INFECTION CONTROL INSIGHTS FOR HOSPITAL ANIMAL-ASSISTED INTERVENTION PROGRAM IMPLEMENTATION: FROM STAKEHOLDER PERSPECTIVES TO MICROBIAL DYNAMICS

by
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Abstract

Background: While animal-assisted intervention (AAI) programs have shown significant benefits to patients, there are concerns regarding their use in healthcare settings limiting utilization. This works aims to enhance the adoption and use of hospital AAI programs and understand the positive and negative outcomes of implemented control measures. We hypothesize that a One Health framework will aid in the understanding and improvement of hospital AAI infection control concerns. This dissertation will 1) collect perspectives on concerns and control measures to understand perceived risks, and 2) examine microbial dynamics to understand actual risks.

Methods: The first two chapters are literature reviews to identify knowledge gaps and provide rationale for the thesis research. The next two chapters are based on a qualitative study interviewing key stakeholders in hospital AAI programs. The last two chapters describe research that sampled for both hospital pathogens and whole microbial communities to pilot test a canine decolonization approach as an infection control intervention.

Results: The literature reviews revealed a lack of data on the risks associated with hospital AAI, and a One Health approach can be used to address this knowledge gap. The qualitative findings indicated occupational health benefits are limited by administrative and infection risk barriers, but these could be overcome through collaboration and leadership. Microbial findings suggest the canine decolonization intervention blocked the microbial contribution from the therapy dog and reduced rare microbiota on the dog, yet did not prevent all microbial sharing, indicating the dog as only one possible pathway for transmission.

Conclusions: The results from this thesis support the hypothesis that a holistic One Health approach can assist in understanding and designing interventions to improve hospital AAI programs. The qualitative findings stress the importance of understanding practical considerations for program implementation. In the quantitative study, allocation of the relative contribution for all potential microbial transmission pathways, and the determination of potentially negative unintended consequences of infection control policies, can inform the design of appropriate and effective control measures. This thesis suggests that a One Health framework should be used for future research in hospital AAI to ensure the sustainability of these valuable programs.

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Chapter 1: Introduction

1.1 Background

Holistic systems-thinking is needed to solve complex public health problems. The One Health framework is an example of such an approach, as it examines the interconnections between humans, animals, and the environment. The goal of this research is to delve into the positives and negatives of human-animal-environment interactions within a healthcare setting, particularly the use of animals as an adjunctive therapy modality, with the objective to support, protect, and enhance these programs.

The One Health Concept

One Health recognizes the inextricable linkage of humans, animals, and their shared environment (Destoumieux-Garzon et al., 2018). It is defined as any added value in human and animal health and wellbeing, environmental sustainability and protection, or economic incentive, that can be achieved by closer cooperation of various disciplines, including human, animal, and environmental health, which could not be accomplished if the sectors work separately (AVMA, 2008). It involves collaborative problem solving—locally, nationally, and globally. Previous research, ranging from vaccination campaigns to early emerging disease detection, shows that a One Health approach provides a clear benefit for the health of humans and animals alike (Rabinowitz et al., 2013; Zinsstag et al., 2011). Public health problems are frequently complex, transboundary, multifactorial, and across species, and if approached from a purely medical, veterinary, or ecological standpoint, it is unlikely that sustainable mitigation strategies will be produced. Therefore, a One Health framework is critical to address many current public health issues.

This concept has never been more evident than now, as this dissertation is written during a worldwide coronavirus pandemic (SARS-CoV-2, COVID-19). The One Health concept first grew in popularity when the Wildlife Conservation Society used the term in their guiding principles, linking the health of humans and domestic animals with the health of ecosystems, issued to address public health challenges during the first SARs outbreak of 2003-2004 (Mackenzie & Jeggo, 2019; Wildlife Conservation Society, 2004).

The roots of One Health are in nineteenth-century comparative medicine, which used animal models to advance human medicine. In 1984, Calvin Schwabe identified 'One Medicine' as considering "the close systematic interaction of humans and animals for nutrition, livelihood, and health" (Zinsstag et al., 2011). While most One Health research has centered on zoonosis, or the spread of disease from animals (either wildlife or domestic) to humans, Hodgson and Darling introduced the concept of "zooeyia" to the One Health field in 2011 as "the positive inverse of zoonosis", the multiple benefits to human health from interacting and bonding with animals, which provided the evidence base for the philosophical construct of the human-animal bond (Hodgson & Darling, 2011). The human-animal bond is a mutually beneficial and dynamic relationship between people and animals that is influenced by behaviors essential to the health and wellbeing of both. This includes, but is not limited to, emotional, psychological, and physical interactions of people, animals, and the environment (Hines, 2003).

Animal-Assisted Interventions

The strength of the human-animal bond and its potential implications for human health and wellness is the fundamental premise of animal-assisted interventions (AAI). AAI is an umbrella term that is any intervention that intentionally includes or incorporates animals in health, education, and human services for therapeutic or ameliorative process

in humans (Dudzik, 2018). It includes animal-assisted activities, programs for motivational, educational, and recreational purposes such as classroom reading animals and animals for trauma support. It also includes animal-assisted therapy, structured therapeutic programs with a targeted clinical outcome or goal delivered by health professionals, such as animal use in physical therapy. Both forms of AAI are used in healthcare settings, either for the purpose of positive distraction to patients or as a targeted therapy modality in patient care.

AAI is a perfect example of a One Health approach. It incorporates the health of humans as a direct result of animal exposure and interaction. The environmental impact on human-animal interactions within AAI incorporates the hospital's social, cultural, political, and economic factors. In fact, the One Health framework previously has been recommended as a beneficial application to AAI research (Chalmers & Dell, 2016; Hediger et al., 2019), specifically to understand the synergistic or antagonist effect on the health of humans and the health of the therapy animals.

However, the One Health concept can also be used to examine the dynamic balance of positive and negative impacts of AAI programs. While numerous health outcomes have been reported in patients experiencing AAI (Kamioka et al., 2014; Maujean et al., 2015), there are potential challenges to incorporating animals into a hospital setting, which can include children with poor immune function. AAI programs may enhance the exchange of pathogens between therapy animals and people. Hospitals can be incubators for infectious disease agents, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridioides (Clostridium) difficile,* and *Pseudomonas aeruginosa*. While these hospital-acquired pathogens are enhanced by the close contact and antimicrobial selective pressure inherent to a healthcare setting, therapy animals may unwittingly

serve as disease recipients and mechanical vectors, or an interactive fomite. It is possible that contact between therapy animals and individuals may lead to subsequent infection in both. While research on this potential negative outcome is lacking, research has shown that dogs can carry hospital-associated pathogens, which could potentially be transmitted to patients with whom they interact (Dalton et al., 2020).

The "Hygiene Hypothesis" and Microbial Interactions between People and Animals

An additional dimension to this dynamic process is the idea that microbes, including pathogens, function in the context of their holistic microbial community. A better understanding of that microbial community, and shifts within that community, will better elucidate pathways and mechanisms of the potential pathogenic risk of AAI programs. This is important as our total microbial communities, or microbiome, plays a critical role in health homeostasis. Previous microbiome work has shown that transmission of non-native microbes could alter hosts' microbial species diversity and community structure, which could positively or negatively influence the risk of pathogen colonization, and ultimately could be associated with disease (Grice & Segre, 2011). Conversely, a high level of microbial diversity within a host niche may confer protection against the acquisition of pathogen bacterial species and ultimately improve health outcomes (Chehoud et al., 2013; Rosenthal et al., 2011). This leads into the concept of the hygiene hypothesis or germ theory, which imparts that a broad range of exposures "train" developing immune systems to tolerate a variety of environmental allergens, reducing risk for inflammatory conditions, such as atopy, hypersensitivity disorders, and obesity (Strachan, 1989; Wold, 1998).

The hygiene hypothesis applies to the One Health concept, and AAI specifically, when

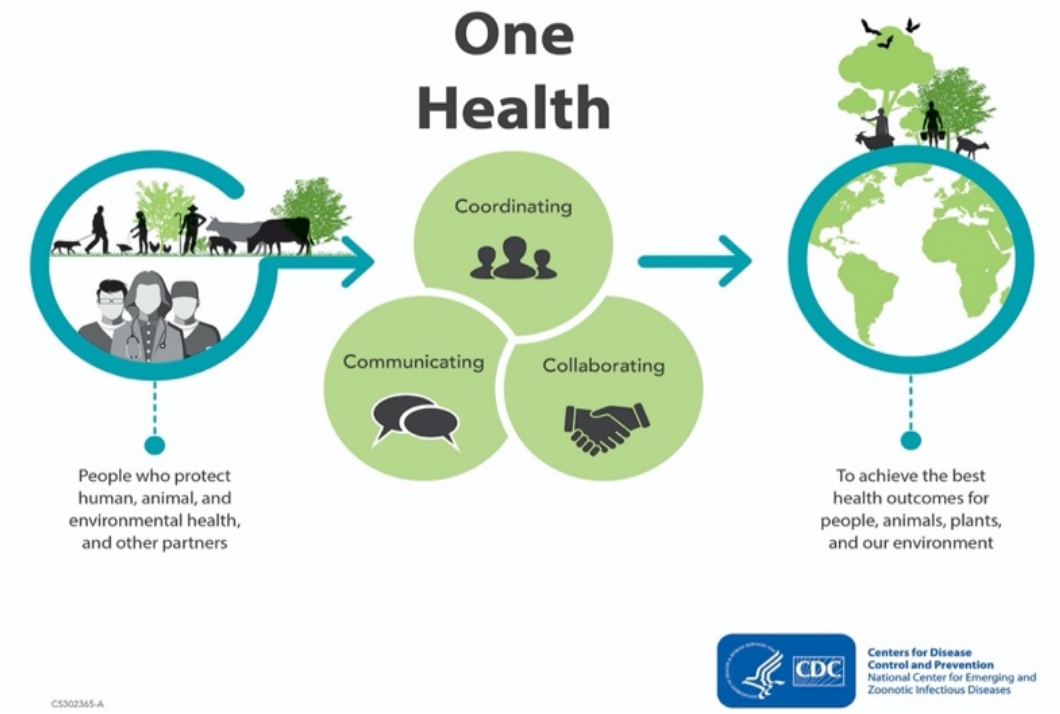
examining research surrounding the microbial shifts as a result of pet ownership. In addition to the mental and physical benefits of pet ownership described earlier as a rationale for AAI, there are also benefits of pet ownership through the mechanism of the microbiome. Pet ownership is associated with a composition of more unique microbiota that are more frequently shared between owners (Misic et al., 2015; Song et al., 2013). Following the hygiene hypothesis, early life pet exposure is associated a decreased incidence of these immune conditions and is best demonstrated where exposure to diverse microbes from farming environments, including animals, is protective against the development of asthma (Azad et al., 2013; Carlsen et al., 2012; Fall et al., 2015; Stein et al., 2016).

Qualitative Methods for One Health and AAI Studies

A key component of One Health research is the need to take a systems-thinking holistic approach to understand and address wicked problems. On the micro-scale, this relates to our broad understanding of microbial communities. On the macro-scale, this conveys the need to understand perspectives and opinions from multiple stakeholders. Collaboration and diversity are key components of the One Health framework (refer to the CDC image below). Understanding problems of a complex nature necessitates involving a diverse group of individuals, communities, organizations, and professional bodies. The use of qualitative research methods best embodies this multi-stakeholder engagement.

Qualitative research is the collection and analysis of unstructured and non-numerical data to examine events in their natural settings, attempting to interpret phenomena in terms of the meanings, experiences, and views of affected and effected populations. When performed well, qualitative methodologies can help One Health researchers develop impactful research questions, create more accurate and contextually relevant

parameters for quantitative studies, and produce policy recommendations and interventions attuned to the political and socio-cultural context of their implementation. Qualitative methods have already been successfully integrated into One Health-based studies, such as pet owners' vaccination reluctance and parasitic control programs (Bardosh et al., 2014; Wera et al., 2016), as well as the field of AAI to better understand the benefits to patients (Conniff et al., 2005; Pedersen et al., 2012; Shen et al., 2018).



1.2 Research Hypothesis and Specific Aims

The dynamic process of potential positive and negative consequences resulting from AAI necessitates a harmonized approach to understand the balance of zoonosis and microbial transmission, what could be considered a negative, and the positives associated with the human-animal bond. This is achieved through the utilization of the One Health framework. The goal of this dissertation is to take a systems-thinking approach to begin to understand the complex subtleties that occur during an AAI session by considering all potential pathways and stakeholders. This understanding is critical in order to identify best practices to improve AAI programs and enhance their utilization, the objective of this and future research.

Working towards this objective, *we hypothesize that the application of the One Health framework, both on the micro- and macro- scale, will increase understanding of AAI programs in healthcare settings in order to identify potential targets for improved program implementation*. We will test our hypothesis through two independent aims.

Aim 1: Identify Occupational Health Benefits and Concerns of Key Stakeholders Regarding Hospital-Based Animal-Assisted Intervention Programs

Aim 1 will address an urgent need to evaluate opinions of program safety and infection control policies from various occupational key stakeholder groups, as infection control concerns could challenge not only use but the effectiveness of AAI programs. This aim also seeks to understand the effectiveness of hospital-based AAI programs to reduce healthcare worker (HCW) stress, a leading occupational hazard in this cohort. To date, no research has evaluated the efficacy of AAI as a valid therapy to reduce stress in this

vulnerable yet essential worker population, as well as assess infection control beliefs and practices for professional personnel who work with hospital-based AAI programs. We will collect qualitative data on the knowledge, beliefs, and practices regarding occupational stress reduction and infectious disease risk mitigation strategies for AAI programs, from HCWs and therapy animal handlers. This work will inform future research efforts and contribute valuable knowledge to the appropriate and safe implementation of hospital-based AAI programs to ensure their sustainability as a beneficial resource in holistic health for occupational groups and patients.

Aim 1 Research Question:

Focusing on key stakeholders involved in hospital-based AAI programs, we identified knowledge, beliefs, and practices of 1) AAI program benefits for HCW occupational stress reduction and 2) concerns and control strategies for infectious disease transmission during AAI.

Aim 1 Objectives:

1. Characterize opinions of hospital-based AAI programs as an efficacious and effective occupational stress reduction intervention.
2. Elucidate concerns and current practices of infection control during AAI programs, and thoughts on novel interventions.

This work will contribute foundational evidence regarding the risk and benefits of AAI programs as a method to promote the health and well-being of patients and HCW. Results generated by this research project will begin to address a critical knowledge gap in the benefit and risk of increasingly frequent hospital AAI programs and raise awareness of AAI hazards and previously undescribed benefits. The disseminated results of this study will contribute rigorous scientific evidence to inform guidelines in the

utilization of AAI for stress management in an occupational setting. These guidelines will focus on improving the positive aspects of AAI, while considering interventions or strategies to minimize the potential risk from pathogens. This work will have important applications for AAI programs within a hospital setting and may even be extended for AAI in other occupational settings.

Aim 2: Characterize Microbiome Alterations of Patients and Therapy Dogs during Hospital Animal-Assisted Intervention Programs

Therapy animals may contribute both general non-native microbes and hospital-associated pathogenic ones to patients with whom they interact, both of which can alter human host microbiome. To date, no published studies have evaluated whether interactions among therapy dogs and patients in an AAI program can alter microbial communities in either. Understanding microbial sharing between pediatric populations and therapy animals, as well as associated factors that drive microbial transmission, has implications for both infection control measures and potential beneficial outcomes related to hospital AAI programs. For this aim, we collected microbial samples from pediatric patients, therapy animals, and the hospital environment, as part of a pilot study to understand the effectiveness of a canine decolonization as an infection control intervention.

Aim 2 Research Question:

Within the context of an infection control pilot study, we examined if the microbiome of patients and therapy animals will be altered after interaction during a hospital AAI session.

Aim 2 Objectives:

1. Quantify the degree of microbial sharing between therapy dogs and patients, and determine factors that modify this microbial sharing, namely contact level between the patients and therapy dogs.

2. Explore the effect of a therapy dog decolonization protocol on the therapy dog's microbiome.

3. Explore the effect of a therapy dog decolonization protocol on microbial sharing between therapy dogs and patients.

Understanding both the beneficial and detrimental aspects of microbial sharing between humans and therapy animals, and risk factors for altered sharing, will address safety concerns of hospital use of AAI programs. If we identify modifiable risk factors in patients or therapy dogs for negative microbial outcomes, these could be targets to address in order to improve the safety and sustainability of AAI programs and increase its utilization as a valid alternative patient therapy in the healthcare field. Findings will inform future research into whether exposure to animal microbes may benefit human microbiota or contribute to the correction of disease-state dysbiosis. This work will have implications for other studies that assess microbial sharing in the context of the human-animal bond and contribute to a foundational understanding of the dynamics of microbial profiles, which may be useful in the prevention and treatment of diseases in individuals in the future.

Dissertation Chapters that Address Each Aim

Chapters 2 and 3 are literature reviews and commentaries that provide further background and scope to this research field and highlight specific knowledge gaps as a rationale for this dissertation.

Chapter 4 describes stakeholder perspectives on AAI program barriers and facilitators for our qualitative Aim 1.

Chapter 5 is a targeted commentary, translating the qualitative results in Aim 1 to hospital administrators and infection control audiences.

Chapter 6 portrays microbial community shifts in the therapy dog as a result of the decolonization intervention (Aim 2.2).

Chapter 7 focuses on microbial sharing between patients and the therapy dogs, both of hospital pathogens and entire microbial communities, and explores factors that modifies this sharing in Aim 2.

Chapter 8, the conclusion, ties together all the original research within this dissertation as it relates to the set hypothesis and research goal. Each chapter uniquely and independently moves forward the state of knowledge on the positives and negatives of hospital AAI programs through the application of the One Health framework, with the purpose of preserving these beneficial programs.

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Chapter 2: One Health in Hospitals: How Understanding the Dynamics of People, Animals, and the Hospital Built-Environment Can Be Used to Better Inform Interventions for Antimicrobial-Resistant Gram-Positive Infections

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2.0 Cover Page

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2.1 Abstract

Despite improvements in hospital infection prevention and control, healthcare associated infections (HAIs) remain a challenge with significant patient morbidity, mortality, and cost for the healthcare system. In this review, we use a One Health framework (human, animal, and environmental health) to explain the epidemiology, demonstrate key knowledge gaps in infection prevention policy, and explore improvements to control Gram-positive pathogens in the healthcare environment. We discuss patient and healthcare worker interactions with the hospital environment that can lead to transmission of the most common Gram-positive hospital pathogens – methicillin-resistant *Staphylococcus aureus*, *Clostridioides* (*Clostridium) difficile,* and vancomycin-resistant *Enterococcus* – and detail interventions that target these two One Health domains. We discuss the role of animals in the healthcare settings, knowledge gaps regarding their role in pathogen transmission, and the absence of infection risk mitigation strategies targeting animals. We advocate for novel infection prevention and control programs, founded on the pillars of One Health, to reduce Gram-positive hospital-associated pathogen transmission.

Keywords

Infection prevention, infection control, hospital-associated infections, hospital environment, HAI interventions, One Health

2.2 Introduction

One Health approaches are based on the belief that we cannot truly understand human, animal, and environmental health by addressing each in isolation. In order to address complex public health challenges, we must understand the interconnectedness of these domains with a holistic methodology. Similar to other systems-thinking models, One Health focuses equally or more on the relationships between the factors in the system, rather than on the individual-level factors themselves.

The One Health paradigm has origins in the recognition that diseases often emerge from interactions of humans and animals, termed initially as “one medicine”, and incorporated preventative and public health. It has since grown to include environmental science and eco-health to encompass the shared environment role (Destoumieux-Garzon et al., 2018). The combined assessment of health risks across the three domains; humans, animals, and the environment; involves design and implementation of intervention strategies that address all three sectors with a goal to produce assimilated knowledge. The One Health concept has been successfully applied to fields such as emerging zoonotic disease outbreak investigation and biosecurity risk across humans and animals (Destoumieux-Garzon et al., 2018; Okello et al., 2014).

But how does One Health impact our healthcare system? Hospitals serve as an incubator that incorporates dynamic microbial inputs from the community from both people and animals, as illustrated in Figure 1. Antimicrobial use exerts selective pressure on these incoming microbial ecosystems, shifting to a higher prevalence of resistant organisms. Microbial ecosystems are defined for this paper as the composition, and the networks, of the entire microorganism population within a single niche or site. Individuals in the

hospital (both patients and employees) may become colonized with hospital-associated multidrug-resistant organisms (MDRO) and then are discharged back to the community, creating a cyclic feedback loop (Dulon et al., 2014; Patel et al., 2017; Xue & Gyi, 2012). Finally, MDRO acquisition and infection is more likely diagnosed in the hospital setting, resulting in the hospital serving as both a surveillance point and multiplier for resistant organisms and infections, which underscores the need to describe community and hospital-based risk factors that influence the hospital environment.

The application of One Health principles to hospital infection prevention and control has not been described previously. In the clinical setting, One Health can provide practical ways to incorporate environmental and animal contact considerations into patient care. While the concept has been endorsed by major medical and public health organizations, studies of physicians reveal limited awareness to the environmental health aspects of medical problems in the patient care settings, as well as low awareness levels about prevention or treatment of zoonotic diseases from animals (Allen, 2015; Hamilton et al., 2005). Therefore, the purpose of this review is to use a One Health lens to describe the relationship between the hospital environment and patient care specifically for Gram-positive hospital-associated pathogens, and to identify how animals fit into this relationship (Figure 1). A broad literature search was conducted to identify information relevant to the scope of this work, see Figure 2. Articles published prior to June 2019 were considered for review.

2.3 Hospital-Associated Gram-Positive Pathogens

Healthcare-associated infections (HAI) are an increasingly prevalent threat in the Unites States healthcare system. The Centers for Disease Control and Prevention's National Healthcare Surveillance Network (CDC-NHSN), a US surveillance system, estimates that about one in 31 hospitalized patients acquires an HAI (Centers for Disease Control and Prevention., 2017). This review focuses on Gram-positive bacterial pathogens, a significant cause of HAIs, which may survive longer on dry surfaces than Gram-negative bacteria (Barbut, 2015; Beard-Pegler et al., 1988). Methicillin-resistant *Staphylococcus aureus* (MRSA) was the first pathogen where spread through the hospital environment was documented, though targeted hospital efforts are contributing to its decline in the past decade (Centers For Disease Control and Prevention, 2019; Evans et al., 2017). It is relevant to One Health, as some MRSA strains and other multidrug-resistant staphylococci are associated with animals, livestock in particular (Larsen et al., 2015; Price et al., 2012).

The second most common hospital associated Gram-positive pathogen is *Clostridioides difficile* (genus recently reclassified from *Clostridium* (Lawson et al., 2016)). Rates of resistance and transmission depends on strain, with higher rates seen in the PCR ribotype 027 and 078 epidemic strains, and documented resistance to quinolones, clindamycin, rifamycins, erythromycin, chloramphenicol, tetracycline and even imipenem (McDonald et al., 2018). It is included in this review because it is the most common hospital-acquired infection pathogen (~500,000 infections annually with up to 30,000 deaths in the US) and antibiotic prescribing for other infections (such as MRSA) can be a risk factor for *C. difficile* infection; conversely treatment with the recommended

vancomycin protocol has been shown to lead to our third Gram-positive pathogen of concern (McDonald et al., 2018).

The third Gram-positive pathogen we cover in this review, of increasing concern as a hospital-associated pathogen, is vancomycin-resistant *Enterococcus* (VRE). While not credited with the same degree of pathogenicity as MRSA or *C. difficile*, VRE causes infections in vulnerable patients, including outbreaks that are difficult to control due to its resistance to routine cleaning. All three important Gram-positive pathogens are able to survive in the environment for days to months and have low infectious doses—as low as 5 spores (*C. difficile*) or 4 CFUs (MRSA)— where inadequate environmental approaches can pose an ongoing risk of transmission to hospital patients (Dancer, 2014).

2.4 The Hospital Environment

The Hospital Built-Environment

Critical to a One Health approach is the role of the environment, including the unique characteristics of the built environment. The built environment is defined as the infrastructure created by people for spaces where they live and work, with consideration for how physical properties of these buildings influence health (Dannenberg & Capon, 2106). The hospital environment can facilitate transmission of pathogens responsible for HAIs. The inanimate environment can be a MDRO reservoir (Mills, 2015; Rock et al., 2018), with environmental contamination responsible for approximately 10–30% of patient MDRO acquisitions (Anderson et al., 2017).

Table 1 summarizes select key studies on the role of the hospital environment in MDRO and other pathogen transmission. Contamination of high-touch surfaces with MDROs such as methicillin-resistant *Staphylococcus aureus* (Knelson et al., 2014; Lei et al., 2017), vancomycin-resistant *Enterococcus* (Knelson et al., 2014; Ray et al., 2002), and *Clostridioides difficile* (Sitzlar et al., 2013; Weber et al., 2010) for prolonged time periods has been well documented, and thus can serve as a potential reservoir for onward infections to patients and healthcare workers. Multiple studies have shown that there is higher HAI risk for patients who are in rooms that were previously occupied by an HAI-positive patient, even after routine cleaning and disinfection (Huang et al., 2006; Mitchell et al., 2015; Shaughnessy et al., 2011).

Aspects of the hospital's built-environment and design, including different surface materials, can influence microbial transmission. Plipat et. al. showed that MRSA may more easily and in higher burden contaminate porous surfaces, but when those

contaminated porous surfaces are touched by patients or healthcare workers they are less likely to transfer MRSA compared with non-porous surfaces (Plipat et al., 2013). Another example of hospital design is private versus open shared rooms. A review of over one million inpatient records from 335 US hospitals found a 10% increase in private rooms was associated with an 8.6% overall decrease in hospital-associated catheter infections (O'Neill et al., 2018; Stiller et al., 2016). Other hospital level risk factors for patient HAI acquisition include larger hospital size and higher patient density and clustering (Archibald et al., 1997; Davis et al., 2017a; Dickstein et al., 2016; Gohil et al., 2015; Ray et al., 2016; Sousa et al., 2018). Hospitals that are highly connected to one another through a shared health-care system or through a referral system have more patient MRSA bacteremia incidence rates (partial correlation coefficient r = 0.33 (0.28 to 0.38)) (Donker et al., 2012; Gibbons et al., 2016). Another key hospital design consideration is hospital-acquired pathogen strains may enter into the community through improperly treated hospital wastewater effluent, including MRSA and VRE (Hocquet et al., 2016), although discussion of this topic is beyond the scope of this paper.

Hospital Fomites

Inanimate objects within the hospital can frequently become contaminated with pathogens and serve as sources for contamination and potential colonization for individuals who come in contact with them. These important fomites can travel between hospital rooms and patients, serving as a mechanical vector in pathogen spread. Nearly any item in contact with skin can serve as a fomite in pathogen transmission, from wearables like white coats and ties to pens, medical devices, and mobile telephones. Hospital objects have been extensively sampled for pathogen carriage and colonization, with prevalence rates as high as 55% for stethoscopes, 52% for neckties, and 50% for

rings (Haun et al., 2016). Concise reviews of the major reservoirs have been published previously by the Centers for Disease Control and Prevention's "Guidelines for Environmental Infection Control in Health-Care Facilities" (Centers for Disease Control and Prevention., 2003) and in the International Society for Infectious Disease's "A Guide to Infection Control in the Hospital" (International Society for Infectious Disease, 2018). Other possible dissemination routes for pathogens, including. *S. aureus* and *C. difficile*, is airborne dispersion (Best et al., 2010; Gehanno et al., 2009; Roberts et al., 2008), promoting spread among the hospital environment and individuals.

The Hospital Microbial Ecosystem

However, human exposure to resistant pathogens occurs in the context of microbial ecosystems, and the hospital built environment can be a source for a number of other microorganisms that are less often pathogenic but can serve as potential reservoirs of resistant genes. A hospital microbiome can harbor a diverse set of antimicrobial resistance genes that are extremely relevant to human health, and these ultimately could be reflected in HAI rates. For example, there is evidence for frequent horizontal transfer of the mobile genetic element Staphylococcal Cassette Chromosome *mec* (SCC*mec*) gene, which encodes for methicillin resistance, between *S. aureus* and coagulase-negative *Staphylococcus* (Otto, 2013). Coagulase-negative staphylococci are not traditionally regarded as pathogenic, but share the same ecological niche in the human anterior nares, leading to the opportunity for horizontal gene transfer (Otto, 2013). Understanding other potential sources of antimicrobial-resistant genes is fundamentally important in combating and understanding MDRO epidemiology. Bacterial diversity also varies among different hospital areas – it has been shown that the halls, living rooms, patient rooms, and rest rooms exhibit more diverse bacterial compositions than that of the

isolated ICU (Lax & Gilbert, 2015). Different ICU management practices, including more rigorous sanitation protocols, could exert selective pressure and foster survival of microorganisms that express genes for resistance to common disinfectants and antimicrobial agents (Christoff et al., 2019).

Within the hospital built-environment, humans are a predominant source of colonizing microbes. Researchers found that bacteria in a patient room resembled the skin microbiota of the patient occupying the room and became more similar throughout the patient's stay (Brooks et al., 2014). Additionally, they reported that patients acquire microorganisms that were present in the room before patient admission, indicating transfer both ways between patients and the hospital environment of all microorganisms—not just pathogens (Brooks et al., 2014). This means that patients and hospital workers likely alter the hospital's microbial composition in the specific areas they occupy, resulting in unique micro-environments within the larger hospital. While this currently is an understudied research area, a better understanding of how microorganisms colonize, persist, and change in the hospital environment has the potential to elucidate major infection sources beyond attempts to focus on specific pathogens, and provide key insights into human health.

2.5 Human Factors

Patient Characteristics

Human factors are critical when assessing One Health in hospitals in the context of HAI transmission. According to some estimates, 5–10% of patients will develop an infection while in the hospital (Yokoe & Classen, 2008). Multiple studies have shown that around 10% of patients who enter hospitals are asymptomatically colonized with at least one type of MDRO, emphasizing the substantial influx of MDRO from community settings into the hospital (Chen et al., 2019). A mathematical model of hospital pathogen spread showed that increasing the patient MDRO prevalence at admission to 12%, or doubling the average length of hospital stay, almost tripled the predicted overall prevalence of MDRO-colonized patients within the hospital (D'Agata et al., 2012). Established factors associated with increased risk of nosocomial infection include prolonged antimicrobial therapy, comorbidity with chronic health conditions, compromised immune function, and close proximity to other patients infected or colonized with an MDRO (Xue & Gyi, 2012). Higher patient density, from both higher influx or longer length of patient stay, can increase direct contact rates between patients which could increase the probability of direct transmission of MDRO. In addition, because patients shed bacteria into their local environments, patient density can also increase contamination of the environment and environmental fomites, thereby increasing the indirect transmission of MDRO (Xue & Gyi, 2012). An increasing reservoir of MDRO through increases in patient admission or length of stay is important to address when assessing the efficacy of infection control interventions. If the reservoir of MDRO increases, then the benefits of preventive strategies may be minimized. Studies have shown higher prevalence of HAIs in hospitals within more densely-packed urban centers, hospitals in lower socioeconomic

neighborhoods, and hospitals in communities where the majority of residents are racial and ethnic minorities, independent of hospital risk factors (Bagger et al., 2004; David & Daum, 2010; Klevens et al., 2007; Morin & Hadler, 2001).

Patients are often prescribed antibiotics as part of their hospital care, occasionally untargeted and unnecessarily, as published reports have estimated that 23%-46% of antibiotic prescriptions are inappropriate (Buehrle et al., 2019; Fleming-Dutra et al., 2016; Gonzales et al., 2001; Lim et al., 2020; Ray et al., 2019; Sharland et al., 2019). This widespread antibiotic use places selective pressure on bacterial ecosystems, enhancing survival of bacteria with resistant genes. Such pressure has been shown to affect horizontal gene transfer rates between bacterial species (Davies & Davies, 2010). While most hospitals have antimicrobial stewardship programs that implement guidelines for judicious antimicrobial use, often antibiotic use is critical to patient care. This often creates an environment that is conducive to the persistence of resistant pathogens. It has been well-documented that selective pressure from antimicrobials increases the MDRO bacterial load colonizing patients, and that the higher bacterial load leads to greater patient skin and hospital environmental contamination (Donskey, 2013). Conversely, the absence of selective pressure from antimicrobials results in lower MDRO bacterial loads and leads to a lower likelihood of skin and environmental contamination (Schinasi et al., 2013). The genes from resistant bacteria can spread to the hospital environment and other individuals in the hospital, then spread to the greater community. Cycling of such strains from the community can be another route for re-entry into the hospital.

Role of Healthcare Workers

A primary transmission route of hospital-associated pathogens for patients is through contaminated healthcare workers (HCW). Thirty to forty percent of HAIs may be spread

by contaminated healthcare worker hands—hands that were contaminated either from direct contact with infected or colonized patients, or from their environment (Weber et al., 2010). Even without direct patient contact, healthcare workers can serve as vectors and spread pathogens between environmental surfaces throughout the hospital (Creamer et al., 2010). A meta-analysis and systematic review calculated that the pooled MRSA prevalence among HCW in non-outbreak settings was 4.4% (95% CI, 3.98%-4.88%), with nursing staff at increased risk for MRSA carriage; nursing staff had an odds ratio for MRSA colonization of 2.58 (95% CI 1.83-3.66) when compared with other healthcare staff (Dulon et al., 2014). While contamination is typically found on HCW hands, other wearable fomites, such as stethoscopes, digital devices, white coats, and neckties, can commonly be contaminated with bacterial pathogens including MRSA (Bearman et al., 2014; Haun et al., 2016). Studies have concluded that pathogen transmission from colonized patients to HCW gowns and gloves is substantial, particularly for those whose job duties involve high contact activities (Roghmann et al., 2015).

In addition to the potential role HCWs play as vectors, increasing the risk of colonization and infection to patients, there is also the occupational safety concern for infection to the workers themselves. Hospital employees serve a critical function in society; a decreased labor force due to illness from infectious disease can have detrimental economic consequences (Lui et al., 2018). In a 10-year study across Dutch hospitals, there were 17 reported MRSA outbreaks: 13 outbreaks involved HCWs, and in 8 cases HCW acquired MRSA infections despite following the current safety precautions, showing that HCWs are at risk as much or more so than the patients during these outbreak situations (Blok et al., 2003). Other occupational safety conditions, such as elevated stress, poor supervision and leadership, and weak communication networks, can increase

nosocomial pathogen spread (Stock et al., 2016). Increased patient density and overcrowding combined with understaffing may lead to failure of MRSA control programs through decreased HCW hand-hygiene compliance, increased patient and staff movement between hospital wards, and overburdening of screening and isolation facilities (Clements et al., 2008). Subsequently, high MRSA incidence leads to increased inpatient length of stay, which can exacerbate conditions of overcrowding and foster a feedback loop that perpetuates HAIs (Clements et al., 2008). Similar to patients, HCWs could play a more active role in community transmission due to the greater frequency of hospital exposure, although this hypothesis has not been tested.

In addition to patients and HCWs, a hospital receives many daily visitors who contribute to the microbial composition of the hospital environment. It is estimated that the prevalence of pathogen colonization, including Community-Associated MRSA (CA-MRSA), in healthy asymptomatic individuals ranges from 0.2 to 7.4% (Casey et al., 2013; Kim et al., 2018b; Turner et al., 2019). These studies showing higher prevalence rates in community visitors compared to common patient or HCW carriage rates may be partly due to success of infection prevention and control policies such as environmental cleaning and hand hygiene compliance in HCW and patients (DeLeo et al., 2010). Of note, individuals who visit the hospitals may be there for contractual service, such as for deliveries. Because these individuals are not considered employees of the hospital, they may not be as well trained on infection control measures nor may be subject to the infection control policies and practices that are job requirements of hospital-employed HCW. This is another understudied area in existing literature.

2.6 Animals in the Hospital

The final aspect of One Health that has received less attention in the context of hospital-associated pathogen control is the roles of animals. Table 2 summarizes selected studies that describe the relationship between humans and animals in the spread of infectious diseases. Animals are potential sources of pathogens, including ones commonly considered nosocomial, which can spread to humans. It has been documented in multiple studies that MRSA strains found in companion animals such as dogs and cats are identical to epidemic strains found in human hospitals (Leonard et al., 2006; Malik et al., 2006; O'Mahony et al., 2005). There are many ways that animals, and their corresponding and unique microbial ecosystems, can positively and negatively enhance transmission of infectious pathogens. Exposure to animals, from pets in the home to farm animal exposure, can increase an individual's overall microbial diversity, which can then be protective against colonization of opportunistic pathogens (Bai et al., 2016; Hogan et al., 2019; Zipperer et al., 2016). This balance of being both a supply and deterrent of human pathogen colonization is the reason why animals are so essential to examine in any context, including the hospital environment. Our understanding regarding direction of transmission, colonization persistence, animal-human transmission rate, animal carriage and inter-species transmission risk factors, and the significance of companion animals as reservoirs for human pathogens are all incomplete.

Pets in the Home

There have been numerous examples of microbial sharing between people and their pets in the household, and pet ownership is a risk factor to acquire, maintain and spread potential pathogenic bacteria. For example, Ferriera et. al. found, in 49 MRSA-infected

outpatients households, 4 cases of MRSA colonization in companion animals (8.2%), 3 of which shared PFGE patterns from their owners, and no MRSA positive pets in the negative human control households (Ferreira et al., 2011). That study also found a human who was infected with MRSA resided with a dog colonized with methicillin-resistant *Staphylococcus pseudintermedius*, a common veterinary pathogen in companion animals that occupies a similar niche as *S. aureus* and causes similar disease conditions in animals. It was hypothesized that SCC*mec* could have transferred between the related bacteria (Ferreira et al., 2011). Another study found similar findings; one of the 8 (12.5%) study households of MRSA-infected humans contained a MRSA-positive pet; conversely they also evaluated human colonization in homes with a MRSA-carrier pet and determined that over 25% (6/22; 27.3%) owners were MRSA-positive (Faires et al., 2009). This higher association of pathogen carriage for humans and pets in the same households, and the identification of indistinguishable MRSA isolates in both pets and humans in contact with them, strongly suggests interspecies transmission but it does not indicate the direction of transmission. However, given the preponderance of common human MRSA clones in household pets, it is possible that animals become contaminated through contact with colonized or infected humans and that they in turn serve as a source of re-infection or re-colonization (Harrison et al., 2014). Given that pets may clear carriage or contamination with removal from infected owners, veterinary guidance recommends contact isolation for household pets in the case of recurrent MRSA infection among humans in the household (Morris et al., 2017).

Pets in the Hospital

Animals can contribute to the hospital microbial ecosystems by directly entering the hospital. A patient may require a service animal, which according to the Americans with

Disability Act, have the legal right to enter the hospital. Therapy animals are employed in many healthcare settings and may visit multiple patients and visitors during their time in the hospital. Therapy animals are particularly important because they can visit multiple patients, multiple wards, and even multiple hospitals all within the same day (Dalton et al., 2018; Lefebvre et al., 2008a), indicating their potential as an effective mechanical vector in the spread of pathogens. Finally, some hospitals allow for periodic or routine visits from patients' personal pet(s) during inpatient care; in a survey of 337 SHEA member hospitals, 121 (36%) healthcare facilities allowed personal pet visitations, of which 7 (5.8%) did not have formal guidelines in place (Murthy et al., 2015). In addition, resident animals in healthcare facilities have been known to be vectors of hospital-pathogens, such as the case reports of a cat residing in a geriatric rehabilitation ward, or a nurse's visiting pet dog that were implicated as the sources of MRSA outbreaks (Cefai et al., 1994; Scott et al., 1988). Since then, few studies have evaluated zoonotic disease carriage of therapy animals living in or entering the hospital. Lefebvre et. al. found that 80 out of 102 (80%) asymptomatic therapy dogs who visited hospitals had a zoonotic pathogen positive fecal sample. The primary pathogen was *C. difficile*, which was isolated from 58 (58%) fecal specimens; 71% (41/58) of these were toxigenic and many were genotypically indistinguishable from the major strain implicated in ongoing outbreaks of highly virulent human *C. difficile* acute disease (Lefebvre et al., 2006a, 2006c). The group also identified that acquisition rates of MRSA and *C. difficile* were 4.7 and 2.4 times higher, respectively among therapy animals compared to household dogs, indicating their increased contact with hospitals could increase exposures to HAIs, similar to human risk factors (Lefebvre et al., 2009). Service animals, therapy animals, and personal pets will have different exposures, and thus have different microbial compositions. Just as patients can bring microbes into the hospital from the community,

animals can also serve as a vector between the hospital and community, and their unique microbial ecosystems could impact this vector function.

Food Animals

In addition to household pets, food animals, such as beef and dairy cows, poultry, and swine, each have unique microbial compositions and can influence pathogens circulating in the community and the hospital. Although the use of healthcare-prescribed antimicrobials in humans is an important risk factor in MDRO colonization in the population and environment, the use of antimicrobials in food animal production also contributes—at times substantially—to the reservoir of resistance (Silbergeld et al., 2008). Medically important antimicrobial drugs may be used in food animal production, as well as companion animal practice, contributing to selection for and emergence of pathogens resistant to specific drugs, including those of critical importance to human medicine. Food animal uses of antimicrobial drugs can influence the hospital environment indirectly via MDRO-contaminated meat or other food products, indirectly via exposure of community members who live in proximity to agricultural production, and directly via animal contact. For example, in a study matching MRSA-colonized incoming patient cases to non-colonized control patients, cases had over 4 times higher odds of living near swine-rearing facilities (Schinasi et al., 2014). Another study found that MRSA carriage in HCWs in contact with livestock is 10-fold higher than in other HCWs (Wulf et al., 2008). Similarly, patients exposed to pigs or veal calves in Denmark were shown to have three times higher incidence of MRSA colonization (van Rijen et al., 2008). Finally, in another study, 373 (9.7%) patients coming from a high-density farming region were MRSA-positive, which is similar to what is found in other non-rural settings, but 292 (78%) had livestock-associated MRSA strains rather than HA- or

general CA- strains (van de Sande-Bruinsma et al., 2015). For more detail, other reviews have been published which discuss the role of livestock and food agriculture operations in the spread of community pathogens (Goerge et al., 2017; McEwen & Collignon, 2018; O'Connor et al., 2017; Richter et al., 2015).

2.7 Interventions to Reduce Exposure

The challenge of complex microbial and pathogen inputs from community sources to the hospital environment—and the pathogen dynamics among individuals who are treated, visit, and work within this setting—requires an integrative perspective to design interventions to reduce the risk of human exposure, colonization, and infection. Therefore, focusing on individuals by themselves or a single type of MDRO may provide incomplete answers. Microbes, including pathogens, circulate between the hospital environment and the larger community, with individuals and animals serving as mechanical vectors. Most interventions are designed to target only one sector, but multimodal strategies may be more successful to break this cyclic feedback loop. Addressing the hospital environment and animal sectors can reduce human exposure of microbes and pathogens, and human-focused interventions can reduce colonization risk. We will discuss interventions within each One Health domains, as shown in Figure 3, and their effectiveness to address community-level factors and patient infectious outcomes. For this review, effective interventions are defined as those which reduce or nullify exposure or colonization risk yet are feasible to implement in a clinical setting, using the CDC NIOSH's (National Institute of Occupational Safety and Health) Hierarchy of Controls as a strategy for ranking the effectiveness of interventions, as shown in Figure 4, where those grouped in the top of the graphic are potentially more effective and protective than those at the bottom. For MDRO control, elimination or substitution, the most effective forms of prevention against hazards would equate to elimination of the source of pathogen, such as creating policies that control animals into the hospital, thus limiting the risk of "sick" animals potentially carrying zoonotic MDRO into the hospital. Engineering and administrative controls, such as changing hospital

design or altering hospital safety culture, can be effective but do not nullify the exposure hazard. Personal protective equipment (PPE), such as gloves and gowns, are the most simplistic form of control measures, as they rely heavily on human motivation and are prone to human error, so should not be the sole means of infection control, as evident by multiple studies showing variance in PPE compliance (Ganczak & Szych, 2007; Harrod et al., 2019; McGovern et al., 2000; Michalsen et al., 1997).

Hospital Interventions

Interventions targeted at the environmental sector have been shown to have downstream benefits on the microbial carriage and colonization of humans (Dancer, 2009; Dettenkofer et al., 2004; Sitzlar et al., 2013). In the literature, interventions targeting the hospital environment are centered on "hands-on" manual cleaning/disinfection protocols and "no-touch" decolonization technologies and isolation through facility or administrative design or through other engineering controls. Cleaning with detergents has been shown to reduce MRSA levels that exist in the healthcare environment; however, detergents can be inferior at killing microbes compared to disinfectants, and cleaning products can become contaminated, furthering the spread of pathogens in the hospital (Dharan et al., 1999; Rutala & Weber, 2001). Disinfectants, while shown to decrease bacterial burden on a surface, can also release toxic fumes and can cause allergic and hypersensitivity reactions in HCW, which may limit the feasibility of increased use (Quinn et al., 2015; Rutala et al., 2008). Cleaning activities are behaviors and therefore may be more effective when monitored, either by direct observation, which is relatively easy and inexpensive but susceptible to human error, or with fluorescent markers, which offer an objective assessment of residual contamination after cleaning (Hota et al., 2009; Snyder et al., 2013). A number of studies suggest that targeted

cleaning focused on highly-touched common fomites is more effective than general cleaning, not only in efficacy of actual decontamination but also in effectiveness, since this intervention is feasible to implement frequently (Lei et al., 2017; Plipat et al., 2013). However, there are limitations to typical cleaning procedures. Microbial properties of organisms, including biofilm development, can make them more resistant to detergents, and even common disinfectants (Pidot et al., 2018; Vickery et al., 2012). A randomized controlled study that evaluated increasing daily cleaning frequency and targeted disinfection showed only modest decreases in patient VRE infections (relative risk 0.63, 95% CI 0.41–0.97, p=0.034), and no changes in the incidence of *S. aureus* bacteremia (RR 0.82, 0.60–1.12, p=0.22) or *C. difficile* infection (RR 1.07, 0.88–1.30, p=0.47) (Mitchell et al., 2019). This indicates that cleaning itself is imperfect, possibly prone to human error. This is best captured in a natural experimental study by Vietri et. al., which found that a hospital move and adoption of radical new cleaning procedures did not result in a statistical decrease for MRSA colonization rates in patients and HCW (Vietri et al., 2004).

"No-touch" technologies include decolonization strategies that may be less prone to human error. These include UV irradiation, which has been shown to be effective as a terminal disinfectant process after initial cleaning preformed to remove debris, but was seen to vary substantially based on location in a room relative to the UV device (Boyce et al., 2016; Rock et al., 2016). In addition to patient isolation rooms, aspects of the hospital built-environment design can contribute to infection control. Chiefly, certain surface materials have antimicrobial properties, although these have been found to be variable (Chyderiotis et al., 2018). Kim et. al found that the use of titanium dioxide-based photocatalyst antimicrobial coating on common environmental touch surfaces significantly decreased MRSA acquisition rates in hospital patients (hazard ratio of

contracting hospital-acquired pneumonia during the intervention period compared to baseline period: 0.46; 95% confidence interval 0.23–0.94; p = 0.03) (Kim et al., 2018a). Other no-touch environmental interventions include aerosolized hydrogen peroxide vapor, HEPA-filtration systems, and negative-pressure rooms, which minimize aerosolized microbes and have been shown to be effective against MRSA and *C. difficile* (Boswell & Fox, 2006; Falagas et al., 2011; Farbman et al., 2013). If utilized, it is recommended these strategies are used as adjuncts to best cleaning and disinfection practices. Unanswered questions remain – when to use disinfectants versus detergents, when to focus on no-touch decontamination processes versus hands-on manual cleaning, and how best to monitor interventions and measure their effectiveness.

Human Interventions

Human-centered interventions reported in the literature have focused primarily on hygiene: patient decolonization, HCW hand hygiene, and wearable fomites decontamination. A meta-analysis evaluating patient washing with chlorhexidine washcloths and wipes in a hospital setting identified a total HAI rate reduction (odds ratio (OR): 0.74; 95% confidence interval (CI): 0.60-0.90; p = 0.002), although studies had moderate heterogeneity (I(2) = 36%) (Afonso et al., 2013). This effect was more evident in the Gram-positive subgroup (OR: 0.55; 95% CI: 0.31-0.99; p = 0.05) (Afonso et al., 2013). HCW hand-hygiene campaigns are a major component of multi-faceted infection control interventions, and a separate meta-analysis showed it had the strongest effectiveness for reducing nosocomial infection rates (median effect 49%, effect range 12.7–100%) compared to other interventions (Murni et al., 2013). However, hand-hygiene campaigns alone had a modest effect size. Other facets of a bundled infection prevention and control bundle include antibiotic stewardship, another key pillar of

human-centered infection control (Murni et al., 2013). Part of this may be due to the imprecise relationship between HCW's risk perceptions and how these perceptions affect their use of risk-mitigating strategies. In fact, demographic, individual and organizational factors, including management structures, were found to influence risk perceptions and HCW's adoption of infection control strategies (Murni et al., 2013). Studies that have evaluated reasons for this disparity and ways to improve behavior to prompt adequate hand-hygiene protocol addressed determinants of knowledge, awareness, action control, and facilitation of behavior. Fewer studies addressed social influence, attitude, self-efficacy, and intention, but the study authors found that addressing combinations of different determinants showed better results (Huis et al., 2012). Increased surveillance and targeted interventions against those colonized have been shown to be effective in some circumstances (van Rijen & Kluytmans, 2009; van Trijp et al., 2007). However such strategies have not been sufficient to control outbreaks in other situations (Kurup et al., 2010; Peterson et al., 2010; Pierce et al., 2017) and are generally not recommended due to the high resource burden (Weber et al., 2007). Contact precautions and isolation of patients known to be colonized with target pathogens has also been shown to be effective, although this is not a substitute for proper hygiene protocols (Mangini et al., 2007).

A recent advance in human-centered interventions is the adoption of human factors engineering, which is a discipline that studies the capabilities and limitations of humans and the design of devices and systems for improved performance. In the context of hospital infection control, this deals with designing spaces and opportunities for individuals to avoid exposure and colonization to pathogens, a form of administrative control. This has the potential to identify major underlying causes and contributors to a problem. It goes beyond education and training, which are often the focus of infection

prevention interventions, to modify an individual's context so that default decisions align with healthy and desired actions. It utilizes environmental design, such as handwashing or antiseptic alcohol stations at the exits of patient rooms and one-way human traffic flows, in a way that minimizes exposure to healthcare workers and other patients to effect downstream reductions in the contamination of other hospital surfaces and individuals (Stiller et al., 2016). This relies heavily on proper leadership for both implementation and oversight. Human factors engineering systems models with audit and feedback, when applied, can increase effective room cleaning and disinfection, decreasing bacterial bioburden in the patient room (Rock et al., 2019a, 2019b). An example of this is the addition goal setting and HCW engagement, resulting in a hospital safety climate, was associated with improved compliance (pooled odds ratio 1.35, 95% confidence interval 1.04 to 1.76; I(2)=81%) compared to the standard of training and education, observation and feedback, and reminders (Luangasanatip et al., 2015).

Animal Interventions

Just as animals have not been extensively examined in their role as vectors of pathogens and other microbes, there are also few studies on interventions in animals in either a hospital or community setting. Just as intervention programs focus on hand hygiene protocols in HCW because of their role as vectors of hospital-associated pathogen transmission between patients and the hospital environment, therapy and service animals may also fill a similar niche, but infection control programs that target animals in healthcare settings are lacking (Murthy et al., 2015). There are recommended guidelines for animals entering into the hospital environment (service animals, therapy animals, personal pet visitations) (Lefebvre et al., 2008a; Murthy et al., 2015), but the evidence of the recommended protocols' effectiveness is based largely on extrapolation

from human data and many recommended interventions have not been validated in animals. Numerous documents on the control of MRSA in people have been published (Centers For Disease Control and Prevention, 2019; Dancer, 2014), and many of the principles may be applied to control in animals. However, caution should be exercised in extrapolating guidelines for MDRO control in people to animals because there may be significant differences in disease epidemiology (Morris et al., 2017; Weese et al., 2004). Because of their unique microorganism ecosystems and their role as an interactive fomite – a living moveable system independently interacting with individuals and its environment – controls focused on inanimate environmental surfaces may not be effective for animals that enter the hospital or such strategies may result in unintended effects.

While antimicrobial stewardship in human medicine has been shown to decrease HAI prevalence in patients (Barlam et al., 2016), in a four-year study across Australia, the level of antimicrobial exposure in dogs and cats was less than half that for human exposure, and critically-important antimicrobials accounted for only 8% of all the antimicrobials prescribed over the study period (Yvonne et al., 2018), so improvement of judicious use of antimicrobials in companion animals may not yield many benefits in some settings. At present, no controlled studies have been conducted to provide data on key questions such as transmission between animals and humans in the hospital, and efficacy of decolonization procedures in animals. Further research is needed in interventions within this One Health domain. For future studies that adopt a One Health approach to evaluate transmission pathways to patients that involve consideration of human, animal, and environmental reservoirs, relevant checklists for study conduct and reporting exist (Davis et al., 2017b; Sargeant et al., 2016).

2.8 Discussion

In this review, we have used a One Health framework to discuss the importance of addressing the hospital environment, the individuals who are treated, work, and visit the hospital, and the animals that directly and indirectly contribute microbial ecosystems, in the prevention and control of hospital-associated pathogens. Hospitals are located within human and animal communities, and the microbial ecosystems of the hospital can be influenced by community-level factors, from individuals who enter the hospital that serve as vectors in the spread of microbes, including pathogens, between the hospital and community. Animals who enter the hospital can also serve in this role and may have altered vector function based on their unique microbial composition, which will be different based on the role they serve (service animals vs. therapy animal vs. personal pet). Antimicrobial pressure in hospitals can be an incubator for MDRO; the cyclic loop between the hospital and community then will continue to foster resistant microbial ecosystems over time.

We have examined current interventions targeted at the hospital environment and to the patients and HCW in the hospital, and the efficacy and drawbacks of each. It has been shown that the most effective intervention programs are multi-modal and designed to minimize individual pathogen exposure before such exposure progresses to colonization and infection. However, environmental decontamination and human hygiene practices decrease but do not eliminate the risk of colonization in other individuals and HAI rates seen in the hospital. A One Health approach may assist in the development of novel research and multi-modal intervention approaches by considering the relationship between the patient, the HCWs, and the hospital environment, and the role of the community. This includes known community-level risk factors for MRSA colonization in

patients, such as pet ownership or living in an animal agriculture community (Leonard et al., 2006; Malik et al., 2006; Rodrigues et al., 2018; van de Sande-Bruinsma et al., 2015).

The largest knowledge gap this review exposed was the lack of data within the animal One Health domain. Little research has been done to explore pathogen transmission between animals and humans, within a home or hospital setting, and no studies have looked at the role of decontamination of the animal sector to see if this minimizes bacterial burden on the animal and has downstream effects on reduced transmission to individuals in contact. Compounding this is the need to understand microbial ecosystem dynamics in the context of hospital spread, particularly as such dynamics relate to microbial ecosystems unique to animals or humans, and how such ecosystems may even provide protection against the acquisition of pathogens through the sharing of potentially "beneficial" commensal microorganisms (Ege et al., 2011; Song et al., 2013; Trinh et al., 2018).

Conclusions

The complexities of hospital infection control deserve the joint focus of various disciplines. An integrated approach is needed to guide both research pathways and public policy mediations. Utilizing a One Health framework in this brief review allowed us to visualize key gaps in the current knowledge base surrounding hospital infection control and can help direct future research and implementation efforts by suggesting opportunities for advancement in non-traditional conduits.

2.9 Tables and Figures

Table 1: Key Studies that Examine the Role of Environment in Patient Infectious Disease Outcomes

Relation	Organism	Comments	Reference
Increased Acquisition			
ENV -> Patient	MRSA	Outbreak of MRSA in hospital that lasted two years was found in hospital dust with the same genotype.	(Rampling et al., 2001)
ENV -> Patient	Not specific	Patients assigned to shared bay rooms had a 21 percent greater relative risk of a central line infection (p = 0.005), compared with patients assigned to private rooms. At the hospital level, a 10% increase in private rooms was associated with an 8.6% decrease in central line infections (p<0.001), regardless of individual patients' room assignment.	(O'Neill et al., 2018)
ENV -> Patient	MRSA	Three of 26 patients who acquired MRSA while in the intensive care unit acquired MRSA from the environment; strains from the patients and their immediate environment were indistinguishable	(Hardy et al., 2006)
ENV-> HCW	VRE	Contact with contaminated surfaces in the rooms of colonized patients results in transfer of VRE to gloved hands, despite cleaning with disinfectants	(Ray et al., 2002)
ENV -> HCW	*C. difficile*	Increasing levels of environmental contamination was positively associated with increasing amounts of *C. difficile* on the hands of healthcare workers, particularly for environmental sites that patients touch	(Verity et al., 2001)
Patient -> ENV	*C. difficile*	Surfaces in rooms exposed to a *C. difficile* patient had significantly increased odds of being contaminated with *C. difficile*, compared to surfaces in unexposed patient rooms	(Faires et al., 2013)
Patient -> HCW	MRSA	Two-thirds of staff enter a room containing an MRSA patient will acquire the patient's strain on gloved hands or apron, even without touching patient directly (40%)	(Boyce, 2007)
Patient -> Patient	MRSA, VRE	Admission to a room previously occupied by an MRSA-positive patient or a VRE-positive patient significantly increased the odds of acquisition for MRSA and VRE.	(Huang et al., 2006)
Patient -> Patient	*C. difficile*	Prior room occupant with CDI was a positive risk factor for new patient CDI acquisition, hazard ratio 2.35 p = .01	(Shaughnessy et al., 2011)

Patient -> Patient	Several (MRSA, *C. difficile*, VRE)	Pooled acquisition odds ratio of 2.14 (95% confidence interval (CI), 1.65e2.77) for several bacteria from prior occupants, Gram positive 1.89 (95% CI: 1.62–2.21)	(Mitchell et al., 2015)
Patient -> ENV -> HCW	MRSA	In the colonized patient's room, HCW exposure occurred more predominantly through the indirect (patient to surfaces to HCW) mode compared to the direct (patient to HCW) mode.	(Plipat et al., 2013)
Cleaning/Removal Reduces Human Acquisition			
ENV -> Patient	MRSA	Enhanced cleaning during an outbreak decreased the number of new affected patients, stopped outbreak, and saved an estimated £28,000.	(Rampling et al., 2001)
ENV -> Patient	General	Lower infection rates associated with routine disinfection of surfaces (mainly floors)	(Dettenkofer et al., 2004)
ENV -> Patient	*C. difficile*	Daily disinfectant high touch surfaces and dedicated cleaning staff reduced CDI positive cultures by 60%	(Sitzlar et al., 2013)
ENV -> Patient	*C. difficile*	Hydrogen peroxide vapor decontamination reduced CDI rate by 37%	(Manian et al., 2013)
ENV -> Patient	VRE	Hydrogen peroxide vapor reduced VRE by 80%	(Passaretti et al., 2013)
ENV -> Patient	MRSA	Reduction in acquired MRSA infections with enhanced targeted cleaning compared to routine cleaning, despite higher MRSA patient-days and bed occupancy rates during enhanced cleaning periods (P = 0.032: 95% CI 7.7%, 92.3%). Genotyping identified indistinguishable strains from both hand-touch sites and patients	(Dancer et al., 2009)
ENV -> HCW	VRE	Decreasing VRE contamination of environmental surfaces decreases hand colonization of VRE and VRE acquisition rates	(Hayden et al., 2006)

MRSA = methicillin-resistant *Staphylococcus aureus*, CDI = *C. difficile* infection, VRE = vancomycin-resistant *Enterococcus*, ENV = hospital environment, HCW = healthcare worker

Table 2: Selected Studies on Potential Transmission of Pathogens between Humans and Animals in Various Settings

Organism	Comments	Reference
Ecological		
MRSA	MRSA strains found in companion animals such as dogs and cats are identical to epidemic strains found in human hospitals	(Leonard & Markey, 2008)
MRSA	Resistance patterns and genetic make-up of MRSA isolates from dogs and cats are generally indistinguishable from the most prevalent hospital-associated MRSA strains in the human population	(O'Mahony et al., 2005)
MRSA	Increase in companion animal MRSA, including MDRO, same clonal lines as CA&HA-MRSA	(Couto et al., 2016)
MRSA	Phylogenomic analyses showed that companion animal isolates were interspersed throughout the epidemic MRSA pandemic clade and clustered with human isolates from the United Kingdom suggesting a human source for isolates infecting companion animals	(Harrison et al., 2014)
Pet Ownership		
MRSA	Transmission of MRSA occurs between humans and companion animals and vice versa	(Malik et al., 2006)
MRSA	Identification of indistinguishable MRSA isolates in both pets and humans in contact with them	(Baptiste et al., 2005)
MRSA	MRSA was found in pets from MRSA-positive owners in 4/49 (8.2%) vs. none of the pets of the 50 uninfected human controls. ¾ of these pairs had concordant PFGE pattern	(Ferreira et al., 2011)
MRSA	MRSA-infected animal was initially identified, at least one MRSA-colonized person was identified in over one-quarter (6/22; 27.3%) of the study households. By contrast, only one of the 8 (12.5%) study households of MRSA-infected humans contained a MRSA-colonized pet	(Faires et al., 2009)
Enterococcus	76% of the isolates from companion dogs had belonged to hospital-adapted clonal complex, screening of 18 healthy humans living in contact with 13 of the dogs under study resulted in the identification of a single, intermittent carrier. This person carried one of the sequence types recovered from his dog	(Damborg et al., 2009)
MRSA	Identical strains from both pets and their owners were identified. Typical livestock-associated *S. aureus* lineages were observed in humans and/or companion animals and hospital and/or community-acquired *S. aureus* lineages were detected among pets.	(Gomez-Sanz et al., 2013)
C. difficile	PFGE patterns of some dog and human *C. difficile* isolates were over 90% similar	(Kwon et al., 2012)

Livestock		
MRSA	373 (9.7%) patients coming from a high-density farming area were positive for MRSA, 292 (78%) had livestock-associated MRSA strains and 81 (22%) non-LA-MRSA strains	(van de Sande-Bruinsma et al., 2015)
MRSA	Patients exposed to pigs or veal calves were shown to have 3 times higher incidence of MRSA colonization	(van Rijen et al., 2008)
MRSA	MRSA carriage in HCWs in contact with livestock is 10-fold higher than in other HCWs	(Wulf et al., 2008)
Hospital		
MRSA	Dog was implicated as a reservoir for the re-infection of two nurses after their treatment to eliminate carriage of MRSA	(Cefai et al., 1994)
MRSA	Cat residing in a geriatric rehabilitation ward was implicated as the source of MRSA for nurses and patients	(Scott et al., 1988)
MRSA, *C. difficile*	Zoonotic agents were isolated from 80 out of 102 (80%) dogs who visit hospitals, primary pathogen was *Clostridium* [sic] *difficile*, which was isolated from 58 (58%) fecal specimens, Seventy-one percent (41/58) of these isolates were toxigenic	(Lefebvre et al., 2006c)
MRSA	Acquisition of MRSA by a pet therapy dog that had visited an elderly care ward in a healthcare facility	(Enoch et al., 2005)
MRSA, *C. difficile*	Rates of acquisition of MRSA and *C. difficile* were 4.7 and 2.4 times as high, respectively, among dogs that visited human health-care facilities, C. dif. 4% was toxigenic, MRSA hospital origin clone	(Lefebvre et al., 2009)
C. difficile	Canine fecal isolate from healthy dog who visits hospitals was indistinguishable from the major strain implicated in outbreaks of highly virulent CDAD, which were occurring at increased frequency in the facility around the time the dog's fecal specimen was collected	(Lefebvre et al., 2006a)
Veterinary Hospitals		
MRSA	Cluster of five canine postoperative wound cases infected with MRSA were found to be associated with asymptomatic carriage of MRSA in one of the attending veterinary surgeons. The human and canine isolates were corresponded to the predominant epidemic strain prevalent in hospitals at this time	(Leonard et al., 2006)
MRSA	MRSA was isolated from 16% (14/88) of household contacts or veterinary personnel and in all 6 identified cases at least one human isolate identical to the initial animal isolate was found.	(Weese et al., 2006)
MRSA	Comparison of genetic markers shows that identical or very similar strains disseminate among animals and veterinary personnel. Companion animals harbor PVL-positive clones - Twenty-six pets and five veterinary personnel carried PVL-positive S. aureus	(Drougka et al., 2016)

MR Staph	Risk factors for nasal colonization by MRS in healthy humans: (i) being a veterinary professional (veterinarian and veterinary nurse) ($p < 0.0001$, odds ratio [OR] = 6.369, 95% confidence interval [CI, 2.683-15.122]), or have contacted with one MRSA- or MRSP-positive animal ($p = 0.0361$, OR = 2.742, 95% CI [1.067-7.045]	(Rodrigues et al., 2018)
MRSA	One veterinary nurse, who carried Panton Valentine leucocidin-positive ST338 MRSA, also owned a ST749 MRSP-positive dog	(Worthing et al., 2018)
MRSA	MRSA was isolated from 14 staff (17.9%), four dogs (9%), and three environmental sites (10%), which all had the same PFGE pattern.	(Loeffler et al., 2010)

MRSA = methicillin-resistant *Staphylococcus aureus*, *C. difficile* = *Clostridioides difficile*, HCW = healthcare worker

Figure 1: Interaction of Humans, Animals, Hospital Environment, and the Community in Hospital-Associated Pathogen Transmission

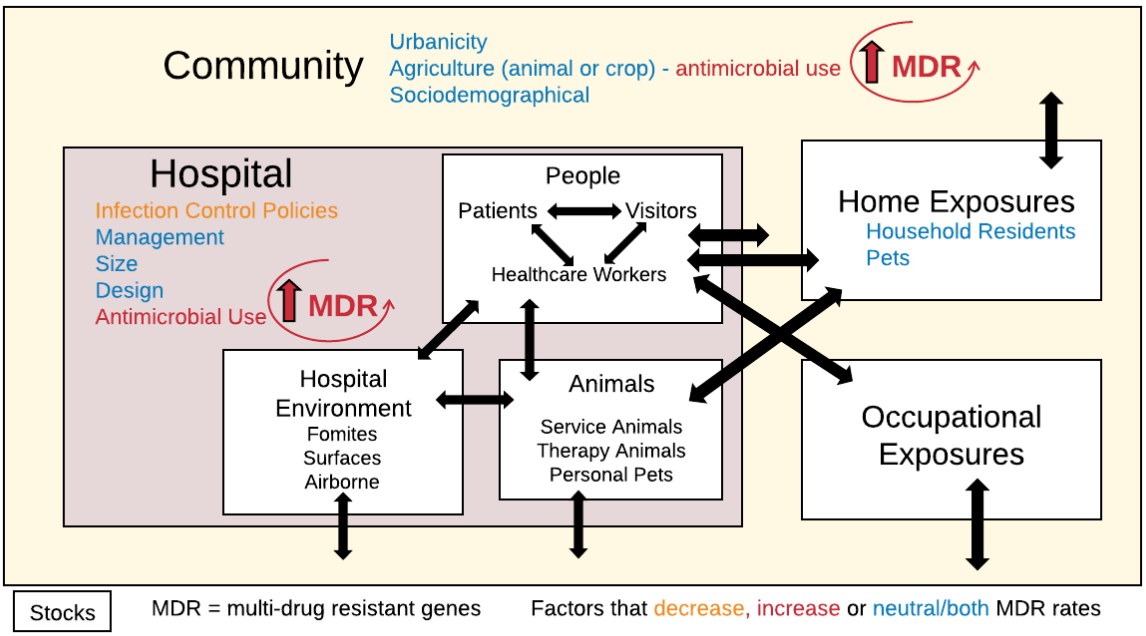


Figure 2: Literature Search Methodology

Databases:
- PubMed
- EMBASE
- Scopus
- Web of Science
- CINAHL

Search Terms: (adjusted based on database)
- Hospital or Healthcare AND
- Infection Control or Policy OR
- Multi-drug Resistant Organisms OR
- Pathogens OR
- Hospital-Associated Infections/Pathogens OR
- MRSA or VRE or C. difficle OR
- One Health

Figure 3: Examples of Infection Prevention and Control Strategies within the One Health Domains

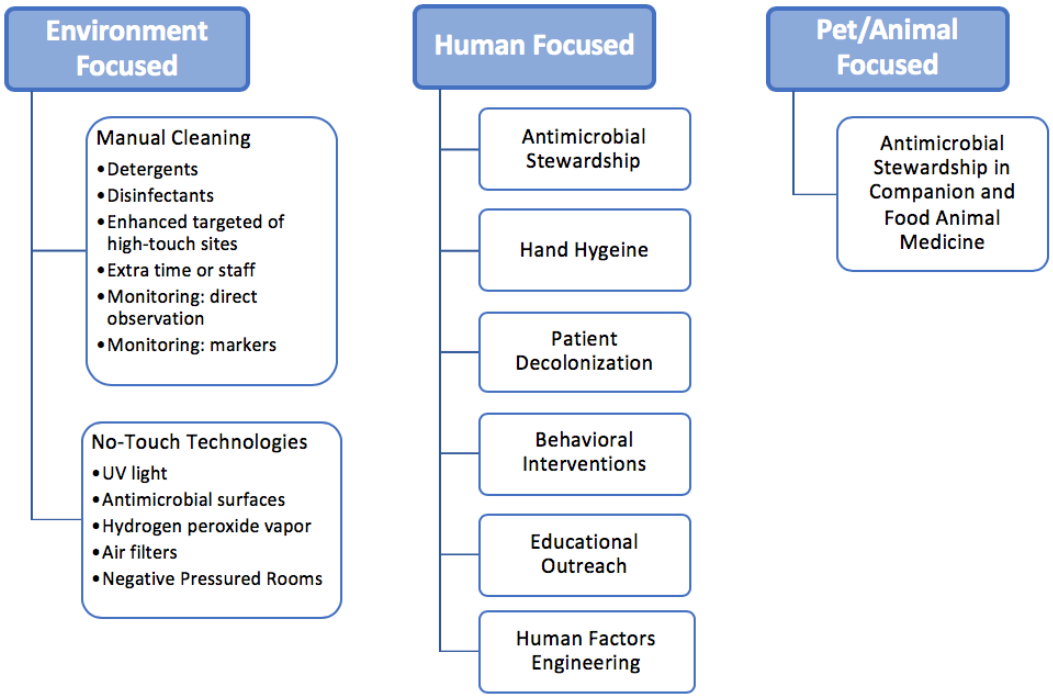
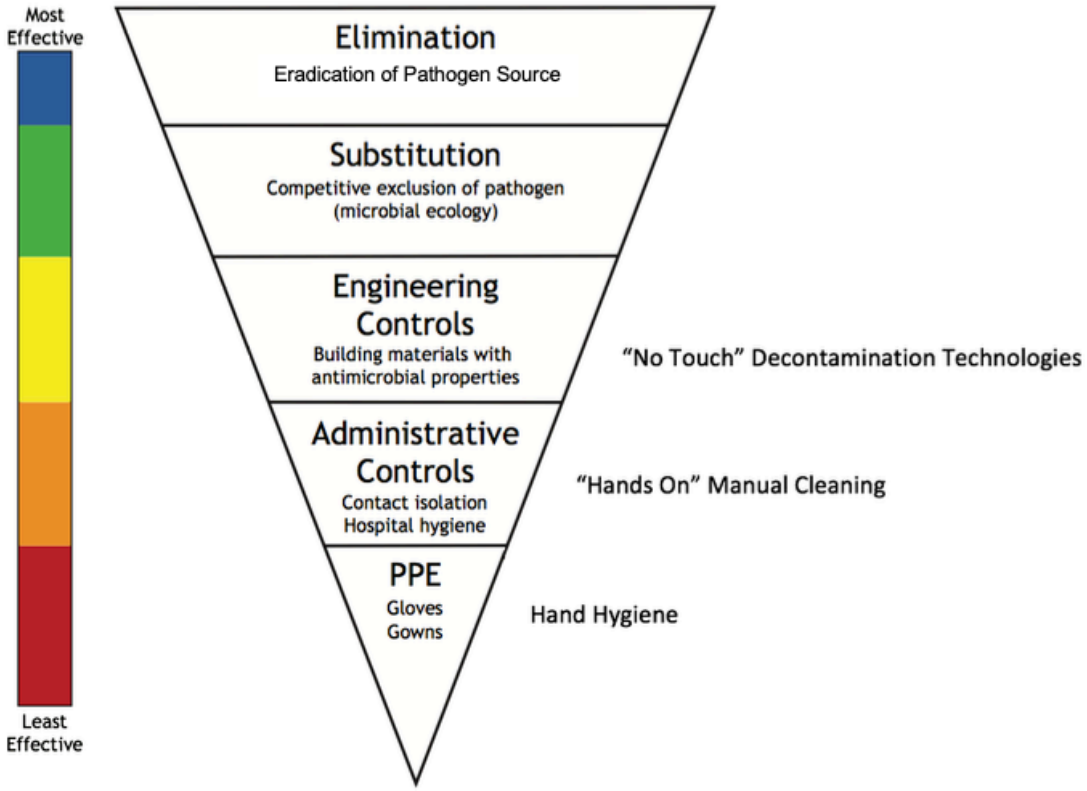


Figure 4: How Infectious Disease Intervention Strategies relate to the Hierarchy of Controls



Legend: Adapted from the National Institute for Occupational Safety and Health (NIOSH, www.cdc.gov/niosh/topics/hierarchy); PPE: personal protective Equipment

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Chapter 3: Risks Associated with Animal-Assisted Intervention Programs: A Literature Review

3.0 Cover Page

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3.1 Abstract

The benefits of animal-assisted interventions (AAI), to utilize companion animals as an adjunctive treatment modality, is well-established and a burgeoning research field. However, few studies have evaluated the potential hazards of these programs, such as the potential for therapy animals to transfer hospital-associated pathogens between individuals and the hospital environment. Here we review the current literature on the possible risks of hospital-based AAI programs, including zoonotic pathogen transmission. We identified twenty-nine articles encompassing reviews of infection control guidelines and epidemiological studies on zoonotic pathogen prevalence in AAI. We observed substantial heterogeneity in infection control practices among hospital AAI programs. Few data confirmed pathogen transmission between therapy animals and patients. Given AAI's known benefits, we recommend that future research utilize a One Health framework to evaluate microbial dynamics among therapy animals, patients, and hospital environments. This framework may best promote safe practices to ensure the sustainability of these valuable AAI programs.

Keywords: Animal-assisted interventions; zoonotic infections; hospital-associated infections; hospital infection control

Highlights:

- Despite the many benefits of animal-assisted interventions (AAI) for patients, there is a risk of therapy animals becoming vectors of hospital pathogens.
- There is an absence of literature on transmission of hospital pathogens between patients and therapy animals during an AAI session.
- More research is needed to improve the safety and utilization of this important adjunctive therapy.

3.2 Introduction

The emotional benefits of human-companion animal relationships are well established in the scientific literature (Serpell, 1996). This concept has extended into the development of animal-assisted interventions (AAI), in which visiting animals participate as an adjunctive treatment in holistic patient care. AAI programs are increasingly popular in various healthcare settings and utilized for patients with widely diverse conditions, including mental health disorders and cancer. Research into the benefits of AAI continues to expand, with the many advantages of these programs supported by numerous epidemiological studies and meta-analyses that standardize and integrate these findings. These data support the hypothesis that AAI programs reduce patient stress, pain, and anxiety levels when incorporated into patients' treatment plans (Bert et al., 2016; Kamioka et al., 2014; Lundqvist et al., 2017; Maujean et al., 2015; Serpell et al., 2017).

However, infection control is a persistent problem in healthcare settings, both in routine care and in the use of complementary therapies. Similar to known fomites in hospitals, such as door handles and clinicians' stethoscopes (Haun et al., 2016), therapy animals may unwittingly serve as mechanical vectors of hospital-associated pathogens, and contribute to the transmission of these pathogens between patients, or otherwise within the hospital environment. Patients can experience different levels of animal exposure from petting and licking, which can result in contamination of both the patient and the animal, thereby providing the opportunity for the spread of microorganisms (Lefebvre & Weese, 2009). Therapy animals also have the potential to introduce zoonotic pathogens directly into the hospital environment, for example, via the consumption of contaminated foods (Lefebvre et al., 2008b). Contamination by a pathogen could

potentially lead to pathogen replication and stable colonization; this is concerning not only for the possible risk of progression to infection, but also for the risk that the therapy animal may serve as a reservoir and spread these pathogens to the home and larger community (Enoch et al., 2005). Such perceptions of potential infection control challenges and resulting harm could limit the use of AAI programs and detract from their employment as a valid and valuable adjunctive therapy for patients.

This review examines the current literature that focuses on potential hazards associated with hospital-based AAI therapy programs. We assessed both the breadth and quality of existing literature regarding infection control in AAI programs; these are discussed in the context of known and hypothetical pathways of microbial transmission. By identifying knowledge gaps, we provide focus for future research efforts and intervention strategies that will ultimately promote the sustainability of these AAI programs.

3.3 Methods

Search Strategy

This review utilized a more flexible search strategy in order to optimize capture of the peer-reviewed literature related to the risk of animal-assisted therapy. Multiple search approaches and terminology were employed to capture existing evidence relating to animal-assisted interventions for patients as a whole. Several unique terms can apply to AAI, such as animal-assisted therapy, animal-assisted activities, or pet therapy, therefore the search strategy was intentionally broad.

The literature search on risks of animal use in hospitals was carried out using the following databases: PubMed, Scopus, Embase, Web of Science, CINAHL, and Cochrane Trials. The search was completed concurrently and independently by two of the authors (KRD, KBW), and the search strategy was framed using PICO (Population, Intervention/Exposure, Comparators, Outcomes) terms (Miller & Forrest, 2001). The Population was identified as healthcare-based AAI programs using any therapy animals, not just canines. The Intervention/Exposure and Comparators were kept flexible and were dependent on study design. The Outcomes were any potential hazards associated with AAI, particularly infectious disease, microbial, or biological risks. Study designs accepted for review remained flexible and included original epidemiological research, literature reviews, commentaries, and case-reports.

Search Terms

In collaboration with a librarian, we performed a systematic search using the terms listed below on the respective databases; search terms were adjusted according to individual database terminologies, and searches were restricted to title/abstract. We used the

following search strategy for the PubMed database: animal assist* OR pet assist* OR dog assist* OR pet therap* OR dog therap* OR animal therap* OR “animal facilitated” OR “pet facilitated” OR "therapeutic animal" OR "therapeutic animals" OR "therapeutic canine" OR "therapeutic canines" OR "therapeutic dog" OR "therapeutic dogs" OR [Animal Assisted Intervention MeSH Term]. Similar keywords were used to conduct searches within the other selected databases.

Inclusion and Exclusion Criteria

The articles identified from this broad search were then individually and independently screened by two of the authors (KRD, KBW), based on the title and abstract, for inclusion based on the following criteria:

- Did the article explain possible complications or hazards to either therapy animals or patients that can occur during a hospital AAI therapy session?
- Did the article describe an epidemiological study demonstrating the risk of animals within health care environments?
- Did the article provide novel commentary on current guidelines, or recommend new guidelines, for reducing associated risks of animals within healthcare environments?

Articles that did not address any of the above criteria, or written in a language other than English, were excluded. Eligible studies underwent full-text review to further confirm eligibility (by KRD & KBW, arbiter MFD). After full-text review, references were examined to look for additional relevant articles that fit the inclusion criteria. We then extracted data from the selected studies on the research aims, study design, study population, exposure characteristics, type of intervention (if any), reported outcomes, and results. These data were then synthesized by study goals and outcomes.

3.4 Results

Search Outcomes

The initial database search returned a total of 5480 unique results (maximum number of returned articles from Embase), as shown in the flow diagram in **Figure 1**. After title and abstract screening of these articles, 110 were deemed potentially relevant based on the inclusion criteria. The remaining 5370 articles did not meet our prespecified criteria for inclusion, most commonly because the excluded articles evaluated the benefits of AAI programs on patient care. Upon full-text review of the 110 potentially relevant articles, 86 articles were removed because they did not satisfy the inclusion criteria. An additional five articles were added after reviewing the reference lists of the remaining included papers. These five articles were not found in the initial database search because they were either 1) not located in the selected databases or 2) had improperly labeled keywords. A summary of the final 29 total articles reviewed can be found in **Tables 1 and 2**. Thirteen articles were reviews or commentaries of current AAI guidelines that refer to therapy animals in healthcare settings, and sixteen articles were data-acquiring or epidemiological studies (6 cohort studies, 5 cross-sectional studies, 4 case reports, and 1 ecological study). Most studies focused on therapy animals broadly or therapy dogs exclusively, but three studies included cats (Boyle et al., 2019; Coughlan et al., 2010; Sillery et al., 2004).

Commentaries and Review Articles

Of the 13 commentaries and reviews, there were a total of 7 commentaries and letters to the editors and 6 systematic or unstructured literature review articles. Four of the six reviews (Brodie et al., 2002; Cimolai, 2015; Guay, 2001; Sehulster & Chinn, 2003) and four of the seven commentaries (Disalvo et al., 2006; Khan & Farrag, 2000; Lefebvre et

al., 2008a; Murthy et al., 2015) focused on risks associated with infection control. The remaining articles primarily discussed AAI benefits, with only a brief mention of hazard reduction. Zoonotic infection and pathogen transmission were the primary hazards discussed, although some papers mentioned injury risk. One article, endorsed by the Society for Healthcare Epidemiology of America (SHEA), is the current source for the medical community on general guidance for animals in healthcare settings, both summarizing existing policies in hospitals and recommending practical directives to minimize risk (Murthy et al., 2015). In this article, the authors also acknowledge that this field remains insufficiently studied (Murthy et al., 2015). There was a consensus among the reviews and commentaries that with proper hospital infection control protocols in place, the risks associated with animal-assisted activities are minimized. All articles recommended using standardized regulations across healthcare facilities for infection control practices for patients and therapy animals. Three of the articles strongly recommended utilizing expert consultation in various animal and human health care fields, as well as environmental microbiology, to evaluate all possible routes of pathogen transmission (Chalmers & Dell, 2016; Disalvo et al., 2006; Waltner-Toews, 1993).

Epidemiological Studies

The three studies that surveyed hospital infection control policies demonstrated dissimilarities across hospitals. Among the combined 186 facilities surveyed, infection control policies regarding therapy animals varied, with 13% (Linder et al., 2017b; Murthy et al., 2015) to 90% (Waltner-Toews, 1993) of healthcare facilities having no existing standardized policies. Only 28% of facilities required documentation that the animal was healthy, and only 29% allowed solely registered therapy animals (Linder et al., 2017b). In addition to clinical practice policy discrepancies, animal handler knowledge of infectious

disease concerns and adherence to infection control policies varied across and within institutions. Lefebvre et al. found that 20% of 90 surveyed handlers did not practice any infection control and 40% of these handlers were unable to name one zoonotic disease or pathogen that may be transmitted by means of their dog, while Boyle et. al. found that 70% of their 40 handler respondents expressed no concerns regarding infectious disease transmission in AAI settings (Boyle et al., 2019; Lefebvre et al., 2006b). These institutional and individual discrepancies in AAI programs drive diversity in infection control practices both across and within healthcare facilities.

Three studies reviewed electronic medical records to compare a change in the rate of diagnosed infections from AAI exposure. One study evaluated hospital-wide infection rates one year after the introduction of an AAI program in a pediatric hospital and, comparing these rates to the previous year, found no changes in overall infections or detected pathogens reported by the hospital's infection control committee (Caprilli & Messeri, 2006). Another prospective cohort study followed 11 adult cardiac patients after receiving multiple AAI therapy sessions (average of 13 visits) and found no reports of infection in participants observed during the study period, but did not compare the AAI participants to a control group (Snipelisky et al., 2016). However, another electronic medical record review study identified eight newly-acquired infections two weeks post AAI therapy in nineteen pediatric oncology patients, but could not definitively attribute these infections to the therapy animal visit as there was no control group of hospitalized pediatric oncology patients not receiving AAI therapy (Chubak et al., 2017).

The ten investigative epidemiological studies described cases of either animals or human patients becoming contaminated as a result of an AAI visit. The strongest weight of evidence was from prospective cohort studies in therapy animals (three studies, see

Table 1). Among these studies, the largest sample size was 200 therapy dogs, with most studies ranging from 10 to 20. In addition, the same group of investigators conducted most of these studies and utilized the same cohort of therapy dogs (Lefebvre et al., 2006a, 2008b, 2009, 2006c; Lefebvre & Weese, 2009). These studies focused on zoonotic pathogen carriage in therapy animals, and detailed cross-sectional prevalence and longitudinal incidence. They observed asymptomatic carriage of both hospital-associated and novel pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium*/*Clostridioides difficile*, *Salmonella*, *Pasteurella*, and intestinal helminths. This investigator group sampled therapy animals longitudinally over 12 months, and detected incidence rate ratios for therapy dogs with hospital exposure compared to no hospital exposure of 4.7 for MRSA acquisition and 2.4 for *C. difficile* acquisition (Lefebvre et al., 2009). They also identified risk factors for acquiring or being colonized with these pathogens, such as a raw meat diet, being fed treats by patients, and licking patients. One of these studies uniquely sampled therapy animals' human handlers for hospital-associated pathogen contamination before and after an AAI visit and demonstrated no contamination related to the AAI visit on the handlers' hands (N=26) (Lefebvre & Weese, 2009). The five other epidemiological studies, not from that investigator group and study population, surveilled therapy animals and found a positive association between therapy visits and zoonotic pathogens. Two were case reports of zoonotic pathogens found in therapy animals (Enoch et al., 2005; Sillery et al., 2004). The three cohort studies found prevalence rates of zoonotic pathogen carriage in therapy animals of 11.8% (Boyle et al., 2019), 18.2% (Coughlan et al., 2010), and 24.3% (Gerardi et al., 2018).

Unfortunately, all of these studies ignored assessment of the human patient, as well as assessment of other individuals involved in AAI, such as healthcare workers, visitors,

and, with the exception of the one study mentioned above, the therapy animal handlers. No studies evaluated the hospital environment as a source of pathogens, and the literature included scant data on the clinical health outcomes of the animals themselves. Furthermore, no studies systematically measured risk other than zoonotic pathogens/infectious diseases, such as phobias, allergies, or injuries.

3.5 Discussion

While most of the literature currently available on animal-assisted interventions centers mainly on positive human psychosocial outcomes, there is an apparent lack of information and guiding data surrounding the potential infection control challenges to the inclusion of therapy animals in a healthcare setting. As evidenced by the relatively few and mostly small epidemiological studies discussed in this review (n=10), therapy animals can harbor hospital-associated pathogens, and while not validated in controlled research, these data are consistent with the hypothesis that animal contact with patient populations may increase the animal's risk for contamination with pathogens. This is best evident in the study that showed therapy dogs that visit hospitals have almost five times higher odds of carrying MRSA as therapy dogs who visit other locations, such as schools (Lefebvre et al., 2009). Additional research is needed to investigate whether therapy animals can serve as pathogen vectors, from being contaminated by contact with one patient, and then transmitting these pathogens to another patient, leading to pathogen exchange. This is critical to test since many patients served by these therapy animals have a compromised health status and may be at higher risk of infection compared to the general population.

While there are proposed guidelines published for AAI in hospitals, senior care facilities, and for individual animal therapy organizations, there are significant differences in infection control policies across these groups (Serpell et al., 2020). This can cause confusion among therapy animal handlers and individuals who participate in AAI programs and may be complicated by a lack of standardized, evidence-based standard-of-care protocols that can be universally adopted. Current guidelines, including the SHEA guidelines, are based on biological plausibility and originate from hospital fomite

research and zoonotic transmission in other situations (pets in the home, etc.). Yet it is likely that therapy animals, with their unique exposures and ability to serve as an interactive living fomite, may have microbial communities that are different from standard pet animals. Therefore, exposure to animals in an AAI setting may fundamentally differ from exposure to household pets. This unique exposure profile could logically result in different risk factors and protective factors for pathogen contamination for both participants and the therapy animals. As such, infection control guidelines that rely on previous research on fomites and pet ownership may not realistically reflect adequate control measures for therapy animal exposures.

Our review confirmed an even greater lack of quantitative research on hazards other than infectious disease agents in the context of AAI studies. While some articles commented on the risks of phobias, injuries, negative cultural perception of animals, and allergies, none examined these risk factors empirically. Explanations for few study findings in this area include that these highly-trained animals minimize the potential risk of injury and that patients, along with their supervising medical team, will self-select to participate in these programs, thus reducing therapy animal contact by those patients who have phobias or allergies.

Our review also suggested a lack of effective educational campaigns and open communication networks between hospital infection control departments and therapy animal handlers regarding infection risk. This was suggested both by the variability in control practices among institutions and by the knowledge disparities among handlers observed in multiple studies (Boyle et al., 2019; Lefebvre et al., 2006b; Linder et al., 2017b). Without these communication channels, therapy animal handlers may not have a clear understanding of the rationale for infection control protocols, as well as the

potential risks towards the patients, their therapy animals, and even the handlers themselves. Continued efforts from infection control departments and hospital program facilitators to provide knowledge-based motivation to adhere to hospital-enacted infection control protocols are essential, directed to both therapy animal handlers and healthcare workers involved in AAI sessions. Without such cohesive collaborations, hospital protocols created for AAI programs can be misinterpreted or poorly executed. In order to minimize the potential risk for all involved, attention should be paid to outreach and education programs that promote safe practices for both therapy animal handlers and hospital staff. In addition to efforts to harmonize infection control regulations across healthcare facilities, individuals involved in AAI should work within the hospital to integrate AAI programs into the overall institutional safety culture in order to maximize the benefits of these programs.

A strong point of the established research is the evaluation of risk factors for pathogen carriage by therapy animals, namely animals fed a raw-food diet and those that have increased interaction with patients (through licking and being fed treats) are more likely to carry zoonotic pathogens. Studies that focus on risk factors can inform interventions to minimize pathogen carriage by therapy animals, and potentially decrease transmission to the patients with whom they subsequently interact. Expanding this work to studies that examine patient-level risk factors (such as concurrent disease conditions or specific animal-contact behaviors) or AAI-level risk factors (such as the number of patients interacting with the animal) will additionally inform the safety practices of these programs and have significant clinical impact. Clear hospital communication channels that impart infection control guidelines, backed by robust evidence-based science on potential risk factors, can empower healthcare workers and handlers to identify and minimize behaviors that pose risk to patients, therapy animals, and themselves.

The most significant knowledge gap is the lack of epidemiological data demonstrating or testing the transmission of zoonotic and hospital-associated pathogens related to AAI therapy sessions. The few published studies have small sample sizes (only two studies included more than 100 animals) and limited longitudinal data (only four retrospective or prospective cohort studies, two from the same cohort). This clearly limits statistical power to demonstrate even associations between pathogen carriage and AAI visits, much less actual illnesses associated with such carriage. Other than those three cohorts, most studies were cross-sectional or case reports, which limits causal inference because of their inherent inability to establish temporality, control for confounding, or account for interpersonal variability. The data from these cross-sectional studies and case reports, therefore, have minimal weight in our understanding of how AAI exposure may relate to pathogen carriage in therapy animals, patients, healthcare workers, and the hospital environment.

At present, the studies that have assessed microbial sharing during a therapy session focused only on the microbial carriage of the therapy animal. Testing only the therapy animal demonstrates carriage of a zoonotic pathogen at a single time point, and does not capture a transmission event. Data and evidence for transmission between patients, animals, and the environment are limited without sampling of all these components. Identification of a transmission event requires longitudinal multi-source sampling (humans, animals, and the environment) with molecular typing to identify and distinguish specific microorganisms. Such data are required to trace the source, pathway, and directionality among therapy animals, the hospital environment, and all individuals involved, including patients, visitors, healthcare workers, and therapy animal handlers.

Longitudinal sampling will also allow insight into whether microbial exposure and transient contamination from AAI conditions can progress into stable bacterial replication and colonization, and then progress to a possible infection in both individuals and therapy animals. In the context of hospital-associated pathogens, it is established that exposure is necessary, but not always sufficient, to progress to infection (Weber & Rutala, 2013); longitudinal sampling can capture these stages of progression, and identify risk factors that promote such progression. This is particularly relevant to clinical outcomes in AAI patient participants, many of whom are children or have compromised health status, making pathogen exposure more likely to progress to an infection. Longitudinal sampling of the therapy animal will also test whether these animals can serve as a vector of disease within and between different hospitals, and in the greater community outside of the hospital, as well as evaluate health outcomes in the animals themselves. With only a few published studies conducted in a small number of single hospitals, and often including the same cohort, the present data are clearly of limited generalizability to other populations.

3.6 Conclusions

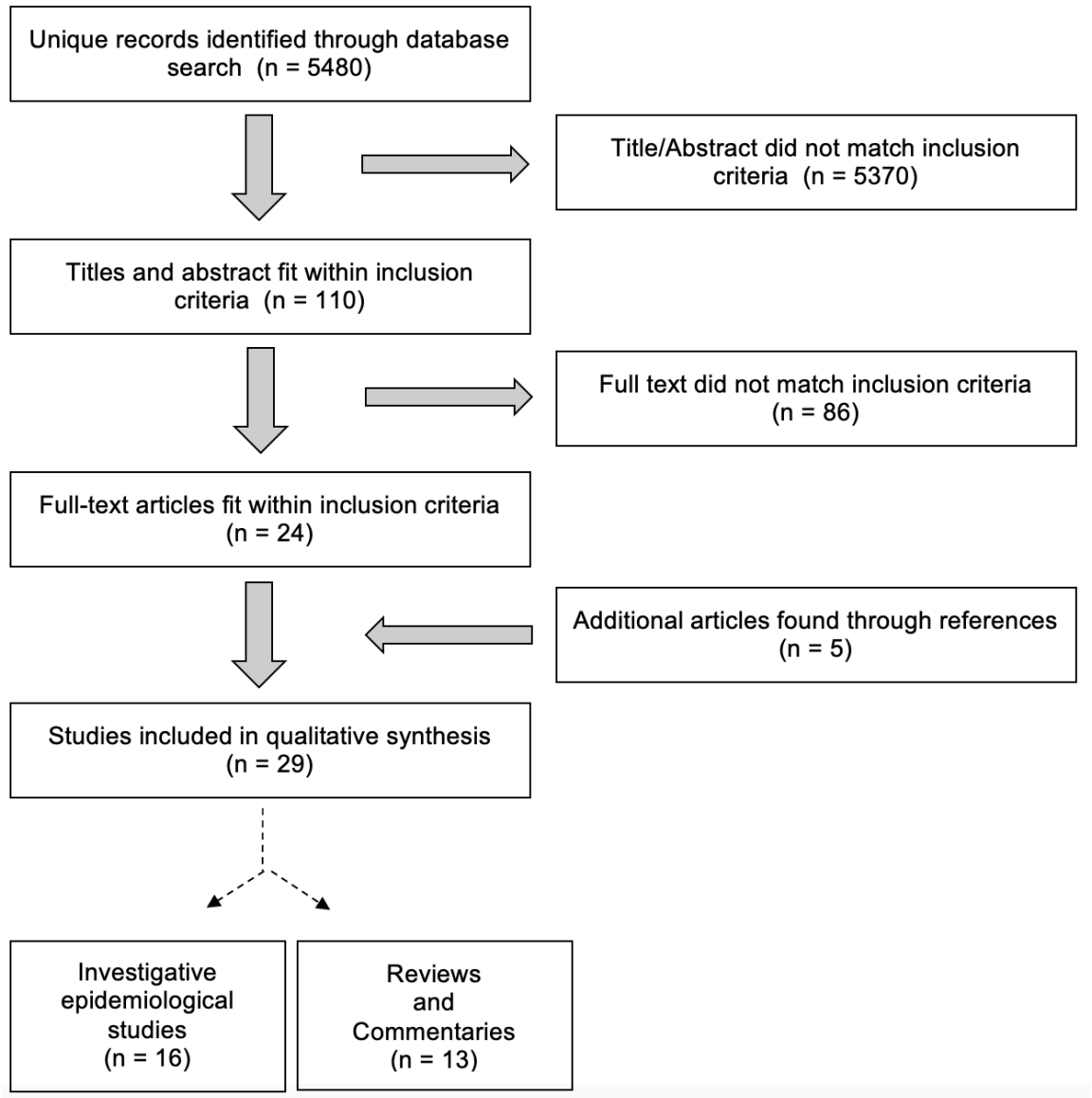
Future work in this area should aim to investigate the potential hazards that can occur during a therapy visit, both in terms of potential injury and infection control, and seek to quantify these possible associated hazards, while confirming these hazards do not interfere with the known benefits of AAI. It is recommended that future studies employ a One Health framework, a systems-thinking approach that addresses concerns at the nexus of human health, animal health, and the health of their shared environment, paying particular attention to the relationship between the entities rather than looking at them in isolation (Destoumieux-Garzon et al., 2018). This framework may facilitate future investigations and provide a more holistic view of the microbial dynamics between therapy animals, hospital patients, and the hospital environment.

While further research into risk identification is necessary, clinicians and other healthcare workers who implement or are debating implementing an AAI program must also consider their hospital and patient needs, given the clear and established benefits of these adjunctive programs. A rational decision process involves a cost/benefit risk assessment that provides insight into the likely consequences of a proposed action. Balanced with this is the concept of the precautionary principle, which states that without a risk assessment involving hazard identification and analysis, one should minimize exposure to the potential risk. In the case of AAI programs, while there is an ongoing need for corroborating research, the recommended guidelines for animals in the healthcare setting can provide a starting point and scaffold for infection control policies that, when properly applied and followed, have potential to minimize the known and unknown risk factors, while still maintaining the known benefits as an adjunctive patient therapy, with the ultimate goal of making AAI more accessible and sustainable for

patients. Promotion of judiciously executed AAI programs will increase attention to its usage as a complementary therapy, and prompt awareness of the need for further insight into its safety and value as a critical tool for patient benefit.

3.7 Tables and Figures

Figure 1. PRISMA* Flow Diagram for Search Strategy



* Preferred recording of items for systemic reviews and meta-analyses (Moher et al., 2009)

Table 1. Overview of the Articles Examined: Epidemiological Studies, listed by type and chronologically

Authors, Year	Study Design	Goals	Evaluated	Measurements	Covariates	Findings
(Boyle et al., 2019)	Epidemiological Retrospective Cohort Study and Survey Review	Prevalence of zoonotic pathogens in therapy animals, and survey of handlers' understanding of the risks of zoonoses and their adherence to infection control practices	Screening test results from 22 dogs and 2 cats, with a survey of 40 registered therapy animal handlers.	Annual fecal parasitic float and bacterial culture, nasal & perianal MRSA/MRSP skin cultures; One-time structured quantitative surveys of handlers	N/A	17 total positive results of the 118 infectious disease screenings performed, 14 of which were potentially zoonotic organisms. 70% of handlers expressed no concerns regarding infectious disease transmission in AAI settings.
(Gerardi et al., 2018)	Epidemiological Cross-sectional Study	Study looked for protozoan *Giardia duodenalis* and zoonotic gastrointestinal nematodes over the three-month study period in dogs training for AAI.	Fecal samples from 74 dogs, and demographic questionnaire data	Fecal parasitic exams	Dog age, breed, sex, health status,	Authors found 18/74 (24.3%) positive fecal samples - 8 with *Giardia*, 3 with co-infections of multiple gastrointestinal parasites.
(Linder et al., 2017a)	Epidemiological Cross-Sectional Survey	Surveyed healthcare facilities, as well as AAI organizations, about animal visitation guidelines.	45 eldercare facilities, 45 hospitals, and 27 therapy animal organizations	Survey assessed existing health and safety policies related to AAI programs	N/A	Health and safety policies varied widely and potentially compromised human and animal safety. Hospitals had stricter guidelines than elderly care facilities, which had stricter guidelines that AAI organizations.
(Chubak et al., 2017)	Epidemiological Retrospective Cohort Study and Survey Review	Pilot study on the risk of hospital-acquired infections following an AAI session in a pediatric oncology inpatient clinic	Electronic medical records from 19 pediatric patients, as well as patient, parent, and healthcare provider surveys.	Newly acquired infection cases of the participants for 14 days following an AAI session	NA	Eight of the 19 patients developed a hospital-associated infection following an AAI session. However, this could not be attributed to AAI therapy sessions, as there was no control group to compare whether the infections resulted from exposure to AAI versus exposure to the hospital.
(Snipelisky et al., 2016)	Epidemiological Retrospective Cohort Study	Pilot study to test the feasibility, receptiveness and safety of AAI in hospitalized patients	11 patients followed for 12 months, receiving 146 therapy sessions.	Medical record review for documented infections; also surveys	N/A	Authors found that while maintaining strict institutional infection control policy, no reports of infection or issues with intravenous lines, central lines, or

		awaiting heart transplantation.		of patient receptiveness to AAI therapy.		ventricular assist devices, were observed during the study period.
(Coughlan et al., 2010)	Epidemiological Prospective Cohort Study	Prevalence rates of MRSA in 12 resident animals at hospice	11 cats and 1 dog, over course of 8 weeks	1 nasal swab per week	Health status of animal	Author found 2 of the 11 cats were positive for MRSA (5 out of 8 samples for one animal, and 2 out of 8 samples for the other), all USA100 healthcare-associated strains.
(Lefebvre & Weese, 2009)	Letter to the Editor: Case Report	To show the potential for therapy animals to become colonized, not just transiently contaminants, with nosocomial infections	26 therapy dogs with 26 human handlers	Paws and haircoat of each dog, and handler's hands, before and after therapy visit		No positive pre-visit samples, 1 dog (4%) acquired *C. difficile* after a visit, and one human was positive for MRSA after petting a therapy dog, suggesting that dogs can became contaminated with pathogens during AAI visits, and can transmit pathogens to humans.
(Lefebvre et al., 2009)	Epidemiological prospective cohort and nested case-control studies	To compare the risk of acquiring a pathogen between therapy dogs that visited hospitals versus therapy dogs that visited other venues (classrooms, etc.)	96 therapy dogs that visited hospitals and 98 dogs that visited other AAI events.	Fecal and nasal samples from the dogs were collected every 2 months for a year	Dog diet, dog illnesses, and antimicrobial use within the home	Therapy dogs that visited hospitals were almost 5 times more likely to be contaminated with healthcare associated pathogens (IRR 4.7 MRSA, 2.9 *C. difficile*). Amongst those, therapy dogs that licked patients' hands were more likely to be contaminated.
(Lefebvre et al., 2008b)	Epidemiological Prospective Cohort Study	To determine if pathogen shedding is different in therapy dogs fed raw meat diet versus not	200 therapy dogs	Fecal samples collected every 2 months for 1 year	Clinical diarrhea, pig-ear consumption	Therapy dogs fed a raw meat diet were significantly more likely to shed pathogens, including antibiotic resistant strains. The authors recommended these dogs be excluded from AAI programs.
(Lefebvre et al., 2006c)	Epidemiological Cross-Sectional Study	Evaluate dogs visiting hospitals for possible zoonotic disease pathogens	102 visitation dogs (includes therapy animals and pets visiting owners)	Fecal sample, hair-coat brushings and one rectal, aural, nasal, oral and pharyngeal swab were collected from each dog and tested for 18 specific pathogens.	Canine demographic details and medical history	Zoonotic pathogens were found in 80 of the 102 dogs (80%), which indicates that these dogs can spread pathogens. The authors concluded that more information is needed on risk factors and transmission routes to better inform infection control policies

(Lefebvre et al., 2006b)	Epidemiological Cross- Sectional Survey	To determine the distribution of canine-visitation programs in Ontario and to characterize the nature of the programs the dogs are affiliated with.	Surveys from 223 hospitals and 90 therapy dog handlers	Surveys from hospitals regarding their usage of AAI programs. Surveys from therapy dog handlers regarding where they volunteer.	Hospital type (acute versus chronic care), dog demographics (age, sex, breed).	Acute care wards were 5.1 times more likely than other wards to prohibit therapy animals. Handlers reported highly variable screening protocols and infection control practices; 18 owners (20%) said they did not practice any infection control and 36 owners (40%) were unable to name one zoonotic disease
(Lefebvre et al., 2006a)	Letter to the Editor: Case Report	Report of a toxin-variant strain of *C. difficile* in an apparently healthy therapy dog.	1 dog that was a part of the cross-sectional study described above	Fecal sample	N/A	This canine isolate is indistinguishable from the major strain implicated in outbreaks of highly virulent CDAD around the world. The recurrent exposure of this dog to human healthcare settings suggests that the animal acquired this strain during visits to the hospital.
(Caprilli & Messeri, 2006)	Ecological hospital-based medical record review	Determine rates of hospital-acquired infections before and after the implementation of an AAI program, and patient-reported enjoyment	138 pediatric patient participants and aggregated hospital-wide infection rates	Cases of newly acquired infections prior to introducing therapy dogs, and one year after dogs present in hospital	NA	Authors found constant rates of hospital infections after 1 year of dogs being present in the hospital weekly, compared to the previous year, and no documented contagious diseases were transmitted by dogs during their presence in the hospital.
(Enoch et al., 2005)	Letter to the Editor: Case Report	Describe a case of a therapy dog acquiring MRSA during a therapy visit to a hospital	1 dog	Nasal, head and paw swabs before and after therapy visit	N/A	The dog was negative for MRSA on entering the hospital, but was found positive when leaving, indicating patients may spread MRSA to therapy dogs.
(Sillery et al., 2004)	Letter to the Editor: Case Report	Describe a case of a patient with *Pasteurella* peritonitis that was suspected to be transmitted from the pet cat.	1 human patient with a pet cat	N/A	N/A	Therapy animals can potentially transmit *Pasteurella multocida*, a pathogen that can cause peritonitis in patients undergoing peritoneal dialysis. This is the first documented case of suspected transmission of the pathogen from animals, and introduces a novel control point for AAI programs.

(Waltner-Toews, 1993)	Epidemiological Cross-Sectional Survey	First documented attempt to understand risk associated with AAI. Surveyed animal care facilities to determine the prevalence of AAI programs, concerns and experiences with AAI, and zoonotic disease precautions taken to prevent transmission	150 systematically selected United States animal care agencies and 74 Canadian humane societies	N/A	N/A	Half of the respondents expressed concern over zoonotic diseases, but few were based on actual experience. Less than half consulted with a human health professional about infection control and only 10% had written guidelines for prevention of zoonotic disease transmission.

Table 2. Overview of the Articles Examined: Reviews, Guidelines, and Commentaries, listed by type and chronologically

First Author, Year	Study Design	Goals	Evaluated	Measurements	Covariates	Findings
(Bert et al., 2016)	Systematic Review	Review current literature of positive clinical outcomes and negative risk to patients from therapy animals	11 papers looking at the risk of therapy animals, which include both epidemiological studies and protocol guidelines.	N/A	N/A	Concluded AAI for hospitalized patients useful and safe for a wide range of diseases
(Chalmers & Dell, 2016)	Commentary	Applying One Health principles to decrease risk in therapy dog programs and further research	Did not include number of papers formally reviewed	N/A	N/A	Author gives a framework for studying therapy programs in the animal-human-environment interface.
(Hardin et al., 2016)	Commentary	Describe implementation of a pet therapy program that includes guidelines for the prevention of transmitted infections.	Did not include number of papers formally reviewed	N/A	N/A	Guidelines were in place in a hospital for sixteen years with no documented cases of disease transmission, supporting that a pet therapy program can be put into place safely with proper regulation
(Cimolai, 2015)	Letter to the Editor: Brief Review	Short review of current studies/case reports of zoonotic infections from pets	Did not include number of papers formally reviewed	N/A	N/A	Author concludes that therapy programs do provide opportunities for patients to become exposed to zoonotic infections and requires strict infection control policies, not a relaxation of guidelines.
(Murthy et al., 2015), Society of Healthcare Epidemiology of America (SHEA) Writing Group	Commentary	Provide general guidance to the medical community regarding management of animals in healthcare, specifically in terms of hazard reduction.	Did not include number of papers formally reviewed	N/A	N/A	Created guidelines for animal-assisted therapies, service animals, research animals, and personal pet visitation. Also recommends additional research be performed to better understand the risks and benefits of allowing animals in the healthcare setting for specific purposes

(Snipelisky & Burton, 2014)	Review	Review current published information regarding the efficacy of AAI in the inpatient population, and to review safety concerns associated with AAI.	Reviewed 44 articles (26 clinical studies, 15 review articles, 1 case report and 2 letters to the editor). Five studies addressed infection concerns.	N/A	N/A	The authors' review of the literature showed that, in the inpatient setting, AAI is an effective therapy among patients of all ages and with various medical problems and is safe, with no transmitted infections reported. Found only 5 studies that addressed infection concerns in the inpatient setting.
(Silveira et al., 2011)	Commentary	Guidelines for a hospital-based AAI program, which has been effective for a hospital in San Paolo, Italy	Did not include number of papers formally reviewed	N/A	N/A	AAI programs can be properly implemented in hospitals if strict attention is paid to animal inclusion criteria and infection control.
(Lefebvre et al., 2008a)	Commentary	Provides standard guidelines for animal-assisted interventions in health care facilities, considering the available evidence.	Did not include number of papers formally reviewed	N/A	N/A	Created strict guidelines, centered on evidenced-based literature, for AAI programs to reduce risk of colonization and transmission of hospital-associated infections for the animals and people.
(Disalvo et al., 2006)	Commentary	Compared guidelines for therapy animals in hospitals to guidelines for service dogs and family pet visitation	Did not include number of papers formally reviewed	N/A	N/A	Argued that therapy animals should have strict guidelines to reduce adverse events such as phobias, allergies, and zoonotic diseases.
(Sehulster & Chinn, 2003)	Review	Centralized CDC guidelines for environmental infection-control strategies and engineering controls to effectively prevent nosocomial infections in healthcare fields.	Did not include number of papers formally reviewed	N/A	N/A	Discussed general infection control policies, but also included therapy animal programs. Recommended minimizing contact with animal bodily fluids, and implementing hand hygiene after each contact. Recommended careful selection of therapy animals and bathing to reduce allergens.

(Brodie et al., 2002)	Review	Review of current literature focusing on health risk to patients	Did not include number of papers formally reviewed	N/A	N/A	Zoonoses, allergies and bites - the three issues surrounding pet therapy causing greatest concern - have the potential to be controlled in a supervised health care setting, and can be minimized by taking simple measures.
(Guay, 2001)	Review	Review of the most common zoonotic infections that might be expected in the long-term care setting from AAI, with recommendations for prevention and control.	Did not include number of papers formally reviewed	N/A	N/A	Recommends infection control policies and procedures, geared toward management and prevention of the different zoonotic illnesses discussed, should be developed and implemented in all nursing homes offering pet-assisted therapy.
(Khan & Farrag, 2000)	Commentary	Critique of current animal therapy programs guidelines in the context of hazard reduction	Did not include number of papers formally reviewed	N/A	N/A	If put into place properly, animal therapy programs can have significant benefit to patients, with minimal risk of animal associated health hazards.

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Chapter 4: Perceptions and Practices of Key Stakeholder Groups in Hospital Animal-Assisted Intervention Programs on Occupational Benefits and Perceived Risks

4.0 Cover Page

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4.1 Abstract

Background: Animal-assisted intervention programs, used widely for patient benefit, have increasingly been used for healthcare workers (HCW) to reduce occupational stress. However, there are barriers to these programs which limit their utilization, for both patients and HCW, specifically infectious disease concerns. The aim of the research project is to identify barriers and facilitators to program use for healthcare worker benefit, and determine knowledge, beliefs, and practices regarding infectious disease risk and control policies, in order to understand the contextual parameters of program implementation.

Methods: We collected perceptions of key stakeholders involved with hospital AAI programs (HCW and AAI workers) through semi-structured in-depth interviews. We used framework analysis to guide thematic coding, completed independently by three researchers.

Results: We interviewed 37 total participants. We divided our themes into two topic areas: program use for HCW and perceived infectious disease risk. Use for healthcare workers included perspectives on the benefits for HCW and program barriers and facilitators (specifically collaboration and leadership). Perceived risk included opinions on infectious concerns with AAI, thoughts on control measures to reduce this risk, and responsibility for safety during these programs.

Conclusions: While significant benefits were reported for HCW, they were limited by administrative barriers and hazard concerns. Facilitators to surmount these barriers are best implemented with collaboration across the hospital and appropriate leadership to roles to direct safe program implementation. With these barriers addressed through

targeted facilitators in the form of evidence-backed guidelines, AAI programs can be used to benefit both patients and HCW.

4.2 Introduction

The numerous benefits of the human-animal bond have extended into the use of animals in healthcare facilities as an adjunctive therapy for patient wellbeing. These animal-assisted intervention (AAI) programs have been shown to reduce stress, pain, and anxiety in patients (Bert et al., 2016; Kamioka et al., 2014; Tsai et al., 2010). One novel use of these programs is for the benefit of healthcare workers (HCWs) in charge of patients, given the critical occupational burden that faces them from high-demand workloads, and secondary traumatic stress from acute negative work experiences. Such stressors can lead to physical, mental, or emotional symptoms such as burnout, depression, and anxiety (Hall et al., 2016; Pradas-Hernandez et al., 2018). Significantly, these symptoms can influence HCW job satisfaction and performance, which have downstream effects on poor patient care (Hall et al., 2016; Monsalve-Reyes et al., 2018). This indicates a crucial need for stress-reduction interventions for HCW, and many hospitals are adopting AAI to address this need. To date, no research has evaluated the effectiveness of AAI as a valid therapy to reduce stress in this vulnerable yet essential worker population. If evidence shows that AAI programs can improve occupational health and wellbeing, this will be a previously undescribed benefit of these programs and further promote the human-animal bond in healthcare settings.

Despite the demonstrated benefits to patients, and potential benefits to HCW, there is still hesitancy in the adoption of AAI programs for both populations. At the forefront of these challenges is the concern for potential exposure to and spread of infectious disease agents to individuals who participate, a challenge that HCW acknowledge (Linder et al., 2017). Previous research has demonstrated that therapy animals and patients who interact with them are at higher risk of exposure to hospital-associated pathogens

(Dalton et al., 2020; Lefebvre et al., 2009). This indicates the possibility for other individuals involved in AAI to become contaminated, including HCW who can transmit microbes to other patients in their care. While guidelines designed to reduce this infectious disease risk have been developed (Murthy et al., 2015), stakeholders at the forefront of these therapy sessions need to be aware of the potential risk and be motivated to deploy these control interventions. Thus, hospital infection control strategies for AAI therapy need to be effective yet practical to implement in the field, with engagement from HCW and other key stakeholders. There is currently no research on the infection control beliefs and practices for key personnel who work with hospital-based AAI programs. Understanding key stakeholders' concerns will allow for the development of interventions relevant to real-world hospital conditions and will be foundational to future research in this area. Proper implementation and adherence of control strategies will improve the safety and perception of safety for these crucial AAI programs, and increase their utilization for the benefit of both patients and HCW.

Therefore, this research aims to collect perceptions of key stakeholders involved with hospital AAI programs on 1) the use of hospital-based AAI programs as an efficacious and practical occupational stress reduction intervention and 2) concerns and current practices of infection control during AAI programs. This qualitative study will use interviews to formulate more accurate and contextually relevant data, a process that has shown to be successful in studies on human-animal interaction, AAI programs, and hospital infection control (Degeling & Rock, 2020; Pedersen et al., 2012; Seibert et al., 2014). This work will contribute foundational evidence regarding the risks and benefits of AAI programs to promote the health and wellbeing of workers and volunteers by preserving the human-animal bond. The ultimate outcome for this qualitative research project is to guide reduction of potential hazards associated with AAI programs by

improving their safety, so that these programs can be sustainable as a validated method to holistically improve human and animal wellbeing.

4.3 Methods

Study Population

The Johns Hopkins Bloomberg School of Public Health Institutional Review Board reviewed all instruments and study materials and approved this project. To document and describe the perspectives and opinions of hospital-based AAI programs on issues related to risks and benefits, we conducted a series of in-depth interviews with key stakeholders. Key stakeholders included healthcare workers (doctors, nurses, and other patient-care staff) and AAI workers (volunteer handlers and program directors) who work/volunteer in hospitals with existing animal-assisted intervention programs. All stakeholders were over 18 years old and fluent in English. We identified potential study participants from existing contacts and connections through concurrent research studies. Secondarily, we used snowball sampling to identify additional participants (Sadler et al., 2010). Participants were recruited via an email that introduced the research team and study goals.

Interviews

A semi-structured interview guide was developed by KRD using programmatic framework analysis, a deductive process focused on exploring predefined key concepts within the data (Gale et al., 2013). Prior to implementation, the interview guide was edited by co-authors (KR, RT, JA, MFD), and beta-tested with knowledgeable contacts. The interview questions addressed relevant themes connected to the participants' experiences with hospital animal-assisted intervention, specifically regarding possible concerns and benefits to healthcare workers.

Interviews took place with participants via an online web-conference software between

May to July 2020 (in-person interviewers were not possible due to COVID-19 contact restrictions in place at the time). Before the start of every interview, participants gave written consent via an electronic signature; occasionally oral consent was obtained from those unable to provide the electronic signature. All interviews were audio-recorded, with participants made aware of the recording before the start. The interviews were conducted by one of three research team members (KRD, WCA, or PC) and typically lasted between 40 to 60 minutes.

Data Analysis

Audio-recordings from the interviews were transcribed verbatim with the interviewees' permission. All transcripts were then coded using a combination of previously established deductive codes and inductive codes that arose from the data, as per the programmatic framework analysis guidelines (Gale et al., 2013). Each transcript was coded by at least two research members (all coded by KRD, and WCA or PC coding half each). The researchers' diverse professional backgrounds and perspectives facilitated openness to different interpretations during both the interview process and data analysis; the first author has a background in veterinary science and human-animal interaction, the second has a background in mental health and social work, and the third has a background in social disparities and environmental justice. To ensure rigor and inter-coder reliability, the researchers utilized "dialogical intersubjectivity" or open group discussion among both the three researchers and the wider co-author team for constant comparison of codes to ensure group consensus (Brinkmann & Kvale, 2015; Saldaña, 2015).

Codes were then grouped into major themes and sub-themes (Malterud, 2001) to formulate new concepts on the topics. The final step was to explore how these themes

were related to each other in a synergistic fashion. Throughout the analysis, the authors reiteratively returned to the interview texts to check that the evolving themes and sub-themes reflected the meanings conveyed by the participants. Representative quotes from the interviews were selected to best illustrate each theme and/or sub-theme.

4.4 Results

Enrollment and Recruitment

We completed interviews with 37 participants, which are described by occupation in **Table 1**. The interviews lasted from 25 minutes to 1 hour and 5 minutes, with an average time of 42 minutes. Participants were almost equally split between healthcare workers (51%) and individuals directly involved with AAI programs (49%). Three of the volunteer handlers were also healthcare workers, and all AAI program directors were hospital employees.

Major Themes

Based on our chosen framework analysis methodology, we planned our interviews to focus on the following two main topic areas: 1) the use of AAI programs for occupational HCW, and 2) perceived risks associated with hospital AAI programs. After data collection, we then organized our themes and sub-themes within each of these two topic areas as shown in **Table 2**.

Topic Area 1 – Program Use for Healthcare Workers

The first topic area that was selected as a focus *a priori* for the interviews was on the implementation of AAI programs for HCW usage, particularly best practices in establishing and sustaining sessions that are exclusively for HCW.

All participants, both HCW and AAI workers, felt that these programs, originally designed as complementary interventions to improve patient wellbeing, could be adapted and used for occupational purposes. Some participants even commented that staff needed these programs more than patients. Within this topic area are opinions in three major themes; 1) benefits to HCW from AAI programs, 2) barriers to HCW AAI,

and 3) facilitators to overcome the barriers.

Theme 1.1: Benefits to HCW

All participants reported that AAI programs could benefit HCW, in ways that are similar and unique to patients' benefits. Participants felt that benefits from AAI programs to HCW would be heterogeneous depending on personality and coping styles, as well as job function (better for more stressful jobs such as residents and night-shift workers). Reported benefits to HCW were aggregated into three main sub-themes.

Sub-Theme 1.1.1. Stress Reliever and Morale Booster

Similar to sessions for patients, participants felt that AAI programs for staff would be a positive distraction or a break from their regular routine. Terms such as "mindfulness" or "reset" were used to describe the positive distraction from these programs for HCWs. The benefits were reported even after brief interactions, with the therapy animal working "instantaneously." The most commonly reported effect from AAI programs used for staff was the concept of stress reduction. Both HCW and AAI workers reported that occupational stress in this cohort is a significant problem, and these therapy animals could reduce this stress burden.

> HCW: "I think that engaging with a dog in a meaningful way de-stresses people."
>
> HCW: "I think there's also something when you're petting a dog, your body relaxes. You feel more at ease and less stressed."
>
> AAI Worker: "I think it's easy to confuse reducing stress with things that are just very pleasant. There's nothing wrong with just having a few pleasant moments, … yet I think pet therapy goes beyond that and actually reduces the grit of the health care workers' day in the moment for stress reduction."

Beyond reducing stress, participants felt that these programs bolstered morale and mood in HCW receiving this therapy, both for programs directed towards HCW and as

bystanders to patient-centered programs. This was reported on a personal level and a group level, in that having a therapy animal visit a unit or department raising the collective mood in the workplace. It was also mentioned that these positive benefits could reinforce the commitment of the hospital to holistic employee wellbeing.

> AAI Worker: “I just think to me it would just be natural that, yes, it would make healthcare employees happier.”
>
> AAI Worker: “Some of the managers have reported that when the dogs have come and visited that they feel like the staff is just in a better mood.”
>
> HCW: “I would think some of the reasons are not just maybe the immediate effect of having that dog, but some of it's also morale boosting. It's maybe an indication that the institution you're working for cares about things like that, and they're trying to help you have a better work experience.”

Sub-Theme 1.1.2. Improved Job Function

Participants reported that HCW benefited from AAI programs through improved job function. This was through its use as an adjunctive therapy modality in patient care, a unique “tool in the toolbox,” resulting in improved clinical outcomes and facilitated communication with patients. In addition, the positive benefits of stress reduction and morale bolstering in HCW also translated into better workplace performance by creating increased employee engagement and resilience.

> HCW: “I get an indirect benefit when my patients get a benefit. It's good for me to see them having that positive experience in the hospital and sometimes helps me build another level of rapport with them, which helps me do my job better.”
>
> AAI Worker: “We know that if our staff are happier and less stressed, that our patients are as well, that carries over to better patient care.”

Sub-Theme 1.1.3. Gateway to Other Therapy

The final benefit to HCW that was observed from participant responses was the concept that the therapy animals could serve a mechanism for open communication. Both AAI

workers and HCW reported feeling more open and freer to discuss mental health and other workplace stress-related factors with a therapy animal present.

> AAI Worker: "They can share their emotion with a dog that they're not going to do with another person or coworker while they're at work."
>
> HCW: "There's definitely something to that human-animal connection. People feel more comfortable disclosing information, I feel like, when the dog is there."

In addition, HCW were more likely to utilize other stress intervention modalities, such as professional counseling, if combined with AAI programs. The therapy animals served as both an incentive and a non-threatening bridge to what could be considered an "intimidating" or "unneeded" therapy. When combined, it was reported that these therapy programs would appeal to a greater audience, as well as address needs from a broader range of personalities, coping styles, and problems.

> AAI Worker: "We talk about the dog as sort of like a gateway to some other therapeutic interactions where people might be more open to talking to a specialist if they're, like, petting the dog while they do it."
>
> HCW: "I have never gone to [*a counseling session*] because it's something that I tend to deal with more internally. But if they're like, come play with some big, fluffy golden retrievers for an hour, I'd be like great, I'm there. And I might be more willing to open up about stuff if I'm already in the room."

Theme 1.2: Barriers to Programs for HCW

Despite the reported benefits, not all departments and hospitals were able to use AAI programs for their staff. Many of the stated barriers were the same administrative hurdles that were reported as barriers to program use for patients, such as an insufficient number of trained volunteer therapy animals and handlers. Other issues that were common to patient-use barriers included HCW's fear of and allergies to the therapy animals. However, there were issues that were specific to the use of AAI in this population. Infectious disease concerns arose as a barrier to program utilization for HCW and patients; these concerns are addressed in more depth later (*infra* Topic Area

2). The other program barriers are broken down into three sub-themes.

Sub-Theme 1.2.1. Conflicting Timing and Location with Normal Clinical Functions

The most frequently reported barrier to program utilization for HCW was their conflicting priorities to their routine job duties. Many participants reported being unable to find time outside of their patient care responsibilities to focus on wellness initiatives, including pet therapy. Handlers also reported this as a barrier when they would attempt to include HCWs in their sessions. Timing issues dealt with both the difficulty of finding a suitable time for HCW-directed sessions, and how long those visits should last in order to be beneficial and worthwhile. The lack of convenience and accessibility of the location for AAI visits was also reported as a potential drawback.

> HCW: "I can't remember a time when a particularly difficult day has coincided with a dog being available for me to go visit. And if there was, I imagine that probably the timing would be difficult."
>
> AAI Worker: "Our volunteer dogs can only be on site for an hour, and so, for that reason, they typically don't work a lot with our staff."
>
> HCW: "You can't spend 10 minutes getting somewhere for something that lasts 10 minutes to spend 10 minutes getting back. It has to be very convenient for your workday."
>
> HCW: "We don't have a lot of true spaces where staff can gather to utilize some type of modality of therapy for themselves. So, I think that's a real barrier."
>
> HCW: "Is it something I look forward to? Yes. But I'm only ever able to go if I have a free moment to do so. So, it's not like I get to choose the pet therapy over my work."
>
> AAI Worker: "I think *[healthcare workers]*, they've got other job responsibilities and duties, and so that's always in the back of your mind."

Sub-Theme 1.2.2. Prioritizing Patient Needs Before Staff

The final primary barrier to HCW AAI sessions was the concept that many HCW felt these sessions should be used for patients. HCW felt that using these programs for

themselves, especially knowing the constrained availability of therapy animal dogs and handlers, would remove this limited resource for patients. This concept was also supported by handlers and AAI program directors, who felt the need to prioritize patients because of individual choices or management pressures.

> HCW: "I guess the times I've heard of them have always been kind of patient-directed and usually, for instance, programs like that, they, I don't know, I always get the impression that medical people, especially doctors, are not necessarily welcome … I feel like it's kind of for the kids and not for me, I guess."
>
> AAI Worker: "I found that if I'm walking the dog around the unit, a lot of the staff feel like I'm taking the dog away from their patient."
>
> AAI Worker: "We've always tried to do some level of *[staff visits]*, although we would always prioritize, like, a patient need over that."
>
> AAI Worker: "The other component is that *[the therapy dog training organization]* really wants these dogs to be working with the patients and families. They know that the staff need a little bit of support now and then, but for the majority of work they really want it to be focused on the patients … we really want to keep the patients and families at the forefront of why we're having these programs exist."

Sub-Theme 1.2.3. Infection Risk as a Barrier to HCW Program Use

Our *a priori* chosen topic area on infection disease risk in AAI was found *post hoc* to be a sub-theme within the HCW program use topic area, namely that infectious risk was reported as a barrier to the establishment and sustainability of programs for HCW. As such, this sub-theme will be addressed in more depth later (*infra* Topic Area 2).

Theme 1.3: Facilitators to Programs for HCW

In addition to discussing barriers of AAI programs for HCW, opinions on ways to overcome these barriers were also examined. Again, many of the facilitators described to increase program use for HCW could also be used to increase their use for patients. Facilitators were grouped into three sub-themes.

Sub-Theme 1.3.1. General Implementation Thoughts

Ideas were collected on general ways to run these HCW-directed AAI programs from participants. This included best practices from successful staff programs, and potential solutions to hurdles for those who face obstacles to these programs. Many of these facilitators dealt with the best timing and location of sessions. Staff were divided on whether visits would be most effective as scheduled sessions or flexible, emergent sessions. Frequently, staff reported that these programs should be combined with existing scheduled occurrences, such as regular meetings or routine support events. This also goes along with perspectives on finding a convenient location to maximize HCW engagement, such as bringing the therapy dog directly to the department and finding a separate location from patients, such as an employee-only break room.

> HCW: "I think if there was just a centralized, I don't know, almost kind of like, … if a pet did rounds in a similar way as *[the doctors]*. Right. You knew between 2:00 and 3:00 they'd be on the floor. I think that would be, that'd be the most feasible way to do it."
>
> HCW: "I actually think just walking the dog even in the halls and having some unscheduled time for who happens to be there is a valuable thing."
>
> AAI Worker: "I tell *[staff leadership]* that they should make sure that they have a separate room set aside for this. So the staff doesn't feel like they're being, they're taking this time away from the kids."
>
> HCW: "If there was kind of, I guess, a more adult friendly space for the session to take place in, I think that would be a great way to do it."

Another frequent solution to implementation barriers was the idea of having facility dogs, which is a therapy dog that works in the hospital full time. Facility dogs were reported to be frequently used for healthcare worker stress reduction, including one hospital that had a facility dog exclusively for HCW.

> HCW: "Facility dogs are being used and because they are in the hospital for a full workweek as service animals, they're able to more often be utilized … because

they are there all day, every day."

AAI Worker: "I think it's like one of the best opportunities the hospital can provide, because they can rotate staff so *[the facility dog]* will be in a room and staff come and go based on their schedule because she'll be there for like a prolonged period of time."

Sub-Theme 1.3.2. Importance of Appropriate Staffing

A frequently reported facilitator was the value of having adequate staffing to support AAI programs. This was reported in terms of having adequate coverage so that HCW could participate in AAI sessions and not be burdened by clinical duties. The importance of having a staff member in a leadership position, at the institutional and unit level, to take care of appropriate scheduling and administrative tasks was also stressed as a critical factor for HCW AAI program success.

HCW: "Nursing, therapist, everybody participated, and everybody supported each other. The nurses covered for each other. We scheduled around it. We made it happen because everybody wanted to participate *[in the AAI session]*."

AAI Worker: "Having somebody to coordinate the program is essential."

AAI Worker: "The great thing about a certain dedicated person would be that that was their primary responsibility would be to provide some level of staff support. And in my mind, that person would have a lot more flexibility in terms of where they could go … I think we could reach a lot more staff that way."

Sub-Theme 1.3.3. Importance of Collaboration and Advocates

The last sub-theme identified to aid hospital leadership and staff in implementing HCW-focused AAI sessions was the concept of collaboration across hospital departments and management, including having advocates to promote the value of these programs for staff. These advocates are described as champions in hospital leadership, but also in the greater community who fund the therapy dogs and staff to run these hospital programs. Advocates were reported to be instrumental in securing hospital "buy-in" and increased

collaboration.

> HCW: "I think without a champion, it would not get done … their setting up the protocol, not giving up when they hit barriers, making partnerships with places like legal-- I think it wouldn't get done without them, to be honest."
>
> AAI Worker: "*[Our physician champion]* was the one that kind of went to bat work for us. He has a real passion for it, and he thought, as well, it would help the staff. And so he was the one that spoke up and got things going … and got leadership team behind it … and just making sure that all the appropriate parties are involved and making sure they feel like they have some input into the program and what it would look like."
>
> HCW: "I think it would need to be like a donor who understands the benefit of it … I just think there have to be at least some support initially from the hospital and then move it out into the community. Yeah. And I think there are people who would definitely support it. You know, that we wouldn't have to convince that that how beneficial it is."
>
> AAI Worker: "One of the things I did to help speed things along was I put together a *[AAI]* therapy advisory team - I've got somebody from infection control, from risk, from general counsel, from family partners, from medicine, and from allergy sitting on that team … I think that advisory team is really helpful because we have a lot of people with a lot of different experience. That's been really helpful in getting things done."

Topic Area 2 – Perceived Infectious Disease Risk

The second topic area that was selected as a focus *a priori* for the interviews was the concept of the risk of infectious disease exposure and transmission during AAI programs. This referred to risks to the patients, HCWs, handlers, and therapy dogs. Interviews also concentrated on opinions of infection control policies in place in the hospital.

Participants stated various levels of perceived risk involved in these problems, as well as differences in perspectives on control measures to reduce risk. This level of risk was for AAI programs overall, including sessions for patients and HCW. It was found in the data

that the two topic areas overlapped, in that infectious disease risks were stated to be a barrier to program implementation, both for patients and HCW (*supra* Theme 1.2). Within this topic area are opinions in three major themes; 1) perceived concerns in AAI programs, 2) control measures, and 3) safety responsibility.

Theme 2.1: Concerns

Participants discussed general opinions on hazards associated with AAI programs, and described specific incidences that supported these concerns. Concerns for these programs centered mainly on four sub-themes.

Sub-Theme 2.1.1. Infectious and Non-Infectious Concerns

For infectious disease risks, the most common concern was the therapy animal serving as an intermediate vector in the spread of pathogenic microbes between patients, HCW, or even the handlers. While the study focused primarily on opinions regarding infectious disease risk, participants frequently commented on other hazards, such as phobias and allergies to therapy animals, and dog misbehavior (biting, jumping, etc.). Another non-infectious hazard was the therapy animal handler inadvertently causing distress to the patient (through probing questions or privacy issues), but these latter issues were reported as minimal concerns.

> HCW: "I think that, you know, there is concern that there may be sort of zoonotic transmission of germs from dogs to patients, particularly in patients who don't have an immune system to sort of adequately fight off those germs."
>
> HCW: "I'm concerned about multiple people are touching the same animal. Whatever the person before me passed on, is it staying on the dog? Is it just like another surface that I can just pick it up off of?"
>
> AAI Worker: "I understand the concerns of transferring illness from one person to another with the dog is a factor."

Participants mentioned that these concerns, particularly infectious disease concerns, were compounded by the lack of available research and data in this area.

> AAI Worker: “I'm curious if there are studies that are suggesting the dogs are bringing in any awful thing.”
>
> HCW: “How much extra risk does a dog confer versus me running around that whole hospital?”

Sub-Theme 2.1.2. Negative Perceptions of the Programs

Participants reported a barrier to AAI program use was the negative perceptions surrounding having animals in the hospital. While none of the participants reported having these negative perceptions, it was reported they often dealt with individuals (patients/visitors and co-workers) who did. These second-hand perceptions included the idea that the animals were unclean, a “dirty dog”, or would misbehave. Participants reported that part of the root cause of this misinformation was a lack of understanding in the training needed to be a therapy animal and the difference between a service animal (used for disability), a therapy animal (used for treatment), emotional support or other companion animal (with no training requirement), and personal pets (again with no training requirement), and the distinction in allowance regulations into the hospital for each group.

> HCW: “People are surprised that you can have a dog in a hospital and so just always wanting it to be a really good forward-facing appearance so that you have a positive perception of just the professionalism and all that is associated with it.”
>
> HCW: “I think there is a lot of misnomers when it comes to animals and their cleanliness.”
>
> AAI Worker: “I just worry that less-than-adequately-trained dogs may harm the overall environment for hospital dogs.”

Sub-Theme 2.1.3. Source or Cause of Infectious Disease Risk

Participants commented on what they felt was the likely source or reason for these infectious disease risks. Answers included the patients and other individuals, the therapy animal, or the hospital environment, with participants mentioning a combination of all three sources.

> HCW: "I would guess it would be all the other people who are there, who are present. It's not just going to be the kid; it's going to be the kid and their parents who are there and all the other kids and their parents are there."
>
> AAI Worker: "Sometimes the dog gets tired and then sits on the floor of the hospital. You wonder, is the floor clean? I hope it is. That's the only time that I worry."

Sub-Theme 2.1.4. Not Concerned About the Programs

While various concerns mentioned above were expressed, a majority of the participants were overall not concerned about these programs and felt the risk for infectious disease was low. Most participants related this to confidence in the control measures in place and adherence to those controls. Many participants also stated that people are unlikely to get infectious diseases from a dog. These opinions were shared equally between healthcare workers and AAI workers, and across the individual roles within each group.

> HCW: "I've always been a little bit more of a pragmatist on things like that. You eliminate all risks. And so, I think it's probably a pretty minimal risk."
>
> HCW: "There really have been zero reports of dogs transmitting anything in the hospital environment. I think we're all very cognizant of the rules about contact isolation, but fortunately, the dogs don't get a lot of the human diseases and humans don't get a lot of the dog diseases."
>
> AAI Worker: "No, I've no concern about *[the dog]* transmitting to a patient. I mean, I've never heard of it. And dogs don't spread diseases. … I don't see that a dog is any more of a vector than any doctor who walked in the room. I mean, but we don't think of doctors bringing in disease, but we all bring in bacteria, germs or whatever. I don't see the dog as more of a vector just because he likes to roll in the mud."

Theme 2.2: Controls

Data were collected on knowledge and attitudes about control strategies in place to

minimize infectious disease risk in hospital AAI programs. These attitudes were aggregated into four sub-themes.

Sub-Theme 2.2.1. General Thoughts on Control Strategies and Their Goals

Participants shared their thoughts on current policies, and the suspected rationale for these policies, when asked about the goals of hospital infection control strategies. It was mentioned by both HCW and AAI workers that communication and dissemination of these control strategies and any policy updates are critical to program success and can vary across hospitals and departments. A majority of participants responded that the end goal for these control strategies was ultimately to protect the patient population, but others mentioned protecting the safety of visitors, employees, volunteer handlers, and the therapy animals themselves. Overall, all participants felt control measures and rules were necessary to reduce infectious disease risk and other hazards.

> HCW: "Making sure that there's wide dissemination and knowledge about the protocols and policies that are out there so that confusion doesn't happen."
>
> HCW: "We tend to take infection control very seriously, and so for the dog to get through the proper channels, there would have been important policies in place to protect the children."
>
> AAI Worker: "I think the *[volunteer handlers]* who do it are totally into it. They're proud of their dogs and they just want to do the right thing. You just want these kids to be happy and you want them to get better … the rules are there for a reason to protect us as well as the patients."

Sub-Theme 2.2.2. Targets of Control Strategies

Participants were asked which component of the AAI session should be the focus of control strategies: the therapy animals, the patients and other individuals, or the hospital environment. Most participants felt that all three components needed to be addressed in order to comprehensively reduce risk. For those who did select one component, the

hospital environment was the component that participants felt should be targeted. Participants, especially AAI workers, felt, in general, that there were more controls directed towards the therapy animals than towards individuals or the hospital environment.

> HCW: “I mean, I really think all three. I think you need to control which patients participate, hand hygiene, and I think the handlers are controlling the cleanliness of the dog, and the hospital environment should be clean.”
>
> HCW: “I think there's less risk to the animal itself. And I think if you are kind of focusing on the hospital environment, you're able to cover adequately the patient and staff.”
>
> AAI Worker: “I think it's a three-pronged approach. You have to have it all. It's like a stool, if you have two legs, it's going to tip over. You really need all three. You do need the hospital controls. You do need to screen your dogs and have the right dogs. And I lump handlers in with the dogs, teams I guess I should say. And the patients have to be the appropriate patients for the dog, and they have to do the hand hygiene.”

Sub-Theme 2.2.3. Effectiveness of Control Strategies

Participants were asked how successful the current control strategies were towards reducing infection risk of individuals and therapy animals in AAI programs, and measures not currently being done that could be added. Almost all participants felt control strategies in place were effective as long as they were followed and cited not having any reported negative incidences as evidence of their effectiveness. Participants shared measures that they were currently doing to increase safety during the visits, above the required protocols, including spacing out the time and location of visits to minimize patient-patient contact, and additional cleaning of the hospital environment, the dog, and dog items (leash, collar, vest, etc.). Also discussed were other possible add-on control measures, such as increased hand-hygiene signs in the hospital’s main lobby and protocols for post-visit dog and handler infection control.

> HCW: “I think that overall the process that we have has really proven to be very effective and very safe since we've had little to no incidents with any of the programs … I feel like our policy is pretty comprehensive because it definitely touches on dog behavior, human behavior, infections coming into the hospital, like infections from patient to patient interacting with the dog.”
>
> AAI Worker: “I don't know that they've had any incidences. They must be effective. I can't really imagine doing more, to be honest with you.”
>
> AAI Worker: “But I haven't really seen a lot of focus that is directed that much on either after-care, like after the visit or like addressing the needs, the kind of particular needs of the animal or the handler.”
>
> HCW: “Sometimes several times a day we'll wipe *[the therapy animal]* down *[with antiseptic wipes]*. But we just decided to do that ourselves. Our Infection Prevention team didn't tell us to do that. But I saw that a lot of places were doing that, so we just decided to do that practice as well.”

Sub-Theme 2.2.4. Adherence to Control Strategies

Participants reported that in general adherence to current infection control strategies was very high. Volunteer handlers especially mentioned that they did not want to do or not do any actions that would take away the allowance of them being in the hospital. The measure that was stated to have the most variability of adherence was the hand hygiene of patients, visitors, and staff. Other policies, such as no contact precaution patients and pre-visit dog bathing, were said to be adhered to very strictly. It was reported that these control strategies could occasionally be a barrier to participating in AAI sessions by both therapy animal teams and HCW. Handlers mentioned that bathing the dog before every therapy session was not always feasible or healthy for the dog.

> AAI Worker: “We're pretty vigilant. It's really drilled into us. And it's a privilege to go there. So you don't want to do anything to remove that privilege for yourself or for the others.”
>
> HCW: “The one that's probably broken most often is the *[hand hygiene]* and some handlers are more and that.... I think, like in a clinical setting on the unit, it's probably adhered to better than when the dog gets down into more of the public spaces and there aren't the antiseptic dispensers everywhere … that doesn't seem to be followed as closely.”

> AAI Worker: “Folks are supposed to foam up before they pet the dog. I would say that one's not 100-percent adhered to … but, we're very good about not breaking those rules. We don't want to lose the capacity to have our dogs there. It's not worth it.”

Theme 2.3: Responsibility

A theme that arose from the data was the concept of who is in charge of safety during these visits, and what training goes into preparing these individuals for that responsibility. Perceptions in this theme were broken into three sub-themes.

Sub-Theme 2.3.1. Individual in Charge of Program Safety

Opinions were split between participants on who was responsible. Some stated that the volunteer handler was the person primarily in charge of protecting safety, particularly those programs where the volunteer would see patients without the escort of a hospital employee. Other participants said it was a combined responsibility, where the hospital employee was in charge of the patient and the handler was in charge of the dog. It was also mentioned that hospital leadership (both AAI program directors and hospital administration), as well as the organizations certifying the therapy dog teams, had an important role in the safety of these visits, since they were in charge of designing control measures and ensuring adherence.

> AAI Worker: “It's my job. That's my volunteer position to handle my animals properly, to abide by the rules and to have a safe and happy experience with the children.”
>
> HCW: “I would say in my experience the therapist needs to lead the session, but really I feel like the handler and the therapist have equal responsibility in the safety. My goal-- mine is to keep my patient safe, and I think the handler should keep the dog safe, so if they're both safe we're good.”

Sub-Theme 2.3.2. Training of Handlers and Other Responsible Parties

Since handlers were frequently reported to be in charge of these visits, opinions on the level of training they received to reduce infectious disease risks were reviewed, and how effective their training was in making sure they are comfortable to lead these AAI visits. In general, participants felt the training was adequate, with both the volunteers stating they felt prepared and HCW commenting on the knowledge of volunteer handlers.

> HCW: "I can understand for being super cautious with that too. So I think just a volunteer, making sure that that person has an understanding and the training to be interacting with a lot of different families and different circumstances and experiences day to day."
>
> HCW: "It was interesting to see the dogs were very well trained. They were gentle. And the provider who came with them was also well-trained, was really good with working with the kids."
>
> AAI Worker: "Handlers should try to educate themselves about that so they can be advocates for themselves and for their *[animal]* partners to have a safer experience."
>
> AAI Worker: "I would say that really good training of your volunteers is important, in addition to having the best dogs. You get back what you put in … that's why I put so much training into our volunteers, because they're going to be the point person."

Sub-Theme 2.3.3. Risk to Handlers and Therapy Animals

Responsibility and training were related to the potential risks that the therapy animal team undertook during these visits. In addition to infection risk to both the handler and the dog, other possible concerns specific to the hander included how seeing patients in physical or mental distress could be alarming. For the therapy animal, concerns were of stress or burnout during the visits, and the risk of physical harm.

> HCW: "I think about the handlers a lot because our program is volunteer handlers, that they're walking into, in my case, a pediatric intensive care unit, which might be something if it's their first visit, that is something they've never encountered. And so I want to make sure that what the handler experiences isn't beyond their ability to cope with it, and that they're well prepared."

AAI Worker: “I've had two or three incidents where somebody was a little too rough with *[the therapy dog]*, not intentionally, but they just don't quite have control over their motor skills. So, making sure you maintain safety for the handler and dog as well, I think is really important.”

AAI Worker: “You don't want to scare people away from participating, but you want them to make an informed decision about, you know, risks that they might be undertaking.”

4.5 Discussion

This study evaluated perspectives on risk and benefits in hospital AAI programs from key stakeholders, including healthcare workers and AAI workers. The qualitative methodology study design, which has been previously shown to be effective at identifying benefits for AAI in patient populations (Shen, Abrahamson 2016), allowed us the obtain knowledge, beliefs, and practices from individuals who are intimately involved in these programs. We found major themes within each of the two topic areas; program use for staff including benefits, barriers, and facilitators, and infectious disease risk, including concerns, control measures, and responsibility. These themes link together and can provide insight into appropriate program implementation.

Perceived Risk influences Program Utilization, for Staff and Patients

The benefits of AAI programs for staff—stress reduction, morale booster, improved job function, and gateway to other therapy—were stressed throughout the interviews by both HCW and AAI workers. Stress reduction and morale bolstering have been previously shown in adult patient populations (Ein et al., 2018; Waite et al., 2018), however even though HCW face different occupational stressors than patients, they expressed similar benefits. Stress reductions interventions directed towards healthcare workers have been associated with improved job function, such as mental health counseling, yoga/mediation, and group bonding discussions (Brand et al., 2017; Hall et al., 2016; Pradas-Hernandez et al., 2018), yet this was the first study to show the potential utility of AAI for this purpose. An interesting finding that arose was how AAI sessions could be combined with other proven therapy programs to have a potential multiplicative beneficial effect, as well as be more inclusive of people with different personalities and coping styles. For program implementation, it may be advantageous if therapy dog

handlers receive training in basic human stress reduction techniques, which could be applied to patients and HCW.

However, the benefits of AAI programs are limited by the reported barriers described by participants; that timing and location of programs can conflict with clinical duties, and conflict with agreement that the top priority for AAI programs was to target patients. These opinions were shared equally by both HCW and AAI workers. However, participants also conveyed various facilitators that could be used to resolve these program obstacles. There were diverse opinions on how best to implement these AAI programs, in terms of timing and location, reflecting the need for individualized programs based on unique hospital and department staff needs and schedules. Having appropriate staffing to cover clinical roles was perceived to reduce the burden on HCW, so they would feel they have adequate time to join in AAI programs. The importance of leadership roles was particularly highlighted, both within the department to help with staff scheduling, and at the administration and management level, to advocate for the use of these programs as an important tool for HCW wellbeing, independent of their patient benefit. AAI was reported to be a finite resource, in terms of staff support, number and availability of therapy dog teams, and program funding, limiting its use for patients and even more so for HCW, who would rather it be used for patients. However, with successful advocacy and administrative buy-in, these programs could obtain the support they need to grow, to create a “win-win” situation for patient and HCW wellbeing. With these facilitators in place, this can overcome many of the barriers and lead to an increase in program utilization for HCW benefit. Leadership and program advocates could push that HCW involvement be part of the mission statement of hospital AAI programs, and harmonize the benefits for patients and HCW.

The other topic area was risks related to hospital AAI programs, both for patients and staff, and both HCW and AAI workers primarily reported infectious disease concerns. Nonetheless, while concerns, and the source of those concerns, were explored, a surprising number of participants reported that they had few concerns for these programs. The lack of concern was mainly attributed to the efficacy of (with strong adherence to) control measures. This is reflected in published guidelines from major healthcare organizations that promote AAI therapy as a low-risk activity (Murthy et al., 2015). Yet, there is a drawback to this lack of concern— this could be a barrier to properly designed and applied control measures that would reaffirm people who do have concerns and hesitancy for AAI, particularly those in positions of power (leadership/management). The best situation is if individuals on the ground (HCW and AAI workers) are aware of the risk, understand the magnitude of the risk (how serious it is in reference to other procedures), and know the appropriate methods to reduce that risk. Previous qualitative studies have shown that HCW perceptions and attitudes affect the implementation of precautions to prevent transmission of hospital pathogens and have identified communication and knowledge as a vital component of those attitudes (Nichols & Badger, 2008; Saint et al., 2008; Seibert et al., 2014; Yiwen et al., 2010). It is necessary that staff be aware of and understand existing policies, including their rationale, which relates back to the role of leadership in proper training and communication. Interestingly, in this study, most participants commented on the low risk of therapy dogs in the context of the dogs bringing an infectious agent into the hospital, but only a few talked about the role of the dog as a potential vector, and even fewer discussed the role of the handler. Research has shown that therapy animals can carry hospital-associated pathogens (Dalton et al., 2020), therefore acknowledging this potential risk and focusing on ways to minimize this risk is critical for the continued

safety of these programs.

Program benefits may be strengthened by understanding potential risk, the design and implementation of appropriate control measures, and ensured adherence and monitoring from the designated responsible parties. Infectious disease concerns are one of the major barriers to program utilization for both patients and HCW. This barrier is addressed through control strategies, leadership, and collaboration, which will ensure the continued use and potential expansion of these beneficial programs. Like many other human-animal bond programs, a comprehensive and holistic outlook is needed into order to ensure program sustainability.

Limitations

While this research has many strengths and innovations, there are a few limitations. The first is that the majority of our participants worked or volunteered at pediatric hospitals, rather than adult hospitals. While AAI programs are more frequently used in pediatric populations (Linder et al., 2017), capturing opinions on adult populations may lead to potentially different perspectives and more widespread findings that could be applied to other settings, such as nursing homes and long-term care facilities. Second, it was recognized there were significant differences in protocols across hospitals, and the majority of our participants were from three hospitals. Including more hospitals with heterogeneous program implementation guidelines, staff knowledge and buy-in, and infection control policies may lead to different findings.

Future Directions

The findings from this research can be used to design a wide-reaching quantitative survey, which can capture differences across patient populations and hospital protocols.

Qualitative data has been used successfully to design and implement quantitative surveys, due to its intricate ability to provide in-depth context to a topic matter, which will allow future research to design survey questions that are appropriate, unambiguous and meaningful (Degeling & Rock, 2020). Particularly since the field of human-animal interactions is so complex and multi-faceted, this qualitative groundwork will lead to more suitable objective means and measurements.

The results of this study, and future work in this field, can significantly impact the preservation of hospital-based AAI programs. While it has long been known how beneficial these programs are for patients, their use in HCW populations is a novel application. Given how critical the problem of occupational stress and burnout is to this population, novel strategies are needed. These foundational results suggest their positive usage for HCW, which could potentially be extended to other high-stress occupations, such as first responders. Evidence-based guidelines that address both administrative and hazard concerns will make possible the safe and effective implementation of hospital AAI programs, and reassure hospital administrations and other leadership roles of the value of the human-animal connection in this setting.

4.6 Tables

Table 1: Participant Recruitment Job Classifications

Study Population	**Total**
Healthcare Workers	19 (51%)
Physicians	4
Nurses	6
Child Life Specialists	3
Rehabilitation Therapists (PT/OT)	2
Clinical Social Workers and Psychologists	4
AAI Workers	18 (49%)
Volunteer Handlers	13
AAI Program Directors	5
Total	37

Table 2: Themes and Sub-Themes from Qualitative Data

Topic Area 1: Program Use for Healthcare Workers		
Theme 1.1: Benefits	Theme 1.2: Barriers	Theme 1.3: Facilitators
Stress reliever and morale booster	Conflict with routine clinical duties	General implementation thoughts
Improved job function	AAI priority for patients over staff	Importance of appropriate staffing for coverage and leadership
Gateway to other therapy	Infection disease risks *(expanded into Topic 2)*	Importance of collaboration across the hospital and having program advocates

Topic Area 2: Perceived Infectious Disease Risks		
Theme 2.1: Concerns	Theme 2.2: Controls	Theme 2.3: Responsibility
Infectious and non-infectious concerns	General thoughts on control strategies and their goals	Individuals in charge of safety during these programs
Negative perceptions of the program	Targets of control strategies	Effectiveness of the training for individuals doing these programs
Source or cause of infectious concerns	Effectiveness of control strategies and purposed changes	Risk to handlers and therapy animals
Not concerned about these programs	Adherence to control strategies and barriers to adherence	

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Chapter 5: A Conceptual Framework to Address Barriers for Animal-Assisted Intervention Programs in Healthcare Facilities: Perspectives from a Qualitative Study

5.0 Cover Page

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5.1 Article

Animal-assisted intervention (AAI) programs have been used extensively in healthcare facilities due to their numerous reported benefits to patients (Bert et al., 2016; Kamioka et al., 2014; Waite et al., 2018). These programs have also increasingly been used for healthcare workers, as a targeted intervention to reduce occupational stress and burnout symptoms (Abrahamson et al., 2016). However, barriers, specifically infection control concerns, prevent AAI programs from being used in many hospitals and populations.

This qualitative pilot study aimed to assess key stakeholders' opinions on benefits and concerns related to hospital AAI programs, particularly occupational health benefits for hospital staff and infectious disease concerns. We report on key stakeholders' perspectives and experiences and, through these reports, develop a conceptual framework to recommend measures in order to better implement and support these programs.

As part of a larger study on hospital AAI program-related risks and exposures, we interviewed 37 healthcare workers and therapy animal handlers from multiple hospitals. We thematically coded interview transcriptions based on deductive programmatic framework analysis. The study underwent research ethics review and approval. See [*Chapter 4*] for further details on methodology and study participants.

Participants reported that these programs did benefit hospital staff by reducing stress and bolstering morale. This indirectly led to an improvement in job performance through increased employee engagement, as well as directly providing an "additional tool in their toolbox" for improved patient care. Finally, these programs were reported to be a gateway and incentive to other therapy programs, such as mental health counseling.

Administrative barriers were reported, mainly prioritizing these programs for patients and balancing routine clinical functions. Participants conveyed that these administrative barriers could be overcome with appropriate staffing and leadership, as well as collaboration across the hospital and management "buy-in," to underscore their importance for staff usage.

Infection concerns were reported as a frequent barrier to program implementation, both for patient and healthcare worker use. Participants described their concern of the dog serving as an intermediary vector in the spread of pathogens between patients, staff, and the hospital environment. However, many of the participants, both pet therapy handlers and healthcare workers, felt this risk was minimal through the adherence of effective control measures, which should target the animal, the patients, and the hospital, designed with practical input from multiple stakeholders. The primary facilitator to appropriate enactment of control measures was the designation of individuals responsible for safety, including staff leadership and volunteer handlers, and relevant training of all individuals involved with these programs, about potential risks and ways to mitigate risk.

Through these reports, we developed a conceptual framework (**Figure 1**), adapted from the Consolidated Framework for Implementation Research (CFIR) (CFIR Research Team, 2017) and the Environmental Protection Agency's (EPA) Risk Management Framework (US EPA, 2014), that links our major themes in the context of program implementation. Hospital objectives and needs feed into program implementation, part of which is addressing program barriers through facilitators. Perceived barriers, both administrative and infection risk as described, can be addressed through a risk management framework: 1) identify the hazard (e.g., infection concerns), 2) assess and

characterize said hazard, and 3) manage that hazard through the enactment and monitoring of mitigation strategies (control measures). This results in an adaptive, tailored protocol based on individual program needs. Critical to the design and execution of program implementation is multi-stakeholder engagement and hospital leadership roles, to ensure diverse, comprehensive input and protocol adherence. Implementing adaptive AAI programs, through targeted facilitators, results in program benefits for both patients and staff, since many program barriers and facilitators are for both. This ultimately creates a reinforcing feedback loop of improved program implementation by substantiating hospital needs.

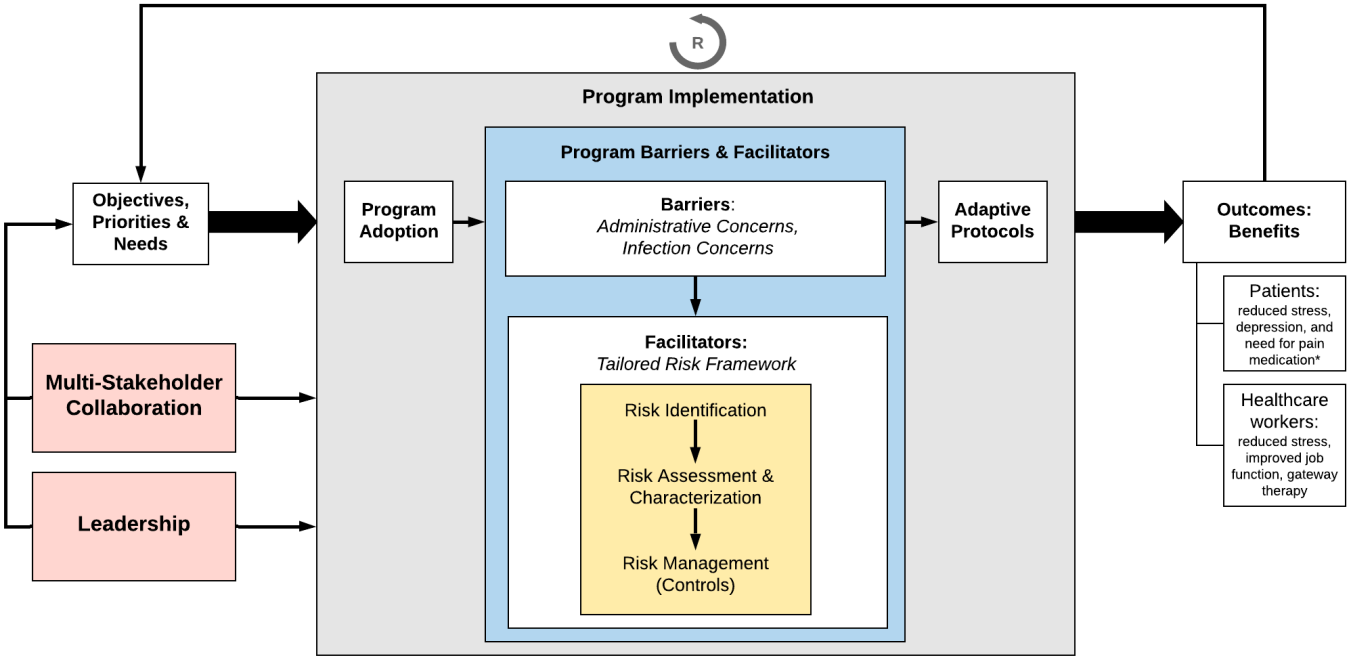
Our qualitative study provided insight into the appropriate AAI program implementation, both directed towards patients and HCW, based on the unique experiences and perspectives from individuals who are actively involved in these programs and have crucial roles in their administration. Through participant reports and the development of our conceptual framework, we identified three major areas for program improvement. First is the need for a tailored risk assessment to understand barriers unique to individual programs, hospitals, departments, and patient populations, to develop tailored adaptive protocols. Secondly, hospital leadership roles are essential to ensure training and appropriate communication of these policies critical to program success. Lastly, collaboration across the hospital is needed to design protocols for AAI programs with input from multiple stakeholder groups. This will ensure that program guidelines are comprehensive and practical.

Understanding diverse perspectives and issues from those on the ground can be used to develop targeted interventions and guidelines. The resulting conceptual framework model can serve as a scaffold guideline for those hospitals wishing to start or extend AAI

programs, noteworthy for hospital administrators, particularly those involved in infectious disease control and epidemiology, and occupational health and safety. The detailed level of contextual qualitative data obtained from our participants can be utilized to develop a practical quantitative survey in order to collect data from a wider scope of hospitals and participant groups and to increase the generalizability of the research findings and recommendations. The results of this, and future work, will have significant implications in the utilization and preservation of these valuable AAI programs.

5.2 Figure

Figure 1: Conceptual Framework for Hospital Animal-Assisted Intervention Program Implementation



Adapted from CFIR and EPA Risk Framework (yellow box). Blue box = program barriers and facilitators, grey box = program implementation, red boxes = external influences. Circled arrow with R = positive reinforcing feedback loop, where appropriate program implementation leads to an increase in program benefits, which validates and increases hospital needs for these programs.

* Most commonly documented patient benefits from systematic reviews of previous literature (Bert et al., 2016; Kamioka et al., 2014; Waite et al., 2018)

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Chapter 6: Impact of a Chlorhexidine Decolonization on Nasal and Dermal Microbiome in Therapy Dogs in Hospital Animal-Assisted Intervention Programs: A Pilot Study

6.0 Cover Page

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6.1 Abstract

Therapy animals in hospital-based animal-assisted intervention programs are an invaluable part of holistic patient care. However, these dogs may be exposed to hospital-associated pathogens through these activities. This pilot study sought to examine a therapy-dog decolonization strategy for infection control by exploring the effects on the therapy's dog entire microbial composition. We found that the chlorhexidine decolonization intervention altered microbial alpha diversity and shifted microbial structures in these therapy dogs, particularly more phylogenetically rare taxa. Specifically, the intervention reduced the abundance of *Staphylococcus pseudintermedius* but did not reduce levels of *S. aureus*, a common human hospital microbe. These preliminary findings hint at the importance of taking into consideration holistic microbial communities when undertaking infection control strategies and stress the need for further research to understand the unintended consequences of their usage and possible secondary health consequences on therapy dog health.

6.2 Introduction

The benefits of the human-animal bond have extended into the use of animal-assisted interventions, which are increasingly used in healthcare facilities for their widely recognized benefits (Kamioka et al., 2014; Waite et al., 2018). However, risks to both the patients and therapy animals from exposure to hospital-associated pathogens are not fully characterized. Previous work has shown that therapy animals that volunteer in hospitals are five times more likely to carry methicillin-resistant *Staphylococcus aureus* compared to therapy animals that volunteer in other non-healthcare settings (Lefebvre et al., 2009). Infection control strategies designed to reduce the spread of pathogens between patients and therapy animals have been considered to improve program safety and increase their beneficial utilization.

A common infection control practice is the use of disinfectants on frequently touched environmental surfaces, or fomites. This can include the fur and gear of therapy animals. Topical disinfectants have been shown in previous research to reduce the bacterial burden of culture-based *Staphylococcus aureus* on therapy animals, as well as reduce the transmission to patients (Dalton et al., 2018). However, disinfectants have been shown to alter the microbial composition of both humans and dogs. In humans, topical disinfectant effects were dependent on personalized and body site-specific colonization signatures but lowered overall microbial diversity level (SanMiguel et al., 2018). In dogs, chlorhexidine disinfectants are frequently used to treat atopic dermatitis, which is characterized by a higher abundance of staphylococcal species and lower overall diversity (Chermprapai et al., 2019; Tress et al., 2017). Treatment with a topical disinfectant and targeted antimicrobials restored the dermal microbiome in atopic patients (Bradley et al., 2016). It is unclear what impact topical disinfectants might have on the skin and

nasal microbial communities of healthy therapy animals. Therapy animals, with their frequent hospital exposure, may have unique microbial compositions compared to normal pet dogs. These distinct communities could then be differentially affected by the disinfectant.

Therefore, the goal of this research is to describe the skin and nasal microbial composition of therapy dogs and how this composition is influenced by the use of a chlorhexidine decolonization intervention. The results of this work will inform the design of more extensive studies, with implications for infection control strategies. Such work is critical to minimize unintended consequences to the health of these volunteer therapy animals from interventions such as the use of disinfectants.

6.3 Methods

Study Population

This pilot study was conducted in a mid-Atlantic hospital between July 2016 and May 2017. The study protocol was approved by all applicable institutional review boards, institutional animal care and use committees, and scientific review committees prior to data collection. Canine participants were registered therapy animals volunteering at an academic hospital's animal-assisted intervention program. These therapy visits were group sessions, lasting one hour, where multiple pediatric patients interacted with the animals.

Data Collection

Enrolled therapy dogs underwent two observational control visits, where they adhered to existing hospital guidelines, requiring the dog to be bathed using an over-the-counter shampoo of the owner's choice within 24 hours prior to entering the hospital. Matched samples were collected from all individuals before and after the therapy session. All sample collection was done by trained research staff.

A detailed description of sample collection is described elsewhere, see [*Chapter 7*]. Briefly, we obtained nasal, oral, inguinal, and perineal samples from the therapy dog before and after every therapy session. Samples were collected using sterile flocked swabs (Puritan, Guilford, ME, USA), which were stored at -80°C until processing. Handlers were asked survey questions about their therapy dog's medical history and volunteer work at every visit. We captured the total number of patients that interacted with the dog at every visit.

Intervention

After two control visits, the therapy dog team underwent two intervention visits using a two-part decolonization intervention on the therapy dog. First, the therapy dog handler used a 4% chlorhexidine-based veterinary prescription shampoo (DUOXO Ceva, Libourne, France) prior to the study visit. Second, during the therapy visit, the dog was wiped down with 3% chlorhexidine wet cloths (DUOXO Ceva, Libourne, France) down the dorsal head and back, "the petting zone". Handlers were given information about both products before usage. The same data collection protocol was implemented for these intervention visits, as described above.

Laboratory Processing for Microbial Communities

A detailed description of laboratory and sequencing protocols are described, see [*Chapter 7*]. DNA was extracted from the thawed sterile flocked swabs, and the V1-3 region of the 16S rRNA gene was PCR-amplified and sequenced using established protocols for microbial composition analysis using the Illumina MiSeq (Illumina, San Diego, CA) at the University of Pennsylvania Next Generation Sequencing Core (Fadrosh et al., 2014).

QIIMEv2.7 was used to match sequencing reads to samples (Bolyen et al., 2019), and the DADA2 pipeline was used for quality filtering and clustering samples into features (amplicon sequence variants, ASVs) (Callahan et al., 2016). ASVs were matched to taxonomy and phylogeny using established pipelines, see [*Chapter 7*]. Unidentified sequences not matched to taxonomy on our classifier were manually entered into the NCBI BLAST database for taxonomic classification. Quality control was ensured through

identifying likely taxa contaminants through negative controls collected during field sampling, DNA extraction, and sequencing (Davis et al., 2018).

Statistical Analysis

Statistical analyses were performed in RStudio v1.1.423 (R Development Core Team, 2010). To maintain the maximum number of samples for comparison, the sequencing data was not rarefied for statistical analysis. Taxa tables, and matching phylogeny and taxonomy, were analyzed using the phyloseq pipeline to calculate alpha (within sample) and beta (between samples) diversity metrics (McMurdie & Holmes, 2013). The negative binomial-based model DESeq2 program was used to identify differential abundance of key taxa between groups (Love et al., 2014). Kruskal-Wallis nonparametric one-way analysis of variance test was used to examine differential alpha diversity between all groups, and Wilcoxon rank-sum test was used for pair-wise comparisons between groups, both adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) correction.

6.4 Results

Study Population and Samples

A total of 4 dogs were included in the study over 13 visits, with 5 intervention study visits, shown in **Table 1**. Ages were equally distributed, and more dogs were female. Therapy dog handlers reported recent veterinary antibiotic usage in the last month in 38% of the visits, and a recent veterinary hospital visit in the last month in 23% of the visits. Therapy dog handlers reported being involved in AAI programs more than once a week after 38% of the visits. Of the 13 visits, 54% had more than 3 patients interacting with the dog during the therapy visit. A total of 100 swabs were collected for microbial analysis - 26 each nasal, oral and perineal swabs, and 22 inguinal samples. All samples were matched for pre- and post-visits.

Taxa Abundance

The relative abundance of taxa was different both across sample locations and individual dogs, as shown in **Figure 1.A-D**. Both the nasal and oral samples tended to be dominated by key taxa, such as *Staphylococcus* (mean relative abundance 0.111), *Porphyromonas* (mean 0.099), *Corynebacterium* (mean 0.095), and *Moraxella* (mean 0.073) genera, while inguinal samples had a higher number of more unique taxa.

The intervention impacted levels of the top genera in different ways, also shown in **Figure 1.E**. The intervention reduced the mean relative abundance of *Staphylococcus*, *Corynebacterium*, and *Capnocytophaga* taxa (DESeq $p<0.0001$). Conversely, *Conchiformibius* and *Fusobacterium* were increased in intervention visits (DESeq $p<0.0001$). No significant difference was found in taxa between pre- and post-visit samples overall, and within each site.

Staphylococcal Species Abundance

Figure 2 represents the relative abundance of the top three *Staphylococcus* species - *S. aureus*, *pseudintermedius*, and *schleiferi*, and demonstrated no significant changes between pre and post samples (absolute abundance depicted in **Supplement Figure 1**). However, there was a significant difference in the relative abundance of *S. pseudintermedius* between control and intervention samples among pre samples (relative abundance 0.043 in control and 0.0008 intervention, Wilcoxon rank-sum test p=0.002) and post samples (relative abundance 0.042 in control and 0.004 intervention, Wilcoxon rank-sum test p=0.008).

S. schleiferi abundance was also shown to be decreased due to the intervention (mean relative abundance 0.026 in control and 0 in intervention, Wilcoxon p=0.036), with equal association seen in both pre and post samples. *S. aureus* levels were not significantly different between control and intervention visits, within pre or post samples.

Alpha Diversity

Alpha diversity by site was evaluated with Shannon and Faith's phylogenetic metrics, shown in **Figure 3.A&B**. When comparing across anatomical sites, nasal, oral and perineal samples were more similar to each other in alpha diversity levels, which were all statistically different than the overall alpha diversity in inguinal samples (Kruskal-Wallis test $p<0.001$ for all pairwise comparisons with inguinal samples, for Shannon and Faith's). There was no statistical difference in Wilcoxon rank-sum test when comparing the overall alpha diversity levels from pre- to post-visit, in all samples and within each site, and across individual dogs.

In individual-level changes, shown in **Figure 3.C&D**, there was an overall increase in alpha diversity after control visits (mean Shannon change 0.18, mean Faith change 6.54) and an overall decrease in intervention visits (mean Shannon change -0.26, mean Faith change -1.93). Perineal and nasal samples showed the most substantial difference (significant difference in Faith metric using Wilcoxon rank-sum test $p<0.05$). This same effect was seen in both pre and post samples. All other comparisons of diversity levels at each sample site, both overall and within pre and post samples, were not significant.

Supplement Table 1 shows how additional dog demographics, such as age, sex, and medical history, impacted alpha diversity levels. Significant associations were observed based on recent antibiotic usage and veterinary hospital visit, as well as reported AAI frequency (the number of times the dog participated in AAI programs) and the number of patients in the visit.

Beta Diversity

Principal coordinate analysis plots are displayed in **Figure 4**, overall and within each site, using both weighted UniFrac and unweighted UniFrac distance. Clustering was observed by sample site (PERMANOVA FDR-corrected $p<0.001$ for both weighted and unweighted UniFrac distance) and by subject overall and within each individual site (PERMANOVA $p<0.001$ for both weighted and unweighted UniFrac distance). There were no differences in microbial composition when comparing before versus after the visit, overall and within each site.

There was a difference in microbial composition between samples in control visits and intervention visits (PERMANOVA $p=0.03$ unweighted and $p=0.009$ weighted). The impact of the intervention on microbial composition was different based on the sample

site. For unweighted UniFrac, only perineal samples showed microbial composition differences between control and intervention visits (PERMANOVA p=0.03). Using the weighted UniFrac metric, only nasal samples had a significant PERMANOVA p-value below 0.05. There was no difference in intervention effect when stratifying by pre or post visit.

Supplement Table 1 shows the distance between two samples by dog demographic factors, such as age, sex, and medical history. There was a significant difference in the microbial composition of dogs based on their age, sex, and recent antibiotic usage, using both unweighted and weighted UniFrac distance. Recent veterinary hospital exposure and the number of patients in the therapy visit were shown to impact the unweighted but not weighted UniFrac distance, while reported AAI frequency did not have an association.

6.5 Discussion

The research aimed to explore the microbiota of healthy, non-atopic dogs that participate in an animal-assisted intervention program and to examine the influence of topical chlorhexidine use on therapy dogs in the context of a pilot infection control intervention. We found that body sites were uniquely affected by the chlorhexidine intervention, and more phylogenetically rare taxa and dogs-specific taxa such as *S. pseudintermedius* were shown to be reduced post-intervention.

Therapy Dogs Compared to Normal Pet Dogs

Similar to normal companion dogs, therapy dogs showed unique patterns across body sites. Samples were more similar to the same site on another individual dog than to another site on the same individual, confirming that the ecological body site niche is a more significant determinant of microbiota composition (Chermprapai et al., 2019; Cuscó et al., 2017; Grice et al., 2009; Misic et al., 2015). As with humans, the skin microbiota in our canine participants varied between different body sites, presumably because of differences in the local cutaneous microclimate. Previous studies have shown that the canine bacterial community is diverse and variable across different body sites within the same dog, and across the same site in different dogs (Hoffmann et al., 2014).

Alpha diversity metrics, assessed by Shannon's and Faith's Phylogenetic diversity, were shown to be unique across body sites, with nasal samples dominated by few key taxa and inguinal samples having a higher number of more unique taxa. Similar to previous studies, therapy dogs had higher diversity levels in haired regions (inguinal skin) than mucosal areas and mucocutaneous junctions (Hoffmann et al., 2014). *Staphylococcus* was increased in these therapy dogs, particularly in nasal samples, compared to prior

reports that *Moraxellla* tends to be the dominant taxa (Bradley et al., 2016; Tress et al., 2017). Nonetheless, *Staphylococcus* spp. in these therapy dogs was less than what is reported in dogs with underlying pathologies, such as atopic dermatitis, pyoderma, or chronic rhinosinusitis (Bradley et al., 2016; Tress et al., 2017; Weese, 2013). Although no comparison dogs were sampled for this pilot study, the differences between this study and the literature may suggest that frequent hospital exposures experienced by these dogs could affect their microbial composition. This same finding has been reported from research on healthcare workers when comparing their microbial composition to the general population (Rosenthal et al., 2013).

Effect of the Decolonization Intervention on Microbiota

Diversity metrics, both alpha (within-sample) and beta (between-sample), was shown to be influenced by the chlorhexidine in similar ways. Dogs tended to have increased alpha diversity in control visits from pre to post samples, and decreased diversity from pre to post samples in intervention visits. There were minimal changes in alpha levels within samples comparing pre to post samples, as well as minimal changes in beta differences in microbial composition between pre samples compared to between post samples. However, there was a significant difference between control versus intervention samples. Intervention samples tended to have lower alpha diversity and have significantly different microbial compositions compared to control samples. This association was more robust when using phylogenetically weighted metrics (Faith's alpha diversity and weighted UniFrac beta diversity) and within nasal and perineal sites.

Taking the results from both alpha and beta diversity together, the differences appreciated due to the chlorhexidine intervention are driven primarily by more phylogenetically rare taxa rather than common taxa. Previous studies on pet dogs (Davis,

2016; Oh et al., 2015; Song et al., 2013) have shown that dogs have more diverse unique microbial communities compared to their human counterparts. It can be proposed that these phylogenetically rare taxa originate from the dog, which are reduced by the dog decolonization. Nasal and perineal sites, which both tend to have lower diversity levels overall, are more influenced by this disturbance. This is an interesting finding, that a topical treatment could be associated with altered microbiome on sites not directly exposed to the chlorhexidine (shampoo just on the skin, and wipes just on the dorsal back/head).

To determine which microorganisms were associated with this change in diversity, we evaluated the abundance of identified taxa, which were differentially impacted by the chlorhexidine intervention. *Staphylococcus*, *Corynebacterium*, and *Capnocytophaga* species were shown to be reduced during the intervention, while *Fusobacterium* and *Conchiformibus* tended to be increased during the intervention. *Staphylococcus* and *Corynebacterium* spp. have been shown to be higher in abundance in dogs with medical conditions, such as atopic dermatitis (Hoffmann et al., 2014; Pierezan et al., 2016). In one study, *Capnocytophaga* was found in be increased in nasal neoplastic samples compared to healthy nasal samples (Tress et al., 2017). Studies on the effect of chlorhexidine in human skin have also identified an association with decreases in overall diversity levels and decreases in specific *Staphylococcus* and *Corynebacterium* taxa (SanMiguel et al., 2018).

Due to its clinical significance, *Staphylococcus* was further evaluated at the species level. The chlorhexidine intervention impacted the abundance of *S. pseudintermedius* and to a lesser degree *S. schleiferi*, more so than *S. aureus*, the three dominant staphylococcal species observed. Both *S. pseudintermedius* and *S. schleiferi* were shown to be decreased

during the intervention, significantly so for *S. pseudintermedius*, while *S. aureus* slightly increased abundance in intervention visits (in both relative and absolute levels). Again, even though the intervention was used just on the skin, nasal samples showed the greatest difference. This is not surprising because *Staphylococcus* species frequently colonize the nose in dogs (Iverson et al., 2015; Weese & van Duijkeren, 2010). *S. pseudintermedius* and *S. schleiferi* tend to be dog-specific microbiota and tend to only incidentally contaminant humans (Weese & van Duijkeren, 2010).

It is uncertain from our single timepoint samples if the intervention selectively removed or reduced certain taxa, such as dog-specific *S. pseudintermedius, S. schleiferi,* and phylogenetically diverse microbiota. Another possibility is that the decolonization removed or reduced all microbiota equally, but prior to sampling, the therapy dog was recolonized with microbiota that are more commonly associated with humans or the hospital environment. This would result in what appeared to be no change in the abundance of common taxa, such as *S. aureus*. The source of this re-colonization could be from hospital exposure, from interaction with other individuals while going to the therapy visit (prior to our pre-visit sampling), or even from the therapy handler.

Limitations and Future Directions

A limitation of this pilot study is that our samples only reflect carriage of microorganisms at one timepoint. We cannot make inferences from our data on whether these microbial exposures and observed changes are transient contamination or stable colonization. Future research in this field will examine the temporal progression and stability of microbial community alterations due to the decolonization; abundance of key taxa of clinical concern and dog-specific microbiota, as well as overall diversity levels. Further study would also benefit from understanding the secondary health consequences

of the decolonization intervention within this therapy dog population, such as the role of *S. pseudintermedius* as a protective commensal versus opportunistic pathogen, and possible competition with *S. aureus*. The zoonotic potential of both is important to consider as these therapy dogs frequently interact with patients with compromised immune function.

Conclusions

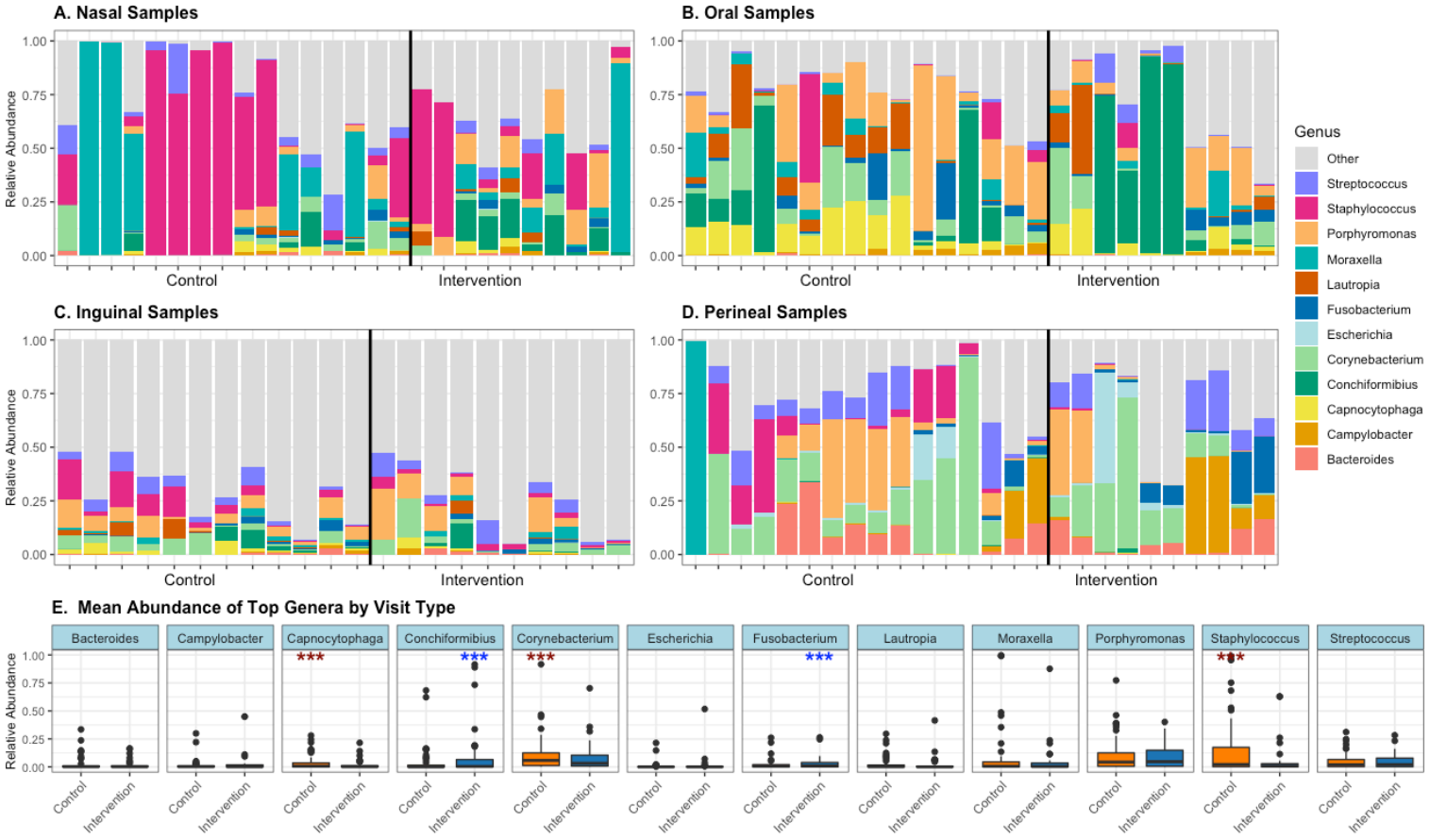
This study benefits from being the first to examine the microbiota of therapy dogs and the effect of a decolonization intervention on therapy animals in hospital animal-assisted intervention programs. Understanding cutaneous microbial ecology is essential to create future targeted therapies that might require not only a reduction in exposure to pathogenic bacteria, but also a promotion of the symbiotic commensal microbiota. This pilot study presents the feasibility and importance of assessing holistic microbial communities in this essential canine worker population. The study demonstrates the potential for infection control practices, designed to limit exposure to pathogens, to alter microbial communities more broadly, with unknown consequences. This has important implications for handlers and practitioners in charge of these therapy dogs' care and hospital administration, on the importance of considering the holistic microbial environment when designing interventions to keep these hospital animal-assisted intervention programs safe for patients and the therapy dogs.

6.6 Tables and Figures

Table 1: Study Population

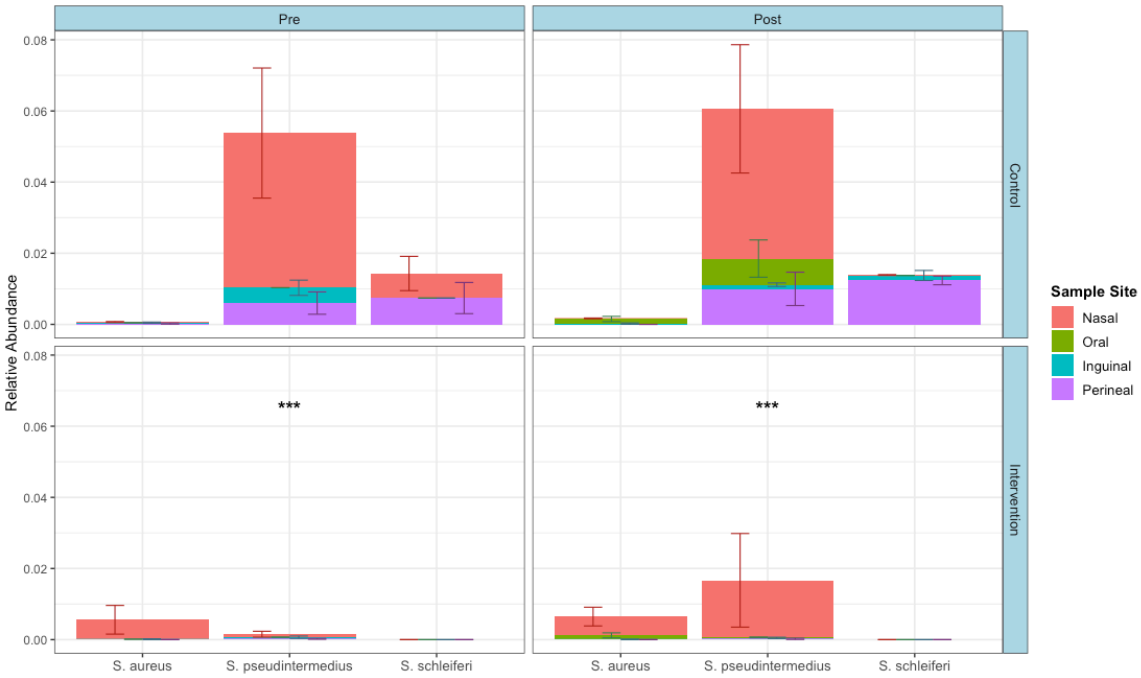
	Total
Unique Dogs	4
Age < 6 years old	2 (50%)
Male	1 (25%)
Study Visits	13
Intervention Visits	5 (38.5%)
Antibiotics Last Month	5 (38.5%)
Veterinary Hospital Visit Last Month	3 (23%)
AAI Frequency >1 week	5 (38.5%)
Patients in Visits Total > 3	7 (54%)

Figure 1: Relative Abundance of Top Genera, by Site and Visit Type *(genera with mean abundance >25%)*



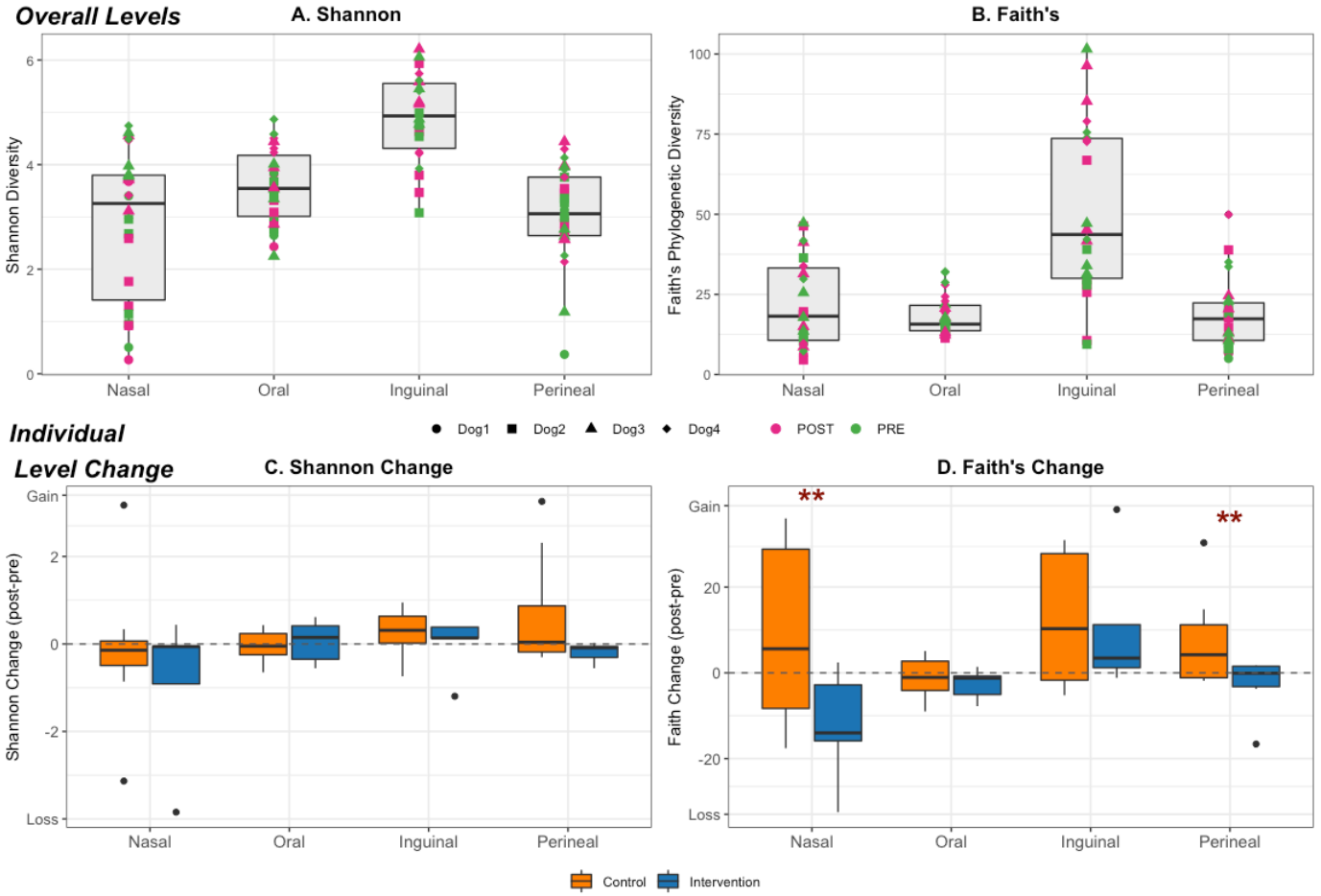
A-D: Bars represent individual sample-level relative abundance of genera that have a mean abundance above 25%, stratified by site. Black horizontal bar divides samples taken from control visits and intervention visits. E: Mean relative abundance of top genera by visit type, aggregated pre/post samples and different sites. *** DESeq results p<0.0001 for differential abundance by visit type, red = higher in control, blue = higher in intervention

Figure 2: Relative Abundance of Key Staphylococcal Species, by Visit Type and Time



Bars are aggregated mean relative abundance of top three *Staphylococcus* species, colored by sample site, with error bars for standard error.
*** Wilcoxon Rank-Sum Test continuity-corrected $p<0.01$ Control vs Intervention.

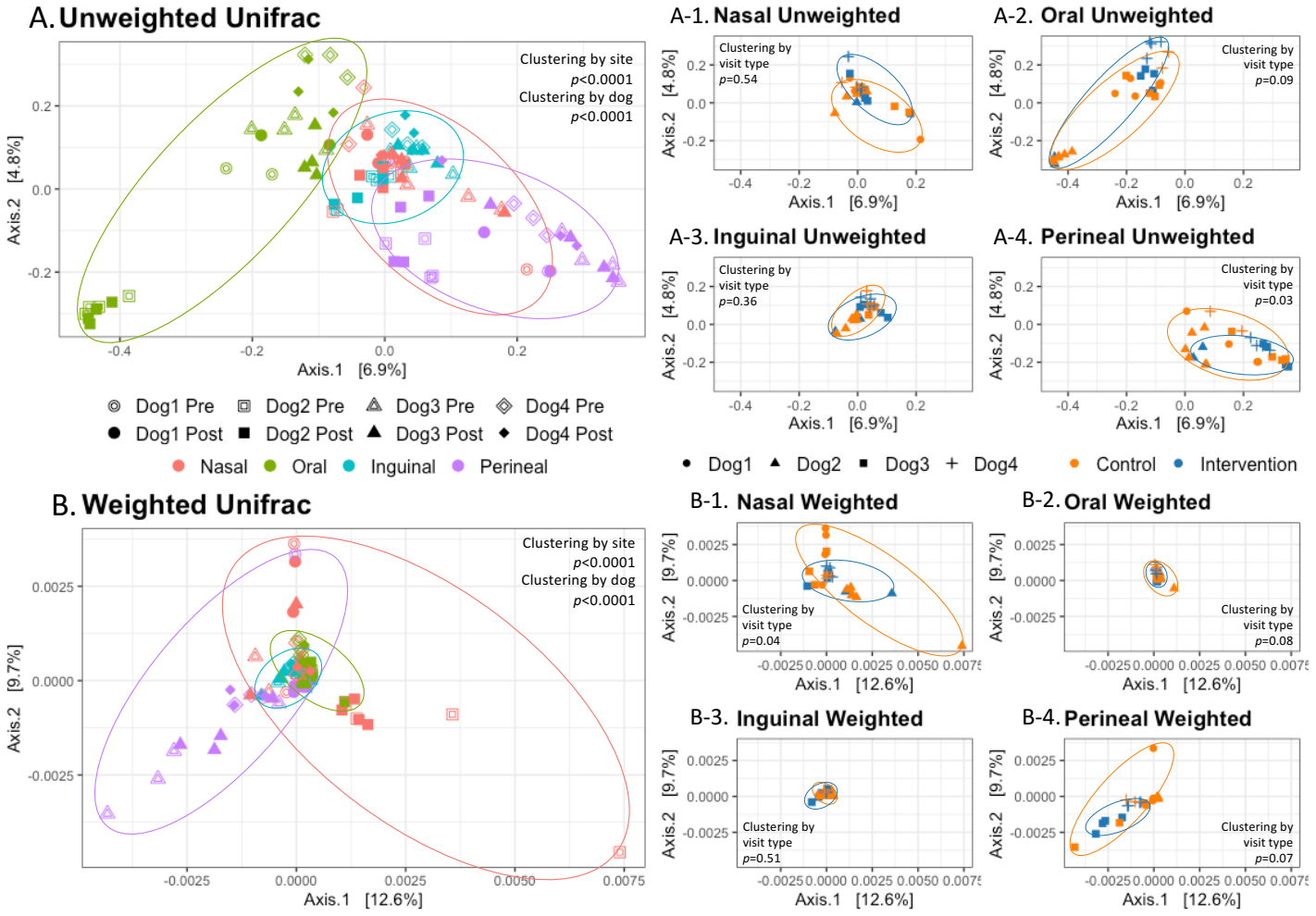
Figure 3: Shannon and Faith's Alpha Diversity Levels by Sample Site *(overall and changes during visit)*



A & B aggregated alpha diversity levels (Shannon A, and Faith B), by sample site, C & D individual level change (post-pre visit) alpha diversity levels by sample site
*** Wilcoxon-Test p<0.05", "Control vs Intervention

Figure 4: Principal Coordinate Plots for Unweighted and Weighted UniFrac Beta Diversity Levels by Dog and Site, and by Visit Type within Each Site

Clustering assessed by adonis PERMANOVA model with FDR-corrected p-value



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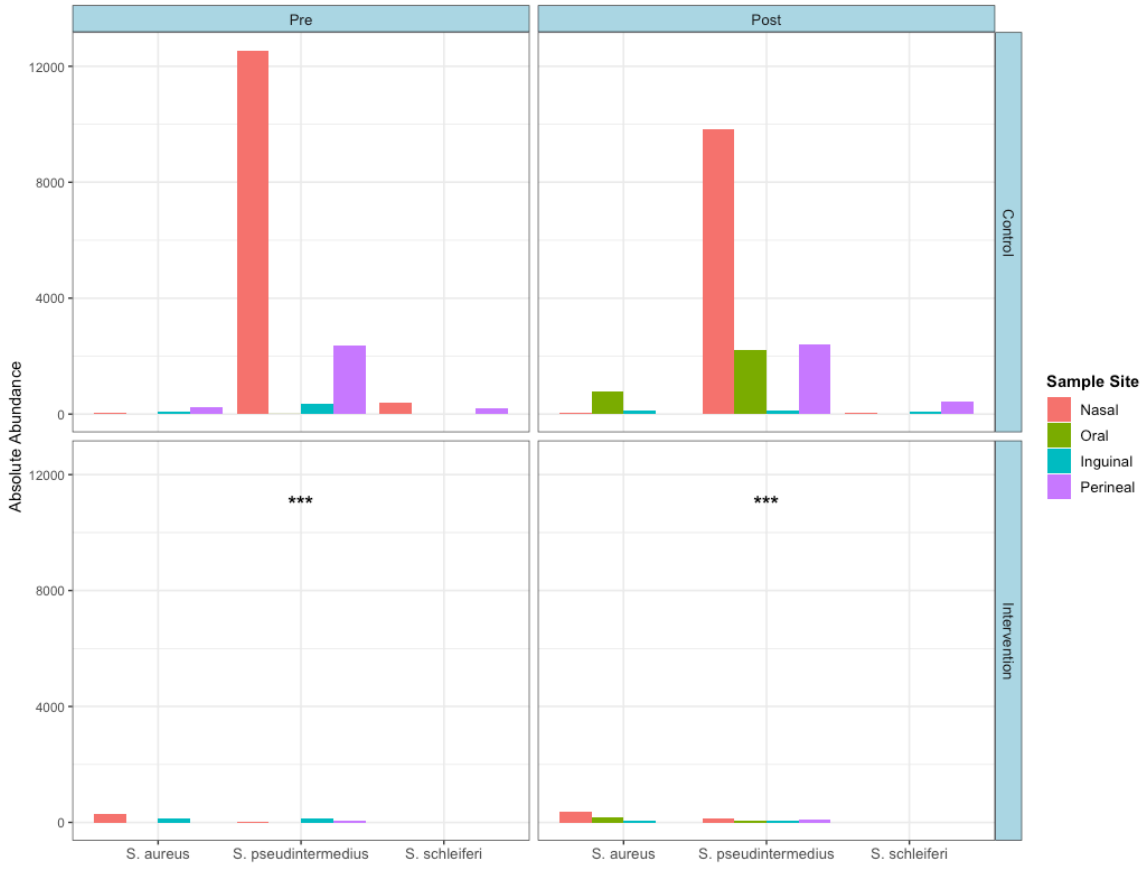
6.8 Supplementary Materials

Supplement Figure 1: Absolute Abundance of Staphylococcal Species by Site



Bars are aggregated mean absolute abundance of top three *Staphylococcus* species dodged by sample site, stratified by pre and post visit and visit type.

*** p<0.0001 DESeq differential absolute abundance by visit type (overall abundance and within nasal samples)

Supplement Table 1: Changes in Alpha and Beta Diversity Levels based on Dog Factors

	Alpha Diversity					Beta Diversity			
	Shannon		Faith			Unweighted UniFrac		Unweighted UniFrac	
	Mean (SD)	KW * p-value	Mean (SD)	KW p-value		Distance within groups+; mean (SD)	PERMANOVA p	Distance between groups; mean (SD)	PERMANOVA p
Age									
<6 years old	3.55 (1.36)	0.9556	30.1 (20.3)	0.1218		0.638 (0.119)	**0.0001**	0.756 (0.193)	**0.0001**
>6 years old	3.54 (1.2)		33.3 (16.8)			0.662 (0.118)		0.737 (0.224)	
					between group distance+	0.662 (0.105)		0.777 (0.224)	
Gender									
Male	3.15 (1.13)	0.0097	26.0 (12.4)	0.0064		0.623 (0.141)	**0.0001**	0.709 (0.224)	**0.0001**
Female	3.74 (1.29)		34.4 (20.1)			0.657 (0.109)		0.768 (0.201)	
					between group distance	0.665 (0.108)		0.769 (0.177)	
Antibiotics last month									
Yes	3.03 (1.23)	**0.0001**	24.3 (12.0)	0.0016		0.617 (0.137)	**0.0001**	0.745 (0.227)	**0.0001**
No	3.87 (1.19)		32.2 (20.2)			0.661 (0.104)		0.756 (0.192)	
					between group distance	0.667 (0.137)		0.773 (0.184)	
Hospital last month									
Yes	2.88 (1.0)	0.0012	21.1 (7.54)	0.0032		0.578 (0.118)	**0.0002**	0.738 (0.213)	0.0148
No	3.74 (1.28)		34.3 (19.4)			0.570 (0.106)		0.768 (0.193)	
					between group distance	0.647 (0.117)		0.758 (0.192)	
AAI frequency									
>1week	3.12 (1.27	0.0084	24.5 (13.3)	**0.0002**		0.628 (0.120)	0.0053	0.775 (0.223)	0.0018
<1week	3.79 (1.21)		36.5 (19.7)			0.664 (0.106)		0.748 (0.178)	
					between group distance	0.66 (0.115)		0.773 (0.198)	
Child Total									
> 3	3.92 (1.2)	**0.0001**	35.9 (19.1)	0.0014		0.664 (0.103)	**0.0002**	0.752 (0.193)	0.0018
≤ 3	3.07 (1.2)		20.2 (16.1)			0.631 (0.125)		0.768 (0.202)	
					between group distance	0.664 (0.112)		0.768 (0.192	

*KW = Kruskal-Wallis test for median alpha differences between groups

+ Beta distance presented as within group distance (eg. mean distance on PCoA microbial composition plot between two young dogs) or between groups (eg. mean distance on PCoA plot between a young and old dog). PERMANOVA model for beta distance differences between groups with FDR-corrected p-value.

Example: Dogs without antibiotics in last month had higher Shannon alpha diversity, and were significantly different in microbial composition for both weighted and unweighted UniFrac distance, compared to those who received antibiotics recently

Chapter 7: Microbial Sharing between Pediatric Patients and Therapy Animals during Hospital Animal-Assisted Intervention Programs

7.0 Cover Page

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7.1 Abstract

Hospital animal-assisted intervention programs are a validated and valuable part of holistic patient wellness. However, concerns of microbial transmission limit program utilization in healthcare settings. This pilot study evaluated the potential for microbial sharing between pediatric patients and therapy dogs, both pathogens and general microbiota, and determined if patient-dog contact level and a dog decolonization protocol modified this sharing. Patients, therapy animals, and the hospital environment were sampled before and after every group therapy session. It was found that microorganisms were transmitted between patients and therapy animals, as evidenced by changes in the relative abundance and overall diversity levels of the microbiome and changes in rates of cultured *Staphylococcus aureus*. Higher contact was associated with increased sharing between patients and therapy animals, and between patients. A topical chlorhexidine-based dog decolonization intervention was associated with lower microbial sharing between therapy dogs and patients, particularly from the removal of rare-dog microbiota, but did not significantly affect sharing between patients. This suggests that the therapy animal is not the only source of microorganisms during these group hospital AAI sessions, and other pathways of exposure to patients should be further explored to determine their relative importance. Infection control protocols should be designed with these implications in mind.

7.2 Introduction

Throughout history, companion animals have demonstrated societal benefits, including improved owner mental health and fitness. This concept has led to their use in healthcare settings; hospital-based Animal-Assisted Intervention (AAI) therapy is the use of animals, typically dogs, as an alternative treatment to improve physical, mental and social functions in holistic in- or out-patient care. AAI has been widely implemented as a therapy modality in a range of physio-social conditions in various settings in healthcare facilities, and is increasingly popular, especially for pediatric patients. Research into the effectiveness and overall benefits of AAI is increasing, with the most common benefits including a reduction in patients' requirement for pain medication, enhanced socialization, and reduced stress and anxiety (Bert et al., 2016; Charry-Sanchez et al., 2018b, 2018a; Kamioka et al., 2014; Waite et al., 2018).

Conversely, one must consider the potential risk of incorporating animals into this type of setting, which includes individuals with decreased immune function. Not only are allergies and phobias potential problems, but there is a potential for zoonotic disease transmission, the spread of diseases from animals to humans. Further, hospitals can be incubators for infectious disease agents, such as methicillin-resistant *Staphylococcus aureus* (MRSA), that more typically spread human-to-human or via the environment. While close contact and antimicrobial selective pressure inherent to healthcare settings enhance pathogen circulation, therapy animals may unwittingly serve as mechanical vectors of transmission. Current research on the hazards associated with AAI has shown that therapy dogs can carry common hospital-associated pathogens (Boyle et al., 2019; Dalton et al., 2020; Lefebvre et al., 2009). But, the evidence is lacking on the spread of

these pathogens to humans, potential subsequent infections in both people and therapy animals, and the role of the hospital environment.

However, we know that microbes, including pathogens, function in the context of their holistic microbial community, and other microbiota besides pathogens may be transmitted during these AAI sessions. Specifically, dogs have unique microbial compositions (Hoffmann et al., 2014; Oh et al., 2015; Swanson et al., 2011), which, compared to humans, could result in a distinct ability to acquire, carry, and spread hospital-associated pathogens, as well as uniquely influence the microbial composition of individuals they come into contact, in a way that is fundamentally different than contact with other people or objects in the environment. This is best illustrated when we look into the research surrounding the microbial shifts resulting from pet ownership, which is associated with more diverse microbial compositions that are more frequently shared between pet owners (Misic et al., 2015; Song et al., 2013). Early life pet ownership is associated with decreased incidents of various immune dysfunctions, and exposure to diverse microbes from farming environments, including animals, is protective against the development of asthma in children (Azad et al., 2013; Fall et al., 2015; Stein et al., 2016; Tun et al., 2017). However, these studies refer to chronic exposure from living with pets. It is uncertain if these same microbial shifts will occur with transient, often less than one hour, exposure of patients to a therapy animal.

This pilot study aimed to explore the potential for microbial sharing between pediatric patients, therapy animals, and the hospital environment during animal-assisted intervention programs. We hypothesized that therapy dogs could serve as intermediary mechanical vectors in the transmission of microbes between the hospital environment and patients, increasing patients' risk of microbial exposure due to interaction with the

therapy animal, as shown in **Figure 1**. We examined if the level of contact between patients and therapy dogs modifies this microbial sharing. We deployed a novel adaptation of an existing FDA-approved topical treatment as a targeted intervention on the therapy animal intended to reduce the risk for therapy animals to enhance microbial transmission among patients and mitigate potential risks from exposure to infectious agents to patients participating in AAI. We secondarily hypothesized that this intervention, aimed to decrease bacterial colonization in the therapy animal, will have downstream effects on microbial composition in patients. Finally, we wanted to ensure that the intervention did not impact the potential benefits from these sessions. This research will aid clinicians and healthcare managers in the proper implementation of AAI therapy, to ensure the safety and sustainability of these valuable programs in the future.

7.3 Methods

I. Study Population

This pilot study was conducted at a pediatric oncology outpatient unit in a mid-Atlantic hospital between July 2016 and May 2017. At the time of this study, the department had an established group therapy dog program. The study protocol was approved by all applicable institutional review boards, institutional animal care and use committees, and scientific review committees prior to data collection. All participants, ages 2 to 20, were cleared by their primary clinician before being eligible to both participate in the therapy session and enroll in the pilot study. Parents of child-patients provided written informed consent. The therapy dog program schedules one therapy team (one dog with one human handler) per week for one hour, during which approved patients could visit the dog. Frequently, multiple patients interacted with the dog at the same time. Parents and non-patient siblings also interacted with the therapy dogs and handlers but were not included in the study.

II. Data Collection

For enrolled therapy dog teams, the first two study visits used the existing therapy dog program protocols, which required the therapy animal to be bathed 24 hours before entering the hospital. The overall goal of sample collection was to collect samples prior to dog-patient interaction and then again following interaction from the hospital environment, the therapy dog, and all patient participants as part of the session (see **Supplement Figure 1**). Trained research staff performed all sample collection.

II.a. Environment

Prior to the therapy dog entering the gymnasium, we collected samples of floor dust from a standardized area with a vacuum filter and a sterile electrostatic cloth (Swiffer™, Proctor & Gamble, Cincinnati, OH, USA), as described in other studies (Davis et al., 2012). Once the study visit was completed and all the participants and therapy team had left, we resampled the same sites using the same protocol.

II.b. Therapy Dogs

When the therapy team entered the gymnasium, the dog was sampled with swabs; Copan E-swabs (Copan Diagnostics, Murrieta, CA, USA) for targeted culture and sterile flocked swabs (Puritan, Guilford, ME, USA) for microbial communities. Sites sampled included the nasal and oral mucosa, and inguinal and perineal skin. A sterile electrostatic cloth was run along the dorsal surface of the dog's back, in the "petting zone." During this collection, we asked handlers questions about the dog's recent medical history, such as antimicrobial and other medication usages, and recent diagnoses or surgeries. After initial sampling was complete, the dog interacted with patients for the full hour, then was resampled at the same sites using the same protocol.

II.c. Patients

Prior to interacting with the therapy dog, we collected nasal samples (Copan E-swabs for culture and sterile flocked swabs for microbial community analysis) from participants who enrolled in the study. At that time, we took blood pressure and heart rate measurements, and asked participants questions about their mental wellbeing. During the visit, we observed interactions of the study participants with the dog, making notes on types and frequencies of certain behaviors (petting, hugging, etc.) and the total length of time the patient interacted with the dog. After the patient was done visiting the dog,

we collected the same swabs, vital measurements, and mental wellbeing questions from participants.

Blank sterile flocked swabs were collected at every visit as a microbiome negative control. The Copan E-swabs were stored at 4°C until processing within one week of collection, and the sterile flocked swabs and vacuum dust were stored at -80°C.

III. Intervention

In the study design, the therapy dog team was to complete two observational control visits abiding established hospital protocol, then cross-over to two intervention visits with modifications to the hospital therapy dog protocol. Prior to the first intervention visit, the handler was given a 4% chlorhexidine-based veterinary prescription shampoo (DUOXO Ceva, Libourne, France) to use 24 hours before the study visit. During the therapy visit, the dog was wiped down along the dorsal petting zone with a 3% chlorhexidine wet cloths (DUOXO Ceva, Libourne, France) every 5 to 10 minutes. Handlers were given information about both products before usage. We implemented the same data collection protocol for these intervention visits as described above.

IV. Laboratory Processing - Microbial Communities

IV.a. Sequencing

The sterile flocked swabs and vacuum filter dust were thawed prior to DNA extraction. Refer to the [*Supplement*] for the detailed sequencing protocol, and as previously described (Misic et al., 2015). For each set of extractions, one blank swab exposed to laboratory air was processed as a negative laboratory control. Prior to sequencing, the total DNA concentration was obtained from PicoGreen instrument, and the 16S rRNA

gene copies per unit DNA was evaluated using quantitative PCR. The V1-3 region of the 16S rRNAgene was amplified using barcoded primers (27F, 534R) for the Illumina platform as previously described (Fadrosh et al., 2014). Sequencing was performed on the MiSeq instrument (Illumina, San Diego, CA) using 300 base paired-end chemistry at the University of Pennsylvania Next Generation Sequencing Core. Microbial Mock Communities B (Even-Low v5.1, BEI Resources, NIAID NIH HMP) were amplified and sequenced as positive controls.

IV.b. 16S rRNA Gene Analysis and Quality Control

QIIMEv2.7 was used for paired-end read assembly and quality filtering for the sequences from all samples (Bolyen et al., 2019). DADA2 plug-in for QIIME2.7 was used to remove chimeric sequences and sequences greater than 300bp in length, and cluster sequences into amplicon sequence variants (ASVs) (Callahan et al., 2016). ASVs were matched to phylogeny using mafft program for multiple masked sequence alignment (Katoh et al., 2002) and FastTree to generate a phylogenetic tree from the masked alignment (Price et al., 2010). Taxonomy assignment used a Naive-Bayes classifier (Wang et al., 2007) that was trained on our dataset (trimmed to 300bp and matched to our primers), applying Greengenes13.8 99% OTU match (McDonald et al., 2012). Results from our taxonomic classification was confirmed by comparing the identification of the known Mock Community samples. For quality control purposes, suspected contaminants were identified and removed from the resulting feature table using the 'decontam' R package, based on the prevalence of taxa in the negative controls and the frequency of taxa as a function of the total DNA concentration and the 16S rRNA copies from qPCR (Davis et al., 2018). Contaminants were identified independently at each processing step (field sampling, DNA extraction, and sequencing) and were sequentially removed.

V. Laboratory Processing - Targeted Culture

Copan E-swab and electrostatic cloth samples were processed at the Johns Hopkins Clinical Microbiology laboratory or a laboratory lead by the study PI specializing in *Staphylococcus aureus*. Refer to [*Supplement]* for detailed culture laboratory protocols.

VI. Statistical Analysis

Statistical analysis was performed in RStudio v1.1.423 (R Development Core Team, 2010).

V.a. Microbiome

To maintain the maximum number of samples for comparison, the sequencing data was not rarefied for statistical analysis. Taxa tables, and matching phylogeny and taxonomy, were analyzed using the phyloseq pipeline to calculate alpha and beta diversity metrics (McMurdie & Holmes, 2013). Differential abundance of specific taxa between groups were analyzed using DESeq2 (Love et al., 2014). Kruskal-Wallis nonparametric one-way analysis of variance test examined differential alpha diversity between all groups, and Wilcoxon rank-sum test was used for pair-wise comparisons between groups, both adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) correction. To determine which factors were most important in determining microbial composition, statistical tests were performed using the non-parametric permutational multivariate analysis of variance (PERMANOVA) with weighted and unweighted UniFrac distance metrics.

V.b. Targeted Culture

Crude prevalence rates of *S. aureus* and MRSA based on qualitative culture were calculated for the patients, therapy animals, and hospital environment. Changes in prevalence of *S. aureus* was calculated before versus after therapy dog interaction, stratified by control and intervention visits and by contact level, and compared using non-parametric descriptive chi-squared test. Changes in quantitative *S. aureus* bacterial burden was assessed with statistical test of difference (Welch's t-test for mean difference and Wilcoxon rank-sum test for median difference) by visit type and contact level.

7.4 Results

I. Study Population

A total of four dogs were included in the study over 13 visits, with 5 (38%) intervention study visits. Forty-nine pediatric oncology patients elected to enroll in the study, as shown in **Table 1**, with a mean age of 11.7 years old (SD 4.7). Four participants returned in following weeks to be re-enrolled in the study for a total of 45 unique patients, but each visit was treated as an individual entry. There was a mean of 3.8 participants at each therapy visit (SD 1.4, range 2-6). 39 participants (79.6%) reported owning a pet at home, with 30 (61.2%) owning a dog.

Individual contact behaviors and total patient-dog interaction time is presented in **Supplement Table 1**. The frequency of key behaviors and total time spent with the therapy dog was aggregated to create an ordinal contact score. The median score was a threshold to create a binary contact level of "High" or "Low" contact. 51% of patients were classified as "High" contact, and this was evenly distributed across visit types.

II. Samples

A total of 445 swabs were collected for microbial analysis, as shown in **Table 1.** This includes 203 for microbiome analysis and 242 for targeted culture analysis. An additional 33 samples were processed for microbiome quality control. Eight patients elected to not provide any swab samples, due to either fear or scheduling conflicts. Two patients did not provide pre-visit culture swabs, and three patients did not provide any post-visit swabs. Two inguinal samples were not captured from dogs, due to protocol changes during the study.

III. Microbial Sharing Results in Distinct Patient Microbial Communities based on Contact Level and Visit Type

To analyze microbial communities in patients and therapy dogs, the V1-3 region of the 16S rRNA gene was amplified and sequenced from swabs. Information on the sequencing library and quality control measures can be found in **Supplement Table 2**.

III.a. Beta Diversity Distribution

Supplement Figure 2 shows the overall distribution of samples in principal coordinate analysis plots for both unweighted and weighted UniFrac beta diversity metrics, by hosts (patient, dog or hospital environment), site, and pre- and post-visit status. Loose clustering was observed by host and sample site, but not by pre and post sample. Clustering was also not observed by individual subject or visit membership. Overall the axes accounted for a maximum of 7.8% variation in unweighted UniFrac and 33.5% variation in weighted UniFrac.

III.b. Beta Diversity Distance

As a result of microbial sharing, patients were more similar to other patients after the visits in their microbial composition distance (beta diversity) (PERMANOVA pre vs. post FDR-p<0.001) and were more similar to therapy dogs (PERMANOVA pre vs. post FDR-p<0.001) (example calculation **Supplement Figure 3**, results **Supplement Figure 4** and **Supplement Table 3**).

When accounting for the difference in microbial composition after the visits compared to before, patients with high contact were more similar to other patients (**Figure 2.A**) and to the therapy dog (**Figure 2.C**) after the visits, compared to low contact patients, using

unweighted UniFrac metric (PERMANOVA FDR-p=0.0001-0.0003). The same pattern was observed in both control and intervention visits. When looking at the weighted UniFrac metric, high contact patients were more similar to other patients in control visits (p=0.0005), but not in intervention visit (**Figure 2.B**). The reverse trend was seen where both high and low contact patients were equally more similar in microbial composition to the therapy dog in intervention visits (p=0.0001, 0.0005), but not in control visits (**Figure 2.D**).

III.c. Alpha Diversity

Alpha rarefaction curves are presented in presented in **Supplement Figure 5.** There was a statistical difference in alpha diversity levels between sites and hosts, as measured by the Shannon (**Figure 3.A)** and Faith's Phylogenetic (**Figure 3.B**) metrics (Kruskal Wallis p<0.001). When evaluating pairwise comparisons across the different combination of sites, nasal samples from the kids and dogs are similar in diversity levels to dog oral and perineal samples, all of which are statistically different than dog inguinal and dust samples (Wilcoxon test p<0.0001), which are similar to each other. There was no effect difference when stratifying these by pre or post and by visit type.

When looking at individual level changes in alpha diversity that occur during a therapy visit, in high-contact patients there was an overall increase in within-sample diversity levels during control visits, and an overall decrease during intervention visits, while either no difference or the opposite difference occurred in low-contact patients, as shown in **Figure 3.C-F.** There was a significant difference between alpha change in control versus intervention visits in high contact patients using Faith's metric (Kruskal Wallis p=0.05), but not a significant difference using the Shannon metric.

III.d. Relative Abundance

There was a difference in the abundance of microorganisms across both host and sample location, as shown in **Figure 4.A**, which shows the percent relative abundance of the top 25 most abundant genera. There were some species that were statistically differentially abundant when comparing across sites, including *Staphylococcus* species in the nasal samples of both patients and dogs. Patient and dog nasal samples had similar microbial compositions, with *Staphylococcus* species being dominant, but dog nasal samples had a greater abundance of *Moraxella* compared to patients' greater abundance of *Streptococcus*. Relative abundance mean values by host and site are presented in **Supplement Table 4**.

Patients had altered microbial abundance based on contact level and visit type, as seen in **Figure 4.B&C**. Within control visits, patients with low contact had a higher abundance of *Streptococcus* species after the visits compared to before, but there was no difference in abundance for any genera in high-contact patients between pre- or post-visit samples. Within intervention visits, patients had greater abundance of *Streptococcus* species before the visit and greater abundance of *Staphylococcus* species after the visit. This effect was observed for both high and low contact patients. When further evaluating which species was driving the change, *S. epidermidis* (and not *S. aureus*) was the dominant Staphylococcal species (**Supplement Figure 6**).

IV. Culture Detection Confirms Microbial Sharing of Clinically Important Staphylococcus aureus is Altered by Contact and Visit Type

Because *Staphylococcus* species in humans can be commensal (*S. epidermidis*) or potential pathogens (*S. aureus*), species identification of *Staphylococcus* was determined via microbial culture using a highly sensitive protocol.

IV.a. Exposure

Staphylococcus aureus was detected from child patients and dogs as shown in **Table 2**. The primary outcome evaluated was *S. aureus* and MRSA exposure, or if a patient had a negative/non-detectable level of *S. aureus* or MRSA prior to the therapy dog session, but detectable *S. aureus* or MRSA after the session. **Table 2** shows that the hospital environment was the most commonly contaminated, or positive detection, of both *S. aureus* and MRSA, and the dogs were less commonly contaminated in intervention visits. Patients who had higher contact with the dog were more commonly exposed to *S. aureus* and MRSA, but that higher association was reduced in intervention visits, particularly for MRSA.

Among those patients with *S. aureus* exposure, we preformed *spa*-typing to classify positive isolates, within 7 visits. **Supplement Figure 7** shows nine unique *spa* types were identified in our positive samples from patients and therapy dogs, with potential crossover of detected isolates between patients and between patients and therapy dogs.

IV.b. Quantification

Since our binary culture detection was highly sensitive, we further evaluated *S. aureus* burden with quantitative PCR (qPCR). **Figure 5** shows the log transformed difference

(post-pre visit) of *S. aureus fem* gene copies (/1ul sample) within patients. In control visits, high contact patients had a significant gain in mean gene copies compared to low contact patients (mean 2.45 high, -1.66 low, Welch's t-test p=0.08). There was a significant loss of mean gene copies in intervention visits compared to control visits, in high contact patients (mean 2.45 control, -1.71 intervention, Welch's t-test p=0.04).

We also tested quantification of *S. aureus* on the therapy dog "petting zone" back samples, to confirm effectiveness of the decolonization intervention (**Supplement Figure 8**). Overall, there was a significant decrease in culture-based CFU count in intervention visits compared to control visits (change CFU count 47 control, -33 intervention, Welch's t-test mean difference p=0.05).

V. The Intervention Did Not Diminish Positive Patient Benefits

We lastly wanted to confirm that our novel application protocol for therapy dog decolonization did not alter the positive physical and mental health benefits reported from AAI programs. **Supplement Table 5** shows a decrease in both blood pressure and heart rate in patients after the visit, as well as a decrease in reported negative mental wellbeing status associated with being in the hospital. Both of the benefits were not changed when stratifying by control and intervention visits (negative t-test).

7.5 Discussion

This innovative yet pragmatic pilot study explored microbial transmission, both key pathogens of clinical concern and general bacterial communities, among pediatric patients and therapy animals during hospital-based AAI programs. This study was the first to sample patients, therapy animals, and the hospital environment before and after every group therapy session, and the first to explore microbial community dynamics in this setting. As a result of microbial sharing that occurred during the AAI sessions, we found microbial compositions of patients were altered, both overall diversity levels and relative abundance of specific taxa, via molecular sequencing. This sharing was also seen with culture-based analysis for *Staphylococcus aureus*, a common hospital-associated pathogen.

We explored the effect of contact level between patients and therapy dogs on microbial sharing and found that higher contact was associated with increased sharing between patients and therapy animals, and among patients. Finally, we determined that a decolonization intervention targeted to the therapy dog modifies the association between contact level and microbial sharing between therapy animals and patients, and between patients. This indicates that pathways of microbial exposure to patients, including the therapy animal, should be further explored during group hospital AAI sessions to identify their relative importance and determine their relevance to infection control strategies.

Distinct Microbial Profiles of Patients and Therapy Dogs

Patients, therapy dogs, and the hospital environment had distinct microbial communities, as evident by their difference in the relative abundance of key species,

difference in alpha diversity levels, and unique clustering of microbial composition in beta diversity. Whereas human and dog nasal sites tend to be dominated by a few taxa at relatively high abundance (namely *Staphylococcus*, *Streptococcus*, and *Moraxella*), dog oral, perineal and especially inguinal sites, as well as hospital environment dust, harbored a more even mixture of a variety of taxa, resulting in higher alpha diversity levels, and distinct beta diversity clusters on PCoA plots.

Microbial community shifts were shown to occur in patients and therapy dogs during an AAI therapy session. This is demonstrated by the increase in within sample alpha diversity levels in patients and dogs using Shannon and Faith's Phylogenetic metrics, more similar microbial compositions after the visits using the weighted and unweighted UniFrac distance metrics, and change in the relative abundance of species taxa, specifically *Staphylococcus*. Culture-based analysis was additionally used to identify which patients were exposed to viable *Staphylococcus* during AAI visits. It is important to note that the culture protocol has been demonstrated to have a limit of detection between 10 and 100 CFUs (Davis et al., 2012), and to be more sensitive than typical protocols used in clinical microbiology laboratories (Davis et al., 2016); it is possible for exposure as defined in this study to be transient contamination that would neither result in colonization nor infection.

Closer Contact Between the Patient and Therapy Dog Increased Microbial Sharing

Patient-dog contact level was shown to modify microbial sharing between patients and therapy dogs and between patients. While contact level was assessed primarily as an indicator of interactions between a patient and a therapy animal, this contact score also is representative of interactions of the patient to other aspects of the therapy visits, shown in **Figure 1**. A patient with a high contact score will have higher contact with the

therapy dog and with other patients and individuals, including the therapy dog handler, and with the hospital environment. Thus, high contact increases all pathways shown in **Figure 1**, and was positively associated with increased microbial sharing. Patients with high contact were more likely to be exposed to both *Staphylococcus aureus* and MRSA during a visit based on culture-based detection. In quantitative burden, patients with high contact also had significantly higher levels of *S. aureus* gene changes during the visit compared to low contact patients. Overall, higher observed contact level resulted in increased exposure to *S. aureus* during a therapy visit.

Beta diversity distance, represented by both unweighted and weighted UniFrac metric, is the most convincing demonstration of microbial sharing, as it evaluated shifts in the microbial community structure that occurred during the visits. The unweighted UniFrac metric does not take into consideration the phylogenetic distance between different taxa. Using this metric, patients with high contact were more similar to other patients after the visit compared to low-contact patients, presumably due to microbial sharing among patients, and were also more similar to therapy dogs after the visit compared to low-contact patients, indicating high contact level resulted in more overall microbial sharing between patients and dogs. For the weighted UniFrac metric, which factors in phylogenetic distinction between microbial compositions, there was not a significant change in microbial composition differences between patients and dogs, indicating that there was not significant sharing of phylogenetically rare taxa between patients and dogs, but there was significant sharing of rare taxa among high-contact patients.

Contact level was shown to be associated with within-sample alpha diversity levels, in that high contact patients had increased levels of both Shannon's and Faith's Phylogenetic alpha diversity after the visit compared to before the visit. Conversely, low-

contact patients showed no change in Shannon's metric and a decrease in Faith's phylogenetic metric after the visit. Overall, increased interaction with various aspects of the therapy programs in high-contact patients was associated with increased within sample bacterial diversity. Faith's phylogenetic diversity, as opposed to Shannon's diversity, considers more phylogenetically rare taxa, so it is more unique microbiota that are driving the increased alpha diversity in patient samples.

Taken together, these findings suggest that rare taxa are shared among patients, resulting in increased within-sample diversity, but are not as commonly shared between patients and dog. Our PCoA distributions and relative abundance results, in addition to previous studies on pet dogs (Davis, 2016; Oh et al., 2015; Ross et al., 2018; Song et al., 2013), have shown that dogs have diverse unique microbial communities compared to humans, which could possibly be driving the differences seen in weighted beta metrics in patient-to-dog composition difference compared to patient-to-patient composition difference. This denotes that dogs can serve as intermediary vectors in the spread of human-origin common microbiota between patients, but may not be sharing their own unique microbiota to patients. Yet there was still significant sharing of rare taxa among patients and an increase in within sample diversity levels driven by rare taxa in patients. This indicates that the therapy animal is only one potential pathway of microbial transmission during these group AAI therapy sessions and may not be as significant as an influence in the transmission of microorganisms as other pathways in **Figure 1**.

Canine Decolonization Intervention Modified Microbial Sharing

As part of this study design, we tested a novel application of a common veterinary disinfectant to therapy dogs and how that canine decolonization intervention influenced microbial sharing among patients. The intervention involved changing the dog's regular

pre-visit bathing routine to a chlorhexidine-based shampoo and wiping the dog with chlorhexidine wipes at regular 5-10-minute intervals during the therapy session. The goal of the intervention was not only to reduce the bacterial burden on the dog, but to lessen the dog's ability to serve as an intermediary vector in the spread of microorganisms between patients, or between other sources to patients. In terms of the pathways in **Figure 1**, the intervention blocked the contributions of the dog.

Our intervention was shown to be effective in its primary objective - to reduce the bacterial burden on the dog. This was observed in both decreased levels of binary *S. aureus* levels before and after the therapy visit in dogs in intervention visits compared to control visits, as well as decreased quantitative bacterial burden of *Staphylococcus aureus*, assessed by CFU level.

We determined that the dog decolonization intervention modifies the relationship that we observed with high-contact patients and increased microbial sharing. The decolonization intervention was shown to affect more phylogenetically rare taxa, as different effects were seen using phylogenetically weighted versus phylogenetically unweighted diversity estimates. Since the intervention worked on the dogs' microbiota, it allowed us to isolate the therapy animal's microbial contribution to patient microbial sharing. Within intervention visits with the therapy dog microbiota removed, microbial sharing of common taxa was still observed among patients and between patients and therapy dogs. But, unlike in control visits, rare taxa were not shared among patients. The intervention blocked the pathway of microbial sharing between patients of rare phylogenetically diverse taxa, also reflected in a decrease in within patient sample phylogenetically rare alpha diversity, but not the sharing of common taxa. If the therapy dog was the only or primary source of microbial sharing to patients during AAI sessions,

we would expect to see reduced sharing of both common and rare taxa between patients and dogs in intervention visits when the therapy dog pathway is blocked, and if the therapy dog served as a major intermediary point, we would expect to see reduced sharing among patients. Since we only see this pattern with phylogenetically rare taxa, not common taxa, this reinforces the concept that while the therapy dog can serve as an intermediary point, the dog is one of only many possible pathways, and these other pathways may be greater contributors to microbial changes seen in patients.

The most important outcome affected by the intervention, which best demonstrates microbial sharing between patients and therapy dogs, is the microbial community shifts as evaluated by the unweighted and weighted UniFrac beta distance metrics. Significant sharing was observed between high-contact patients within intervention visits, as significant as in control visits, using the unweighted UniFrac metric. However, using the weighted UniFrac metric, as opposed to in control visits, there was no difference in microbial composition between patients in intervention visits at either contact level. This indicates that sharing of common microbiota still occurs between patients, even with the intervention blocking the dog pathway, but patients are now sharing fewer phylogenetically rare taxa between them in intervention visits.

The intervention also altered the beta distance between patients and therapy dogs. Using the unweighted UniFrac metric, control and intervention visits both had similar patterns. High-contact patients were more similar in microbial composition to the therapy dog after intervention visits, indicating that the intervention did not alter microbial sharing of common taxa between patients and therapy dogs. However, using the phylogenetically weighted UniFrac metric, patients of both high and low contact were more similar in microbial composition to therapy dogs after the visit, opposite to control

visits were both contact levels were less similar. Unlike in previous examples where microbial composition similarities appeared to be due to the spread of microbiota among individual patients, it is possible that this microbial community shift is due to the effect of the decolonization on the dog's microbiota. The decolonization selectively removes unique dog taxa from the dog itself, resulting in the microbial compositions of the therapy dogs being more similar to the microbial compositions of patients.

Similar to beta diversity compositional differences, altered alpha diversity levels demonstrated the effect of reduced patient exposure to rare taxa as a result of the intervention, indicating that our canine-centered decolonization had indirect effects on the microbial diversity levels within patient samples. In intervention visits, there was a slight decrease in Shannon metrics within high contact patients after the visit – the opposite trend in control visits – yet there were minimal changes to low contact patients. This effect was more substantial when looking at Faith's phylogenetic metric. When the therapy dog's microbial contribution was removed by the intervention, patients with high contact had lowered diversity levels after the visit compared to before the visit, particularly a reduction in rare taxa. High-contact patients in intervention visits also had significantly decreased alpha diversity levels than their high-contact counterparts in control visits.

The intervention also was associated with changes in the abundance of specific taxa. High-contact patients who interacted with decolonized therapy dogs had higher relative abundance of staphylococcal species post visit compared to high contact patients post control visits. Instead of *S. aureus*, this change was primarily driven by *S. epidermidis*, a predominant human nasal commensal. Since this metric compares relative, not absolute, abundance within each sample group, it is not surprising that human commensals are of

greater relative abundance in intervention visits than control visits, since patients are exposed to fewer taxa from the therapy dog.

We also found changes in cultured levels of *Staphylococcus aureus* based on the intervention. For binary *S. aureus* exposure, the intervention did not directly reduce the incidence of *S. aureus* and MRSA detection in patients before or after the visit. However, it nullified the risk of exposure in patients with high contact, so that there was no difference in the likelihood of exposure in high-contact and low-contact patients within intervention visits. Essentially, all patients had an equal chance of becoming exposed to *S. aureus*, regardless of contact level. It did not completely eliminate the risk— there were still detectable concentrations in patients post intervention visits—but it reduced sharing from one pathway (the therapy dog) shown in **Figure 1**. The same effect could also be observed in the quantitative qPCR results, where high contact patients had significantly higher mean *S. aureus fem* gene change compared to low contact patients in control visits, but no difference based on contact level in intervention, where the therapy dog pathway is blocked. The dissimilar impact on high-contact rather than low-contact patients is not surprising, since the intervention targeted the therapy dog.

Overall, while the intervention indirectly affected patient microbial composition, diversity levels, and sharing, it primarily worked on the therapy's dog microbial composition. Because we still observed equal microbial sharing among patients in both control and intervention visits, this is another potential indicator that the dog is only one possible pathway of microbial transmission during these group therapy sessions. While the therapy dog can be vector in the spread of microbes, as shown in our culture-based *S. aureus* results, other pathways, shown in **Figure 1**, may have a weightier influence on the microbial alterations observed in patients as a result of the therapy visit. This

concept has important implications when considering the design and implementation of control policies for these AAI programs; targeting the dog alone may be insufficient to prevent spread of microorganisms, specifically pathogens.

Canine Decolonization Did Not Negatively Impact Patient AAI Experience

It is important to note that the intervention did not diminish the positive benefits we observed from patients who participated in these visits, both a decrease in heart rate and blood pressure, and a decrease in self-reported negative feelings. This is critically important in the design of any intervention to improve safety - that the intervention does not detract from the ultimate goal of the therapy session to improve holistic patient health.

Strengths, Limitations, and Future Directions

While designed as a pilot study to assess feasibility, this is the first study to the authors' knowledge to expressly target microbial transmission that occurs during hospital AAI programs by sampling multiple components before and after each visit. Previous studies to date have focused exclusively on carriage in the therapy animal or have assessed aggregated rates of infection diagnosis in departments with or without AAI programs (Dalton et al., 2020). By sampling multiple components—the patients, the therapy animals, and the hospital environment—we can begin to elucidate exposure pathways from these individual data points. In addition to our sampling strategy, this study is the first to assess the contact level between patients and therapy dogs as a risk factor. Human-animal contact level has been previously described to be a risk factor in the exposure and acquisition of pathogens in the case of pet ownership (Morris et al., 2012; Rodrigues et al., 2018), but it was unknown if the same positive association would be

seen with the brief contacts between patients and therapy animals. This study also benefits from the novel deployment of an established canine decolonization procedure, adapted from veterinary clinical protocols for canine dermatology patients, to decolonize therapy animals as an infection control strategy. It was found that the intervention did decrease the role of the therapy dog both to spread its own unique microbiota to patients, but also to reduce its role as an intermediary vector in the spread of microorganisms between patients or other individuals and the hospital environment. This intervention appeared to be effective to limit exposures to *S. aureus*, and further, it did not detract from patient enjoyment and the overall positive goal of these therapy sessions.

While novel, this study does have practical drawbacks that the researchers were unable to address in the study design. Its primary purpose was to determine the feasibility to conduct a larger infection control trial, including the implementation of the decolonization intervention. As such, a limitation is the smaller sample size, particularly when considering the number of unique dogs. Sampling other sites, both on the patients and in the hospital environment, as well as other individuals, such as healthcare workers and the handlers, may have led to alternative hypotheses. As shown by the *spa*-typing results, multiple pathways demonstrated in **Figure 1** prove challenging to examine, and blanket statements inferring directionality of transmission from therapy dogs to patients or vise-versa should be taken with caution. Finally, the purpose of this experiment was to assess microbial exposure at one time point. It is uncertain from our data if the changes observed during the visit will be temporally stable and, if so, for how long. We also cannot make any claims as to the health outcomes related to these microbial community shifts, particularly related to the exposure of potentially pathogenic microorganisms and to rare taxa from the therapy dog.

Future work in this topic will expand the study design to include AAI sessions that involve only one child per dog, thus providing more insight into potential microbial pathways, and increase the generalizability of findings to other situations. To also increase generalizability, future plans are to sample within different hospital departments with varying compositions of patient, and various hospitals. Lastly, we seek to explore the temporal stability of these microbial shifts observed in patients and determine if it leads to clinically significant outcomes. This is especially important when considering the exposure to rare dog taxa, given that early-life exposure to pets is associated with decreased incidence of allergic and atopic diseases in children (Havstad et al., 2011; Mandhane et al., 2009), and having a diverse microbiome is protective against numerous health outcomes and can be protective against colonization from pathogens (Grice & Segre, 2011; Naik et al., 2012). If we can show that exposure to therapy animals, even briefly during AAI programs, can benefit microbial diversity and microbial community resilience over a longer-term, this will be a previously undescribed benefit to AAI and may increase its utilization in patient care. Many hospitals and individual practitioners are hesitant to adopt these known beneficial programs, given the uncertainty surrounding their risk with regards to infection control. The goal of this and future work is to address those concerns, and to design and implement practical guidelines and recommendations for the safe implementation of these programs.

7.6 Conclusions

The results of this work could have significant clinical implications in terms of infection control. These findings indicate that, while there is microbial sharing between the patients and dogs and the potential for the dog to serve as an intermediary vector of microbial spread, other potential transmission pathways (patient-to-patient, and hospital-to-patient) were also important for microbial sharing during group visits. Infection control efforts during these visits should reflect all the possible pathways of microbial transmission.

Conversely, the therapy dog could be a source of more unique microbes to patients. As hospital exposure and certain therapies have been shown to decrease microbial diversity in patients, therapy dog exposure can possibly provide a novel way to counterbalance this imbalance and share potential beneficial microorganisms that could be protective against hospital pathogen exposure. This pilot study shows that microbial community alterations in patients and therapy dogs during these therapy programs warrants additional research, which will make these programs safer and more sustainable.

Figure 1: Microbial Pathways during Animal-Assisted Intervention Programs

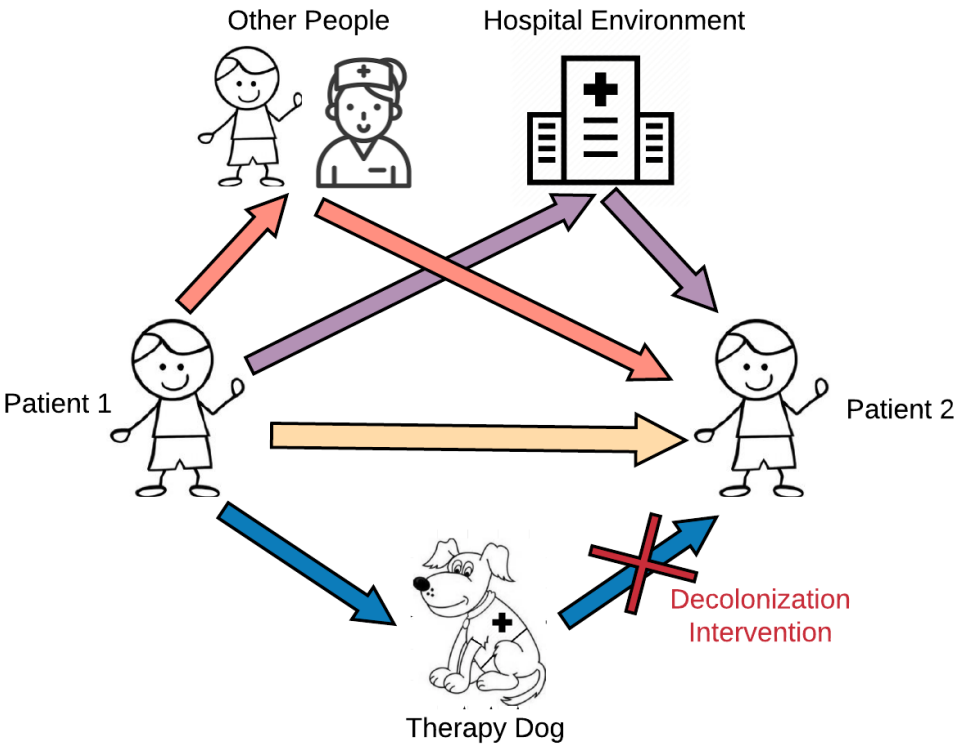
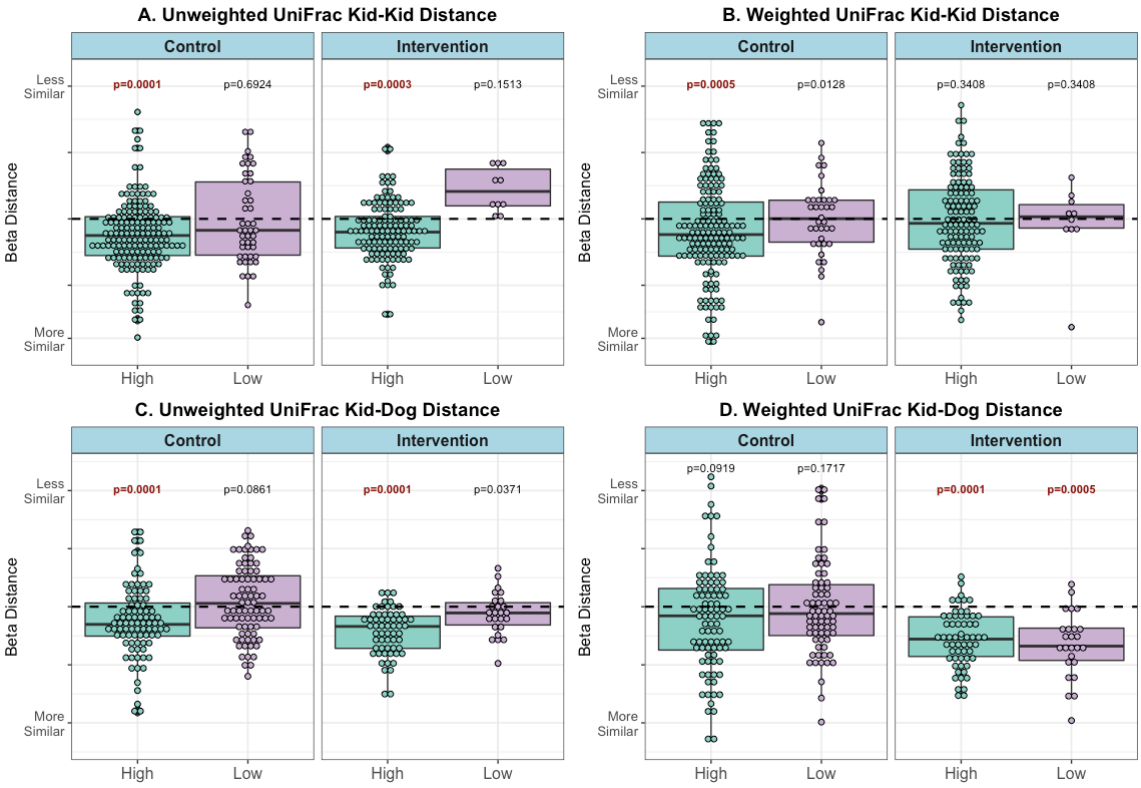


Table 1: Study Population and Samples

	All Visits	Control Visits	Intervention Visits
Study Population			
Patients		N (% total)	N (% total)
N total sampled	49 *45	26 (53%) *23	23 (47%) *22
Male (%)	31 (63%)	15 (58%)	16 (69%)
Age (y), mean (range)	11.68 (1.9-20.4)	11.07 (1.9-18.4)	12.41 (3.5-20.4)
High Contact (%)	25 (51%)	12 (46%)	13 (56%)
Visits		N (% total)	N (% total)
Total	13	8 (62%)	5 (38%)
Patients per visit, mean (range)	3.77 (2-6)	3.25 (2-5)	4.6 (3-6)
Therapy Dogs			
N Unique Dogs	4		
Male (%)	1 (25%)		
Age (y), mean (range)	6.43 (1.5-12)		
Samples			
Culture		N (% total)	N (% total)
From Patients	90	46 (51%)	44 (48%)
From Dogs	126	76 (60%)	50 (40%)
From Environment	26	16 (62%)	10 (38%)
Microbiome		N (% total)	N (% total)
From Patients	79	43 (54%)	36 (45%)
From Dogs	100	60 (60%)	40 (40%)
From Environment	24	16 (62%)	10 (38%)
Field Blanks	12	7 (58%)	5 (42%)
Laboratory Controls	21		

*45 patients with microbial samples collected, 23 in control and 22 in intervention

Figure 2: Beta Distance for Microbial Composition Difference, by Contact Level and Visit Type (post – pre visit)

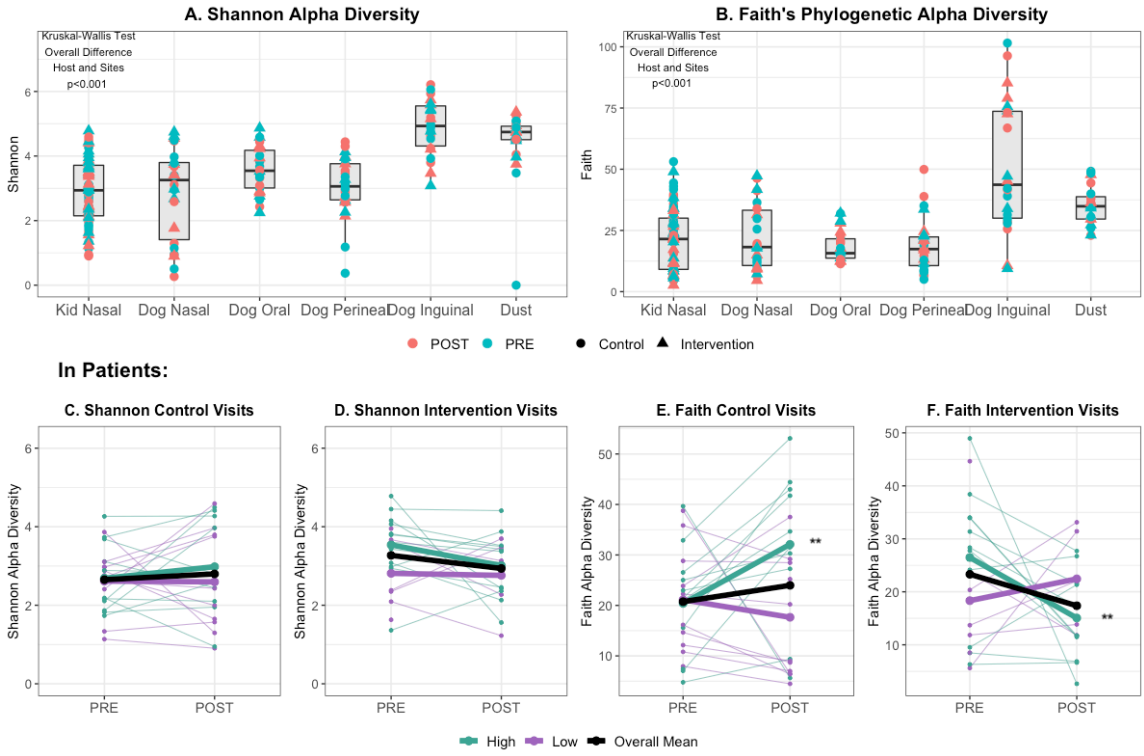


PERMANOVA model p value results for difference in microbial composition beta distance between patients pre compared microbial composition beta distance between patients post visit (kid-kid) or difference in microbial composition beta distance between patients and therapy dogs pre compared microbial composition beta distance between patients and therapy dogs post visit (kid-dog), within each stratification (visit type and contact level).

Refer to **Supplement Figure 3&4** for example caluclations and pre/post distances

BOLD FDR-corrected p <0.005

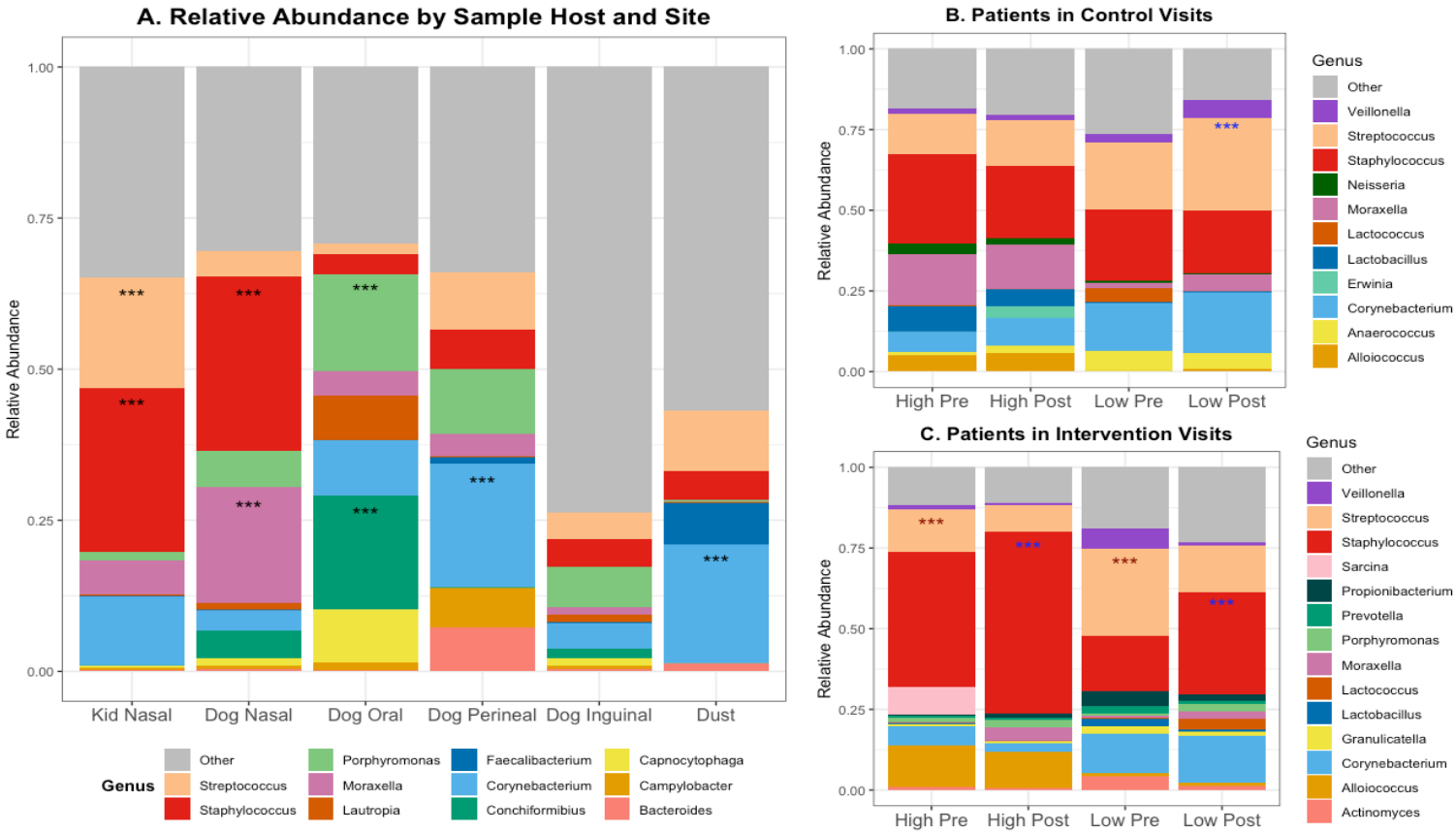
Figure 3: Alpha Diversity by Sample Host and Site, and Within Patient Samples



Thin lines = within subject changes, bold lines = aggregated group means

** Kruskal-Wallis test p=0.05 for median difference in change in alpha diversity level (post-pre) in control vs intervention (in high contact patients)

Figure 4: Relative Abundance of Top 20 Genera



*** Benjamini-Hochberg adjusted p-values <0.001 for differential abundant genera using a negative binomial model (DESeq) between sample sites

Within Patients: **Blue** *** = higher in post samples, **Red** *** = higher in pre samples

Mean total DNA concentration in patients in control = 6.28, in intervention = 4.42 (ng/ul)

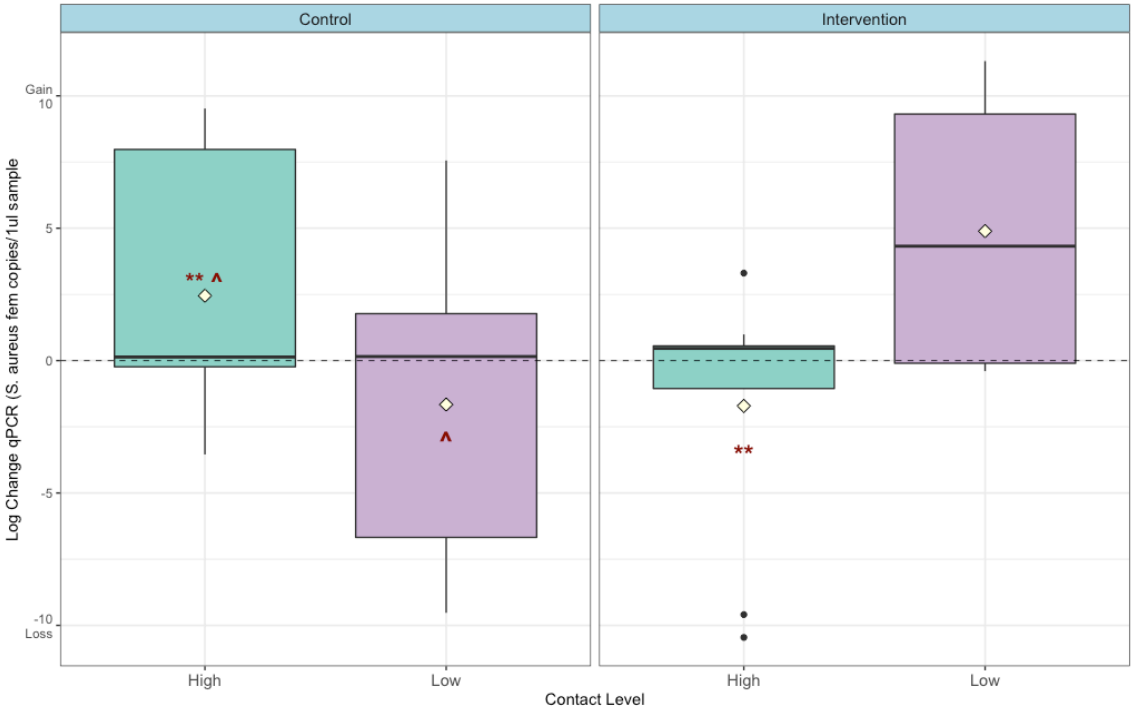
Mean qPCR 16S gene copies in patients in control = 22254, in intervention = 8691 (/ul DNA)

Table 2: *Staphylococcus aureus* Exposure based on Culture Data

	***Staphylococcus aureus* detection**			**MRSA detection**		
	All Visits	**Control Visits**	**Intervention Visits**	**All Visits**	**Control Visits**	**Intervention Visits**
Overview of Detection						
Patients						
Pre N= 45	24 (53%)	12 (52%)	12 (55%)	20 (44%)	10 (43%)	10 (45%)
Post N= 45	25 (56%)	13 (56%)	12 (55%)	18 (40%)	10 (43%)	8 (36%)
Therapy Dogs (any site)						
Pre N= 13	10 (77%)	7 (88%)	3 (60%)	6 (46%)	4 (50%)	2 (40%)
Post N= 13	9 (69%)	7 (88%) +	2 (40%) +	8 (62%)	7 (88%) ++	1 (20%) ++
Environment						
Pre N= 13	13 (100%)	8 (100%)	5 (100%)	12 (92%)	7 (88%)	5 (100%)
Post N= 13	13 (100%)	8 (100%)	5 (100%)	11 (85%)	7 (88%)	4 (80%)
Exposure (pre negative - post detect) ~						
All Patients	8 (18%)	5 (22%)	3 (14%)	5 (11%)	4 (17%)	1 (5%)
High Contact N= 23	6 (26%)	4 (36%)	2 (17%)	5 (22%) **	4 (36%) **	1 (8%)
Low Contact N= 22	2 (9%)	1 (8%)	1 (10%)	0 **	0 **	0

Culture-based detection of *Staphylococcus aureus* (PCR *nuc* gene positive) and methicillin-resistant *Staphylococcus aureus* (PCR *nuc* and *mec* gene positive), stratified by visit type. Presented as total number positive and percent of total (in all visits and within visit type and contact level).
N = total number of samples (patients and environment) or sampling points (therapy dogs, since aggregated site total)
~ Exposure = an individual's pre-visit sample is PCR negative (non-detectable staphylococcal levels on PCR) and post-visit sample is PCR positive.
++ $p<0.05$ + $p<0.1$ chi-squared difference cases control vs intervention
** $p<0.05$ * $p<0.1$ chi-squared difference cases high vs low contact

Figure 5: Patient qPCR *Staphylococcus aureus* gene Gain and Loss by Contact Level and Visit Type (post-pre, log transformed)



diamonds = means
** Welch's T-test difference means control-intervention p<0.05
^ Welch's T-test difference means high-low contact p<0.1

7.8 References

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7.9 Supplementary Materials

Supplement: Detailed DNA Extraction Protocol

The Puritan swab samples were thawed, and 0.5 µL of Ready-Lyse Lysozyme (Epicentre Biotechnologies, Madison, WI) was added to each tube and incubated for 1 h with shaking at 600 rpm and 37°C. The swab was re- moved, placed into a spin basket, and centrifuged for 1 min at 9,400 × g to extract any remaining liquid. The sample was then added to a glass bead tube (0.5 mm; MO BIO, Carlsbad, CA) and vortexed for 10 min at maximum setting. The samples were then incubated in a heat block for 30 min at 65°C and 600 rpm, followed by ice for 5 min and a brief spin. A 150 µL of Protein Precipitation Buffer (Epicentre Biotechnologies, Madison, WI) was added, and the samples were vortexed briefly, then centrifuged at 22,000 × g for 10 min. The supernatant was removed and the protein pellet was discarded. The supernatant was mixed with 500 µL isopropanol and inverted to mix. The mixture was added to a spin column from the Genomic DNA Isolation Kit (Life Technologies, Grand Island, NY), and the remaining steps were followed according to manufacturer's protocol. The samples were eluted with 50 µL Elution Buffer (Life Technologies, Grand Island, NY).

Supplement: Detailed Laboratory Culture Protocol

Refer to previous studies for detailed laboratory protocols (Davis JCM 2016). Briefly, samples were qualitatively cultured (presence/absence) for *S. aureus* using a highly sensitive protocol, and confirmed with polymerase chain reaction (PCR) for the *nuc* gene (presumptive *S. aureus*) and universal *mec* gene (for methicillin-resistance, presumptive MRSA) (Shahbazian 2017). Therapy dog dorsal petting zone samples were quantitatively cultured (via counts of bacterial colony forming units, CFUs) on Baird-Parker media (Hardy Diagnostics, Santa Maria, CA, USA), while patient samples were qualitatively evaluated using real-time qualitative PCR for the staphylococcal *femB* gene (Klotz 2003). A subset of positive isolates from both patients and dogs were subjected to sequencing of the *spa* gene, and *spa*-typing was performed for classification (Karynski 2008).

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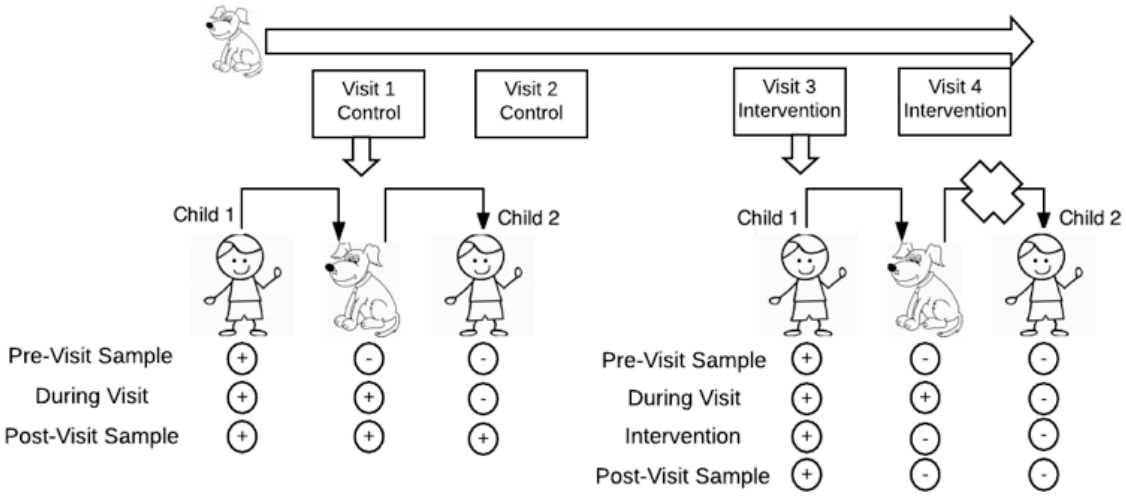
Supplement Figure 1: Study Design and Sampling Points



Supplement Table 1: AAI Behavioral Observations and Patient-Therapy Dog Contact Scores

Observed Interaction Behaviors	**Patients Observed**
N *	46
Total time spent with dog, in minutes mean (range)	14 (2-42)
Interact with Dog N (%)	44 (95.7)
Sat on Floor N (%)	28 (61.9)
Touch Head N (%)	43 (93.5)
Touch Back N (%)	27 (58.7)
Touch Belly N (%)	13 (28.2)
Touch Paws N (%)	11 (23.9)
Feed Dog N (%)	24 (52.2)
Walk Dog N (%)	10 (21.7)
Kiss Dog N (%)	2 (4.3)
Hug Dog N (%)	5 (10.9)
Contact Score Level Calculation	
Interact Score+ mean (range)	7.89 (0-17)
Interact Score x Time ^ mean (range) median (IQR)	 127 (0-403) 108 (56.25-197.75)
Contact Score Level High (≥median) N (%) Low (<median) N (%)	 25 (51%) 24 (49%)

* observations not recorded for 3 patients

+ score based on total tally of individual behaviors, weighted based on closeness of contact: 1 point for interact with dog, walk dog, and sat on floor, 2 points touches, 3 points for feed, hug, or kiss dog.

^ score multiplied by total time with dog

Supplement Table 2A: Microbial Community targeted 16S rRNA gene Sequencing Library Results

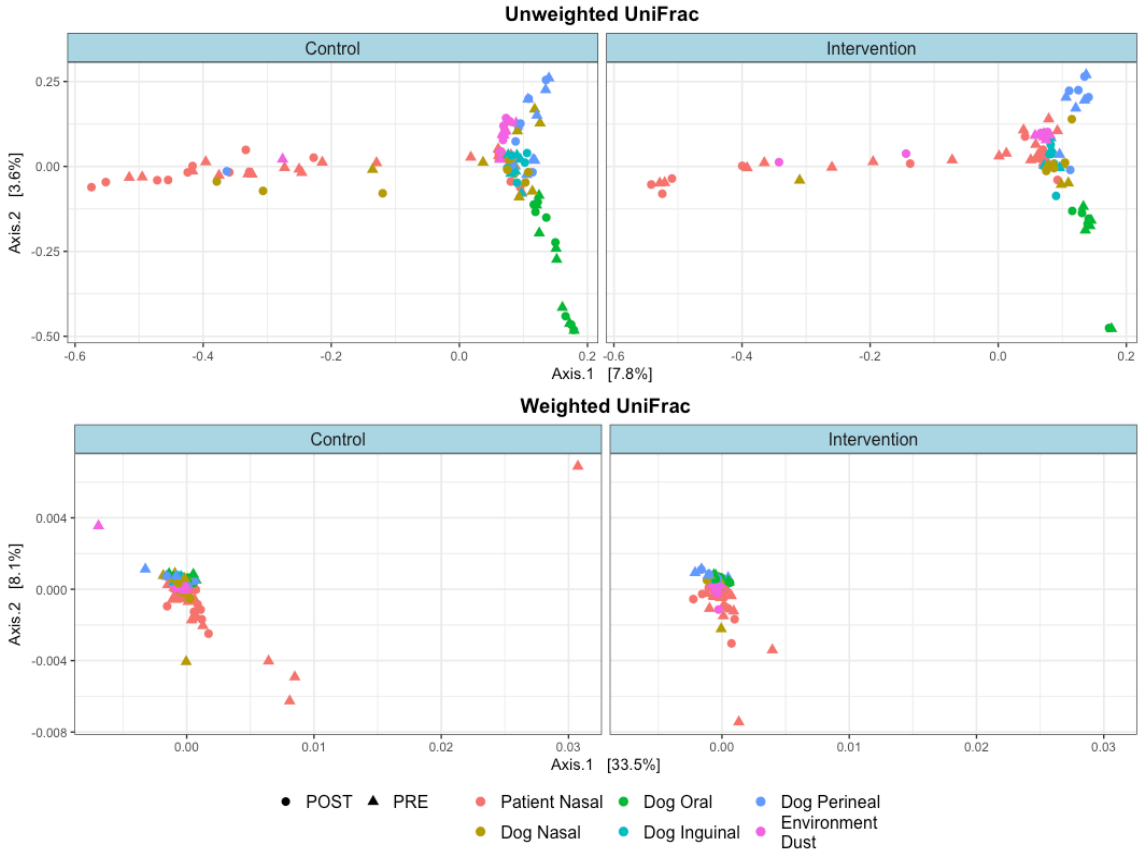
Read Counts				
Sample	**Min**	**Mean**	**Median**	**Max**
Total	1	10736	13342	21890
Child N	164	11639	14100	19430
Dog All N MO I R	711 711 4980 941 12745	12559 9315 14144 11389 15207	14448 8598 14989 13140 14967	21890 21890 16502 17373 18503
Environment	1	12051	13048	16109
Field Blank	520	4676	4307	10064
Controls Extraction Sequence Mock	 189 1 1	 2357 26.2 4.5	 2296 8 3.5	 5207 117 10
Total DNA Concentration (ng/ul)				
Total	0.04	8.517	3	41.39
Child N	0.05	5.434	2.25	31.67
Dog All N MO I R	0.16 0.16 0.6 0.18 1.49	11.001 3.92 18.8 3.19 16.9	7.05 0.975 19 2.14 13.9	41.39 18.5 41.1 9.46 41.39
Environment	0.07	19.77	19.98	38.82
Field Blank	0.2	0.7717	0.745	1.61
Controls Extraction Sequence Mock	 0.06 0.08 0.04	 0.327 0.2267 0.105	 0.31 0.16 0.08	 0.67 0.7 0.22
qPCR 16S gene copies (/ul DNA)				
Total	43	1.42e6	4570	6.26e7
Child N	111	16073	2470	2.58e5
Dog All N MO I R	208 208 1080 314 838	1.41e6 7630 1.72e6 10782 3.69e6	10850 1730 2.24e5 3940 95000	6.26e7 70100 2.52e7 77600 6.26e7
Environment	185e5	7.94e6	5.91e6	2.45e7
Field Blank	88	481	405	1040
Controls Extraction Sequence Mock	 56.6 61.9 42.8	 460 344 233	 273 293 181	 1400 729 475

Supplement Table 2B: Microbial Community Sequencing Library Decontamination

Decontamination Stage	Number Contaminants (% removed)	Common Genera	Prevalence
Starting Taxa	**14183 total ASVs**		
Sequencing Controls	166 contaminants (1.17%)	*Corynebacterium*, *Sphingomonas*, *Streptococcus*, *Bacillus*	832nd most abundant
Extract Controls	149 contaminants (1.06%)	*Corynebacterium*, *Streptococcus*, *Staphylococcus Sphingomonas*	591st most abundant
Field Blanks	188 contaminants (1.36%)	*Corynebacterium, Streptococcus, Staphylococcus Sphingomonas*	705th most abundant
Final Taxa	**13680 total ASVs** (3.55%)		

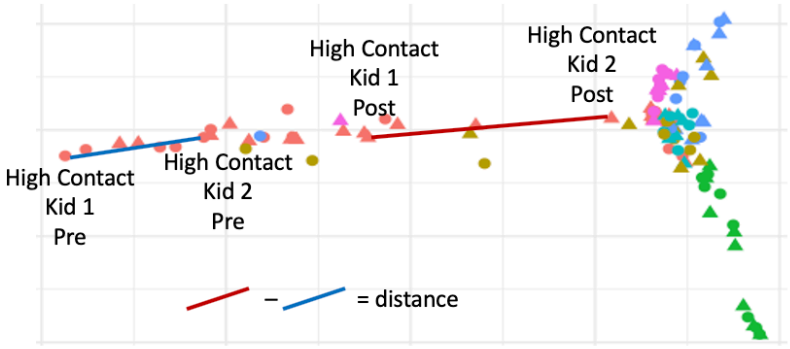
Using 'decontam' package

Supplement Figure 2: Beta Diversity Principle Coordinates Analysis Plots

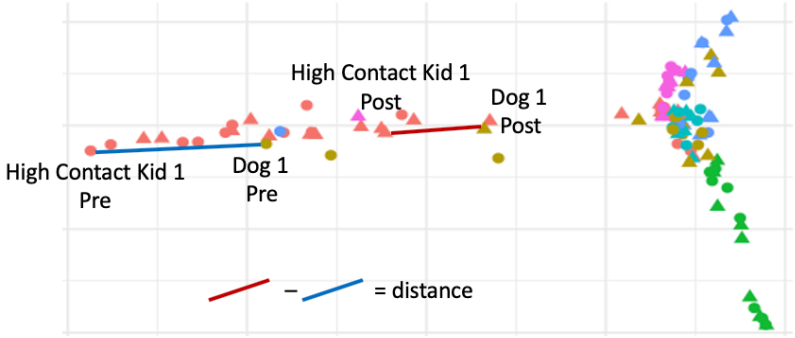


Supplement Figure 3: Graphical Example for Calculations of Beta Distance in Figure 2

A. Kid-Kid Distance Example

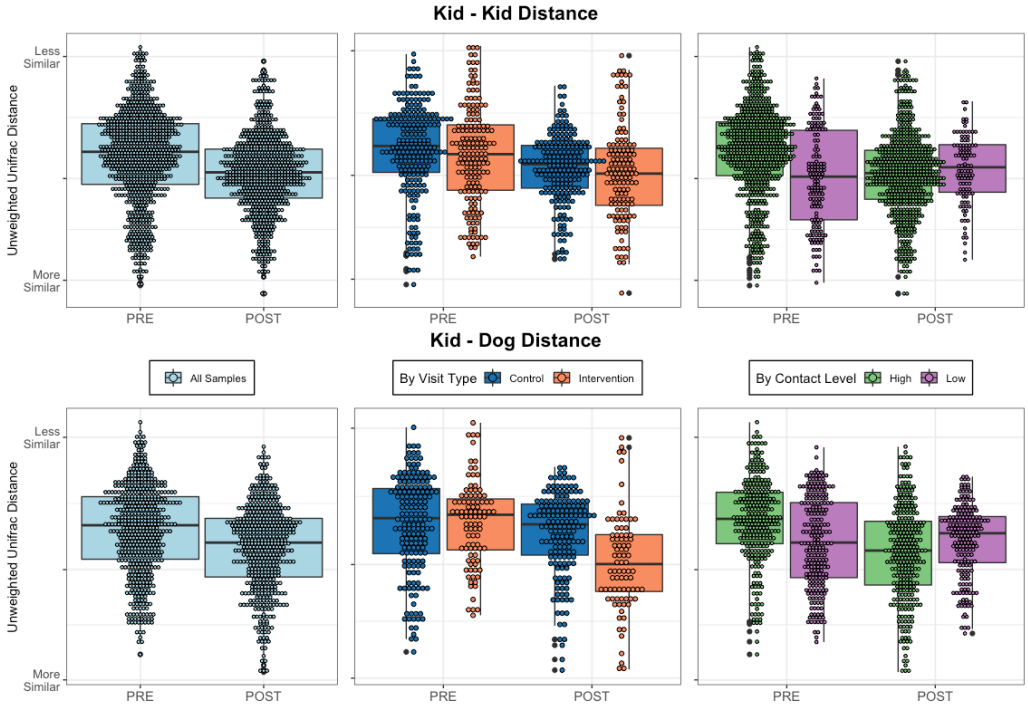


B. Kid-Dog Distance Example

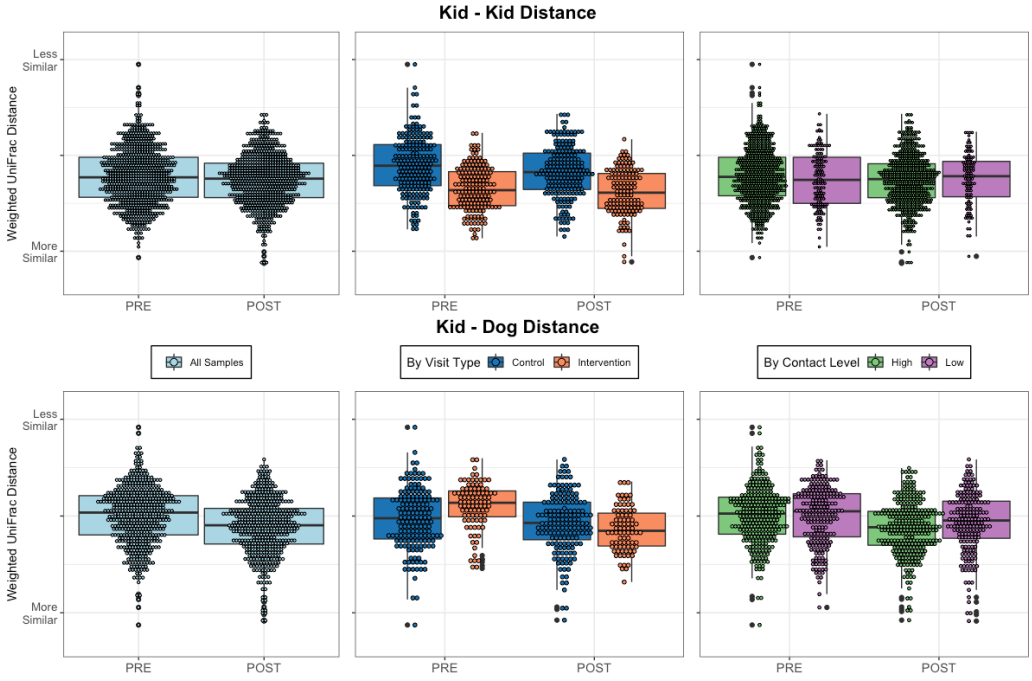


Supplement Figure 4: Visit Type and Contact Level in Microbial Composition Differences Between Patients and Between Patients and Therapy Dogs

A. Unweighted UniFrac Distance



B. Weighted UniFrac Distance



Supplement Table 3: Microbial Composition Differences between Patients and Between Patients and Therapy Dogs Before the Visit Compared to After Visit, Based on Visit Type and Contact Score

Results for Beta Distance via PERMANOVA model

Group	Metric	Kid-Kid Distance		Kid-Dog Distance	
		F-statistic	p	F-statistic	p
Unadjusted Effect Pre versus Post					
All Samples	Unweighted UniFrac	47.068	**0.0001**	38.168	**0.0001**
	Weighted UniFrac	19.33	**0.0001**	36.378	**0.0001**
Control Visits	Unweighted UniFrac	15.926	**0.0002**	2.294	0.128
	Weighted UniFrac	17.78	**0.0001**	4.274	0.025
Intervention Visits	Unweighted UniFrac	8.737	*0.003*	35.188	**0.0001**
	Weighted UniFrac	1.049	0.313	44.689	**0.0001**
High Contact	Unweighted UniFrac	89.538	**0.0001**	82.758	**0.0001**
	Weighted UniFrac	16.017	**0.0001**	28.701	**0.0001**
Low Contact	Unweighted UniFrac	2.418	0.118	0.067	0.829
	Weighted UniFrac	0.474	0.514	9.766	*0.001*
Multivariate Adjusted Effect					
Pre versus Post visit	Unweighted UniFrac	47.642	**0.0001**	38.626	**0.0001**
	Weighted UniFrac	20.962	**0.0001**	36.422	**0.0001**
Contact Level	Unweighted UniFrac	10.317	**0.0002**	2.245	0.135
	Weighted UniFrac	6.691	**0.0003**	0.829	0.328
Visit Type	Unweighted UniFrac	1.325	0.263	4.728	0.011
	Weighted UniFrac	58.887	**0.0001**	2.138	0.094

PERMANOVA FDR-corrected **p<0.001**, *p 0.01-0.001*

Unadjusted Effect = difference in microbial composition distance between patients in pre-visit samples compared to microbial composition distance between patients in post-visit samples (kid-kid distance), or significant difference in microbial composition distance between patients and therapy dogs in pre-visit samples compared to microbial composition distance between patients and therapy dogs in post-visit samples (kid-dog distance) within each exposure group.

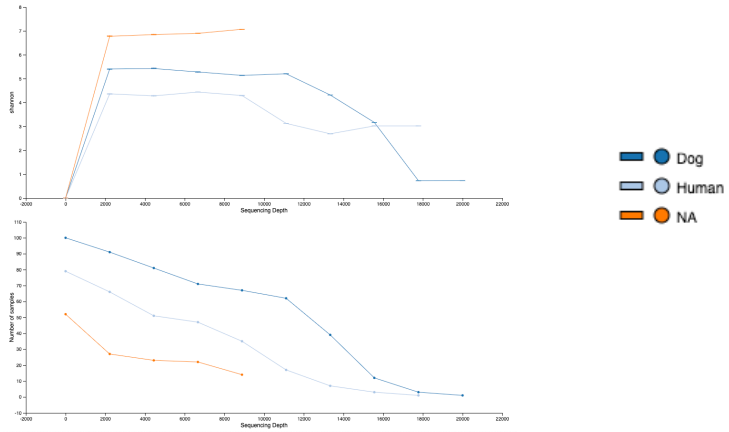
Example interpretation – In control visits, there is a significant difference in the microbial composition between patients before the visits compared to after the visit (p=0.0002 unweighted, 0.0001 weighted)

Adjusted Effect = independent effect of each exposure of the microbial composition distance between patients (kid-kid distance) or microbial composition distance between patients and therapy dogs (kid-dog distance).

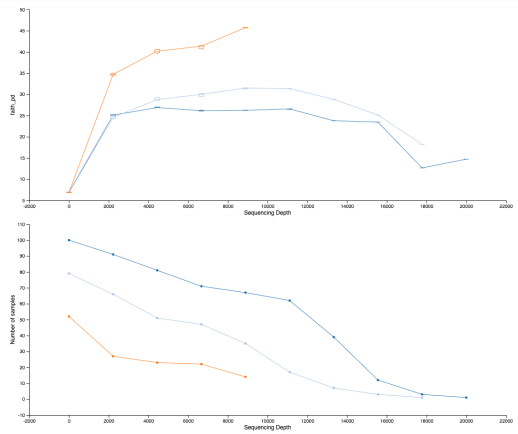
Example interpretation – There is a significant difference in the microbial composition between patients with high contact compared to microbial composition between patients with low contact, independent of collection time (pre versus post) or visit type (control versus intervention) (p=0.0002 unweighted, 0.0003 weighted)

Supplement Figure 5: Alpha Diversity Curves by Host and Sample Site

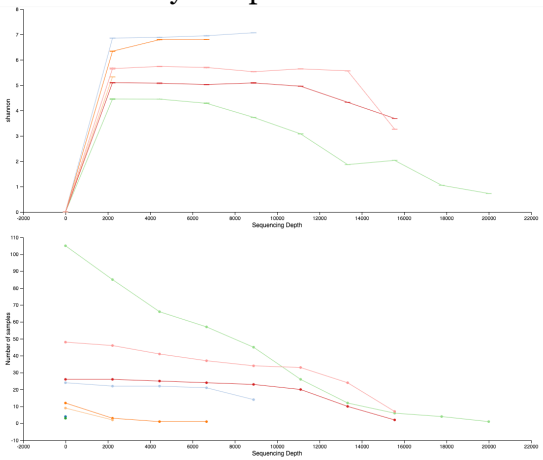
A. Shannon Curves by Host



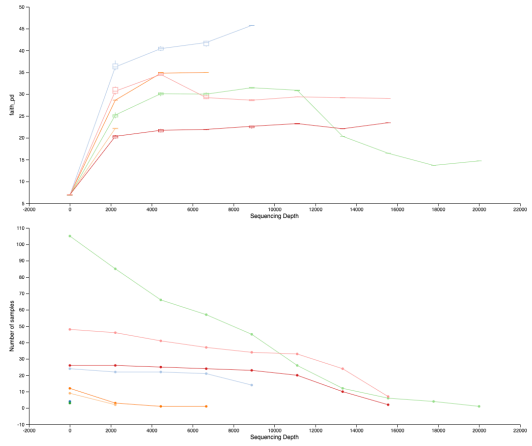
B. Faith Curves by Host



C. Shannon Curves by Sample Site



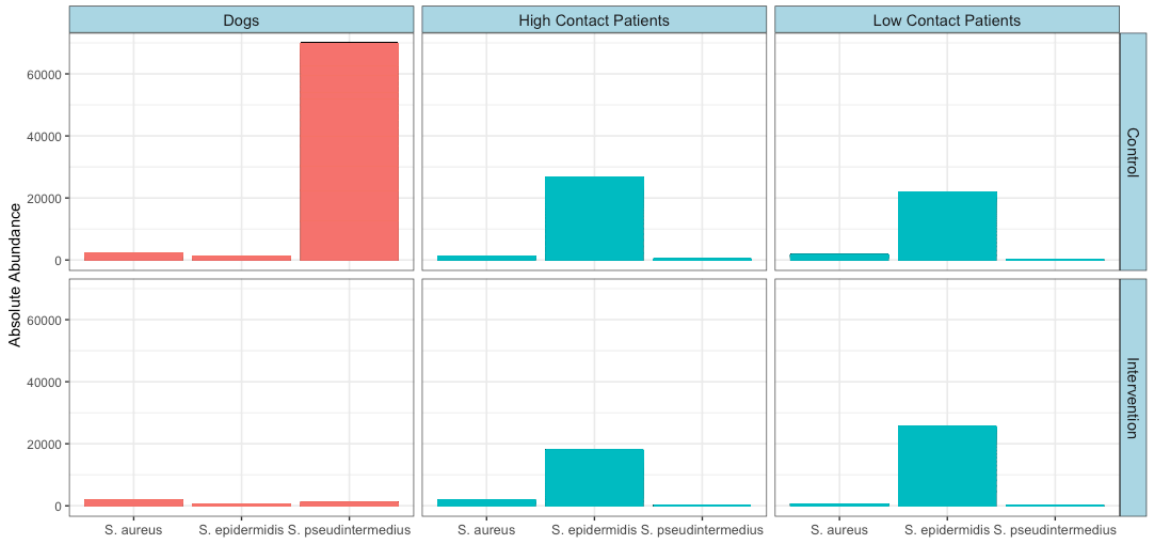
D. Faith Curves by Sample Site



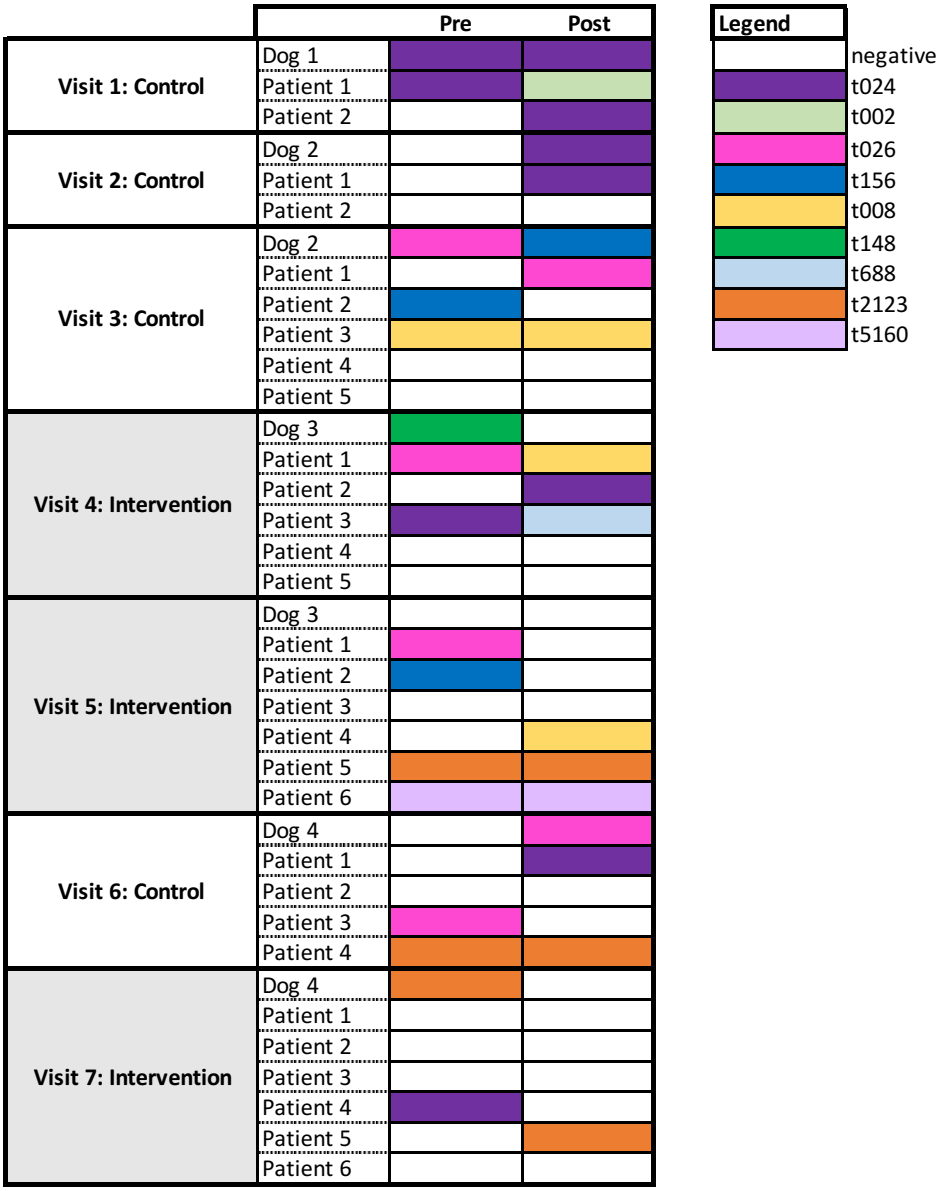
Supplement Table 4: Relative Abundance by Host and Site by Phyla and Genus (Taxa > 3%)

Taxon (Phyla & Genus)	Patient Nasal	Dog Nasal	Dog Oral	Dog Perineal	Dog Inguinal	Environment
Actinobacteria	0.0483	0.0330	0.0432	0.2035	0.0197	0.0522
Corynebacterium	0.1130	0.0330	0.0922	0.2035	0.0431	0.1968
Micrococcus						0.0313
Actinomyces						
Bacteroidetes	0.0137	0.0213	0.0893	0.0704	0.0236	0.0248
Porphyromonas		0.0602	0.1604	0.1065	0.0673	
Capnocytophaga			0.0883			
Bacteroides				0.0734		
Prevotella				0.0312		0.0365
Firmicutes	0.0667	0.1147	0.0212	0.0360	0.0341	0.0633
Staphylococcus	0.2714	0.2886	0.0333	0.0649	0.0453	0.0465
Streptococcus	0.1834	0.0411		0.0952	0.0432	0.1011
Faecalibacterium						0.0688
Blautia				0.0433		
Alloiococcus	0.0382					
Lactobacillus						0.0369
Dorea				0.0317		
Fusobacteria		0.0120	0.0415	0.0370	0.0103	
Fusobacterium			0.0415	0.0370		
Proteobacteria	0.0368	0.0832	0.0559	0.0420	0.0191	0.0204
Moraxella	0.0572	0.1927	0.0396	0.0386		
Conchiformibius		0.0462	0.1879			
Lautropia			0.0741			
Campylobacter				0.0648		
Escherichia				0.0435		
Pantoea						0.0427
Neisseria			0.0408			
Sphingomonas					0.0349	
Pseudomonas					0.0345	
Spirochaetes			0.0274			

Supplement Figure 6: Absolute Abundance of Key *Staphylococcus* Species

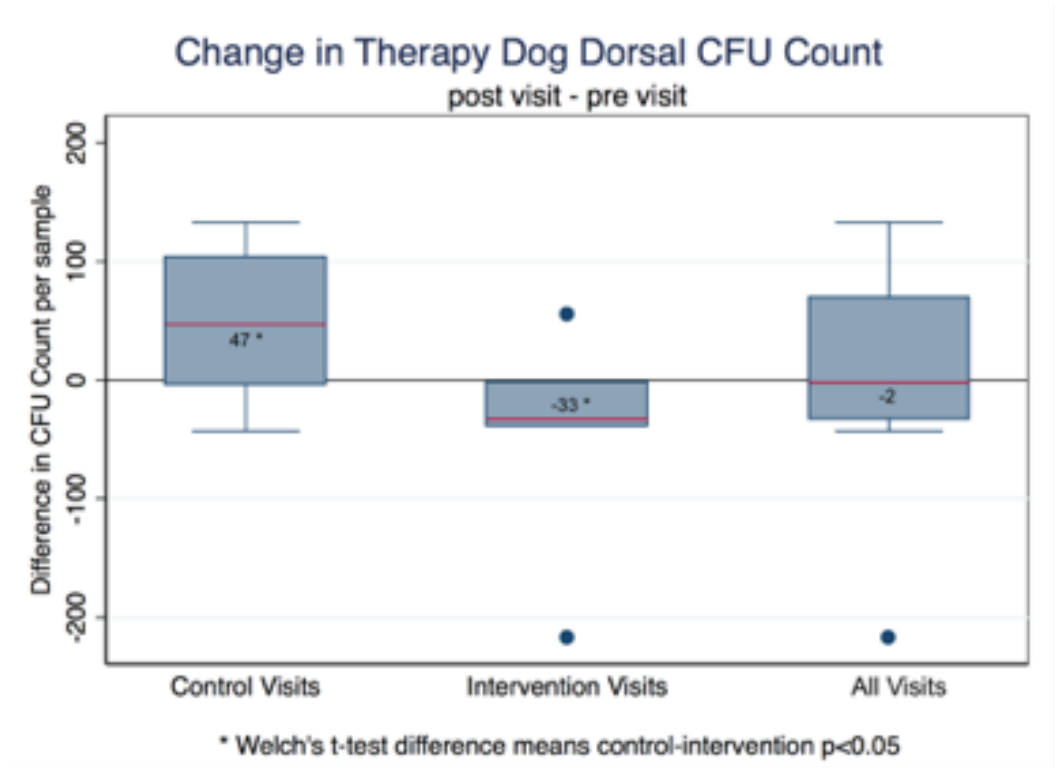


Supplement Figure 7: *spa*-Typing of *Staphylococcus aureus* Isolates from Patients and Therapy Dogs



Results shown only for visits where at least one patient had *Staphylococcus aureus* exposure (negative pre-visit, positive post-visit)

Supplement Figure 8: Gain and Loss in *Staphylococcus aureus* Bacterial Burden in Therapy Dogs via Culture-Based CFU (Colony-Forming Unit) Count Difference (post-pre visit)



Supplement Table 5: Patient Physical and Mental Wellbeing Benefits during Control and Intervention Visits

	All Visits	Control Visits	Intervention Visits
Physical Parameters			
Systolic Blood Pressure Mean Difference post-pre	-5.8 (11.2)	-4.8 (10.4)	-7.3 (12.5)
Diastolic Blood Pressure Mean Difference post-pre	-2.99 (10.6)	-1.2 (12.9)	-5.5 (5.7)
Heart Rate Mean Difference post-pre	-2.78 (7.9)	-3.46 (9.8)	-1.82(4.5)
Mental Wellbeing Parameters			
Reports of Pain* Mean Difference post-pre	-0.06 (0.44)	-0.13 (0.45)	0 (0.43)
Reports of Worry* Mean Difference post-pre	-0.22 (0.69)	-0.33 (82)	-0.09 (0.53)
Reports of Sadness* Mean Difference post-pre	-0.08 (0.41)	-0.17 (0.48)	0 (0.31)

* Graded on Likert Scale 1-5, with 5 being more negative feeling (painful/worried/sad), hence a negative value mean difference reflects feeling more positive after the visit.

No significant t-test in differences of means between control and intervention visits

Chapter 8: Conclusions

8.1 Summary of Findings

Animal-assisted intervention (AAI) programs are a validated and valuable part of holistic patient care in hospitals, and their use has extended to healthcare worker benefits. However, concerns regarding these programs limit their beneficial utilization, namely the possibility of infectious disease spread between patients and other individuals, the therapy animal, and the hospital environment. As such, these concerns would be best addressed by a One Health approach, a harmonized, collaborative effort among human, animal, and environmental stakeholders.

The objective of this thesis research was to apply the One Health framework as a systems-thinking approach to understand collaboration at the macro-level (multi-stakeholder engagement and contributions to implementation practices) and the micro-level (the shared microbial communities between AAI participants). Through this all-encompassing viewpoint, this work has focused on identifying modifiable factors to address infection control and safety in hospital AAI for all individuals involved; the patients, healthcare workers, therapy dogs and their handlers, and the hospital environment. This thesis has approached infection control in hospital AAI programs through multiple angles - from understanding its effectiveness and unintended consequences on the microbial scale, to understanding compliance and potential improvements from individuals who are managing or participating in these programs. Taken together, this work advocates for the sustainability of these valuable programs by identifying areas for potential improvement in implementation.

Chapter 2 reviewed the literature surrounding hospital-associated pathogens and argued for the utilization of a One Health approach to control hospital-acquired infections.

Chapter 3 identified knowledge gaps in current research on hazards associated with hospital AAI programs, specifically infectious disease risks. Both of these literature review chapters set the foundation for our original research. Chapter 4 used in-depth interviews with key stakeholders in AAI programs (healthcare workers and AAI workers) to identify barriers and facilitators to program use for healthcare worker benefit, and determine knowledge, beliefs, and practices regarding infectious disease risk and control policies, in order to understand the contextual parameters for enhanced program implementation. Chapter 5 uses this data to create a conceptual framework to improve program implementation targeted to hospital administrators and hospital infection control specialists.

Chapters 6 and 7 used targeted amplicon metagenomics of samples from patients and therapy dogs to understand AAI's collective positive and negative dynamism on the microscopic scale. Explicitly, the microbial community alterations and sharing that occur between individuals during an AAI session, and the impact of an infection control intervention (dog decolonization) on the burden and sharing of not just pathogens, but all microbiota (the microbiome). Chapter 6 specifically looks at the impact of the decolonization intervention on therapy dog microbiota to identify both effectiveness and safety to minimize unintended consequences and therefore enhance sustainability of this intervention modality for both human and animal health. Chapter 7 further unpacked microbiome changes in child patients as a result of microbial sharing with the therapy dog, and how patient-dog contact level and the dog decolonization intervention modifies this sharing.

Research within this dissertation is significant to inform intervention strategies that target risk reductions of bacterial contamination during AAI programs and provide the

groundwork for further research. The main key findings from this dissertation research, to be used for further study design, are:

1. The lack of data on infectious disease risks to participants in hospital AAI leads to hesitancy in program adoption and underutilization of these beneficial programs. The lack of data was identified in Chapter 3 and confirmed from on-the-ground stakeholders in Chapter 4. This lack of data also relates to a lack of understanding and lowered concern regarding infectious disease risk, also identified in Chapter 4, which could be a barrier to the adoption of control measures and program improvement.

2. This lack of information and program hesitancy is best addressed by multi-stakeholder collaboration, in the form of program advocates across and outside the hospital to design practical risk mitigation strategies, and impactful leadership to direct implementation and train individuals on these appropriate risk mitigation strategies. This concept of holistic engagement was argued in Chapter 2, reported by stakeholders in Chapter 4, and hallmark recommendation in Chapter 5.

3. This holistic outlook, backed by multi-stakeholder collaboration, can be used to design risk mitigation strategies, namely infection control intervention, to improve the safety of these programs. This includes conducting an individual risk assessment within a hospital's AAI program (Chapter 4), but it also deals with understanding collaboration at the microscopic level, namely acknowledging microbial transmission, including pathogens, as a function of the entire microbial community. Control interventions may impact the microbiome, which may have downstream implications for the effectiveness of reducing pathogen transmission

(Chapter 7). Understanding microbial transmissions, within the context of all possible transmission pathways and exposure routes, allowed this research to determine that the therapy dog is only one potential pathway and may not contribute substantially to the infectious disease risk during these AAI programs.

4. In addition to understanding all potential routes of transmission, a holistic outlook will, more importantly, allow for the determination of any unintended consequences from risk mitigation strategies. This was first identified in Chapter 4, where therapy animal handlers reported concerns for the dogs' health as a result of control measures, and was further explored in Chapters 6 and 7. Our decolonization intervention had the unintended consequence of being associated with a reduction in dog-specific microbiota, and sharing of dog-specific phylogenetically rare microbiota to and between patients. This could have secondary health impacts—both beneficial (reduction of dog pathogens) and detrimental (reduction of commensal flora). It is critically important to ensure the safety of all individuals involved in these programs, including the therapy dog teams. As the low number of therapy dog teams was reported to be a limited resource and a barrier to program implementation, any risk mitigation shown to have negative health consequences in the dog would further lower this critical resource and hinder program implementation.

As evidenced by our key findings, this dissertation is a complete and comprehensive body of research that marks the first body of work to connect qualitative and quantitative study designs to understand how beliefs and practices overlap with microbial transmission dynamics and program safety in hospital AAI. In addition to the novelty of this thesis as a whole, each chapter advances the state of current knowledge on AAI

program implementation, as identified by our literature review chapters. By applying a One Health framework to AAI program safety, this research highlighted the importance of considering all potential stakeholders. This is in terms of gaining program support and understanding barriers to program safety, as well as beginning to understand the multiple pathways of microbial sharing. Previous research has focused on microbial carriage on just the therapy animal (Dalton et al., 2020), while our research extends that to explore sharing between therapy dogs and patients. Furthermore, while previous studies have commented on the importance of stakeholder buy-in for hospital infection control (Seibert et al., 2014; Yiwen et al., 2010), none have explored knowledge, belief, and practices in the context of AAI programs. A hallmark of this dissertation, and the One Health framework, is stakeholder collaboration. In addition to collecting perspective from those individuals on the ground, it was essential to translate the research to reach stakeholders involved in hospital leadership. While guidelines directed towards this critical population have been previously published (Lefebvre et al., 2008; Murthy et al., 2015), our Chapter 5 commentary backs those recommendations with novel findings from a mixed-methods study design. Overall, this dissertation research achieved its primary goal of addressing AAI program safety through a One Health approach.

8.2 Implications for Public Health and Policy

The findings from this dissertation can be used to advance the knowledge of program safety and implementation for hospital AAI programs, which has public health and policy implications. The findings are perhaps most relevant for hospital administrators and hospital infection control epidemiologists who are in charge of these programs. Our Chapter 5 commentary directly translate the research findings from our qualitative work into actionable guidelines for this population, while Chapter 7 makes recommendations based on microbial pathways, that all microbial transmission pathways must be considering in the design of infection control programs in order to be effective and safe. However, these results will also be applicable to individuals directly involved in these programs, including healthcare workers and therapy animal handlers. Therapy animal handlers, and other individuals involved in the care of the therapy animals such as veterinarians and certification organizations, will also benefit from these safety guidelines, particularly recommendations from Chapter 6 on unintended consequences of infection control measures to the therapy dogs, to protect this valuable, limited resource. The findings overall from this dissertation can be used to improve hospital infection control policies.

In addition to infection control policies, this research strongly advocates for the adoption of a One Health framework in research studies at the human-animal interface. A hallmark of the One Health approach is the importance of collaboration across disciplines. This research significantly benefitted from the inclusion of a mixed-methods study design and the incorporation of perspective from multiple individuals with diverse backgrounds. This stresses the need for future studies in the field of AAI and other human-animal public health areas to work with specialists with varied experiences. This

includes human-animal interaction specialists, microbiologists, human and animal medical professionals, environmental exposure scientists, and quantitative and qualitative researchers. Working together with these multiple disciplines will create more comprehensive study designs that translate into accurate and practical findings.

8.3 Future Directions

This thesis lays the groundwork for future research intended to support and extend hospital-based AAI programs. While the studies within this dissertation are exploratory and focused in scope, their preliminary results suggest the appropriateness of the study designs and inclusion of the One Health framework. Additional research, using the same rigorous study designs, would benefit the field of AAI as a whole and all participants involved. As a result of this thesis, it is recommended that two major avenues of research be pursued.

The first is additional qualitative analysis, focusing on program implementation in a wide-ranging variety of hospitals, departments, and patient populations. We discovered in our data that there is significant heterogeneity in program adoption, implementation, and adherence. This finding is also confirmed with quantitative survey results from other studies (Linder et al., 2017). As such, perspectives on barriers and facilitators may be fundamentally different across different programs, and our recommendations may not hold true for all AAI programs. Reaching out to new stakeholder groups, both in different geographic locations and job roles, will improve the generalizability and strength of our recommendations. It became apparent in our data that concerns regarding infection are directly related to program leadership and hospital buy-in, so understanding the unique circumstances regarding program implementation across a broader array of settings will have important implications for best practices and program safety. A benefit to qualitative data is that it can be used to create targeted, practical, and relevant quantitative studies, such as survey questionnaires. This could be a potential avenue to capture a greater participant population across a diverse background of experiences and opinions. Combined with qualitative interviews of a subset of

participants, this mixed-methods design can improve the validity of our findings and subsequent policy recommendations for best practices of program implementation to improve AAI benefits and minimize risks.

The second recommended future research area is to explore further microbial transmission that occurs during AAI programs. In addition to the limitation of a fixed sample size in our quantitative microbial studies, our results reflect only microbial carriage at one timepoint. Future research would benefit from understanding the temporal stability of the observed microbiome and pathogen changes during these programs. Likewise, this research highlighted the importance of other potential microbial pathways, such as between patients and healthcare workers or therapy animal handlers — this could be another avenue for future exploration. This research showed how infection control interventions could impact the microbiome of both patients and therapy dogs, and alter microbial sharing, yet we tested only one intervention strategy. Other possible infection control strategies, particularly those identified from our qualitative research, could be examined to understand the unique microbial impacts of different interventions. Finally, distinguishing the clinical significance of these microbial shifts in both patients and therapy dogs will have a critical influence on engaging hospital administrators in program implementation. If these observed microbial shifts lead to differential health outcomes, either negative or positive, this will have significant implications for the safety, effectiveness, and overall use of AAI programs in hospitals.

8.4 Final Remarks

While undertaking this dissertation, it became profoundly clear how important animal-assisted intervention programs are to the patients, the healthcare workers, and the therapy dog teams. These programs are a vital part of holistic patient health, directly observed from the impacts the therapy dog had on patients and healthcare workers, even with brief interactions. It is perhaps the most compelling example of the unequivocal power of the human-animal bond. The need for alternative holistic social support systems has never been more critical than during this time of a worldwide pandemic. The driving force behind all study goals within this thesis is the preservation and proliferative uptake of these indispensable programs. This can only be achieved through the recognition and minimization of barriers to program implementation, including infection risks to all individuals. By understanding and addressing these risks, we can enrich these programs and enhance their use across healthcare facilities. A holistic understanding of the risks and barriers, appreciated through a One Health framework, can best capture the minute and multi-faceted complexities within AAI programs. It is the hope with this dissertation, and the subsequent research that follows, that we can protect hospital AAI programs so they may continue to be used for all who benefit from them.

8.5 References

Dalton, K. R., Waite, K. B., Ruble, K., Carroll, K. C., DeLone, A., Frankenfield, P., … Davis, M. F. (2020). Risks Associated with Animal-Assisted Intervention Programs: A Literature Review. *Complementary Therapies in Clinical Practice*, *39*, 101–145. https://doi.org/10.1101/2020.02.19.20025130

Lefebvre, S. L., Golab, J. S., Christensen, E., Castrodale, L., Aureden, K., Bialachowski, A., … Weese, J. S. (2008). Guidelines for animal-assisted interventions in health care facilities. *Am J Infect Control*, *36*(7), 78–85. https://doi.org/10.1016/j.ajic.2007.09.005

Linder, D. E., Siebens, H. C., Mueller, M. K., Gibbs, D. M., & Freeman, L. M. (2017). Animal-assisted interventions: A national survey of health and safety policies in hospitals, eldercare facilities, and therapy animal organizations. *Am J Infect Control*, *45*(8), 883–887. https://doi.org/10.1016/j.ajic.2017.04.287

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Seibert, D. J., Speroni, K. G., Oh, K. M., Devoe, M. C., & Jacobsen, K. H. (2014). Preventing transmission of MRSA: A qualitative study of health care workers' attitudes and suggestions. *American Journal of Infection Control*, *42*(4), 405–411. https://doi.org/10.1016/j.ajic.2013.10.008

Yiwen, K., Hegney, D., & Drury, V. (2010). A comprehensive systematic review of healthcare workers' perceptions of risk from exposure to emerging acute respiratory infectious diseases and the perceived effectiveness of strategies used to facilitate healthy coping in acute hospital and community he. *JBI Library of Systematic Reviews*, *8*(23), 917–971.

CURRICULUM VITAE

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PERSONAL DATA

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EDUCATION AND TRAINING

Postdoc	Current
Johns Hopkins School of Public Health	
Ph.D.	2020
Johns Hopkins School of Public Health	
Environmental Epidemiology and Exposure Science	
Clinical Research Fellow	2017
Johns Hopkins School of Public Health	
Environmental Microbiology	
M.P.H.	2016
Johns Hopkins School of Public Health	
Infectious Disease	
V.M.D.	2013
University of Pennsylvania, School of Veterinary Medicine	
Veterinary Public Health	
B.S.	2008
SUNY Stony Brook University	
Biology and Anthropology	

MEDICAL OR OTHER LICENSURE

Licensed veterinarian in Maryland, New Jersey, and Pennsylvania	2013
USDA veterinary accreditation:	
Maryland	2015
New Jersey	2013
Veterinary Medical Certification	2013

Professional Experience

Relief Veterinarian 2015-2019
Banfield Pet Hospitals in North Maryland region
Provided veterinary preventative services, and other veterinary clinical duties

Associate Veterinarian 2013-2015
Banfield Pet Hospital, Mount Laurel, New Jersey
Provided veterinary preventative, general medicine, surgical and emergency services in an AAHA-certified three-doctor practice, was primary medical doctor and trained on-boarding doctors.

Professional Activities

Society Membership & Leadership

Infectious Disease Society of America (IDSA)	2018-present
Society for Healthcare Epidemiology in America (SHEA)	2018-present
International Society for Environmental Epidemiology (ISEE)	2017-present
Humane Society Veterinary Medical Association	2015-present
American Veterinary Medical Association (AVMA)	2009-present
Maryland Veterinary Medical Association (MVMA)	2015-2019
American Public Health Association (APHA)	2015-2017

Consortium Activities

Mid-Atlantic Vector-borne Disease Inter-Agency Workgroup	2015-present
CDC / Maryland Department of Health Lyme Corp Outreach Group	2015-2017

Editorial Activities

Peer-review Activities

Reviewed for the following journals:

American Journal of Infection Control
Environmental International
Zoonoses and Public Health

Honors & Awards

IDweek2018 Kass Award	2018
IDweek2018 Oral Abstract Media Release and Press Conference Recognition	2018
Delta Omega Honors Society Poster Competition Runner Up Laboratory Science	2017

Department of Environmental Health Research Retreat
Poster Award Runner Up 2017

Department of Environmental Health Sciences
MPH Capstone Award 2016

FDA Center for Excellence in Regulatory Science and
Innovation (CERSI) Award 2015

University of Pennsylvania School of Vet Medicine,
Student Inspiration Award 2012

PUBLICATIONS

The following link provides access to all published work:

All works:
https://scholar.google.com/citations?user=UshXcZUAAAAJ&hl=en

Currently indexed by PubMed:
https://www-ncbi-nlm-nih-gov.proxy1.library.jhu.edu/myncbi/kathryn.dalton.1/bibliography/public/

JOURNAL ARTICLES (PEER-REVIEWED)

Dalton KR, Waite K, Ruble K, Carroll KC, DeLone A, Frankenfield P, Serpell J, Thorpe R, Morris DO, Agnew J, Rubenstein R, and Davis MF. Risks Associated with Animal-Assisted Intervention Programs: A Literature Review. Complementary Therapies in Clinical Practice 2020, May;39:101145. DOI: 10.1016/j.ctcp.2020.101145.
PrePrint version: medRxiv 2020.02.19.20025130.
DOI: 10.1101/2020.02.19.20025130.

Dalton KR, Rock C, Carroll KC, and Davis MF. One Health in Hospitals: How understanding the dynamics of people, animals, and the hospital built environment can be used to better inform interventions for antimicrobial-resistant Gram-positive infections. Antimicrobial Resistance & Infection Control 2020, June;9(78). DOI: 10.1186/s13756-020-00737-2. PMID: 32487220.

Davis, M.F., Ludwig, S., Josephs-Spaulding, J., **Dalton, K**., Newman, M., Balcer-Whaley, S.L., Peng, R., Keet, C., McCormack, M.C. and Matsui, E.C., 2018. Environmental exposure to Staphylococcus aureus and SEB are associated with asthma symptoms and worse lung function among low-income, urban children with asthma. Journal of Allergy and Clinical Immunology, 141(2), p.AB193. DOI:10.1016/j.jaci.2017.12.612

Leibler, J.H., **Dalton, K.,** Pekosz, A., Gray, G.C. and Silbergeld, E.K., 2017. Epizootics in industrial livestock production: preventable gaps in biosecurity and biocontainment. Zoonoses and public health, 64(2), pp.137-145. DOI: 10.1111/zph.12292

Preprint Publications

K.R. Dalton; Spicer, K.; Ludwig, S; Clemons-Erby, D.; Green, T.; Rule, A.M.; Koehler, K.; McCormack, M.C.; Davis, M.F.; Evaluation of Field Sampling Techniques for Environmental Microbial Exposure: Assessing Efficacy and Feasibility. bioRxiv 2020.06.14.150722; DOI: 10.1101/2020.06.14.150722

Baron PA, Love DC, Ludwig S, **Dalton K**, Larsen J, Innes GK, and Heaney CD, Davis MF. Microbial food safety in the Maryland direct-to-consumer poultry supply chain. bioRxiv 643106. doi: https://doi.org/10.1101/643106.

Teaching

Capstone/Master's Thesis Advisees

Kimberley Guyer, D.V.M., current iM.P.H. student 2020-present

Julianna Nechin, current Sc.M. student (MMI) 2019-present

Summer Student Advisees

Sabrina Waugh (CO State SVM), veterinary student 2019

Zoë Johnson (MI State SVM), current M.H.S. student 2017

Research Assistants

Peter Campbell (current medical student at UMBC) 2020-present

William Altekruse (current social work graduate student UMBC) 2020-present

Teaching Assistantship

One Health Tools 2018-present
to Promote & Evaluate Healthy and Sustainable Communities
Johns Hopkins Bloomberg School of Public Health
Course Faculty Instructor: Meghan F. Davis
3.0 credits, Fourth Term
Enrollment: 2020 — 18; 2019 – 25; 2018 – 21
2018, 2019 & 2020 Excellence in Teaching, based on student course evaluation feedback
* Helped to design this course, gave two lectures, and directed interactive group sessions

Essentials of One Health 2019-present
Johns Hopkins Bloomberg School of Public Health
Course Faculty Instructor: Meghan F. Davis
0.5 credits, First, Third & Fourth Terms
Part of the "Cells to Society" public health curriculum
Enrollment 2019-20: First term – 150; Third term – 80; Fourth term – TBD

Foundations of Occupational Health 2018
Johns Hopkins Bloomberg School of Public Health
Course Faculty Instructor: Maureen Cadorette
3 credits, First Term

Case Studies in Food Animal Production and Public Health 2017
Johns Hopkins Bloomberg School of Public Health
Course Faculty Instructor: Keeve Nachmann
3 credits, Fourth Term

RESEARCH GRANT PARTICIPATION

CURRENT GRANTS

No number (Dalton) 2019-present
Johns Hopkins ERC
Identifying Occupational Health Benefits and Concerns of Key Stakeholders Regarding Hospital-Based Animal-Assisted Intervention Programs: A Pilot Study to Inform Program Implementation.
$10,000
Role: Principal Investigator (no effort covered)
Main Grant Objective: Conduct qualitative interviews on key stakeholders in hospital animal-assisted intervention programs in order to understand barriers and facilitators to program implementation as a stress-reduction mechanism in healthcare workers. Principal Responsibilities: As student PI, I designed the project, wrote for initial funding, submitted for IRB approval, hired and trained research assistants, conducted or supervised interviews, preformed or supervised coded qualitative data analysis, and transcript finding into a manuscript for publication.

No number (Dalton) 2018-present
NIOSH Johns Hopkins Education and Research Center Training Award (T42)

RHD097692A (Davis) 2018-2022
R01, Eunice Kennedy Shriver National Institute of Child Health & Development
Clinical trial of a disinfectant intervention in therapy dogs to combat hospital-associated pathogens and promote sustainability of Animal-Assisted visitation programs
$1,857,348
Role: Postdoctoral Fellow Co-Investigator
Main Grant Objective: Leadership of one independent aim, to assess holistic microbial community alterations during a hospital animal-assisted intervention program, and the effect of a chlorhexidine-based intervention on acquisition of hospital-associated pathogens and microbial communities by patients during AAI sessions via a multicenter randomized controlled trial
Principal Responsibilities: Assist with overall study management for multicenter clinical trial, aid in study design, supervise and train sample collection and

laboratory assessment, supervise or perform data management and data analysis on microbial community analysis, give presentations, prepare manuscripts.

Previous Grants

No number
American Kennel Club Canine Health Foundation 2018 - 2019
Clinician-Scientist Fellowship
$12,000

No number (Davis/Fanzo) 2017-2018
Johns Hopkins Practical Ethics Award
The law of unintended consequences: Will the implementation of California SB27 impact animal health and well-being?
$67,500
Role: Student Investigator (no effort)
Main Grant Objective: To characterize the immediate impact of SB27 on animal health and welfare and examine ethical trade-offs associated with the California law.
Principal Responsibilities: conducted farmer interviews, assist with preparation of manuscripts.

D15CA-802 (Chen) 2014-2015
Morris Animal Foundation (extramural)
Animal Assistance Therapy: Ensuring animal health and program sustainability in the context of hospital-associated infections
$10,000
Role: Study Coordinator (no effort)
Main Grant Objective: To demonstrate whether a dog intervention to decontaminate fur during AAT visits can reduce transmission of HAIs between patients and animals.
Principal Responsibilities: Study design, sample collection, laboratory and data analysis, manuscripts.

Academic Service

University (Johns Hopkins)

One Health Student Group
Co-Founder 2015
President 2015-2018
Senior Advisor 2018-present

Department (Environmental Health and Engineering)

Environmental Health and Engineering Practice Committee
Student Representative 2018-present
Environmental Health and Engineering Student Group
Treasurer 2017-2020

Dalton KR, Waite KB, Agnew JA, Barnett DJ, David MF. The COVET Study: Preliminary Findings from the Ongoing Veterinary and Animal Care Workers' Perceived Risk and Willingness to Respond to the COVID-19 Pandemic. World One Health Congress. Oct 30 – Nov 3, 2020. (Presenting author, Oral presentation).

Dalton KR, Carroll KC, Grice EA, Davis MF. Exploring Microbial Community Alterations during Hospital Animal-Assisted Intervention Programs. ID Week. Oct 21-25, 2020. (Presenting author, Poster presentation).

Dalton K, Ruble K, Carroll K, Grice E, and Davis MF. Emerging exposures and health effects in the hospital environment. International Society of Environmental Epidemiology (On Places II, S03), August 25-28, 2019, abstract published in Environmental Epidemiology (Presenting author, Oral presentation).

Dalton K, Ruble K, Delone L, Frankenfield P, Walker D, Ludwig S†, Ross TL, Jaskulski J, Carroll KC, Rankin S, Morris DO, Chen A, and Davis MF. Reduction in the spread of hospital-associated infections among pediatric oncology patients in a group animal-assisted visitation program from a canine intervention. ID Week (Abstract #72940). October 4, 2018, abstract published in Open Forum Infectious Diseases. (Presenting author, Oral presentation and press conference)

Davis MF, **Dalton K**, Johnson Z, Ludwig S, Sabella K, Newman M, Balcer-Whaley S, Keet C, McCormack MC, Carroll KC, and Matsui EC. Household pets and recovery of Moraxella catarrhalis and other respiratory pathogens from children with asthma. ID Week (Abstract #71914). October 6, 2018, abstract published in Open Forum Infectious Diseases. (Poster session)

Innes G, **Dalton K**, Gould CA, Markos A, Nachman K, Frattaroli S, Fanzo J, Barnhill A, and Davis MF. Antibiotic resistance and societal consequences: perspectives from animal agriculture producers and other stakeholders. 8th Symposium on Antimicrobial Resistance in Animals and the Environment. July 1-3, 2019 (Poster presentation)

Davis MF, Ludwig S, **Dalton K**, Exum N, Schwab K, Kosek M, Koehler K, Rule A, Lautenbach E, McCormack M, and Matsui E. Assessment of indoor microbial exposures. International Society of Exposure Science & International Society for Environmental Epidemiology joint conference (Abstract#300180). August 28, 2018. (Poster session)

Davis MF, Ludwig S, Josephs-Spaulding J, **Dalton K,** Newman M, Balcer-Whaley S, Peng R, Keet C, McCormack MC, Matsui EC. Environmental exposure to Staphylococcus aureus and SEB are associated with asthma symptoms and worse lung function among low-income, urban children with asthma. The American Academy of Allergy, Asthma, and Immunology Annual Meeting, (Abstract# 33436). March 4, 2018, abstract published in the Journal of Allergy and Clinical Immunology.