Title
The Hospital as Environment: Assessing and Improving the Efficacy and Impacts of Interventions Designed to Reduce Hospital Acquired Infections

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Los Angeles

The Hospital as Environment: Assessing and Improving the Efficacy and Impacts of Interventions Designed to Reduce Hospital Acquired Infections

A dissertation in partial satisfaction of the requirements for the Doctor of Philosophy in Environmental Health Sciences

by

Evelyn Natalia Alvarez

2018
ABSTRACT OF THE DISSERTATION

The Hospital as Environment: Assessing and Improving the Efficacy and Impacts of Interventions Designed to Reduce Hospital Acquired Infections

by

Evelyn Natalia Alvarez

Doctor of Philosophy in Environmental Health Sciences
University of California, Los Angeles, 2018

Professor Hilary Godwin, Co-Chair
Richard J. Jackson, Co-Chair

The overarching goal of the work described herein is to examine strategies for improving the safety of hospital environments. Specifically, I examine the evidence-base used to approve antimicrobials that could be linked to health outcomes, consider the cost-effectiveness of emerging infection prevention technologies, such as antimicrobial copper surfaces, and assess the psychosocial impacts of pediatric isolation precautions. There has been considerable interest in evaluating the in vitro antimicrobial efficacy of copper alloy surfaces as demonstrated by the numerous in vitro studies conducted in the past decade, prompting us to consider the clinical efficacy of such emerging technologies. The first section provides a critical review of the U.S. Environmental Protection Agency (US EPA) antimicrobial registration process and of the scholarly literature to investigate the current state of the hospital with regards to hospital-acquired infections (HAIs) and whether improvements could be made at the policy level to address this. We reviewed current literature on the national rates of HAIs,
current hospital infection prevention practices, and emerging technologies, in particular copper alloy surfaces, that aim to decrease the rate of HAIs. Based on review of these findings, we recommended that antimicrobials for usage in hospital settings be subject to more rigorous regulatory scrutiny, requiring clinical evidence of efficacy if public health claims are made, and we proposed a revised paradigm of registering antimicrobials for use in hospital settings. The second section reports an assessment of the cost-effectiveness and public health benefits of emerging hospital technologies, such as copper alloy surfaces, that have previously been demonstrated to have strong *in vitro* effectiveness against common hospital pathogens. We compared the cost and performance of standard surfaces with that of copper alloy surfaces based on results from the first clinical study conducted evaluating the *in vivo* efficacy of copper alloy against common hospital pathogens. With reasonable estimates and data from the literature, our cost-effectiveness model indicated that copper alloy surfaces are a moderately cost-effective strategy for hospitals to adopt in the prevention of HAIs but have minimal incremental effectiveness compared to standard surfaces as measured in quality-adjusted life years (QALYs). In the future, this methodology could be used to determine if copper alloy surfaces are a cost-effective strategy for hospitals to adopt based on the availability of more clinical evidence. The third section, addresses a critical gap in the literature on qualitative data on isolation precautions for pediatric patients. In this study, we conducted semi-structured, open-ended interviews with children who were under isolation precautions (or have been in the past) to learn about how this vulnerable population, through their own lens, copes with isolation policies to identify areas of improvement in the pediatric isolation experience. Studying the hospital as home to the vulnerable allows a unique opportunity to give voice to key vulnerable populations that are susceptible to HAIs. Together, these studies highlight the importance of
using evidence-based approaches to guide when hospitals should adopt emerging HAI technologies or modify existing interventions and services.
The dissertation of Evelyn Natalia Alvarez is approved.

Brian Cole
Gerald F. Kominski
Daniel Z. Uslan
Hilary Godwin, Committee Co-Chair
Richard J. Jackson, Committee Co-Chair

University of California, Los Angeles
2018
DEDICATION

My dissertation is dedicated to my grandfather.

His painful experience with a deadly hospital acquired infection inspired me to look into this subject.

I miss you every day.

Thank you for always believing in me and supporting me.
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ABBREVIATIONS USED HEREIN

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td>ATP</td>
<td>Antimicrobial Testing Program</td>
</tr>
<tr>
<td>CAUTI</td>
<td>Catheter-Associated Urinary Tract Infection</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CDI</td>
<td>Clostridium difficile infection</td>
</tr>
<tr>
<td>C/E</td>
<td>Cost-effectiveness ratio</td>
</tr>
<tr>
<td>CLABSI</td>
<td>Central Line-Associated Bloodstream Infections</td>
</tr>
<tr>
<td>CLS</td>
<td>Child Life Specialist</td>
</tr>
<tr>
<td>CMS</td>
<td>Centers for Medicare and Medicaid Services</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Enterococcus faecium, Staphylococcus aureus, Clostridium difficile, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterobacter species</td>
</tr>
<tr>
<td>FIFRA</td>
<td>Federal Insecticide, Fungicide, and Rodenticide Act</td>
</tr>
<tr>
<td>HAIs</td>
<td>Hospital-Acquired Infections or Healthcare-Associated Infections</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>IP</td>
<td>Infection Prevention</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of Stay</td>
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<tr>
<td>MDRO</td>
<td>Multi-Drug Resistant Organism</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-Adjusted Life Year</td>
</tr>
<tr>
<td>RRMC</td>
<td>Ronald Reagan Medical Center</td>
</tr>
<tr>
<td>STPP</td>
<td>Sustainable Technology and Policy Program</td>
</tr>
<tr>
<td>US EPA</td>
<td>United States Environmental Protection Agency</td>
</tr>
<tr>
<td>VAP</td>
<td>Ventilator-Associated Pneumonia</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin-Resistant Enterococcus</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness to pay</td>
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</tbody>
</table>
I would like to take some time to thank the village that helped me get through these past 7 years of my life, without whom I would not have been able to complete my PhD. Whether present or in heaven, you have all woven different pieces of the tapestry of this journey.

To begin, I’d like to thank my advisor, Dr. Hilary Godwin, for never giving up on me. From organizational skills to crafting better narratives, she has helped me tackle academia with a strong skillset, and I’m a better researcher for it. Her countless hours providing me with constructive feedback on my manuscripts and dissertation have also taught me how to effectively give feedback to my own students, and I’m a better instructor for it. In sharing sad moments of my life with her, like the passing of my grandfather while I was beginning my PhD program, she taught me how to transform loss into inspiration, and to look forward. It is in this way that my dissertation was born.

I’d like to thank my collaborators, committee members, funders, and those who helped me with various parts of my dissertation. I’m completely indebted to the amazing Child Life Specialist, Megan Pike, without whom my vision for Chapter 4 would not have been a reality. Thank you to all staff at UCLA Mattel Children’s Hospital for facilitating this study and for allowing us to hear children’s perspectives on isolation precautions. Chapter 2 and Appendix A are published manuscripts that Dr. Daniel Uslan, Dr. Peter Sinsheimer, and Dr. Malloy in addition to Dr. Godwin helped to write and revise. Dr. Gerald Kominski helped me conceptualize and revise Chapter 4. To my other committee members, Dr. Jackson and Dr. Brian Cole, thank you for your support and feedback, and your dedication to building healthy communities. To Dr. Uslan, thank you for all of your support since Day 1! Thank you to Dr. Kominski for being extremely generous with his time in helping me understand cost-
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Sitting sedentary and typing a thesis is no joke, so never has exercise been more important. In the beginning of my PhD program, Dr. Gina Ann Garcia and Sergio Guevara taught me that working out could be also be fun through high intensity interval training classes that pushed me beyond my limits and motivated to make exercise a fundamentally important part of my daily life. To Claire Berngartt and Billy Blanks, whom I met later in this journey, thank you for alleviating my PhD-induced stress through your tough but extremely fun workouts. Thank you to the team of amazing gym trainers at the John Wooden Center who put in so much time and effort into teaching daily classes to help keep students healthy. I’m a stronger person for it.
To my grandparents who raised me, thank you for believing your little girl would grow up to do something special – si se puede, guelos!

To Kenny, thank you for always being by my side and accepting my newfound thesis nocturnality. Thank you for being my rock during such a challenging part of my life.
EDUCATION

2016……………PhD Candidate in Environmental Health Sciences, University of California, Los Angeles

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2011-2012………California Wellness Fellowship

2011-2012………Eugene Cota-Robles Fellowship

2011…………….UCLA National Science Foundation Alliance for Graduate Education and the Professoriate Competitive Edge Award

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PUBLICATIONS

• Alvarez E, Uslan D, Malloy T, Sinsheimer P, Godwin H. Response to Perspectives from the field in response to ‘it is time to revise our approach to registering antimicrobial agents [by the environmental protection Agency] for health care settings. Am J Infect Control. 2017; 45(1):100–
102.


**PRESENTATIONS**

- Guest lecture, “Intro to Environmental Health Sciences” for a UCLA course, Environment 12 in August 2014 and August 2015

- Poster on the “Evaluation of the Regulatory Paradigm for Testing Antimicrobials for Use in Clinical Settings” for the American Public Health Association (APHA) 2014 Conference in New Orleans, LA.

- Lecture on “Climate Change and Allergies/Asthma” for public health professionals as part of a workshop series for the Los Angeles County Department of Public Health LADPH on December 4th, 2013.

- Poster on the “Efficacy of Commercially Available Antimicrobial Copper Surfaces Against Common Nosocomial Pathogens” for Infectious Disease Week IDW 2013 in Atlanta, GA.
INTRODUCTION

Hospital-associated infections (HAIs) contribute to increased morbidity, mortality, and healthcare costs. A key priority is to shift our focus from treating HAIs to preventing their occurrence. A second priority is to adopt infection prevention strategies that are rooted in best practices and that are cost-effective. A third priority is to better understand the psychosocial implications of HAIs and their management in order to avoid harming vulnerable populations. Our goal is to conduct research that helps to inform policies and practices to preventing HAIs. I specifically chose to focus my research on three areas: antimicrobial regulation, cost-effectiveness of emerging HAI interventions, and children as a vulnerable population to HAIs.

THE STATE OF THE HOSPITAL AS ENVIRONMENT

Healthcare-associated infections (HAIs) result in more than 95,000 deaths in the United States each year, and significant morbidity and mortality worldwide. The five most costly types of infections in the United States (central line-associated bloodstream infections, ventilator-associated pneumonia, surgical site infections, Clostridium difficile infections, and catheter-associated urinary tract infections) resulted in $9.8 billion in associated costs in 2012. A growing body of evidence suggests that 50% of HAIs are preventable, and that use of evidence-based interventions could significantly reduce the incidence of HAIs. Effective,
evidence-based approaches to prevention of HAI s could save not only lives, but also an estimated $5.7-$31.5 billion per year in the United States alone.\textsuperscript{7}

It is particularly important to focus on \textit{prevention} of HAI s because many of the pathogens responsible for causing infections in healthcare settings are resistant to antibiotics and hence hard to treat. Infections caused by multidrug-resistant organisms (MDROs) lead to significant mortality and morbidity, prolonged length of hospital stay, and excessive costs. One resistant organism alone, methicillin-resistant \textit{Staphylococcus aureus} (MRSA), kills more Americans every year (~19,000) than emphysema, HIV/AIDS, Parkinson’s disease, and homicide combined.\textsuperscript{8} All told, about 23,000 deaths in the USA are caused annually by antibiotic-resistant bacterial infections.\textsuperscript{9} The overuse or misuse of antimicrobial agents is the crucial component of the emergence and spread of MDROs.

The Infectious Diseases Society of America has highlighted a group of highly problematic antibiotic-resistant organisms that are responsible for a substantial proportion of HAI s, which are referred to as “ESCAPE” pathogens: \textit{Enterococcus faecium, Staphylococcus aureus, Clostridium difficile, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter} species.\textsuperscript{10-12} ESCAPE pathogens are currently responsible for the majority of U.S. hospital infections and no longer respond effectively to antibiotics, hence the “ESCAPE” terminology.\textsuperscript{10,11} Furthermore, several of these ESCAPE pathogens are responsible for \textit{Clostridium difficile} infection (CDI), whose rates are higher in the elderly,\textsuperscript{13} and CLABSIs (central line-associated bloodstream infections), whose rates are higher in children and neonates compared with adults,\textsuperscript{14,15} - both are vulnerable populations of interest in \textbf{Chapter 3 and Chapter 4}, respectively. The Centers for Medicare and Medicaid Services (CMS) stopped reimbursing hospitals for costs attributed to treating CLABSIs as of 2008.\textsuperscript{15} CDI is responsible
for a U.S. economic burden exceeding $1 billion per year, so similarly to CLABSIs, insurance reimbursement is also strained.\textsuperscript{13} Hence, the focus of many interventions has been to address some of these specific infection routes of ESCAPE pathogens.

**THE ANTIBIOTIC PIPELINE**

Despite the increasing prevalence of antibiotic-resistant infections, the pipeline for new antibiotics has slowed to a trickle. The development of antibiotics is time-consuming and expensive and has a low success rate.\textsuperscript{16} Relatively few new antibiotics have been developed in the last \textasciitilde{}40 years due to low financial incentives.\textsuperscript{17} The market for antibiotics is limited because antibiotics are not taken chronically and are usually prescribed for a window of 1-4 weeks depending on the type of infection. As a result, the potential for pharmaceutical companies to profit from developing new drugs is limited. The rise of antimicrobial resistance with a diminishing antibiotic pipeline, therefore poses a serious threat worldwide. By contrast, cardiovascular drugs are highly profitable because they are typically taken for years if not decades.

Additionally, when new antibiotics are developed and approved for use, doctors are advised to limit their use to prevent antibiotic resistance to the new drugs from evolving, which limits the potential market for the drugs. If antimicrobial drugs are used extensively, then antibiotic resistance can occur, making the drug ineffective, limiting the length of time for which there is a large market. Therefore, drug companies frequently perceive that potential profits from sales of new antibiotics will not cover the costs of developing and testing these new drugs. With limited treatment options, infection prevention is key to efforts to combatting HAIs.
Research and evidence are needed to provide an evidence base for prevention efforts. Three areas in which research is particularly needed include: (1) improved policy approaches to disinfecting hospital environments (2) improved decision-making about which infection control-practices to employ in specific settings and (3) improved understanding of the behavioral effects of isolation practices in a vulnerable population.

IMPROVED APPROACHES TO REGULATING ANTIMICROBIALS USED IN CLINICAL ENVIRONMENTS

Several new technologies have emerged in recent years that are aimed at improving disinfection in clinical environments, but the current process for registering these technologies for use does not require companies to demonstrate that they improve clinical outcomes. Examples include touchless technologies such as airborne hydrogen peroxide and ultraviolet devices,¹⁸ as well as antimicrobial-coated devices (e.g., copper alloy surfaces and silver-coated endotracheal tubes, ETTs). Because manufacturers are currently not required to demonstrate clinical efficacy before marketing these products for use in clinical settings with public health claims, infection prevention (IP) practitioners must make decisions about whether to implement these products without having a strong evidence base about their health benefits. Studies are needed that assess the clinical efficacy of these products, and changes to the way in which antimicrobials are registered need to be addressed. Better health outcomes would be achieved if the registration process required proof of clinical efficacy for antimicrobial products, and health savings would also be observed as expenditures on non-evidenced based antimicrobial products decrease.
IMPROVED DECISION-MAKING ABOUT WHICH INFECTION CONTROL PRACTICES TO EMPLOY IN SPECIFIC SETTINGS

Studies and tools are also needed that will allow Infection Prevention (IP) staff to make informed, evidence-based decisions about which infection control practices are most suited for their specific clinical setting. The IP guidelines issued by the CDC and the Joint Commission allow for IP staff to select the practices that are most appropriate for their own organization, given the specific challenges and constraints that they face. One problem is that it is difficult for IP staff to know whether new antimicrobial options are more cost-effective than existing approaches. Tools are needed that would allow hospital stakeholders to systematically compare the costs and benefits of current and proposed infection control practices in their organization.

To understand how to improve infection prevention, practitioners need to understand why some approaches work better than others. For example, key barriers identified in the literature as potential reasons why healthcare workers have low compliance rates with hand-hygiene practice recommendations are skin irritation caused by hand-hygiene agents, inaccessible hand-hygiene supplies, interference with worker-patient relationships, priority of care (i.e., the patient’s needs are given priority over hand hygiene), wearing of gloves, forgetfulness, lack of knowledge of the guidelines, insufficient time for hand hygiene, high workload and understaffing, and a lack of scientific information revealing the significant impact hand hygiene has on HAI rates. Some perceived barriers to adherence with hand-hygiene recommendations have been assessed or quantified in observational studies but have not been explored in terms of more rigorous clinical studies.
Passive infection prevention approaches, such as copper alloy surfaces, offer a promising alternative to traditional “active compliance” infection prevention approaches (e.g., hand hygiene practices by healthcare workers) that have limited success due to low compliance. However, prior to adopting new interventions, IP professionals need access to data demonstrating that these novel approaches actually decrease the transmission of infectious disease.

A decision analysis framework for this area would be valuable in that it would allow stakeholders to weigh the pros and cons of different infection control interventions. Ideally, this decision-analysis framework would also allow IP staff to directly compare the costs of specific infection control practices to the hospital costs that would be incurred from additional HAIs that would occur if the practices were not in place. Several studies reported in the research literature allow these costs to be estimated. For example, the excess hospital costs associated with only four healthcare-associated infections may equal the entire annual budget for hand-hygiene products used in inpatient-care areas. Just one severe surgical site infection, lower respiratory tract infection, or bloodstream infection may cost the hospital more than the entire annual budget for antiseptic agents used for hand hygiene. Several studies have provided quantitative estimates of the benefit of hand-hygiene-promotion programs. These studies demonstrate that preventing even a small number of HAIs per year leads to savings that exceed any incremental costs of improved hand-hygiene products long-term. However, because similar cost analyses are not available for some of the newer types of IP interventions, it is difficult for IP staff to evaluate whether the costs of these new interventions outweigh any additional reductions in disease burden, let alone whether they should be implemented in conjunction with existing practices or should be used instead of current IP interventions.
Assessing and improving the efficacy and impacts of interventions to reduce HAIs also involves examining the perspective of a vulnerable population that previously had not had its voice heard. To get a comprehensive understanding of the scope of HAIs, it is important to study the vulnerable populations they target. One of the ways hospitals deal with prevention of HAIs is by employing isolation precautions, the advantages and disadvantages of which have been discussed in the peer-reviewed literature. Largely absent from the literature is a discussion of the psychosocial effects of isolation on a particularly vulnerable population: children. Children are even more vulnerable to the impacts of isolation given they can miss key developmental milestones. Furthermore, many children in isolation are chronically ill, and are repeatedly hospitalized. A prior study in which parents of pediatric isolation patients (but not the children themselves) were surveyed revealed themes of confusion, loss of control, and anxiety. Chronically ill children have shared more stories of loneliness, fear, and unpleasant emotions even before hospitalization, therefore subsequent isolation may exacerbate preexisting depression and feelings of loneliness and alienation. In the 1950s and 1960s, researchers John Bowlby and James Robertson provided seminal evidence on the harmful effects of social isolation on developing children. They theorized that hospitalized children’s responses could be categorized in three separate phases: protest, despair, and detachment.

In response to this work, hospitals have begun to change the way they handle pediatric hospitalization, and thus, changes to hospital visiting policies now incorporate recommendations to allow parents to room in, provide a wide-array of play equipment, and
provide health care professionals specifically trained to educate and support hospitalized children.33-35 Despite these advances, pediatric isolation is still commonly employed in cases where the patient is particularly vulnerable to infection or when the patient has an antibiotic-resistant infection.29 After an internal risk assessment demonstrated the costs and risks of isolation outweighed benefits at Ronald Reagan Medical Center (RRMC), contact isolation precautions for MRSA and VRE were discontinued as of July 1st, 2014.38 However, at the time this was written (December 2018), contact isolation precautions were still routinely employed for CDI at RRMC and protective isolation measures for transplant patients and other immune-suppressed patients are still in effect.

There exists a paucity of recent research examining the psychosocial effects of pediatric isolation. Better understanding of these effects would allow doctors to assess whether the benefits of isolation for infection control reasons outweigh the potential harms to the patient. Critically, such research would also provide insights into how to develop strategies that would help to ameliorate these harms.

ORGANIZATION OF THIS THESIS

Chapter 2 (previously published in the American Journal of Infection Control) provides a critical review of the literature to analyze the current framework the U.S. EPA uses for the registration of antimicrobial products for use in hospital settings. The review addresses three key questions about the state of infection prevention strategies in a U.S. context: What are the challenges related to the U.S. EPA approval of antimicrobial products for use in clinical settings? What are the limitations of relying on in vitro data for approving antimicrobial products for clinical settings? What is the recommended improved process for the registration of antimicrobial products
for clinical settings to stop the trend of HAIs? We found that the U.S. EPA’s reliance on *in vitro* self-reported data for approval of antimicrobials used in hospitals has the potential to affect HAI outcomes. Previously, only one study had been reported on a randomized control trial evaluating the clinical efficacy of copper surfaces in a hospital setting, and this study has been critiqued because of the pathophysiology of the clinical isolates obtained and the statistical analyses performed.

UCLA researchers are currently investigating the question of whether copper alloy surfaces have clinical efficacy. I have collaborated with the lead researchers on the UCLA copper alloy clinical trial (Dr. Uslan and Dr. Sinsheimer) to analyze the framework that was used to register copper surfaces as antimicrobial products for use in hospital settings to assess whether the regulatory process for antimicrobial surfaces is sufficiently evidence-based. In collaboration with this team, I have been able to develop recommendations on how to improve the process for registration of antimicrobial products in clinical settings. Thus, we proposed a more rigorous framework for the registration of antimicrobials for healthcare settings based on clinical data requirements. This work was published in the *American Journal of Infection Control.* In **Appendix A** (previously published in the *American Journal of Infection Control* as a response to our first publication), we provide a timeline to contrast the lack of clinical data regarding the specific case study of copper alloy with the prominence of *in vitro* studies, concluding with the recommendation for more clinical studies to be conducted on copper alloy surfaces in hospitals.

To address the need for tools that would allow hospital stakeholders to easily make cost effective, evidence-based decisions on what IP technologies and measures to adopt for their respective institutions, I developed a decision analytic model for comparing the cost-effectiveness of different IP interventions (**Chapter 3**). To develop the model, I examined the cost-effectiveness of a proposed infection control intervention (copper alloy surfaces) at
UCLA’s RRMC as a case study. Because there is a particular need for IP practitioners to compare the costs and benefits of new interventions (e.g., antimicrobial surfaces) with standard interventions (e.g., hand hygiene practices), we used the model to evaluate and compare the costs and effectiveness of implementing copper surfaces in RRMC in comparison to standard surfaces used in RRMC.

This work, coupled with the results of the pending UCLA clinical study on antimicrobial copper surfaces, will help to inform individuals deciding whether to deploy antimicrobial copper surfaces on a large scale across hospitals. In addition, the lessons learned from this study will be used to aid hospital stakeholders in evaluating the cost-effectiveness of other infection prevention measures in their own institutions.

Prompted by our research in Chapter 2, we sought to focus on the vulnerable populations that are most affected by HAIs, specifically children. We identified key gaps in the literature related to how pediatric patients experience isolation. Therefore, in Chapter 4 (accepted for publication in Clinical Child Psychology and Psychiatry), we assess how children experience pediatric isolation when it is used as a tool for infection control at UCLA Mattel Children’s Hospital. We conducted semi-structured interviews with pediatric isolation patients and surveyed their parents to explore the psychosocial effects of pediatric isolation as a tool for infection control and identified characteristics and behaviors that build resiliency. My collaborator, Child Life Specialist (CLS), Megan Pike, administered our semi-structured, open-ended interviews with pediatric isolation patients and a survey for their parents. In Chapter 4, I synthesize and analyze the resulting interview and survey data to develop recommendations regarding pediatric isolation practices.

Studying perceptions of isolation is particularly important because prior studies in the literature have reported that most children are not fully aware of why they are put in isolation.29
Striving for a balance between keeping isolated pediatric patients physically healthy while maintaining their mental health and allowing them to achieve near-milestone development should be an attainable goal for hospitals.

We anticipated that additional themes would arise because the voices of the children would also be heard. The three topics we based the interview questions on concentrate on three themes: (1) Creating a Comforting Environment, (2) Identifying Patient Concerns, and (3) Identifying Possible Areas of Pediatric Patient Experience Improvement. We collected this data via our CLS collaborator, Megan Pike, developed a coding methodology to identify recurring concerns, and synthesized the data to develop a cohesive narrative of the responses as they pertain to the four final themes resulting from the coding methodology. Appendix B provides the open-ended children interview questions used and Appendix C provides the parent survey questions used in the study. Appendix D contains the Child Life Training Guide developed for this study to outline the basic patient recruitment and enrollment process for the CLS conducting the interviews.

Chapter 5 provides a synthesis of the overarching findings and conclusions reached through this research and recommendations for future studies:

- The work described in Chapter 2 suggests that policies and programs targeted at HAIs are supposed to be based on the best available evidence to support their use, and in fact, many are. However, our research has highlighted that clinical studies, which are the gold standard, are often times not employed in the decision-making process for antimicrobials, and in our particular case study, copper alloy antimicrobial surfaces, more clinical studies need to be conducted to ascertain if there is a pathway to reduced rates of HAIs in actual patient populations and not just in in vitro controlled
The work in Chapter 3 provides key insights into the cost-effectiveness of our case study from Chapter 2, copper alloy antimicrobial surfaces. Based on the scientific literature along with reasonable estimates, copper alloy surfaces provide minimal incremental effectiveness and moderate cost-effectiveness compared to standard surfaces. However, more clinical and cost-effectiveness studies are needed to address this literature gap.

The work described in Chapter 4 suggests that qualitative studies evaluating pediatric isolation through the lens of the children themselves are needed not just to address the pediatric literature gap but to also identify best practices especially when it involves a key vulnerable population.

Together, these studies elucidate something that is taken for granted in the hospital environment: the clinical efficacy of infection prevention policies and programs.
REFERENCES:


It is Time to Revise our Approach to Registering Antimicrobials for Healthcare Settings

(This chapter was published in the *American Journal of Infection Control, 2016, 44(2): 228-232* )

ABSTRACT

**Background:** Healthcare-associated infections (HAIs) are on the rise worldwide and control of HAIs is a top priority for U.S. healthcare systems. Antimicrobial products are an important part of our arsenal for controlling and preventing HAIs. Furthermore, misuse of antimicrobials can result in an increased burden of antibiotic-resistant organisms. Despite this, federal regulations do not require manufacturers to provide clinical evidence of the efficacy of new antimicrobials prior to registration for use in clinical settings, even if public health claims are made by the manufacturer. This is a problem because several studies have shown that effectiveness of an antimicrobial in a laboratory assay does not necessarily mean that use of that antimicrobial in a clinical setting will result in a reduction of HAIs.

**Objectives:** Here, we examine as a case study the recent registration of copper as an antimicrobial surface by the U.S. Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which highlights the lack of clinical evidence required of hospital antimicrobial registrants.

**Discussion:** We discuss how this example illustrates why the current requirements under FIFRA for registration of antimicrobials to be used in clinical settings do not serve the public’s best
interest. In addition, we propose how the regulatory requirements might be amended to improve public safety.

**Conclusions:** Given the importance of antimicrobials in preventing HAIs and how the use of antimicrobials in the environment impacts antibiotic resistance, the integration of a clinical data requirement for antimicrobial registration is needed.
INTRODUCTION

Healthcare-associated infections (HAIs) result in more than 75,000 deaths in the United States each year\(^1,2\) and countless more worldwide. Effective, evidence-based approaches could save not only lives, but also an estimated $5.7-$31.5 billion per year in the United States alone.\(^3\) A major mechanism for transmission of HAIs is via contaminated surfaces in healthcare settings\(^4\). Even after environmental cleaning, clinically relevant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and *Clostridium difficile* (C. difficile) can persist in healthcare environments where they can then be transferred to other patients.

A promising new method of infection control is the use of antimicrobial surfaces such as copper alloys. The use of antimicrobial surfaces in healthcare settings is intuitively appealing because it can conceivably provide constant antimicrobial activity with a low likelihood for recontamination.\(^5\) Replacing hospital high-touch surfaces, such as bed rails, with a copper alloy has been shown to reduce quantitative microbial burden (>90%), including the burden for key organisms that cause infections.\(^6\) In addition, antimicrobial surfaces may employ novel mechanisms of activity that may be harder for organisms to evade.

Copper surfaces have been shown to kill a wide range of microbes *in vitro*, including organisms responsible for HAIs such as MRSA and *C. difficile*.\(^6\) A single randomized control trial has been conducted on copper alloy surfaces in clinical settings.\(^7\) The results demonstrated that patients staying in intensive care unit rooms with copper alloy surfaces had significantly lower rates of HAIs and/or colonization with MRSA or VRE compared with patients in control rooms.\(^7\) However, additional studies are needed to reproduce these findings and to assess the clinical effect of copper alloy surfaces in other patient populations and settings.
On the basis of the *in vitro* studies alone, copper alloys were registered as an antimicrobial surface by the U.S. Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Currently, the EPA currently does not require clinical evidence of efficacy for registration of antimicrobial agents, which is in stark contrast to the Food and Drug Administration (FDA), which requires evidence of clinical efficacy to approve antimicrobial products. A significant concern is that the registration of copper sets forth public health claims that have not yet been clinically demonstrated, which can lead to confusion for consumers. This is problematic because public health claims allowed by the EPA are based on *in vitro* assays and not on clinical evidence of disease reduction.

The registration of copper alloy as an antimicrobial agent reveals flaws in the registration process that need to be addressed. It is reasonable to anticipate that the general public might mistakenly believe that EPA-approved antimicrobial public health claims are based on clinical evidence. To address this concern, the Copper Development Association (CDA) created a section on their Web site (www.antimicrobialcopper.com) with the intent of providing clarifying statements to aid potential users of antimicrobial copper in understanding the difference between conclusions found in peer-reviewed literature and EPA-registered product label claims. In their clarification of public health claims associated with copper alloy products, the CDA states that “while Antimicrobial Copper surfaces have been shown to reduce microbial contamination, they do not necessarily prevent cross-contamination.” Nonetheless, we are concerned that manufacturers are allowed to make public health claims that are based on *in vitro* assay efficacy and not on clinical data. We believe that public health claims for antimicrobial products designed for use in hospital settings should be reserved for products for
which there is compelling clinical evidence of efficacy, ideally published in the peer-reviewed literature.

**THE CURRENT PROCESS OF REGISTRATION FOR ANTIMICROBIAL PRODUCTS**

Currently, manufacturers wishing to register antimicrobial agents must demonstrate the efficacy of these agents *in vitro* (*i.e.*, using bacterial cultures in a laboratory) and must demonstrate that the agents can be used without causing unreasonable risk to humans and the environment.\(^8\) If the prescribed standards are met, the product is issued an EPA registration identification number that can appear on the product’s label along with public health claims. (See Figures 2.1 and 2.2)

Public health claims can be made for registered sterilants, disinfectants, virucides, sanitizers, or tuberculocides if they show *in vitro* efficacy against microorganisms that are pathogenic to humans.\(^8\) Although the EPA has not explicitly defined what a public health claim is, it does define public health antimicrobial pesticide products as “those products that bear a claim to control pest microorganisms that pose a threat to human health, and whose presence cannot readily be observed by the user, including but not limited to, microorganisms infectious to man in any area of the inanimate environment.”\(^8\) The EPA distinguishes between “public health” and “non-public health” antimicrobial pesticide products. A product can bear a non-public health claim when the aim is to control microorganisms of economic or aesthetic significance and when there is no risk of infection or disease in humans.

Antimicrobial agents used for purposes of infection control in healthcare settings are also subject to post-regulatory scrutiny through the EPA Antimicrobial Testing Program (ATP), which requires efficacy testing after a product is brought to market. Products that do not continue to meet ATP post-regulatory standards can be subject to further action, including
removal of disinfectant claims from product labels, cancellation of product registration, and/or removal of the product from the marketplace. Nonetheless, even these post-regulatory standards do not require demonstration of clinical evidence. Adding requirements that manufacturers provide clinical data either before initial registration or as part of the ATP would ensure that antimicrobial agents used in clinical settings not only reduce microbial burden on surfaces, but actually reduce the incidence of HAIs.

The regulatory requirements for antimicrobial agents used in healthcare settings stand in stark contrast to those for antibiotics (i.e., antimicrobial agents used to treat humans). Antibiotic agents are regulated in the United States by the Food and Drug Administration, which requires demonstration of efficacy through clinical trials before approval. The way that antimicrobial products are used in clinical settings (often large-scale, hospital wide implementation) can have a critical influence on hospital resource use. Clinical studies would ensure that a product’s cost merits implementation. The benefits that hospitals would actually encounter if the infection control products they use are clinically effective are profound. However, given the escalating costs of healthcare in the United States, implementation of expensive products that are not clinically effective is highly undesirable, particularly if such implementation results in decreased use of other practices that are known to be effective but may require more individual effort (e.g., good hand hygiene practices). If the EPA has already weighed the advantages and disadvantages of requiring clinical efficacy data for antimicrobial registration, and has deemed such a requirement intractable, then that decision-making process should be made more transparent.
Conceptual flaws in the current antimicrobial pesticide registration requirements were highlighted by the process used for registration of copper alloys as antimicrobial surfaces by the EPA. In 2004, the CDA approached the EPA with the intent of registering 5 copper-based alloys that constituted a new type of antimicrobial product: a surface. Because a standard protocol for assaying the antimicrobial activity of surfaces was not available, the EPA approved the registration of copper alloy surfaces based on data obtained by the manufacturers using an unofficial modification of an existing protocol for sanitizers. Typically, the required test protocol used to evaluate the efficacy of 1-time use antimicrobial products (e.g. sanitizers) measures the percentage of microbes killed in 5 minutes. Although copper alloys do not meet the criteria set by the EPA for sanitizers based on this 5-minute kill assay, the CDA argued that antimicrobial surfaces provide sustained antimicrobial activity, and that their efficacy should be assayed over a longer period of time, recommending that 2 hours be used. However, the 2-hour time period selected by the CDA for this assay appears not to have been based on third-party standards of what constitutes efficient and effective sustained antimicrobial activity.

In response to such concerns, the EPA decided to require data from 3 modified Good Laboratory Practices test protocols before registering a copper surface: efficacy as a sanitizer (bacterial count after 2 hours), residual self-sanitizing activity (bacterial count before and after 6 wet and dry wear cycles during which bacteria are added), and continuous reduction of
bacterial contaminants (bacteria are inoculated onto an alloy surface 8 times in a 24-hour period without intermediate cleaning or wiping). \(^{11-14}\)

We believe that robust clinical studies should also have been required either before registration of antimicrobial surfaces or, at a minimum, during the ATP process (Figure 2.2). The first completed clinical study evaluating copper alloy surfaces’ effect on decreasing HAIs\(^7\) stands in sharp contrast to the more than 400 research articles that have been published on the clinical efficacy of good hand hygiene practices.\(^{15}\) Furthermore, some concerns have been raised about the single copper surface clinical trial that has been published, including criticisms about the reporting of study outcomes and interobserver variability in detecting MRSA in that study.\(^{16,17}\) The study findings have also been criticized for being inconsistent with the known pathophysiology of intensive care unit-acquired HAIs. Salgado et al reported a >50% reduction in risk of HAIs with use of copper alloy surfaces, which is surprising given that the major route of HAI transmission is generally considered to be direct person-to-person contact, and a patient’s endogenous flora is known to be a major source of health care-associated pathogens.\(^{17}\) Clearly, larger and better-designed clinical studies are needed to test the effects of copper alloy surfaces on HAI incidence in health care settings before hospital administrators and the general public can be confident that antimicrobial surfaces are worth the investment.

Despite the absence of compelling clinical studies, the EPA concluded that the copper alloy products were “rigorously tested and have demonstrated antimicrobial activity.”\(^{18,19}\) The EPA also concluded that the use of these products could provide a benefit as “a supplement to existing infection control measures.”\(^{19}\) Reassuringly, the EPA mandated that the CDA develop and implement an antimicrobial copper alloy stewardship plan designed to support the responsible use of antimicrobial copper products in anticipation of concerns that some
companies would make exaggerated claims on copper’s antimicrobial activity. Under the stewardship plan, the CDA has agreed to submit to the EPA materials representative of advertisements intended for use for at least the first 24 months after registration and until the EPA terminates this condition.

Based on this approval, the CDA has been allowed to market copper surfaces to hospitals and other healthcare providers with “public health claims,” including that the copper surfaces “[kill] 99.9% of bacteria within two hours.” Based on the results of the *in vitro* data they provided, the CDA may also specify the type of bacteria that the copper alloy kills: MRSA, VRE, *Staphylococcus aureus*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *E. coli* O157:H7. A complete list of public health claims that the EPA has allowed the CDA to make for copper surfaces that are registered as antimicrobials is provided in Table 2.1.

On October 2, 2014, the EPA released a new protocol that is recommended for evaluation of copper and copper-alloy surfaces and asked for public comments. This protocol includes standards for assessing both the effects of mechanical abrasion and chemical solutions on the surfaces as well as a detailed protocol for assessing the ability of surfaces to kill bacteria after 1 hour of exposure. The protocol also specifies surface performance standards and other controls to be used but has since reverted to its “Performance Test Guidelines for Sanitizers” as it continues to develop a more standardized approach to registering antimicrobial surfaces. According to the EPA web site, the EPA anticipates that they will require this testing for all currently registered copper alloy surfaces in the future. This is an excellent first step. However, it does not address the need for clinical data. In addition, independent scientific studies are needed to determine whether other parameters besides the amount of bacteria killed...
at a single time point (*e.g.*, the area under a kill curve plotted as a function of time) may be more appropriate measures of “sustained activity” for antimicrobial surfaces.

**THE NEED FOR EVIDENCE-BASED APPROACHES TO REDUCE HEALTHCARE-ASSOCIATED INFECTIONS**

One of the reasons that clinical studies are so important when assessing the efficacy of antimicrobial agents in healthcare settings is that there is still considerable uncertainty regarding how to extrapolate a decrease in microbial burden to benefits in human health.\(^{23}\) In the case of hand hygiene, a decrease in microbial burden has been shown to correlate with a decrease in infectious disease outcomes through epidemiologic studies that extend beyond *in vitro* efficacy tests. However, the connection between bacterial burden on surfaces and patient outcomes is not so clear. Surface cleaning, the number of times practitioner hands come in contact with patient, and a variety of confounding factors can influence microbial count, which may affect disease burden. Furthermore, we do not currently have an objective measure of how much the microbial burden on a surface would need to be reduced to prevent transmission of HAIs. Better methods are needed to be able to make a more concrete assessment of what microbial loads on different types of surfaces result in infection in humans for a variety of different organisms.

Better, evidence-based, approaches are needed not only to determine whether a product should be registered as an antimicrobial surface, but also to improve disinfection and cleaning practices in healthcare settings more broadly. Hospital accreditation standards set by The Joint Commission require that environmental surfaces in patient care areas be cleaned and disinfected when visibly contaminated or at least daily, but do not specify protocols or
procedures for determining quantitative bacterial counts or cleanliness.\textsuperscript{24} The Society for Healthcare Epidemiology of America (SHEA) provides recommendations to hospital accreditation institutions such as the Joint Commission via its Compendium of Strategies to Prevent Healthcare-Associated Infections in Acute Care Hospitals, but these are not federally mandated requirements.\textsuperscript{24,25} The standards recommended by The Joint Commission “are designed to assist hospitals, both large and small, in developing and maintaining an effective program that covers a wide range of situations.”\textsuperscript{24}

Some insights into how to move toward more evidence-based approaches to disinfection and cleaning in healthcare settings can be gained by looking at practices used in the food industry.\textsuperscript{18} The food industry has adopted an integrated and risk-based approach to manage cleaning practices in a cost-effective manner. This approach includes a preliminary visual assessment, rapid sensitive tests for organic deposits and specific microbiology-based investigations. Although surfaces in the food industry are not completely analogous to surfaces in hospitals, there are some surfaces that are frequently touched, similar to a hospital environment, and the potential for surface contamination to cause disease is great in both settings.

An important issue is how much bacteria on a surface should be considered unacceptable. Dancer\textsuperscript{18} proposed that there should be a standard set of <1 CFU/cm\textsuperscript{2} indicator organisms (\textit{i.e.}, those associated with infection risk or potential outbreaks such as MRSA, multi-drug resistant Gram-negative bacilli, and \textit{C. difficile}) present in the clinical environment and that mandatory repeat sampling should be conducted if an organism is detected that is sufficient to cause an outbreak. Likewise, several UK studies have advocated for a standard that would recommend a hand contact surface in a hospital to have <2.5 CFU/cm\textsuperscript{2} indicator
organisms with routine environmental culturing to identify epidemic sources.\textsuperscript{19,26} However, this approach is not always practical, particularly in resource-limited settings, because environmental culturing is expensive (~$100 per culture), labor intensive, and has a slow turnaround time. Adenosine Triphosphate bioluminescence assays are currently being developed and validated as surrogate tests, which we believe show promise and are likely to be more practical than routine environment culturing.\textsuperscript{27} These assays can be used to quantify the quality of different cleaning practices in clinical settings.\textsuperscript{28} However, a significant limitation of the adenosine triphosphate assay is that it is not specific for any 1 bacterium or even for disease-causing bacteria in general. Benign and beneficial bacterial are ubiquitous in most environments and can cause a false positive signal with this approach. Clearly, additional methods are needed that allow for rapid, selective and cost-effective analysis of microbes on surfaces.

**THE PATH FORWARD**

Antimicrobial surfaces hold tremendous potential as a new way to reduce bacterial loads in healthcare settings. Since the registration of copper alloys as antimicrobial surfaces, a wide range of copper-based products, including door knobs, counter tops, hand rails, intravenous line poles, and other objects found in healthcare settings, are now being manufactured and marketed as being antimicrobial. These products are currently being marketed with public health claims (Table 2.1) despite a paucity of clinical evidence that using these products in healthcare settings actually reduces HAIs. This is particularly concerning because these items are expensive and use valuable (non-renewable) raw materials compared with clinically proven, more economical, and less resource-intensive measures such as good hand hygiene practices.
The EPA’s proposed protocol that is specific for copper surfaces\textsuperscript{20} is an excellent step in the right direction. However, there still remains a need for independent scientific studies that can guide decisions about how to best measure sustained antimicrobial activity. In addition, we believe that there needs to be a better evidence base that links antimicrobial activity of products in vitro to improved clinical outcomes before products are registered for use in clinical settings. At a minimum, clinical efficacy data should be required as part of ongoing requirements post-registration through the ATP.

We note that the EPA is currently developing a new “Agency Confirmed Efficacy” designation under the ATP.\textsuperscript{29} On a voluntary basis, registrants can submit additional in vitro efficacy data for their antimicrobial products to obtain the “Agency Confirmed Efficacy” designation. This is a critical step in creating greater accountability on the part of antimicrobial registrants by assessing whether additional scrutiny of a certain class of antimicrobials is warranted.

In the meantime, applying evidence-based food industry cleaning standards modified for hospital settings could also aid in the development of better antimicrobial efficacy tests to provide a benchmark of necessary microbial reduction. Ultimately a better understanding of the role of the environment in transmission of HAIs, including dynamics of organism transmission, the role of specific reservoirs, and how to optimally reduce these reservoirs, will lead to more effective use of antimicrobial agents in health care settings that can translate into a much needed reduction in HAIs.
Figure 2. 1. Simplified schematic of the EPA antimicrobial registration process. Schematic simplifying the antimicrobial testing process under FIFRA.
Figure 2. EPA Antimicrobial Registration Process. Schematic depicting the current Antimicrobial Certification Program process (ACP) under FIFRA and possible stages at which clinical data could be required. Currently, registrants are only required to provide in vitro efficacy data. Following review of documentation received from company, EPA rules on whether product merits registration based on fulfillment of efficacy test protocols. Antimicrobials that are used in healthcare settings are subject to post-regulatory scrutiny through the EPA’s Antimicrobial Testing Program (ATP). Requiring clinical studies that demonstrate improved health outcomes either prior to registration or through the ATP would significantly improve confidence in public health claims and would ensure better health outcomes.
Table 2.1. **EPA Approved Public Health Claims.** Public health claims that the EPA has approved for copper alloys that have been registered as antimicrobial surfaces

<table>
<thead>
<tr>
<th>EPA-Approved Public Health Claims</th>
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</thead>
<tbody>
<tr>
<td>Public Health Claims Approved by the US Environmental Protection Agency (EPA) for registered copper alloy antimicrobial surfaces</td>
</tr>
<tr>
<td>This surface continuously reduces bacterial* contamination.</td>
</tr>
<tr>
<td>This surface provides continuous/ongoing/persistent antimicrobial action even with repeated exposures</td>
</tr>
<tr>
<td>This surface continuously kills over 90% bacteria* after repeated exposures during a day</td>
</tr>
<tr>
<td>This surface prevents the buildup of disease-causing bacteria*</td>
</tr>
<tr>
<td>This surface delivers continuous, long-lasting antibacterial* activity</td>
</tr>
<tr>
<td>*Registrant must include list of tested organisms</td>
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REFERENCES:


CHAPTER 3

Cost-Effectiveness of Implementing Copper Alloy Surfaces in an Urban Hospital Setting
(Prepared for submission to *Coatings*)

ABSTRACT

**Background:** Healthcare-associated infections (HAIs) are responsible for significant patient morbidity and mortality. Thus, there has been a considerable effort in assessing the *in vitro* and recently, the clinical efficacy of copper alloy surfaces in hospitals, however, their cost-effectiveness has not been evaluated. Here, we model the cost-effectiveness of implementing copper alloy surfaces in the intensive care unit (ICU) of an urban hospital compared to the current surface type in place.

**Methods:** A cost-effectiveness analysis (CEA) based on results from a randomized clinical trial as well as probabilities for outcomes related to HAIs were obtained from the published literature and expert opinion. A decision-analytical model using TreeAge Pro 2018 was built to model events and costs. Cost effectiveness was evaluated using a three-stage Monte Carlo simulation with 10,000 trials and one-way sensitivity analysis.

**Results:** Using conservative ranges, the results of the Monte Carlo simulation and one-way sensitivity analysis suggest that the implementation of copper alloy surfaces to prevent HAIs was moderately cost-effective compared with standard surfaces, with only an incremental effectiveness (IE) of 0.29 days (~7 hours) measured in quality-adjusted life years (QALYs) and an overall incremental CE (cost-effectiveness) ratio of $10,500 per QALY relative to standard surfaces.
**Conclusions:** In comparison with current surfaces, the introduction of copper alloy surfaces for the prevention of HAIs were only moderately cost-effective with minimal incremental effectiveness compared to standard surfaces based on available data. However, more clinical and cost-effectiveness studies are needed.
INTRODUCTION

Healthcare-associated infections (HAIs) are the main cause of preventable death and disability in hospital patients.¹ An estimated 1.7 million HAIs are reported each year in U.S. Hospitals with approximately 100,000 annual deaths attributable to HAIs.²,³ The annual direct medical cost of HAIs in U.S. hospitals is $35.7-$45 billion.⁴ A focus on evidence-based approaches to target HAIs has opened the door to novel passive approaches such as antimicrobial-coated surfaces for their in vitro efficacy against common nosocomial pathogens.

Since high-touch surfaces in hospitals are associated with the transmission of HAIs,⁵ researchers have been exploring antimicrobial surfaces (such as copper alloys) for use in hospital settings, and some clinical data is now available for cost-effectiveness analysis.⁶ Numerous studies have reported on the in vitro efficacy of copper alloy against pathogens responsible for HAIs.⁷-¹³ These studies have highlighted the need for data on clinical outcomes associated with antimicrobial surfaces, (e.g. infection reduction).¹⁴,¹⁵ As this emerging application of antimicrobial surfaces in hospital settings continues to gain interest and appeal from hospital stakeholders, assessing the cost-effectiveness of this approach is critical given that the availability of resources differs by hospital and that infection control needs differ based on the populations that each hospital serves.

Since HAIs affect a growing number of Americans each year, preventing them through cost-effective measures could be highly beneficial for hospital administrators, insurance companies, doctors, patients and their families, and society at large. A particular type of infection of interest to infection prevention (IP) staff is Clostridium difficile infection (CDI), which disproportionately affects the elderly, who are also at higher risk of CDI complications than younger persons.¹⁶ CDI is associated with significant morbidity and mortality, and affects
gut microbiota that has been disrupted due to antibiotic use. Patients who get CDI are at significantly higher risk of getting re-infected, hence there is an urgency to address this particular type of HAI. Therefore, we decided to focus on CDI for this study with the understanding that its pathway to infection is mediated by high-touch surfaces.

To date, no model has been reported for evaluating the cost-effectiveness of copper alloy surfaces in hospital settings. Furthermore, no model has been reported for any antimicrobial surface in clinical settings that could be adapted to help hospital stakeholders weigh their options. However, there have been cost-effectiveness studies reported that examine non-surface HAI interventions, such as triclosan-coated sutures, Staphylococcus aureus screening and decolonization of lung transplant patients, and multi-faceted infection prevention programs. Therefore, developing a decision analytic model evaluating the cost-effectiveness of surfaces is timely and practical.

A randomized controlled trial to address the clinical efficacy of copper alloy antimicrobial surfaces in hospitals would require hospital funding or researchers to seek out alternative funding sources, but this would enable researchers to gather more clinical data for modeling the cost-effectiveness of these emerging technologies. To date, there has been only one completed randomized controlled trial (by Salgado et al 2013) reported in the peer-reviewed literature that evaluates the clinical efficacy of copper alloy surfaces. This study provides clinical data for our model, which is supplemented with estimated costs and probabilities derived from the literature on HAI endpoints. Decision analytic models also allow us to use hypothetical cohorts of patients in the absence of clinical data through Monte Carlo simulations. This model offers some insights into the economic viability of copper alloy antimicrobial surface implementation in hospital settings.
Because copper alloy antimicrobial surfaces have a higher cost compared to standard surfaces, identifying situations in which copper alloy surfaces could be advantageous is of importance. Copper alloy surfaces in hospitals are an interesting case study to assess cost-effectiveness for because they are emerging in the literature as a potential way to address HAIs yet there is to date no cost-effectiveness studies conducted on them. The goal of this study was to develop a decision analytic model to assess the cost effectiveness of copper alloy surfaces compared to conventional surfaces for the prevention of HAIs in a hospital setting.

MATERIALS AND METHODS

Methods Used in Previous Study

We used data presented in Salgado et al 2013, which is the first clinical trial on copper alloy surfaces at the time of this work (December 2018). In Salgado et al 2013, two patient arms are denoted for three different hospitals: one for the control (non-copper surfaces) and one for the experimental group (copper alloy surfaces). Patients were randomly assigned to a room at admission for a total of 650 admissions to 16 study rooms (8 copper, 8 standard) in the ICU occurring between July 12, 2010 and June 14 2011. Environmental sampling of high-touch surfaces took place across all sites, and more complete data and methods for this study can be found in Salgado et al 2013. The HAI and colonization rate in the copper rooms was 7.14% compared to 12.81% in the non-copper rooms.6

Statistical Tests Used in Previous Study

Using clinical data from Salgado et al 2013, we were able to establish our model parameters and data points. A Shapiro-Wilks was employed by Salgado et al 2013 to assess
normality, and differences between the new option and the standard option were analyzed using t-tests. Categorical differences between the two groups were analyzed using the chi-square significance test. Logistic regression models were also applied in Salgado et al 2013 to determine whether individual factors such as age or sex could be confounding factors to control for. Results used in our model are presented as predicted probabilities based on clinical data from Salgado et al 2013 as well as the literature.

Methods Used in this Study: Decision Model

In Chapter 2, we focused on the in vitro efficacy of copper alloy surfaces and highlighted the need to obtain more clinical data to answer the question of clinical efficacy. In this chapter, we delve into how this clinical information can help to simulate the cost-effectiveness of using an emerging technology such as copper alloy versus a standard option.

Using TreeAge Pro 2018, we developed a simple decision analytic model (Figure 3.1) to model the average pathway costs and savings for a patient who is admitted into a room with copper alloy surfaces compared to conventional surfaces. Figure 3.2 features the decision tree with the rollback feature, which indicates the values and some of the equations used in the study. Table 3.1 lists the values and key assumptions made for our model.

Using some of the clinical data (i.e., incidence of HAIs in copper alloy rooms versus standard rooms) coupled with retrofitting costs, direct costs of HAIs, and quality-adjusted life years (QALYs) associated with CDI, we obtain an incremental cost-effectiveness ratio (ICER), which is our primary outcome of effectiveness in our model. A Monte Carlo simulation was also conducted for a hypothetical cohort for a total of 10,000 unique trials. In each simulation, one-way sensitivity analysis varied each parameter throughout the ranges listed in Table 3.1 independently.
Cost of HAIs and New Option

The decision to employ copper alloy surfaces in a hospital setting is initially costly: stakeholders must outfit a room’s high-touch surfaces (i.e., bed rails, IV poles, etc.) for an estimated cost of $4,000 per room. This is an added cost absorbed by hospitals but with possible net monetary benefits for society. As it may be impractical for a hospital to retrofit every room with antimicrobial copper alloy surfaces, exploring what situations this would be advantageous for is useful. Our model identifies the possible net monetary benefits of implementing copper alloy antimicrobial surfaces in hospitals.

The cost of retrofitting with copper alloy surfaces per room was obtained from colleagues currently conducting a randomized controlled trial on copper alloy surfaces at the University of California, Los Angeles. Since decision trees are usually conducted at the individual level, values had to be converted from the aggregate to the individual level. Therefore, the cost of the new option per person can be determined by the cost of retrofitting an ICU room with copper alloy divided by the annual average number of ICU patients to use a hospital room multiplied by the average lifetime of copper alloy surfaces. Dividing 365 days by the ICU average length of stay (LOS) as reported in the literature, gives us our ICU patients per bed for the equation:

For baseline values:

\[
\text{cost of copper per bed/(ICU patients per bed * bed life)}
\]

\[
= \frac{7,000}{(365/3.43)\times 1.25}
\]

\[
= \$52.68
\]

To be conservative in our estimates, we ran the model across the ranges listed in Table 3.1, making $13.33 the low estimate. We acknowledge that these costs may not be representative of
real costs and that the annual occupancy of an ICU hospital room could be more or less than our assumption. We also used a conservative estimate of the lifetime of copper alloy surfaces, since environmental degradation of surfaces could occur. Therefore, the lifetime of copper alloy surfaces was simulated across a range of 0.5-2 years\textsuperscript{21}. For LOS, we applied a range of 2-5 days based on the literature indicating an average of 3.43 days LOS in the ICU\textsuperscript{23} as depicted in Table 3.1.

The annual cost of HAIs was obtained from a Centers for Disease Control and Prevention (CDC) report on the direct costs of HAIs.\textsuperscript{4} The cost-effectiveness analysis was conducted from a societal perspective, hence the values associated with CDI reflect total lifetime related infection costs. Since these values had to be adjusted to 2018 costs, the average cost of an HAI after applying the 2018 Consumer Price Index (CPI) index is:

\[
= \frac{\text{October 2018 CPI-U}}{\text{February 2007 CPI-U}} \times (\text{low estimate of CDI per patient costs}) \\
= (869.303/487.881) \times \text{low estimate adjusted to 2007 } \text{S using CPI-U} \\
= (1.78) \times \text{low estimate adjusted to 2007 } \text{S using CPI-U} \\
\sim \$10,000
\]

Similarly, for the high estimate, adjusting for 2018 costs:

\[
= \frac{\text{October 2018 CPI-U}}{\text{February 2007 CPI-U}} \times (\text{high estimate of CDI per patient costs}) \\
= (869.303/487.881) \times \text{low estimate adjusted to 2007 } \text{S using CPI-U} \\
= (1.78) \times \text{high estimate adjusted to 2007 } \text{S using CPI-U} \\
\sim \$15,000
\]

For our model, we used a more conservative high estimate of $20,000.

Because we wished to evaluate the cost-effectiveness of an added intervention compared to an existing standard option (as opposed to assessing the question of whether to employ copper
alloy surfaces or conventional surfaces), the cost of the standard option was set as $0. The standard option was selected as conventional surfaces (as opposed to, for instance, handwashing) because the research question we are addressing is whether is it cost-effective to implement copper surfaces where conventional surfaces exist. Researchers wishing to assess whether it is cost-effective to implement copper alloy or conventional surfaces for a new hospital under construction could investigate the average total upfront cost of stainless steel/plastic surfaces for a hospital room and compare it to the total upfront cost of adding copper alloy surfaces. The scope of this study was to assess the cost-effectiveness of copper alloy surfaces where conventional surfaces exist.

Cost-Effectiveness Analysis

To assess cost-effectiveness of the two copper alloy surfaces, we developed a three stage Monte Carlo microsimulation using 10,000 trials and calculated the 95% confidence ellipsoid for the scatterplot of incremental cost-effective ratios (ICERs) resulting from this microsimulation. All cost-effectiveness analyses were conducted using TreeAge Pro 2018 Decision Analysis software (Williamstown, MA). In our model, the unit of effectiveness is determined by QALYs, which is defined as being equal to one year of perfect health. Based on findings from the literature that approximately 0.91 QALYs are gained if a person in the 70-79 year range does not get a CDI, we used a range of 0.9-1 for the variable of QALYs for CDI. For QALYs associated with getting a CDI, we used a range of 0.6-0.8 QALYs based on the literature indicating that a CDI is associated with 0.7 QALYs. Since there are multiple potential routes of transmission for HAIs, (e.g., Central Line Associated Bloodstream Infection (CLABSI), Catheter Associated Urinary Tract Infection (CAUTI), or Ventilator Associated
Pneumonia (VAP), and CDI), we decided to focus on CDI because it disproportionately affects vulnerable populations and because of its transmission pathway being affected by high-touch surfaces. QALYs associated with prevention of an HAI through each of these routes varies according to previous studies conducted.

This decision model was used to determine the cost-effectiveness of copper alloy surfaces by using the incremental cost-effectiveness ratio, determined as:

\[
\text{ICER} = \frac{\text{Cost}_{\text{Copper Alloy Surfaces}} - \text{Cost}_{\text{Standard Option}}}{\text{Effectiveness}_{\text{Copper Alloy Surfaces}} - \text{Effectiveness}_{\text{Standard Option}}}
\]

The ICER is the ratio of overall difference in cost between a patient being put in a copper alloy retrofitted room versus being put in a standard room divided by the incremental difference in effectiveness (as determined by QALYs). Therefore, the ICER can be interpreted as the cost per additional QALY gained when a patient is put in a copper alloy room. In addition to a Monte Carlo microsimulation, we also conducted one-way sensitivity analysis to address uncertainty.

RESULTS

The results of the Monte Carlo simulation analysis indicated that relative to the standard option, the new option only produced minimal effectiveness, with an incremental effectiveness of only 0.00080 QALYs or 0.08% QALYs, which translates to about 0.29 days (~7 hours) of increased effectiveness compared to the standard option (Table 3.2). Therefore, relative to the standard option, the new option produced better lifetime QALYs per person (0.00080), however, at a higher lifetime cost ($8.40) (Table 3.2), indicating that this intervention had an ICER of ~$10,500 per QALY. These findings are consistent with the one-way sensitivity
analysis (Figure 3.4) conducted using the ranges used in Table 3.1. Our HAI incidence rates (which were not specific to CDI) were based on results from the clinical trial by Salgado et al 2013 where copper alloy was 5.67% more effective than the standard option at preventing HAI or colonization. High and low ranges for copper alloy were conservatively chosen to mimic extremely low effectiveness to high effectiveness, and the high range value doubles that of the results from Salgado et al 2013 (Table 3.2). Therefore, our range estimates aimed to simulate a scenario where we erred on the side of caution with regards to the effectiveness of the new option compared to the standard option to account for a wide range of effectiveness given the lack of robust clinical evidence on the effectiveness of copper alloy surfaces (Table 3.2).

For our probabilistic sensitivity analysis based on the Monte Carlo microsimulation, the new option is more cost-effective 50% of the time when the willingness to pay is greater than $20,000 (Figure 3.3). This is well below the standard willingness to pay of $50,000, however, this depends on how much a stakeholder is willing to pay for the additional unit of effectiveness. The percentage of iterations that are considered cost-effective are greater than those for the standard option only when the WTP is greater than $20,000, therefore, a WTP less than $20,000 would not render the new option cost-effective compared to the standard option. Any WTP less than $20,000 would not render an additional unit of effectiveness compared to the standard option, meaning that copper alloy surfaces employed with a WTP greater than $20,000 could be considered moderately cost-effective. Given the incremental effectiveness of copper alloy surfaces is so low (0.0008 QALY), it is uncertain if the cost per person, even though it is low, is justified for this intervention. It would be up to individual stakeholders to decide whether the cost is negligible enough to justify the implementation of copper alloy surfaces despite its moderate cost-effectiveness.
To assess the uncertainty and strength of our model and to account for error in our estimates, we conducted one-way sensitivity analyses. We assumed that the standard option cost is $0 because these surfaces are in place in most urban hospitals. Therefore, the only cost in the analysis is for the annual cost of treatment of a CDI and for the cost of retrofitting a room to copper alloy surfaces. One-way sensitivity analyses were conducted for each of the key assumption variables shown with the ranges indicated in Table 3.1. Figure 3.4 indicates that as the effectiveness of the new option increases, the ICER decreases for the most part, which is expected. For the standard option, as the effectiveness of copper increases (plateaus initially), the ICER decreases and becomes negative, indicating that the standard option is now leading to savings, however, negative ICERs are difficult to interpret.25,26

The net monetary benefits (NMB) graph (Figure 3.5) shows a combination of cost-effectiveness and willingness to pay being analyzed as a variable where the probability of the new option preventing an HAI changes. The highest net benefits value, defined as the highest monetary savings, determines the most cost-effective strategy under the assumption that a WTP is set at $50,000. The NMB is higher for the new option than the standard option when new option effectiveness is greater than 0.05 (Figure 3.5). If we are certain that the probability of the new option preventing an HAI is greater than 0.05, copper alloy surfaces could be a slightly more cost-effective option. If the probability of the new option preventing an HAI is less than 0.89, the recommended option would be the standard option. Because this is based on data from one clinical trial, it would be a hasty generalization to deem retrofitting a room to copper the recommended option over keeping standard surfaces.

A tornado diagram is a graphical way to display univariate (or one-way) sensitivity analyses that has been commonly used in cost-effectiveness analysis. Tornado diagrams
indicate which parameters were more sensitive to variation by the length of the bar, the longest bars indicating more sensitivity to variation and the biggest impact on the ICER. **Figure 3.6** is a tornado diagram of the standard option versus the new option based on the ICER, and indicates that copper effectiveness and cost of copper per patient are the most sensitive parameters to variation and have the biggest impact on the ICER, whereas, QALYs associated with HAI was the least sensitive to variation and had the least impact on the ICER. As copper effectiveness increases, copper effectiveness has a positive impact (depicted as blue) on the ICER, which decreases. As cost of copper per patient increases, copper effectiveness has a negative impact (depicted as red) on the ICER, which increases. Cost of HAIs as well as the probability of an HAI at baseline also did not have much of an impact on ICER. The Expected Value (EV) for the ICER resulting from the cost-effectiveness analysis is $10,500, less than a standard $50,000 willingness to pay, so this is a relatively small ICER.

The analysis of the scatterplot of the 10,000 ICERs resulting from the Monte Carlo simulation revealed that in 35% of trials, costs were lower in the new option with an additional improvement in QALYs (*i.e.*, IC < 0 and IE > 0) (**Figure 3.7**). For 29% of trials, costs were greater in the new option but with an additional improvement in QALYs (*i.e.*, IC > 0 and IE > 0) with an ICER < $50,000 (**Figure 3.7**). Similarly, in 36% of trials, costs were greater in the new option but also with an additional improvement in QALYS (*i.e.*, IC > 0 and IE > 0) but with an ICER > $50,000 (Figure 4.7). We set our willingness to pay (WTP) at $50,000 as that is the standard value used by most medical cost-effectiveness studies and it is commonly accepted that an ICER < $50,000 is cost-effective and that an ICER > $100,000 is not. The ICER is a measure of how much each additional unit of effectiveness costs and is determined by the increasing cost divided by the increase in effectiveness. By comparing the ICER to the WTP
(where WTP is the limit on what one is willing to pay for an additional unit of effectiveness), a decision can be made on whether one should choose the new option. The C/E is the cost per unit of effectiveness.

In Table 3.2, based on a WTP of $50,000, the results indicate that an ICER of $10,500 is less than the WTP, which implies that the new option is moderately cost-effective with a minimal incremental effectiveness of 0.08% QALYs. Figure 3.7 demonstrates that with reasonable assumptions, the new option is not a significant cost saver compared to the standard option given that more than 36% of the points on the scatterplot lie above the WTP threshold of $50,000. Figure 3.7 depicts a WTP set as $50,000 (ceiling ICER) as demonstrated by the dotted line, hence any points that lie on that mean will have an ICER of $50,000. The region below the line indicates the points that are cost-effective with the ellipsis denoting a 95% confidence interval. 36% of the Monte Carlo iterations that were run through the model lie below the WTP, therefore indicating that only 64% of these iterations were considered cost-effective with a WTP of $50,000.

DISCUSSION

Knowing which infection prevention strategies are worth implementing in hospitals is challenging to hospital administrators. Cost-effectiveness can provide information that can be used in the decision-making process. In this study, we were interested in understanding the costs and cost-effectiveness of a novel infection prevention technology since currently there are no cost-effectiveness studies on copper alloy.

Our findings demonstrate that copper alloy surfaces in ICU rooms are only moderately cost-effective with only an incremental effectiveness of 0.08%. More studies on the clinical effectiveness of copper alloy should be conducted to be able to have more compelling evidence
to support and recommend the new option. The probabilistic sensitivity analysis revealed that the new option is moderately cost-effective compared to the standard option since the resulting ICER was $10,500, which is less than the WTP set at the standard $50,000. When conducting a Monte Carlo simulation with 10,000 trials, results indicate that the percentage of iterations that are considered cost-effective by the model changes after an intersection point of required effectiveness (Figure 3.5) and scatterplot results indicate 36% of trials are above a WTP of $50,000. Furthermore, more studies are needed to provide more reliable estimates. Therefore, it is not entirely clear from this data if the recommended option should be the new option over the standard option.

The strengths of our analytic decision model include the unique opportunity to evaluate the cost-effectiveness of a novel approach to HAI prevention, that being passive antimicrobial surfaces that are gaining momentum in industry. Additionally, our model explores the value of retrofitting existing hospital rooms to copper alloy surfaces in comparison to a standard option. Since the majority of hospitals have this standard option in place, they can explore the added value of adding copper alloy surfaces.

Although the study is useful in opening the door for researchers to model the cost-effectiveness of a novel approach, antimicrobial surfaces, it does come with notable limitations. Firstly, since our model is based on incidence means and results from the only randomized controlled trial on clinical efficacy of copper alloy surfaces from Salgado et al 2013, the study’s environmental settings also have to be extrapolated to the model. Salgado et al 2013 conducted the study in an ICU setting, which is a critical setting in a hospital compared to standard inpatient rooms, surgical operating rooms, pre-operation rooms and others. Secondly, there is a need for more clinical studies evaluating the clinical effectiveness of copper alloy surfaces in hospitals to
be able to get more precise values for the model, representative of more hospital environments, as we cannot simply rely on findings from one study for cost-effectiveness analysis. Thirdly, Salgado et al. did not consider the degradation of copper alloy surfaces over time in their study. It is likely that some degradation of surfaces occurred as that is what is being witnessed in the current UCLA clinical study on copper alloy surfaces.\(^{21}\)

It would be worthwhile to simulate the cost-effectiveness of copper alloy surfaces in other hospital room settings where the incidence of HAIs may differ, for instance, in the operating room or in pediatric wards. Additionally, our model was simplified to include the CDI route of transmission of HAIs, but there are multiple routes to consider including CLABSI, CAUTI and VAP. Lastly, the results from Salgado et al 2013\(^6\) could be stratified by pathogen type, i.e. MRSA, MSSA (Methicillin-Sensitive *Staphylococcus aureus*), *C. diff* (*Clostridium difficile*), *E. coli* (*Escherichia coli*), VRE (Vancomycin-resistant *Enterococcus*), and others since they each have different risks and incidences. Therefore, a more complex model could be created to assess the cost-effectiveness of copper surfaces compared to interventions other than standard surfaces, such as handwashing educational programs, hand sanitizer usage, and other public health interventions including the elimination of certain contact precautions.

**CONCLUSION**

Copper alloy surfaces in a hospital setting have demonstrated *in vitro* antimicrobial properties as well as a reduction in HAIs, however, they are expensive to implement. Therefore, it is important for hospital administrators to evaluate if copper alloy surfaces are an effective technology to implement in their respective hospital settings.

Our model indicates that copper antimicrobial surfaces for use in an urban hospital setting may only be moderately cost-effective compared to standard surfaces based on one-way
sensitivity and probabilistic sensitivity analysis conducted on our model. However, more clinical studies are needed to obtain stronger data for model inputs. More cost-effectiveness studies could therefore be conducted based on the availability of more clinical data. Results of the Monte Carlo microsimulation showed that 36% of trials run were above the standard WTP of $50,000, therefore rendering the new option only moderately cost-effective. Furthermore, the incremental effectiveness of the new option was only 0.08% based on reasonable estimates. Our model is a good starting point for assessing the cost-effectiveness of novel HAI interventions such as antimicrobial surfaces in hospitals, and we hope that it will inform discussions on the viability of antimicrobial copper surfaces in hospitals with the aim of reducing the rate of HAIs, and therefore improving outcomes for patients.
Figure 3.1. Decision tree model structure. Simplified decision tree model structure for evaluating the cost-effectiveness of copper alloy surface implementation in hospitals using results from Salgado et al. 2013, the first completed randomized control trial examining copper alloy surface clinical efficacy.
Figure 3.2. Decision tree model structure (rollback feature). Simplified decision tree model structure for evaluating the cost-effectiveness of copper alloy surface implementation in hospitals using results from Salgado et al. 2013⁶, the first completed randomized control trial examining copper alloy surface clinical efficacy. Here, the rollback features indicate the model inputs and values from Table 3.1 that are part of the decision tree model calculations.
Table 3. 1. Key Assumptions of Cost-Effectiveness Analysis. Table of inputs and values used for the decision tree model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Low</th>
<th>High</th>
<th>Distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of Standard Option(^a)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td>Authors’ Assumption</td>
</tr>
<tr>
<td>Cost of Copper Alloy High-touch Surfaces per room</td>
<td>$7,000</td>
<td>$4,000</td>
<td>$10,000</td>
<td>Uniform</td>
<td>Expert Input</td>
</tr>
<tr>
<td>Cost of Copper Alloy High-touch Surfaces per Patient(^b)</td>
<td>$52.68</td>
<td>$13.33</td>
<td>$400</td>
<td>Uniform</td>
<td>Expert Input</td>
</tr>
<tr>
<td>Effectiveness of Copper</td>
<td>0.08</td>
<td>0.01</td>
<td>0.15</td>
<td>Uniform</td>
<td>Salgado et al 2013(^6)</td>
</tr>
<tr>
<td>Probability of HAI at Baseline (standard surfaces)</td>
<td>0.04</td>
<td>0.03</td>
<td>0.05</td>
<td>Beta</td>
<td>Salgado et al 2013(^6)</td>
</tr>
<tr>
<td>Probability of HAI w/ Copper</td>
<td>0.0368</td>
<td>0.01</td>
<td>0.08</td>
<td>N/A</td>
<td>Salgado et al 2013(^6)</td>
</tr>
<tr>
<td>QALYs(^*) for CDI Infection</td>
<td>0.7</td>
<td>0.6</td>
<td>0.8</td>
<td>Beta</td>
<td>Lapointe-Shaw et al 2016(^17)</td>
</tr>
<tr>
<td>QALYs(^*) for no HAI</td>
<td>0.95</td>
<td>0.9</td>
<td>1</td>
<td>Beta</td>
<td>Gold et al 1998(^24)</td>
</tr>
<tr>
<td>Annual Number of Patients per Bed(^c)</td>
<td>106.3</td>
<td>50</td>
<td>150</td>
<td>N/A</td>
<td>Assumption; Hunter et al. 2014(^23)</td>
</tr>
<tr>
<td>Useful Life of ICU Beds in Years(^d)</td>
<td>1.25</td>
<td>0.5</td>
<td>2</td>
<td>Uniform</td>
<td>Expert Opinion(^1), Rubenfire 2015(^4), CDC 2003(^28), CDC 2002(^29)</td>
</tr>
<tr>
<td>Annual Cost of an HAI (CDI specific)</td>
<td>$15,000</td>
<td>$10,000</td>
<td>$20,000</td>
<td>Gamma</td>
<td>Scott 2009(^4)</td>
</tr>
<tr>
<td>Length of Stay (LOS)</td>
<td>3.43 days</td>
<td>2 days</td>
<td>5 days</td>
<td>Triangular</td>
<td>Hunter et al. 2014(^23)</td>
</tr>
</tbody>
</table>

All costs listed are per person.

\(^a\) Total cost of standard option was determined to be $0 since standard surfaces are already in place, no additional funds were used for this option, and no standard or estimate is available in the literature or from the first study’s authors.
b. Total cost of new option is $4,000 per room (costs of retrofitting high-touch surfaces in an ICU room). Therefore, the cost per person is: cost of new option/(number of patients * lifetime of copper). We used a slightly more conservative estimate.

c. Number of patients per bed determined by: 365 days/LOS

d. There is a lack of data on this in the literature as hospital guidelines only dictate to replace beds when needed based on contact with certain fungi and other pathogens, but we provide estimates from business reports, CDC’s Hospital Guidelines on Bed Replacement as well as expert input\textsuperscript{21,22,28,29}. Since hospital guidelines do not specify a time frame for replacing hospital beds, we used expert opinion, which suggested a range of 1-2 years. We used a more conservative lower range.

*QALYs: Quality-Adjusted Life Years
Figure 3.3. Cost-Effectiveness Acceptability Curve. The new option (copper alloy) is more cost-effective 50% of the time when the willingness to pay is greater than $20,000. The blue squares correspond to the new option (copper alloy) and the red triangles correspond to the standard option.
Table 3. 2. Summary of Cost-Effectiveness Analysis. Summary of cost-effectiveness rankings based on our model. QALYs = Quality-Adjusted Life Years; CE = Cost Effectiveness

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Effectiveness in QALYs</th>
<th>Incremental Effectiveness (IE) in QALYs</th>
<th>Average HAI-related Costs</th>
<th>Incremental Cost (IC)</th>
<th>Average CE Ratio</th>
<th>Incremental CE Ratio (ICER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Option</td>
<td>0.94000</td>
<td>-</td>
<td>$553.48</td>
<td>$0</td>
<td>$589</td>
<td>-</td>
</tr>
<tr>
<td>New Option: Copper Alloy</td>
<td>0.94080</td>
<td>0.00080</td>
<td>$561.88</td>
<td>$8.40</td>
<td>$597</td>
<td>$10,497</td>
</tr>
</tbody>
</table>
Figure 3.4. One-Way Cost Effectiveness (CE) Sensitivity Analysis. Graph depicting how as the effectiveness of the new option (Copper) increases, the ICER (the cost associated with gaining one unit in effectiveness, in this case, a QALY) decreases for both the standard and the new options. The blue circles correspond to the new option (copper alloy) and the red triangles correspond to the standard option.
Figure 3.5. Sensitivity Analysis - Net Monetary Benefits Graph. Graph indicating monetary benefits associated with each option. Note an intersection of strategies at 0.05 copper effectiveness, where the new option starts to gain more net monetary benefits than the standard option. The blue squares correspond to the new option (copper alloy) and the red triangles correspond to the standard option.
Figure 3.6. Tornado diagram of the standard option vs. the new option (copper alloy). Tornado analysis based on ICER depicting the variables of copper effectiveness and cost of copper per patient as being the variables that have the biggest impact on the ICER. As copper effectiveness increases, this has a positive impact on the ICER, which decreases, and as cost of copper per patient increases, this has a negative impact on the ICER, which increases. Cost of HAIs as well as the probability of an HAI at baseline and the QALYs associated with HAIs did not have much of an impact on ICER. The Expected Value (EV) for the ICER resulting from the cost-effectiveness analysis is $10,500, less than a standard $50,000 willingness to pay, so this is a relatively small ICER.
Figure 3. 7. Incremental Cost-Effectiveness Scatterplot of New Option vs. Standard Option. The x-axis represents the incremental effectiveness and the y-axis represents that incremental costs, and each blue point on the graph represents a pair of values that show the incremental effectiveness and incremental cost for that particular simulation (out of 10,000), therefore a point at 0,0 means that there was no change in cost or effectiveness with a change in strategy. Using 10,000 Monte Carlo microsimulation trials, 35% of cases had incremental cost (IC) <0 and incremental effectiveness (IE) > 0; 29% had IC > 0 and IE > 0, and Incremental Cost-Effectiveness Ratio (ICER) < 50,000; 36% had IC > 0 and IE > 0, and ICER > 50,000.
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28. CDC (Centers for Disease Control and Prevention). Guidelines for environmental infection control in health-care facilities. MMWR. 2003;52(RR10); 1-42. Accessed: November 4, 2018. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5210a1.htm CfDCaPCMGfEICiH-CFRoCaHICPAC.

CHAPTER 4

Children’s and Parents’ Views on Hospital Contact isolation: A Qualitative Study to Highlight Children’s Perspectives

(Accepted for publication in Clinical Child Psychology and Psychiatry)

ABSTRACT

Background: To date, there has been a paucity of studies conducted on the experiences of children under hospital contact isolation precautions. Furthermore, the studies that have examined children’s experiences at the hospital typically reflect the perspectives of their parents, and few have directly involved interviews with children themselves, and even fewer with children in isolation.

Methods: To address this gap, we conducted semi-structured, open-ended interviews with hospitalized children to assess their experiences of being placed in isolation. Where possible, the children’s parents also completed written surveys to assess parental perspectives on their child’s experiences.

Results: Two important findings of the study were the children’s resilience during a difficult time and children's varying awareness of the pathophysiology of infections as it relates to isolation precautions. Examination of the parent-child dyads elucidated some discordance between parents’ and children’s perspectives on how children experienced their isolation, on what the children’s preferred activities were while in isolation, and how much children understood about the reasons they were in isolation.
**Conclusion:** This study supports earlier studies that suggest that the benefits of isolation procedures may be outweighed by how negatively isolation is experienced by patients, particularly when the patients are children. It also highlights the need for child-friendly isolation signs. Because parental and child perceptions differed in cases where data from both were available, this study suggests larger studies on children’s perspectives and/or on parent-child dyads are needed.
INTRODUCTION

Hospitalization has been shown to be distressing for children;\textsuperscript{1,2} this distress is exacerbated when a child is put under isolation contact precautions. Each year, more than 3 million children are hospitalized in the United States\textsuperscript{3} and many of these children are put under contact isolation precautions if they have an active infection, are colonized, or are immunocompromised. This isolation often prevents children from going to the playroom or interacting with other children. It is unclear, however, how children perceive the overall state of being under hospital isolation precautions. Hospital isolation signs are designed for adults and although they use pictures to detail requirements for entry (\textit{e.g.}, appropriate personal protective equipment, PPE), children may not fully understand their implications. Furthermore, the experience of being in isolation at the hospital needs to be explored from the perspectives of the children themselves.

To date, studies exploring children’s experiences at the hospital have primarily been conducted through parents’ perspectives and not through asking children directly. Parents of hospitalized children perceive that their children experience high levels of stress and anxiety\textsuperscript{4,5} but there still remains a literature gap with regards to children’s perspectives. One older study from 1978 examined the emotional reactions of 123 hospitalized children and their mothers during standard isolation (which limited visitation through glass partitions), but this study was conducted using written surveys of parents and behavioral observations by nurses only.\textsuperscript{6} A study from 1972 on twins revealed that isolation was correlated with learning disorders and impairment of intellectual capacity. However, newer studies need to be conducted as naming and social conventions have changed over the last thirty years.\textsuperscript{7} A more recent study involved interviews with 29 families who had children with chronic illness and were receiving hospital treatment\textsuperscript{8} and another study evaluated the psychological impact of isolation precautions on older
Health practitioners’ emotional reactions to providing care for hospitalized children have been examined as well as older adult patient family members’ psychological well-being. Intervention have focused on supporting parents and how they cope with having a hospitalized child, once again, with an emphasis on alleviating parents’ psychological distress as opposed to children’s distress. Figure 4.1 includes a timeline highlighting the gap in the literature on qualitative data on pediatric isolation through the children’s lens.

A systematic review of studies evaluating adverse effects of isolation in hospitalized patients found that the majority of these studies surveyed adults and there were only two studies that included children. One of the studies involving children assessed interactions between a medical team with their pediatric patients during morning rounds, and data were collected on the quantity and quality of care. The other study involving children makes recommendations to guide the implementation of strategies and practices to prevent the transmission of methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and other multi-drug resistant organisms (MDROs). Neither of these studies employed semi-structured interviews or any other qualitative methodology to explore the experiences of children who were under hospital isolation. There exists a key opportunity to gain insight into the pediatric isolation hospital experience through the lens of children. Only one study (in Turkey) has attempted to examine children’s perceptions of the hospital experience, but it did so through collecting data using a pediatric information form and questionnaire. Although these researchers obtained information directly from children, the study was more quantitative than qualitative and hence did not provide a nuanced assessment of the experiences of isolation from the children’s perspective.
A more complex understanding of how children experience isolation could provide a valuable evidence base for mitigating the negative impacts of isolation. Child Life Specialists (CLSs) are charged with the unique duty of helping children and their families cope with the hardships of hospitalization. They work closely with children, and are charged with using “evidence-based, developmentally appropriate interventions including therapeutic play, preparation and education that reduce fear, anxiety, and pain.” They are uniquely poised to administer semi-structured, open-ended interviews with hospitalized children, and provide unique insights into children’s perspectives on isolation. Such information could help to guide the CLSs in the development of evidence-based interventions tailored to children under isolation precautions.

To address the literature gap, we conducted semi-structured, open-ended interviews with children (N = 8) who had been or were at the time of the study under hospital contact precautions. A CLS who was familiar to the patients conducted the interviews and asked children questions directly to assess their experiences of being placed in isolation while hospitalized. Where possible, children’s parents (N = 3) also completed a written survey to assess parental perspectives on their child’s experiences so that concordance between parental and child perspectives could be assessed.

METHODS

Interviews

Semi-structured interviews were conducted to explore children’s perspectives of being under isolation precautions, and written surveys were collected from parents to assess parent-child concordance across various themes. Please see Appendix B for the open-ended interview
questions used for children and Appendix C for the survey questions used for parents.

Appendix D provides the Child Life Training Guide developed for this study that outlines the basic patient recruitment and enrollment processes used by the CLS who conducted the interviews. Interview and survey questions were based on three a priori themes: (1) Creating a comforting environment, (2) identifying patient concerns, and (3) identifying possible ways to improve the experiences of pediatric patients. The University of California, Los Angeles Institutional Review Board approved this study (IRB# 16-001999).

All interviews were conducted between August 2017 and January 2018. The interviews with children lasted 15-30 minutes. It is uncertain how long it took for the parents to fill out the survey, but the intended target range was ~30 minutes. The research took place in Los Angeles, California, and participant recruitment was facilitated by a CLS at UCLA Mattel Children’s Hospital. All recruited patients were admitted to this hospital at the time of the interviews and some were under isolation during the interview time, with one patient having been under isolation precautions various times in the past. All children were being treated for various conditions ranging from active infections to complications related to a liver transplant. UCLA Mattel Children’s hospital is located in a relatively affluent area but the pediatric population that is served by this facility range from low to high socio-economic status, and many of the patients are from Spanish-only speaking households. The CLS helping with the study was trained to recruit children who fit the study criteria (ages 7-15, who had been in the past or were currently under contact, droplet, spore and/or neutropenic precautions) and to obtain proper parental consent and child assent.

Parental consent and child assent were obtained per the university’s Institutional Review Board (IRB). One CLS with a special interest in researching children’s perspectives on isolation
precautions conducted the interviews and recorded them in addition to taking notes. The parent survey was created as a way for the researchers to identify common themes as well as discordance between children and their parents relating to the experience of being under isolation precautions. The CLS who conducted the interviews had previously expressed interest in conducting this type of study and reached out to UCLA Infection Prevention staff for possible collaboration opportunities. Other CLSs working with children at UCLA Mattel Children’s Hospital were briefed on the study details to make them aware of the study.

*Child Life Specialist Training Guide*

We developed a Child Life Specialist Training Guide (*Appendix D*) to facilitate the interviews with children as well as to provide an interview protocol for the CLS. The training guide included guidance for how to keep questions open-ended so as to encourage children who were reticent to vocalize their feelings. The training guide also included instruction on how to recruit patients who fit the study criteria as well as subsequent ways to recruit parent-child dyads. The training guide was presented to CLS staff and revisions were made based on feedback from this meeting.

Interviews with children were conducted face-to-face by an experienced CLS. Parents were given hard copies of the parent survey and were asked to fill out the survey and to hand it back or mail it back to the Child Life office. Parental consent and child assent were obtained per the university’s Institutional Review Board (IRB). One CLS with a special interest in researching children’s perspectives on isolation precautions conducted the interviews and recorded them in addition to taking notes.
Parents and children provided consent and assent, respectively. The interviewer took notes and summarized important details on a hard copy of the child interview questions during the recorded interview. The interviewer also checked with the interviewee to ensure she had correctly understood their responses and provided notes to the researcher on body language that could not be captured via the recording.

The parent survey was created as a way for the researchers to identify common themes as well as discordance between children and their parents relating to the experience of being under isolation precautions. Parents were offered a self-addressed stamped envelope (SASE) to return their own written surveys, but each of the parents that were part of the parent-child dyads submitted their surveys directly to the CLS. Responses were received from 3 parents, and 8 children completed the interviews. Table 4.1 provides the parent/child de-identifiers used for the study along with other subject information.

Data analysis

All the interviews were audio-recorded and transcribed verbatim electronically using Dedoose data analysis software (version 8.1). Transcripts of each data set (8 children, 3 parents) were read to identify common themes between all children interviews as well as commonalities and inconsistencies between children and parent answers. The researchers then met to discuss their overall impressions of the child interviews and parent surveys as well as the analysis approach. Each data set was analyzed separately before comparisons were made across all children interviews and across children-parent dyads. Figure 4.2 illustrates an example of a coded passage from a child interview. Four key themes emerged from the analysis that were common across both data sets (children and parents): (1) child and parent awareness of the
pathophysiology of infections and parent/child synchrony on awareness of isolation state, (2) parent and children’s struggles with isolation precautions, (3) difficulty in self-reflecting during a trying time, and (4) identifying areas for potential improvement in patient experience (Figure 4.3)

RESULTS

Interviews were conducted with eight children ages 7-15 years, five of which were accompanied by their mother (C002, C003, C005, C006, C008) and three of which did not have a parent present during the interview (C001, C004, C009) either because the parents preferred to step out of the room or because the parents were not present at the time of the interview, some due to their work schedule (Table 4.1). Two of the children’s parents filled out an accompanying parent survey, thus creating two parent-child dyads. One additional parent was part of the study (P007) whose child was too ill to be included, however, her mother still wanted to complete a survey.

Child and parent awareness of the pathophysiology of infections and parent/child synchrony on awareness of isolation state

In general, children demonstrated an adequate awareness of being under a special type of situation (isolation) at the hospital that required them to be in their hospital room. However, the children interviewed here had varying levels of difficulty describing why they came to the hospital in the first place and how the doctors were helping them. Some seemed reluctant to respond at first, but would respond when further prompted with a reiteration or rephrasing of a question. They also varied in their understanding of the pathophysiology of infections as well as
the enormity of their condition. One child referred to ‘fevers’ when asked about what part of his body gets sick. Another child, in particular, believed she would leave soon when in fact she was a long-term, frequent inpatient. One child illustrated a lack of awareness that there are some type of isolation precautions, (e.g., neutropenic precautions) that are in place to protect a child who does not have an active infection but rather a compromised immune system, hence, isolation in this case aims to protect the child from others potentially exposing him/her to an infection.

(Responding to: Do you remember why had you had to come here?) Well, it's just that I was like vomiting on my bed and then I woke up and I then started vomiting again and that's why my mom called the ambulance and I gotta come back here cause I'm sick. But I hope that I will go soon on Sunday or Saturday, I don't know yet. (C001, female, 8 years)

(Responding to: Do you know how they are helping you right now?) Well, they're helping me like getting all the bugs out of surgery [...] out of my stomach? (C001, female, 8 years)

(Responding to: Has there ever been a time when you were in the hospital but you were not allowed to go out and play?) I dunno. (Could you go to the playroom right now?) No? (How come?) Cuz I'm sick, and I make people cough. (C006, male, 7 years)

(Responding to: Is there like a special word or name for being stuck in your room?) Isolation? (C004, male, 11 years)

(Responding to: is there something that happens to make the hospital put these signs on or are they always on?) I think that some of them are not on and some of them are also on. Yeah, because when you're sick they leave them on and when you're not sick they don't leave them on. (C001, female, 8 years)

(Responding to: Do you know why you come to the hospital?) Because you get sick. What part of your body gets sick? fevers. Do you know what the doctors are doing for you right now? I dunno. Do you want to know? Uh-hum. (C009, male, 13 years)

(Responding to: And you know what these [signs] means?) It means I’m not allowed to touch people or things outside my room. (Why is that?) Because, uh, germs can spread, yeah. (C003, male 15 years)
However, in the 2 parent-child dyads, accounts from parents indicated some discordance between children’s awareness of why they were in the hospital and parents’ belief and confidence that their child did know why he/she was at the hospital or how the doctors were helping the child get better.

**DYAD 1:**
(Responding to: does your child know why he/she is in the hospital?) *Yes.* (P002, Mother of son, 8 years)

(Responding to: [...] do you remember how come you had to come to the hospital this time? It's ok if you don't.) *I don't remember [laughs].* (C002, male, 8 years)

**DYAD 2:**
(Responding to: does your child know what the nurses and doctors are going to do for him/her today?) *Yes.* (P004, Mother of son, 11 years)

(Responding to: what are they doing for you right now?) *umm...I forgot.* (C004, male, 11)

Furthermore, the results from the parent-child dyads revealed that there was sometimes some discordance between what a parent believed their child’s preferred activities were compared to what the child him- or herself delineated as his or her preferred activities.

**DYAD 1:**
(Responding to: what kinds of arts/crafts activities does your child enjoy the most at the hospital?) *painting, play doh, building* (P002, Mother of son, 8 years)

(Responding to: Is there anything that has made it easier for you when you can’t go to the playroom and have to stay in your room?) *video games, ipad, having mom or dad here.* (C002, male, 8 years)

**DYAD 2:**
(Responding to: what kinds of arts/crafts activities does your child enjoy the most at the hospital?) *coloring, things that have to [be] put together.* (P004, Mother of son, 11 years)

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Most of the children interviewed in this study understood that being under isolation precautions is correlated with them not being able to visit the playroom, but their degree of reflected awareness of reasons for not being able to visit the playroom varied.

(Responding to: Is there anything that has made it easier for you when you can’t go to the playroom and have to stay in your room?) video game systems. (C004, male, 11 years)

Parent and children’s struggles with isolation precautions

Both parents from the parent-child dyads understood that isolation, though difficult, is necessary for protecting not just the health of their child but of others around them. Furthermore, both parents indicated that their fears about their children’s isolation were related to the children being inactive as a result of staying in their room.

(Responding to: How do you feel about your child being in isolation? Are you currently using resources available to you to cope with this situation?) Although it is inconvenient and limits physical activity, it’s necessary to keep everyone safe. A strong support system is really helpful during these tough situations. (P004, Mother of son, 11 years)
Child resiliency and strength are evident in how some of the children cope with their state of isolation.

(Responding to: How do you feel about your child being in isolation? Are you currently using resources available to you to cope with this situation?) *It is necessary, yes.* (P002, Mother of son, 8 years)

(Responding to: what concerns you the most when your child is in isolation at the hospital?) *He just stays in bed.* (P004, Mother of son, 11 years)

(Responding to: what concerns you the most when your child is in isolation at the hospital?) *Not having enough distraction.* (P002, Mother of son, 8 years)

(Responding to what concerns you the most when your child is in isolation at the hospital?) *How long he will be in isolation and why [he’s] like that.* (P007, mother of son)

(Responding to: what’s the worst thing about being on isolation? *Ummm...well nothing as long as I have my technology and that’s the thing that I can answer 5-7 with one sentence.* (…you memorized these questions?) *Well, the tablet video games, and I’m not gonna specify which video games cuz I don’t want them to get stolen.* (Oh, have you ever worried about stuff getting stolen here?) *Yes, I actually had like a scare where I had a bunch of video games and they’re like inside the sheets and we couldn’t find them and they were inside the linens.* (C005, male, 14 years)

(Responding to: do you feel sick in your body right now? *umm no not really.* (Well, I'm glad your body feels alright.) (C001, female, 8 years)

(Responding to: So, if you’re in the hospital for a long time and someone comes into your room what’s like the best thing they can say to you?) *You’re going home tomorrow!* *[emphatic] ohh, that’d be a good one!* *Yes, ma’am, I’ve been here for two months.* (C005, male, 14 years)

(Responding to: Are you on isolation right now?) *No.* (Are you glad?) *Yes.* (Yeah, knock on wood.) *But we don’t have anywhere to knock on wood!* *[playful]*. (C005, male, 14 years)

(Responding to: What is the hardest thing about being in your room when you can’t go to the playroom?) *You feel stuck.* *[sadness in tone]*. (C009, male, 13 years)

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One child did not seem to mind that he could not go to the playroom.

Children confirmed concerns voiced by parents in the study that isolation stifles children’s activity. Several children speak about feeling sad and/or lonely when they have to stay in their rooms. Some children speak to the importance and value of having volunteers play with them.

(Responding to: …so how about that time when you couldn't leave your room, what was the worst part of that or the hardest part?) I couldn't do much? (C002, male, 8 years)

(Responding to: Is there anything that makes it easier for you when you have to stay in your room and you can't go to the playroom?) Well, [I] just like some people to come play with me and bring me some toys and play with me. (C001, female, 8 years)

(Responding to: when thinking back to a time when you were on isolation, what's the worst thing about that?) When I can't go to the playroom or I can't touch anything. ([…] can you explain more about not being able to touch anything?) Um, I won't be able to touch, um, anyone who wants to give me like a high five or anything [sadness invoked in tone of voice]. (C003, male, 15 years)

(Responding to: what’s the worst part [of isolation]?) Feeling sad and being on isolation. (C001, female, 8 years)
(Responding to: Do you have any other thoughts on things we should be doing to help kids out when they’re in isolation.) *Maybe someone to play with or something like that?* (So you don’t get like super super bored?) *Uh-huh. Sometimes kids get really bored very easily. I learn from experience!*  (C003, male, 15 years)

**Difficulty of self-reflection during a trying time**

For some of the children interviewed, talking about video games was a rare emphatic point in the interview.

(Responding to: Is there anything that makes it better or easier? Umm...this! [presumably points to video games] (The game systems?) Uh-huh. (C004, male, 11 years)

(Responding to: for how many hours do you think you can play a video game?) 24 hours! (C003, male, 15 years)

Several children struggled with elaborating more deeply about what they like to hear when they’re at the hospital.

(Responding to: what do you like for people to tell you when you’re in the hospital?) *TV?*  (The TV? You like people to tell you to watch TV or that you can watch TV?) *I can watch TV?* (That you get to watch TV? Ok.) (C006, male, 7 years)

(Responding to: What's something that someone could say when you're in the hospital that you would not like them to say?) *I dunno.*  (C006, male, 7 years)

(Responding to: when you're on isolation, is there anything that makes it easier or makes it better?) *ummm...not really.*  (Not really? Anything that like, anything you would suggest?) *Umm...I dunno.*  (C003, male, 15 years)
One child who had numerous silent moments and seemed too hesitant or shy to answer any of the interview questions, had a marked moment of gregariousness when prompted to talk about video games.

(Responding to: Why do you think that game is so popular?) So, all I have to do is crash into someone really quick. [mumbles] wrong thing, [laughter] So, my best length ever was 19,750. (C002, male, 8 years)

Additionally, the importance of the playroom in an isolated child’s happiness is noted across children and parent data sets. Both parents and children understand the comfort that the playroom provides.

(Responding to: you told me that when you have isolation that it makes you sad…can you tell me a little bit about why?) Because I really don't want to be on isolation because I really want to have fun at the playroom. (Yeah?) yeah, well when I was not very sick I did not have those on [referring to isolation signs] and then I get to go to the playroom. (C001, female, 8 years)

(Responding to: so, when thinking back to a time when you were on isolation, what's the worst thing about that?) When I can't go to the playroom or I can't touch anything. (C003, male, 15 years)

(Responding to: what's the worst part about being in isolation? Not getting toys? (Not getting toys? ...tell me more about not getting toys when you're on isolation?) Umm, I don't get to go there and choose. (You don't get to go there and what?) Choose. (C004, male, 11 years)

(Responding to: what is your child’s favorite time of the day when he/she is at the hospital?) Whenever the playroom is open. (P002, Mother of male, 8 years)

Identifying areas for potential improvement in patient experience

One young child (aged 8 years old) who, understandably, did not comprehend every detail of the isolation signs, elucidated that she thought her door needed to always remain closed
even though she would have preferred to have it open, possibly for comfort. This conversation with the CLS conducting the interview provided an opportunity for the CLS to identify and correct the patient’s misconceptions. Another child expressed contentment when he learned that the door could remain open, as he prefers, when he is under isolation precautions.

(Responding to: do they make you keep your door closed when you're on isolation?) *I think they like leave it like a little bit closed.* (Do you like your door closed or open?) *I like my door open a lot.* (Can we read the words on this sign? Because there's a picture here and it says?) [child reads]"Door may remain open” (C001, female, 8 years)

(Responding to: What happens to a kid when they’re on isolation?) *I don’t know why they got the door sign.* (Want me to read the door sign? ‘Door may remain open.’) *Oh.* (So, you are someone who likes to have his door open all the time, right?) *Me, yes.* (You have told me before that it’s scary when the door is shut, right?) *Uh-hm.* (So this sign says, it’s ok for you to leave his door open. Does that make, you’re smiling, you happy?) *Yes.* (What are your thoughts when people have to wear a mask and a gown?) *That’s weird [laughing].* (C009, male, 13 years)

Another child exhibited some confusion in answering a question about who engages in activities with him while he is under isolation precautions, perhaps whimsically alluding to the importance of siblings’ presence in a young child’s life.

(Responding to: Who plays with you all the stuff?) *With my brother?* (Mother responds) *No, right here your brother doesn’t come to the hospital.* (C006, male, 7 years)

Some children provided specific things they prefer to hear during isolation whereas other children had more emphatic feelings about things they do not like to hear during isolation and elucidate feelings of stigmatization related to the experience of being under isolation precautions,
using vivid metaphor and description. One parent who was not part of the child-parent dyads expressed some simple things her child likes to hear when he is at the hospital.

(Responding to: What else do you like people to tell you when you're in the hospital?) I go to child life? (Oh, that you get to go to child life? What do you like to do in child life?) Just get legos. (Do you like to go there to play the legos or to get them and come back to your room?) Get them and go back to my room? (But you like to go pick them out of yourself?) Yeah. (C006, male, 7 years)

(Responding to: What do you like for people to say to you?) Well, I ask and talk and play with them [referring to volunteers] and ask a lot of questions to them. (You like to be able to ask questions?) Yes. (What kind of questions do you like to ask?) Well, I like to ask yes or no questions…or if you want to play with me questions? (C001, female, 8 years)

(Responding to: You’re stuck in your room, what’s the worst thing that someone can say to you?) You have to go to the PICU. Basically, you’re going into a room that you feel, that’s like so like isolated you can’t even leave and you feel like you’re an animal in the zoo. (What makes you feel like you’re an animal in the zoo? Everybody can see inside your room? Because the walls are glass?) Yes. (C005, male, 14 years)

(Responding to: What words or sentences does your child like to hear when he/she is at the hospital? How about at home?) He likes to hear “hi cutie, how you feel today?” At home he loves to hear whistle from everybody. (C007, mother of son)

One child expressed interest in having the CLS explain the significance of the isolation signs to him. Another child provided detailed feedback on ways video game systems could be disseminated in ways that would facilitate play with other children in other rooms.

(Responding to: Do you always have these signs [child is shown an isolation sign] on your door or only sometimes?) Sometimes? (Do you want me to tell you what they’re for?) Yeah. (These signs are on the door when kids are in isolation. So, isolation is what it means like how mommy was explaining to you. When you can't go to the playroom, when you have a cough, when you're sick, when we have to wear the gowns and the masks, and when they're might be germs that we can't spread to other people, right? Do you have questions now about these signs now?) No. (C006, male, 7 years)

(Responding to: So, can you play Wii or Wii U in your room here?) Only the Wii, the Wii U
is for PICU only. (Do you wish you had it on this floor?) Yes. (So, some game systems in some parts of the hospital you can’t play, and that’s annoying? And you would like to have lots of access to lots of different game systems?) Yeah. (What else would you like to have?) Bingo [child continues to explain at length a version of an electronic version of Bingo that could be played with kids in different rooms while under isolation precautions]. (C005, male, 14 years)

One child expressed interest in knowing what the spore isolation precautions sign entailed since his room had this sign up a couple of times throughout his stays.

(Responding to: Are you saying you want to know what the pink one means [referring to spore isolation precautions isolation sign]? Yeah. [child read signs out loud] (…so, when you have the pink sign, you’re not allowed to use the alcohol hand rub, only allowed to wash hands with soap and water.) (C005, male 14 years)

In one of the dyads, the child and parent were in agreement about what the child does not like to hear when he is in isolation.

DYAD 1: (Responding to: is there anything that you do not like people to say to you when you're in the hospital?) You're gonna get IV. NOOOO. [Emphatic] (C002, male, 8 years)

(Responding to: what words or sentences does your child NOT like to hear when he/she is at the hospital?) He needs labs drawn, or an IV. (P002, mother of male, 8 years)

The parent who was not part of a parent-child dyad stated that her child’s least favorite thing to do at the hospital was something that the staff would normally avoid anyway.

(Responding to: What is your child’s LEAST favorite thing to do at the hospital?) …to bother him when [he’s] sleeping. (P007, mother of son)
DISCUSSION

Main Findings

The primary aim of this study was to explore children’s perspectives of being under hospital contact isolation. Gaining insight into how children feel when they are under isolation precautions could provide valuable feedback in areas of improving a child’s hospital experience. Four key themes emerged from the analysis of children interviews and parent surveys: (1) Varying child and parent awareness of the pathophysiology of infections and parent/child synchrony on awareness of isolation state, (2) parent and children’s struggles with isolation precautions, (3) difficulty in self-reflection during a trying time, and (4) identifying areas for potential improvement in patient experience.

An important finding from this study was that the children interviewed had varying degrees of awareness of the pathophysiology of infections as it relates to isolation precautions. Some children who were or have been at some point under neutropenic precautions (C003, C009) expressed a lack of understanding of those type of precautions entailed from a pathophysiological perspective, (i.e., precautions in this case are to protect the child from others as opposed to protecting others from the child). Creating more awareness of the differences between the various types of isolation precautions (contact, droplet, spore and neutropenic), perhaps via the CLSs, is warranted as children expressed a desire to know more about their state of isolation.

Analysis of the parent-child dyads elucidated some discordance between parents’ and children’s perspectives on how the children experienced their isolation, on what the children’s preferred activities were while in isolation, and how much children understand about the reasons they are in isolation. Giving parents (ideally in the first language of the parents) the tools needed
to communicate the concept of isolation precautions to children as well as encouraging them to converse with their children on their preferred activities during their hospital stay could help address these issues.

Another significant finding of the study was the children’s resilience during a difficult, trying time. One child (C005, male, 14 years), who was also a recurring inpatient showed strength throughout his interview by joking with the CLS and his mother, stating to the recorder before answering the first interview question that “if you hear any laughing or chuckling in the background, that’s not me, that’s my mother.” Additionally, it could be that humor in this type of hardship could be a helpful coping strategy that allows the child to externalize as opposed to internalize any form of negative emotions. C003 (male, 15 years) also used humor as a potential coping strategy during the interview by speaking of himself in third person (referring to himself as ‘Nugget’) and using sarcasm to playfully engage with the CLS.

C005 also reflected that he felt that being under isolation precautions, “makes [him] feel like [he is] an animal in a zoo” because “everyone can see inside [his] room.” Given this child’s resilience and high level of feedback on the negative emotions experienced during isolation, hospital staff and administrators should have a conversation on how to de-stigmatize the concept of isolation precautions. CLSs are well poised to do this, and this study has reaffirmed the importance and value that CLSs represent to children, in addition to the therapeutic value the interviews provided to the children in this study.

A gradual sense of empowerment from the interview’s start to its end was witnessed in the way some of the children in the study opened up about their feelings on isolation and in the way some of them took interest in holding the recorder as they answered questions, perhaps invoking a sense of control and agency over their situation. The interviews provided some of the
children, in particular C001 and C003, a platform to speak out during a time where everything else, including their health status, is out of the children’s control.

Furthermore, as analysis of these interviews suggests that children want to be informed of their hospital status and they like to be given the ability to choose from various options when possible (e.g., choosing from a set of activities or toys when they are under isolation precautions and cannot go to the playroom, as exemplified by C004 and C006). Incorporating choice into play has been associated with a reduction of anxiety in hospitalized children.\textsuperscript{17} The CLS who interviewed the children often incorporated play (e.g., play-doh, drawing, and legos) during the interviews to keep them engaged, and always made them aware of the different choices they had. It would be valuable to expand this study and incorporate a more structured drawing and writing activity, which has been demonstrated to be of therapeutic value in reducing children’s anxiety in other settings. For instance, another prior study involved children being asked to draw a picture of a hospitalized child and write an accompanying story as part of a storytelling technique.\textsuperscript{18}

Verbalizing an imminent departure from the hospital could be a coping mechanism used by a child (C001, female, 8 years) to try to take control over a situation that may seem out of control. Regardless, the child’s distinctive reflection and willingness to speak profoundly about her situation, speaks to her desire to have her perspective heard and stands in contrast to the other children who struggled a bit more with self-reflection.

\textit{Interpretation of findings}

This study supports earlier studies that suggested that any clinical benefits of isolation procedures may be outweighed by how negatively isolation is experienced by patients, particularly when the patients are children. It is important to note that the clinical value of
isolation procedures is not always clear. One prior study evaluated before and after rates of MRSA and VRE after discontinuing routine MRSA contact precautions and found no increased rates of MRSA or VRE after one year. Moreover, discontinuation of contact precautions translated to hospital savings of $643,776 in one year. Contact precautions have also been associated with fewer visits by healthcare workers compared with patients not on contact precautions. Since children constitute a vulnerable population, it is possible that discontinuing routine contact precautions for MRSA or VRE could also provide a significant benefit to children from a psychosocial standpoint, as well as monetary savings to health systems. Because removing contact precautions can result in increased time for direct patient care, removing contact precautions could potentially improve a hospitalized child’s overall experience and care.

It was evident from interviews conducted herein that many of the children we interviewed experienced difficulties in self-reflection, which permeated through their narratives. This was perhaps indicative of the hardships that being in isolation poses to a child’s creativity and ability to express his. Clearly, some children had trouble expressing ideas that could improve their experience while in isolation. Among the children we interviewed, playing video games provided a respite from being in isolation, but perhaps could indicate a form of escapism taking place, since the children do have other toys available to them in their rooms. Furthermore, as one child whimsically illustrated, the presence of siblings is important and given their absence during isolation, other methods such as video conferencing or FaceTiming with siblings should be encouraged and facilitated.

In addition, de-stigmatizing parents’ beliefs of video games as being harmful might also be worth exploring. Research has demonstrated that video games have the potential to promote healthful behavior by increasing physical activity and nutritional knowledge, hence moving past
the stigma attached to video games. Video games offer opportunities for self-reflection and expression and can figuratively take children who are in isolation beyond their bodily or environmental restrictions. Discordance observed in this study between children and parents’ beliefs of children’s preferred activities at the hospital suggests that parents may not want to admit that their children prefer to play video games instead of more intellectual activities such as drawing, painting or constructing cities with legos. De-stigmatizing children’s use of video games as a distraction could help alleviate some of the pressure parents feel to keep their child active and intellectually engaged when at the hospital. Research has elucidated that parents of hospitalized children who are content with their hospital situation (e.g., feeling encouraged that they are doing the right thing for their child) are better able to support their child. Therefore, communicating some of these results might alleviate some of the concerns that parents may have about their children playing video games while under isolation.

Implications for future research

Video games can offer a form of attractive entertainment to a child in isolation, and perhaps a form of escapism from their current state, and our study has elucidated the importance of video games in the isolated child’s hospital experience. Given parent and child fears of the inactivity that isolation creates, a novel approach to video games could be appealing – active video games (AVGs). AVGs can increase physical activity in children and decrease a sedentary lifestyle in the way they are engineered and designed, and thus provide a unique opportunity for children under isolation precautions. Most of the children recruited for this study who voiced enthusiasm and lengthy rapport when talking about video games did so for video games that did not exhibit an active or AVG component.
Immersive Virtual Reality (VR) has also been shown to be effective in treating psychological distress in children, as well as increasing positive emotions.\textsuperscript{23} Research has also shown significant decreases in cortisol levels in adult populations exposed to animal-assisted activities (AAAs). Furthermore, AAAs have also been shown to improve positive mood in hospitalized children but more randomized controlled trials with larger recruitment are needed to explore their effectiveness.\textsuperscript{24} Hospital administrators could consider amplifying efforts in these research areas or increase the availability of such interventions in isolated children’s rooms if their respective policies permit them.

UCLA Mattel Children’s Hospital has in place a volunteer program whereby musicians, artists, students, and celebrities can come visit children who are not under isolation precautions. Since several children spoke to the need to have more volunteers (C001, C003) when they’re under isolation precautions, it is timely to revisit visitation policies to see if they can be improved, perhaps using virtual mechanisms such as Skype or FaceTime.

Since our sample only included one female, future research could also expand on finding more significant differences between girls’ and boys’ experiences in isolation that could better inform practices and interventions. Increasing study subject numbers and recruiting more girls could help facilitate more findings on differences between girls’ and boys’ experiences in isolation.

\textit{Strengths and limitations of this study}

Our hope is that in the future, other researchers interested in the hospital environment as it pertains to children’s health and psychological well-being will conduct studies similar to this one but with higher subject recruitment numbers. Given that children are a key vulnerable
population, it is important to fill in these literature gaps to showcase more of the child’s perspective. Interventions to improve the hospital experience for children who have to be under some form of isolation will therefore be more evidence-based and will also provide practitioners such as CLSs with a more substantiated way to provide the best care for hospitalized children, which is in line with their mission. Future studies could explore children’s, parents’ and CLS’s perspectives on isolation precautions together as a way to obtain a better understanding of the complexities of child hospitalization.

Children are not small adults. It is important not to apply what has been learned psychosocially about hospitalized adults to our pediatric population. There are better ways to survey the pediatric voice itself than solely relying on the parents’ perspective or relying on research conducted on hospitalized adults. Interview as a form of research methodology cannot only elucidate important findings but can also be empowering to subjects who are willing to tell their story to those who will ask and listen.\(^8,25\) The results of this study suggest that children’s experiences while under contact precautions could be improved through educational tools such as children-friendly isolation signs and child-friendly pamphlets with animations explaining germ transmission.

Lastly, the importance of parent-child dyads in this type of research cannot be stressed enough. Since some parent-child discordance was observed with regards to children’s likes and dislikes at the hospital, it would also be helpful for researchers to continue pairing hospitalized children’s interviews with parents’ perspectives as we did for this study. Our parent-child dyad completion rate was low (\(N = 2\)) due to the fact that the parental component was a take-home survey as opposed to a recorded interview and because parents caring for sick children are likely to feel overwhelmed. The impetus for this decision was primarily based on increasing our
children subject number without putting additional research burden on the parent who may not always be available and with their child during their isolation period due to work constraints or caring for their other children. Incentives to involve parents more directly through a recorded interview for completion of parent-child dyads could be worthwhile to explore.

CONCLUSION

A review of the literature reveals that there is a paucity of studies that examine hospitalized children’s perspectives with an even lesser focus on children who are under hospital contact isolation precautions. Here, we addressed this literature gap by providing the results of an original research study in which children who are or have been under contact isolation precautions were interviewed directly. Critically, we were able to pair some of these children’s interviews with the surveyed perspectives of their parents.

This study’s findings have implications for future researchers interested in expanding on the common themes found: (1) varying child and parent awareness of the pathophysiology of infections and parent/child synchrony on awareness of isolation state, (2) parent and children’s struggles with isolation precautions, (3) difficulty in self-reflection during a trying time, and (4) identifying areas for potential improvement in patient experience. Parent-child discordance suggests some potential ways to improve how children experience isolation. We recommend giving parents the tools needed to improve communication with their children during medical hardships. In addition, it may be helpful to de-stigmatize a hospitalized child’s desire to play video games. Given the emphatic reliance on video games during isolation that children in this study expressed, it would be helpful to explore more active forms of video games and other entertainment for children in isolation. Lastly, given some children in this study revealed
uncertainty regarding the meaning of some of the precautions on isolation signs, we therefore suggest that hospitals explore different (more child-friendly) ways to explain isolation precautions to children and their parents.

In summary, we believe that our study addresses an important gap in the literature involving a very vulnerable population’s perspective that merits further exploration.
Figure 4.1. Detailed timeline depicting gaps in the literature. Timeline indicates gaps in the literature from 1960-current on studies that employ research tools such as qualitative interviews to assess isolation contact precautions through the pediatric lens. The majority of these studies involve the parents’ or health professionals’ perspectives and not the children’s.
Table 4. Parent/child de-identifiers used and other subject information. The study included two parent-child dyads. Age range for children was 7-15 years, with the majority of children being male and most being accompanied by a parent during time of interview. Most children were on both contact and droplet precautions, and half were on contact, droplet, and spore precautions. Only two were on neutropenic precautions. Type of isolation precautions pertains to the time of interview and previous history of isolation, therefore not all types of precautions were experienced at the same time.

<table>
<thead>
<tr>
<th>Child</th>
<th>Parent</th>
<th>Age</th>
<th>Gender of Child</th>
<th>Type of Isolation Precautions</th>
<th>Accompanied by Parent During Interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>C001</td>
<td>Not enrolled</td>
<td>8</td>
<td>F</td>
<td>Contact, droplet</td>
<td>N</td>
</tr>
<tr>
<td>C002</td>
<td>P002</td>
<td>8</td>
<td>M</td>
<td>Contact, droplet</td>
<td>Y</td>
</tr>
<tr>
<td>C003</td>
<td>Not enrolled</td>
<td>15</td>
<td>M</td>
<td>Contact, droplet, spore, neutropenic</td>
<td>Y</td>
</tr>
<tr>
<td>C004</td>
<td>P004</td>
<td>11</td>
<td>M</td>
<td>Contact</td>
<td>N</td>
</tr>
<tr>
<td>C005</td>
<td>Not enrolled</td>
<td>14</td>
<td>M</td>
<td>Contact, droplet, spore</td>
<td>Y</td>
</tr>
<tr>
<td>C006</td>
<td>Not enrolled</td>
<td>7</td>
<td>M</td>
<td>Contact, droplet, spore</td>
<td>Y</td>
</tr>
<tr>
<td>Not enrolled</td>
<td>P007</td>
<td>N/A</td>
<td>M</td>
<td>Contact, droplet</td>
<td>N/A</td>
</tr>
<tr>
<td>C008</td>
<td>Not enrolled</td>
<td>14</td>
<td>M</td>
<td>Contact, droplet</td>
<td>Y</td>
</tr>
<tr>
<td>C009</td>
<td>Not enrolled</td>
<td>13</td>
<td>M</td>
<td>Contact, droplet, spore, neutropenic</td>
<td>N</td>
</tr>
<tr>
<td>Visualization of Coding</td>
<td>Codes</td>
<td>Overall Theme</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>------------------------</td>
<td>---------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#C001: “Because I really don’t want to be on isolation because I really want to have fun in the playroom.”</td>
<td>-Sadness -Playroom Nostalgia</td>
<td>-Identifying areas for potential improvement in patient experience</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLS: “And in the playroom, you can’t wear all this stuff, right?”</td>
<td>-Identification of Understanding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#C001: “Yeah”</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.2. Visualization of Coding.** Example of a coded excerpt from interview transcripts, illustrating how color was used to differentiate between sentences that have been tagged with different codes (sadness, playroom nostalgia, and identification of understanding) and how some can subsequently be coded with an overall theme (eg., identifying areas for potential improvement in patient experience).
Figure 4.3. Children Interview and Parent Survey Emerging Themes. The themes resulting from coded transcripts of children interviews and parent surveys. Interview and survey questions were based on three *a priori* themes: (1) Creating a comforting environment, (2) identifying patient concerns, and (3) identifying possible ways to improve the experiences of pediatric patients. Subsequent coding of interviews resulted in the four final themes in Figure 4.3: (1) varying child and parent awareness of the pathophysiology of infections and parent/child synchrony on awareness of isolation state, (2) parent and children’s struggles with isolation precautions, (3) difficulty in self-reflection during a trying time, and (4) identifying areas for potential improvement in patient experience.
REFERENCES:


CHAPTER 5

Overarching Conclusions and Recommendations for Future Studies

INTRODUCTION

Hospital administrators face pressure to adopt infection prevention strategies that are effective, affordable, and that will be well received and adopted by hospital staff and patients. As highlighted in Chapter 3 and Chapter 4, vulnerable populations such as the elderly and children continue to be disproportionately affected by hospital-acquired infections (HAIs), particularly by *Clostridium difficile* infection (CDI) and central line-associated bloodstream infections (CLABSIs), respectively. Because CDI recurrence in the elderly is common and because children have to be put under isolation for certain CLABSIs, it is important to investigate emerging technologies that can alleviate this burden.

Even though the most costly type of HAI, CLABSIs, has decreased 46% between 2008 and 2013, hospital stakeholders have a vested interest in examining evidence-based strategies to continue decreasing HAIs such as CLABSIs and CDI. Motivations for examining evidence-based infection prevention strategies is four-fold:

1. HAIs remain the primary cause of preventable death and disability in hospitalized patients.¹
2. Children are the most impacted age group by CLABSI.²
3. 70-80% of CDIs occur in the elderly.³
4. Centers for Medicare Services (CMS) has stopped reimbursing for CLABSIs and could do the same for other HAIs.⁴
In this thesis, we have provided a research base to support evidence-based infection prevention strategies through the following work:

(1) **Chapter 2**: I examined how antimicrobial products are currently registered and reviewed by the United States Environmental Protection Agency (US EPA) and make recommendations for how this process could be improved so that it is better informed by clinical data (previously published in the *American Journal of Infection Control*). Appendix A includes a response commentary with a timeline contrasting antimicrobial copper *in vitro* studies with clinical studies (previously published in the *American Journal of Infection Control*).

(2) **Chapter 3**: I developed a decision analysis model that allows decision-makers to incorporate cost-effectiveness data when deciding whether to adopt or maintain specific infection control practices. Specifically, we compared the cost-effectiveness of copper surfaces to standard surfaces at RRMC in light of emerging infection prevention technologies (prepared for submission to the *American Journal of Infection Control*).

(3) **Chapter 4**: I assessed the psychosocial effects of pediatric isolation as part of infection control practices by working with UCLA Mattel Children’s Hospital Chase Child Life hospital staff to develop and administer interviews and questionnaires for children and their parents. An examination of the psychosocial effects of pediatric isolation practices related to infection control addresses a significant gap in the literature first identified through our research in Chapter 2 (submitted for publication and under review in *Clinical Child Psychology and Psychiatry*).

Taken together, this work addresses the need for better evidence-based, cost-effective approaches to reduce HAIs, calls for the identification of positive deviants and best practices that
might improve the pediatric isolation experience, and recommends that clinical data be required as part of the registration process for antimicrobials that are intended for use in healthcare settings— all of which focus on the hospital environment, which is inextricably linked to health. In this chapter, we summarize the overarching themes that emerged from our work as well as pivot to the path forward for future studies based on lessons learned from our research.

**IN VITRO EFFICACY DOES NOT NECESSARILY TRANSLATE TO CLINICAL EFFICACY**

The goal of the work presented in Chapter 2 was to learn more about how antimicrobials are registered in healthcare settings. Given lack of clinical evidence-based standards that our antimicrobial regulatory framework is based on, our research reflects the need for more governmental (or hospital) accountability for better clinically effective Infection Prevention (IP) interventions.

**COST-EFFECTIVENESS OF EMERGING IP TECHNOLOGIES**

The work we conducted in Chapter 2 also highlighted the need for more evidence-based approaches to selecting new IP strategies. In Chapter 3, we developed a model to assess the cost-effectiveness of copper alloy antimicrobial surfaces compared to the current standard surfaces in RRMC. To improve health outcomes, hospital administrators must be able to ascertain if a certain infection prevention technology or program is cost-effective for their respective institution to adopt. Evidence-based IP technologies that are cost-effective are therefore of interest for hospital stakeholders to incorporate. Based on limited clinical data available, we were able to model the decision of choosing a novel IP technology such as copper alloy surfaces compared to maintaining
the standard surfaces. Our model determined that copper alloy surfaces are moderately cost-effective for a hospital to adopt based on the QALYs saved, the minimal incremental clinical effectiveness of copper alloy, and the current average cost per person of retrofitting one room to copper alloy but more clinical and cost-effectiveness studies are needed to assess if copper alloy surfaces for use in hospitals is a strategy worth implementing.

BETTER UNDERSTANDING PEDIATRIC CARE NEEDS AND PROGRAM PREFERENCES

Assessing the psychosocial effects of pediatric isolation at UCLA Mattel Children’s Hospital through our work in Chapter 4 provided a better understanding of pediatric care needs and program preferences. A literature review on the subject revealed a paucity of recent research regarding the psychosocial effects of isolation on children. The few studies that had been performed previously each called for a need to conduct more research.7,8 Furthermore, the few prior studies in the literature that had examined the psychosocial effects of pediatric isolation, particularly in contexts that are relevant to HAIs, had all done so through the lens of the parent.7 Those studies that had focused on pediatric isolation related to ESCAPE pathogens were over 30 years old.7 All of these point to the need for more and newer research in this area.

To address this gap, we developed a set of interview questions for children and their caregivers that focused on three a priori topics: (1) Creating a comforting environment, (2) identifying patient concerns, and (3) identifying possible ways to improve the experiences of pediatric patients. After coding interview transcripts, the data is synthesized into four final, posteriori themes: (1) varying child and parent awareness of the pathophysiology of infections and parent/child synchrony on awareness of isolation state, (2) parent and children’s struggles with
isolation precautions, (3) difficulty in self-reflection during a trying time, and (4) identifying areas for potential improvement in patient experience. The results of this study suggest that while isolation is a commonly used strategy, more evidence is needed to inform isolation practices, particularly when isolation is used for vulnerable populations like children. Studying the psychosocial effects of pediatric isolation enabled us to address research gaps, identify positive deviants, and disseminate best practices that will aim to improve the patient experience of this key, vulnerable population that has so much at stake.

Insights from the interviews we conducted will be of direct value not only to stakeholders at the hospital where the work was conducted, but also to other hospitalized children. Specifically, this study suggests that pediatric patient experience, in particular for those pediatric patients who are currently in isolation or who will be in isolation can be improved by:

- making sure children under contact isolation precautions understand the pathophysiology of HAIs in basic terms
- including more active video games (AVGs) in pediatric patient rooms
- disseminating coping strategies that work for some children under contact precautions
- and conducting a risk-benefit analysis of certain isolation precautions in a pediatric setting.

Additionally, as anticipated, some of the children’s and parents’ responses revealed low cost opportunities to ameliorate the pediatric isolation experience such as creating child-friendly isolation signs, destigmatizing video games (in particular those with an active component such as AVGs), and encouraging parent-child discussions on their preferred activities while under contact isolation precautions.
Prior research has shown that Child Life Specialists (CLSs) in pediatric settings are essential to formulating effective interventions because they have expertise in providing information that is developmentally sensitive to the child's level of understanding. The qualitative data that we obtained from open-ended interviews conducted by our CLS collaborator at UCLA Mattel Children’s Hospital led to the identification of positive deviants, patients who have unique coping strategies that seem to enable them to thrive. Identification of positive deviance is an approach to fostering positive change based on the observation that in any setting, there are individuals who use uncommon but successful coping strategies that enable them to find better solutions to a problem at hand than their peers, despite facing similar challenges. Informing stakeholders on effective coping strategies that can be more widely disseminated can be helpful for the pediatric community. Our interview data in Chapter 4 elucidated positive deviance strategies that can be more widely disseminated in order to improve the pediatric patient experience.

Overall, this work can inform the development of more effective, evidence-based programs that are targeted at such a key vulnerable hospital population. Studies on adult patients in isolation indicate that many patients believe more information regarding their care and isolation precautions would result in a better isolation experience. We believe that for children, information regarding isolation could decrease the risk of misconceptions regarding reasons for their isolation. The results of the work we conducted in Chapter 4 will also allow staff to provide developmentally-appropriate information to isolated children as supported in the literature.

LESSONS LEARNED AND THE PATH FORWARD

The studies resulting from my research help to further the field of infection prevention as it pertains to shifting towards a more evidence-based hospital culture, from clinical environment to stakeholder input and collaboration. Chapter 2 elucidates a new way of registering antimicrobial
agents for use in hospital settings that is based on clinical efficacy as opposed to just *in vitro* efficacy. Looking forward, larger and better-designed clinical studies are needed to test the effects of copper alloy surfaces on HAI incidence in healthcare settings before hospital administrators and the general public can be confident that antimicrobial surfaces are worth the investment. As more clinical data for infection prevention practices becomes available, researchers and hospital stakeholders will be able to use cost-effectiveness models like the one discussed in Chapter 3 to simulate costs of choosing one option over the other across a set of variables.

If we want more hospital programs and interventions that will improve the pediatric hospital experience, then we need more programs and interventions that solicit children’s voices, ideally through qualitative research tools as we have done through our open-ended interviews and questionnaires so we get their stakeholder buy-in. As mentioned in Chapter 4, our hope is that more researchers will follow suit and conduct larger qualitative studies with more resources to examine how to improve the hospital environment for children, particularly for children under isolation precautions, to gain more perspective on children’s voices. Studies that include more child-parent dyads or triads with CLSs will further highlight areas that could be improved in the pediatric isolation experience by including all three stakeholders’ perspectives. Furthermore, a risk-benefit analysis should be conducted, similar to the one conducted in Martin et al 2016¹⁰ or to the cost-effectiveness study conducted in Chapter 3, to determine across a rigorous set of variables, if contact precautions in a pediatric setting pose more risk than benefit in terms of its effects on patient experience. Together, these studies highlight that the hospital environment can be improved by assessing and improving the efficacy and impacts of interventions designed to reduce HAIs.
REFERENCES:

5. Alvarez E, Uslan D, Malloy T, Sinsheimer P, Godwin H. Response to "Perspectives from the field in response to 'It is time to revise our approach to registering antimicrobial agents [by the Environmental Protection Agency] for health care settings'". Am J Infect Control. 2017;45(1):100-102.
6. Alvarez E, Uslan D, Malloy T, Sinsheimer P, Godwin H. Response to "Perspectives from the field in response to 'It is time to revise our approach to registering antimicrobial agents [by the Environmental Protection Agency] for health care settings'". Am J Infect Control. 2017;45(1):100-102.


APPENDIX A

Supporting Information for CHAPTER 2
Response to “Perspectives from the field in response to: It is time to revise our approach
to registering antimicrobial agents [by the EPA] for healthcare settings

(A manuscript published in the American Journal of Infection Control, 2017, 45(1): 100–102)

ABSTRACT

In this response, firstly, we express our satisfaction with the responding authors agreement with our call to action to require clinical studies in the U.S. EPA registration of antimicrobial surfaces. Secondly, we reaffirm our stance on requiring clinical evidence before registration, and we present salient counterarguments as to why this should be of crucial importance to the scientific process. Thirdly, we address a discrepancy made in Schmidt et al 2016 where the authors mistakenly ascribe clinical relevance to an in vitro study.

We also include a literature timeline to visually juxtapose the robust body of in vitro studies to the paucity of clinical studies of antimicrobial copper alloy surfaces. Lastly, we highlight an ongoing UCLA study representative of the level of rigor we hope to see in clinical studies of antimicrobial surfaces. We believe that this piece will be of significant interest to the readers of Environmental Health Perspectives, and will address the key elements addressed in Schmidt et al 2016 that need correction and further clarification.
We appreciate the perspectives from Schmidt et al on our commentary (“It is time to revise our approach to registering antimicrobial agents for health care settings)"1 published in the American Journal of Infection Control in 2016. The impetus for this commentary was to start a discussion on the utilization of clinical data as part of the U.S Environmental Protection Agency (U.S. EPA) antimicrobial registration process, and we welcome the opportunity to discuss this important issue further.

Our commentary (Alvarez et al 2016)1 explores the value of requiring clinical studies as part of the registration process of antimicrobials under the jurisdiction of the U.S. EPA. We agree with responding authors on the importance of our call to action on requiring clinical evidence of antimicrobial products for use in clinical settings, which are inextricably linked to public health.

However, where we diverge is on the importance of requiring the clinical effectiveness study component before registration versus post registration. We believe that it is important to conduct such clinical studies of effectiveness on antimicrobials before registration because otherwise we will continue to adopt innovations that may not make an actual difference in disease rates. EPA registration for “antimicrobial” surfaces has facilitated adoption of copper surfaces for this purpose in hospital built environments, despite a paucity of high-quality evidence demonstrating clinical efficacy (See Figures A.1 and A.2). A robust body of evidence is necessary to support clinical outcomes and for the scientific community to fully embrace the validity of copper antimicrobial surfaces. In the case of in vitro studies of copper alloy surfaces, the body of evidence is robust (See Figures A.1 and A.2). Our argument is that well-designed, high-quality studies showing clinical outcomes of relevance should be performed before registration and before any public health-related claims are made.
We would like to emphasize that there is only one published clinical study to date evaluating copper surfaces in hospitals (Salgado et al 2013), not multiple clinical studies, as suggested by the respondents. The responding authors state that “It should be noted that in addition to the clinical trial reported by Salgado et al 2013, another trial, conducted in Santiago, Chile in a pediatric setting, correlated reductions to the environmental microbial burden and infection rates.” Thorough review of the original manuscript by Schmidt et al 2016 reveals that this study reported data on microbial counts within a clinical environment but the authors did not correlate these data with clinical outcomes. As such, this does not constitute a “clinical study”.

Furthermore, the responding authors appear to claim that the outcome of the clinical study in this particular case validates EPA’s reliance on in vitro testing in all cases. The question of whether an in vitro study is a valid method (i.e., whether it provides reliable data relevant to the performance question) cannot be resolved by relying upon the outcome in a single case. The responding authors make a hasty generalization by suggesting otherwise. Therefore, we maintain our position that while there is a robust body of evidence to support the in vitro effectiveness of copper alloy surfaces (See Figures A.1 and A.2), at the time that the surfaces were first registered, there was not a robust body of evidence to support their clinical effectiveness.

With regards to the responding authors’ comments on the EPA’s transparency of the registration process, we would like to emphasize what is mentioned in our original manuscript: if the EPA has already considered the advantages and disadvantages of requiring clinical efficacy data for registration, then that decision-making process should be made more transparent. When an unofficial modification of an existing protocol for sanitizers was accepted
for copper alloy registration purposes, at the time, this decision-making process was opaque. We understand that the protocols for registration are available on public websites, but our commentary addressed the lack of transparency with regards to exceptions made to the copper alloy surface registration, not on the online availability of protocols.

In calling for a requirement for reliable clinical evidence, we acknowledge that generating high quality repeatable patient-based data is challenging. That said, recent federal funding from the Agency for Healthcare Research and Quality (AHRQ) has been provided to develop and implement the first large-scale robust clinical trial focused on the use of copper surfaces to prevent hospital-associated infections (HAIs) in intensive care unit (ICU) patients. This study, being carried out by two of the authors of this commentary, Dr. Uslan and Dr. Sinsheimer, has been able by design to incorporate key elements associated with classical clinical trial studies.

*In vitro* efficacy testing was conducted to quantify the antimicrobial capacity of a number of commercially-available copper-based materials. The specific copper-based material selected had an *in vitro* efficacy comparable to 100% copper, was gun-metal grey – masking its copper content, was able to be cost-effectively coated onto a wide range of existing ICU assets located in close proximity to ICU patients (i.e., bed-rails, overbed tables), and was durable enough to withstand the rigors of an ICU. A sham material, manufactured by the same firm producing the copper-base material, was developed for the clinical trial which looks visually indistinguishable from the selected copper-based material, and can also be cost-effectively coated onto existing ICU assets. The sham material has the same durability qualities as the copper-based material, and was demonstrated in *in vitro* testing to have zero antimicrobial activity. By matching coloration of the sham material with the active material, this study has
been able to blind care providers as to which ICU rooms have assets coated with antimicrobial copper and which rooms have assets coated with the sham material, blinding ICU personnel documenting HAIs among ICU patients, and blinding the infectious disease physicians responsible for validating each HAI claim.

While such rigorous prospective clinical trials are time consuming and expensive to implement, having designed and implemented such a trial demonstrates the feasibility of evaluating whether indeed ICU patients in rooms with assets coated with antimicrobial copper have a lower risk of developing an HAI than ICU patients in rooms with assets coated with sham material. Furthermore, regardless of whether clinical trials are conducted before or after registration, the cost of such trials remains the same. If antimicrobial copper surfaces are able to lower HAI risk in this first study and if these findings are replicated, this not only provides the necessary evidence base for EPA registration of copper surfaces as antimicrobial but also triggers decision makers involved in health care in the United States and worldwide policy to consider the cost-effectiveness of integrating antimicrobial copper materials into full range of ICU assets located in close proximity to patients. Such a finding would also trigger additional research focused on developing clinical evidence of HAI reduction associated with antimicrobial copper beyond the ICU.

We appreciate the responding authors’ concern over the implementation of a clinical evidence requirement before registration of antimicrobial products, but we stand our ground in recommending the implementation of a clinical evidence requirement before registration of antimicrobial products for healthcare settings. Furthermore, despite the large number of antimicrobial copper in vitro studies, there is only one published antimicrobial copper surface clinical study, which does not constitute a robust body of evidence.
Figure A. 1. Timeline of copper alloy studies. Visual representation quantitatively comparing and contrasting in vitro and clinical studies assessing the antimicrobial properties of copper alloy surfaces.
Figure A. 2. Detailed authorship timeline of copper alloy studies. Peer-reviewed papers of *in vitro* and clinical studies using copper alloy surfaces as a testing material. Notice the paucity of clinical studies to date.\textsuperscript{2,5-15}
REFERENCES:

1. Alvarez E, Uslan D, Malloy T, Sinsheimer P, Godwin H. Response to "Perspectives from the field in response to 'It is time to revise our approach to registering antimicrobial agents [by the Environmental Protection Agency] for health care settings". Am J Infect Control. 2017;45(1):100-102.


APPENDIX B

Supporting Information for CHAPTER 4

*Interview Questions for Children*
APPENDIX B: Interview Questions for Children in Isolation at Mattel Children’s Hospital
UCLA (UCLA IRB #16-001999)

Intake Form
Interview Open-Ended Questions
Mattel Children’s Hospital UCLA

(STAFF ONLY)

Study Subject ID#: ________________________________________________________________

Interviewer Initials: ______________________________________________________________

Date of Interview: ________________________________________________________________

Child Age: _____________________________________________________________________

Reason for Isolation (Checkbox):

☐ Contact
☐ Droplet
☐ Spore
☐ Neutropenic

Length of Isolation: ________________________________________________________________

One or more parent(s) with children during interview? Yes/No (circle)

If circled Yes, circle which parent(s) are with child: Mother/Father (circle)

If NO, is child unaccompanied by parents during his/her stay for the entire duration or for part of it? Circle Answer.

If answered for part of it, then indicate how many times a week on average a parent accompanies the child: ______________________________

Non-Parent Caretaker with child during interview? Yes/No (circle)

(For Child)
Hi (Child's name) - Today, I would like to learn more about you and what being in the hospital is like for you.

[Give children the choice of drawing or doing an arts and crafts activity (i.e. play-doh, legos) while they answer questions if possible]

*Topic(s): Open-ended* (You can ask variations of each question depending on how child is responding. You can also try prefacing/rephrasing questions with “what sorts of situations make you feel this way?” or “can you tell me more about how you feel?”)

**Interview Questions**

1. What words or sentences do you like to hear when you have to stay in your room?

2. Which ones do you **NOT** want to hear?

3. Right now, can you go outside or to the playroom?

4. If not, do you know why not?

5. What is the hardest thing about being in your room when you can't go to the playroom? *(Does it make you mad or sad?)*

6. Is there anything that has made it easier for you when you can't go to the playroom and have to stay in your room?

7. Can you tell me what it is?

8. How come you had to come in to the hospital at first?
9. Has there ever been a time when you were not allowed to go outside or to the playroom?

10. Can you tell me what this is? *(Show child enclosed isolation sign from binder).*
APPENDIX C

Supporting Information for CHAPTER 4

Survey Questions for Parents
APPENDIX C: Survey Questions for Parents/Caretakers of Children in Isolation (UCLA IRB #16-001999)

(STAFF ONLY)

Study Subject ID#: _________________________________________________________________

Date of Survey: _________________________________________________________________

Type of Isolation (Checkbox):

☐ Droplet
☐ Spore
☐ Contact/Spore
☐ Neutropenic

Length of Isolation: _______________________________________________________________

(For Parent)

In order to provide the best hospital experience for children in isolation at Mattel Children's Hospital UCLA, we are asking for your permission and participation in our questionnaire study. If you agree to participate, you will be asked to fill out the parent survey along with the parent permission form so that we can ask your child some questions regarding his/her feelings about being in isolation. We seek to better understand the psychosocial effects of pediatric isolation, so we would greatly appreciate you and your child’s participation in the study. The study findings will better inform hospital staff in minimizing the detrimental effects of being in pediatric isolation and will ensure that Mattel Children’s Hospital UCLA continues to provide the best standard of care for children in isolation.

Survey Questions

Topic 1: Creating a Comfortable Environment
1. What words or sentences does your child like to hear when he/she is at the hospital? How about at home?

2. What words or sentences does your child **NOT** like to hear when he/she is at the hospital? How about at home?

3. What kinds of pictures or photos does your child like to see when he/she is at the hospital? How about at home?

4. What kinds of pictures or photos does your child **NOT** like to see when he/she is at the hospital? How about at home?

5. What kinds of arts/crafts activities does your child enjoy the most at the hospital? How about at home?

6. What kinds of arts/crafts activities does your child enjoy the least at the hospital? How about at home?

7. What is your child’s favorite time of the day when he/she is at the hospital? How about at home?

8. Is there a toy or game that your child likes the most at the hospital? What about at home?

9. What is your child’s favorite thing to do at the hospital? What about at home?

10. What is your child’s **LEAST** favorite thing to do at the hospital? What about at home?
Topic 2: Identifying Patient Concerns

1. What does your child worry about the most when he/she is in the hospital? How about at home?

2. What is the reason your child had to come in to the hospital at first?

3. Does your child know why he/she is in the hospital?

4. Does your child know why he/she is still here?

5. Does your child know what an infection is? If yes, what does he/she say it is?

6. What bothers your child the most when he/she is at the hospital?

Topic 3: Identifying Possible Areas of Pediatric Patient Experience Improvement

1. Does your child know what the nurses and doctors are going to do for him/her today? If not, would you like your child to know what the nurses and doctors are going to do for him/her today?

2. Does your child ever feel like he/she can't talk about his/her feelings?

3. What do you think your child would benefit from having at the hospital during isolation (i.e. more interactive TV programming, educational video games, skype or facetime with parents if away, etc?)
4. What concerns you the most when your child is in isolation at the hospital?

5. How do you feel about your child being in isolation? Are you currently utilizing resources available to you (i.e. family support, religious practices, mental health services, etc.) to cope with this situation? Why or why not?

6. What can Mattel Children’s Hospital UCLA do to make you and your child feel better during isolation?

Thank you very much for your participation in our study!
APPENDIX D

Supporting Information for CHAPTER 4

Child Life Training Manual
APPENDIX D: Child Life Training Manual

CHILD LIFE TRAINING MANUAL FOR STUDY ON PSYCHOSOCIAL EFFECTS OF PEDIATRIC ISOLATION (IRB# 16-001999)

BACKGROUND

What if there was adequate research to elucidate best practices for children who undergo hospital isolation due to the growing threat of superbugs?

Hospital-associated infections (HAIs) contribute to increased morbidity, mortality, and healthcare costs. A key priority is to shift our focus from treating HAIs as they occur to preventing HAIs in the first place, but a second priority is to better understand the psychosocial implications of HAIs and their management, so that hospital practices don’t inadvertently harm vulnerable populations (Strauss and Corbin 1998). The study we propose to conduct at Mattel Children’s Hospital UCLA aims to examine the psychosocial effects of pediatric isolation practices related to infection control. For this study, we propose to work with Mattel Children’s Hospital infection prevention staff and Chase Child Life hospital staff at UCLA to develop and administer a questionnaire to children in isolation and their parents to assess the psychosocial effects of pediatric isolation as part of infection control practices. A report summarizing evidence-based recommendations regarding isolation practices post-study will be delivered to Mattel Children’s Hospital at UCLA.

As a first step towards completing this study, a literature review was conducted on both the psychosocial impacts of pediatric isolation and on practices that have resulted in positive outcomes for isolation patients. This review revealed a paucity of recent research regarding the psychosocial effects of isolation on children, and the few studies that delve on this call for the urgent need to conduct more research (Koller et al. 2006; Bradley 2001). Furthermore, the few studies that do examine the psychosocial effects
of pediatric isolation, particularly in contexts that are relevant to HAIs, do so in the context of parental or caretaker perspectives (Koller et al. 2006). Most of these studies that do focus on pediatric isolation are over 30 years old (Koller et al. 2006; Kretzer and Larson 2001).

**PERSPECTIVE AND TIME HORIZON**

This study aims to represent the perspective of the child who is undergoing isolation as well as his/her parent(s) or caretakers. The study will take place for approximately 12 weeks.

**Study Goal:** Assess the psychosocial effects of pediatric isolation at Mattel Children’s Hospital UCLA to better understand pediatric care needs and program preferences and to inform development of more effective, evidence-based programs.

**SCREENING CRITERIA**

Inclusion Criteria: Children who are admitted as inpatients to Mattel Children’s Hospital UCLA who fit the following criteria:

- Have been under contact, droplet, spore or neutropenic precautions for at least 24 hours or more at the time of interview potential
- Are not under contact, droplet, spore, or neutropenic precautions but have been previously for longer than 24 hours. (Isolation must have taken place at ages 7-12).
- Are English and/or Spanish speakers
- Are in the age range of 7-12 years of age
- Parent(s)/legal guardian are willing to participate in parent survey portion of study and can consent to their child participating in children interview portion of study.

Exclusion Criteria:

- Out-patients
• In-patients are neither currently nor have been previously under contact, droplet, spore, or neutropenic precautions
• Children whose parents don’t give consent for their participation
• Children who do not give their assent to participate in the study
• Children who are not feeling well enough to speak
• Children who do not recall their isolation experience (if previously under contact isolation precautions).

RECRUITMENT PROCEDURE

If a child meets inclusion criteria after chart review, Chase Child Life specialists will ask parent or caretaker (if there with child) to sign consent form.

The Child Life specialist will also hand a survey to the parents to be filled out at their discretion (anytime within 3 weeks of receiving survey). Parents can turn survey in to Chase Child Life staff or mail to our office via an enclosed self-addressed stamped envelope included with the survey. Materials sent by email should be postmarked within 3 weeks of date that parents received survey from Child Life.

CHILD INTERVIEW & PARENT SURVEY PROCEDURES

Child Interview Procedure

Chase Child Life staff will conduct 15-30 minute interviews with each recruited child, ideally alone with the child, after parent/caretaker gives consent.

• Interviews will be recorded.
• Child Life specialist should start by having child tell a story (see interview guide for details) in as much detail as possible as a technique to get kids to be more conversational.
• If interview is interrupted, child life specialist can stop recording, and continue whenever there is another opportunity (ideally, the same day, if possible).

**Parent Survey Procedure:**

• Child Life Staff will give parent(s)/caretakers a printed-out survey with SASE to be filled out at their discretion.

• They will be given the option to fill it out there and hand back in person, or take home and mail back to our office.

**Physician Notification:**

• Child Life specialist should notify each child’s physician about his or her participation in the study after parent permission is obtained.

### REFERENCES


