Risk Factors for Emerging and Reemerging Infectious Diseases in Children

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ABSTRACT

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This dissertation assesses the factors that lead to the emergence of infectious diseases in children, particularly the emergence of multidrug-resistant organisms (MDROs) and diarrheal pathogens in vulnerable pediatric populations. It includes three manuscripts. The initial study is a systematic review that summarized the role of antibiotic exposure on the acquisition of MDROs in children. Twenty-nine studies met the inclusion criteria and a positive association between prior antibiotic use and subsequent colonization or infection with an MDRO was identified in most studies. There were wide variations among study sites, populations, and definitions of antibiotic use and MDROs. Therefore, limited inferences could be made on which components of antibiotic exposure have the greatest impact on MDRO development.

The second analysis examines the relationship between prior stay at a pediatric long-term care (LTC) facility and infection with an MDRO among hospitalized children. This study included 2,945 infections in 258,664 pediatric admissions from 2006 through 2016. At least 1 MDRO was identified in 10% of infections. Of the 1,198 children who had previously resided in a pediatric LTC facility, only 1 child (0.08%) had an MDRO infection. However, prior receipt of pediatric LTC was associated with an increased likelihood of infection (OR 2.4, CI95 1.66 – 3.43), *C. difficile* infection (OR 2.57, CI95 1.26 – 5.25), days of antibiotic use (OR 1.01, CI95 1.01 – 1.02), length of stay (OR 1.01, CI95 1.01 – 1.01), and death (OR 4.38, CI95 2.93 – 6.55).

The concluding study evaluates the association between animals living in or near the home and diarrheal disease in children. This research is a secondary analysis of the Global Enteric Multicenter Study case control study, which investigated the epidemiology of diarrheal

illness in children <5 in sub-Saharan Africa and south Asia. Of 9,439 cases and 13,128 controls, 87% had ≥1 animal in their home. In a multivariable analysis adjusting for exclusive breastfeeding, water source, sanitation facility, number of children <5 years in the household, and wealth index, any animal on a child's compound decreased the odds of diarrhea by 33% (aOR 0.66, CI_{95} 0.59 – 0.74). However, children with diarrhea who had an animal present were not more likely to have a positive stool culture.

Overall, the three studies provide a thorough analysis of several factors associated with the infectious disease emergence in children, particularly as related to MDROs and diarrheal disease. Environmental characteristics, including antibiotic use and interaction with animals, were shown to be important factors for emergent infectious disease across diverse settings. The development of pediatric infection prevention interventions should take into consideration environmental risk factors in order to effectively mitigate the risks posed infectious disease emergence.

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DEDICATION

This dissertation is dedicated to Cohort Support, namely Melissa Beauchemin and Richard Dorritie. When I started this journey, I had no idea how much cohort support would become an integral component of these past three years. Somehow, we are all still standing. We did it, folks.

CHAPTER ONE

Introduction

Despite advances in infection prevention and the development of antimicrobial therapies, infectious diseases have remained a significant cause of global morbidity and mortality. According to the World Health Organization, infectious diseases cause about a quarter of deaths worldwide and are a significant contributor to lifetime disability (1, 2). In 2016, infectious diseases were responsible for almost 9 million deaths of which half were due to a respiratory infection or diarrheal disease (3).

Emerging infectious diseases, i.e., those that "have newly appeared in a population or have existed previously but are rapidly increasing in incidence or geographic range" (4), constitute a major threat to public health. While the total number of infectious disease cases has decreased in recent decades, since 1980, the rate of infectious disease outbreaks and the diversity of pathogens causing disease have been significantly increasing, even when controlling for the impact of globalization and increased surveillance (5). This dissertation examines the impact that emerging and re-emerging infectious diseases have on children.

Causes of Emerging Infectious Diseases

Numerous factors are implicated in the emergence and reemergence of infectious diseases including but not limited to human susceptibility, climate change, warfare, poverty and social inequality, microbial adaptation, and economic development (6). These generalized causes are important for understanding the grander socioeconomic and environmental interactions precipitating emerging infectious diseases, however, they can be less applicable in identifying public health prevention and control interventions. For the purpose of this dissertation, two specific modes of infectious disease emergence were studied: antibiotic use and zoonotic transmission.

Antibiotic use. More than one fifth of all known emerging infectious diseases are associated with drug-resistant organisms (7). While advances have been made in the development of novel antibiotics, infections due to multidrug-resistant organisms (MDRO) are on the rise with an increasing burden of morbidity in children. Multidrug- and carbapenem-resistant *Pseudomonas aeruginosa* in children has been increasing steadily throughout the early 2000s, with almost 25% of isolates tested showing multidrug-resistance in 2012 (8). Similar findings have been reported in studies of carbapenem-resistant Enterobacteriaceae, with significant increases of an emerging resistant strain that was not identified in children until 2011 (9, 10).

Exposure to antibiotics has been identified one primary driver for the acquisition of a MDRO (11), which is further exacerbated by inappropriate antibiotic use. A study on viral pneumonia found that most individuals were administered courses of antibiotics greater than 3 days despite laboratory diagnosis with a viral pathogen and that those individuals were at more than 2 times the risk for subsequent acquisition with an MDRO (12). Even though much of the current research has evaluated antibiotic use and MDRO colonization and not infection, colonization with an MDRO has been shown to not only increase the risk of an infection with that particular organism but also to increase the risk of colonization and/or infection with other MDRO (13). Despite growing concerns over increases in antibiotic resistance, antibiotic use has largely remained consistent and there is evidence that broad-spectrum antibiotics are increasingly being used (14).

Furthermore, some populations, such as residents of long-term care (LTC) facilities are more likely to receive not only more antibiotics but broad-spectrum antibiotics as well. Prior research has shown that an estimated 47-79% of adults living in LTC facilities receive at least

one course of antibiotics a year at a rate of 0.4-23.5 courses per 1,000 resident days (15, 16). Similar findings were reported for residents of pediatric LTC facilities, who may be at greater risk for colonization and/or infection with an MDRO not only for increased antibiotic use but also for their comorbidities and complexity of care (17).

Zoonotic transmission. Emerging diseases are two times as likely to be caused by a zoonotic pathogen as compared to a non-zoonotic one (18). Over the past few decades, zoonotic infections have increased with over half of all outbreaks and almost two-thirds of all infectious diseases being traced back to an animal source (5). While wildlife constitute the majority reservoir population of zoonotic pathogens, a significant proportion of these emerging infectious diseases spreading to humans are due to interactions with livestock (7). Middle East Respiratory Syndrome has been associated with domesticated dromedary camels (19), Severe Acute Respiratory Syndrome was sourced to wet markets in China (20), an outbreak of Nipah virus was traced back to industrial pig farming (21), and the emergence of antimicrobial resistant organisms has been linked to industrial animal agriculture (22). As the volume of animal products consumed continues to increase worldwide (23), it is likely that livestock will become an ever-increasing source of emerging infectious diseases.

Emerging Infectious Diseases Impact on Vulnerable Populations

The burden of infectious diseases disproportionately affects vulnerable populations such as those living in developing countries as well as those at the extremes of age (1, 24). Individuals living in a low-income country are more likely to die from a respiratory infection or diarrheal disease than any other cause (3). Many of these infections also have the greatest impact on children, especially those younger than 5 years old, with an estimated 6 million children dying each year as the result of an infectious disease, accounting for 68% of all childhood deaths in

those < 5 years old (25). Both antibiotic use and zoonotic transmission have profound impacts on the emergence of infectious disease in these vulnerable populations, therefore this dissertation focuses on the acquisition of MDROs and the incidence of diarrheal disease.

Emergence of multidrug-resistant organisms in hospitalized children. Antibiotic exposure primarily leads to the development of MDRO in all populations, but it is children who oftentimes experience the greatest effects from MDRO acquisition, especially among those who are critically ill and/or hospitalized. An estimated 5-10% of healthcare-associated infections (HAI) that occur each year in hospitalized children are caused by an MDRO (26). Infection with an MDRO is known to increase the risk of mortality, lengthen hospitalization, and cost more than an infection with a non-MDRO among hospitalized patients (27, 28). Critically ill children are at increased risk for a MDRO HAI due to their relatively high use of invasive devices, frequency of procedures, increased exposure to antibiotics, and prolonged length of stay (29-31). In addition to those risks, critically ill hospitalized children are likely to experience greater negative consequences of MDRO infection, with an estimated two times the risk of mortality for children with an MDRO versus non-MDRO HAI (32).

Hospitalized children who are admitted from pediatric LTC facilities likely have an even greater risk of MDRO acquisition. In addition to widespread antibiotic use in this population, these children are also more likely to have invasive device use, increased care needs, and be immunologically immature (17, 33). However, previous research in pediatric LTC facilities has largely been limited to describing the prevalence of MDRO colonization, e.g., methicillin-resistant *Staphylococcus aureus* and multidrug-resistant gram-negative bacilli (34, 35). Understanding the role that antibiotic use has in the development of MDRO will help to prevent the continued emergence of these pathogens in this at-risk population.

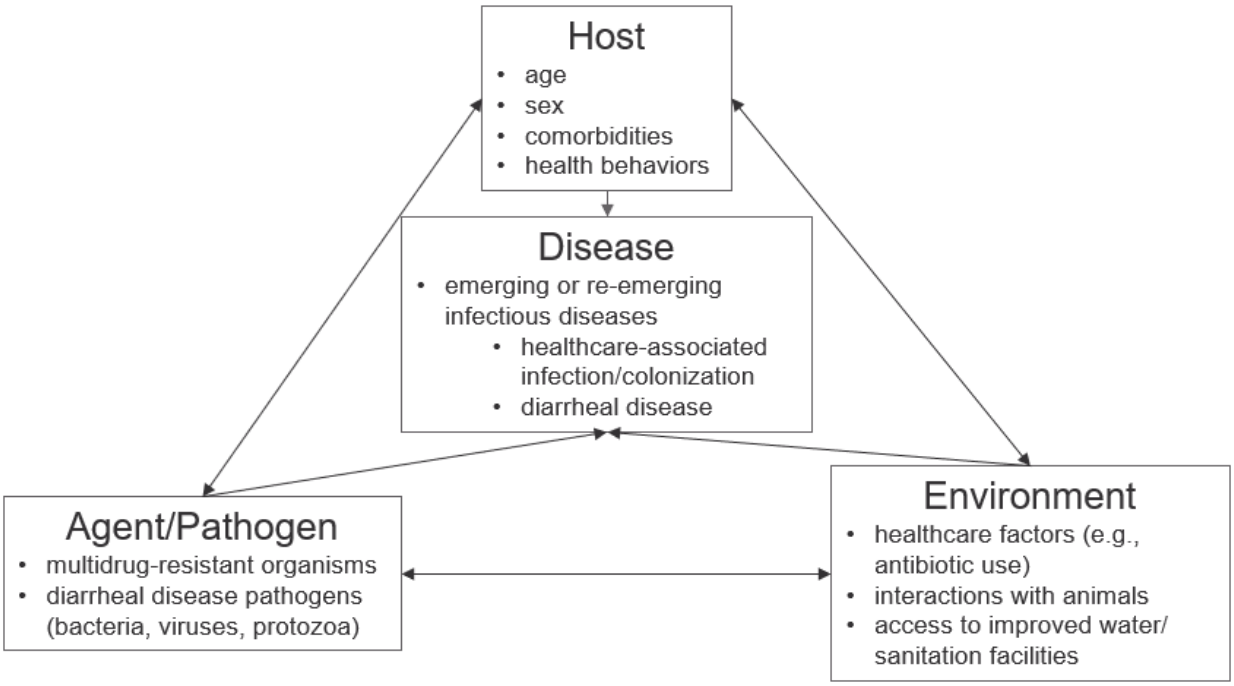
Diarrheal disease. One of the most common infections caused by zoonotic transmission is diarrheal illness, which was responsible for 1.6 million deaths worldwide in 2016 (36). Children carry an unequal burden of diarrheal disease. It is a major cause of death throughout much of the world for children younger than 5 years old, particularly for those living in low- or middle-income countries. In 2016, there were an estimated 1.1 billion new cases of diarrhea and an associated 446,000 deaths in children less than 5 years of age (36, 37). Many factors contribute to the incidence of diarrhea in this population, including duration of breastfeeding and access to improved water and sanitation facilities, but of increasing concern is how interactions with animals may be associated with disease emergence (38). Livestock and companion animals have been identified as a reservoir for many diarrheal pathogens such as *Campylobacter* spp., *Escherichia coli, and Salmonella* spp. (39), which are known to cause a significant proportion of diarrheal illness in children less than 5 years old (40). Most studies investigating the interactions between humans and animals and subsequent diarrheal disease have focused primarily on developed countries with large animal agriculture and companion animal industries (39, 41). Since the burden of diarrheal disease primarily impacts developing and/or low-income countries, it is important to gain greater understanding of the interactions between humans and animals and how that may impact the incidence of diarrheal illness in young children living in low resourced areas. Furthering our understanding of the human-animal exchange of pathogens may help to inform the design of improved interventions for the prevention of diarrhea, especially in children.

Theoretical Framework

This dissertation was guided by the epidemiologic triad of disease, which is comprised of four constructs: host, agent, environment, and disease (42). This model fits this dissertation's

investigation of the relationship between predictors related to the emergence and reemergence of infectious diseases (Figure 1.1). The host includes factors such as age, sex, and comorbidities, and only refers to human hosts. Agent includes the bacterial, viral, and parasitic pathogens causing infections in humans, e.g., MDRO, diarrheal disease pathogens, and Shiga toxin-producing *E. coli*. Environment refers to factors extrinsic of the host and agent that occur prior to the onset of an infectious disease. The environmental factors influencing the development of disease can vary greatly. For this dissertation, environment included healthcare factors (e.g., antibiotic use), interactions with animals (e.g., livestock), and characteristics of the lived environment, (e.g., use of improved sanitation facility).

Figure 1.1: Epidemiologic triad of disease



Specific Aims

To gain further insight into the factors leading to the emergence and re-emergence of infectious diseases in vulnerable populations, with a focus on antimicrobial resistance and diarrheal disease, this dissertation aims to accomplish the following:

Aim 1: To explore the relationship between antibiotic use and subsequent colonization or infection with a multidrug-resistant organism in hospitalized children

Aim 2: To determine the relationship between prior stay in a pediatric long-term care facility and subsequent infection with a multidrug-resistant organism in hospitalized children

Aim 3a: To assess the association of living in close proximity to animals on presence of diarrheal disease in children less than 5 years of age

Aim 3b: To evaluate the relationship between type of animal and pathogen present in children with diarrhea

CHAPTER TWO

Prior Antibiotic Use and Acquisition of Multidrug-Resistant Organisms in Hospitalized Children: A Systematic Review

Abstract

Objective: Multidrug-resistant organisms (MDRO) cause about 5-10% of infections in hospitalized children, leading to an increased risk of death, prolonged hospitalization, and additional costs. Antibiotic exposure is considered a driving factor of MDRO acquisition, however there is a lack of consensus regarding the impact of antibiotic factors, especially in children. We conducted a systematic review to examine the relationship between antibiotic use and subsequent healthcare-associated infection or colonization with a MDRO in children.

Design: Systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guideline.

Methods: Pubmed and Embase were searched for all English, peer-reviewed original research studies published before September 2018. Included studies evaluated hospitalized children, antibiotic use as an exposure, and bacterial MDRO as an outcome.

Results: Of the 535 studies initially identified, 29 met the inclusion criteria. Overall, a positive association was identified in most studies evaluating a specific antibiotic exposure (81%, n=17/21), duration of antibiotics (75%, n=9/12), and number of antibiotics received (67%, n=2/3). Those studies that evaluated any antibiotic exposure had mixed results (50%, n=5/10). There were wide variations among study sites, populations, and definitions of antibiotic use and MDROs.

Conclusions: Published research evaluating this relationship is limited and was of mixed quality. Limitations include observation bias in recall of antibiotic exposure, variations in case definitions, and lack of evaluation of antibiotic dosing and appropriateness. Additional studies exploring the impact of antibiotic use and MDRO acquisition may be needed to develop effective antibiotic stewardship programs for hospitalized children.

Introduction

Multidrug-resistant organisms (MDRO) cause about 5-10% of infections in hospitalized children (26). While there is no standard definition, a MDRO is generally an organism resistant to one or more classes of antibiotics to which it has been traditionally susceptible (43). Such organisms have long been associated with increased risk of mortality, longer hospitalizations, and additional costs when compared with non-MDRO infections with the same species (28).

Over the past two decades, the prevalence of MDRO has been increasing, particularly in children. Researchers examining *Pseudomonas aeruginosa* found a 4% increase each year in multidrug-resistant strains beginning in 1999, with over a quarter of isolates multidrug-resistant by 2012 (8). Similarly, studies of Enterobacteriaceae have shown significant increases in carbapenem-resistance, an emerging strain that was not consistently identified in children until 2011 (10). In the United States, pediatric multidrug-resistant Gram-negative enteric *Enterobacteriaceae* infections in hospitalized children increased 7.5-fold between 2007 and 2015 (9). Similarly, the rate of children hospitalized with vancomycin-resistant enterococcal infections increased from 53 per million in 1997 to 120 per million 2012, resulting in an average 2 day longer hospitalization and an additional $8233 USD in hospital costs (44).

About one third of children with MRSA bacteremia experience treatment failure and there is an estimated 50% increase in odds of a serious complication, e.g., need for extracorporeal membrane oxygenation or death, for every 1 day increase in bacteremia duration (45). For hospitalized children who are critically ill, the consequences are more severe as their odds of death are two times greater if they have an infection with an MDRO as opposed to a non-MDRO (32). Furthermore, critically ill children are at increased risk for an infection with an

MDRO due to increased invasive device use and procedures, antibiotic exposure, and longer hospital stays (2, 29, 31).

Although it is well-established that antibiotic exposure is highly correlated with MDRO acquisition, there is no general consensus on which drugs and dosages lead to resistance, especially in children (46-48). Infections in children differ from those in adults and therefore often require different antibiotic management (49), which may lead to varying resistance patterns in children as compared to adults. While individual studies have examined the relationship between antibiotic use and acquisition of MDRO in hospitalized children, but the data from these studies has not been synthesized. In order to address the emergence of MDRO in critically ill children, it is necessary to understand the specific role of antibiotic use. Therefore, we conducted a systematic review of the research literature to examine the relationship between antibiotic use and subsequent healthcare-associated infection or colonization with a MDRO in hospitalized children.

Methods

Inclusion and exclusion criteria. This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guideline.(50) The following inclusion criteria were used: 1) conducted only in children hospitalized at an acute care facility, 2) study predictor was a measure of antibiotic use, 3) study outcome was an HAI or healthcare-associated colonization (HAC) with a bacterial MDRO as defined by the study authors, 4) published in English, and 5) original research. HAI and HAC were considered hospital-associated if they occurred > 48 hours after admission and before discharge. Tuberculosis and case studies were excluded from this review.

Search strategy. An initial search of two biomedical literature databases, Embase and PubMed, was conducted in November 2017 with subsequent searches conducted through September 2018. Search terms included combinations of keywords and/or Medical Subject Headings, when appropriate, which were linked with Boolean operators. Embase and Pubmed search terms are described in the Appendix.

Study screening and quality assessment. Throughout the screening and quality assessment, two reviewers (MM and MB) evaluated each article. Any discrepancies between reviewers were discussed with a third reviewer (EL) until consensus was reached. The following process was employed to evaluate articles for inclusion in the study. Firstly, articles were screened for duplication. Secondly, the titles and abstracts were reviewed for relevance. Thirdly, appropriate articles were retrieved and the full text was assessed to determine if they met the inclusion criteria. Fourthly, references of included studies were hand searched to identify additional studies not identified during the original database search.

The final included articles were reviewed using the Newcastle and Ottawa tools for quality assessment for cohort and case control studies (51). While both tools have a maximum score of 9, not all items were relevant for each of the included studies. To address the variance in denominators, scores were presented as percentages. Studies were determined a priori to be of high quality if they scored > 75%, unclear quality if the scored 50 - 75%, and of low quality if they scored < 50%.

Results

Overall, 535 studies were identified during the initial database searches. Twenty articles were duplicates, which resulted in 515 articles to be assessed for relevance. After title, abstract and full text review, 20 studies met the inclusion criteria. An additional nine articles were found

during hand searching of the 20 studies, bringing the total number of articles in the review to 29. The screening process and exclusion criteria are summarized in Figure 1. The studies included 4,598 hospitalized children in whom there were 4,606 HAI and/or HAC of which 34% (1,577) were due to a MDRO. A detailed description of each study is provided in Table 2.1.

Study designs, sample, and association between antibiotic use and MDRO. The articles included in this review were all observational studies: 12 were cohort studies (seven retrospective (52-57) and five prospective (58-62)) and 17 were case control studies (63-80). The study sample for all articles were hospitalized children, although their ages differed among the studies. Seven included specific age ranges (53, 56, 58, 60, 63, 74, 75), 10 included only neonates (52, 54, 57, 59, 61, 62, 65, 70, 71, 80), and 12 did not provide an age range for the children included (55, 64, 66-69, 72, 73, 76-79).

Organisms included in the articles were Enterobacteriaceae (n=10) (52, 55, 59, 68, 69, 74-78), *Klebsiella pneumoniae* (n=8) (54, 56, 60, 61, 67, 71, 79, 80), *Escherichia coli* (n=5) (56, 66, 70, 79, 80), Gram-negative bacteria (n=3) (53, 63, 72), *Acinetobacter baumannii* (n=3) (62, 65, 73), *Enterococcus faecalis* or *E. faecium* (n=1) (64), *Pseudomonas aeruginosa* (n=1) (57), *Serratia marcescens* (n=1) (61), and *Streptococcus pneumoniae* (n=1) (58). For HAI, eight studies included all types of infections (52, 54, 57, 58, 62, 63, 74, 80), five were bloodstream infections (BSI) (53, 56, 60, 64, 79), one was urinary tract infections (UTI) (75), one was ventilator-associated pneumonia (VAP) (65), and one was respiratory tract infections (RTI) (55). All HAI were specified as occurring during the hospitalization, however only six studies provided HAI case definitions (52-54, 63-65). Five studies examined HAC only (59, 67, 72, 76, 78), and eight did not distinguish between HAI and HAC (61, 66, 68-71, 73, 77).

Ascertainment of antibiotic exposure differed across studies; 86% (n=25) abstracted antibiotic use from the medical record (52, 53, 55-57, 59-62, 64-68, 70-80), 3% (n=1) utilized both parental recall and the medical record (58), and 10% (n=3) did not explicitly state how antibiotic exposure was ascertained (54, 63, 69). Each study varied in its definitions of antibiotic use and HAI/HAC with a MDRO. For the antibiotic exposure, measures of use included previous receipt of particular antibiotic classes or drugs (n=21) (52, 53, 56-60, 62, 65, 67-74, 76, 78-80), receipt of any antibiotics (n=10) (53, 54, 56, 58, 63, 66, 72, 74, 76, 78), duration of antibiotic therapy (n=11) (52, 55, 61, 62, 64, 66, 72, 75, 77, 78, 80), and number of antibiotics received (n=3) (52, 75, 77). The period of exposure timing varied from two weeks to six months (53, 55-58, 60, 62-64, 66, 68, 73, 74, 79); 15 studies did not provide any specific period (52, 54, 59, 61, 65, 67, 69-72, 75-78, 80). MDRO was limited to a specific bacteria (n=12) (54, 57, 58, 60, 62, 64-67, 70, 71, 73) or grouping of bacteria (n=17) (52, 53, 55, 56, 59, 61, 63, 68, 69, 72, 74-80). The summary of findings of the impact of antibiotic exposure measures and subsequent MDRO acquisition is presented in Table 2.2.

Quality assessment of included articles. The majority of studies had quality scores >50% (mean score 81%, range 44-100%) (Table 2.1), with 66% of high quality (n=19), 31% of unclear quality (n=9), and 3% of low quality (n=1). Overall, case control studies were marginally higher quality than the cohort studies (mean score 82% and 79%, respectively). For case control studies, all had adequate case definitions and the same method of ascertainment for cases and controls. Since all case control studies were medical record reviews, the non-response rate was not applicable nor reported. For cohort studies, all were representative of the exposed cohort, had proper selection of non-exposed cohort, the outcome of interest was not present at the beginning of the study, and had adequate follow-up. The most common low-quality measure

was lack of definition of controls or ascertainment of exposure; 10 of the studies had either incomplete or no appropriate controls in their analysis. The overall quality assessment for each quality measure is presented in Table 2.3 and the individual quality assessment for each study is provided in the Appendix.

Discussion

Overall, previous antibiotic use was significantly associated with MDRO colonization and/or infection in hospitalized children. Half of the included studies reported a significant relationship between prior exposure to any antibiotic and subsequent HAI or HAC with an MDRO (53, 56, 66, 72, 78) and most of the studies examining the association between a particular antibiotic or antibiotic class found a positive association (53, 56-60, 62, 65, 67-69, 72, 73, 76, 78-80). Many of the agents evaluated were broad-spectrum, highlighting the importance of narrowing antibiotics to targeted therapy when possible. These findings are in line with previous research which has shown that the continued use of broad-spectrum antibiotics increases the risk of development of MDROs (81). Yet despite the growing concerns over antibiotic resistance, there is evidence that broad-spectrum antibiotics are increasingly being used (14). Therefore, given the findings in this systematic review in addition to prior research, antibiotics for which there is concern for the development of drug-resistance, i.e. broad-spectrum agents, should be a main focus of antimicrobial stewardship programs.

Duration of antibiotic use was also consistently significantly associated with MDRO infection and/or colonization in hospitalized children, even though there were wide variations among duration measurement. Of the studies that evaluated antibiotic duration, 75% linked days of therapy to HAC or HAI with an MDRO (55, 61, 62, 64, 66, 70, 75, 77, 78). These findings are consistent with similar studies in adults. Ruhe et al. found that prolonged beta-lactam use

increased the risk of penicillin-resistant *S. pneumoniae* bacteremia (82). Similarly, longer courses of imipenem and ciprofloxacin have been associated with higher rates of HAI caused by drug-resistant *Pseudomonas aeruginosa* (83). Additionally, prolonged antibiotic duration is associated with increases in adverse drug reactions (84). Given research showing that an estimated 12-30% of antibiotic days of therapy in hospitalized patients is inappropriate (85-87), duration of therapy represents another important target for antibiotic stewardship initiatives.

The importance of pediatric considerations in antimicrobial stewardship is warranted. Limited antibiotics exist for the treatment of MDRO infections and current efforts to develop new antibacterial drugs are lacking, especially for children (88). Additionally, children exposed to antibiotics and subsequently develop MDROs may have long-term sequelae related to the exposure and infection. Recent research on the effect of early exposure to antibiotics on the microbiome has linked antibiotic use to wide range of negative health outcomes including obesity, metabolic disease, and autoimmune disorders (89). Furthermore, antibiotic resistant organisms have been shown to persist in the microbiome of children exposed to antibiotics (90), increasing not only the individual child's risk of infection with an MDRO but also increasing the potential risk of spread throughout their communities (13).

While important insights can be gained from the studies appraised in this systematic review, there also are several limitations. All of the studies included were observational and the majority were case control followed by retrospective cohort designs. Therefore, ascertainment of antibiotic exposure may be subject to observation bias, especially for studies that relied on recall of exposure. Even though the majority of studies cited the use of the medical record for determining antibiotic exposure, it was not clear whether the included courses were limited to those received during the hospital admission or if they also included other clinical settings,

potentially based on parental recall. Parents of children with an infection, particularly if the infection is difficult to treat, i.e., caused by an MDRO, may be more likely to recall past antibiotic courses. For those studies that used the medical record to determine antibiotic exposure, they may have been limited to only antibiotics prescribed within the hospital or healthcare system. However, the most common prescription drug provided to children in the outpatient setting is antibiotics (91), which may lead to an underrepresentation of antibiotic exposure in studies that relied solely on ascertainment from the medical record.

Also, there were wide variations in how antibiotic exposure was defined. Only 52% of studies provided a defined window of antibiotic exposure, e.g., within 30 days prior to infection onset and less than half evaluated a specific measure of antibiotic use, e.g., duration of therapy. Due to the wide variation in definitions of antibiotic exposure, it was not possible to synthesize these results in a meta-analysis. Additionally, none of the studies examined antimicrobial dosing. One systematic review of antimicrobial dosing in adults identified low antibiotic dosing as a significant contributor to antibiotic resistance (92). In children, the provision of appropriate antibiotics is complicated by a variety of factors including weight-based dosing and limited antibiotic choices due to concerns about safety (93, 94). Inappropriate dosing of antibiotic courses may partly drive the development of MDROs in this population.

Research on the relationship between antibiotic use and MDRO infection in hospitalized children is limited and of mixed quality. Antibiotic stewardship programs are considered one of the mainstays of MDRO prevention in children (95), however research evaluating the effectiveness of these programs have either not evaluated their impact on MDRO acquisition or have had little to no effect (47), Because hospitalized children represent a unique and vulnerable population and the impact of MDRO infections in this group of patients is likely to have long-

lasting effects (96), additional studies are needed to further elucidate the relationship of antibiotic exposure and subsequent MDRO HAI and to determine the best targets for intervention in antibiotic stewardship programs.

Figure 2.1: Flow diagram of study selection for comparison of prior antibiotic use and subsequent health care-associated infection or colonization with multidrug-resistant bacteria

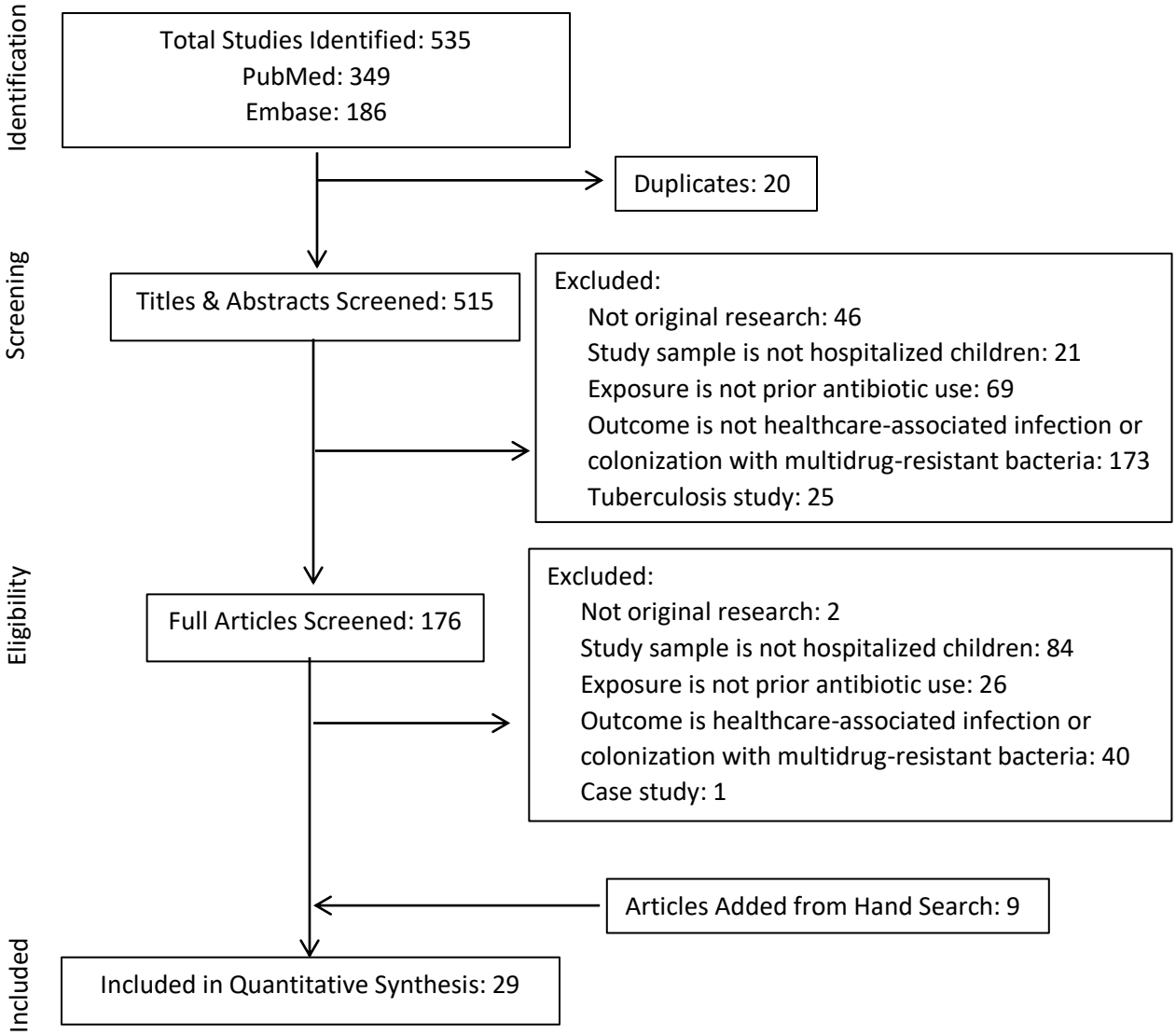


Table 2.1: Description of studies comparing prior antibiotic use and subsequent health care-associated infection or colonization with multidrug-resistant bacteria in hospitalized children

Author, Quality Score	Subjects	Setting	Study Design	Antibiotic Exposure	Outcome & Comparison	Association of Interest
Allen, U. D. et al., 88%	548 children with *Escherichia coli* positive urinary cultures	Tertiary care pediatric center, Canada, Dec 1992-1994	Case control, 1:1	Antibiotic therapy or prophylaxis for > 4 wk in past 6 mo, any antibiotic prophylaxis	T-S[1] resistant *E. coli* isolates versus T-S sensitive *E. coli* isolates	In cases compared to controls: antibiotics > 4 weeks in past 6 mo, aOR 23.4, 95% CI 12.0-47.6; any antibiotic prophylaxis, OR 12.9, 95% CI 7.8-21.4
Arhoune, B. et al., 67%	164 neonates with 169 positive rectal swabs for Enterobacteriaceae; 127 ESBL[2], 37 non-ESBL	Neonatal ICU[3], Morocco, Feb-Jul 2013	Prospective cohort	Combination therapy of ceftriaxone and gentamicin	ESBL versus non-ESBL colonization	In neonates with ESBL versus non-ESBL: ceftriaxone and gentamicin, p=0.03
Arrifin, H. et al., 78%	29 children ≤ 12 yr with neutropenia and fever for > 2 hr with 31 episodes of *Klebsiella pneumoniae* BSI[4]: 16 CRKP[5] and 15 CSKP[6]	Pediatric oncology unit, Malaysia, Jan 1996- Dec 1997	Prospective cohort	Receipt of broad-spectrum or 3° cephalosporin antibiotics within 2 weeks prior to BSI, prophylaxis with T-S	CRKP versus CSKP bacteremia	In children with CRKP versus CSKP bacteremia: broad-spectrum antibiotic, OR 28.0, 95% CI 4.0-194.5; 3° cephalosporin, OR 11.1, 95% CI 1.3-95.2; prophylaxis with T-S, non-significant
Asensio, A. et al., 75%	42 children hospitalized in the pediatric ICU; 10 with MRKP[7] colonization or infection, 32 controls	Pediatric ICU, Spain, Oct 1997-Apr 1998	Case control	Exposure to any aminoglycoside, gentamicin, tobramycin, 3° cephalosporin, 3° cephalosporin and gentamicin/tobramycin	Infected or colonized with MRKP versus control	In cases compared to controls: aminoglycoside, OR 12, 95% CI 1.8-129; gentamicin, OR 4.3, 95% CI 0.7-25.5; tobramycin, OR 6.4, 95% CI 0.6-85.7; 3° cephalosporin, OR 17.8, 95% CI 1.8-411; 3° cephalosporin and gentamicin/tobramycin, aOR 31.2, 95% CI 3.3-298

Table 2.1, continued: Description of studies comparing prior antibiotic use and subsequent health care-associated infection or colonization with multidrug-resistant bacteria in hospitalized children

Author, Quality Score	Sample Size	Study Sample	Study Design	Antibiotic Exposure	Outcome & Comparison	Association of Interest
Chiotos, K. et al., 88%	189 children with positive cultures (colonization or infection) with Enterobacteriacae: 63 CRE[8] and 126 CSE[9]	3 children's hospitals, USA, Jan 1, 2011-Oct 15, 2015	Case control	Fluoroquinolone, antipseudomonal, or carbapenem given >48h in the 3 months prior to culture	Infected or colonized CRE versus CSE	For cases versus controls: fluoroquinolone, OR 1.92, 95% CI 0.57-6.52; carbapenem, OR 12.67, 95% CI 3.75-42.8; antipseudomonal, aOR 5.20, 95% CI 1.71-15.9
Chiu, S. et al., 44%	70 infants with 76 Enterobacteriaceae HAI[10]: 34 ESBL and 42 non-ESBL	Neonatal ICU, Taiwan, Jan -Dec 2001	Retrospective cohort	Number of antibiotics received, receipt of 3˚ cephalosporin, duration of 3˚ cephalosporin	ESBL versus non-ESBL HAI	In infants with ESBL versus non-ESBL: number of antibiotics received, p=not significant; receipt of 3˚ cephalosporin, p=0.874; duration of 3˚ cephalosporin p=0.94
Crivaro, V. et al., 78%	167 neonates; 100 with ESBL *S. marcescens* and/or *K. pneumoniae* colonization/infection	Neonatal ICU, Italy, Nov-Apr, 2004	Prospective cohort	Receipt of ampicillin/ gentamicin, days of ampicillin/gentamicin	ESBL versus non-ESBL culture	For neonates with ESBL vs non-ESBL: receipt of ampicillin/gentamicin (p=0.002); days of ampicillin/gentamicin therapy, aOR 1.316, 95% CI 1.021-1.695
de Oliveira Costa, P. et al., 63%	76 children ≤ 18 yr with 101 HAI: 47 MDR-GNB[11] and 54 non-MDR-GNB	Pediatric ICU, Brazil, Jan 2009-Dec 2012	Case control	Receipt of any antibiotics in previous 30 days	MDR-GNB versus non-MDR-GNB HAI	For cases versus controls: previous antibiotic therapy, aOR 3.082, 95% CI 0.296-32.049
Deeks, S. L. et al., 89%	274 children ≤ 5 yr with invasive *Streptococcus pneumoniae* HAI: 99 PRSP[7] and 175 PSSP[8]	13 hospitals in Uruguay and Argentina, Jun 1993-Oct 1996	Prospective cohort	Receipt of any antibiotic and receipt of ampicillin/penicillin in prior 3 months	PRSP versus PSSP HAI	For children with PRSP vs PSSP HAI: antibiotic use, OR 1.2, 95% CI 0.7-1.9; ampicillin/penicillin, aOR 2.9, 95% CI 1.5-5.7

Table 2.1, continued: Description of studies comparing prior antibiotic use and subsequent health care-associated infection or colonization with multidrug-resistant bacteria in hospitalized children

Author, Quality Score	Sample Size	Study Sample	Study Design	Antibiotic Exposure	Outcome & Comparison	Association of Interest
Dirajlal-Fargo, S. et al., 63%	65 children: 13 with CRE positive culture and 52 with no CRE isolated from any specimens	Children's hospital, USA, Aug 2009-2011	Case control	Receipt of penicillin, 3° cephalosporin, carbapenem, fluoroquinolone, T-S	CRE positive culture versus no CRE isolated	For cases vs controls: penicillin, aOR 30.4, 95% CI 3.8-238.8; 3° cephalosporin, aOR 7.3, 95% CI 1.8-29.8; carbapenem, aOR 12.7, 95% CI 2.6-61.5; fluoroquinolone, aOR 14.0, 95% CI 2.9-66.6; T-S, aOR 8.2, 95% CI 2.1-31.8
Gaynes, R. P. et al., 88%	16 infants infected or colonized with MR[14]-*E. coli* and 16 matched controls	Neonatal ICU, USA, Jan 1981-Sep 1982	Case control	Receipt of penicillins, mean total doses of penicillins, receipt of aminoglycosides, mean total doses of aminoglycosides	Infected or colonized with MR-*E. coli* versus controls	For cases vs controls: penicillins, p=not significant; mean total doses of penicillins, p=not significant; aminoglycosides, p=not significant; mean total doses of aminoglycosides, p<0.03
Gupta, A. et al., 75%	73 infants: 19 infected or colonized with ESBL *K. pneumoniae* and 54 with negative surveillance cultures	Neonatal ICU, USA, April – June 2001	Case control	Receipt of cefotaxime	Infected or colonized with ESBL *K. pneumoniae* versus controls	For cases vs controls: cefotaxime, OR 0.44, 95% CI 0.02-4.25
Haas, E. J. et al., 88%	339 children with *Enterococcus faecalis* or *E. faecium* BSI: 39 VRE[15] and 300 VSE[16]	Children's hospital, USA, 2001-2006	Case control	Days of vancomycin exposure in prior 30 days	VRE versus VSE BSI	For cases versus controls: days of vancomycin, aOR 1.25, 95% CI 1.14-1.38

Table 2.1, continued: Description of studies comparing prior antibiotic use and subsequent health care-associated infection or colonization with multidrug-resistant bacteria in hospitalized children

Author, Quality Score	Sample Size	Study Sample	Study Design	Antibiotic Exposure	Outcome & Comparison	Association of Interest
Huang, Y. et al., 78%	39 infants with nosocomial infections caused by *E. coli* or *K. pneumoniae*: 22 ESBL and 17 non-ESBL	Neonatal ICU, China, Jan 2000-Dec 2002	Retrospective cohort	Prior use of 3° cephalosporin, days on 3° cephalosporin, prior use of beta-lactamase inhibitor	Children with ESBL versus non-ESBL *E. coli* or *K. pneumoniae* HAI	In children with ESBL versus non-ESBL HAI: 3° cephalosporin, aOR 12.8, 95% CI 1.1-143.8; days on 3° cephalosporin, p=0.190; beta-lactamase inhibitor, OR 0.508, 95% CI 0.14-1.84
Karaaslan, A. et al., 50%	398 children: 176 colonized with CR-GNB[17] and 222 non-colonized controls	Tertiary hospital, Turkey, Mar-Oct 2013	Case control	Receipt of any antibiotic, carbapenem, ceftriaxone, ampicillin, vancomycin; median days of antibiotic therapy	CR-GNB colonization versus non-colonized	For cases versus controls: any antibiotic, OR 2.9, 95% CI 1.7-5.1; carbapenem, aOR 3.9, 95% CI 1.6-9.2; ceftriaxone, OR 3.5, 95% CI 1.8-6.9; ampicillin, OR 3.1, 95% CI 1.2-7.8; vancomycin, OR 7.04, 95% CI 4.1-11.9; median days of antibiotic therapy, p=0.001
Katragkou, A. et al., 75%	78 children: 26 cases with IRAB[18] colonization or infection and 52 controls with no isolation of IRAB	Pediatric ICU, Greece, Jul 2001-Dec 2003	Case control, matched 1:2	Antibiotic exposure at 15 days/30 days pre-isolation of IRAB or discharge: 2° cephalosporins, 3° cephalosporins, cefepime, colistin, carbapenems, aminoglycosides, metronidazole, glycopeptides, quinolones, clindamycin, other beta-lactams, other antibiotics	Nosocomial acquisition of IRAB colonization or infection versus no isolation of IRAB	For cases versus controls: carbapenems 15 days, carbapenems 30 days, and aminoglycosides 30 days, all p<0.0001; other beta-lactams, p=0.01; aminoglycosides 15 days, aOR 1.175, 95% CI 1.025-1.347; all other antibiotic exposures, p>0.10

Table 2.1, continued: Description of studies comparing prior antibiotic use and subsequent health care-associated infection or colonization with multidrug-resistant bacteria in hospitalized children

Author, Quality Score	Sample Size	Study Sample	Study Design	Antibiotic Exposure	Outcome & Comparison	Association of Interest
Kim, Y. et al., 89%	142 children < 18 yr with *E. coli* or *K. pneumoniae* BSI: 49 ESBL and 93 non-ESBL	Children's hospital, Korea, Nov 1993-Dec 1998	Retrospective cohort	Within previous 1 month: receipt of any antibiotics, extended-spectrum cephalosporins, antibiotics other than extended-spectrum cephalosporins	ESBL BSI versus non-ESBL BSI	For children with ESBL versus non-ESBL BSI: any antibiotics, p=0.001; extended-spectrum cephalosporins, p=0.001; antibiotics other than extended-spectrum cephalosporins, p=not significant
Logan, L. K. et al., 100%	120 children ≤ 17 yr: 30 ESBL-producing bacterial infections, 30 non-ESBL-producing bacterial infections, and 60 negative culture controls	Tertiary-care hospital and public teaching hospital, USA, Jan 2008-Dec 2011	Case control	Antibiotic exposure in the 40 days prior to bacterial culture for any antibiotics, 3° cephalosporins, and fluoroquinolones	ESBL bacterial infections or versus control	For cases versus controls: any antibiotics, p=0.058; 3° cephalosporins, p=0.16, fluoroquinolones, p=0.11
Nieminen, O. et al., 100%	78 children <16 yr with UTI[19]: 22 ESBL and 56 ESBL-negative controls	Hospital pediatric department, Finland, 2005-2014	Case control	Mean days on antibiotics, intravenous antibiotics, and oral antibiotics; mean number of different antibiotics used; antibiotic prophylaxis	ESBL vs non-ESBL UTI	For cases versus controls: mean days on antibiotics, p=0.000; mean days on intravenous antibiotics, p=0.052; mean days on oral antibiotics, p=0.020; mean number of different antibiotics used, p=0.000; antibiotic prophylaxis, aOR 3.14, 95% CI 0.59-16.54

Table 2.1, continued: Description of studies comparing prior antibiotic use and subsequent health care-associated infection or colonization with multidrug-resistant bacteria in hospitalized children

Author, Quality Score	Sample Size	Study Sample	Study Design	Antibiotic Exposure	Outcome & Comparison	Association of Interest
Nolan, S. M. et al., 100%	78 children: 16 colonized with VRE and 62 matched controls who were negative for VRE	Pediatric oncology patients at a children's hospital, USA, Jun 2006-Dec 2007	Case control	Receipt of any antibiotic, fluoroquinolones, gylcopeptides, 3° cephalosporins, aminoglycosides, antianaerobes, and carbapenems	VRE colonization versus non-VRE colonization	For cases versus controls: any antibiotic, p>0.99; fluoroquinolone, OR 4.65, 95% CI 1.23-17.56; glycopeptide, OR 2.34, 95% CI 0.76-7.21; 3° cephalosporin, OR 2.51 0.73-8.57; aminoglycoside, OR 1.54, 95% CI 0.47-5.08; antianaerobe, OR 0.85, 95% CI 0.22-3.31; carbapenem, p>0.99
Nourse, C. et al., 88%	55 children: 14 cases with VRE infection or colonization and 41 matched controls negative for VRE	Pediatric oncology patients at a children's hospital, Ireland, Dec 25, 1995-Mar 31, 1996	Case control	Number of antibiotics received; days on any antibiotic, intravenous antibiotics, ceftazidime, amikacin, and teicoplanin	VRE infection or colonization versus VRE negative cultures	For cases versus controls: number of antibiotics, OR 6.78, 95% CI 1.34-34.3; total antibiotic days, OR 4.07, 95 % CI 1.08-15.3; intravenous antibiotic days, OR 4.07, 95 % CI 1.08-15.3; days on ceftazidime, OR 11.5, 95% CI 2.2-59.9; days on amikacin, OR 10.7, 1.4-81.5; days on teicoplanin, OR 12.3, 95% CI 2.25-67.5
Ozsurekci, Y. et al., 89%	97 children 1 mo – 18 yr with GNB BSI: 31 CR-GNB and 66 CS-GNB[20]	Pediatric infectious diseases department at hospital, Turkey, Jan 2014-Feb 2015	Retrospective cohort	Class of antibiotic used ≤48 hr in the previous 14 d: beta-lactams, piperacillin-tazobactam, carbapenems, fluroquinolones, aminoglycosides, glycopeptides, anaerobicidal; no prior antibiotic exposure	Children with CR-GNB BSI versus CS-GNB	In children with CR-GNB versus CS-GNB BSI: carbapenem, p<0.001, fluoroquinolones, p=0.004, glycopeptides, p=0.001, no prior antibiotic use, p<0.001; all other associations

Table 2.1, continued: Description of studies comparing prior antibiotic use and subsequent health care-associated infection or colonization with multidrug-resistant bacteria in hospitalized children

Author, Quality Score	Sample Size	Study Sample	Study Design	Antibiotic Exposure	Outcome & Comparison	Association of Interest
Pessoa-Silva, C. L. et al., 67%	383 neonates with 13 ESBL *K. pneumoniae* HAI	Neonatal ICU, Brazil, Aug 1, 1997-May 30, 1999	Retrospective cohort	Any antimicrobial use prior to HAI	Incidence of ESBL *K. pneumoniae* HAI	Incidence of ESBL *K. pneumoniae* HAI: antimicrobial use, IRR 3.23, 95% CI 0.99-10.49
Rao, Y. B. et al., 78%	188 neonates with *Pseudomonas aeruginosa* infections: 73 IRPA[21] and 115 ISPA[22]	8 level III neonatal ICUs, China, Jan-Dec 2014	Retrospective cohort	Receipt of imipenem, piperacillin-sulbactam, 3° cephalosporin, and/or vancomycin < 2 weeks prior to hospitalization	IRPA versus ISPA	In neonates with IRPA versus ISPA infections: imipenem treatment and IRPA vs ISPA, aOR 6.41, 95% CI 1.93-21.33; piperacillin-sulbactam, p=0.715; 3° cephalosporin, p<0.001; vancomycin, p=0.537
Renk, H. et al., 100%	123 children with 167 Enterobacteriaceae RTI[23]: 116 non-MDR-E[24] and 51 MDR-E	Children's hospital, Germany, 2005-2014	Retrospective cohort	Antibiotic therapy ≥ 7 days in the 30 days prior to RTI	Children with MDR-E versus non-MDR-E RTI	For children with MDR-E versus non-MDR-E RTI: antibiotic therapy, aOR 4.56, 95% CI 1.69-12.30
Rubin, L. G. et al., 63%	22 children: 8 cases colonized with VRE and 14 controls with negative cultures	Pediatric oncology at children's hospital, USA, Mar 1990-Mar 1991	Case control	Mean days of any antibiotic or vancomycin; receipt of any antibiotic or vancomycin	Colonization with VRE versus negative culture	For cases vs controls: mean days vancomycin, p=0.0004; any vancomycin therapy, RR=8.8, p=0.0002; mean days any antibiotic, p=0.0068; any antibiotic, RR=3.9, p=0.0068

Table 2.1, continued: Description of studies comparing prior antibiotic use and subsequent health care-associated infection or colonization with multidrug-resistant bacteria in hospitalized children

Author, Quality Score	Sample Size	Study Sample	Study Design	Antibiotic Exposure	Outcome & Comparison	Association of Interest
Sultan, A. M. & Seliem, W. A., 89%	124 neonates with *Acinetobacter baumannii* HAI: 91 CRAB[25] and 33 CSAB[26]	Neonatal ICU, Egypt, Jan 2013-Jun 2014	Prospective cohort	Systemic antibiotics administered for ≥ 24 in the 14 days prior to HAI including previous exposure of carbapenems, cephalosporins, aminoglycosides, and vancomycin; and median duration of antibiotic therapy in days	CRAB versus CSAB HAI	For children with CRAB versus CSAB HAI: carbapenem, aOR 124.7, 95% CI 45.2-588.1; cephalosporin, p=0.07; aminoglycoside, aOR 22.6, 95% CI 1.1-864.9; vancomycin, p=0.79; days of antibiotic therapy, p<0.05
Thatrimontrichai, A. et al., 88%	76 neonates with *A. baumannii* VAP[27]: 63 CRAB and 13 CSAB	Neonatal ICU, Thailand, Jan 1 2009-Dec 31 2014	Case control	Class of antibiotic therapy used prior VAP including penicillins, vancomycin, cephalosporins, lactamase inhibitors, carbapenems, colistin, and aminoglycosides	Neonates with CRAB versus CSAB	For cases versus controls: cephalosporin, aOR 4.4, 95% 1.2-15.6; all other associations not significant
Zaoutis, T. E. et al., 100%	140 children with *E. coli* or *K.* spp. BSI: 35 cases with ESBL and 105 controls with non-ESBL	Children's hospital, USA, May 1, 1999-Sept 30, 2003	Case control	Antibiotic use in previous 30 days prior to infection including 3° cephalosporins, ceftazidime, extended-spectrum penicillins, carbapenems, anti-anaerobes, aminoglycosides, and quinolones	ESBL versus non-ESBL BSI	For cases versus controls: 3° cephalosporin, aOR 5.82, 95% CI 1.92-17.68; ceftazidime, p=0.000; extended-spectrum penicillins, p=0.073; carbapenems, p=0.015; anti-anaerobes, p=0.131; aminoglycosides, p=0.034; quinolones, p=0.154; T-S, p=0.000

[1]T-S = trimethoprim-sulfamethoxazole
[2]ESBL = extended-spectrum beta-lactamase producing
[3]ICU = intensive care unit
[4]BSI = bloodstream infection
[5]CRKP = ceftazidime-resistant *Klebsiella pneumoniae*
[6]CSKP = ceftazidime-susceptible *K. pneumonia*
[7]MRKP = multidrug-resistant *K. pneumonia*
[8]CRE = carbapenem-resistant Enterobacteriaceae
[9]CRE = carbapenem-sensitive Enterobacteriaceae
[10]HAI = healthcare-associated infection
[11]MDR-GNB = multidrug-resistant Gram-negative bacteria
[12]PRSP = penicillin-resistant *Streptococcus pneumoniae*
[13]PSSP = penicillin-susceptible *S. pneumonia*
[14]MR = multidrug-resistant
[15]VRE = vancomycin-resistant *Enterococcus*
[16]VSE = vancomycin-susceptible *Enterococcus*
[17]CR-GNB = carbapenem-resistant GNB
[18]IRAB = imipenem-resistant *Acinetobacter baumannii*
[19]UTI = urinary tract infection
[20]CS-GNB = Carbapenem-susceptibility GNB
[21]IRPA = imipenem-resistant *Pseudomonas aeruginosa*
[22]ISPA = imipenem-susceptible *P. aeruginosa*
[23]RTI = Respiratory tract infection
[24]MDR-E = Multidrug-resistant Enterobacteriaceae
[25]CRAB = Carbapenem-resistant *Acinetobacter baumannii*
[26]CSAB = Carbapenem-susceptible *Acinetobacter baumannii*
[27]VAP = Ventilator-associated pneumonia

Table 2.2: Summary of findings from systematic review evaluating the relationship between antibiotic exposure and subsequent infection or colonization with a multidrug-resistant organism among hospitalized children

Antibiotic Exposure	Positive Association with MDROs	Not Significant
Any antibiotic, n=10[1]	5	5
Specific antibiotic, n=21	17	4
Duration of antibiotic, n=12	9	3
Number received, n=3	2	1

[1] n is the number of studies that evaluated the antibiotic exposure category; each study evaluated one or more categories of antibiotic exposure.

Table 2.3: Assessment of study quality using the Newcastle-Ottawa scale for case control and cohort studies

Quality Measure	Yes N (%)[1]	No N (%)	Not Applicable N (%)
Selection			
Representativeness of the cases/exposed cohort	28 (97)	1 (3)	0 (0)
Selection of the controls/non-exposed cohort	27 (93)	2 (7)	0 (0)
Definition of controls *or* Ascertainment of exposure	19 (66)	10 (34)	0 (0)
Adequacy of case definition *or* Outcome of interest was not present at start of study	100 (100)	0 (0)	0 (0)
Comparability			
Comparability of cases and controls/cohorts on the basis of the design or analysis	24 (86)	4 (14)	0 (0)
Exposure/Outcome			
Assessment of exposure/ outcome	24 (83)	5 (17)	0 (0)
Non-response rate *or* Follow-up long enough for outcomes to occur	7 (29)	4 (14)	18 (62)
Same methods of ascertainment for cases and controls *or* Adequacy of follow up of cohorts	100 (100)	0 (0)	0 (0)
Total Score,[2] mean % (range)	**81% (44-100%)**		

[1] For each category of Yes, No, and Not Applicable, N is the number of studies and % is out of 29, which is the total number of studies evaluated in the systematic review.
[2] Total score is percentage of met criteria for the Newcastle Ottawa tool.

CHAPTER THREE

Low Prevalence of Multidrug-Resistant Infections in Hospitalized Children who Have a History of Pediatric Long-Term Care

Abstract

Background: Infections caused by multidrug-resistant organisms (MDROs) are a significant burden for hospitalized children. Due to their multiple comorbidities, high acuity, relatively high use of invasive devices, and frequent antibiotic treatment, hospitalized children who have previously stayed in a pediatric long-term care (LTC) facility may be at increased risk for infection with MDROs. This study aimed to assess the relationship between prior stay in pediatric LTC and infection with an MDRO.

Methods: A retrospective cohort study was conducted of children ≤ 18 years old admitted to one of four hospitals in the New York City metropolitan area. Data were collected from the electronic medical records for outcome and exposure variables including demographic, clinical, and microbial factors. Infections included pneumonia, bloodstream, surgical site, and urinary tract infections. MDROs were defined using the Centers for Disease Control and Prevention surveillance guidelines. Logistic regression was used to evaluate the association between previous stay in a pediatric LTC facility and infection with an MDRO.

Results: During the study period, 77,454 children had 258,664 admissions, of which 1% (n=2945) had an infection. At least 1 MDRO was identified in 10% of infections (n=305); the most common MDRO was methicillin-resistant *Staphylococcus aureus* (49%) followed by multidrug-resistant (MDR) *Klebsiella spp.* (19%), VRE (12%), MDR *Pseudomonas spp.* (12%), carbapenem-resistant Enterococcus (5%), and MDR *Acinetobacter spp.* (2%). Only 1 child who had previously resided in a pediatric LTC facility had an MDRO infection. Prior stay in a LTC facility was associated with an increased likelihood of infection (OR 2.4, CI95 1.66 – 3.43), *C. difficile* infection (OR 2.57, CI95 1.26 – 5.25), days of antibiotic use (OR 1.01, CI95 1.01 – 1.02), length of stay (OR 1.01, CI95 1.01 – 1.01), and death (OR 4.38, CI95 2.93 – 6.55).

Conclusions: MDROs do not appear to be a major contributor to infections among hospitalized children who have resided in pediatric LTC facilities. However, these children were more likely to have other negative outcomes during their hospitalizations including increased antibiotic exposure, *C. difficile* infections, and prolonged hospital stays. Further research is needed to assess the risks for negative outcomes during hospitalization for children who receive pediatric LTC.

Background

Infections caused by antibiotic-resistant organisms are a significant burden for hospitalized children. An estimated 5-10% of pediatric healthcare-associated infections (HAIs) are caused by multidrug-resistant organisms (MDROs), which are resistant to at least one class of antibiotics to which they are normally susceptible (26, 43). Infection with an MDRO has been shown to increase the risk of mortality, lengthen hospitalization, and cost more than infections with a non-MDRO (28). These negative outcomes become even more pronounced for critically ill children as those hospitalized in an intensive care unit with a HAI have almost twice the risk of death if their infection is caused by an MDRO versus a non-MDRO (32).

While efforts such as antimicrobial stewardship programs to limit the development of MDROs have been implemented, the prevalence of infections due to MDROs has been increasing over the past decade with a profound effect in children. From 2007-2015, infections with multidrug-resistant Enterobacteriaceae significantly increased in hospitalized children from 0.2% to 1.5%, and almost 25% of these infections were HAIs (9). Similarly, among pediatric infections caused by *Pseudomonas aeruginosa,* the proportion of multidrug-resistant isolates increased by 4% each year from 15.4% to 26% between 1999 and 2012 (8).

Children who have previously resided in a pediatric long-term care (LTC) facilities may contribute to the rise of MDROs, particularly among hospitalized patients. This population typically has multiple comorbidities, high acuity, relatively high use of invasive devices, and frequent antibiotic treatment, which may increase their risk for infection with MDROs (17, 29-31). Also, children receiving pediatric LTC are often transferred to acute care related to infections (97). Given their increased risk factors for MDRO infection along with their frequent hospitalizations, the pediatric LTC population may be a source of transmission of MDROs from

the community and into the acute care setting, or vice versa. Therefore, the primary aim of this study was to determine the relationship between prior stay at a pediatric LTC facility and infection with an MDRO versus non-MDRO among children hospitalized in acute care settings. Secondary aims were to assess prior stay at a pediatric LTC facility with any infection (MDRO or non-MDRO), antibiotic exposure, length of hospitalization, and death.

Methods

Study design and setting. We conducted a retrospective cohort study using data from a comprehensive dataset of electronic medical record clinical information for all patients admitted to four hospitals in a large academic healthcare system in New York City (Nursing Intensity of Patient Care Needs and Rates of Healthcare-Associated Infections; Agency for Healthcare Research and Quality, R01 HS024915). The four medical facilities include a 221-bed community hospital, a 283-bed pediatric acute care hospital, a 647-bed adult tertiary/quaternary care hospital and a 914-bed adult and pediatric tertiary/quaternary care hospital. All admissions from January 1, 2006 through December 31, 2016 were included for patients ≤ 18 years of age on the day of their admission. Data were collected from the electronic medical record pertaining to demographic (e.g., age, sex, and admission source), clinical (e.g., infection type, invasive device use, antibiotic use, and length of stay), and microbial (e.g., pathogen and susceptibilities) factors.

Outcomes. HAI and community-acquired infections were identified using electronic algorithms based on the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network's (NHSN) surveillance case definitions, as previously described (98). The algorithms use data from the electronic medical record and administrative records including ICD-9 diagnosis codes, microbiology and microscopy results, and antibiotic susceptibility

reports to identify infections. The following infections were identified in this study: bloodstream infections (BSI), pneumonia, surgical site infections (SSI), urinary tract infections (UTI), and *Clostrioides difficile* infection. Commonly implicated organisms in both healthcare associated and community acquired infections were evaluated for antibiotic resistance including *Staphylococcus aureus, Enterobacter* spp., enterococci, *Escherichia coli, Klebsiella spp., Acinetobacter spp., and Pseudomonas spp*. For this study, an organism was identified as an MDRO based on common resistance patterns to key antimicrobial agents (43), as recommended for surveillance by the CDC's National Healthcare Safety Network (99). Multidrug-resistant *Pseudomonas spp*. was also included as an MDRO in this study as it is a common infection-causing pathogen in hospital settings and is considered a serious antimicrobial resistance threat by the CDC (100). Table 3.1 lists the organisms of interest along with the antimicrobial agents assessed to identify MDROs. Only infections with susceptibility testing completed were included in the study. Additional outcomes evaluated included days of antibiotic use during hospitalization, length of stay, and death.

Exposures. History of stay in a LTC facility was assessed dichotomously based on administrative records indicating whether a child had ever been admitted to one of the four hospitals from LTC. Other variables evaluated prior to onset of infection included demographic characteristics (age in years at time of admission, sex, and race), relevant comorbidities (diabetes mellitus or history of organ transplant), relevant treatments and interventions (antibiotics use prior to onset of infection, procedure in operating room, presence of tracheostomy, mechanical ventilation, feeding tube, urinary catheter, and central line), and factors related to hospitalization (admission to the pediatric acute care hospital versus any other and stay in intensive care unit).

Data analysis. The relationship between prior stay in pediatric LTC and the outcomes of infection, antibiotic use, length of stay, and death were assessed using logistic regression with repeated subjects to account for multiple hospitalizations per patient. For patients with an infection, the association between previous stay in a pediatric LTC facility and infection caused by an MDRO was assessed using the same method. The potential confounders in the analysis of infection and infection with an MDRO were the previously described demographic characteristics, relevant comorbidities, treatments and interventions, and factors related to hospitalization. Only the first infection for each hospitalization was evaluated for presence of an MDRO, regardless of other infections that may have occurred during the same stay, as this study did not aim to evaluate acquired resistance during hospitalization. Statistical significance was defined a priori at 0.05.

Results

From 2006 through 2016, 77,454 children had 258,664 admissions, of which 1% (n=2,945) had an infection. The most common infection was UTI (n=1,529, 52%) followed by BSI (n=839, 28%), pneumonia (n=313, 11%), and SSI (n=264, 9%). Fourteen percent of infections were associated with more than 1 organism (n=426): 2 organisms (n=362, 12%), 3 organisms (n=55, 2%), 4 organisms (n=7, 0.2%), and 5 organisms (n=2, 0.07%). There were 323 MDROs identified in 305 infections accounting for 10% of the infections in hospitalized children; 49% of MDROs were methicillin-resistant *Staphylococcus aureus* (MRSA) (n=158/323), 19% were multidrug-resistant *Klebsiella spp.* (n=61/323), 12% were vancomycin-resistant Enterococcus (n=40/323), 12% were multidrug-resistant *Pseudomonas spp.* (n=40/323), 5% were carbapenem-resistant Enterobacteriaceae (n=16/323), and 2% were multidrug-resistant

Acinetobacter spp. (n=8/323). Table 3.2 provides the complete list of identified organisms implicated in infections.

There were 1,128 acute care admissions of children who previously received pediatric LTC. The prevalence of infection among children who had received pediatric LTC was 3% (n=30/1,128), whereas among children who never received pediatric LTC, the prevalence of infection was 1% (n=2,915/257,536). Only one child with a history of pediatric LTC had an infection with an MDRO. The prevalence of MDRO infection was 0.09% (n=1/1,128) and 0.12% (n=304/257,536) among children with and without a previous stay in pediatric LTC, respectively. Children who had a history of residing in a pediatric LTC facility were 2.4 (CI_{95} 1.66 – 3.43) times more likely to have an infection during their hospitalization compared to children who never received pediatric LTC. The associations between the assessed covariates and infection as well as infection with an MDRO are provided in Tables 3.3 and 3.4, respectively. Previous stay in an LTC facility was also associated with an increased likelihood of *C. difficile* infection (OR 2.57, CI_{95} 1.26 – 5.25), total days of antibiotic use (OR 1.01, CI_{95} 1.01 – 1.02), length of stay (OR 1.01, CI_{95} 1.01 – 1.01), and death (OR 4.38, CI_{95} 2.93 – 6.55).

Discussion

These data did not suggest that MDROs were a major contributor to infections among hospitalized children who have resided in pediatric LTC facilities. Rates of infections with an MDRO among hospitalized children at four New York metropolitan area hospitals were lower than reported in previous research (10, 101). As this study only evaluated the first infection per hospital admission, the prevalence of these organisms would likely be greater if all infections were included. Even though prevalence is relatively low, MDROs continue to be a significant concern among healthcare providers who work with this population. In a survey of pediatric

LTC providers, multidrug-resistant bacteria were the most frequently cited concern related to infection prevention and control (102). In our study, children who had a history of stay at a pediatric LTC facility had significantly longer duration of total antibiotic use during hospitalization and it is well established that antibiotic use is a primary driver of MDRO acquisition (11). We were unable to capture outpatient antibiotic use in this study, however, children who have received pediatric LTC are known to frequently receive antibiotics (17) and are likely exposed to more courses of antibiotics compared to other hospitalized children. Therefore, these children would appear to be at greater risk to acquire an MDRO while hospitalized, however this was not substantiated by our results. Since we only included the first infection for each acute care admission, it is possible that we missed the acquisition of an MDRO during the hospital stay, which may be more likely in the pediatric LTC population. Children who have previously resided in a pediatric LTC facility may not be at greater risk for infection with an MDRO upon admission but due to their significantly longer length of stay and greater antibiotic use during the hospital stay, they may have an increased risk of acquiring an MDRO throughout their hospitalization. Additionally, the use of an electronic algorithm based on the CDC NHSN surveillance case definitions may have been inappropriate for detecting infections for this study. Children who receive pediatric LTC may differ in their presentation of infection due to their complex and chronic medical conditions, and previous assessments of surveillance case definitions have been shown to be inadequate in this population (33, 103, 104). It is possible that the infections that were not captured in this population are more likely to be caused by an MDRO, e.g., respiratory and skin and soft tissue infections.

In addition to longer exposure to antibiotics, children who resided in pediatric LTC had increased odds of infection, length of stay, and death. This finding highlights the vulnerability of

the pediatric LTC population in acute care settings and may warrant specialized considerations for their medical care when hospitalized. *C. difficile* infection is increasingly concerning as antibiotic-resistant strains emerge, and children who previously stayed in a pediatric LTC facility may be at greater risk for this complication (105). Previous studies have reported a rise in *C. difficile* infections over the past two decades, particularly in children with complex chronic conditions (106-108). Prolonged antibiotic use is known to lead to the development of *C. difficile* infections (109), and longer hospitalizations may also provide greater opportunity for these children to become infected.

There were several limitations to this study. Since there was only one MDRO infection in children who had a previous stay in a pediatric LTC facility during our study period, we were unable to assess this relationship. While this may indicate a low prevalence of MDROs in this population, it is likely that we did not capture many of the admissions from pediatric LTC facilities as this research was focused at one hospital system. Children residing in pediatric LTC facilities often have complex and chronic medical conditions which require them to receive specialized care (33). While we included one of the main pediatric acute care facilities in the region, it is possible that these children are being transferred other pediatric hospitals or to local community hospitals for emergent care.

Also, we did not assess longitudinal trends of MDRO acquisition, including the potential for colonization. Prior studies have shown that colonization with an MDRO only increases the risk of an infection with that particular organism but also to increase the risk of colonization and/or infection with other MDROs (13). Future research should evaluate MDRO colonization in vulnerable pediatric populations, including those who have received care in pediatric LTC facilities. Lastly, we limited our organisms and infections of interest to those most prevalent in

the hospital setting and of greatest concern for development of multidrug-resistance. Other types of antimicrobial-resistant organisms, e.g., multidrug-resistant *Streptococcus spp.* and infections, e.g., skin and soft tissue infections, were not accounted for and may be of greater impact in the pediatric LTC population (97, 110).

In conclusion, infection with an MDRO was not common in children with a history of residing in a pediatric LTC facility, however these children were more likely to have other negative outcomes during their hospitalizations including increased non-MDRO and *C. difficile* infections, *C. difficile* infections, and length of stay. While children who have resided in pediatric LTC are a small proportion of pediatric patients, they are a particularly vulnerable population and may be in need of specialized care considerations. Further research is needed to evaluate the additional risks children at pediatric LTC facilities may have during hospitalization and the best ways to mitigate them.

Table 3.1: Key antimicrobial agents for determining multidrug-resistance of bacteria

Organism	Definition of Resistance
Acinetobacter	At least 3 antimicrobial classes of the following: β-lactams (piperacillin or piperacillin-tazobactam), aminoglycosides (amikacin, gentamicin, or tobramycin), carbapenems (imipenem or meropenem), cephalosporins (cefepime or ceftazidime), fluoroquinolones (ciprofloxacin or levofloxacin), sulbactams (ampicillin-sulbactam)
Enterococci	Vancomycin
Klebsiella	Ceftazidime, cefotaxime, ceftriaxone, or cefepime
Pseudomonas	At least 3 antimicrobial classes of the following: β-lactams (piperacillin or piperacillin-tazobactam), aminoglycosides (amikacin, gentamicin, or tobramycin), carbapenems (imipenem or meropenem), cephalosporins (cefepime or ceftazidime), fluoroquinolones (ciprofloxacin or levofloxacin), sulbactams (ampicillin-sulbactam)
Staphylococcus	Oxacillin
Enterobacteriaceae	*Escherichia coli*, *Enterobacter spp.*, or *Klebsiella spp.* resistant to carbapenems (ertapenem, imipenem, or meropenem)

Table 3.2: Organisms causing infections in hospitalized children, 2006 – 2016

Organism	N = 3446 (%)
Acinetobacter spp.	80 (3)
Multidrug-resistant	8 (10)
Enterobacter spp.	215 (7)
Carbapenem-resistant	1 (0)
Enterococci	460 (15)
Vancomycin-resistant	40 (9)
Escherichia coli	1281 (41)
Carbapenem-resistant	6 (0)
Klebsiella spp.	518 (17)
Carbapenem-resistant	9 (2)
Cephalosporin-resistant	61 (12)
Pseudomonas spp.	320 (10)
Multidrug-resistant	40 (13)
Staphylococcus aureus	572 (18)
Methicillin-resistant	158 (28)

Table 3.3: Characteristics of hospitalized children with and without infections, 2006 – 2016

Characteristics	Infection N = 2945 (%)	No Infection N = 255,719 (%)	p-value	OR (95% CI)
Previous stay in pediatric long-term care	30 (1)	1098 (0)	<0.001	2.39 (1.62 – 3.51)
Demographics				
Age in years, mean (SD)	4.47 (5.53)	3.15 (5.48)	<0.001	1.04 (1.03 – 1.05)
Male	1495 (51)	133,355 (52)	0.28	0.95 (0.86 – 1.05)
White	1044 (35)	80,976 (32)	<0.001	1.19 (1.07 – 1.31)
Prior conditions				
Diabetes mellitus	47 (2)	1896 (1)	<0.001	2.12 (1.53 – 2.94)
History of transplant	159 (5)	2468 (1)	<0.001	5.72 (4.55 – 7.18)
Invasive device use				
Feeding tube	48 (2)	1060 (0)	<0.001	3.98 (2.97 – 5.34)
Mechanical ventilation	560 (19)	10,007 (4)	<0.001	5.77 (5.20 – 6.39)
Urinary catheter	513 (17)	21,172 (8)	<0.001	2.34 (2.11 – 2.58)
Central venous line	670 (23)	19,696 (8)	<0.001	3.53 (3.20 – 3.90)
Hospitalization				
Admission to children's hospital	1949 (66)	124,328 (49)	<0.001	2.07 (1.86 – 2.30)
Stay in intensive care unit	737 (25)	85,195 (33)	<0.001	0.67 (0.61 – 0.73)
Operating room procedure	518 (18)	36,864 (14)	<0.001	1.27 (1.15 – 1.40)
Receipt of any antibiotic	890 (30)	135,330 (53)	<0.001	0.39 (0.35 – 0.42)

Table 3.4: Characteristics of hospitalized children with infections with and without a multidrug-resistant organism, 2006 – 2016

Characteristics	MDRO N = 305 (%)	No MDRO N = 2640 (%)	p-value	OR (95% CI)
Previous stay in pediatric long-term care	1 (0)	29 (1)	0.23	0.30 (0.04 – 2.20)
Demographics				
Age in years, mean (SD)	4.47 (5.53)	3.15 (5.48)	<0.001	1.04 (1.02 – 1.06)
Male	163 (53)	1332 (50)	0.41	1.13 (0.85 – 1.50)
White	128 (42)	916 (35)	0.04	1.36 (1.02 – 1.82)
Prior conditions				
Diabetes mellitus	5 (2)	42 (2)	0.94	1.03 (0.42 – 2.56)
History of transplant	18 (6)	141 (5)	0.68	1.11 (0.66 – 1.87)
Invasive device use				
Feeding tube	8 (3)	40 (2)	0.16	1.75 (0.81 – 3.81)
Mechanical ventilation	74 (24)	486 (18)	0.02	1.42 (1.07 – 1.89)
Urinary catheter	69 (23)	444 (17)	0.02	1.45 (1.07 – 1.95)
Central venous line	103 (34)	567 (21)	<0.001	1.86 (1.42 – 2.44)
Hospitalization				
Admission to children's hospital	230 (75)	1719 (65)	0.001	1.64 (1.22 – 2.21)
Stay in intensive care unit	89 (29)	648 (25)	0.10	1.27 (0.96 – 1.67)
Operating room procedure	67 (22)	451 (17)	0.04	1.37 (1.01 – 1.84)
Receipt of any antibiotic	139 (46)	751 (28)	<0.001	2.11 (1.63 – 2.73)

CHAPTER FOUR

The Association between Living with Animals and Diarrhea in Children Less Than 5 Years Old

Abstract

Background: Diarrheal disease is one of three major causes of death in children <5 years. Because livestock and pets are reservoirs of diarrheal pathogens, we assessed the relationship between animals living in or near the home and diarrheal disease in children.

Methods: We conducted a secondary analysis of the Global Enteric Multicenter Study case control study of the epidemiology of diarrheal illness in children <5 in sub-Saharan Africa and south Asia. Diarrheal cases from 12/1/2007 to 3/3/2011 were matched 1:1-3 by age, sex, timing (within 14d of case) and location (same or nearby village) to community controls without diarrhea in the previous 7 days. Cases and controls reported whether animals lived at or near their home and provided stool samples. Associations between animals and diarrhea and diarrheal pathogens were assessed using conditional logistic regression.

Results: Of 9,439 cases and 13,128 controls, 87% had ≥1 animal in their home. Adjusting for exclusive breastfeeding, water source, sanitation facility, number of children <5 years in the household, and wealth index, any animal on a child's compound decreased the odds of diarrhea by 33% (aOR 0.66, CI_{95} 0.59 – 0.74). Children with diarrhea who had an animal present were not more likely to have a positive stool culture.

Conclusions: In contrast to prior research, having an animal at the home did not increase the risk of childhood diarrhea. Risk of diarrheal disease in children in low-to-middle income countries may depend on type and number of animals. Further understanding of human-animal pathogen exchange may inform prevention interventions.

Background

Diarrheal disease is a major contributor to global morbidity and mortality for children younger than 5 years old, with an estimated incidence of 1.1 billion new cases and 446,000 deaths in 2016 (36, 37). Compared to children without diarrhea of the same age, those with moderate-to-severe diarrhea (diarrhea) are 8.5 times more likely to die in the following 60 days, with greater than two-thirds of diarrhea-related deaths happening after a week of the initial case (111). In addition to increasing the risk of death, there are significant long-term effects associated with the incidence of diarrhea in these children. Diarrheal disease has been associated with greater risk for subsequent infections and stunted growth (112, 113). The risk for stunting increases with the number of cases of diarrhea experienced in early childhood (114).

Many factors contribute to the incidence of diarrhea in children younger than 5, including duration of breastfeeding and access to improved water and sanitation facilities, but of increasing concern is how interactions with animals may be associated with disease emergence (38). One of the most common infections caused by zoonotic transmission is diarrheal illness (36). Livestock and companion animals are known reservoirs of diarrheal pathogens including *Campylobacter* spp., *Escherichia coli, and Salmonella* spp. (39), and these pathogens are among the leading causative agents of diarrhea in children younger than 5 years of age (40).

While previous studies have investigated companion animals and livestock as contributors to human diarrheal disease, few have investigated this association in sub-Saharan Africa and/or Southeast Asia, where diarrhea remains a leading cause of death in children (39, 115, 116). An analysis of Demographic and Health Surveys from 30 countries in sub-Saharan Africa found mixed results when comparing number of livestock owned and diarrhea in young children (117). Similarly, a study by Headey et al. evaluating the relationship between exposure

to animal feces in the homestead environment and diarrhea in children younger than 2 years old living in Ethiopia, Bangladesh, and Vietnam did not conclusively identify a significant association (118). However, both studies relied on parental recall for the identification of diarrhea in the previous 2-weeks, which may have led to misclassification.

Worldwide, the highest incidence of diarrhea as well as the greatest burden of severe disease is in Africa and Southeast Asia (119). Increased understanding of the relationship between the presence of animals near the home and the incidence diarrhea in children younger than 5 years old can enable public health practitioners to implement better interventions to improve the health of vulnerable children in developing countries. Thus, the purpose of this study was to gain further insight into diarrheal disease as it relates to the interaction between people, animals, and their shared environment. The aim of this study was to assess the association between living in close proximity to animals and presence of diarrheal disease in children less than 5 years of age.

Methods

Study sites. We conducted a secondary analysis of the Global Enteric Multicenter Study (GEMS), which was a multi-site case control study that described the epidemiology of and evaluated the risk factors for diarrheal illness in children < 5 years old living in sub-Saharan Africa and South Asia (120). The GEMS study sites were located in seven countries: Bangladesh, India, Pakistan, The Gambia, Kenya, Mali, and Mozambique. Enrollment in GEMS occurred between December 1, 2007 and March 3, 2011. As per the global access commitment of the Bill and Melinda Gates Foundation, the funders of GEMS, these data were publicly available following approval of a written request for its use from the University of Maryland

(121). As the data is provided de-identified no additional Institutional Review Board review was needed for this secondary analysis.

Enrollment criteria. The methodology of the GEMS study has been previously described (120). Cases were defined as children 0-59 months of age who presented to a study site sentinel health center with acute diarrhea. For each case, 1-3 children were enrolled as controls. Children enrolled as controls were in the same surveillance region, enrolled within 14 days of the case, had no history of diarrhea in the previous 7 days, and were matched to the case for age, sex, and location of residence (e.g., village or neighborhood). This study included all 22,568 cases and controls from the original GEMS study (111). Previous analyses of the GEMS dataset have not assessed the association between living with animals and incidence of diarrhea across study sites nor have they determined the relationship between types of animals at the home and pathogens present in the stool. Conan et al. examined animal-related exposures and incidence of diarrhea among a subset of children enrolled in GEMS in western Kenya, however, this was only among children living in households with domestic animals (122).

Data collection. During GEMS, an enrollment questionnaire was administered to all children and completed by the child's caregiver. This form included information pertaining to demographic (e.g., age, sex), environmental (e.g., living conditions, water sources, hygiene behaviors), clinical (e.g., symptoms, diarrhea frequency and consistency, treatment), and health care utilization (e.g., visits to health care center and health-related costs) factors. Additional clinical data ascertained at the time of enrollment included physical characteristics (e.g., weight, height, and signs of dehydration) and laboratory findings from stool samples. Laboratory testing of stool samples from both cases and controls included bacterial culture; multiplex polymerase chain reaction (PCR) assay for enterotoxigenic, enteropathogenic, and enteroaggregative *E. coli*

pathotypes; viral immunoassays; multiplex PCR assay for RNA viruses; and immunoassays for protozoa pathogens. A detailed description of diagnostic microbiologic methods employed in GEMS has been previously published (123). Further information regarding demographic and environmental factors were gathered during follow-up visits 60 days after the initial visit to the child's home, which provided additional data on water sources and sanitation facilities.

Variable definitions. The primary predictor was the presence of animals in the living environment or compound of enrolled children. Animal presence was assessed as a dichotomous variable, e.g., present or not, as well as a categorical variable. The animal categories included in this analysis were goat, sheep, dog, cat, cattle, rodents, fowl (chicken, duck, or other birds), donkey and/or horse, and pig. The secondary predictor was animal type, i.e., the dichotomous presence or absence of each of at least one animal in each category. Animal types were further categorized into two groups: livestock and companion animals. Livestock were defined as cattle, goats, and/or sheep. Companion animals were defined as dogs and/or cats. Lastly, the number of types of animals present were evaluated, e.g., presence of fowl and sheep at a child's home would be counted as two animal types present.

The primary outcome was diarrhea, defined as at least 3 loose stools within a 24-hour period that occurred at least 7 days after any previous diarrheal episode and included one or more of the following additional symptoms: sunken eyes, loss of skin turgor, need for intravenous rehydration, dysentery, and/or hospitalization with diarrhea or dysentery (120). The secondary outcome was the presence of a pathogen in the stool of children who had diarrhea. Pathogens were identified from fecal specimens and/or rectal swabs of cases and categories of pathogens (i.e., bacteria, viruses, and protozoa) and specific organisms (e.g., Shiga toxin-producing *E. coli*, rotavirus, and *Cryptosporidium* spp.) were evaluated.

Covariates evaluated as potential confounders include country of residence, breastfeeding, other children < 5 years old living in the household, access to an improved water source, and private sanitation facility. These factors have been previously identified as risk factors for diarrheal disease (38). Country of residence was the location of the study site for the study participant. Breastfeeding was defined as a child being either partially or exclusively breastfed. The number of children < 5 years old was evaluated as a continuous variable. Use of improved water sources and sanitation facilities were determined using definitions from the World Health Organization (124). Improved water source included use of piped water, boreholes or tube wells, protected/covered wells or springs, rainwater, and/or bought water (tank, bottles, etc.). Private, improved sanitation facility included use of a flush toilet, ventilated improved pit latrine, traditional pit toilet, ventilated improved pit with water seal, and/or pour flush toilet and is not shared with another household (125). A measure of wealth was also included in the analysis to account for the potential confounding relationship between animal ownership and higher socioeconomic status. The GEMS study generated wealth index quintiles (WIQ) for enrolled households using principal component analysis (120). Factors in the WIQ included home construction materials and ownership of household items and/or amenities, e.g., owning a television and presence of a flush toilet.

Statistical analysis. Descriptive statistics for predictors, potential confounders, and outcomes were calculated for the primary and secondary aims of this study. The primary and secondary aims were evaluated using multivariable conditional logistic regression, with strata defined by the matching of cases and controls. Breastfeeding, other children < 5 years old living in the household, access to an improved water source, private sanitation facility, and WIQ were included as potential confounders (38). The final models were determined using backwards

step-wise elimination. All confounders except WIQ were retained in the final model if they were statistically significant at $p<0.05$. WIQ was forced into the models to account for differences in sociodemographic characteristics between cases and controls. All statistical analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

From 12/1/2007 to 3/3/2011, there were 22,567 children enrolled in GEMS, including 9,439 cases with diarrhea and 13,128 controls. The average age was 17.7 months and 57% (n=12,821) were male. Eighteen percent (n=4,097) resided in Mali, 17% (n=3,859) in Bangladesh, 16% (n=3,582) in India, 15% (n=3,359) in Kenya, 14% (n=3,096) in Pakistan, 12% (n=2,598) in The Gambia, and 9% (n=1,976) in Mozambique. Eighty-seven percent of children had at least 1 animal present at their home. The most common animal present was rodent (n=14,502, 64%) followed by fowl (n=12,151, 54%), cat (n=9,893, 44%), dog (n=9,598, 43%), goat (n=5,617, 25%), cow (n=5,267, 23%), sheep (n=3,771, 17%), donkey and/or horse (n=1,478, 7%), and pig (n=456, 2%).

Relationship between proximity to animals and moderate-to-severe diarrhea. The characteristics of cases and controls are described in Table 4.1. When adjusting for exclusive breastfeeding, access to an improved water source, private access to an improved sanitation facility, the number of children younger than 5 years old living in the household, and wealth index, the presence of any animal on a child's compound decreased the odds of diarrhea by 33% (aOR 0.66, CI_{95} 0.59 – 0.74). Only cattle, donkeys and/or horses, pigs, and rodents had a significant association with diarrhea. However, these types of animals had differing associations with diarrhea, even after adjusting for confounding. Presence of cattle or of donkeys and/or

horses at a child's household increased the odds of diarrhea, being 1.20 times more likely with cattle (aOR CI_{95} 1.10 – 1.30) and 2.17 times more likely with donkeys and/or horses (aOR CI_{95} 1.84 – 2.56). In contrast, pigs on a child's compound decreased the odds of diarrhea by 43% (aOR 0.57, CI_{95} 0.45 – 0.72) and rodents decreased the odds of diarrhea by 12% (aOR 0.88, CI_{95} 0.81 – 0.95). Similarly, having three to five different types of animals on child's compound decreased the odds of diarrhea by 10% compared to children with zero to two different types, controlling for confounding (aOR 0.90, CI_{95} 0.83 – 0.98). Whereas the presence of six to eight different types of animals, compared to zero to two, increased the odds of diarrhea by 1.33 times (aOR CI_{95} 1.17 – 1.52). The complete multivariable results are provided in Table 4.2.

Relationship between proximity to animals and pathogens causing moderate-to-severe diarrhea. The majority of children enrolled in GEMS had at least one pathogen identified in their stool: 83% of cases (n=7,860) and 72% of controls (n=9,419) (OR 2.07, 1.93 – 2.23). For children with diarrhea, the most common was bacteria (n=5,408, 69%) followed by viruses (n=3,202, 41%) and protozoa (n=2,864, 36%). Sixty-three percent (n=4,965) of children with diarrhea had more than one pathogen identified: 36% (n=2,805) had two different pathogen types, i.e., bacteria and virus, virus and protozoa, protozoa and bacteria, isolated in their stool and 5% (n=404) had bacteria, virus, and protozoa isolated. Bacteria was isolated in 84%, viruses in 35%, and protozoa in 45% of diarrheal stool specimens. The complete description of pathogens identified in children with diarrhea is listed in Table 4.3. Children with diarrhea who had an animal present on their compound were not more likely to be infected with a bacterial (aOR 0.96, CI_{95} 0.82 – 1.13), viral (aOR 0.95, CI_{95} 0.80 – 1.12), or protozoal organism (aOR 0.94, CI_{95} 0.80 – 1.11) when controlling for potential confounders.

Discussion

Overall, in this study we found that having an animal present at the home does not consistently increase the risk of childhood diarrhea, and the relationship appears to be driven by the type of animal as well as the number of animals present. In our study, the presence of cattle, donkeys, and/or horses was associated with increased odds of diarrhea, whereas rats and swine were not. Other studies conducted in low- to middle-income countries have found mixed results when determining the relationship between childhood diarrhea and exposure to animals, particularly livestock (39, 117, 118, 126). Given these differences, there may be additional environmental factors at play that are driving this relationship. Large animals such as cattle, donkeys, and horses are reservoirs for different pathogens than swine and rodents. In GEMS, the three most common pathogens identified in children with diarrhea were *E. coli*, rotavirus, and *Giardia* spp. While it is well established that cattle are a reservoir for enterohemorrhagic *E. coli* (127), the overwhelming majority of *E. coli* identified were enteroaggregative, enteropathogenic, and enterotoxigenic *E. coli*. Whereas there is some evidence that cattle may be a reservoir for some strains of enteropathogenic and enterotoxigenic *E. coli* (128, 129), no known animal reservoir has been identified for enteroaggregative *E. coli* (127). Swine and cattle have both been implicated as reservoirs of rotavirus (130) and *Giardia* spp. is commonly found in domesticated animals, including livestock, dogs, and cats (131).

The transmission pathway from animal presence at a child's home and incidence of diarrhea is not well understood. Contamination of drinking water with diarrheal pathogens may be a mechanism by which exposure to animals can lead to diarrheal disease. Barnes et al. found that domestic animal ownership was significantly associated with contamination of drinking water with enteropathogenic organisms in Kenya (132). In a GEMS sub-study, a subset of cases

and controls in western Kenya underwent additional assessments for potential zoonotic pathogens in the stool of domestic animals at the children's homesteads as well as other factors that may increase or decrease the risk of diarrhea (122). While Conan et al. (120) did not find a significant relationship between the pathogens identified in the domestic animals and diarrhea in children, in our study, having an animal appeared to be protective. Conan et al. did note that engaging in basic health behaviors, e.g., handwashing after animal contact, reduced the risk for diarrhea. Similar studies evaluating the impact of interventions aimed at improving water, sanitation, and hygiene conditions on childhood diarrhea have had limited success (133-136). However, these interventions did not account for the influence of animal contact on childhood diarrhea. Broadening infection control measures to address preventive health behaviors with animals in and around the home may lead to greater decreases in childhood diarrhea.

In this study, we did not find an association between presence of animals and type of pathogen in children with diarrhea when controlling for other known risk factors for diarrheal illness. However, almost three-quarters of children enrolled as controls had a pathogen identified in their stool. These children may have had asymptomatic infections, which have been identified in previous research investigating diarrheal illness in children living in low-resourced countries (137). Asymptomatic enteric infections are common in children and their impact is not fully understood (138-140). Previous research has linked asymptomatic enteric infections to negative health outcomes in children, such as growth faltering and malnutrition (138), leading some researchers to state that child growth rather than diarrheal incidence may be a more accurate measure of child health as related to sanitation (141). In this study, we were unable to evaluate the relationship between animal presence at the homestead and colonization or asymptomatic infection with a pathogen. Further research is needed to fully elucidate the role

that these pathogens play in the health of young children and the possible influence of animal exposure, especially for those who have additional factors which put them at risk for diarrheal disease.

There were several limitations to this study. Firstly, the GEMS study asked participants only about presence of animals on their compounds and not about whether children had direct contact with animals, animal waste, or specific pathogens. Interaction with animals may be influenced by a range of household characteristics that are protective against the incidence of diarrhea, such as socioeconomic status. Even though household wealth, as measured by WIQ, was not identified as a confounder of the relationship between animal presence and childhood diarrhea, it remained significantly associated with diarrhea in children. While this particular measure of socioeconomic status did not rise to the level of confounding, there may be unmeasured confounding related to this construct that was not captured in this study. Secondly, as this was a secondary data analysis, the purpose of GEMS was not to evaluate the impact of animal presence on childhood diarrhea. Further investigation is needed to determine the impact of animals on childhood diarrhea, especially given the varying associations identified among animal types in this study. Lastly, as the GEMS study is a case-control study, it is not possible to determine causality between animal presence and childhood diarrhea. However, given the large sample size and the robustness of the study design, the findings offer important insight into the potential effects that living with animals may have on childhood diarrhea incidence.

In conclusion, animal exposure may increase or decrease the risk for diarrheal disease in young children living in low-to-middle income countries, depending on the type and number of animal exposures. Furthering our understanding of the human-animal exchange of pathogens may help to inform the design of improved interventions for the prevention of diarrhea,

especially in children. Additional research is needed to gain greater understanding of this relationship.

Table 4.1: Characteristics of children with and without moderate-to-severe diarrhea living in South Asia and Sub-Saharan Africa, 2007 - 2011

	Cases N = 9,439 (%)	Controls N = 13,128 (%)	p-value	OR	CI_{95} Min	CI_{95} Max
Exclusively breastfed	710 (8)	1,105 (8)	0.01	0.68	0.60	0.77
Access to improved water source	7,936 (84)	11,149 (85)	<0.01	0.83	0.74	0.93
Access to private improved sanitation facility	4,714 (50)	7,235 (55)	<0.01	0.89	0.83	0.96
Mean number of children < 5 years old in household (SD)	2.48 (2.20)	2.50 (2.37)	<0.01	0.98	0.96	0.99
Wealth index quintile						
1 (Poorest)	2,027 (21)	2,510 (19)	Ref	--	--	--
2	1,813 (19)	2,590 (20)	<0.01	0.89	0.81	0.97
3	1,993 (21)	2,834 (22)	<0.01	0.89	0.82	0.97
4	1,779 (19)	2,521 (19)	0.02	0.90	0.83	0.99
5 (Wealthiest)	1,821 (19)	2,672 (20)	0.01	0.89	0.81	0.97
Animal present on compound	8,119 (86)	11,542 (88)	<0.01	0.66	0.59	0.74
Type of animal present						
Cat	4,086 (43)	5,807 (44)	0.16	1.06	0.98	1.15
Cattle	2,223 (24)	3,044 (23)	<0.01	1.17	1.08	1.27
Dog	3,910 (41)	5,688 (43)	0.48	0.97	0.90	1.05
Donkey and/or horse	705 (7)	773 (6)	<0.01	2.17	1.84	2.56
Fowl	4,980 (53)	7,171 (55)	0.83	0.99	0.93	1.06
Goat	2,283 (24)	3,334 (25)	0.11	0.94	0.86	1.02
Pig	314 (3)	142 (1)	<0.01	0.56	0.44	0.71
Rodents	6,041 (64)	8,461 (64)	<0.01	0.88	0.81	0.94
Sheep	1,603 (17)	2,168 (17)	0.95	1.00	0.91	1.10
Number of types of animals present						
0-2	4,513 (48)	5,921 (45)	Ref	--	--	--
3-5	4,019 (43)	6,240 (48)	<0.01	1.13	1.04	1.22
6-8	907 (10)	967 (7)	<0.01	0.76	0.67	0.87

[1]Bolded characteristics are statistically significant at p <0.05

Table 4.2a: Multivariable analysis of animal exposure and children with and without moderate-to-severe diarrhea living in South Asia and Sub-Saharan Africa, 2007 - 2011

Characteristic	p-value	aOR	CI_{95} Min	CI_{95} Max
Exclusively breastfed	<0.01	0.68	0.60	0.77
Access to improved water source	<0.01	0.83	0.74	0.94
Access to private improved sanitation facility	<0.01	0.91	0.84	0.97
Mean number of children < 5 years old in household	0.03	0.98	0.97	1.00
Wealth income quintile				
1 (Poorest)	Ref	--	--	--
2	0.01	0.90	0.82	0.98
3	0.04	0.91	0.84	1.00
4	0.19	0.94	0.86	1.03
5 (Wealthiest)	0.26	0.95	0.86	1.04
Animal present on compound	<0.01	0.66	0.59	0.74

Table 4.2b: Multivariable analysis of cattle exposure and children with and without moderate-to-severe diarrhea living in South Asia and Sub-Saharan Africa, 2007 - 2011

Characteristic	p-value	aOR	CI_{95} Min	CI_{95} Max
Exclusively breastfed	<0.01	0.68	0.60	0.77
Access to improved water source	<0.01	0.83	0.74	0.94
Access to private improved sanitation facility	<0.01	0.91	0.84	0.97
Mean number of children < 5 years old in household	<0.01	0.98	0.96	0.99
Wealth income quintile				
1 (Poorest)	Ref	--	--	--
2	<0.01	0.89	0.82	0.97
3	0.02	0.90	0.83	0.98
4	0.08	0.92	0.84	1.01
5 (Wealthiest)	0.13	0.93	0.84	1.02
Cattle present on compound	<0.01	1.20	1.10	1.30

Table 4.2c: Multivariable analysis of donkey and/or horse exposure and children with and without moderate-to-severe diarrhea living in South Asia and Sub-Saharan Africa, 2007 - 2011

Characteristic	p-value	aOR	CI_{95} Min	CI_{95} Max
Exclusively breastfed	<0.01	0.69	0.61	0.78
Access to improved water source	<0.01	0.83	0.74	0.94
Access to private improved sanitation facility	0.01	0.91	0.85	0.98
Mean number of children < 5 years old in household	<0.01	0.98	0.96	0.99
Wealth income quintile				
1 (Poorest)	Ref	--	--	--
2	<0.01	0.89	0.82	0.97
3	0.04	0.91	0.83	0.99
4	0.12	0.93	0.85	1.02
5 (Wealthiest)	0.18	0.94	0.85	1.03
Donkey and/or horse present on compound	<0.01	2.17	1.84	2.56

Table 4.2d: Multivariable analysis of pig exposure and children with and without moderate-to-severe diarrhea living in South Asia and Sub-Saharan Africa, 2007 - 2011

Characteristic	p-value	aOR	CI_{95} Min	CI_{95} Max
Exclusively breastfed	<0.01	0.68	0.60	0.78
Access to improved water source	<0.01	0.83	0.74	0.94
Access to private improved sanitation facility	0.01	0.91	0.84	0.98
Mean number of children < 5 years old in household	0.01	0.98	0.96	1.00
Wealth income quintile				
1 (Poorest)	Ref	--	--	--
2	0.01	0.90	0.82	0.98
3	0.04	0.91	0.84	1.00
4	0.16	0.94	0.86	1.03
5 (Wealthiest)	0.22	0.94	0.86	1.04
Pig present on compound	<0.01	0.57	0.45	0.72

Table 4.2e: Multivariable analysis of rodent exposure and children with and without moderate-to-severe diarrhea living in South Asia and Sub-Saharan Africa, 2007 - 2011

Characteristic	p-value	aOR	CI_{95} Min	CI_{95} Max
Exclusively breastfed	<0.01	0.68	0.60	0.77
Access to improved water source	<0.01	0.83	0.74	0.94
Access to private improved sanitation facility	<0.01	0.91	0.85	0.98
Mean number of children < 5 years old in household	0.02	0.98	0.96	1.00
Wealth income quintile				
1 (Poorest)	Ref	--	--	--
2	0.01	0.89	0.82	0.98
3	0.03	0.91	0.83	0.99
4	0.13	0.93	0.85	1.02
5 (Wealthiest)	0.18	0.94	0.85	1.03
Rodent present on compound	<0.01	0.88	0.81	0.95

Table 4.2f: Multivariable analysis of rodent exposure and children with and without moderate-to-severe diarrhea living in South Asia and Sub-Saharan Africa, 2007 - 2011

Characteristic	p-value	aOR	CI_{95} Min	CI_{95} Max
Exclusively breastfed	<0.01	0.68	0.60	0.77
Access to improved water source	<0.01	0.83	0.73	0.93
Access to private improved sanitation facility	0.02	0.92	0.85	0.99
Mean number of children < 5 years old in household	<0.01	0.98	0.96	0.99
Wealth income quintile				
1 (Poorest)	Ref	--	--	--
2	0.01	0.89	0.82	0.97
3	0.02	0.90	0.83	0.99
4	0.14	0.93	0.85	1.02
5 (Wealthiest)	0.18	0.94	0.85	1.03
Number of types of animals present				
0-2	Ref	--	--	--
3-5	0.01	0.90	0.83	0.98
6-8	<0.01	1.34	1.17	1.52

Table 4.3: Pathogens identified in children with moderate-to-severe diarrhea living in South Asia and sub-Saharan Africa, 2007 - 2011

Pathogen	Count (%) n = 7,860
Bacteria	5,408 (69)
Escherichia coli	4,003 (44)
Enteroaggregative *E. coli* (EAEC)	1,846
Enterohemorrhagic *E. coli* (EHEC)	6
Enteropathogenic *E. coli* (EPEC)	1,084
Enterotoxigenic *E. coli* (ETEC)	1,067
Campylobacter spp.	1,171 (15)
Shigella spp.	1,092 (14)
Aeromonas spp.	655 (8)
Vibrio cholerae O1	179 (2)
Salmonella spp.	5 (0)
Viruses[1]	3,202 (41)
Rotavirus	1,747 (22)
Norovirus	741 (9)
Adenovirus	380 (5)
Sapovirus	325 (4)
Astrovirus	238 (3)
Protozoa[2]	2,864 (36)
Giardia spp.	1,786 (23)
Cryptosporidium spp.	1,123 (14)
Entamoeba histolytica	279 (4)

[1] Six children did not have viral testing.

[2] One child did not have protozoal testing.

CHAPTER 5

Conclusion

The aim of this dissertation was to describe the factors associated with the emergence and re-emergence of infectious diseases in children, in particular multidrug-resistant organisms (MDROs) and diarrheal disease. To achieve this, three studies were undertaken to assess potential risk factors for infectious disease emergence. The first study was a systematic review exploring the relationship between antibiotic use and subsequent colonization or infection with a MDRO in hospitalized children. The second was a 11-year retrospective cohort study in four New York City hospitals evaluating the association between prior stay in a pediatric long-term care (LTC) facility and subsequent infection with a MDRO infection in hospitalized children. The third study was a secondary analysis of a case control study in seven countries in South Asia and sub-Saharan Africa examining the association of living in close proximity to animals on presence of diarrheal disease in children less than 5 years of age.

Summary of Results and Key Findings

Chapter Two describes the first study of the dissertation. The systematic review in Chapter Two summarized the existing literature related to the acquisition of a MDRO following antibiotic exposure in hospitalized children. Twenty-nine research articles met the inclusion criteria and included a total of 4,598 hospitalized children and 4,606 healthcare-associated infections and/or colonization, of which 34% were due to a MDRO. Overall, previous antibiotic use was found to be associated with MDRO colonization and/or infection in hospitalized children; a positive association with MDROs and a specific antibiotic exposure was reported in 81% (17/21) of studies, duration of antibiotic use in 75% (9/12), number of antibiotics received in 66% (2/3), and any antibiotic exposure in 50% (5/10). However, there was wide variation in the definitions of antibiotic exposition and MDRO, which limited the ability to synthesize the current research. Having a comprehensive understanding of the components of antibiotic use

that lead to MDRO development in children would enable healthcare providers to create effective antibiotic stewardship programs for the prevention of MDRO infections.

Chapter Three describes the second study of this dissertation. The purpose of this study was to further understand the acquisition of MDROs in hospitalized children. To accomplish this, a retrospective cohort study was conducted to assess the likelihood of infection with an MDRO in hospitalized children who had previously received pediatric LTC, an especially vulnerable population. From 2006 through 2016, there were 77,454 children who had 258,664 admissions, of which 1% (2,945) had an infection. A MDRO was detected in 10% of infections, however, only 1 child who previously resided in pediatric LTC had a MDRO infection. Prior stay in a LTC facility was associated with an increased likelihood of MDRO and non-MDRO infections, *Clostrioides difficile* infection, days of antibiotic use, length of stay, and death.

These findings are important for several reasons. First, in this study, MDROs were not a major contributor to infections among hospitalized children who had previously resided in a pediatric LTC facility. While this may indicate a low prevalence of MDROs in this population, it is inconsistent with what would be expected given the high risk characteristics of children who receive pediatric LTC. One possible explanation is that infections are not being adequately captured by the electronic algorithm utilized, which was based upon the National Healthcare Safety Network surveillance case definitions (142). These definitions were developed for the identification of acute care healthcare-associated infections (HAIs) and are not tailored to pediatrics. Due to the medical complexity of children who receive pediatric LTC, the presentation of infection may differ from other hospitalized populations and therefore these surveillance definitions may lead to the underreporting of infections (103). Infections that were not captured in this population may be more likely to be caused by an MDRO, e.g., respiratory

and skin and soft tissue infections. Second, hospitalized children with a history of LTC were significantly more likely to experience a number of negative outcomes during their acute care stay including *C. difficile* infection, prolonged antibiotic use, increased length of stay, and death. Each of these outcomes warrants special consideration during hospitalizations among children admitted from LTC settings. Of particular concern is the higher rates of infection with *C. difficile* among these children because of the emergence of antibiotic-resistant as well as highly virulent strains (105).

Chapter Four describes the third study of this dissertation. In this chapter, the research aim was to determine the association of living in close proximity to animals on the presence of diarrheal disease in children younger than five years old. A secondary analysis of a three-year case control study was conducted to identify factors related to animal exposure and diarrheal disease in young children. Of 9,439 cases with diarrhea and 13,128 uninfected controls, 87% had ≥1 animal in their home. Any animal present on a child's compound decreased the odds of diarrhea by 33%, when controlling for exclusive breastfeeding, water source, sanitation facility, number of children <5 years in the household, and wealth index.

The findings of this study provided new knowledge to this area of research. Specifically, in contrast to previous studies (39, 117, 118, 126), having an animal at or near the home did not consistently increase the risk of childhood diarrhea. This relationship appears to be driven by type and number of animals present. Cattle, donkeys, and horses were associated with an increased risk of diarrhea, whereas rats and swine were not. Furthermore, the number of different types of animals present initially had a protective effect against diarrhea in young children but there appears to be a threshold where the inverse becomes true and more animal types leads to an increased risk for diarrhea. Therefore, it is important to consider the many

aspects of animal exposure when developing infection control interventions to limit the incidence of childhood diarrhea.

Among children with diarrhea, there did not appear to be a significant relationship between the organism identified in their stool and the presence of animals at the home. However, this finding may be related to the inability to distinguish between diarrhea disease-causing pathogens and colonization with an enteric organism because the majority of children had a gastrointestinal pathogen detected in their stool, regardless of whether they had diarrhea. Prior research has shown that asymptomatic enteric infections in children are linked to negative health outcomes, including growth faltering and malnutrition. Given the association between diarrhea and animal presence at a child's home, it is possible that exposure to animals may also lead to asymptomatic infections or colonization with an enteric pathogen. While this study was unable to evaluate this relationship, this finding highlights an important gap in the current research and warrants further investigation.

Strengths and Limitations

This dissertation provides a detailed analysis of factors related to the emergence of infectious diseases in children. By including diverse populations, i.e., children in both inpatient and outpatient settings worldwide, and multiple disease-related outcomes, i.e., acquisition of an MDRO and diarrheal disease, a thorough examination of the environmental, host, and pathogen characteristics implicated in infectious disease emergence was conducted. Also, the three studies each included a large sample size, which increased the power and decreased the margin of error of the findings.

There are limitations to this dissertation. First, pathogen emergence is linked to time and none of the included studies were longitudinal in design. Future research should build upon

these initial findings to elucidate how the relationship changes over time between the potential risk factors identified and the emergence of infectious diseases. Second, Chapters Three and Four were both retrospective, observational studies and as such causality could not be inferred. Lastly, this dissertation relied solely on existing data and therefore the research questions in each study were not the primary purpose of the source datasets. However, due to the large sample size and the robust study design of the parent studies, valuable insight into the factors involved in infections with MDROs and diarrheal disease was gained.

Implications and Future Research

Overall, these three studies provide a comprehensive look at various factors associated with the emergence of infectious diseases in children, particularly as related to MDROs and diarrheal disease. Environmental factors, such as selective pressure of antibiotics and zoonotic transmission, were clearly associated with subsequent infection with an emergent infectious disease across diverse settings.

These findings offer practical and clinical implications for limiting the emergence and re-emergence of pathogens. In the prevention of MDROs, antibiotic use should continue to be a main focal point of infection control efforts. The components of antibiotic use leading to MDRO acquisition are not well understood and further research is needed in order to develop effective antibiotic stewardship programs. Among hospitalized children, the prevalence of MDROs was low, which may indicate that MDROs have yet to become a major issue in this population. However, given the many risk factors present for MDRO acquisition, there is great opportunity for the implementation of surveillance and prevention methods to thwart MDRO development and spread.

Infection prevention and control policies often focus on individual health behaviors, e.g., handwashing, or facility-level practices, e.g., antibiotic stewardship programs, but few have made recommendations for the community environment, e.g., interactions with wildlife. While this dissertation examined the association between animal exposure and diarrheal disease, animals, particularly livestock, have also been implicated in the development of MDROs (143). Infectious disease emergence and spread is not limited to human-to-human interactions and this dissertation provides further evidence that a One Health approach to infection prevention measures is needed.

Judicious use of antimicrobials through the adherence to antimicrobial stewardship programs, specialized infection prevention precautions for at-risk populations, and the encouragement of basic health behaviors, e.g., handwashing, have been well-studied and may greatly limit infections in children. However, even though advances have been made both in the development of antimicrobial therapies and infection prevention and control interventions, infectious diseases, particularly among children, continue to be a major cause of morbidity and mortality worldwide (1, 2). Children are often an under-researched population, yet emerging and reemerging infections in this population may have lasting effects. Young children are particularly at-risk not only for infectious diseases but also for the negative consequences associated with infection, including growth faltering, development of comorbidities, and even death (25, 112, 113). Developing interventions to limit these negative outcomes is a key component of public health programs and additional methods need to be designed to effectively mitigate the risks of emergent infectious diseases in children.

Conclusion

In summary, this dissertation described three studies focused on identifying actionable risk factors to limit the incidence of emerging and reemerging pathogens in children. This work is important given the national focus on emerging infections, global initiatives to reduce morbidity and mortality from infectious disease in children, and the importance of antibiotic stewardship programs on the local, national, and global landscape. The findings from this dissertation provide new knowledge to the field and will inform future interventional studies to reduce infectious disease morbidity in vulnerable populations.

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APPENDICES

Appendix I: Search terms for systematic review

Embase search terms:

('antibiotic therapy'/exp OR 'antibiotic therapy') AND ('antibiotic resistance'/exp OR 'antibiotic resistance') AND ('hospital'/exp OR hospital) AND ('risk factor'/exp OR 'risk factor') AND ('pediatrics'/exp OR pediatrics OR 'child'/exp OR child)

PubMed search terms:

("drug resistance, microbial"[MeSH Terms] OR ("drug"[Title/Abstract] AND "resistance"[Title/Abstract] AND "microbial"[Title/Abstract]) OR "microbial drug resistance"[Title/Abstract] OR ("antibiotic"[Title/Abstract] AND "resistance"[Title/Abstract]) OR "antibiotic resistance"[Title/Abstract]) AND ("hospitals"[MeSH Terms] OR "hospitals"[Title/Abstract] OR "hospital"[Title/Abstract]) AND ("risk factors"[MeSH Terms] OR ("risk"[Title/Abstract] AND "factors"[Title/Abstract]) OR "risk factors"[Title/Abstract]) AND ((("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[Title/Abstract] AND "agents"[Title/Abstract]) OR "anti-bacterial agents"[Title/Abstract] OR "antibiotics"[Title/Abstract])) AND (“dose”[Title/Abstract] OR “duration”[Title/Abstract] OR “indication”[Title/Abstract] OR “appropriate”[Title/Abstract] OR “drug”[Title/Abstract] OR “prophylaxis”[Title/Abstract] OR “therapy”[Title/Abstract])) AND (infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*)

Appendix II: Quality assessment of case control and cohort studies using the Newcastle-Ottawa Quality Assessment Scale

Study		Selection				Comparability	Outcome			
Study	Study Type	Represents cases/ exposed cohort	Selection of the controls/ non-exposed cohort	Definition of controls *or* ascertain-ment of exposure	Adequacy of case definition *or* Outcome absent at study start	Comparability of cases and controls/cohorts based on the design or analysis	Ascertain-ment of exposure/ Assessment of outcome	Non-response rate *or* Long enough follow-up of outcomes	Same methods of ascertain-ment for cases and controls *or* Adequacy of follow up of cohorts	Total Score
Allen, E. D., 1999	Case control	★	★		★	★ ★	★		★	78%
Arhoune, B., 2017	Cohort	★	★	★	★		★		★	67%
Arrifin, H., 2000	Cohort	★	★	★	★	★			★	67%
Asensio, A., 2000	Case control	★	★		★	★	★	N/A	★	75%
Chiotos, K., 2017	Case control	★	★		★	★★	★	N/A	★	88%
Chiu, S., 2005	Cohort	★	★		★				★	44%
Crivaro, V., 2007	Cohort	★	★	★	★	★	★		★	78%
de Oliveira Costa, P., 2015	Case control	★	★		★	★		N/A	★	63%
Deeks, S. L., 1999	Cohort	★	★	★	★	★	★	★	★	89%
Dirajlal-Fargo, S., 2014	Case control	★	★	★	★	★		N/A	★	75%
Gaynes, R. P., 1984	Case control	★	★	★	★	★	★	N/A	★	88%

★Met the Newcastle-Ottawa Quality Assessment Scale criteria for cohort studies; one star per category except for comparability which can be granted two stars

Appendix III, continued: Quality assessment of case control and cohort studies using the Newcastle-Ottawa Quality Assessment Scale

Study		**Selection**				**Comparability**	**Exposure/Outcome**			
Study	Study Type	Represents cases/ exposed cohort	Selection of the controls/ non-exposed cohort	Definition of controls *or* ascertain-ment of exposure	Adequacy of case definition *or* Outcome absent at study start	Comparability of cases and controls/cohorts based on the design or analysis	Ascertain-ment of exposure/ Assessment of outcome	Non-response rate *or* Long enough follow-up of outcomes	Same methods of ascertain-ment for cases and controls *or* Adequacy of follow up of cohorts	Total Score
Gupta, A., 2004	Case control	★	★		★	★		N/A		50%
Haas, E. J., 2010	Case control	★	★	★	★	★	★	N/A	★	88%
Huang, Y., 2007	Cohort	★	★	★	★	★	★		★	88%
Karaaslan, A., 2016	Case control	★				★		N/A	★	38%
Katragkou, A., 2006	Case control	★		★	★	★		N/A	★	63%
Kim, Y., 2002	Cohort	★	★	★	★	★	★		★	78%
Logan, L. K., 2014	Case control	★	★	★	★	★★	★	N/A	★	100%
Nieminen, O., 2017	Case control	★	★	★	★	★★	★	N/A	★	100%
Nolan, S. M., 2009	Case control	★	★	★	★	★★	★	N/A	★	100%
Nourse, C., 1998	Case control	★	★	★	★	★	★	N/A	★	100%
Ozsurekci, Y., 2017	Cohort	★	★	★	★		★		★	56%

★Met the Newcastle-Ottawa Quality Assessment Scale criteria for cohort studies; one star per category except for comparability which can be granted two stars

Appendix III, continued: Quality assessment of case control and cohort studies using the Newcastle-Ottawa Quality Assessment Scale

Study		**Selection**				**Comparability**	**Exposure/Outcome**			
Study	Study Type	Represents cases/ exposed cohort	Selection of the controls/ non-exposed cohort	Definition of controls *or* ascertain-ment of exposure	Adequacy of case definition *or* Outcome absent at study start	Comparability of cases and controls/cohorts based on the design or analysis	Ascertain-ment of exposure/ Assessment of outcome	Non-response rate *or* Long enough follow-up of outcomes	Same methods of ascertain-ment for cases and controls *or* Adequacy of follow up of cohorts	Total Score
Pessoa-Silva, C. L., 2003	Cohort	★	★		★		★	★	★	67%
Rao, Y. B., 2018	Cohort	★	★		★	★★	★	★	★	63%
Renk, H., 2017	Cohort	★	★	★	★	★★	★	★	★	100%
Rubin, L. G., 1992	Case control		★	★	★		★	N/A	★	63%
Sultan, A. M., 2018	Cohort	★	★		★	★	★		★	67%
Thatrimontrichai, A., 2016	Case control	★	★	★	★	★	★	N/A	★	88%
Zaoutis, T. E., 2005	Case control	★	★		★	★★	★	N/A	★	88%

★Met the Newcastle-Ottawa Quality Assessment Scale criteria for cohort studies; one star per category except for comparability which can be granted two stars