not improve predictive performance.[44] Yet, given the

subjectivity of ASA scoring and lack of inter-rater reliability it may be a poor measure to include in risk adjustment.

Operative time or duration of surgery is often used in SSI risk adjustment models though there are issues of construct validity. Surgical duration reflect the complexity of the case due to patient comorbidity or it may represent an inexperienced surgeon. [50] Including this variable may inappropriately adjust SSI rates that are due to poor surgical technique. [41] The use of a laparoscope or endoscope is often included in models as it associated with less risk of infection than traditional surgery. [51] The use of a scope involves creation of several small incisions to perform or assist in the performance of an operation rather than use of a traditional larger incision (i.e., open approach). However, this variable could also be due to reduced case complexity and be a result of patient comorbidity as well.

Comorbidity indices

Comorbidity "defined as the total burden of illnesses unrelated to the principal diagnosis" [39] or the "co-occurrence of multiple chronic diseases and medical conditions within one person." [52] One in four Americans has multiple (two or more) chronic conditions. The number of conditions increases with age; three in four individuals 65 years and older have multiple chronic conditions. [53] Adequately measuring this construct has been challenging. Though a great deal of research has been devoted to developing comorbidity measurements, there is no gold standard. Outlined below are the most common disease-based and medication-based comorbidity indices that have been shown to have good construct validity (the ability of an index to predict a specific outcome in a given population).

The CCI was developed by Charlson et al in 1987 through chart review to predict 1 year in-hospital mortality. The original index included 21 weighted conditions from which a total score is calculated. [39] It has subsequently been adapted by both Deyo and Romano to use *International Disease Classification, Ninth Revision* (ICD-9) codes instead of chart review. Deyo et al adapted the CCI in 1992 for use with ICD-9 codes that correspond to the comorbid conditions. [54] Deyo combined some conditions for a list of 17 comorbidities and their associated codes. [54] Romano et al. also adapted the CCI for use in administrative databases by mapping the conditions to ICD-9 codes. The Romano adaptation includes broader definitions of each conditions that include more codes in the comorbidities. [39] All have been mapped to the tenth revision (ICD-10) codes with similar results. [55] The CCI is the most widely used comorbidity index and has been used in a host of patient populations for other outcomes such as readmission, quality of life indicators, surgical complications, and infectious diseases with mixed results. [39,56]

The validity of using the CCI derived from administrative data has been extensively studied. Two studies compared the CCI derived from self-reported to administrative data, one of which found that CCI discrimination was similar across both derivation methods for a variety of outcomes of patients admitted to emergency departments in Montreal, Canada. [57] Both studies found poor agreement between the two sources with a Cohen's kappa coefficient (κ) of 0.43 (95% confidence interval [CI]: 0.40, 0.47). [57] Another study found varying levels of agreement between self-report and administrative data that ranged from poor to substantial depending on the component condition. [58] Three studies have been conducted to compare the derivation of the CCI in chart review versus administrative data. One study found that CCI scores calculated from

administrative data were lower than those derived from chart review and that the agreement between the two sources ranged from poor to moderate (k 0.30-0.56). [59] Another study found wide ranging agreement between component conditions (k 0.02-0.47), [39] while Jang et al. found good agreement in CCI scores between the two sources using ICD-10 codes (r=0.88). [60]

The Elixhauser index (EI) consists of 30 conditions, identified using ICD-9 codes from administrative data to predict length of hospital stay, hospital charges, and inhospital mortality. [61] These conditions were selected for their relevance to hospitalization other than the primary reason for the hospital stay and the severity of that primary condition. [62] Unlike the CCI, the EI does not use weights for the component conditions in the score. The EI's ability to predict inhospital mortality has ranged from good to excellent in several studies. [39] Quan et al.'s enhanced EI performed the best, using a broader range of ICD-9-CM codes. [55]

A host of studies have looked at head to head comparisons of the CCI to EI. Overall, both demonstrated poor to excellent ability to predict various outcomes. [39] For inhospital mortality the C ranged from 0.63 to 0.88 for the CCI and 0.61-0.86 for the EI. [39] For 1 year mortality the CCI ranged from 0.69-0.91 and EI from 0.65-0.91. [39] Using Medicare claims data, one study showed that a combined comorbidity score performed better than the CCI or EI alone in predicting 30-day mortality in older adults. [62] The CCI and EI components were combined and the weights recalculated, which resulted in a combined score with 20 non-zero weighted conditions. [62] Interestingly, this score included conditions with negative weights (HIV/AIDS and hypertension) implying a protective effect of the comorbidity. [62]

The chronic disease score (CDS) was created in 1992 by von Korff et al. using medications from a population-based pharmacy database to identify comorbidities. Weighted disease categories were created by a panel of experts using selected medications. [63] The CDS has been expanded to 28 disease categories and weighted using regression instead of expert consensus. This modification is the CDS-2 and has been validated in a number of populations. [39] The RxRisk index was developed to be used on all age populations and includes 57 adult and pediatric weighted disease categories. Rx Risk-V was adapted for the Veteran's population using VA data. [39]

Several studies have compared the diagnosis based indices to the medication based indices, with inconsistent results. Mortality outcomes, Deyo CCI predicted better than CDS-1 in one study and RxRisk V predicted better than Deyo in another. [39] The different risk scores had similar predictive ability for hospital readmission, length of stay, hospitalization, spending, and costs. [39] No one model performs best across all outcomes. Usually the model will perform best for an outcome for which it was designed. The Charlson was designed to predict 1 year in-hospital mortality and has had limited success in predicting other outcomes, such as infection with MDROs. McGregor et al. compared the CCI to CDS ability to predict MRSA and VRE in an ICU. [64] The c statistic for CCI was 0.65 and 0.61 for the CDS for the MRSA model and 0.67 for CCI and 0.65 for the CDS in the VRE model. [64]

Innovation

Current risk adjustment methods for both SSI and CLABSI are lacking. The CDC does not consider patient comorbidities beyond diabetes and BMI in their SSI models and no patient-level factors in their models for CLABSI. [42] Little research has been conducted on how adding electronically available comorbid conditions to these risk

models would improve performance.[31,50] The aim of this analysis is to illustrate the effect of risk adjustment by comparing crude SSI and CLABSI rates to adjusted rates across hospitals.

Hospitals with a large burden of patients with more comorbid conditions are expected to have a larger rate of CLABSI and their ranking will improve once the risk adjustment model is applied. Likewise, hospitals that serve healthier patients with fewer comorbidities may decline in their performance ranks when SIRs are adjusted for patient case-mix. These shifts may have consequences on payments and penalties for an individual hospital when all U.S. hospitals are included in this ranking, as currently done by CMS. The results of this aim could potentially change the current CDC risk adjustment methodology for nationally reported SSI and CLABSI rates by incorporating comorbid conditions. Improved methodology can result in a better comparison of hospitals and better information for patients.

CHAPTER III. STUDY DESIGN AND METHODS

A. Aim 1

1. Study Design

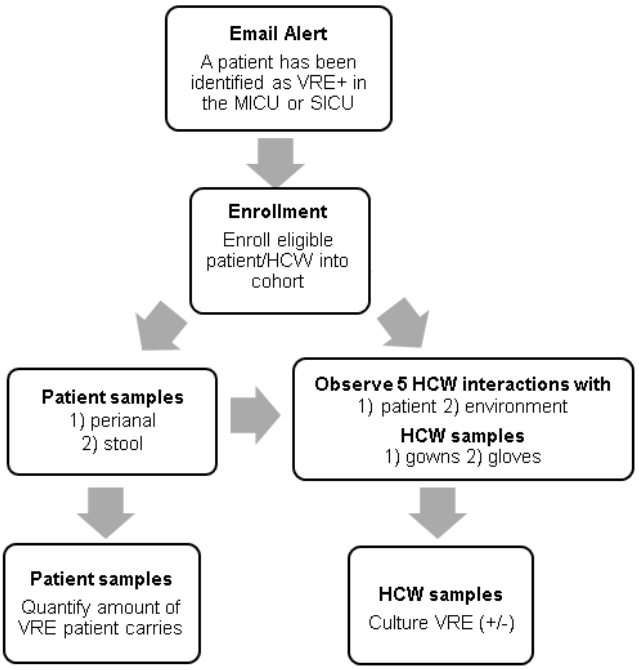
This is a prospective cohort study of 100 ICU patients colonized with VRE designed to examine the relationships between bacterial burden and transfer of VRE to HCWs, and risk factors associated with transmission of VRE to HCWs' gloves or gowns. The transfer of VRE from patient to HCWs' gloves or gowns may serve as a surrogate measure of transmission in ICUs through HCWs. This is important because the transfer of MDRO from HCWs' hands to other patients is thought to be a significant driver of bacterial transmission in hospitals.

2. Participants

One hundred patient participants were sampled from two adult ICUs at University of Maryland Medical Center (UMMC): the Medical ICU (MICU) and Surgical ICU (SICU). These ICUs conduct active surveillance for VRE wherein all patients are screened for VRE at ICU admission, thereafter weekly, and at discharge. This active surveillance is conducted as part of UMMC Hospital Epidemiology and Infection Prevention Standards of Care.

Patients were identified from the hospital microbiology laboratory daily list of all patients currently admitted to MICU or SICU with a new VRE positive culture. The research staff were notified each day of patients with recent (~72 hours) VRE positive rectal surveillance cultures via email alerts associated with hospital microbiology reports. Five HCWs per patient were enrolled for a study total of 500 HCW participants. Please see figure 1 for a schematic of the study design.

Figure 1. Aim 1 study design schematic



The Institutional Review Board at UMMC granted approval for waived consent of patient participants. The research study was described to the HCWs and verbal consent was obtained. Patient and HCW participants who expressed a desire to not participate were not enrolled. The patients selected into the study represent a convenience sample. Patients were enrolled Mondays through Thursdays, for up to 4 patients per week, and no more than 2 patients per day. See Figure 2 for a schematic of the study flow and Table 4 for the demographics of patients enrolled in the study and patients who were not enrolled. One patient was enrolled from the Trauma ICU, who was later dropped from the analysis after the research staff decided to limit enrollment to the MICU and SICU only.

Figure 2. Enrollment and analysis flow chart for Aim 1 study

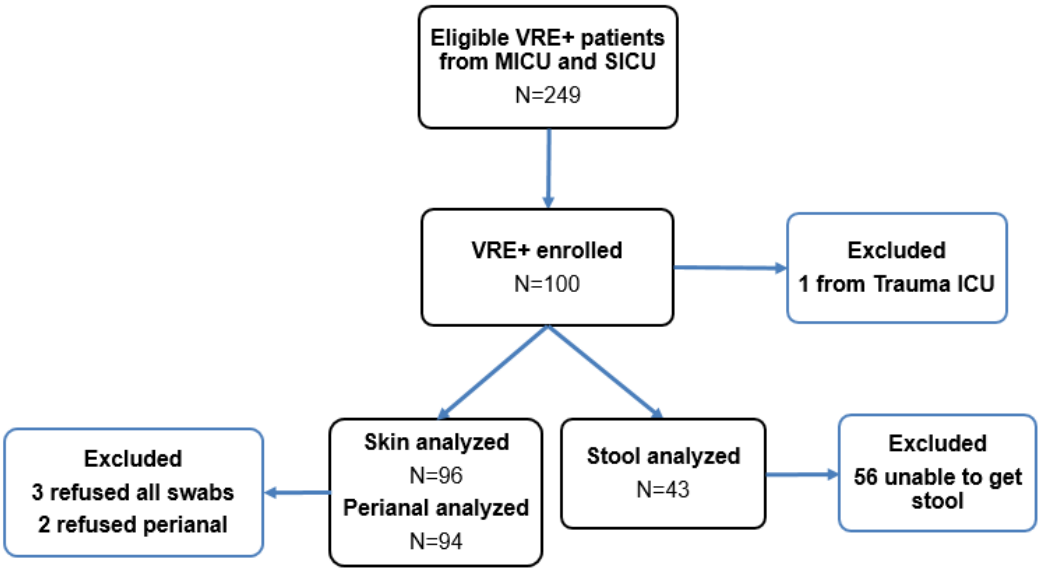


Table 4. Demographic and clinical characteristics of patients enrolled and not enrolled in the VRE study between January 1, 2017 and November 15, 2017

Characteristic	Enrolled N=99*	Not enrolled N=194	P-value
Age in years, mean (SD)	60.8 (12)	57.5 (14)	0.056†
Sex, n (%)			
Female	47 (47)	68 (46)	0.813‡
Male	52 (53)	80 (54)	
Race, n (%)			
American Indian/Alaskan Native	0 (0)	2 (1)	
Black or African American	39 (41)	56 (39)	0.707‡
Hispanic	2 (2)	3 (2)	
White	54 (57)	83 (58)	
ICU location, n (%)			
MICU	60 (61)	82 (55)	0.385‡
SICU	39 (39)	67 (45)	
Elixhauser Index, mean (SD)	7.0 (3)	6.6 (2)	0.253†
Length of ICU stay in days, median (range)	13 (3-118)	8 (1-98)	<0.001§

*Excluded 1 patient from the trauma ICU; †Students' t-test; ‡chi-square test; §Wilcoxon-rank sum test
Abbreviations: ICU, intensive care unit; MICU, medical intensive care unit; SD, standard deviation; and SICU, surgical intensive care unit.

3. Outcome variables

HCW contamination was measured as the presence or absence of VRE on the gloves or gown. Each VRE positive patient identified from surveillance in the SICU is placed on contact precautions. The MICU has a universal contact precautions policy, whereby HCWs are required to where glove and gowns whether the patient has tested positive for

an MDRO or not. Contact precaution protocol requires gloves and gowns to be worn by HCWs before entry into patients' rooms. As such, there was the opportunity to sample the gowns and gloves of each HCW participating in this study without changing standard protocol.

HCWs' gloves and gowns were sampled for the presence of VRE with dual CultureSwabs (BBL; Becton Dickinson, Sparks, MD) after patient care and prior to doffing. The swab was rubbed gently with a twirling motion along the dorsum of each finger and the palm of both the right and left hand. HCWs' gowns were swabbed with a twirling motion twice on each forearm and then by swabbing a "W" along the beltline with a single swab.

Laboratory procedures

HCWs' glove and gown swabs were cultured for the presence of VRE. The swabs were removed from their containers with a Kimwipe, placed into tryptic soy broth with 6.5% NaCl and vortexed for 10 seconds. The swabs were discarded and all tryptic soy broth with 6.5% NaCl tubes were incubated for 24 hours at 35± 2°C. After incubation, 50 µl from each broth tube were inoculated onto a Bile Esculin Azide Agar with 6 µg/mL Vancomycin (BEAV) plate for isolation. The BEAV plates were incubated aerobically at 35± 2°C for 48 hours. Following incubation, colonies were subcultured, identified and speciated by the VITEK II, and were subsequently tested for vancomycin (30µg/mL) susceptibility. All enterococcal isolates were frozen in tryptic soy broth with 15% glycerol and stored at -80°C.

4. Predictor variables and covariates

a. Aim 1a

Predictors

The exposure of interest is the quantity of VRE each patient is colonized with, measured in colony forming units per milliliter (CFU/mL). To measure each patient bacterial burden, we swabbed the patient's perianal area, chest, antecubital fossa, and obtained a stool sample when available. These areas were selected for sampling because prior literature has identified them as highly efficient areas of transmission.[2]

The perianal area was swabbed using aseptic technique with ESwab tubes (FLOQSwab + 1 mL Aimes transport medium). The FLOQSwab was rubbed gently back and forth three times on the skin immediately around the anus, covering an area approximately four centimeters (cm) in diameter. A sterile 10x10 cm^2 template was used to ensure all antecubital fossa and chest skin samples were collected in a standardized fashion between patients. The FLOQSwab was rubbed within the template with a twirling motion to ensure all sides of the swab came in contact with the skin. After collection, the FLOQSwab were placed in the ESwab tubes with 1mL Aimes transport medium.

The stool sample was collected, when available, in Dynarex sterile stool specimen containers. If the patient had a rectal tube, the stool was collected from the colorectal bag using the scooper within the collection tube. For patients without rectal tubes, stool was collected by asking the nurse to save stool after the patient's bowel movement or directly from patient's diaper/padding as applicable. We were able to collect stool from 43 (43%) patients.

All specimen collection tubes were labeled with the study id, specimen number, and collection date.

Laboratory procedures

Patient swabs and stool samples were placed into collection tubes and sent to the MRL for quantification. The swabs from the skin and perianal sample were vortexed separately for one minute, and then the swab heads were removed and discarded. One gram of stool was extracted from the stool container, added to 1mL of 0.9% saline in an Eppendorf tube, and vortexed until well mixed (at least one minute).

One mL of each patient sample was serially diluted using Butterfield's Buffer. BEAV was inoculated with 100 µL of each serial dilution and distributed evenly onto the each agar plate using a cell spreader. Next, 100 µL of the original ESwab sample were inoculated into tryptic soy broth with 6.5% NaCl. The plates and broth tubes were incubated for 48 hours aerobically at 35± 2°C, after which the number of bacterial colonies were counted. If there was no growth on the inoculated plates, 100 µL from the previously inoculated tryptic soy broth with 6.5% NaCl tubes were inoculated onto a BEAV plate. If there was growth on the BEAV agar after 48 hours at 35± 2°C, a count of one CFU was given. Enterococcal identification and speciation were confirmed by the VITEK II. All confirmed enterococcal isolates were frozen in tryptic soy broth with 15% glycerol and stored at -80°C.

Antimicrobial susceptibility testing was conducted using the Kirby-Bauer disk diffusion method on Muller Hinton agar according to the Clinical Laboratory Standards Institute guidelines. A 0.5 McFarland standard was prepared from each isolated enterococci colony, and all isolates were tested with 30 µg/mL vancomycin. Plates were incubated for 24 hours at 35± 2°C, and growth was assessed visually to ensure accurate determination of zone sizes.

Covariates

Patient-level factors of age, race, gender, comorbidities, acute conditions, presence of devices, or diarrhea (for the perianal and skin analyses only). Patient characteristics include the presence of an artificial airway (endotracheal or tracheostomy tube), wound, Foley catheter, intravascular catheter (central line), chest tube, surgical drain, diarrhea, rectal tube and nasogastric tube. These variables were chosen based on prior literature showing increased transmission between patients with devices and HCWs [12] (see Appendix 1 for a replication of the data collection forms).

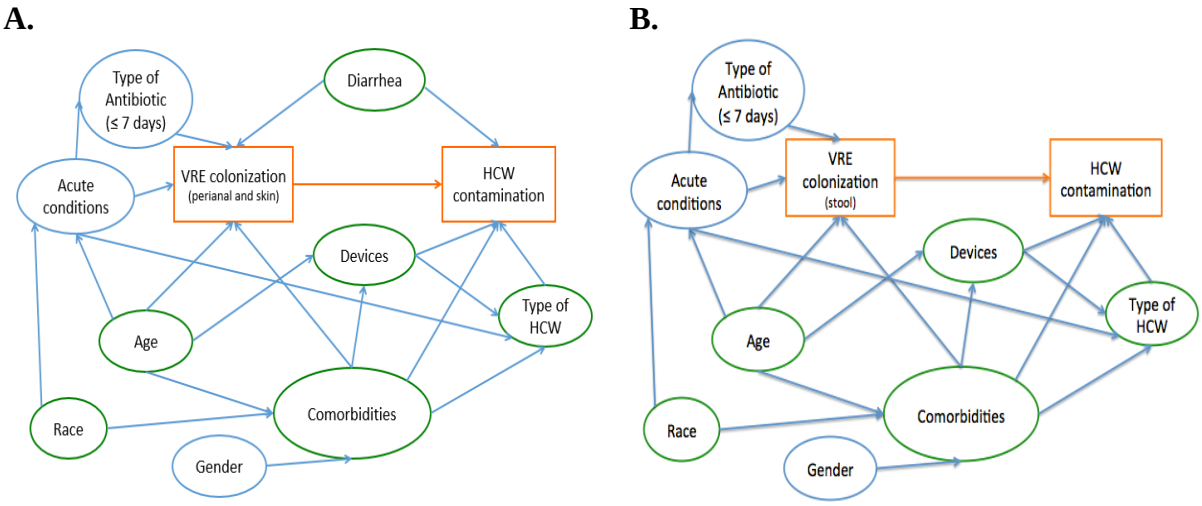
The patient demographics of age, sex, and race were abstracted from the electronic medical record. The Elixhauser Index was used to adjust for comorbidities and was constructed with ICD codes abstracted from the medical record. [65] A random sample of 10% of these abstracted data was compared to the electronic health record to assess the validity of these data. A discussion with patients' HCWs provided us with information on the presence of devices and diarrhea. Because specific patient acute conditions were not captured, the type of ICU was used as a proxy

HCW-level factors included the amount of time the HCW spent in the room (in minutes) and the type of HCW entering the patient room. The types of HCW are: nurse, physician/nurse practitioner (MD/NP), patient care technician (PCT), respiratory technician (RT), physical therapist/occupational therapist (PT/OT), environmental services (EVS), and other. This other category includes nutritionists, dialysis technicians, and the study researchers, among others.

The presence of confounding was assessed based on clinical and statistical knowledge. Figure 3 displays the directed acyclic graph that describes the relationship

between the covariates and the exposure-outcome relationship (3A presents the perianal and skin models and 3B presents the stool model). The exposure and outcome are highlighted in orange boxes and the direction of the association marked by the orange

Figure 3. Directed acyclic graph to identify sufficient set of confounders in Aim 1a. **A)** Perianal and skin models. **B)** Stool model.



arrow. All possible covariates are contained in the circles and the direction of the associations are noted by the arrows. These covariates were selected for their relationship to the exposure (e.g. they may impact the overall quantity of the organism found on the patient) and are also associated with an increased risk of transmission to HCWs. [2,13,66] The minimally sufficient set of covariates needed for confounding control are patient comorbidities, presence of devices, and type of HCW. However, our previous work on using comorbidities has shown that there may be some residual confounding due to low sensitivity of ICD codes used in comorbidity adjustment. [50] Race and age were added to the models to block the path from comorbidities due to the possibility of residual confounding. The minimally sufficient set needed for adjustment are presented in green in Figure 3.

Effect measure modification

Existing literature suggests that patients with diarrhea may have increased bacterial shedding. [14] Increased shedding of bacteria to the environment may lead to an increase in HCWs' glove and gown contamination. Because the relationship between quantitative bacterial load in the stool and HCW contamination may be different depending on the presence of diarrhea, this covariate was explored as potential effect measure modifier in the stool model. No effect measure modification was found when the stool data was stratified by isolated species *E. faecium* and E. faecalis (p for interaction =0.291). The association between bacterial burden and HCW contamination among patients colonized with *E. faecium* was OR: 1.87 (95% CI: 1.28, 2.73) and among those colonized with *E. faecalis* was OR: 1.44 (95% CI: 1.04, 1.98). These preliminary results do not indicate presence of effect measure modification on the odds ratio scale and are not presented in the results.

b. Aim 1b

Predictors

The following predictors were collected on a standardized form during each HCW-patient observation, each of which are categorized into three domains: HCWs' characteristics, patient characteristics (as detailed in covariate section in Aim 1a) and patient care activities.

Patient care activities were categorized into two domains as interactions with the patient's environment and interactions with the patient. Variables collected within the environmental domain included touching the sink, bedside table, vital sign monitor, supply cart, lift, IV pump, ventilator, curtain, trash, computer, barcode scanner, call button. Variables collected within the patient domain include bed rail, bedding, anal/groin

area, skin, wound dressing, bathing/hygiene, catheter/drain, artificial airway, vital signs, giving oral meds, IV tubing/IV meds, transfer in/out of bed, blood draw, glucose monitoring, rectal tube/bag, and suctioning. Each domain on the data collection form had a place to record activities that fell outside these pre-specified activities ("Other, specify"). Please see Appendix 2 for a cross-walk of how these variables were categorized. These patient care activities were chosen based on prior literature showing these interactions were associated with increased transmission of several types of MDROs. [13,23,66,67]

5. Analysis

a. Aim 1a

Bacterial counts were expressed in CFU/mL and were logged transformed ($\log_{10}$ [bacterial burden +1]). The chest and antecubital fossa swabs were collapsed into one variable (referred to herein as skin swabs) by taking the higher of the two measurements. Frequencies and proportions were calculated to describe the demographics, clinical characteristics, and VRE species of the sample. The mean bacterial burden (and 95% CI) of *E. faecium* and *E. faecalis* present in each of the patient samples was estimated. Pearson's correlations were calculated to compare the bacterial burden between each sample.

The association between patient bacterial load and transfer to HCWs' gloves or gowns was estimated using logistic regression models fit by generalized estimating equations (GEE) with an exchangeable correlation matrix to take into account within-patient correlation. Separate models were constructed for VRE burden recovered from the perianal swab, skin swabs, and the stool sample. The association between VRE species

isolated from each of the patient samples and HCW contamination was also estimated using GEE. The use of GEE results in odds ratios (OR) and 95% confidence intervals (95% CI) that estimate the average patient odds of transmission.

Tests for linearity between the continuous variables (bacterial burden in the patient samples, patient age, and duration of time HCWs spent in the room) and the outcome were conducted. To test this assumption, the functional form of these variables were modeled with spline regression. Splines are piece-wise polynomials with the pieces defined by knots. The slopes of each piece, or segment, are allowed to vary and are estimated separately.[68] Knot placement was determined by dividing the continuous variables into quartiles, regressing the quartiles on the outcome, and plotting the median in each quartile against the beta estimate from each model.

The score test, which tests the null hypothesis that the slopes of each segment are equal, was used to test for linearity. Results from the score test for the model where the exposure was bacterial burden from the perianal sample indicates that the linearity assumption holds [X^2=0.15, p=0.929]. Comparing the quasi-likelihood under the independence model criterion[69] (QIC)* (QIC=348.95) between the spline model and a model where bacterial burden (QIC=342.36) was entered as continuous variable shows better fit for the latter model.

The score test for the VRE bacterial burden in the stool model did not indicate any departures from linearity (X^2=2.95, p=0.228) and QIC=201.80. Modeling the exposure continuously also indicated better fit, QIC=200.70 compared to the spline

* QIC is the quasi-likelihood analogue to the Akaike Information Criterion used in maximum likelihood estimator models for variable selection.

model. The assessment of linearity for the skin model used a spline with one knot at the 70th percentile (instead of at the quartiles) because VRE was recovered from only 30% of the patients. Results from the score test for the perianal model (X^2=1.88, p=0.171) indicate that the linearity assumption holds. While the QIC of the spline model is slightly smaller (QIC=360.41) than a model where bacterial burden was entered as continuous variable (QIC=362.33), the skin bacterial burden was modeled continuously due to the results of the score test.

Duration of time the HCW spent in the room was also found to have a non-linear relationship with the outcome (X^2=6.71, p<0.001). The odds of contamination for time spent in the room between 0 - 6 minutes steadily increased, while the time after 6 minutes did not show an additional increased odds of contamination. Age was also found to be non-linear (X^2=5.52, p=0.019) and so a spline was constructed with the knot at the median of 68 years for the perianal and skin models and at the median of 61 years for the stool model.

All the candidate covariates were entered into the models for bacterial burden and VRE species and confounding was assessed as a 10% change in the estimate of the main effect. Covariates that met this criterion for confounding were retained in the final model. None of the covariates met this criterion in the perianal or skin model, so the final model was selected by choosing the model smallest QIC.

b. Aim 1b

Risk factors and transmission to healthcare workers were analyzed using in three ways:

1) The association between type of HCW (nurse, MD/NP, RT, PCT, PT/OT, EVS, other) and HCWs' glove or gown contamination was estimated by looking at the frequency of transmission among the provider types and estimating ORs and 95% CIs using GEE, adjusting for relevant cofounders. Potential confounders identified *a priori* were patient devices, patient comorbidities, diarrhea, age, VRE burden (as measured by the perianal swab) and duration of time (in minutes) the HCW was in the patient's room. Model selection was conducted using a stepwise procedure whereby each combination of confounders were entered into the model and comparing the QIC of each model. The model with the smallest QIC was selected for presentation.

2) The association between touching items in the environment (environmental domain) or on the patient (patient domain) and HCWs' glove or gown contamination. Please see Appendix 2 for details of how the environmental and patient domains were categorized. This analysis was performed using GEE to estimate ORs and 95% CI to account for patient clustering. The same covariates presented in part 1 of this aim 1b were selected as potential confounders and models were selected on the basis of smallest QIC.

3) The association between specific patient-care activities/touching each item (see Appendix 2 for list) and HCWs' glove or gown contamination was estimated ORs and 95% CIs using GEE, adjusting for relevant cofounders (as outlined in part 1). Risk factors significant at $\alpha \leq 0.10$ were considered candidate predictors for the multivariable model. Model building was conducted in a stepwise fashion where the model with the lowest QIC was chosen as the final multivariable model. Odds ratios and 95% CIs from this model were presented and interpreted.

All analyses were conducted using SAS version 9.4 (The SAS Institute, Cary, NC).

6. Sample Size and Power

Sample size was calculated for several levels of transmission proportions in the high and low bacterial load groups. Transmission proportions of VRE between patients with high and low bacterial load are not available in the literature. Instead, a review of the literature estimates average transmission rates of VRE from patient to HCWs ranges from 8.5% to 13%. [23,24] Transmission proportions in each group were estimated based on this average rate. These estimates range from 2% to 10% in the low bacterial load group to 10% to 30% in the high group. Sample size was estimated using proc power in SAS with power set at 80%.

A design effect was estimated to account for clustering at the patient level using the formula: $n_{adj}=n*(1.2+rho*(m-1))$ where correlation (rho) is 0.25 (based on previous work from the group, epicenter grant) and m is a cluster size of 5 (the number of HCWs per patient). [70] The results of these calculations are shown in Table 5. The average transmission rates of VRE in research conducted by Dr. Harris and Dr. Thom have ranged from 8.5% and 13.9%, [24] 11.2% is the average transmission rate. Power calculations were run with a variance inflation factor to estimate the odds ratio and amount of power we would have to detect that association in a clustered design. We assumed there would be an equal proportion of high transmitters and low transmitters (e.g. prevalence of P_2 is 50%). Based on the feasibility of enrolling patients we have selected the highlighted row in the power Table 5 for a sample size of 93 patients. Power calculations were run (using proc power in SAS), which found that this sample size would yield a power of 81% to detect an odds ratio of 3.89.

Table 5. Sample size calculations for Aim 1

Proportion in Low bacterial count	Proportion in High bacterial count	Average transmission percentage	Difference	Number of observations needed per group	Adjusted number of observations needed per group	Adjusted total number of observations needed	Total number of patients needed
0.02	0.15	8.5	0.13	72	158	317	63
0.02	0.20	11	0.18	47	103	207	41
0.02	0.25	13.5	0.23	34	75	150	30
0.05	0.10	7.5	0.05	435	957	1914	383
0.05	0.15	10	0.10	141	310	620	124
0.05	0.17	11	0.12	106	233	466	93
0.05	0.18	11.5	0.13	94	207	414	83
0.05	0.20	12.5	0.15	76	167	334	67
0.05	0.25	15	0.20	49	108	216	43
0.05	0.30	17.5	0.25	36	79	158	32
0.07	0.12	9.5	0.05	539	1186	2372	474
0.07	0.15	11	0.08	239	526	1052	210
0.07	0.17	12	0.10	165	363	726	145
0.10	0.15	12.5	0.05	686	1509	3018	604
0.10	0.20	15	0.10	199	438	876	175

*11.2% average transmission rate based on 8.5% and 13.9% from Harris' group in literature.

B. Aim 2

1. Study Design

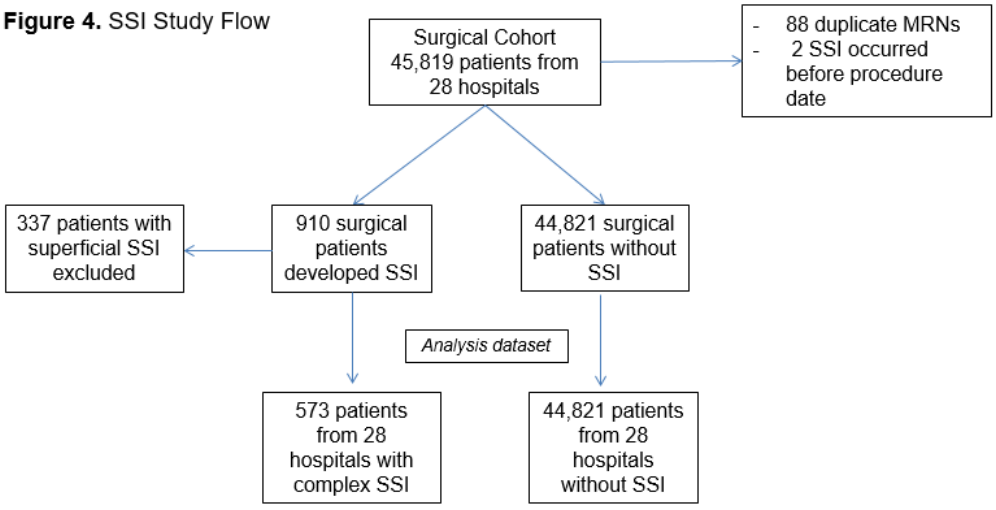
This aim is concerned with building risk adjustment models for SSI and CLABSI. We assembled a retrospective cohort of surgical patients for SSI and ICU patients for CLABSI from hospitals across the US. The hospitals were recruited by Dr. Harris from the Society of Hospital Epidemiologists of America network, a national HAI surveillance database. Premier, a hospital data warehouse, was contracted to provide us with all the electronic health records of surgical (for the SSI aim) and ICU patients (for the CLABSI aim) at these hospitals during the same time period and merge the data with the HAI data sent by the sites. These electronic health records include patient demographics, hospitalization dates, procedure details, and ICD-9 codes. Premier linked the SSI and CLABSI infection data (e.g. type of SSI, date of SSI, date of CLABSI, etc.) provided by the hospitals to the patient medical records in their central data repository. I validated and cleaned the dataset by confirming infection rates and dates with the sites, reviewing the data for consistency and completeness, and performing date range and logic checks.

2. Participants

a. Aim 2a SSI

The SSI cohort consists of all adult (≥18 years old) patients undergoing colectomy, hysterectomy, or knee or hip replacement procedures at the participating hospitals between January 1, 2012 and December 31, 2013 at 28 US hospitals. These procedures were identified from the Premier Quality Advisor™ database ICD-9-CM codes and Current Procedural Terminology codes for the NHSN operative procedure categories. See Figure 4 for a schematic of study flow.

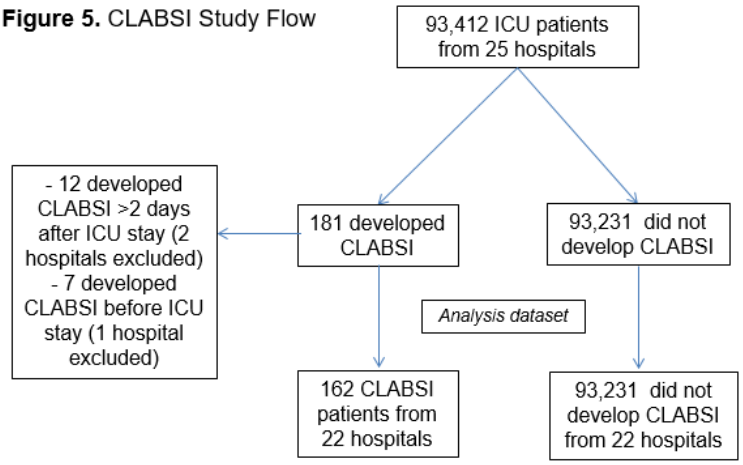
Figure 4. SSI Study Flow



b. Aim2b CLABSI

The CLABSI cohort consists of all adult ICU patients (≥18 years old) hospitalized between January 1, 2012 and December 31, 2013. CLABSI cases were identified by trained IPs at each hospital and then all non-CLABSI patients were selected for analysis from the same ICUs from which the CLABSI cases arose. See Figure 5 for a schematic of study flow. Institutional Review Board approval was obtained by Premier for study oversight and by each participating hospital.

Figure 5. CLABSI Study Flow



*CLABSIs from these hospitals were excluded because the CLABSI dates did not fall within the ICU window. Hospitals without CLABSIs were excluded.

3. Outcome variables

a. Aim 2a SSI

SSIs and CLABSIs were identified by IPs at each hospital using standardized CDC NHSN criteria. [71] SSIs were classified using NHSN definitions of superficial incisional, deep incisional, or organ/space. Patients with superficial SSIs were excluded from this analysis as the risk factors may be different from those with deep incisional and organ/space (complex) SSIs and the morbidity and mortality from complex SSIs are higher. [72] Public reporting excludes superficial SSIs, in part, due to the subjectivity of assessing superficial SSIs and poor comparisons between facilities. [73]

b. Aim2b CLABSI

Patients with CLABSI were identified by trained IPs at each hospital using CDC NHSN definitions. [71] Patients who were diagnosed with CLABSIs either while in the ICU or within two days of being discharged from the ICU were included in the analysis. Patients diagnosed with CLABSIs before ICU stay or >2 days after ICU stay were excluded from the analysis.

4. Predictor variables

a. Aim 2a SSI

For the SSI risk adjustment model, procedure type, patient characteristics including age, race, and comorbidities from either the CCI or EI thought to be associated with SSI based on expert consensus.[74] Procedure type was be entered into the model as a covariate instead of building separate procedure specific models (as is done by the CDC) due to the smaller numbers of procedure-specific SSI outcomes. Age was entered the model as a continuous predictor after confirming that there is a linear relationship with the outcome.[34] Patient race was categorized as black, white, or other. Smoking was selected *a priori* as a potential risk factor for SSI. ICD-9-CM codes for former and current smoking (V15.82 and 305.1) were used to create a variable for 'ever smokers.'[75]

The comorbid conditions thought to be associated with SSI were identified from expert consensus, which has been reported elsewhere.[74] Using Delphi consensus[76,77] nine infectious disease and infection control experts were asked to rate the 35 comorbid conditions found in the Charlson and Elixhauser Indices from 1 (not at all related) to 5 (strongly related), based on perceived relatedness to SSI. These experts rated the following 17 conditions as 3 (somewhat related) or higher: blood loss anemia, chronic pulmonary disease, coagulopathy, congestive heart failure, diabetes without complications, diabetes with complications, hemiplegia or paraplegia, HIV/AIDS, lymphoma, malignancy, peripheral vascular disease, solid tumor with metastasis, severe liver disease, obesity, renal disease, rheumatologic disease, and weight loss (malnutrition).

All available patient ICD-9-CM codes were mapped to comorbid conditions outlined by Quan et al. [65] Multiple ICD-9-CM codes were used in defining comorbidities, but the conditions themselves were operationalized as binary variables; that is, either the presence or absence of a condition. The variables of ASA score and surgery duration were not available in the Premier data set and so are not included in our models.

b. Aim2b CLABSI

In order to compare the CDC methodology to our patient case-mix model two models were constructed as follows: 1) a model containing ICU type, medical school affiliation, and hospital size (CDC methodology) and 2) a model containing ICU type plus patient case-mix variables model. Hospital size was defined in the 2017 CDC NHSN model as a binary variable indicating the number of beds in the hospital ≥276. [33] For the latter model, we identified candidate comorbidity variables using expert consensus, similar to methodology in For CLABSI, these experts rated the following 13 conditions in terms of causality with CLABSI as 3 (somewhat related) or higher: coagulopathy, dementia, diabetes without complications, diabetes with complications, drug abuse, hemiplegia or paraplegia, HIV/AIDS, lymphoma, malignancy, solid tumor with metastasis, severe liver disease, obesity, renal disease, and weight loss (malnutrition). All available patient ICD-9-CM codes were mapped to comorbid conditions outlined by Quan et al. [65]

5. Analysis

a. Aim 2a SSI

Logistic regression with a random intercept for hospital was used to account for the correlation between patients from the same facility. [78] The 17 comorbid conditions identified by experts as mentioned above, along with procedure type, age, race, and smoking status, were entered into the model as potential predictors of SSI and variables were retained using backwards selection if they met the significance level of $\alpha < 0.05$.

The predicted probabilities of an SSI for each patient were calculated from this model without including the random effect in the prediction so that hospital did not influence these values. These predicted probabilities were then used to generate the C-statistic and 95% CI for the model. Calibration, which is how well the model predicts the outcome, was assessed with a calibration curve. The curve was constructed by first dividing the predicted probabilities into deciles of risk. Next the predicted probabilities were plotted against the observed proportion of SSI in deciles. A 45-degree line was added to visually inspect how well the model was calibrated. In a perfectly calibrated model the predicted probabilities will agree with the actual observed risk. In other words, the plotted decile points should line up perfectly on the calibration plot's 45-degree line. [37]

The model was validated using internal-external validation to adjust for optimism in clustered data. [79] In internal-external validation, all candidate predictors were entered into a logistic regression model with a random intercept for hospital, excluding one hospital from each run. The coefficients from the resultant model were then applied to the model for the excluded hospital and the C-statistic estimated. This procedure was run 28 times for each hospital and the C-statistic for each model was estimated. The mean of 28

model C-statistics and 95% CI estimate represents the optimism adjusted C-statistic for the final model.

The proportions of SSIs observed at each hospital were calculated and the hospitals were ranked in ascending order from least to greatest proportion of SSI. The predicted probabilities from the mixed model were summed to estimate the expected number of SSI events for each hospital. The SIR for each hospital was calculated by dividing the observed number of SSIs by the expected number of SSIs predicted by the model, similar to the current NHSN method.[73] Hospitals were then ranked by the risk-adjusted SIRs and compared to the rankings when ordered by the unadjusted SSI proportions.

b. Aim 2b CLABSI

Two risk adjustment models for CLABSI were constructed using discrete time survival analysis, a method that accounts for time at risk.[80] Acquisition of CLABSI on each day in the ICU was modeled as the outcome of a binary regression model with a complementary log-log link. A random intercept for hospital was included in the model to account for the clustering of patients within hospitals. The first model (CDC model) included the candidate predictors ICU type, academic affiliation, and hospital size. The second model (our CDC + patient case-mix model) included the 13 comorbid conditions identified by expert consensus, along with ICU type, age, gender, race, hospital size, and medical school affiliation. These variables were entered into the model as potential predictors of CLABSI. Variables were retained using backwards selection if they met the significance level of alpha <0.05.

From these models, the predicted probabilities of a CLABSI for each patient-day in the ICU was estimated without including the random effect in the prediction so that hospital characteristics did not influence these values. These predicted probabilities were then used to generate the C-statistic and 95% CI for both models. The predicted probabilities were plotted against the observed rate of CLABSI in deciles along a 45-degree line to visually inspect how well the model was calibrated.

To calculate risk-adjusted rates, the predicted probabilities from both risk adjustment models were summed to estimate the expected number of CLABSI events for each hospital. SIRs for each hospital were calculated by dividing the observed number of CLABSIs by the expected number predicted by each model. Hospitals were ranked first by the CDC model SIRs and then by the comorbidity-adjusted SIRs.

Sensitivity analysis

One potential problem with this aim is that ICUs without CLABSIs were excluded from the final dataset. Further, when CLABSI events were limited to those that occurred within two days of ICU discharge (the CDC NHSN definition), three hospitals were also dropped because they did not contribute any CLABSIs to the analysis. Therefore, the incidence rate of CLABSI is overestimated in this analysis. Further, there may be a different distribution of comorbidities among the patients in these excluded ICUs, which may affect the comorbidities included in the risk adjustment model.

A sensitivity analysis was conducted using the three hospitals excluded from the main analysis to re-estimate the CLABSI rate and to re-estimate the risk adjustment model. If there is not a substantial change in the predictors and model discrimination when including these hospitals, this may imply the exclusion of the ICUs from the dataset

would not have substantially altered the results. The results of this analysis are presented in Appendix 3.

All analyses will be conducted using SAS version 9.4 (The SAS Institute, Cary, NC).

6. Sample Size

Traditional sample size calculations were not performed for this aim because there is not a measure of effect that we want to estimate, nor are we trying to detect a difference between two groups. While this is not a purely predictive model, overfitting is a concern in risk adjustment models so we assessed sample size by looking at the events per variable ratio. [81,82] The SSI dataset contains over 45,000 patients and the CLABSI dataset contains over 100,000 patients. There are a total of 52 potential predictors including the comorbid conditions from the CCI and EI, smoking, and demographic characteristics. There are a total of 573 SSIs so the events per variable is appropriate if all predictors are included in the model. However, there were 162 CLABSIs, which means that at most 16 predictors can be included in the model. Please see the analysis section below for details on how predictors were selected.

CHAPTER IV. BACTERIAL BURDEN IS ASSOCIATED WITH INCREASED TRANSMISSION TO HEALTH CARE WORKERS FROM PATIENTS COLONIZED WITH VANCOMYCIN-RESISTANT *ENTEROCOCCUS* [1]

A. Abstract

Background: Healthcare workers (HCWs) are significant vectors for transmission of multidrug- resistant organisms among patients in intensive care units (ICU). We conducted a study of ICU patients on Contact Precautions, colonized with vancomycin-resistant Enterococcus (VRE) to assess whether bacterial burden is associated with transfer to HCWs' gloves or gowns , a surrogate outcome for transmission to subsequent patients.

Methods: From this prospective cohort study we analyzed 96 VRE colonized ICU patients and five HCWs per patient. We obtained samples from patients' perianal, skin, and stool to assess bacterial burden and cultured HCW gloves and gowns for VRE after patient care.

Results: Seventy-one of 479 (15%) HCW-patient interactions led to HCWs' glove or gown contamination with VRE. VRE burden was associated with HCW contamination on the perianal swab (OR: 1.37 [95% CI 1.19, 1.57]); skin swabs (OR: 2.14 [95% CI: 1.51, 3.02)]; and in stool (OR: 1.95 [95% CI: 1.39, 2.72]). Colonization with *E. faecium* was associated with higher bacterial burden and more HCW contamination than colonization with *E. faecalis*.

[1] Submitted to *Clinical Infectious Diseases*

Discussion: Our study shows that ICU patients with higher bacterial burden are more likely to transfer VRE to HCWs. These findings have implications for VRE de-colonization and other infection control interventions.

B. Introduction

Enterococcus make up 14% of all hospital-associated infections (HAI) reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention.[83] Roughly 35.5% of all enterococcal HAIs are resistant to vancomycin (VRE).[84] VRE is responsible for bacteremia, surgical site infections, and urinary tract infections[84] and the cause of approximately 1,300 deaths annually.[1] The two predominant species of VRE are *E. faecium* and *E. faecalis*, which make up roughly 77% and 9% of isolates, respectively.[1]

VRE has a demonstrated propensity for skin colonization, which can increase the risk of catheter-related bacteremia and cross-infection.[85] Patients' skin colonization can also lead to transfer of VRE to the healthcare workers' (HCWs') hands and clothing while providing patient care. This is especially concerning as VRE has been shown to last up to 60 minutes on HCWs' hands in the absence of hand hygiene.[86] This contamination of HCWs can lead to further transfer of VRE to patients' other body sites (cross contamination), the patient's environment, or to other patients in the HCWs' care.[21]

Whether the bacterial load of VRE increases the risk of transmission is thus far unknown. While several studies have found that colonized patients can transmit MDROs, including VRE, to HCWs, these studies suffered from small samples sizes and[2,22-24] associations between patient bacterial burden or colonizing species and HCW contamination were not estimated. Therefore, we conducted a study of ICU patients

colonized with VRE to assess the relationship between bacterial burden and transfer to HCWs' gloves or gowns. These results could have major implications for infection prevention practices, such as Contact Precautions and de-contamination policies for patients with high bacterial carriage.

C. Methods

Study design and participants

We conducted a prospective cohort study to estimate the contribution of bacterial burden on the transfer of VRE from patients to HCWs' gloves and gowns, a surrogate outcome for possible transmission to other patients. One hundred patients were recruited from the medical (MICU) and surgical (SICU) ICUs within the University of Maryland Medical Center (UMMC) between January 1 and November 15, 2017. The MICU is a 29-bed unit that provides care to adult patients with acute or potentially life-threatening medical conditions, while the SICU is a 24-bed unit designed to care for adult surgical patients. These ICUs screen for VRE on admission and once weekly as part of the VRE infection prevention active surveillance program. The research staff were notified each day of patients with recent (within 72 hours) VRE positive rectal surveillance cultures via email alerts associated with hospital microbiology reports. Five HCWs for each patient were approached for participation in the study before engaging in care activities. The University of Maryland Baltimore Institutional Review Board approved this study.

Data collection

We cultured the patients' perianal area, chest, antecubital fossa, and obtained a stool sample when available to measure patient VRE bacterial burden. The perianal area was sampled using aseptic technique with ESwab (Copan Diagnostics, Murrieta, CA).

The swab was rubbed gently back and forth three times on the skin immediately around the anus, covering an area approximately four centimeters (cm) in diameter. The chest and antecubital fossa were chosen because these body sites are likely to be touched by the HCWs and have been examined in previous studies. [2,22,85] These skin sites were sampled using a 10x10 cm^2 template, rubbing the swab within the template with a twirling motion to ensure all sides of the swab came in contact with the skin. Stool samples were collected, when available, in Dynarex sterile stool specimen containers.

Five interactions between HCWs and patients were observed shortly after obtaining the patient swabs. Following patient care, but prior to doffing, the gloves and gown of each HCW were cultured for the presence of VRE. The BBL dual Culturettes (BBL, BD, Sparks, MD) was rubbed gently with a twirling motion along the dorsum of each finger and the palm of both the right and left hand. HCWs' gowns were sampled with a twirling motion twice on each forearm and then in a "W" pattern along the beltline using a single swab.

Patient characteristics including the presence or absence of an artificial airway (endotracheal or tracheostomy tube), Foley catheter, intravascular catheter (central line), chest tube, surgical drain, rectal tube, nasogastric tube, diarrhea, and wound were also collected. *International Classification of Diseases, 10th Revision*, (ICD-10) codes, age, sex, and race, were abstracted from the electronic medical record of each patient. The ICD-10 codes were used to calculate the Elixhauser Index, a validated comorbidity score for hospital inpatients. [65]

Laboratory procedures

HCWs' gown and glove swabs were cultured for the presence of VRE. The swabs were placed into tryptic soy broth with 6.5% NaCl and incubated for 24 hours at 35± 2°C. After incubation, 50 µL from each broth tube were inoculated onto a Bile Esculin Azide Agar with 6 µg/ml vancomycin (BEAV; Remel, Lenexa, KS) plate for isolation. The BEAV plates were incubated aerobically at 35± 2°C for 48 hours. All enterococcal isolates were frozen in tryptic soy broth with 15% glycerol and stored at -80°C.

Patient swabs and stool samples were placed into collection tubes and the swabs from the skin and perianal samples were vortexed separately for one minute. One gram of stool was extracted from the stool container, added to 1mL of 0.9% saline in an Eppendorf tube, and vortexed until well mixed (at least one minute). One mL of each patient sample was serially diluted using Butterfield's Buffer. BEAV was inoculated with 100 µL of each serial dilution and distributed evenly onto the each agar plate using a cell spreader. Also, 100 µL of the original sample was inoculated into tryptic soy broth with 6.5% NaCl. The plates and broth tubes were incubated for 48 hours aerobically at 35± 2°C, after which the number of bacterial colonies were counted. If there was no growth on the inoculated plates, 100 µL from the previously inoculated tryptic soy broth with 6.5% NaCl tubes were inoculated onto a BEAV plate. If there was growth on the BEAV agar after 48 hours at 35± 2°C, a count of one colony forming unit (CFU) was given. Following incubation, colonies were subcultured, identified and speciated by the VITEK II. Antimicrobial susceptibility testing was conducted using the Kirby-Bauer disk diffusion method according to the Clinical Laboratory Standards Institute guidelines.

Statistical analysis

Frequencies with proportions and means with standard deviations (SD) were calculated to describe the demographics, clinical characteristics, and VRE species of the sample. Bacterial counts were logged transformed (log_{10} [VRE bacterial burden +1]) so that those without recovered VRE were included as 0, and counts were modeled in log_{10} CFU/mL for the perianal and stool samples, and log_{10} CFU/cm^2 in the skin samples. The chest and antecubital fossa skin swabs were combined into one variable by taking the higher of the two measurements. Separate models were constructed for VRE burden recovered from each of the patient sampling sites. The association between patient bacterial burden and VRE species with HCWs' glove or gown contamination was estimated using logistic regression fit with generalized estimating equations with an exchangeable correlation matrix accounting for within-patient correlation. These associations were expressed in odds ratios (OR) and 95% CI were calculated. The final model was selected by entering all covariates into the model, with a stepwise variable selection method to choose the model with the smallest QIC. Separate models were constructed for VRE burden recovered from each of the cultured patient sites. Potential confounders were selected *a priori* for all models and included patient age, race, comorbidities, presence of invasive devices, diarrhea, type of HCW (physician/nurse practitioner, nurse, patient care technician, physical/occupational therapist, respiratory technician, or other) and duration of time HCW spent in the room. We estimated the mean bacterial burden and 95% confidence interval (CI) found in each of the samples by species. Pearson's correlations were calculated to compare the bacterial burden between each sample.

All analyses were conducted using SAS version 9.4 (The SAS Institute, Cary, NC).

D. Results

Of the 100 patients enrolled, chest and antecubital fossa skin samples were obtained from 96 patients, perianal swabs from 94 patients, and stool samples from 43 patients. The demographics and clinical characteristics of the patients are presented in Table 6. The mean age of the patient sample was 61 (SD: 13), 51/97 (53%) were white, 50/97 (52%) were men, 58/97 (60%) were from the MICU, and the median number of comorbidities was 6 (range 0 to 14) as measured by the Elixhauser Index. Most patients had at least one invasive device (93%), with a mean of 3 devices (SD: 1.6).

Table 6. Demographics and characteristics of VRE colonized ICU patients enrolled between January 1, 2017 and November 15, 2017

Characteristic	N=96
Age in years, mean (SD)	60.8 (13)
White race	51 (53)
Male sex, n (%)	50 (52)
ICU location, n (%)	
Medical ICU	58 (60)
Surgical ICU	38 (40)
Elixhauser Index, median (range)	6 (0 – 14)
Diarrhea, n (%)	29 (30)
Wound, n (%)	56 (58)
Endotracheal tube, n (%)	50 (52)
Central line, n (%)	68 (71)
Foley catheter, n (%)	55 (57)
Chest tube, n (%)	7 (7)
Surgical drain, n (%)	25 (26)
Rectal tube, n (%)	32 (33)
Nasogastric tube, n (%)	53 (55)
Number of devices, mean (SD)	3 (1.6)

Abbreviations: ICU, intensive care unit; n, number; and SD, standard deviation.

We observed 479 HCW-patient interactions, of which 71/479 (15%) led to HCWs' glove or gown contamination with VRE. Figure 6 shows that patients who transfer VRE to HCWs have higher bacterial distributions in their perianal, skin, and stool samples. Table 7 presents the adjusted odds ratios and 95% CI for HCWs' glove or

gown contamination for each patient sample type, controlling for nasogastric tube, diarrhea, age, and amount of time the HCW spent in the room. In each patient sample there is an association between increasing bacterial burden and HCWs' glove or gown contamination: adjusted OR (aOR) 1.37 (95% CI 1.19, 1.57) for the perianal, aOR: 1.95 (95% CI: 1.39, 2.72), for the stool, and aOR: 2.14 (95% CI: 1.51, 3.02) for the skin samples. This association between skin colonization and HCWs' glove or gown contamination did not change after adjusting for the stool bacterial burden (data not shown).

Figure 6. Bacterial distributions of each sample by transmission to HCWs' gloves or gowns

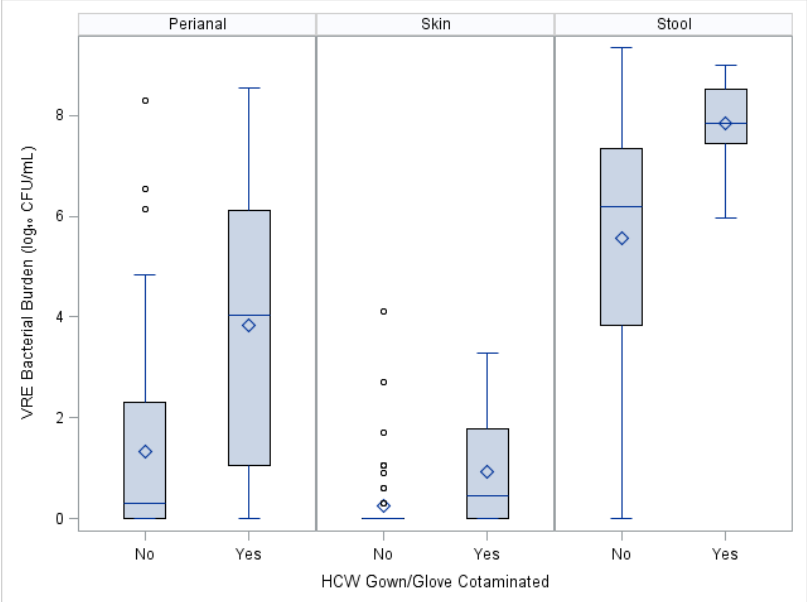


Table 7. Adjusted associations between bacterial burden and HCWs' glove or gown contamination by patient sample type

Patient sample type	OR (95% CI)
Perianal (log_{10} CFU/mL)	1.37 (1.19, 1.57)*
Skin (log_{10} CFU/cm^2)	2.14 (1.51, 3.02)*
Stool (log_{10} CFU/mL)	1.95 (1.39, 2.72)†

Abbreviations: CFU, colony forming units; CI, confidence interval; CM, centimeter; HCW, healthcare worker; mL, milliliter; and OR, odds ratio.
*Adjusted for nasogastric tube, diarrhea, age, and time spent in the room by the healthcare worker
†Adjusted for nasogastric tube, age, and time spent in the room by the healthcare worker

The frequency and mean bacterial burden by VRE species and patient sample type is presented in Table 8. VRE was identified in 60 of the 94 perianal samples collected, ranging from 1 to 1,300,000 CFU/mL. Patients who were colonized with *E. faecium* had an average of 2.4 $\log_{10}$ (95% CI: 0.89, 3.91) colony counts higher than those with *E. faecalis*. VRE was identified on 42 of the 43 collected stool samples, ranging from 0 to 2,250,000,000 CFU/mL. Those colonized with *E. faecium* in the stool had 1.6 $\log_{10}$ (95% CI: -0.39, 3.52) higher bacterial burden than those with *E. faecalis*. VRE was identified in 18 of the 96 samples collected from the patients' chest, with bacterial burden ranging from 1 to 1,910 CFU/cm^2. VRE was identified on 23 of the antecubital fossa swabs obtained from 95 patients, ranging from 1 to 13,300 CFU/cm^2. Patients colonized with *E. faecium* on the skin had 0.97 $\log_{10}$ (95% CI: 0.04, 1.89) higher than those with *E. faecalis*. The amount of bacteria found in the stool was moderately correlated with the amount found in the perianal sample ($r=0.56$, $p<0.001$) and mildly correlated with the amount found on the skin ($r=0.31$, $p<0.001$).

Table 8. Frequency, mean bacterial burden, and odds ratios for transfer to HCWs' gloves or gowns by VRE species and patient sample type

Patient sample type	VRE species*	n/Total (%)	Mean burden† (95% CI)	OR (95% CI) for HCW transfer‡
Perianal	*E. facecium*	49/59 (83%)	3.92 (3.30, 4.55)	9.32 (1.32, 66.03)
	E. faecalis	10/59 (17%)	1.52 (0.16, 2.89)	Reference
Stool	*E. facecium*	36/40 (90%)	7.09 (6.49, 7.69)	1.61 (0.37, 6.89)
	E. faecalis	4/40 (10%)	5.53 (3.72, 7.34)	Reference
Skin	*E. facecium*	26/31 (84%)	1.68 (1.31, 2.06)	1.98 (0.53, 7.41)
	E. faecalis	5/31 (16%)	0.72 (-0.13, 1.57)	Reference

*Other species not listed were identified as *E. avium* and *E. casseliflavus*

†Perianal and stool bacterial loads are expressed in $\log_{10}$ CFU/mL. Skin bacterial load is expressed in $\log_{10}$ CFU/cm^2

‡Adjusted for bacterial burden found in that sample

VRE species is also associated with increased HCWs' glove or gown contamination, controlling for bacterial burden (Table 8). Patients colonized with *E. faecium* on the skin were 9.32 (95% CI: 1.32, 66.03) times as likely to contaminate HCWs' gloves or gowns as those colonized with *E. faecalis*. There was an increased odd of contamination for those colonized with *E. faecium* compared to *E. faecalis* in the perianal and stool samples as well, but these associations did not reach statistical significance.

E. Discussion

This study is the first of its size to quantify VRE bacterial burden and examine its role in the transfer of VRE from colonized patients to HCWs' gowns or gloves. As bacterial burden in all patient samples increases so does the likelihood of HCWs' glove or gown contamination, a potential source of transmission to other patients in the ICU. Previous studies have not examined the association between VRE species and transmission potential. Our results indicate the main driver of this transfer is likely due to *E. faecium*, which is associated with higher colony counts and increases the odds of transfer. Patients colonized with *E. faecium* on their skin were nine times as likely to transfer the bacteria to HCWs as those colonized with *E. faecalis* after adjusting for bacterial burden.

Though we were only able to recover VRE from a small proportion of skin samples (27% from the antecubital fossa and 19% from the chest), there was a 114% increase in HCWs' glove or gown contamination for each $\log_{10}$ increase in skin bacterial burden. This strong association remained even after adjustment for stool bacterial burden. These results indicate that skin may be an efficient means of VRE transfer. Duckro et al. found that the antecubital fossa was the most efficient body site for VRE transmission. In that

study, HCWs contaminated their gloves 100% of the time after touching the patient's antecubital fossa, compared to 60% after contacts with the patient's chest. Our study also found higher bacterial burden on the patients' arms than on their chests. The patient's antecubital fossa is touched often by HCW during clinical care (e.g. for blood draws and blood pressure measurement), resulting in increased bacterial burden and transmission efficiency. As has been suggested previously, this area may also be a habitable environment for VRE. [85]

These results show skin contamination increases odds of VRE transmission and highlight the need for ICUs to invest in decontamination protocols, such as bathing with chlorhexidine gluconate (CHG), for their VRE colonized patients. CHG bathing has been shown to be associated with reductions in the incidence of VRE acquisition and gram-positive bacteremias. [21,87,88] In 2007, Vernon et al. [21] performed a single center clinical trial comparing the effect of three types of bathing routines on VRE acquisition. Compared to soap and water, daily bathing of patients with 2% CHG-saturated clothes resulted in a 60% decrease in VRE acquisition, a 40% reduction of HCWs' glove contamination, and 70% reduction in environmental contamination. [21] Further, the use of CHG bathing resulted in a decrease of inguinal bacterial burden by 2.5 $\log_{10}$ colony counts. [21] The multicenter, cluster-randomized trial conducted by Climo et al. [87] in 2013 similarly found that daily CHG bathing reduced overall MDRO acquisition by 23% and bloodstream infections by 28% compared to cleansing with non-antimicrobial washcloths. Bleasdale et al. [88] , also found that daily CHG bathing compared to soap and water baths lead to a reduction in hospital-acquired bloodstream infections. However this trial and one by Noto et al., [89] did not see a reduction in other HAIs such as urinary tract

infection, ventilator-associated pneumonia, or *Clostridium difficile*. There was no reduction in incidence of bloodstream infections either, though duration of the CHG intervention was only 10 weeks compared to the 24+ weeks in other trials. [89] The longer duration of these other trials may have reduced colonization pressure in the ICU by reducing the amount of bacteria in the environment over time. Further, these results highlight the fact that CHG bathing reduces the bacterial burden of MDROs on the skin, which is a risk factor for infections, such as bacteremia, along with increased HCW and environmental contamination.

Our results indicate that the association with perianal bacterial burden and transfer to HCWs is not as strong as the association seen in the other samples. The odds of HCWs' glove or gown contamination increases by 37% for each $\log_{10}$ increase in VRE isolated from the perianal swab. Even though a greater number of colonies were isolated from the perianal sample than the skin, this area likely not often accessed by HCWs for routine procedures in the ICU. We found a nearly a two-fold increase in the odds of HCW contamination for each $\log_{10}$ increase in stool bacterial burden. Large concentrations of VRE in the stool have been previously found to correlate with skin and environmental contamination. [14]

Potential limitations of this study include the fact that we sampled only a portion of the gloves and gowns instead of using a juicing method that would culture the entire surface area. The transfer rate of VRE may be much higher than we were able to detect. However, we did culture from areas most likely to come in contact with the patient (glove fingers and gown arms), which are most likely involved in transmission. In addition, we did not quantify the bacterial burden recovered from the HCWs' gloves and gowns. As

such, we do not know how much VRE was transferred to HCWs or what amount of VRE is needed for transfer to future patients. Though, had these HCWs not been wearing personal protective equipment (i.e. gowns and gloves), they would have had VRE on their hands and clothing which could lead to a subsequent transmission to other patients. This study was conducted at a single site and in two ICUs. Transmission of VRE between patients and HCWs may vary in other acute care settings due to differences in patient care practices. However, these findings will likely be generalizable to other large-sized, academic hospitals and ICUs with similar patient case-mix. Furthermore, the findings of this study may not be generalizable to other organisms as transmission mechanisms may differ between pathogens.

This study is the first of its size to study the role of VRE bacterial load in transmission to HCWs. Our use of a prospective cohort design established temporality between patient transmission and HCW acquisition of VRE. HCW-patient interactions were observed immediately following patient specimen collection (generally within an hour and no more than four hours). Therefore, it is unlikely that patient VRE burden decreased significantly between patient sample collection and HCW observation. We only sampled from ICUs in our hospital that conducted active surveillance to minimize selection bias. Clinical cultures are often ordered when a patient shows clinical signs and symptoms of an infection. Bias may be introduced if patients identified from clinical cultures are included as these patients may have different risk factors for transmission than patients identified by surveillance cultures. The former patients may be sicker, have greater number of comorbidities and devices, and may be higher transmitters than patients identified through surveillance cultures. Finally, the methods we used to detect

bacterial transmission in the ICU setting were developed and validated by the UMMC hospital epidemiology team and the microbiology research lab. These methods have been adopted by other institutions and are now standard in the literature. [23,24,67,90]

This study demonstrates the role bacterial burden plays in transmission. These results may have major implications for infection prevention practices that aim to lower VRE levels and decrease transmission. Examples include increased CHG bathing for VRE colonized patients in the ICU or for future work on alteration of the human microbiome that could lower levels of VRE colonization.

CHAPTER V. PATIENT CONTACT IS THE MAIN RISK FACTOR FOR VANCOMYCIN-RESISTANT *ENTEROCOCCUS* CONTAMINATION OF HEALTHCARE WORKERS' GLOVES AND GOWNS IN THE INTENSIVE CARE UNIT[1]

A. Abstract

Objective: To determine which healthcare workers (HCW) and patient care activities are risk factors for acquisition of vancomycin-resistant *Enterococcus* (VRE) on HCWs' gloves or gowns after caring for patients with VRE, as a surrogate for transmission to other patients in the intensive care unit (ICU).

Design: Prospective cohort study.

Setting: Medical and surgical ICUs at a tertiary-care academic institution.

Participants: VRE-colonized patients on Contact Precautions and their HCWs.

Methods: Ninety-four VRE-colonized patients and 469 HCW-patient interactions were observed. Research staff recorded patient care activities on a standardized data collection form and cultured HCWs' gloves and gowns for VRE before doffing and exiting patient room.

Results: VRE were isolated from 15% (71/469) of HCWs' gloves or gowns following patient care. Occupational/physical therapists, patient care technicians, nurses, and physicians were more likely than environmental services workers and other HCWs to have contaminated glove or gowns. Compared to touching the environment alone, the odds ratio (OR) for touching the both the patient (or objects in the immediate vicinity of the patient) and the environment was 2.78 (95% CI: 0.99, 7.77) while the OR for touching only the patient (or objects in the immediate vicinity) was 3.65 (95% CI: 1.17,

[1] Submitted to *Infection Control and Hospital Epidemiology*

11.41). Independent risk factors for transmission of VRE to HCWs in a multivariable model were touching the patients' skin (OR: 2.18 [95% CI: 1.15, 4.13]) and transferring the patient in/out of bed (OR: 2.66 [95% CI: 1.15, 6.43]).

Conclusion: Direct patient contact is a major risk factor for HCWs' glove or gown contamination. Interventions should prioritize Contact Precautions and hand hygiene for HCWs whose activities involve touching the patient.

B. Introduction

Vancomycin-resistant *Enterococcus* (VRE) is responsible for bacteremia, surgical site infections, and urinary tract infections, resulting in approximately 1,300 deaths in the US annually, [1] and is the second most common cause of HAIs in the US. [5,91] Patients with VRE bacteremia are 2.5 times as likely to die from their infection as patients with susceptible enterococcal infections. [92]

Healthcare workers (HCW) serve as an intermediate vector for VRE transmission from patient to patient in the intensive care unit (ICU). Research has implicated both the ICU room environment[15, 20,23] [15] and direct patient contact in VRE acquisition. [2,93] However, these studies were either too small or examined a number of multidrug-resistant organisms (MDRO) so that specific care activities related to VRE transmission could not be identified.

Understanding the risk factors for VRE transfer to HCWs can aid in identifying interventions to prevent transmission and reduce VRE acquisition among ICU patients. In this study we sought to determine the frequency of VRE transfer to HCWs' gloves or gowns during routine patient care in the ICU and to identify the care activities most associated with HCW contamination with VRE.

C. Methods

Study design and participants

This was a prospective cohort study to determine which HCW types and patient care activities are risk factors for VRE transmission to HCWs' gloves or gowns , a surrogate for transmission to other patients in the ICU. Between January 1, 2017 and November 15, 2017, 100 VRE colonized patients from the medical (MICU) and surgical (SICU) ICUs were enrolled at the University of Maryland Medical Center (UMMC). The MICU is a 29-bed unit providing medical care to adult patients with acute or life-threatening conditions, while the SICU is a 24-bed unit which cares for adult surgical patients. These ICUs screen for VRE on admission, discharge and once weekly as part of the VRE infection prevention active surveillance program. On each study day, email alerts associated with the hospital microbiology laboratory notified research staff of recent (within 72 hours) VRE positive cultures. Patients with positive rectal surveillance cultures and five HCWs per patient were enrolled in the study. The Institutional Review Board at the University of Maryland, Baltimore granted approval for waived consent of participants.

Data collection

All HCW-patient activities were recorded by research staff on a standardized data collection form. HCW activities were categorized into two domains as interactions with the patient (patient domain) or the patient's environment (environmental domain). The patient domain included direct contact with the patient (such as bathing/hygiene, wound dressing or physical examination) or contact with the objects in direct contact with a patient (such as bed rail, bedding, catheter/drain, artificial airway, vital signs, giving oral

meds, IV tubing/IV meds, rectal tube/bag). The environmental domain included contact with items in the ICU room environment (such as the sink, bedside table, supply cart, lift, curtain, trash, computer medical equipment, and room furniture). (Please see Appendix 1 for a more detailed list). These patient care activities and interactions were chosen based on prior literature showing these interactions were associated with increased transmission of several types of MDROs. [13,90,93,94]

Following patient care, but prior to doffing, the gloves and gown of each HCW were sampled for the presence of VRE with BBL dual Culturettes (BBL, BD, Sparks, MD). With a twirling motion, the swab was rubbed along each finger and the palm of both gloved hands. HCWs' gowns were sampled twice along both forearms and then in a "W" pattern along the beltline using a twirling motion.

Patient demographics including age, sex, and race were abstracted form the electronic medical record. The Elixhauser Index, a validated comorbidity score used for hospitalized patients, [61,95] was calculated from the *International Classification of Diseases, 10th Revision* codes. Study researchers conferred with the nursing staff to obtain clinical characteristics including the presence or absence of an artificial airway (endotracheal or tracheostomy tube), Foley catheter, intravascular catheter (central line), chest tube, surgical drain, rectal tube, nasogastric tube, diarrhea, and wounds. To quantify VRE burden, we cultured the patients' perianal area by gently rubbing ESwabs (Copan Diagnostics, Murrieta, CA), on the skin immediately around the anus.

Laboratory procedures

HCWs' gown and glove swabs were placed into tryptic soy broth with 6.5% NaCl and incubated for 24 hours at 35± 2°C. After incubation, 50 µL from each broth tube

were inoculated onto a Bile Esculin Azide Agar with 6 µg/ml vancomycin (BEAV; Remel, Lenexa, KS) plate incubated aerobically at 35± 2°C for 48 hours. The isolates were frozen in tryptic soy broth with 15% glycerol and stored at -80°C. One mL of each patient perianal sample was serially diluted using Butterfield's Buffer. BEAV was inoculated with 100 µL of each serial dilution and distributed evenly onto the each agar plate using a cell spreader. Next, 100 µL of the original sample was inoculated into tryptic soy broth with 6.5% NaCl. The plates and broth tubes were incubated for 48 hours aerobically at 35± 2°C, after which the number of bacterial colonies were counted. If there was no growth on the inoculated plates, 100 µL from the previously inoculated tryptic soy broth with 6.5% NaCl tubes were inoculated onto a BEAV plate. If there was growth on the BEAV agar after 48 hours at 35± 2°C, a count of one CFU was given. Antimicrobial susceptibility testing was conducted according to the Clinical Laboratory Standards Institute guidelines using the Kirby-Bauer disk diffusion method.

Statistical analysis

Frequencies and proportions were calculated to describe patient demographics and clinical characteristics. Patient bacterial burden (x+1) was log transformed and are expressed in $\log_{10}$ CFU/mL. We estimated the associations: 1) between HCW type (physician/nurse practitioner, nurse, patient care technician, physical/occupational therapist, respiratory therapist, environmental service worker, or other) and HCWs' glove or gown contamination; and 2) specific patient-care activities/interactions and HCWs' glove or gown contamination. Risk factors significant at $\alpha \leq 0.10$ in the previous analyses were considered candidate predictors for the multivariable model. All models were built using logistic regression models fit by generalized estimating equations (GEE) with an

exchangeable correlation matrix to take into account within-patient correlation and conducted in a stepwise fashion where the model with the lowest QIC was chosen as the final multivariable model. Potential confounders were selected *a priori* for all models and included patient age, race, Elixhauser Index, invasive devices, diarrhea, bacterial burden, and duration of time HCW spent in the room.

All analyses were conducted using SAS version 9.4 (The SAS Institute, Cary, NC).

D. Results

The demographics and clinical characteristics of the 94 VRE colonized patients are presented in Table 9. The mean patient age was 61 (SD: 12), 57% were white, 50% were men, 60% were from the MICU, the median Elixhauser Index was 7.2 (range 0 to 14). Ninety-three percent of patients had at least one invasive device, with a mean of 3 devices (range 0 to 6).

Table 9. Demographics and clinical characteristics of VRE colonized ICU patients enrolled between January 1, 2017 and November 15, 2017

Characteristic	Total N=94
Age in years, mean (SD)	60.7 (12)
Male sex, n(%)	47 (50)
White race	51 (57)
Elixhauser Index, median (range)	7.2 (0-14)
ICU location, n (%)	
MICU	56 (60)
SICU	38 (40)
Diarrhea, n (%)	29 (30)
Wound, n (%)	55 (59)
ETT tube, n (%)	48 (51)
Central line, n (%)	67 (71)
Foley catheter, n (%)	55 (59)
Chest tube, n (%)	6 (6)
Surgical drain, n (%)	25 (26)
Rectal tube, n (%)	31 (33)
NG tube, n (%)	52 (55)
No. of devices, median (range)	3 (0-6)

Abbreviations: ICU, intensive care unit; n, number; and SD, standard deviation.

We observed 469 HCW-patient interactions, of which 71/469 (15%) led to HCWs' glove or gown contamination with VRE. Table 10 shows the associations between HCW type and glove or gown contamination. Compared to environmental services and other HCWs (e.g. nutritionists, dialysis technicians, etc.), occupational/physical therapists had the highest odds of glove or gown contamination (OR: 8.66 [95% CI: 1.36, 55.05]), followed by patient care technicians (OR: 7.57 [95% CI: 1.80, 31.79]), nurses (OR: 4.74 [95% CI: 1.63, 13.77]) and physicians/nurse practitioners (OR: 4.26 [95% CI: 1.06, 17.18]).

Table 10. Adjusted associations between HCW-patient interactions and glove or gown contamination by HCW type

HCW type, N=469	HCW-patient interactions n (%)	OR (95% CI)*
Nurse	236 (50)	4.74 (1.63, 13.77)
MD/nurse practitioner	70 (15)	4.26 (1.06, 17.18)
Respiratory technician	37 (8)	3.15 (0.64, 15.54)
Patient care technician	18 (4)	7.57 (1.80, 31.79)
Occupational/physical therapist	12 (3)	8.66 (1.36, 55.05)
Environmental services and other†	96 (20)	Reference

Abbreviations: CI, confidence interval; HCW, healthcare worker; OR, odds ratio; and n, number.
*From a GEE model adjusted for VRE burden, diarrhea, nasogastric tube, and amount of time HCW spent in the room.
†Other includes HCWs such as nutritionists, dialysis technicians, study researchers, etc.

As shown in Table 11, HCWs who touched the patient only were 3.65 (95% CI: 1.17, 11.41) times as likely to contaminate their gloves or gowns as those who touched the environment only. Those who touched both the patient and environment were 2.78 (95 CI: 0.99, 7.77) as likely to have glove or gown contamination as those who touched the environment only. HCWs on average touched 3 different items in the patient domain and 3 different environmental items. The odds of contamination increased with the number of different patient touches (OR: 1.22 [95% CI: 1.05, 1.41) and with the number of different items touched in the environment (OR: 1.07 [95% CI: 0.94, 1.21]).

Table 11. Adjusted associations between contact with patient and environmental domains and HCWs' glove or gown contamination with VRE

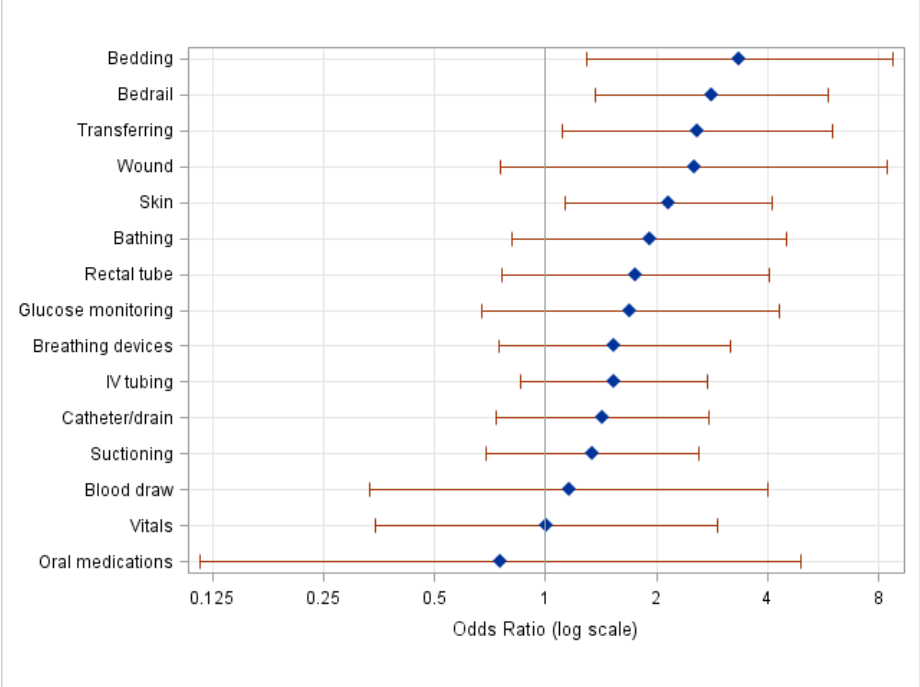
Patient care activity	HCW-patient interactions N=469	Number (%) of interactions that resulted in contamination	OR (95% CI)*
Touched patient domain only, n (%)	50 (11)	10 (20)	3.65 (1.17, 11.41)
Touched both patient and environmental domains, n (%)	333 (71)	57 (17)	2.78 (0.99, 7.77)
Touched environment only, n (%)	83 (18)	4 (5)	Reference
Number of distinct contacts within the patient domain, mean (range)	3 (0 – 12)	--	1.22 (1.05, 1.41)
Number of distinct contacts within the environmental domain, mean (range)	3 (0 – 10)	--	1.07 (0.94, 1.21)

Abbreviations: CI, confidence interval; HCW, healthcare worker; OR, odds ratio; and n, number
*From a GEE model adjusted for VRE burden, diarrhea, nasogastric tube, and HCW time spent in patient room.

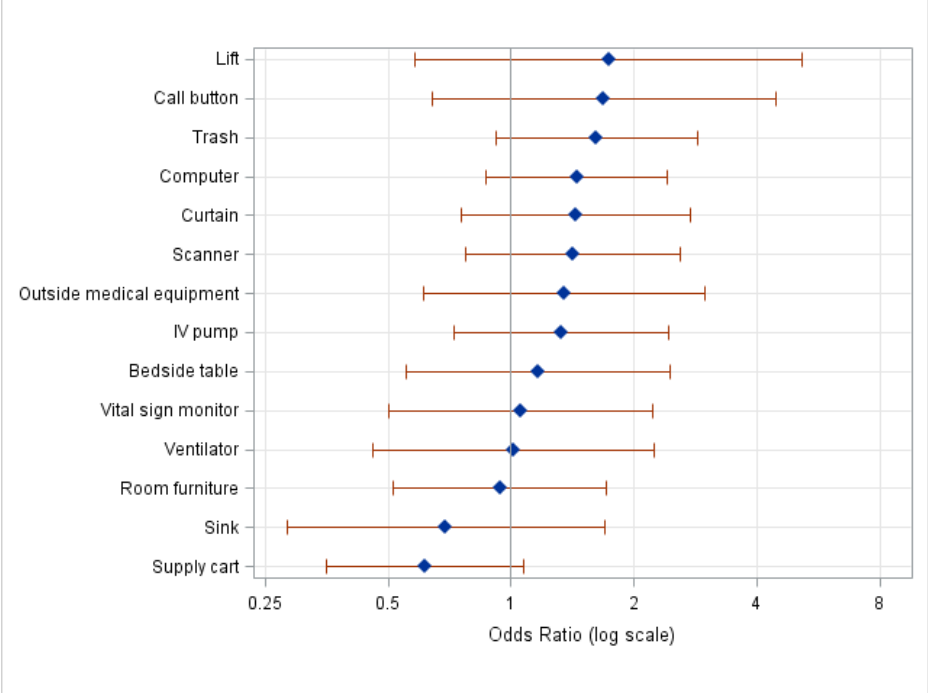
Figures 7a and b show the odds ratios for HCW contamination of each patient care activity in the environment and patient domains adjusted for VRE burden, diarrhea, nasogastric tube, and time the HCWs spent in the room, respectively. Touching items within the patient domain, touching the patient's bedding (OR: 3.36 [95% CI: 1.29, 8.75]), bedrail (OR: 2.83 [95% CI: 1.37, 5.84]), skin (OR: 2.16 [95% CI: 1.13, 4.13]), and transferring the patient in/out of bed (OR: 2.58 [95% CI: 1.11, 5.99]) increased the odds of HCWs' glove or gown contamination. Touching the supply cart was associated with reduced odds of contamination (OR: 0.62 [95% CI: 0.35, 1.08]), while touching trash (OR: 1.62 [95% CI: 0.92, 2.86]), was associated with increased odds. These items were entered into a model with the final model showing touching the patients' skin (OR: 2.18 [95% CI: 1.15, 4.13]) and transferring the patient (OR: 2.66 [95% CI: 1.10, 6.43]) were the risk factors that remained when adjusting for patient VRE burden, diarrhea, nasogastric tube, and time the HCWs spent in the room.

Figure 7. Adjusted odds ratios* and 95% confidence intervals of HCWs' glove or gown contamination for each patient care activity

A) Patient care activities that involve touching items on or near the patient



B) Patient care activities that involve touching items in the ICU room environment



*From a GEE model adjusted for VRE burden, diarrhea, nasogastric tube, and the amount of time the HCW spent in the room.

E. Conclusion

This study found that 15% of the HCWs' gloves or gowns became contaminated with VRE after providing patient care. Touching the patient or items touching the patient was the greatest risk factor for HCW contamination during routine patient care. Because our patient and HCW sample sizes were nearly five times larger than previous studies on gown and glove contamination we were able to identify the risk factors specific to VRE transmission, touching the patient's skin and transferring the patient in or out of bed.

These results are consistent with increased odds of glove and gown contamination observed among the occupational/physical therapists, patient care technicians, nurses, and physicians who are most likely to have direct contact with the patient and perform tasks that would require them to touch or transfer the patient. Further, there was 22% increased odds for each new patient contact, compared with 7% increased odds for each environmental item touched. For example, the odds of glove or gown contamination is increased by 82% if the HCW touches three different patient contacts (the average number of patient touches) versus an increase of 23% if the HCW touches three environmental items.

These results are consistent with another study that found 13% [23] glove or gown contamination, and one study [2] that found 11% transfer to gloves only. Similar to our findings, Snyder et al. [24] identified the presence of nasogastric feeding tubes as a patient-level risk factor for transmission of VRE to HCW. They also found that touching the patient's skin conferred the greatest contamination risk, specifically contact with the patient's catheter, trunk, and lower extremities. [24] Morgan et al. [23] identified duration in the room, performing a physical exam, contact with the ventilator, and environmental

contamination as risk factors for HCW gown or glove contamination with MDRO, but VRE-specific risk factors were not examined. Hayden et al.[93] found that 62% of the 103 HCW-patient interactions resulted in glove contamination, though was unable to distinguish between touching the patient and touching the environment as nearly all HCWs touched the environment, though they did find increased transfer among those who touched both compared those who touched the environment only (70% vs. 52%).[93]

Contrary to previous research,[2,23] our study did not find a strong association between touching items in the environment and HCW contamination. Our findings suggest that patient contact is the main driver of HCW contamination with VRE. A recent study[96] that conducted environmental sampling of all ICU patients (both VRE-positive and VRE-negative) showed that 30% of ICU patients and their bed spaces were positive for VRE. Similar to our findings, these[96] researchers found that high touch items closest to the patient led to increased glove contamination.

Limitations of this study are as follows: we did not culture the entire glove or gown, though we did culture the areas of the gloves (fingers and palm) and gown (arms and waist) most likely to come into contact with the patient and subsequent patients. The methods we used were developed and validated by the UMMC hospital epidemiology team and the microbiology research lab. These methods have been adopted by other institutions and are now standard in the literature.[23,24,90,94] We did not culture the environment or collect data on time of last cleaning and therefore, cannot adjust for the bacterial burden of the environment. Many of the patient care activities were co-occurring, such that we may not have been able to distinguish risk between bundled care

activities. This study was conducted at a single site and may not be generalizable to other hospitals.

Our results indicate that direct patient contact is the major risk factor for HCWs' glove or gown contamination with VRE, a surrogate outcome for transmission to other patients within the ICU. We were also able to estimate the association with VRE transmission for a variety of common patient care activities using a large sample size and prospective design. These findings can help inform novel interventions, such as "red boxes" (areas in which HCWs can conduct clinical assessments without donning personal protective equipment). Further, that we found 15% of HCWs are contaminated with VRE after patient care should add to the debate surrounding whether or not to discontinue Contact Precautions for VRE.[97-99] These findings contribute to the evidence for the use of Contact Precautions and hand hygiene for HCWs whose activities involve touching the patient.

CHAPTER VI. ELECTRONICALLY AVAILABLE COMORBIDITIES SHOULD BE USED IN SURGICAL SITE INFECTION RISK ADJUSTMENT[1]

A. Abstract

Background: Healthcare-associated infections such as surgical site infections (SSI) are used by Centers for Medicare and Medicaid Services (CMS) as pay-for-performance metrics. Risk adjustment allows a fairer comparison of SSI rates across hospitals. Until 2016, Centers for Disease Control and Prevention (CDC) risk adjustment models for pay-for-performance SSI did not adjust for patient comorbidities. New 2016 CDC models only adjust for body mass index and diabetes.

Methods: We performed a multicenter retrospective cohort study of patients undergoing surgical procedures at 28 US hospitals. Demographic data and International Classification of Diseases, Ninth Edition codes were obtained on patients undergoing colectomy, hysterectomy, and knee and hip replacement procedures. Complex SSI were identified by infection preventionists at each hospital using CDC criteria. Model performance was evaluated using measures of discrimination and calibration. Hospitals were ranked by SSI proportion and risk-adjusted standardized infection ratios (SIR) to assess the impact of comorbidity adjustment on public reporting.

Results: Of 45,394 patients at 28 hospitals, 573 (1.3%) developed a complex SSI. A model containing procedure type, age, race, smoking, diabetes, liver disease, obesity, renal failure, and malnutrition, showed good discrimination (c-statistic, 0.73) and calibration. When comparing hospital rankings by crude proportion to risk-adjusted

[1] Jackson SS, Leekha S, Magder LS, Pineles L, Anderson DJ, Trick WE, Woeltje KF, Kaye KS, Lowe TJ, Harris AD. Electronically Available Comorbidities Should Be Used in Surgical Site Infection Risk Adjustment. Clin Infect Dis. 2017 Sep 1;65(5):803-810

ranks, 24/28 (86%) hospitals changed ranks, 16 (57%) changed by two or more ranks, and 4 (14%) changed by more than 10 ranks.

Conclusions: We developed a well-performing risk adjustment model for SSI using electronically-available comorbidities. Comorbidity-based risk adjustment should be strongly considered by the CDC and CMS to adequately compare SSI rates across hospitals.

B. Introduction

Surgical site infection (SSI) is one of the most common healthcare-associated infections and is associated with poor health outcomes such as increased length of stay, reduced quality of life, and even death.[41,72] Therefore, SSI rates are a potentially important healthcare quality metric.

Rates of various healthcare-associated infections including SSI are included prominently in publicly available quality "report cards" with the explicit intent of comparing rates across different facilities. Even beyond reporting, SSI rates are being used by the Centers for Medicare and Medicaid Services (CMS) and private insurers as a performance metric for reimbursement. SSI standardized infection ratios (SIRs) are a component of each hospital's hospital-acquired condition score on which CMS payment reductions are based.[25] However, the patient population at one facility may be significantly different from the population at another facility, and a seemingly large proportion of SSIs at one hospital may be due to a high burden of patients with a number of risk factors (comorbidities) for adverse surgical outcomes rather than poorer quality of care. Therefore, risk adjustment for patient case mix is necessary to make comparisons

meaningful to providers and healthcare centers and to level the playing field for reimbursement policies.[50,100,101]

The CDC's NHSN updated its SSI risk adjustment models to stratify by surgical procedure in 2010, but individual patient-level comorbidity adjustment for surgical procedures are not routinely included in CMS pay-for-performance.[73] Only spinal fusion procedures included diabetes and cesarean delivery included adjustment for body mass index (BMI).[41] A major weakness in the current CDC risk adjustment method is that nearly all SSI models do not include other patient comorbid conditions, many of which are well-described risk factors for SSI,[72,102-104] and thereby fail to adequately account for the contribution of patient case mix to hospital SSI rates. More recently in 2016, diabetes and BMI were added to many models as individual patient case-mix variables,[33] though there may be variability between hospitals as to how these conditions are captured if not in a standardized fashion or through *International Classification of Diseases* (ICD) codes. Other performance measurement systems for SSI, such as the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), collect many more variables than the NHSN system, but often the data collection burden may be too high for some, especially smaller, hospitals.

We hypothesized that patient comorbidities easily obtained from ICD discharge codes could be used to develop a well-performing risk adjustment model for SSI. In fact, most hospitals already send ICD data for all of their Medicare patients to CMS. To test this hypothesis, we built 2 models using procedure type, individual patient demographics, and hospital discharge codes (comorbid conditions) from a large cohort of surgical patients across 28 US hospitals. We then demonstrated the impact of risk adjustment on

SSI rates by comparing the hospital rankings before and after adjustment. To our knowledge, we are the first to develop risk adjustment models specifically for SSI using patient comorbidities derived from ICD codes across multiple patient populations, hospitals, and surgical procedures.

C. Methods

We retrospectively analyzed a cohort of patients undergoing surgery between 1 January 2012 and 31 December 2013 at 28 US hospitals. These procedures were identified from the Premier Quality Advisor database using ICD, Ninth Revision, Clinical Modification (ICD-9-CM) codes and Current Procedural Terminology codes for the NHSN operative procedure categories of colon, abdominal hysterectomy, and knee and hip replacement. We chose these procedures because SSI rates for these procedures are either publicly reported or used for pay-for-performance, or both. Premier's database currently contains data from standard hospital discharge files, including patient demographics, disease state, and information on billed services.

Institutional review board approval was obtained by Premier for study oversight and by each participating hospital. Infection preventionists at each hospital used CDC NHSN criteria [71] to identify SSI. SSIs were classified using NHSN definitions of superficial incisional, deep incisional, or organ/space. Patients with superficial SSI were excluded from this analysis as the risk factors may be different from those with deep incisional and organ/space ("complex") SSI, [72] and the morbidity and mortality from complex SSI is higher. Public reporting excludes superficial SSI, in part due to the subjectivity of assessing superficial SSI and poor comparisons between facilities. [33]

Participating hospitals sent patient SSI details to Premier, where the data were merged with additional administrative and clinical data.

We used 2 methods to build the risk adjustment model: (1) a data-driven model where all comorbid conditions that are components of the Charlson and Elixhauser comorbidity indices were considered as potential predictors and (2) a model that included only the comorbid conditions from either index thought to be associated with SSI based on expert consensus.[105] For both models, procedure type and patient characteristics including age, race, and ICD-9-CM codes were obtained from Premier's merged database. Procedure type was entered into the model as a covariate instead of building separate procedure-specific models due to the smaller numbers of procedure-specific SSI outcomes. Age was entered into both models as a continuous predictor after confirming that a linear relationship existed with the outcome.[34] Patient race was categorized as black, white, or other. Smoking was selected a priori as a potential risk factor for SSI. We used ICD-9-CM codes for former and current smoking (V15.82 and 305.1) to create a variable for "ever smokers."[75] All available patient ICD-9-CM codes were mapped to comorbid conditions outlined by Quan et al.[95] Multiple ICD-9-CM codes were used in defining comorbidities, but the conditions themselves were operationalized as binary variables, that is, either the presence or absence of a condition. The variables of American Society of Anesthesiologists (ASA) score and surgery duration were not available in the Premier data set and so are not included in our models.

For the data-driven model we used the conditions contained in the Deyo adaptation of the Charlson comorbidity index[54] and the Elixhauser comorbidity index[61] to identify comorbidities and their ICD-9-CM codes associated with SSI.[95] Bivariate

associations between SSI and the predictors were assessed using a logistic regression model with a random intercept to account for patient clustering at the hospital level to obtain odds ratios. Demographic characteristics, procedure type, and comorbid conditions found to be significant at the $P < .10$ level in the bivariate analysis were candidates for the data-driven risk adjustment model. If the conditions overlapped between the indices, eg, Elixhauser diabetes and Charlson diabetes, the component with the smaller P value was selected for entry into the model. Separate models were built where components were tied for statistical significance, using the smallest Akaike information criterion as criteria for model selection. [106] These models were fit using maximum likelihood and backwards selection. Variables were retained in the model if they met the significance level of $P < .05$.

For the second model, we only used the comorbid conditions identified from expert consensus, which has been reported elsewhere. [105] In brief, using Delphi consensus, [76,77] 9 infectious disease and infection control experts were asked to rate the 35 comorbid conditions found in the Charlson and Elixhauser indices from 1 (not at all related) to 5 (strongly related), based on perceived relatedness to SSI. These experts rated the following 17 conditions as 3 (somewhat related) or higher: blood loss anemia, chronic pulmonary disease, coagulopathy, congestive heart failure, diabetes without complications, diabetes with complications, hemiplegia or paraplegia, human immunodeficiency virus/AIDS, lymphoma, malignancy, peripheral vascular disease, solid tumor with metastasis, severe liver disease, obesity, renal disease, rheumatologic disease, and weight loss (malnutrition). These 17 conditions, along with procedure type, age, race, and smoking status, were entered into the model as potential predictors of SSI

and variables were retained using backwards selection if they met the significance level of $\alpha < .05$.

We used logistic regression for both risk adjustment strategies and included a random intercept for hospital to account for the correlation between patients from the same facility. [107] The marginal predicted probabilities of an SSI for each patient were calculated from this model without including the random effect in the prediction so that hospital did not influence these values. These predicted probabilities were then used to generate the C-statistic and 95% confidence interval (CI) for the model. The C-statistic is a measure of discrimination, or the model's ability to discriminate between those with and without the outcome. The C-statistic is the chance that the model will assign a higher probability to patients with SSI than without. [34] Values for the C-statistic range from 0.50 (a probability no different from chance) to 1.0 (perfect prediction). Calibration, which is the model's ability to accurately quantify the probability of the outcome, was assessed with a calibration plot. The predicted probabilities were plotted against the observed proportion of SSI in deciles, and a 45-degree line was added to visually inspect how well the model was calibrated. In a perfectly calibrated model the points would rest exactly on the 45-degree line, implying that the predicted risks are equal to the observed frequencies. [36,37]

The expert consensus model was validated using internal-external validation to adjust for optimism in clustered data. [79] The expert consensus predictors were entered into a logistic regression model with a random intercept for hospital, excluding one hospital from each run. The coefficients from the resultant model were applied to the model for the excluded hospital and the C-statistic was estimated. This procedure was run

28 times for each hospital and the C-statistic for each model estimated. The optimism adjusted C-statistic and 95% CI was estimated from the mean of the 28 model C-statistics.

The proportions of SSI observed at each hospital were calculated and the hospitals were ranked in ascending order from least to greatest proportion of SSI. The predicted probabilities from the risk adjustment model were summed to estimate the expected number of SSI events for each hospital. Standardized infection ratios (SIRs) for each hospital were calculated by dividing the observed number of SSIs by the expected number of SSIs predicted by the model, similar to the current NHSN method.[73] An SIR >1 indicates the hospital reported a greater number of SSI than expected, whereas an SIR <1 indicates the hospital reported a lower number of SSI than expected by the model.[33] Hospitals were then ranked by these risk-adjusted SIRs and compared to the rankings when ordered by the unadjusted SSI proportions.

All analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, North Carolina). The calibration plots were generated using "ggplot2" package in R studio (version 0.99.902).

D. Results

There were 28 hospitals in our sample, of which 16 (57%) were teaching hospitals, 20 (71%) had ≤500 beds, and 27 (96%) were located in urban areas. The patient cohort included 45394 patients, of whom 16383 (36%) underwent knee replacement, 12118 (27%) hip replacement, 8959 (20%) colectomy, and 7934 (17%) hysterectomy procedures. Of these surgical patients, 573 (1.3%) developed a deep incisional or organ/space SSI. Three percent (279/8959) of colon procedures, 1.3%

(106/7934) of hysterectomies, 0.8% (102/12118) of hip replacements, and 0.5% (86/16383) of knee replacements resulted in an SSI. There was a median of 6 ICD-9-CM codes (range, 1–69) recorded per patient.

The bivariate associations between the SSI and the comorbid conditions are shown in Table 12. The multivariable data-driven risk adjustment model (Table 13) included the following predictors that were associated with development of an SSI: younger age ($P < .001$), cardiac arrhythmia ($P < .001$), depression ($P < .001$), diabetes uncomplicated ($P = .006$), diabetes complicated ($P < .001$), fluid and electrolyte disorders ($P = .005$), liver disease ($P = .002$), weight loss (malnutrition) ($P < .001$), black race ($P < .001$), white race ($P = .024$), colectomy ($P < .001$), hysterectomy ($P = .003$), and hip replacement ($P = .003$). The multivariable expert consensus model (Table 2) included the following predictors associated with SSI: younger age ($P < .001$), diabetes without complications ($P = .009$), diabetes with complications ($P = .002$), liver disease ($P = .001$), obesity ($P = .021$), renal failure ($P = .029$), weight loss (malnutrition) ($P < .001$), white race ($P = .033$), black race ($P < .001$), smoking ($P = .021$), colectomy ($P < .001$), hysterectomy ($P = .002$), and hip replacement ($P = .002$).

Table 12. Incidence and odds ratios of demographic characteristics and comorbid conditions with SSI in the cohort

Variable	SSI+ n=573 Mean (SD)	n (%)	Odds Ratio (95%CI)	p-value
Age in years, mean (SD)*	59.2 (15.2)		0.98 (0.98, 0.99)	<0.001
Race*				
Black		102 (1.8)	2.22 (1.52, 3.25)	
White		432 (1.2)	1.42 (1.02, 1.98)	<0.001
Other		39 (1.0)	Reference	
Ever smokers*		186 (1.6)	1.38 (1.15, 1.64)	<0.001
Procedure type				
Colectomy		279 (3.1)	4.92 (3.81, 6.39)	
Hip replacement		102 (0.8)	1.53 (1.14, 2.04)	<0.001
Hysterectomy		106 (1.3)	1.98 (1.47, 2.66)	
Knee replacement		86 (0.5)	Reference	
Charlson Comorbidity Index Components				
Cerebrovascular disease		9 (1.2)	0.89 (0.46, 1.71)	0.730
Chronic pulmonary disease*		112 (1.6)	1.34 (1.09, 1.65)	0.005
Congestive heart failure*		45 (2.2)	1.78 (1.31, 2.40)	<0.001
Dementia		2 (1.1)	0.71 (0.18, 2.84)	0.631
Diabetes*		107 (1.5)	1.27 (1.03, 1.57)	0.025
Diabetes with complications*		24 (3.2)	2.65 (1.78, 3.96)	<0.001
Hemiplegia or paraplegia*		3 (2.2)	1.48 (0.48, 4.53)	0.49
HIV/AIDS*		1 (2.6)	2.64 (0.38, 18.18)	0.33
Malignancy*		129 (2.3)	1.64 (1.34, 2.01)	<0.001
Metastatic cancer*		50 (2.5)	1.64 (1.22, 2.19)	<0.001
Mild liver disease		11 (4.3)	3.29 (1.84, 5.89)	<0.001
Moderate or severe liver disease*		4 (4.0)	2.66 (1.02, 6.97)	0.046
Myocardial infarction		33 (1.7)	1.46 (1.03, 2.07)	0.032
Peptic ulcer disease		7 (2.3)	1.89 (0.91, 3.94)	0.088
Peripheral vascular disease*		18 (1.6)	1.29 (0.81, 2.05)	0.282
Renal disease*		67 (2.1)	1.70 (1.32, 2.20)	<0.001
Rheumatologic disease*		21 (1.4)	1.24 (0.81, 1.92)	0.320
Elixhauser Comorbidity Components				
Alcohol abuse		19 (2.1)	1.78 (1.13, 2.80)	0.012
Anemia (blood loss)*		23 (2.2)	1.60 (1.06, 2.42)	0.027
Anemia (deficiency)		23 (2.2)	1.63 (1.08, 2.46)	0.021
Cardiac arrhythmia		147 (2.1)	1.99 (1.66, 2.40)	<0.001
Chronic pulmonary disease*		120 (1.6)	1.37 (1.12, 1.67)	0.002
Coagulopathy*		39 (2.6)	2.00 (1.45, 2.75)	<0.001
Congestive heart failure*		52 (2.2)	1.83 (1.38, 2.42)	<0.001
Depression		126 (1.9)	1.63 (1.34, 1.99)	<0.001
Diabetes complicated*		29 (3.1)	2.48 (1.71, 3.58)	<0.001
Diabetes uncomplicated*		107 (1.5)	1.28 (1.04, 1.58)	0.021
Drug abuse		19 (2.7)	2.19 (1.40, 3.44)	<0.001
Fluid and electrolyte disorders		162 (2.4)	2.18 (1.82, 2.61)	<0.001
HIV/AIDS*		1 (2.6)	2.64 (0.38, 18.18)	0.331
Hypertension complicated		58 (1.9)	1.54 (1.18, 2.02)	0.002
Hypertension uncomplicated		270 (1.2)	0.96 (0.82, 1.13)	0.642
Hypothyroidism		62 (1.0)	0.83 (0.63, 1.07)	0.151
Liver disease*		33 (3.4)	2.68 (1.90, 3.79)	<0.001
Lymphoma*		3 (1.4)	1.15 (0.37, 3.53)	0.810
Malignancy*		125 (2.4)	1.65 (1.35, 2.03)	<0.001
Metastatic cancer*		50 (2.5)	1.64 (1.22, 2.19)	<0.001
Obesity*		138 (1.5)	1.25 (1.03, 1.52)	0.023
Other neurological disorders		34 (2.2)	1.75 (1.24, 2.46)	0.001
Paralysis*		3 (1.3)	0.88 (0.28, 2.70)	0.822
Peptic ulcer disease excluding Bleeding		5 (1.9)	1.59 (0.67, 3.80)	0.300
Peripheral vascular disorder*		25 (1.6)	1.26 (0.85, 1.88)	0.251
Psychoses		11 (2.7)	2.16 (1.20, 3.88)	0.010
Pulmonary circulation disorder		25 (2.8)	2.06 (1.39, 3.07)	<0.001
Renal failure*		67 (2.0)	1.68 (1.30, 2.16)	<0.001
Rheumatoid arthritis*		25 (1.5)	1.25 (0.84, 1.87)	0.271
Valvular disease		22 (1.1)	0.93 (0.61, 1.42)	0.721
Weight loss (malnutrition)*		80 (4.2)	3.30 (2.60, 4.18)	<0.001

*Component identified by expert consensus

Abbreviations: N, number and SSI, surgical site infection

Table 13. Associations between the predictors and SSI in both risk adjustment models

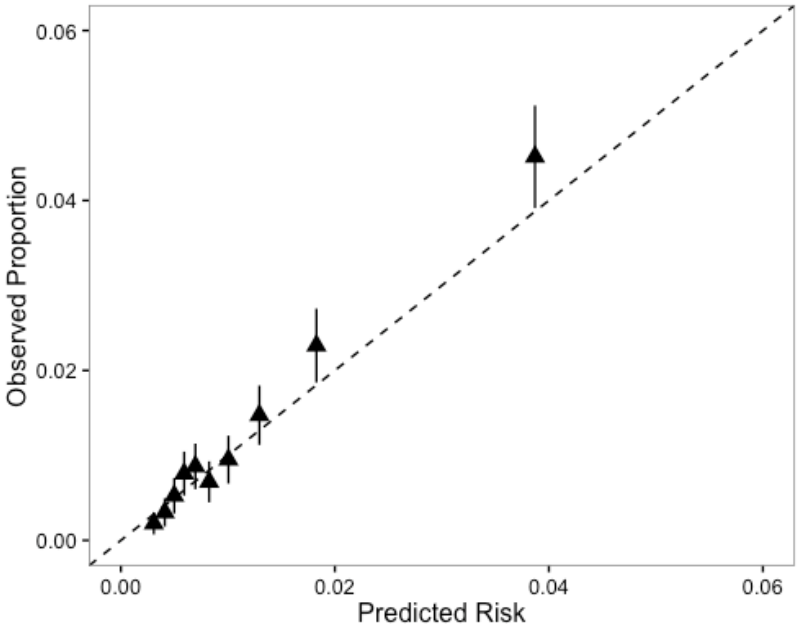
Data Driven Model			
Variable	**OR**	**95% CI**	**p-value**
Age (in years)	0.98	(0.97, 0.99)	<0.001
Cardiac arrhythmia	1.73	(1.40, 2.13)	<0.001
Depression	1.58	(1.28, 1.94)	<0.001
Diabetes uncomplicated	1.37	(1.10, 1.71)	0.006
Diabetes complicated	2.00	(1.34, 2.98)	<0.001
Fluid and electrolyte disorders	1.37	(1.10, 1.70)	0.005
Liver disease	1.82	(1.25, 2.63)	0.002
Procedure type			
Colectomy	3.63	(2.75, 4.78)	<0.001
Hysterectomy	1.60	(1.17, 2.19)	0.003
Hip replacement	1.57	(1.17, 2.10)	0.003
Knee replacement	Ref	--	
Race			
Black	2.07	(1.40, 3.04)	<0.001
White	1.48	(1.04, 2.06)	0.024
Other	Ref	--	
Weight loss (malnutrition)	1.48	(1.12, 1.70)	<0.001

Expert Consensus Model			
Variable	**OR**	**95% CI**	**p-value**
Age (in years)	0.98	(0.98, 0.99)	<0.001
Diabetes uncomplicated	1.35	(1.08. 1.69)	0.009
Diabetes complicated	1.95	(1.29, 2.95)	0.002
Liver disease	1.85	(1.28, 2.68)	0.001
Obesity	1.27	(1.04, 1.56)	0.021
Procedure type			
Colectomy	3.99	(3.04, 5.25)	<0.001
Hysterectomy	1.63	(1.19, 2.22)	0.002
Hip replacement	1.61	(1.20, 2.16)	0.002
Knee replacement	Ref		
Race			
Black	1.94	(1.32, 2.86)	<0.001
White	1.44	(1.03, 2.03)	0.033
Other	Ref		
Renal failure	1.37	(1.03, 1.83)	0.029
Smoking	1.24	(1.03, 1.49)	0.021
Weight loss (malnutrition)	2.68	(2.05, 3.51)	<0.001

The C-statistic was 0.73 (95% CI, .71–.76) for the data-driven model, and 0.73 (95% CI, .71–.75) for the expert consensus model. The validated expert consensus model C-

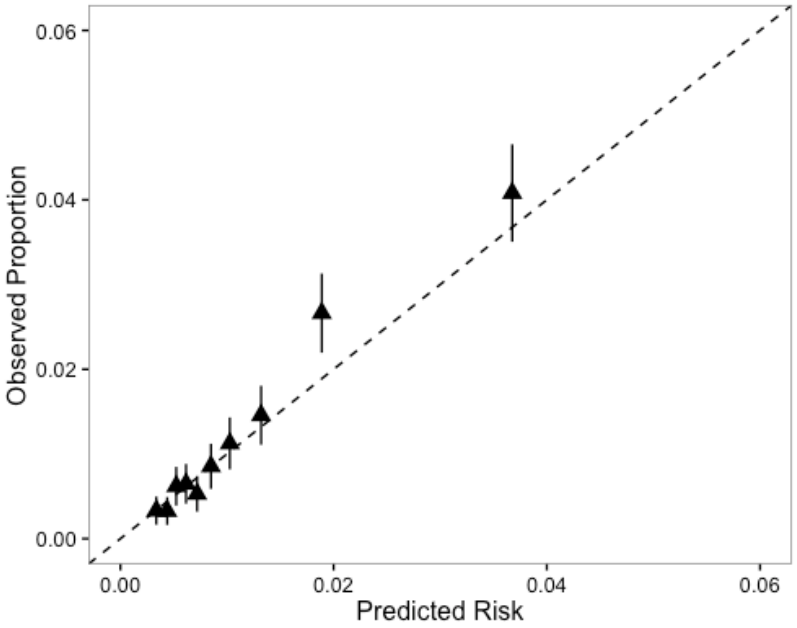
statistic was 0.67 (95% CI, .64–.71). Calibration is illustrated in Figure 8 for the data-driven model and Figure 9 for the expert consensus model. Both calibration plots indicate that the models are well calibrated until the last 2 deciles of risk. This indicates that both models accurately predict SSI for much of the cohort, but the models underestimate the risk of SSI in the higher deciles.

Figure 8. Calibration plot for the data-driven risk adjustment model.



The figure shows the observed proportion of SSI plotted on the y-axis against the risk of SSI predicted by the model on the x-axis. The triangles represent the observed proportions in each model-defined decile of risk and the vertical lines are the 95% CI. The 45-degree line represents perfect model calibration.

Figure 9. Calibration plot for the expert consensus risk adjustment model.



The figure shows the observed proportion of SSI plotted on the y-axis against the risk of SSI predicted by the model on the x-axis. The triangles represent the observed proportions in each model-defined decile of risk and the vertical lines are the 95% CI. The 45-degree line represents perfect model calibration.

The hospital rankings are shown in Table 14. The 28 hospitals were ranked from lowest to highest crude proportion of SSI, and then ranked by the SIRs estimated from the expert consensus risk adjustment model. The rank differences between the crude and adjusted rankings were calculated and the direction of the change noted. When the hospitals were ranked using the expert consensus model, 24 of 28 (86%) hospitals changed ranks, with 16 (57%) changing by ≥4 rankings. Four (14%) hospitals changed position by ≥10 ranks. The rankings changed in a similar manner for the data-driven model (data not shown).

Table 14. Ranking of hospitals (in order of crude rank) before and after risk adjustment by expert consensus divided into quartiles

Hospital	Crude Proportion	Crude Rank	Observed SSI	Expected SSI*	SIR†	Adjusted Rank	Rank Difference	Direction
14	0.0009	1	3	22.8	0.13	1	0	
3	0.0031	2	11	40.0	0.27	2	0	
20	0.0048	3	9	16.9	0.53	4	-1	↓
23	0.0058	4	10	19.8	0.50	3	1	↑
4	0.0060	5	6	7.4	0.81	10	-5	↓
9	0.0068	6	2	1.7	1.21	16	-10	↓
22	0.0070	7	5	6.9	0.73	8	-1	↓
26	0.0070	8	5	7.0	0.72	7	1	↑
19	0.0080	9	11	17.9	0.62	5	4	↑
18	0.0087	10	28	40.5	0.69	6	4	↑
5	0.0088	11	29	35.0	0.83	11	0	
17	0.0106	12	3	2.0	1.49	21	-9	↓
7	0.0113	13	39	28.6	1.36	18	-5	↓
11	0.0143	14	46	33.2	1.39	19	-5	↓
24	0.0147	15	24	17.2	1.40	20	-5	↓
21	0.0152	16	9	7.7	1.17	15	1	↑
2	0.0167	17	30	18.5	1.62	24	-7	↓
8	0.0171	18	18	16.9	1.07	13	5	↑
15	0.0180	19	4	5.0	0.80	9	10	↑
1	0.0202	20	41	32.3	1.27	17	3	↑
6	0.0203	21	34	14.7	2.31	27	-6	↓
10	0.0209	22	56	30.3	1.85	26	-4	↓
13	0.0233	23	4	4.1	0.98	12	11	↑
16	0.0233	24	12	10.7	1.12	14	10	↑
25	0.0244	25	59	37.1	1.59	23	2	↑
12	0.0307	26	52	28.5	1.82	25	1	↑
27	0.0316	27	21	14.0	1.50	22	5	↑
28	0.1111	28	2	0.4	4.72	28	0	

*Number of SSI predicted by the model
†SIR is the observed over the expected number of SSI
Abbreviations: SIR, standardized infection ratio and SSI, surgical site infection

F. Discussion

In this retrospective cohort study, we illustrate the importance of adjusting for individual patient demographic and comorbid conditions when comparing SSI across hospitals using 2 methods of risk adjustment. To our knowledge, this is the first analysis to develop risk adjustment models using patient comorbidities derived from ICD-9-CM codes in a large cohort of surgical patients undergoing several procedures across multiple hospitals. Both

the data-driven and expert consensus models show good discrimination with C-statistics of 0.73, and good calibration across the deciles of risk. When validated, the expert consensus model showed good discrimination, indicating that the model would perform well in other hospital data sets.

We further demonstrate the importance of risk adjustment by showing the change in rankings of the hospitals that resulted when the risk adjustment models were applied. Hospitals with a large burden of patients with comorbid conditions are expected to have a larger proportion of SSI, and their ranking will improve once the risk adjustment model is applied. Likewise, hospitals that serve healthier patients with fewer comorbid conditions may decline in their performance ranks when adjusted for patient case mix. In our study, nearly every hospital changed ranks and approximately half changed by >4 ranks when either risk adjustment methods were applied. These dramatic shifts may have consequences on payments and penalties for an individual hospital when all US hospitals are included in this ranking, as currently done by CMS.

The 2011 CDC models report C-statistics that range from 0.56 to 0.66 for the procedures in our dataset. [41] However, the CDC does not include comorbidities in many of their SSI models. Variables included in most of these procedure-specific models are age, ASA score, surgery duration, wound class, bed size, and academic affiliation. [41] These variables are either not patient specific (eg, medical school affiliation and number of hospital beds) or are subjective (ASA score). Further, the clinical relevance of nonmodifiable risk factors such as bed size and hospital affiliation in risk adjustment is poorly understood. [100] The variable of surgery duration is hard to interpret, as an increase in duration may indicate a more complicated case (patient-level factor) or it may signify a

less skilled surgeon (hospital-level factor). Moreover, adjusting for hospital-level factors may in fact remove the variability in SSI rates explained by surgical or hospital quality of care.

Other risk adjustment models that do include patient comorbidities have been developed including Preventie Ziekenhuisinfecties door Surveillance and ACS-NSQIP. [107,108] When applied to SSI following colorectal resection, these models produced C-statistics of 0.58 for PREZIES and 0.71–0.73 for ACS-NSQIP. [107,108] The NSQIP models, which include comorbid conditions obtained by records review, include many of the same comorbidities as our models, lending further credibility to our approach. The CDC has recognized the value of comorbidity in risk adjustment, and the most recent iterations of the SSI risk models for colon and abdominal hysterectomy procedures include a limited number of comorbidity variables. [33,41] However, our approach provides a more feasible way of collecting and standardizing data on a larger number of relevant comorbidities.

Our expert consensus model has some advantages over the data-driven model. It is much simpler, with fewer variables, than the data-driven model. Candidate comorbid conditions used to develop the consensus model were identified a priori by an expert panel to increase the likelihood of causal relatedness with SSI, and to reduce the possibility that in this large dataset associations were found by chance. [109] Furthermore, discharge diagnoses do not distinguish between conditions that were present on hospital admission and those that are surgical complications, [110] such that the clinical significance of certain comorbidities in the data-driven model is unclear. For example, fluid and electrolyte disorders could be a condition in the causal pathway or a result of the surgery

itself, and including such comorbidities can erroneously inflate the predicted performance of the model. [111] Identifying comorbidities a priori reduces the likelihood of adjusting for conditions that developed postoperatively.

A criticism of the use of ICD-9-CM codes in research is that they fail to capture all patient comorbidities or could reflect codes that maximize reimbursement. [111,112] Indeed, often only the conditions that are likely to have an impact on the admission of interest are coded by the hospital, [113] leading to an underestimation of the prevalence of comorbid conditions among patients. However, claims that ICD-9-CM–based discharge codes incorrectly categorize a patient as having a condition may be overstated. [94,95] Research comparing the Charlson and Elixhauser indices derived from ICD-9-CM codes to those same scores extracted from records review has found that the sensitivity of the individual components varies greatly but that specificity is approximately 98%. [59] Likewise, research has shown the sensitivity of ICD-9-CM codes to identify smokers may be low, but the specificity is nearly 100% when compared to study questionnaires. [75] Furthermore, documentation of comorbidities such as obesity, diabetes, and smoking tend to be higher in surgical patients, owing to the fact that these are known risk factors for postoperative complications. [75] This means that while some patient comorbidities or smokers may be missed (eg, the patient diagnosis was not recorded) due to low sensitivity of the codes, a condition assigned to a patient is likely to be correct. [59,114,115] Therefore, we may in fact be underestimating the prevalence of these conditions in our study sample and incompletely adjusting for comorbidity in our model, resulting in smaller rank changes after adjustment. Despite this limitation, our models still demonstrated good discrimination and calibration.

Our approach has some limitations. Our models' ability to predict SSI in the higher deciles of risk is limited, implying that either important predictors may have been left out of the model or the ICD-9-CM codes failed to correctly identify every patient with a given comorbidity. Our models are not directly comparable to the CDC's because some of the variables used in the NHSN risk adjustment model (ASA score and surgery duration) were not available in the dataset. We were also unable to stratify by procedure type due to the low proportion of complex SSI in our sample. However, colon procedures accounted for the highest and hips/knee replacement for the lowest proportion of SSIs in our dataset. These findings are consistent with the literature, indicating that our results may be generalizable to other hospital groups.[41,108] Another limitation is that we used ICD-9-CM codes and hospitals have recently switched to ICD-10 codes.[95]

Our analysis has a number of strengths. We analyzed patient outcomes in a large number of diverse hospitals in the United States. Infection preventionists used standardized CDC NHSN criteria to identify SSI so that outcome assessment is comparable across hospitals. Because we analyzed deep and organ/space SSI, we likely captured the true incidence of SSI in this cohort.[72] We were able to use comorbid conditions from discharge codes already collected routinely for other purposes, which may be an improvement upon the CDC's risk adjustment model by decreasing the burden of additional data collection. In fact, ICD diagnostic codes are already routinely transmitted to the CMS by hospitals. Use of discharge codes may also encourage the use of risk adjustment among researchers as ICD-9-CM codes are easier to access and are collected on every patient by trained individuals in a standardized fashion. Last, we used

a validation method that demonstrates our model will have good discriminative ability in other data sets.

Our analyses demonstrate the importance of using individual demographic data and comorbidities in risk adjustment models. Further testing of this risk adjustment methodology should be conducted for other infection-related quality improvement measures such as central line–associated bloodstream infections and catheter-associated urinary tract infections. We believe that the CDC and CMS should begin incorporating comorbid conditions obtained by ICD codes into their risk adjustment models.

CHAPTER VII. THE EFFECT OF ADDING COMORBIDITIES TO CURRENT CDC CENTRAL LINE-ASSOCIATED BLOODSTREAM INFECTION (CLABSI) RISK ADJUSTMENT METHODOLOGY[1]

A. Abstract

Background: Risk adjustment is needed to fairly compare central-line–associated bloodstream infection (CLABSI) rates between hospitals. Until 2017, the Centers for Disease Control and Prevention (CDC) methodology adjusted CLABSI rates only by type of intensive care unit (ICU). The 2017 CDC models also adjust for hospital size and medical school affiliation. We hypothesized that risk adjustment would be improved by including patient demographics and comorbidities from electronically available hospital discharge codes.

Methods: Using a cohort design across 22 hospitals, we analyzed data from ICU patients admitted between January 2012 and December 2013. Demographics and International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) discharge codes were obtained for each patient, and CLABSIs were identified by trained infection preventionists. Models adjusting only for ICU type and for ICU type plus patient case mix were built and compared using discrimination and standardized infection ratio (SIR). Hospitals were ranked by SIR for each model to examine and compare the changes in rank.

Results: Overall, 85,849 ICU patients were analyzed and 162 (0.2%) developed CLABSI. The significant variables added to the ICU model were coagulopathy, paralysis,

[1] Jackson SS, Leekha S, Magder LS, Pineles L, Anderson DJ, Trick WE, Woeltje KF, Kaye KS, Stafford K, Thom K, Lowe TJ, Harris AD.The Effect of Adding Comorbidities to Current Centers for Disease Control and Prevention Central-Line-Associated Bloodstream Infection Risk-Adjustment Methodology. *Infect Control Hosp Epidemiol.* 2017 Sep;38(9):1019-1024.

renal failure, malnutrition, and age. The C statistics were 0.55 (95% CI, 0.51–0.59) for the ICU-type model and 0.64 (95% CI, 0.60–0.69) for the ICU-type plus patient case-mix model. When the hospitals were ranked by adjusted SIRs, 10 hospitals (45%) changed rank when comorbidity was added to the ICU-type model.

Conclusion: Our risk-adjustment model for CLABSI using electronically available comorbidities demonstrated better discrimination than did the CDC model. The CDC should strongly consider comorbidity-based risk adjustment to more accurately compare CLABSI rates across hospitals.

B. Introduction

Central-line–associated bloodstream infections (CLABSIs) are responsible for substantial morbidity and mortality among hospitalized patients. Patients with CLABSIs are at a higher risk of death, have longer hospital stays, and incur more healthcare costs than patients without CLABSIs. [116] 1 Since January 2012, hospital reimbursement by the Centers for Medicare and Medicaid Services (CMS) has depended on public reporting of CLABSI rates. CMS hospitals use the operational system of the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) to facilitate reporting. [28]

The CDC uses risk adjustment to more fairly compare CLABSI rates across hospitals. Until 2017, the CDC NSHN adjusted CLABSI rates only by type of intensive care unit (ICU). In 2017, the CDC added hospital size (ie, number of licensed beds) and medical school affiliation as additional risk-adjustment variables. [33] However, neither of these CDC models adjust for individual patient level factors, including comorbid conditions. We hypothesized that risk adjustment could be improved by including

demographics and comorbid conditions from electronically available hospital discharge codes.

C. Methods

Using a cohort design, we retrospectively analyzed ICU patients admitted between January 1, 2012, and December 31, 2013, to 22 US hospitals. Facilities were recruited as part of a partnership between Premier, Inc, the Society for Healthcare Epidemiology of America Research Network, and the University of Maryland School of Medicine. Institutional review board and facility consent were obtained from facilities that voluntarily participated in the study.

Using Premier's Quality Advisor database, we obtained demographic and International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) discharge codes for each adult ICU patient. Patients with CLABSIs were identified by trained infection preventionists at each hospital using CDC NHSN definitions.[71] We also obtained information on the size of the hospital (ie, number of beds) and whether the hospital was associated with an academic medical school.

Risk-adjustment models were built using discrete survival analysis, a method that accounts for time at risk.[80] Specifically, acquisition of CLABSI on each day in the ICU was used as the outcome of a binary regression model with a complementary log-log link. A random intercept for hospital was included in the model to account for the clustering of patients within hospitals.

We constructed 2 models: (1) a model containing only ICU-type (ie, CDC methodology prior to 2017) and (2) a model containing ICU-type plus patient case-mix variables. For the latter model, we identified candidate comorbidity variables using

expert consensus, which has been reported elsewhere. [105] Using a modified Delphi method, 9 infectious disease and infection control experts were asked to rate the 35 comorbid conditions found in the Charlson and Elixhauser comorbidity indices from 1 (not at all related) to 5 (strongly related), based on perceived relatedness to CLABSI. These experts rated the following 14 conditions in terms of causality with CLABSI as 3 (somewhat related) or higher: coagulopathy, dementia, diabetes without complications, diabetes with complications, drug abuse, hemiplegia or paraplegia, HIV/AIDS, lymphoma, malignancy, solid tumor with metastasis, severe liver disease, obesity, renal disease, and weight loss (malnutrition). These 14 conditions (identified using ICD-9-CM codes), along with ICU type, age, gender, race, hospital size, and medical school affiliation were entered into the model as potential predictors of CLABSI. Hospital size was defined in the 2017 CDC NHSN model as a binary variable indicating that the number of beds in the hospital was ≥276. [33] 3 Variables were retained using backward selection if they met the significance level of $\alpha<0.05$.

For both models, we estimated the marginal predicted probabilities of a CLABSI for each patient day in the ICU without including the random effect in the prediction so that hospital characteristics did not influence these values. These predicted probabilities were then used to generate the C statistic and 95% confidence interval (CI) for both models. The C statistic is a measure of discrimination, or the model's ability to discriminate between those with and without the outcome. The C statistic is the chance that the model will assign a higher probability to patients with CLABSIs than without. [106] Values for the C statistic range from 0.50, a probability no different from chance, to 1.0, which is perfect prediction. Calibration, the model's ability to accurately quantify the

probability of the outcome, was assessed with a calibration plot. The predicted probabilities were plotted against the observed proportion of CLABSI in deciles, and a 45° line was added to visually inspect how well the model was calibrated. In a perfectly calibrated model, the points would rest exactly on the 45° line, implying that the predicted risks are equal to the observed rate. [36,37]

Unadjusted CLABSI rates were calculated for each hospital by dividing the number of CLABSIs by the total number of ICU days. To calculate risk-adjusted rates, the predicted probabilities from the risk-adjustment model were summed to estimate the expected number of CLABSI events for each hospital. Standardized infection ratios (SIR) for each hospital were calculated by dividing the observed number of CLABSI by the expected number predicted by the ICU-type plus patient case-mix model. An SIR above 1 indicated that the hospital reported a greater number of CLABSIs than expected, while an SIR below 1 indicated that the hospital reported a lower number of CLABSIs than expected by the model. [73] Hospitals were then ranked by the case-mix risk-adjusted SIRs and compared to the rankings when ordered by the ICU-type–only risk-adjusted SIRs.

All analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC). The calibration plots were generated using the "ggplot2" package in R studio version 0.99.902 software (R Foundation for Statistical Computing, Vienna, Austria).

D. Results

In total, 22 hospitals contributed ICU data. The analysis included 85,849 ICU patients, of whom 162 (0.2%) developed CLABSIs. Of the 22 hospitals, 16 (73%) were large (≥296 beds), 11 (50%) were affiliated with medical schools, and 20 (90%) were located in urban areas. Across hospitals, 22,560 (26%) patients were from 9 medical cardiac critical care

units, 18,157 (21%) were from 8 medical critical care units, 34,537 (40%) were from 14 medical/surgical critical care units, and 10,595 (12%) were from 6 surgical critical care units based on CDC ICU definitions. All patients had a minimum of 9 ICD-9-CM codes, with a median of 27 and a maximum of 65 codes.

Table 15 presents a bivariate analysis of the relationship between CLABSI and patient demographics and comorbidities. Intensive care unit type, age, coagulopathy, paralysis, liver disease, renal failure, and malnutrition were significant at the P<.10 level in the bivariate analysis. Using the medical cardiac care ICU as the reference category, medical/surgical critical care ICU (P=.06) and surgical critical care ICU (P=.03) were predictive of CLABSI, but the medical critical care ICU (P=.40) was not. Table 16 presents the results of the ICU-type plus patient case-mix model. The following variables were added to the ICU-type–only model: coagulopathy (P=.01), paralysis (P=.03), renal failure (P<.01), malnutrition (P<.01), and patient age in 10-year increments (P<.01). Facility hospital size (P=.33) and medical school affiliation (P=.152) were not significant predictors of CLABSI and were therefore dropped from both models.

Table 15. Characteristics of 85,849 Patients With and Without Central-Line–Associated Bloodstream Infection (CLABSI) Admitted to the Intensive Care Unit Between January 1, 2012, and December 31, 2013

Variable	CLABSI n=162		Non-CLABSI n=85,687		Hazard Ratio	p-value
	Mean (SD)	n (%)	Mean (SD)	n (%)	(95%CI)	
Age in years	.60.2 (17.2)		63.0 (16.9)		0.99 (0.98, 1.00)	0.012
Sex						
Female		71 (0.17)		39,094 (99.8)	Reference	
Male		91 (0.18)		46,590 (99.8)	0.96 (0.70, 1.31)	0.793
Race						
Black		42 (0.29)		13,225 (99.7)	1.70 (1.15, 2.52)	0.008
Other		17 (0.17)		6,998 (99.8)	1.44 (0.85, 2.42)	0.175
White		103 (0.15)		65,364 (99.8)	Reference	
ICU type						
Medical cardiac		36 (0.14)		22,524 (99.8)	Reference	
Medical critical care		32 (0.16)		18,125 (99.8)	1.52 (0.85, 2.70)	0.156
Medical/surgical critical care		64 (0.18)		34,473 (99.8)	1.82 (1.03, 3.22)	0.040
Surgical critical care		30 (0.24)		10,565 (99.7)	1.98 1.14 (3.46)	0.016
Coagulopathy		52 (0.39)		12,258 (99.6)	1.70 (1.22, 2.37)	0.002
Dementia		2 (0.24)		751 (99.7)	1.36 (0.34, 5.12)	0.665
Diabetes uncomplicated		39 (0.15)		23,236 (99.8)	0.87 (0.61, 1.26)	0.468
Diabetes complicated		17 (0.23)		6,696 (99.8)	1.22 (0.74, 2.01)	0.446
Drug abuse		9 (0.15)		5,726 (99.8)	0.79 (0.40, 1.55)	0.489
Paralysis		17 (0.45)		3,659 (99.5)	1.89 (1.14, 3.14)	0.013
HIV/AIDS		2 (0.45)		411 (99.5)	1.58 (0.39, 6.40)	0.524
Lymphoma		4 (0.34)		1,057 (99.6)	1.60 (0.59, 4.31)	0.355
Malignancy		9 (0.11)		6,773 (99.9)	0.63 (0.32, 1.24)	0.185
Metastatic cancer		10 (0.24)		3,538 (99.7)	1.42 (0.75, 2.70)	0.281
Liver disease		31 (0.37)		7,667 (99.6)	1.68 (1.13, 2.49)	0.010
Obesity		32 (0.20)		14,956 (99.8)	1.02 (0.69, 1.50)	0.927
Renal disease		56 (0.28)		19,822 (99.7)	1.38 (1.00, 1.92)	0.050
Weight loss (malnutrition)		55 (0.47)		10,804 (99.5)	1.74 (1.25, 2.42)	0.001

Table 16. Hazard Ratios, P Values, and the C Statistic for the ICU-Type Plus Patient Case-Mix Model

Variable	HR (95%CI)	p-value	C-Statistic (95% CI)
ICU type			0.64 (0.60, 0.68)
Medical cardiac	Reference		
Medical critical care	1.33 (0.74, 2.37)	0.400	
Medical/surgical critical care	1.92 (1.08, 3.42)	0.060	
Surgical	1.83 (1.04, 3.20)	0.034	
Coagulopathy			
No	Reference		
Yes	1.65 (1.17, 2.30)	0.004	
Paralysis			
No	Reference		
Yes	1.76 (1.06, 2.93)	0.029	
Renal disease			
No	Reference		
Yes	1.59 (1.13, 2.22)	0.009	
Weight loss			
No	Reference		
Yes	1.56 (1.12, 2.19)	0.010	
Age (per 10 year increase)	0.88 (0.80, 0.96)	0.006	

The C statistics were 0.55 (95% CI, 0.51–0.59) for the ICU-type–only model and 0.64 (95% CI, 0.60–0.69) for the ICU-type plus patient case-mix model, with a statistically significant difference (P<.001) (Figure 10). When the hospitals were ranked by adjusted SIRs and compared (Table 17), 10 hospitals (45%) changed rank (4 increased in rank and 6 decreased in rank) when comorbidities were added to the ICU-type–only model. Figures 11 and 12 show the calibration of the ICU-type–only model and the ICU-type plus patient case-mix model. Our final model shows better calibration than the ICU-type–only model, which overestimated the expected rate relative to the observed CLABSI rate in some subgroups.

Figure 10. Receiver operating characteristic (ROC) curves comparing the intensive care unit (ICU)-type–only model to the ICU-type plus patient case-mix model

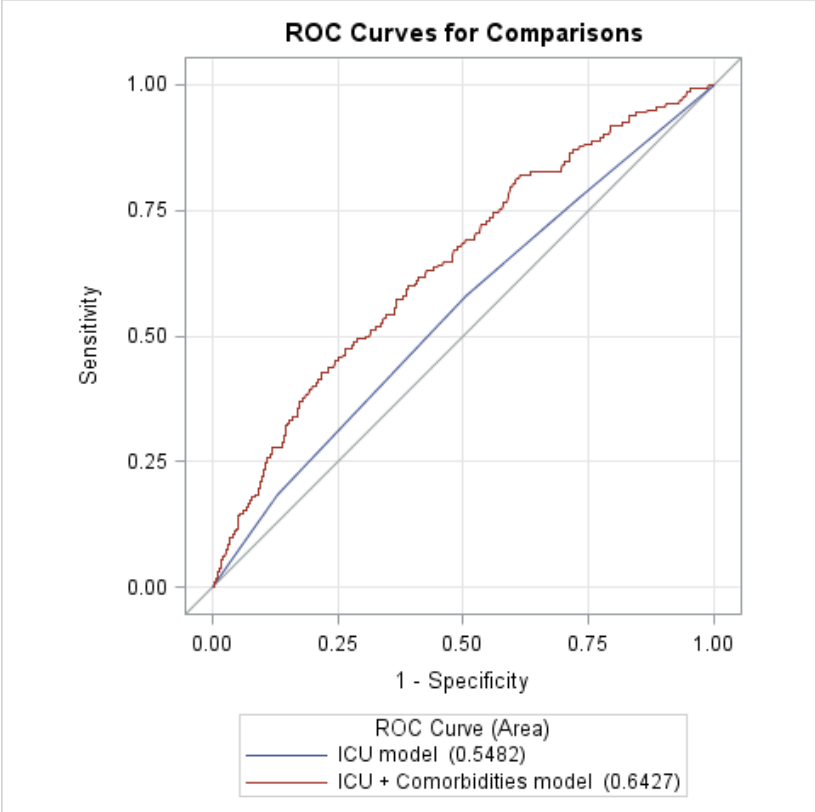


Table 17. Ranking of Hospitals[a] With the Intensive Care Unit (ICU)-Type–Only Model and ICU-Type Plus Patient Case-Mix Risk Adjustment

Hospital	ICU Model SIR	ICU model Rank	ICU+ Comorbidities Model SIR	ICU + Comorbidities Rank	Difference in Rank	Direction
A	0.15	1	0.15	1	0	
B	0.17	2	0.17	2	0	
C	0.20	3	0.23	3	0	
D	0.38	4	0.44	4	0	
E	0.62	5	0.67	5	0	
F	0.68	6	0.70	6	0	
G	0.83	7	0.83	7	0	
H	0.88	8	0.87	8	0	
I	1.03	10	0.94	9	1	↑
J	0.93	9	0.95	10	-1	↓
K	1.06	11	1.00	11	0	
L	1.10	12	1.16	12	0	
M	1.53	18	1.29	13	5	↑
N	1.30	13	1.30	14	-1	↓
O	1.34	14	1.30	15	-1	↓
P	1.36	16	1.37	16	0	
Q	1.61	19	1.38	17	2	↑
R	1.48	17	1.44	18	-1	↓
S	1.35	15	1.50	19	-4	↓
T	2.94	20	2.66	20	0	
U	3.32	22	2.73	21	1	↑
V	3.29	21	3.50	22	-1	↓

[a] In order of ICU-type-only model ranking.

Figure 11. Calibration curve for the ICU model

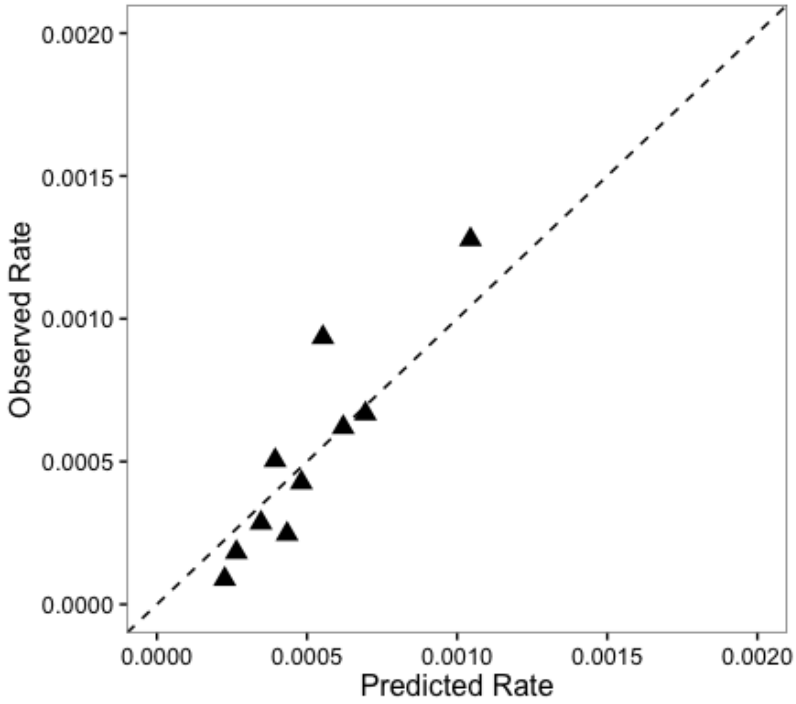
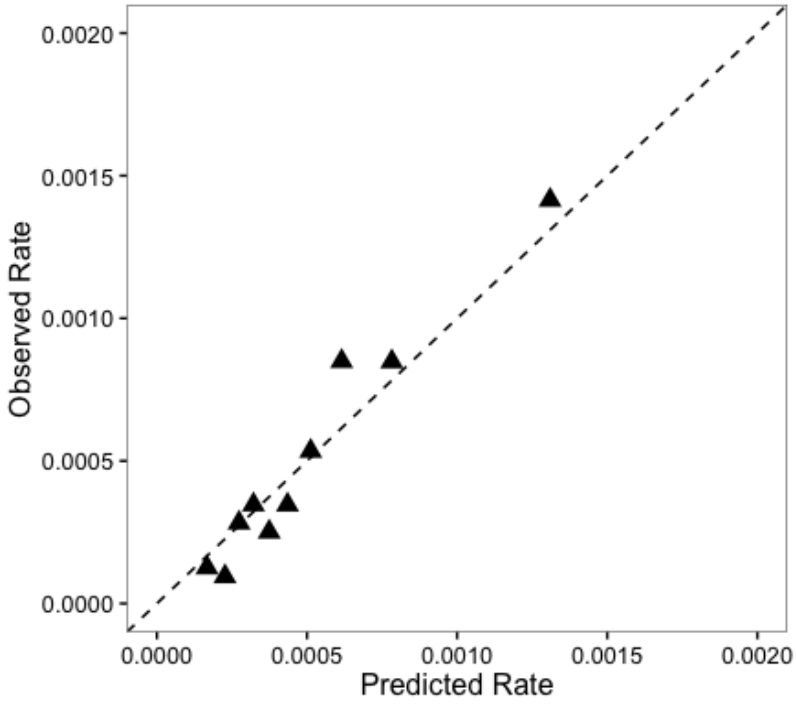


Figure 12. Calibration curve for the ICU plus patient demographics and comorbidities model



F. Discussion

In this retrospective cohort study, we have illustrated the importance of adjusting for patient case-mix variables including comorbid conditions when comparing CLABSI rates across hospitals. Other than the existing CDC model, this analysis is the first in developing risk-adjustment models for CLABSI. Furthermore, the CDC models do not incorporate comorbid conditions or other significant patient factors such as age. Although our model incorporating these factors showed modest discrimination, it showed better discrimination than a model using only ICU type (CDC risk model until 2017). The additional 2017 CDC variables of medical school affiliation and facility hospital size were not statistically significant predictors of CLABSI in our cohort.

We have further demonstrated the importance of risk adjustment by showing the change in rankings of the hospitals that resulted when the risk adjustment model including comorbid conditions was applied. Hospitals with a large burden of patients with more comorbid conditions are expected to have larger CLABSI rates, and their rankings will improve once the risk adjustment model is applied. Likewise, hospitals that serve healthier patients with fewer comorbidities may decline in their performance rankings when SIRs are adjusted for patient case mix. These shifts may have consequences regarding payments and penalties for individual hospitals when all US hospitals are included in this ranking, as is currently done by the CMS.

The CDC models prior to 2017 only adjusted for type of ICU. [73] The new 2017 CDC model added medical school affiliation and facility hospital size as variables. [33] Although these variables are unlikely causally related to CLABSI occurrence, they were probably selected as proxy variables for patient case mix. However, while medical school affiliation may represent a case mix of patients who have more comorbid conditions and

higher severity of illness that merits risk adjustment, it may also represent more inexperienced providers that should not be adjusted for when the intent is to use those adjusted rates for quality-of-care comparisons. Similarly, facility hospital size is likely associated with several patient case-mix and care delivery factors, which make the direction of influence on CLABSI difficult to predict. Indeed, in our large and diverse cohort, neither medical school affiliation nor facility hospital size were significantly associated with CLABSI. Therefore, we suggest that it is better to directly adjust for patient demographics and comorbid conditions when possible.

Our analysis has several strengths. Infection preventionists used standardized CDC NHSN criteria to identify CLABSI such that outcome assessment is comparable across hospitals. We used comorbid conditions from discharge codes already collected routinely for other purposes; therefore, the incorporation of these variables into current national risk adjustment would not require any additional data collection burden on the part of hospitals. In fact, ICD diagnostic codes are already routinely transmitted to CMS by hospitals. The use of discharge codes may also encourage the use of risk adjustment because ICD diagnostic codes are easier to access and are collected on every patient by trained individuals in a standardized fashion.

Our approach has some limitations. Most of our sample consisted of large, urban facilities, which may limit the generalizability of our findings to other hospitals. The Premier database did not have data on central-line days, so we were unable to use this measure for our denominator or to account for patients with >1 line. Our use of ICU days as the denominator may have underestimated the overall CLABSI rate in each unit, which may have misclassified patient time at risk, but we have no reason to believe that this

misclassification is differential. Work by Horstman et al [117] has shown that ICU days correlate strongly with device days and that hospital performance rankings using either measure are also strongly correlated. A criticism of the use of ICD-9-CM codes in research is that they fail to capture all patient comorbidities and could reflect codes that maximize reimbursement. [111,112] Research comparing the Charlson and Elixhauser comorbidity indices derived from ICD-9-CM codes to those same scores extracted from chart review revealed that the sensitivity of the individual components varies greatly but that specificity is nearly 100%.[59,97] Therefore, while some patient comorbidities may have been missed due to low sensitivity of the ICD codes, a condition assigned to a patient is likely to be correct. [59,114,118] Therefore, we may have underestimated the prevalence of these conditions in our study, resulting in smaller rank changes after adjustment. Despite this limitation, our models still demonstrated good discrimination. Another limitation is that we used ICD-9-CM codes and hospitals have recently switched to ICD-10 codes; however, this change is unlikely to affect the discrimination of our model because the identified comorbid conditions can be directly compared between ICD-9-CM and ICD-10. [119]

Our analyses demonstrate the importance of using individual demographic data and comorbidities in risk-adjustment models. We believe that the CDC and CMS should strongly consider incorporating comorbid conditions obtained by electronically available ICD codes into their risk adjustment models for CLABSI.

CHAPTER VIII. DISCUSSION

A. VRE

This study is the first of its size to quantify VRE bacterial burden and examine its role in the transfer of VRE from colonized patients to HCWs' gloves or gowns. As bacterial burden in all patient samples increases so does the odds of HCW glove and gown contamination, a potential source of transmission to other patients in the ICU. We also found that 15% of the HCWs' gowns and gloves were positive for VRE after providing patient care. These results are consistent with another study that found 13%[23] glove or gown contamination, and one study[2] that found 11% transfer to gloves only (this study did not look at transmission to gowns). There was a 114% increase in HCW glove and gown contamination for each $\log_{10}$ increase in skin bacterial burden. This strong association remained even after adjustment for stool bacterial burden.

The strong association between skin bacterial burden and HCW contamination is supported by our other findings that touching the patient was the greatest risk factor for HCW gown and glove contamination during routine patient care. Touching the patient's skin and transferring the patient in or out of bed remained independent risk factors for contamination after adjusting for touching other items in the patients' environment. Other studies have also suggested that skin may be an efficient means of VRE transfer. Duckro et al. found that the antecubital fossa was the most efficient body site for VRE transmission. In that study, HCWs contaminated their gloves 100% of the time after touching the patient's antecubital fossa, compared to 60% after contacts with the patient's chest. Our study also found higher bacterial burden on the patients' arms than on their chests. The patient's antecubital fossa is touched often by HCWs during clinical care (e.g. for blood draws and blood pressure measurement), resulting

in increased bacterial burden on this area and subsequent transmission efficiency. As has been suggested previously, this area may also be a habitable environment for VRE. [85]

Consistent with our findings, Snyder et al. [24] identified presence of a nasogastric feeding tube as a patient-associated risk factor for transmission of VRE to HCW. They also found that touching the patient's skin conferred the greatest contamination risk, specifically contact with the patient's catheter, trunk, and lower extremities. [24] Morgan et al. [23] identified duration in the room, performing a physical exam, contact with the ventilator, and environmental contamination as risk factors for HCW gown and glove contamination with MDROs, but VRE-specific risk factors were not examined. Hayden et al. [93] found that 62% of the 103 HCW-patient interactions resulted in glove contamination, though was unable to distinguish between touching the patient and touching the environment as nearly all HCWs touched the environment, though they did find increased transfer among those who touched both compared those who touched the environment only (70% vs. 52%). [93]

Our results also indicate the main driver of this transfer is likely due to *E. faecium*, which is associated with higher colony counts and increases the odds of transfer. Patients colonized with *E. faecium* on their skin were nine times as likely to transfer the bacteria to HCWs as those colonized with *E. faecalis* after adjusting for bacterial burden. This study was among the first to look at the role of VRE species in bacterial burden and HCW contamination. Previous work in mouse models have found high levels of colonization with *E. faecium*. [120] Future work is needed on how species-specific colonization affects subsequent infection.

B. Risk adjustment

This retrospective cohort study has illustrated the importance of adjusting for patient case-mix variables including comorbid conditions when comparing SSI proportions and CLABSI rates across hospitals. This is the first analysis to develop risk adjustment models using patient

comorbidities derived from ICD-9-CM codes in a large cohort of surgical and ICU patients across multiple hospitals. The SSI model using comorbidities identified by experts showed good discrimination a C-statistic of 0.73 (95% CI: 0.71–0.75). Further, validation indicated the model would perform well in other hospital data sets (C-statistic: 0.67 (95% CI: 0.64–0.71). The CLABSI model which incorporated patient comorbidities showed modest discrimination (C-statistic: 0.64 [95% CI: 0.60–0.69]). This model performed better than one used by the CDC, which accounts for ICU-type only (0.55 [95% CI, 0.51–0.59]).

We have further demonstrated the importance of risk adjustment by showing the change in rankings of the hospitals that resulted when the risk adjustment model included comorbid conditions. Hospitals with a large burden of patients with more comorbidities are expected to have higher SSI and CLABSI rates. Adjustment for underlying case-mix of the hospital population will improve these hospitals' rankings. Likewise, hospitals that serve healthier patients with fewer comorbidities may decline in their performance rankings when SIRs are adjusted for patient case mix. These shifts may have major consequences for individual reimbursement hospitals when all US hospitals are included in this ranking, as is currently done by the CMS.

Variables included in the 2011 CDC SSI procedure-specific models are age, ASA score, surgery duration, wound class, facility size (as measured by the number of patient beds), and academic affiliation. [41] The C-statistics reported from these CDC models range from 0.56 to 0.66 for the same surgical procedures analyzed in our dataset. [41] The CDC models for CLABSIs prior to 2017 only adjusted for type of ICU. [73] The new 2017 CDC model added academic affiliation and facility size as variables. [33] These variables are either not patient specific (eg, medical school affiliation and number of hospital beds) or are subjective (ASA score). The

inclusion of surgery duration is also hard to interpret, as an increase in duration may indicate a more complicated case (patient-level factor) or it may signify a less skilled surgeon (hospital-level factor).

The clinical relevance of non-modifiable risk factors such as facility size and hospital affiliation in risk adjustment is poorly understood. [100] These hospital factors may be proxies for patient population with greater comorbidity and higher severity of illness that merits risk adjustment, but it may also represent more inexperienced providers that should not be adjusted for when the intent is to use those adjusted rates for quality-of-care comparisons. These factors may be better captured by patient demographics and diagnosis codes. Moreover, adjusting for hospital-level factors may in fact remove the variability in HAI rates explained by hospital quality of care. Therefore, we suggest that it is better to directly adjust for patient demographics and comorbid conditions when possible.

C. Strengths and Limitations

1. VRE

VRE bacterial burden has rarely been examined in the acute care setting. This study is the first study of its size to examine the role of VRE bacterial burden in transmission to HCWs' gloves or gowns. Our use of a prospective cohort design established temporality between patient transmission and HCW acquisition of VRE. HCW-patient interactions were observed immediately following patient specimen collection (generally within an hour and no more than four hours). Therefore, it is unlikely that patient VRE burden decreased significantly between sample collection and HCW observation. The methods used in this study to detect bacterial transmission in the ICU setting were developed and validated by the UMMC hospital epidemiology team and the microbiology research laboratory. These methods have been adopted by other institutions and are now standard in the literature. [23,67,90]

We sampled from two ICUs in our hospital that conduct active surveillance. Clinical cultures fail to detect many of those colonized with VRE. Surveillance cultures collected at admission increase detection of VRE carriers in the ICU three-fold. [12] Case finding through active surveillance minimizes selection bias. Because clinical cultures are often ordered when a patient shows signs and symptoms of an infection, bias is introduced if patients are included based on clinical cultures have different risk factors for transmission than patients included based surveillance cultures. The former patients may be sicker, have greater number of comorbidities and devices, and may be higher transmitters than patients identified through surveillance cultures.

We were unable to recover VRE from the perianal swab of 34 patients. There may be many reasons for this. First, it is possible that after the initial positive surveillance culture, some of these patients were successfully de-colonized. Though, there was no difference in time from positive culture to enrollment between those who had recoverable VRE and those who didn't (mean time in both groups was 3.5 days). We obtained a stool samples on 19 of these patients, of which, all but one had detectable VRE in the stool. Second, because VRE was found in the stool of nearly all patients it may be the technique used to swab the patients was not always optimal. Nine interactions with five patients lead to transmission of VRE to HCWs' gloves or gowns in those without VRE detected on the perianal swab, indicating these patients were in fact colonized with VRE. It was not always possible to visualize the anus of patients who could not be turned due to obesity or the presence of breathing tubes and other devices. Bacterial mis-measurement due either to de-colonization or problems with specimen collection would likely attenuate the association found between VRE burden and HCW contamination.

We did not sample the environment directly or sample the HCWs after each task or touch. We may have been unable to tease apart transmission risk factors when care activities were bundled (e.g. touching items in both patient and environmental domains). It is possible that HCWs could have picked up VRE from the environment, touched the patient, and tested positive for VRE on their gloves.

This study was conducted at a single site and in two ICUs. Thus, these results may not be generalizable to other hospitals or ICUs. Transmission of VRE between patients and HCWs may vary in other acute care settings due to differences in patient care practices. However, these findings will most likely be generalizable to other large-sized, academic hospitals and ICUs with similar patient case mix. Furthermore, the findings of this study may not be generalizable to other organisms as transmission mechanisms may differ between pathogens.

2. Risk adjustment

This design has many strengths. We analyzed patient outcomes in a large number of hospitals across the US. IPs used standardized NHSN criteria to identify SSIs and CLABSIs, so that proportions and rates are comparable between hospitals. We used comorbid conditions from discharge codes, which may be an improvement from CDC's risk adjustment model. Use of discharge codes may also lead to improved risk adjustment among researchers and quality improvement professionals as ICD-9 codes are easier to access, take less IP time, and are collected on every patient. Further, for the CLABSI aim we were able to compare our model directly to the CDC's model.

We used comorbidities identified *a priori* by an expert panel to increase the likelihood of causal relatedness with SSI and CLABSI and to reduce the possibility that in this large dataset associations were found by chance. [109] This was especially important for CLABSI where risk

factors are poorly understood. Further, discharge diagnoses do not distinguish between conditions that were present on hospital admission and those that developed while in the hospital. Identifying comorbidities *a priori* increases the likelihood these conditions existed before surgery or hospitalization.

Another major strength of this analysis is the use of internal-external validation to validate the SSI model. This validation method has several advantages over others, such as split sample validation, because it uses all the data to build the model instead of a portion. Further, because the data are not split at random, but use the natural split of the hospital, the validation method is qualifies as external validation. [79] The resulting C-statistic (0.67 [95% CI: 0.64–0.71]) represents a reasonable estimate for another cohort of hospitals with similar case-mix.

Our hypothesis was that the inclusion of comorbid conditions to risk adjustment models will improve the model for SSI outcomes. However, some of the variables currently used by the CDC for risk adjustment of SSI (ASA score, wound class, and surgery duration) were not available to us and a direct comparison of our model to the CDC's model was not possible. Regardless, the addition of these variables would increase the discrimination of our model, so we are likely underestimating discrimination instead of overestimating.

CLABSI rates are determined by number of CLABSIs over central line days. However, substituted ICU days for central line days, which is a good approximation, but not completely accurate as patients may be taken off and on a central line as needed throughout their time in the ICU. While ICU days may overestimate the time patients are exposed and underestimate the rate of CLABSI at each hospital. However, research has shown that rates calculated from ICU days roughly correlate to central line days. [117] More importantly, there was a strong correlation between the hospital performance ranks using either denominator. [117] Hospitals without

CLABSIs were excluded from the analysis, which may overestimated the CLABSI rate and resulted in a different risk adjustment model if the patient case-mix of these excluded hospitals was different from the sample. The sensitivity analysis shows that while the CLABSI rate was slightly overestimated (5.1 vs. 4.7 per 10,000 patient-days), the resultant risk adjustment models and model discrimination were the same.

Another limitation common to both studies is that we may be underestimating the prevalence of comorbidities in our SSI and CLABSI populations with the use of ICD-9 codes to identify comorbid conditions. Research comparing the Charlson and Elixhauser Indices derived from ICD-9-CM codes to those same scores extracted from chart review has found that the sensitivity of the individual components varies greatly by condition.[114] This underestimation may have led to incomplete adjustment for comorbidities in our model and smaller rank changes after adjustment. With more sensitive methods we would expect to see greater model discrimination and larger rank changes.

D. Contribution to the field of healthcare epidemiology

This dissertation focused on two important topics in healthcare epidemiology: 1) VRE transmission to HCWs as a surrogate outcome for patient to patient transmission via HCWs; and 2) risk adjustment methods for two important HAIs, SSIs and CLABSIs.

HAIs caused by MDROs contribute substantially to patient morbidity and mortality in the US. Understanding how transmission occurs and the risk factors for transmission is paramount to testing and implementing infection control policies. Discontinuing Contact Precautions for VRE colonized patients is currently being debated healthcare epidemiologists.[97-99] Our finding that 15% of HCWs' glove or gowns were VRE positive after patient care should add to this debate. Our results may also have significant implications for other infection prevention policies,

especially the finding implicating skin colonization in VRE transmission to HCW. Interventions to consider include increasing the frequency of CHG bathing and the use of "red boxes," small zones at the threshold of patient's room where HCWs can conduct clinical assessments without donning personal protective equipment. [121,122] This red-zone intervention could lead to less use of gloves and gowns for low risk transmission activities. Our research may help expand the red box areas in patient ICU rooms and identify patient-care activities where it may be reasonable for HCWs forgo donning of gloves and gowns. In contrast, high risk transmission activities like touching the patient or transferring the patient in a patient with a high VRE burden, could require more aggressive infection control interventions including double gloving or better gown barriers.

Hospitals in the US are required to report their rates of SSI and CLABSI to CMS for reimbursement[†]. [123] Because certain patient comorbidities are risk factors for these HAIs, risk adjustment models should include comorbid conditions for these rates to be meaningful. Major limitations of current CDC NHSN risk adjustment methods include a lack of identifiable risk factors for CLABSI, and the time and effort spent by hospital personnel collecting and entering patient data into the NHSN database. This dissertation sought to determine whether patient discharge codes could be used successfully to risk adjust SSI and CLABSI rates. This work resulted in the identification of relevant risk factors for SSI and CLABSI, as well as accurate and validated models. We showed that electronic health data is easy to collect and use in risk adjustment models. This work should inform future CDC risk adjustment models and research which compares HAI rates across different hospitals. We hope that this research will lead to better risk adjustment methods by the CDC.

[†] As of 2015, CMS reporting requirements include CLABSI from all adult ICUs and SSI from surgical patients undergoing colectomies and hysterectomies.

CHAPTER IX. APPENDIX 1. DATA COLLECTION FORMS USED

PATIENT INFORMATION FORM

REPID: ________________ Study Number: ________________ Enrollment Date: ________________

Location information

☐ Midtown ☐ UMMC Unit/Ward: __________ Room: ______________

Culture information

☐ MRSA Culture date: ______________________________

☐ CRE Final result date: ______________________________

☐ VRE Accession number: ______________________________

Culture source:
☐ Nasal surveillance swab
☐ Perirectal surveillance swab
☐ Wound
☐ Blood
☐ Sputum
☐ Urine
☐ Other (specify): ________________

Date	Artificial airway (trach/ET tube)	Wound	Foley	Intravascular Catheter (central or PICC line)	Chest Tube	Surgical Drain	Diarrhea	Rectal Tube	NG Tube
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐

HCW cultures obtained

HCW #	Date
1	
2	
3	
4	
5	

Observation Form A
HCW SAMPLES DATA COLLECTION SHEET

HCWID: _____

OBSERVATION DATE: _____

ENTRY TIME: _____ **EXIT TIME:** _____

PROVIDER TYPE:

- ☐ Nurse
- ☐ Respiratory Tech
- ☐ MD/Nurse practitioner
- ☐ Occupational/Physical Therapy
- ☐ Patient Care Tech (PCT)
- ☐ Environmental Services
- ☐ Other (specify):

ENVIRONMENTAL CONTACT	PATIENT CONTACT
☐ Sink	☐ Physical exam
☐ Bed Rail	☐ Wound dressing
☐ Bedding	☐ Bathing/hygiene
☐ Bedside Table	☐ Catheter/drain
☐ Vital Sign Monitor	☐ ETT/trach
☐ Supply Cart	☐ Vital signs
☐ Lift	☐ Giving meds (oral)
☐ IV Pump	☐ IV tubing/IV meds
☐ Ventilator	☐ Transfer in/out of bed
☐ Curtain	☐ Blood draw
☐ Trash	☐ Glucose monitoring
☐ Computer	☐ Rectal tube/bag
☐ Barcode scanner	☐ Suctioning
☐ Call button/remote	
☐ Other (specify below)	☐ Other (specify below)

CHAPTER X. APPENDIX 2. RECATEGORIZATION OF VARIABLES

There are a number of items that the HCW touched during the ICU observation that were written in the Other, specify field. These were categorized into pre-existing categories, where possible. New categories were created for the observations that could not be categorized.

Patient domain:

Field name	Other, specify	Name of variable in analysis
Physical exam	listened to back and chest, listened to chest, listened to chest w/room stethoscope, touched patient while listening to chest w/room st, listend to chest, listened to chest w/stethoscope, listened to chest/back, listened to chest, peg tube, face, feed patient, head, neck, patient head, patient neck, eyes, touched inside of mouth, oral care, handed patient pen and white board, abdomen, arm, back, chest, feet, gown, hand, leg, legs, legs and arms, patient arm, patient arm and chest, patient gown, patient leg, patient leg/foot, patient legs feet, patient wrist/wristband, pt arm, pt chest, pt gown, pt. Gown, put xray film behind patient, shook hand, shoulders, stomach, temp under arm, touched patient, touched patient arm, touched patient foot and head, touched pt leg, touched stomach, ultrasound patient's back, wrist, abdomen, ankle, ankles, axilla, back, arms, foot/leg, patient feet, patient shoulder, pt leg feet, side, skin, touched chest and arm, touched foot, touhed arm and leg, ultrasound, and arm, sock, stomache, thigh, took pulse, took temp, and leg, touched ankle, took off sock and touched foot	**RENAME**: Skin*
Wound dressing	surgical wound, bloody gauze, surgical drain, emptied surgical drain	Wound dressing
Bathing/hygiene		Bathing/hygiene
Catheter	catheter insertion, urine bottle	Catheter
ETT/Trach	Bronchoscopy, intubated patient, Breathing tube/mask, Ng tube, ng tube, inserted ng tube, nasal cannula, ng tube, put mask on patient, take oral temp, throat, nasal canula/face/nose, ng feeding tube	**RENAME**: Breathing devices
Vital signs	BP cuff, took off bp cuff, wire from patient, wires from patient, wires from pt, wires, wires	Vital signs

	attached to pt, wires connected to patient, temp under arm, took pulse, took temp, took pt. oral temp	
Oral meds		Oral Meds
IV tubing	PICC line, central line, central line dressing change, picc line insertion, tube/wires from patient, central line port	IV tubing
Patient transfer	Repositioning patient, helped roll patient, helped to bathroom, repositioned patient, rolled, rolled patient, rolled pt, rolled pt., skin contact with repositioning, turn patient, turned patient over, turned patient, helped patient walk around the room, moved patient, adjusted patient	Patient transfer
Glucose monitoring		Glucose monitoring
Rectal tube	re-inserted rectal tube	Rectal tube
Suctioning	suction tube, sunction tube	Suctioning
Bedrail[†]		**MOVED**: Bedrail
Bedding[†]	Bed straps, bed ties, patient pillow wedge, ice packs, patient ice packs, hip pad, linen on floor,	**MOVED**: Bedding
	perianal specimen, perianal swab, placed bed pan underneath, placed bedpan, bottom, flushed stool and urine, diaper, helped pt with bedpan, helped pt. with toileting, inguinal area, patient's diaper, peri-anal, perianal sample, perianal swab, stool specimen, swabbing, swabbed patient, toileting, wiped patient after bowel movement, cleaned bottom, obtained perianal & stool sample,	**NEW**: Anal/groin skin

[*]Physical exam and touching the patient's skin were collapsed into one variable called skin.
[†]These items were moved from the environmental to patient domain.

Environmental domain:

Field name	Other, specify	Name of variable in analysis
Sink		
Bedside table		
Vital sign monitor		
Supply cart		
Lift		
IV pump		
Ventilator	oxygen pump	
Curtain		
Trash	Medical waste trash, sharps container, pick up trash off floor, red trash, sharpes container, picked up trash off floor, trash on floor	
Computer		
Scanner		
Call Button		
	Bathroom, bathroom door, bathroom door and handle, bathroom door handle, bathroom toilet, toilet, bathorrom door, bed pain stand, bedpan, bed pan, chair, beside chair, counter top, counter, prepping medication, bulletin board, cabinet, door, dry erase marker, flashlight, floor, label maker, light switch, lockbox, marker, window ledge, windowsill, counter label maker, doorway, dry erase board, lock box, pen in room, scissors, dry ersase marker, telemonitor, hanging bag, patient cell phone, drink, patient breakfast tray, food tray, pen from patient, patient's drink, pt drink	**NEW**: Room furniture
	CT scan, EKG, and sonography machine (brought into, dialysis machine, doppler, ultrasound, x-ray machine, xray machine, walker	**NEW:** Outside medical equipment

CHAPTER XI. APPENDIX 3. AIM 2B SENSITIVITY ANALYSIS

Three hospitals were excluded from the original analysis because no CLABSIs had been reported at these hospitals. Because of these exclusions the CLABSI rate may have been overestimated, and the comorbidities selected for and the discrimination of the risk adjustment model may be different. When these three previously excluded hospitals were added back to the analysis the sample size increased from 317,977 ICU patients from 22 hospitals to 344,741 ICU patients from 25 hospitals. There were 162 CLABSIs reported in both analyses. The original analysis had a CLABSI rate of 5.1 per 10,000 patient days and the new analysis has a rate of 4.7 CLABSI per 10,000 patient days.

The ICU-only and ICU plus patient case-mix models were re-constructed in the same way that is detailed in Chapter III. The results of the ICU-type only model comparing the original analysis with the sensitivity analysis are presented in Table 18. The discrimination of the new model is C=0.59 (95% CI: 0.57, 0.61) and of the original model is C=0.55 (95% CI: 0.51, 0.59). The hazard ratios in the new model are not substantially different from the original model. The results of the ICU plus comorbidity model comparing the two analyses are shown in Table 19. The discrimination of the new model is C=0.64 (95% CI: 0.60, 0.68) and from the original model is C=0.64 (95% CI: 0.60, 0.69). The hazard ratios in the new model did not change substantially from the original model.

Table 18. ICU-type only CLABSI model comparing the hazard ratios and C-statistics of the sensitivity analysis with original analysis

Sensitivity analysis (25 hospitals)		**Original analysis (22 hospitals)**	
Variable	**HR 95% CI**	**Variable**	**HR 95% CI**
ICU type		ICU type	
Medical critical care	1.62 (0.91, 2.90)	Medical Critical Care	1.52 (0.85, 2.70)
Medical surgical care	2.11 (1.17, 3.83)	Medical Surgical Care	1.82 (1.03, 3.22)
Surgical critical care	2.00 (1.14, 3.52)	Surgical Critical Care	1.98 (1.14, 3.46)
Medical cardiac care	Reference	Medical cardiac care	Reference
C- statistic	0.59 (0.57, 0.61)	C- statistic	0.55 (0.51, 0.59)

Table 19. ICU-type plus patient case-mix CLABSI model comparing the hazard ratios and C-statistics of the sensitivity analysis with the original analysis

Sensitivity analysis (25 hospitals)		**Original analysis (22 hospitals)**	
Variable	**HR 95% CI**	**Variable**	**HR 95% CI**
ICU type		ICU type	
Medical critical care	1.35 (0.76, 2.41)	Medical critical care	1.52 (0.85, 2.70)
Medical surgical care	1.98 (1.11, 2.18)	Medical surgical care	1.98 (1.14, 3.46)
Surgical critical care	1.83 (1.03, 3.24)	Surgical critical care	1.82 (1.03, 3.22)
Medical cardiac care	Reference	Medical cardiac care	Reference
Coagulopathy	1.65 (1.17, 2.31)	Coagulopathy	1.65 (1.17, 2.30)
Paralysis	1.78 (1.07, 2.95)	Paralysis	1.76 (1.06, 2.93)
Renal failure	1.57 (1.12, 2.19)	Renal failure	1.59 (1.13, 2.22)
Weight Loss	1.56 (1.12, 2.18)	Weight Loss	1.56 (1.12, 2.19)
Age10	0.87 (0.80, 0.96)	Age10	0.88 (0.80, 0.96)
C- statistic	0.64 (0.60, 0.68)	C- statistic	0.64 (0.60, 0.69)

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