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Inter-facility Patient Sharing and the Spread of Carbapenem-resistant Enterobacteriaceae

DISSERTATION

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by

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ABSTRACT OF THE DISSERTATION

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By

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Doctor of Philosophy in Social Ecology

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Carbapenem-resistant Enterobacteriaceae (CRE) are a rapidly emerging group of multiple drug-resistant organisms (MDROs), with a mortality rate reaching 50%, causing the CDC to declare them to be the highest level antibiotic-resistant microorganism threat. Drug resistance limits the available treatments for CRE to older, more toxic antibiotics and makes infection control practices to stop the spread of CRE crucial. Because of its dependence on human factors, the spread of MDROs was examined using a newly proposed social ecological model of CRE epidemiology which considered how factors at three levels - the patient, the hospital, and the nursing home - interact throughout inter-facility patient sharing to influence individual patient carriage of MDROs.

The current research began necessary CRE surveillance by quantifying the current prevalence of CRE and identifying targets for intervention in a region in which CRE is still emerging. The results confirm the importance of containing CRE, which had a high mortality rate (31%) and extensive spread (52 days of healthcare facility exposure per year of follow up for CRE carriers). The results also suggest targets for intervention at the intra-personal level, including high comorbidity; and at the institutional levels, highlighting nursing home facilities. The results of statewide studies show that Southern California UC hospitals having 10 times the rate of CRE carriage than Northern California hospitals. Statewide results

reaffirmed the high mortality rate and extensive healthcare facility exposure of CRE carriers, which were significantly greater than those of non-CRE carriers. They also emphasized the importance of surveillance definitions in the control of infectious disease and demonstrated how the intra-personal factor of the co-colonization among CRE carriers affects the potential impacts of institutional level contact precautions policies in preventing the spread of emerging MDROs.

Understanding the interplay of factors at the intrapersonal and institutional levels that amplify MDRO spread is important to effectively target interventions, such as contact precautions, to reduce the burden of emerging MDROs. As the population in the United States ages, it will be increasingly important to understand how infection prevention policies at nursing home facilities and healthcare facility exposure contribute to the population burden of infectious disease.

Chapter 1

Introduction

1.1 The Burden of Healthcare-Associated Infectious Diseases

The Institute of Medicine has called loss of life in the United States from serious adverse medical events, including healthcare associated infections (HAI), akin to a Boeing 747-8 Aircraft with approximately 400 passengers crashing every two days with no survivors (1). Among hospital inpatients, HAI affect an estimated 648,000 patients each year in the United States (2). However, despite the fact that HAI have afflicted patients throughout the history of healthcare and are now widely recognized as a as an important preventable cause of morbidity and mortality, systematic study of HAI began only in the 1960s and the goal of eliminating HAI remains elusive today.

In the 1960s, hospital infection control programs with a public health approach were instituted at a few large academic hospitals (3), ushering the first large scale HAI surveillance efforts. Understanding the causes and transmission patterns of HAI is crucial to being able

to stop their spread. Therefore, the Centers for Disease Control and Prevention (CDC) launched the first large study of HAI in 1965, when the Comprehensive Hospital Infections Project (CHIP) was piloted. CHIP examined 6 community hospitals, testing methods for surveillance and infection control, and found a mean HAI rate of 1.4% (3; 4). These initial programs were designed with the goal of identifying HAI, establishing the baseline of endemic HAI, identifying nosocomial outbreaks, and promoting infection prevention measures (4).

The full cost of HAI morbidity and mortality in the United States was not revealed until 1976 when a large national study by the CDC estimated that there were 2.1 million such infections per year in 37.7 million hospital admissions in the 1970s (5). The CDCs Study on the Effectiveness of Nosocomial Infection Control (SENIC) project was the first attempt to quantify the impact of HAI in a statistically representative sample of U.S. hospitals (5). The study was undertaken in three phases between 1975 and 1976 (5). In the third phase, CDC staff performed retrospective reviews of 500 patients medical charts before the implementation of infection surveillance and control programs to establish baseline HAI rates and 500 charts after implementation at 338 hospitals to determine the impact of these practices (6). The overall rate of HAI was estimated to be 7.18 infections / 1000 patient days or 5.7 infections per 100 admissions in U.S. acute care hospitals, and 30% were believed to be preventable by appropriate infection control measures (5). Following these results, The Joint Commission on Accreditation of Hospitals (now The Joint Commission) began requiring infection surveillance for hospital accreditation in the United States in 1976 (7; 8).

More than thirty years later, HAI remains a major problem in the United States. A study based on infections reported to the National Nosocomial Infections Surveillance system in 2002 estimated that there were 1.7 million HAI in the United States in 2002 and that 98,987 deaths were caused by or associated with these HAI (9). The next year, in 2003, HAI killed around 40 times as many people as SARS (10). The most recent report of surveillance

data shows that, in 2009-2010, there were nearly 70,000 HAI reported by U.S. hospitals to the National Healthcare Safety Network (NHSN) (11). These NHSN data capture only a small subset of the total HAI in the United States because not all hospitals report to the NHSN, and those that do limit reporting to only a small subset of infection types. Todays best estimate of the full burden of HAI in the United States comes from a point-prevalence survey of 183 hospitals in 10 states which was conducted in 2011. That study estimated 721,800 HAI, more than ten times the number reported to NHSN, in 648,000 patients in acute care hospitals in the United States in 2011 (2).

Of all HAI reported to the NHSN in 2009-2010, nearly 20% were associated with difficult-to-treat pathogens resistant to multiple antibiotics, called multidrug-resistant organisms (MDROs) (11). This included approximately 6,000 methicillin-resistant Staphylococcus aureus (MRSA) HAI, 6,000 multi-drug resistant gram negative bacteria (MDR GNB) HAI, and 2,000 vancomycin-resistant Enterococcus (VRE) HAI (11). Without improvements throughout the healthcare system to decrease HAI, the aging population can be expected to have increased healthcare facility exposure and HAI, including those caused by MDROs.

1.2 The Emergence of Antibiotic Resistance in Healthcare

Antibiotics were developed to treat infections, including HAI, by specifically killing or slowing the growth of bacterial cells but not human cells. Penicillin, an early antibiotic which was first used to treat civilians in the United States in 1942, was deemed a miracle drug due to its ability to kill bacteria causing previously untreatable infections (12) and to save soldiers with wound infections during World War II (13). Despite widespread optimism about antibiotics, Alexander Fleming, the discoverer of penicillin, warned in 1945 that bacteria

could become resistant to penicillin, a phenomenon he had observed in his laboratory in the 1920s, particularly if the drug was given in too low a dose or with the lack of adequate supervision that might come from an oral route of administration (12). However, penicillin-resistant Staphylococcus strains had already begun increasing rapidly in hospitals by 1944, when some studies found more than 10% of strains to be resistant (14). By 1947, a report was published of the proportion of penicillin-resistant Staphylococcus pyogenes in a London hospital increasing from 14.1% to 38% in one year (14).

Resistant bacterial strains develop when antibiotics exert selective pressure, killing the vast majority of bacteria infecting or colonizing the human host and leaving bacteria that survive to reproduce rapidly without competition. Compared to humans, bacteria evolve extremely rapidly due to their large population sizes, high mutation rates and short generation times (15). Many molecular mechanisms of resistance have evolved including specific enzymes which degrade antibiotics, pores and pumps which remove the antibiotic from the bacterial cell before it can take effect, and structural changes to proteins targeted by antibiotics (16).

While mutations producing resistance can spread vertically between generations of bacteria, resistance can spread even more quickly through horizontal transfer of resistance genes directly from one bacterium to another, often through plasmids containing mobile genetic elements (17). Genes conferring resistance to multiple antibiotics can travel together on one plasmid. When a patient receives an antibiotic, selection for one resistance gene on the plasmid also selects for the other resistance genes on the plasmid, compounding the problem of antibiotic resistance.

As a result of these evolutionary processes, the trend, noticed first with penicillin, of the emergence of resistant strains following shortly after the introduction of each new antibiotic has continued. As examples, tetracycline was introduced in 1950 and tetracycline resistance found in 1959, methicillin in 1960 and resistance in 1962, vancomycin in 1972 and resistance in 1988, and ceftazidime in 1985 and resistance in 1987 (18). In 1952, it was observed that,

only one month after the introduction of a new antibiotic into a hospital, health care workers carried resistant strains and were transmitting them to patients (19). Antibiotic resistant strains often appeared in hospitals where they were spread much like other HAI.

Between 1940 and 2004, 20.9% of newly emergent pathogen strains evolved through antibiotic resistance (20). Among these were MRSA and extended-spectrum beta-lactamase-producing bacteria (ESBL). Before 1968, only four cases of MRSA had been reported in the United States, despite such strains making up 15% of staphylococcus isolates in some parts of Europe. By 2008, 76% of a representative sample of S. aureus clinical isolates was found to be MRSA (21). ESBLs were first identified in 1987 (22). Between 1986 and 1993, bloodstream infections caused by Klebsiella pneumoniae went from 0% ESBL to 27% ESBL at one Chicago hospital (22).

In addition to infections caused by bacteria with acquired resistance, another type of infection has become more prominent as a result of selective pressures from antibiotic use. Clostridium difficile was first identified in the 1930s (23). As early as the 1940s, guinea pigs treated with penicillin for gas gangrene developed symptoms of what we would now recognize as C. difficile infection (23). However, decades passed before the connection between antibiotic use and C. difficile was made. It was not noted as the cause of antibiotic-associated pseudomembranous colitis until 1978 (23). Current strains of C. difficile produce an order of magnitude more toxin than older strains and have high resistance to fluoroquinolones (23).

1.3 The Burden of Antibiotic Resistance in Healthcare

Despite recent gains in controlling HAI, antibiotic resistance is increasing in their causative bacterial populations, posing problems for future control. In a study of National Nosocomial Infections Surveillance data from 1986 to 2003, the percentage of Escherichia coli and K.

pneumoniae resistant to third-generation cephalosporins both rose significantly, as did Pseudomonas aeruginosa resistance to imipenem and ceftazidime and Acinetobacter resistance to imipenem, ceftazidime, and amikacin (24). Between 2007-2008 and 2009-2010, the percent of central line infections reported to the NHSN caused by E. coli resistant to extended spectrum cephalosporins rose 54.3% and those caused by carbapenem resistant Acinetobacter baumannii rose by 25.3% (11). Catheter-associated urinary tract infections caused by fluoroquinolone resistant E. coli increased by 15.6% in the same time frame (11). Antibiotic resistant strains have been shown to be no more common in critical care units, where they were previously believed to be clustered, than hospitals at large (11), so HAI treatment options are limited throughout acute care hospitals.

In addition to being more difficult to treat, antibiotic resistant bacteria also pose greater risks to patients. Even asymptomatic carriage of these resistant pathogens is associated with high risk of later infection (25; 26). Compared to bacteremia caused by methicillin-sensitive strains (MSSA), MRSA bacteremia results nearly twice the risk of patient mortality (27). Surgical site infections caused by MRSA are also more dangerous than those caused by MSSA, resulting in more than three times higher risk of death within 90 days and a five day longer hospital stay after infection (28). MRSA bacteremia similarly resulted in longer hospital stays (29). A 2007 study of MRSA in 16.5 million people estimated that the number of invasive MRSA infections in the United States in 2005 was 94,360, resulting in 18,650 in-hospital deaths (30). MRSA surgical site infections also cost almost $14,000 more to treat than those caused by MSSA in 2003 (28), while MRSA bacteremia cost almost $7,000 more to treat in 2005 (29).

As the other leading cause of resistant HAI, antibiotic-resistant Gram-negative bacilli are associated with increased mortality, length of stay, and costs in intensive care units (31). An important source of antibiotic resistance in gram negative bacteria is the production of extended spectrum beta-lactamases. Meta-analysis has found that bloodstream infec-

tion caused by ESBL-producing Enterobacteriaceae is associated with a two-fold increase in mortality compared to those caused by non-ESBL bacteria (32). These poor outcomes are believed to be due to a 5-fold higher proportion of patients with ESBL not receiving effective antibiotics in a timely manner than patients with non-ESBL, for whom a larger proportion of antibiotics are likely to be effective (32). Patients with VRE HAI experience similar outcomes. They have longer hospital stays, about twice as long for VRE versus VSE (33; 34), and higher mortality (35; 33; 34; 36), with 2.5 times the risk of dying from VRE bacteremia compared to VSE (37). Patients with VRE are also more likely to require surgery, ICU care, or transfer to another hospital than patients with VSE (34). Hospitalizations for VRE have been reported to cost, on average, 48%-64% more than those for VSE (33; 34).

In addition to harming hospitalized patients, multi-drug resistant strains of pathogens also can spread within the community outside of hospitals. Community-associated strains of MRSA were first observed in 1981, and by 2005, a MRSA study of 16.5 million people in the United States found that the rate of community-acquired invasive MRSA infections was 4.6 per 100,000 (30).

1.4 Emergence of Carbapenem-resistant Enterobacteriaceae

1.4.1 Molecular Mechanisms of CRE Emergence

Carbapenem-resistant Enterobacteriaceae (CRE) is another group of highly antibiotic-resistant gram negative bacteria that cause serious infections. CRE is not a specific species of bacteria but a group of bacteria which all share resistance to carbapenems. The most common species of bacteria causing CRE HAI are E. coli, K. oxytoca, K. pneumoniae, and Enter-

obacter spp. The CRE strains of these organisms evolved from susceptible strains due to selective pressures from antibiotic use. To evade carbapenem treatment, CRE strains typically utilize one of two mechanisms: (1) coupling of overproduction of AmpC or extended spectrum beta-lactamases with porin mutations or (2) production of carbapenemases (38).

The first mechanism, coupling of a specialized beta-lactamase with porin mutations, was noted first in the United States. AmpC beta-lactamases are naturally occurring on the chromosomes of Enterobacter, Citrobacter, Serratia, and Pseudomonas species; however, more recently, they have been isolated from plasmids in other bacteria (39). The gene MIR-1 was the first Amp-C-type beta lactamase isolated from a plasmid in a strain of one of these other bacterial species, K. pneumoniae, which had caused HAI in eleven patients between 1988 and 1989 (40). Of known chromosomal genes causing naturally occurring resistance, it most closely resembled the ampC gene of Enterobacter cloacae. Plasmids with genes of this AmpC type convey resistance to expanded-spectrum cephalosporins, penicillins, and monobactams but not normally to carbapenems; however, in combination with loss of outer membrane proteins, the gene also conveys resistance to imipenem (39). The overproduced beta-lactamase degrades the carbapenem while the porin loss decreases the outer membrane permeability, slowing carbapenem penetration into the bacteria (41). This mechanism of carbapenem resistance was first described in Enterobacter spp. in 1991 (41) and the first Klebsiella isolates with the mechanism were cultured in 1994 (39). A similar mechanism of imipenem resistance combining loss of a major outer membrane protein and the ESBL gene SHV-2 was reported in 1997 (42). The second mechanism of carbapenem-resistance is mediated by the production of carbapenemase enzymes, most commonly KPC and NDM. The KPC-1 gene was first isolated from K. pneumoniae in 2001 and confers resistance to imipenem, meropenem, extended-spectrum cephalosporins, and aztreonam (43). The NDM-1 gene was first described in 2009 after being isolated from K. pneumoniae; infections caused by bacteria containing this gene can only be treated with fluoroquinolones and colistin (44).

A third carbapenem resistance gene, which is less common in the United states, is found in the OXA-48 strain of CRE and was first identified in Turkey in 2001 (45).

As a result of these molecular mechanisms of resistance, very few antibiotics can be used to treat CRE. The only potentially effective antibiotics are tigecycline (46), polymyxins, some tetracyclines and aminoglycosides (47), and fosfomycin (48), and none of these treatments are ideal. For example, it is difficult to achieve appropriate blood levels of tigecycline, and it may be less effective in severely ill patients (49). Furthermore, in 2010 the FDA issued a warning for tigecycline due to increased mortality relative to comparable drugs and nausea/vomiting in 30% of patients (50). Polymyxins are the most effective in treating CRE but are potentially dangerous due to known neuro- and nephro-toxicity (48; 50) and a lack of standardized dosing (47). While aminoglycosides can be used in combination regimes to treat CRE, they can result in nephrotoxicity, ototoxicity and neuromuscular blockade (50). Fosfomycin is only available as an oral preparation in the U.S., therefore can be used only for treatment of cystitis and no other CRE infections (50). These limited treatment options mean that CRE infections pose substantial risk to patients. Furthermore, pan-resistant cases of CRE have been reported which are resistant to all available antibiotics (51).

1.4.2 Outbreaks and Spread of CRE

In the U.S. the first case of KPC-producing CRE was reported from an isolate from a North Carolina patient in 2001 (43). The first outbreak of CRE in a U.S. hospital occurred in New York City between 2000 and 2001. During a one year period, 24 patients were infected across 4 ICUs which shared medical staff (52). Despite initial staff education sessions on correct aseptic technique, isolation of patients with CRE in private rooms, and creation of a 24-hour infection control on-call service, the outbreak continued (52). Only when it was observed that urine culture had become the primary source of positive cultures and corrections were

made to catheter bag emptying techniques was the outbreak resolved (52). By the end of 2001, K. pneumoniae resistant to carbapenems had been found in 7 New York City hospitals and was believed to be spreading endemically (53).

In 2002-2003, 45% of K. pneumoniae in Brooklyn were resistant to extended-spectrum beta lactamase inhibitors, leaving carbapenems as the antibiotic of choice for their treatment (54). Among these, 3.3% were resistant to carbapenems (54). In October 2003, the gene causing carbapenem resistance in K. pneumoniae was found in a different species, Enterobacter cloacae, heightening concern about the spread of CRE (55). Subsequently, in 2003-4, two additional outbreaks occurred in New York City, both in Brooklyn. Thirty-two patients were found to have carbapenem-resistant K. pneumoniae in the first hospital and 27 in the second (54). Of these cases, 73% were believed to be nosocomial in origin (54). Among the 19 patients with bacteremia examined, 47% died (54). By late 2004, 24% of K. pneumoniae collected from Brooklyn hospitals was CRE (56).

In 2006, one hospital in Brooklyn implemented an intervention in the ICU to attempt to better control CRE, which was spreading despite the use of contact precautions for CRE carriers, daily environmental cleaning, infection control participation on weekday rounds, and rectal surveillance for other MDROs upon admission to the unit and then weekly (57). The intervention added to these infection control activities testing of the screening cultures for CRE, placement of the CRE antibiogram in the medical record, extensive decontamination of the ICU, cohorting patients with CRE to one end of the ICU, the addition of more, free-standing alcohol hand sanitizer dispensers, and meetings on environmental cleaning between infection control and nursing staff (57). Following this intervention, the rate of positive CRE clinical culture decreased from 9.7 to 3.7 per 1,000 patient-days (57). However, despite these gains, CRE prevalence continued to increase throughout the northeastern United States.

As it spread throughout the East Coast of the United States, CRE also began to be observed in clinical cultures abroad in countries including Israel and Greece, and CRE surveillance

was begun. As in the United States, KPC CRE was seen in Greece at least as early as 2001. Between 2001 and 2006, the proportion of K. pneumoniae resistant to imipenem in hospitals in the Greek System for the Surveillance of Antimicrobial Resistance (GSSAR) had risen from 1 to 20% and the fraction of hospitals with at least one CRE isolate was 62.5% by 2007 (58). During this time period, in 2002, Greece had the highest per capita consumption of hospital specific antibiotics (those rarely used in ambulatory care, including third-generation cephalosporins and carbapenems) in Europe (59).

In 2007, two cases of CRE were reported in Europe, both in patients who had been treated in Greece (60; 61). As a result, a study was conducted to examine whether strains of K. pneumoniae with the KPC gene conveying resistance to carbapenems was present throughout the country at hospitals participating in GSSAR (62). This study found that 77% of the 225 isolates received from hospitals belonged to one hyper-epidemic clonal strain, which was also the causative strain in the European patients whose illnesses triggered Greek CRE surveillance (62). A case-control study in Greece found that among patients with carbapenem-sensitive K. pneumoniae, use of fluoroquinolones and carbapenems were risk factors for developing CRE (63).

In 2006, multiple hospitals in Israel began reporting outbreaks of CRE. One hospital saw the percent of carbapenem-resistant K. pneumoniae isolates increase from less than half a percent in 2004 and 2005 to 3.1% of isolates in 2006 (64). Among those cases, 75% were clones, signaling a possible outbreak (64). The strain of K. pneumoniae implicated in the outbreak was later found to be closely related to strains collected during the NYC outbreak (65). Country-wide CRE rates rose from 1.8 cases per 100,000 patient days to 11.8 in the first half of 2006 and 27 by the second half (66). By early 2007, when the rate rose to 41.9 cases per 100,000 patient days, it became apparent that the outbreak had spread country-wide despite increased infection control efforts undertaken at local levels (66).

In order to combat this outbreak, the Israel Ministry of Health implemented a country-wide plan covering approximately 14,000 beds in acute care hospitals in March 2007 to attempt to control CRE (66). This approach mandated public health reporting of positive CRE cultures and isolation of CRE carriers (defined as those who had ever tested positive for CRE), which included self-contained nursing units with dedicated nursing staff who did not treat non-carrier patients. Beginning in May 2007, all hospitals submitted daily census reports confirming isolation precautions and dedicated nursing for each patient with CRE, and any deviations from guidelines were reviewed and responded to by the Ministry of Health. This aggressive approach using regional coordination reduced CRE rates from a peak of 55.5 cases per 100,000 patient days in March 2007 to 11.7 in May 2008 (66). Compliance with the control plan was nearly 100% for all components except dedicated nursing, for which each 10% increase in compliance was associated with a 0.6 case per 100,000 patient-days decrease in CRE rates (66).

In May 2008, two new components were added to the infection prevention plan, intervention in long term care facilities and active CRE surveillance in acute care hospitals (66). In post-acute care hospitals (PACH, equivalent to a U.S. LTACH) the intervention consisted of on-site assessments of facilities and scoring based on infection control measures, weekly CRE census reports which were reviewed along with daily reports from acute care hospitals, guidelines based on ward, including rectal screening upon patient entry to skilled nursing, long term ventilation, and subacute wards (67). Prevalence surveys were conducted to track progress and showed that CRE carriage rates decreased from 16.8% to 12.5% between 2008 and 2011 (67).

Meanwhile, in the United States, CRE spread across the country following the East to West progression commonly seen in MDROs. The next major outbreak occurred in Illinois. In May 2008, K. pneumoniae with CRE resistance caused by the same gene as that in the New York City outbreaks was identified in a Chicago hospital laboratory and additional cases

were subsequently identified throughout the region. Ultimately, the outbreak was traced to a single long term care facility in which an intervention was begun in July 2008 (68). The intervention included daily 2% chlorhexidine bathing for all patients, clarification of cleaning duties belonging to different types of staff to ensure that all surfaces would be cleaned, replacement of bedside curtains, testing of surveillance cultures for CRE, placement of patients with hemodialysis, tracheostomy, or MDRO carriage on contact precautions, and staff education (68). At the start of the intervention, point prevalence surveys showed that 21% of patients were CRE carriers, but after four months of the intervention, no patients had positive CRE screening cultures (68).

In Chicago, the major CRE outbreak resulted from the spread of CRE in long-term acute-care hospitals (LTACHs). LTACHs are defined by the Centers for Medicare and Medicaid Services as certified acute care hospitals which focus on patients who, on average, stay more than 25 days and who may have more than one serious condition, but who may improve with time and care, and return home (69). A 2015 modeling study showed that despite high prevalence of CRE in LTACHs in Chicago, when an intervention bundle including rectal screening cultures for CRE carriage, daily chlorhexidine bathing, and cohorting, transmission could be reduced sufficiently to prevent endemic spread (70). However, a study published the same year reporting the outcomes of a similar intervention in LTACHs found that while the bundle intervention resulted in significantly decreased rates of CRE acquisition, positive CRE clinical culture, CRE bacteremia, and all-cause bacteremia, CRE acquisition did not decline to zero (71). Instead, rates remained plateaued around 2 acquisitions of CRE per 100 patient-weeks (71).

Despite the relative success of these very aggressive interventions undertaken by individual facilities during outbreaks, CRE has continued to spread throughout the United States. By the end of 2010, KPC-producing CRE had been reported in 36 states, Washington, DC, and Puerto Rico (38). In recognition of the wide spread of CRE in the United States and its

epidemiologic importance, the CDC developed an interim surveillance definition for CRE in 2012 (72). In the first six months of 2012, according to data from the National Healthcare Safety Network, 3.9% of short-stay acute care hospitals and 17.8% of LTACHs reported HAI caused by CRE (73). CRE containment has proved similarly difficult abroad. Despite aggressive and resource-intensive measures coordinated at the national level, Israel has not succeeded in eliminating CRE, with the initial dramatic reductions in CRE prevalence eventually plateauing. Similar results were seen with the addition of PACHs to the Israeli intervention program, which initially resulted in further declines in CRE prevalence but these improvements also plateaued prior to elimination of CRE spread. In order to effectively contain CRE, new approaches considering factors at all levels of CRE epidemiology may be necessary.

1.5 The Burden of CRE

While CRE infections remain relatively rare in the United States, they pose a high burden of risk to patients. The mortality associated with CRE infections is significantly higher than infections caused by similar organisms which differ only in that they are susceptible to carbapenem antibiotics; for example when comparing imipenem-resistant Enterobacteriaceae with imipenem-sensitive strains, patients with clinical cultures of resistant strains were five times more likely to die than those with sensitive strains (74). In another study of hospitalized patients, patients who had a clinical microbiology culture positive for carbapenem-resistant strain of K. pneumoniae had 3.9 times the odds of dying as those with a culture for carbapenem-sensitive strains (75).

Compared to bloodstream infections caused by antibiotic-susceptible gram negative organisms, those caused by CRE result in higher mortality (50). A case-control study conducted at one Israeli hospital found that the crude mortality rate among patients with CRE blood-

stream infections was 71.9% and attributable mortality rate was 50% (76). The all-cause mortality in cases in which a patient has an invasive CRE infection is 50% (77).

CRE isolation, regardless of the presence of infection, has been associated with death in the hospital in 29-52% of cases (50). Because of this high mortality, the dearth of medications which can treat CRE, and the rapidity with which CRE spreads through health care facilities, the CDC has designated the threat posed by CRE infections as urgent, the highest level of antibiotic resistant microorganism threat (78). Understanding the spread of CRE is an important step in implementing appropriate infection prevention protocols to mitigate this threat.

1.6 A Social Ecological Model of MDRO Spread

While antibiotic resistance is clearly a product of antibiotic use, what McMichael calls a rare instance of human action actually increasing biodiversity (79), prescribing patterns alone cannot account for the rapid spread of MDROs. Transmission of MDROs between people, rather than de novo evolution of resistance, is the primary factor driving the spread of antibiotic resistant organisms. After promoting the evolution of MDROs through antibiotic use, humans disseminate MDROs as patients move from one hospital or nursing home to another, spreading pathogens to other patients either directly or indirectly through healthcare workers and fomites (80). This phenomenon of patient, and microbe, movement is referred to as inter-facility patient sharing and plays a key role in the transmission of MDRO pathogens. Because of its dependence on human activity, the spread of MDROs can be understood more fully through the use of social ecological models, which consider multiple levels of influence over the health of individuals.

Public health has long taken a social ecological approach to understand multifactorial causes of disease and disability in populations, and to develop effective, sustainable prevention strategies. Beginning with the early 19th century French public health movement, the discipline has emphasized the role of the environment in health, for example with the publication of French epidemiologist Louis-Ren Villerms On Mortality in the Different Sections of Paris, Demonstrating the Relation between Poverty and Disease in 1840. A re-analysis of Villerms data in 2011 showed that indeed, taxes and rent, measures of poverty at that time, were correlated mortality while crowding was not (81). Villerm further addressed social epidemiology by identifying prison type and detention conditions as key factors contributing to mortality among prison inmates and by studying sanitation in working-class work places and communities (81). In the same period, Virchow, now more often known within medicine for his contributions to pathology, conducted a study of typhus in Upper Silesia and concluded that poor governance, poverty, and illiteracy were to blame, leading him to go on to found the field of social medicine (82).

Despite this early social ecological orientation, medicine became increasingly individualistic in its focus as scientific research provided support for contagionism, as early formulations of the germ theory of disease were known, and political conservativism resisted the broader reforms called for by social medicine. Virchows own obstinate resistance to germ theory and disdain for the early work of Semmelweis, who demonstrated the importance of hand washing in the spread of contagious disease, and Koch, whose postulates established a scientific method for determining the causative organism in infectious diseases, further diminished the standing of social medicine (82). With the rise of germ theory, the focus in public health narrowed to emphasize the prevention of single-factor causes of infectious disease (83).

As science and politics evolved, the pendulum of popular opinion in public health swung between an emphasis on individual behaviors and on collective environments. By the 1970s, neoconservativism grew and, with it, an insistence on individualism and the free market as

solutions to health policy in the United States (84). Public health policy took an increasingly individualistic view of health, as exemplified by the Canadian 1974 Lalonde Report and 1979 U.S. Surgeon Generals Report, which placed strong emphasis on individual behaviors (85). Education and persuasion to bring about individual life-style changes were emphasized as public health interventions rather than collective action to change social settings or environment (86). Increasingly, voluntary risk-taking and lifestyle decisions were seen as the key factors determining health status, with suggestions that those who smoked, drove cars, or owned guns should pay increased taxes to compensate for the health effects of their choices (87).

The social ecological model of human behavior was first proposed by Urie Bronfenbrenner in 1974 as an alternative to the dominant model of individual-focused experimental laboratory research, which he argued had little relevance to human behavior in the world (88). Instead, he argued that the human environment, including the immediate situation of the subject and the larger formal and informal social contexts, should be considered when studying human behavior. The subjects ecological environment, then, was a nested arrangement of [social] structures, each contained within the next (88) Research settings then, could be considered ecologically valid if the environmental properties theorized by the researcher aligned with the environment as experienced by the subjects, and ecological experiments investigate the interaction between subject and environment by contrasting environmental systems (88).

Like developmental psychology of the time, early work in health promotion focused primarily on identifying individual risk factors and modifiable individual behaviors for intervention (85). However, increasingly there was recognition of the link between peoples health and their physical and social environments, leading a working group of the World Health Organization defining health promotion as a mediating strategy between people and their environments, synthesizing personal choice and social responsibility in health to create a healthier future in 1984 (89). In 1988, McLeroy and colleagues introduced a social ecological model of health

promotion and proposed that interventions in the field should target both the individual and the individuals social environmental factors (90), drawing from the work of Urie Bronfenbrenner. McLeroy noted that the individual and social environmental factors each affect one another through reciprocal causation, a key component of Bronfenbrenners theory (90). This interdependence and interaction occurs across all levels of the health concern. McLeroy identified these multiple levels of influence impacting a health concern as 1. Intrapersonal factors, 2. Interpersonal processes formed by the individuals social networks, family, friends, and co-workers, 3. Institutional factors such as the organizational characteristics of schools and healthcare facilities, 4. Community factors, the relationships among organizations, and 5. Public policy, consisting of laws and government policies (90). In examining the social ecology of MDRO spread, I will reference this formulation of Bronfenbrenners social ecology model.

As an example of a social ecological model within public health, McLeroy and colleagues pointed to the host-agent-environment model (90), which was popularized by Wade Hampton Frost in 1928 (91). Often, the environmental factors in the model are construed narrowly, for example, environmental factors described in a 2010 model of influenza transmission were limited to descriptors of the very immediate environment such as surface area to volume ratio and host density (92). However, by using a broader definition of the environment which includes the social, cultural, and economic environments of the host at multiple levels, it is possible to expand this model to examine the social ecology of infectious diseases. Mayer and Pizer define the social ecology of infectious diseases as, the scientific study of the ways by which human activities enable microbes to disseminate and evolve, creating favorable conditions for the diverse manifestations of communicable diseases (93).

In the studies described here, I will examine the interaction of the intra-personal patient (host) factors in the first level of the McLeroy model and institutional environmental factors in the third level. Below, I propose an ecological model of CRE epidemiology showing how

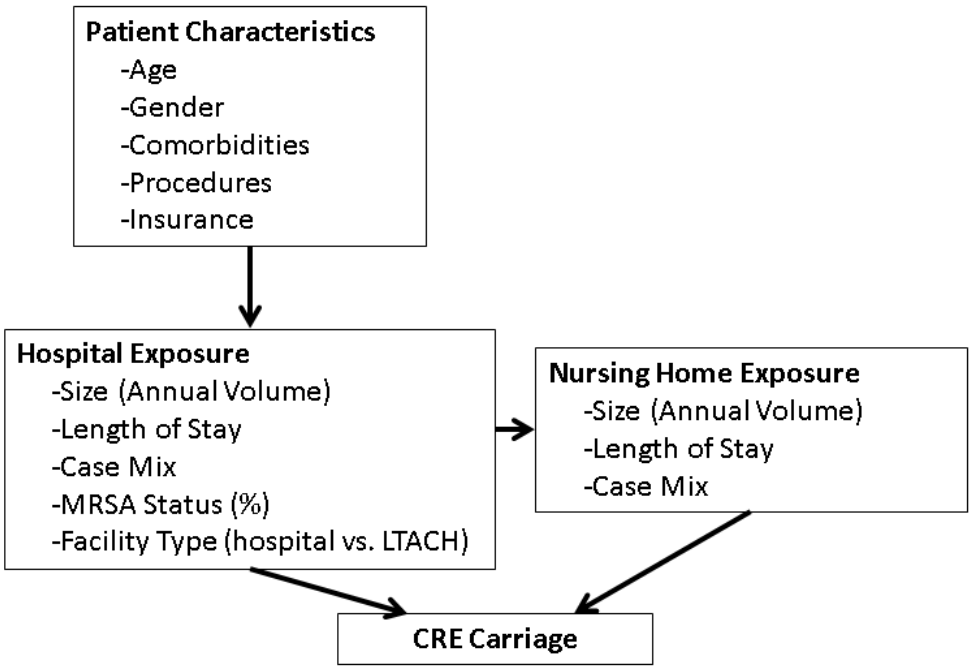


Figure 1.1: An Ecological Model of CRE Epidemiology

factors at three levels - the patient, the hospital, and the nursing home - interact throughout inter-facility patient sharing to influence individual patient carriage of MDROs (Figure 1.1). This multi-level ecological model shows the interplay of the patient, the hospital, and the nursing home characteristics resulting in MDRO carriage, in this example, during the emergence of CRE in California. Patients carrying CRE have high rates of hospitalization and nursing home residence, often moving back and forth between facilities via inter-facility transfer. This strong association between hospital and nursing home stays and CRE carriage makes understanding the role of key characteristics of these social environmental settings critical. A social ecological perspective of CRE epidemiology can improve targeting of interventions for CRE prevention and control.

1.7 Social Ecology of MDRO Spread: The Patient Level

For an infection to occur, there must be a host. Frosts epidemiologic triad named the host as the first factor in the spread of infectious disease, and intrapersonal factors lie at the inner-most nested level of social structures influencing health in McLeroys formulation of Bronfenbrenners social ecological model. To spread MDROs, infected or colonized patients must transmit their pathogens to other patients either directly or indirectly through health-care worker contact or fomites. At the patient level, the ecological model proposed above highlights patient age, gender, comorbidities, procedures, and insurance type as key characteristics related to hospitalization and CRE carriage status. Many of the intrapersonal characteristics in this model of CRE epidemiology have been implicated in prior studies of endemic MDROs.

Age plays a key role in patient health status. Due to increased life expectancy and decreased fertility, the United States population, much like that of other developed nations, is aging. Beginning in 2011, the baby boomers will enter old age as they turn 65 (94). While the percentage of the U.S. population over 65 is expected to increase 135% between 2000 and 2050, the percentage of the population over 85 is projected to make even greater gains, increasing by 350% (95). The increase in the oldest-old group over age 85 is of particular importance to public health, as these individuals typically require the most medical and long term care (94; 95). As the population ages, the percentage of the population with chronic disease is expected to rise, as will their need for healthcare (96). As these demographic and epidemiologic transitions occur, the aging population will have greater exposure to healthcare facilities, such as hospitals and nursing homes, and thus be exposed to higher risk of adverse medical events, such as colonization with healthcare-associated MDROs. Older patient age has been associated with a greater risk of HAI in studies of endemic MDROs (97).

Comorbidities and procedures to place invasive medical devices are also key factors in the spread of endemic MDROs. Invasive medical device use (98; 2; 99), including central catheters (100), urinary catheters, and ventilators, is also significantly associated with a higher risk of HAI. Other factors significantly associated with HAI were comorbidities (97; 101; 102), receipt of dialysis (100), and stay on critical care units (2; 98; 99). Greater antibiotic use also plays a role in HAI caused by MDROs (102), in terms of both number of types of antibiotics (100) and duration of use (97), presumably because antibiotics promote the growth of resistant organisms by eliminating competing organisms.

While these factors play a role in many HAI, the risk factors for CRE have not yet been well-characterized, in part due to limitations posed by the small number of cases in prior studies. One important factor for CRE spread is antibiotic use. A case-control study of patients with no prior history of CRE in whom CRE was detected upon screening found colonization with other MDROs and antibiotic exposure in the prior three months to be significant risk factors for CRE in multivariable analysis (103). In a study of CRE in an Israeli tertiary care hospital, poor functional status, ICU stay, and antibiotic receipt, especially receipt of fluoroquinolones, were found to be independent risk factors for being a CRE carrier (75). In the same study, 31% of cases were found to have previously received carbapenems compared to 0% of controls, meaning that use of these antibiotics was significantly associated with CRE carriage (75). In addition, comorbidities (104; 105) and medical devices have been linked to CRE carriage (106). Certain patient procedures performed in healthcare facilities, such as endoscopy, have been implicated in CRE outbreaks (107; 108; 109; 110). Further investigation of the intrapersonal level factors that contribute to CRE spread is necessary to better understand the interplay of these factors with those at the institutional level.

In addition to their direct effects on CRE risk, individual patient factors affect healthcare service utilization including hospitalization, that is, intrapersonal factors affect patient exposure to institutions and institutional level factors. Patient age, gender, comorbidities, and

insurance type all have been shown to be related to healthcare service utilization. Specifically, older people, women, and those with public only insurance coverage are disproportionately represented among high utilizers of health care (111), as are those with multiple comorbidities (112). Through their association with healthcare utilization, patient level factors also influence patient exposure to hospital and nursing home level risks; for example, they can affect the duration the patient stays in the hospital, the procedures and treatments the patient is exposed to during their hospitalization and even the type of hospital at which they stay.

1.8 Social Ecology of MDRO Spread: The Hospital Level

Because CRE is currently believed to be circulating primarily within healthcare institutions, factors at the institutional level of the social ecological model of infectious disease must be examined. At the hospital institutional level, the ecological model shown above identifies hospital-wide social environmental characteristics such as facility type, facility size, mean length of stay, case mix, and percent of patients with other multi-drug resistant organisms as altering a patients risk of acquiring CRE. Institutional level infection prevention techniques also play a key role in controlling the spread of MDROs.

Certain facility types have been shown to be key locations for transmission and spread of CRE. In particular, long term acute care hospitals (LTACHs) have been shown to be significantly more strongly associated with CRE carriage than short stay acute care hospitals. In 2009 in Israel, a country-wide study of post-acute care facilities found that skilled nursing wards (similar to U.S. LTACHs) were found to have a CRE carriage prevalence of 25.9% (103). In a study of 31 Chicago area hospitals between 2010 and 2011, the adjusted rela-

tive risk of colonization with carbapenem-resistant K. pneumoniae was 5.94 for patients in LTACHs compared with short stay hospitals (113). LTACHs were also found to be important in the epidemiology of CRE in Los Angeles County during 2010 and 2011 when the incidence rate for CRE was found to be 2.54 per 1,000 patient days in LTACHs and 0.31 per 1,000 patient days in short stay acute care hospitals (114). A CDC study of CRE central line associated blood stream infections and catheter associated urinary tract infections reported to the National Healthcare Safety Network found that a larger percentage of LTACHs than short stay acute care hospitals reported CRE during 2012 (73).

Mean facility length of stay and hospital size are key institutional factors in CRE epidemiology. In the Chicago study of carbapenem-resistant K. pneumoniae, LTACHs were found to longer lengths of stay suggesting that length of stay may be an institutional-level factor that impacts the risk of CRE carriage (113). The CDC study of CRE infections associated with medical devices also found that the fraction of hospitals reporting CRE increased with hospital size, with 17.4% of hospitals with 500 or more beds reporting CRE (73). Hospital volume has also been identified as a facility-level factor associated with healthcare associated C. difficile infection rates (115). This trend appears to hold across pathogen types, with larger hospital size associated with higher overall rates of HAI (2).

Case-mix, or the mixture of the complexity levels of patients clinical conditions and consequent resource use at a particular facility, also impacts the spread of MDROs. For example, hospitals associated with medical schools are often tertiary care facilities which care for patients with more severe conditions than community hospitals. A greater fraction of hospitals associated with medical schools reported CRE (9.5% versus 1.9% at hospitals not affiliated with a medical school (73). One intervention that increases complexity in patient care is mechanical ventilation. Mechanical ventilation was shown to occur at high rates in facilities implicated in carbapenem-resistant K. pneumoniae spread in Chicago (113). Similarly, in Israel, wards for patients requiring mechanical ventilation had a relatively high CRE preva-

lence of 11.9% (103). In a study of C. difficile in California, case mix was identified as a facility-level factor associated with infection rates (115).

Common elements of infection prevention programs associated with decreasing spread of MDROs and HAI include healthcare worker hand hygiene, other hospital cleaning and sanitation efforts, use of contact precautions, and isolation of patients with known infections. In the Israeli study of LTACHs, three institutional factors, alcohol-based hand sanitizer in patient rooms, proper glove use in standard precautions, and entry screening for CRE, were associated with lower risk of CRE carriage (67). A 2009 review of 24 hospital-based studies of hand hygiene conducted between 1977 and 2008 found that HAI decreased in 21/24 studies (116). In the 16 studies which evaluated the impact of hand hygiene campaigns, 15 found that hand washing increased (116). Environmental cleaning, particularly of high-touch surfaces near vulnerable patients has been shown to be effective for control of HAI, often when bundled with other infection control measures (117). Environmental contamination with MRSA and VRE has been shown to be decreased by increased disinfectant use, cleaning education, and feedback (118). Another study showed that environmental cleaning education reduced contamination of surfaces and healthcare worker hands with CRE and significantly decreased the risk of transmission of VRE between patients in an MICU where VRE was endemic (119). Significant decreases in infection incidence were also seen for C. difficile in two studies of bleach disinfection for hospital wards on which C. difficile was highly endemic (120; 121). Contact precautions, which require healthcare providers to don gowns and gloves when caring for designated patients, are an important barrier in preventing the spread of HAI. In a study of environmental and hand contamination from patients with VRE, when healthcare workers entered the rooms of patients with VRE, those who did not wear gloves contaminated their hands 37% of the time, versus 5% for those who wore gloves, a significant difference (122). Separating patients known to carry pathogens from patients without those pathogens is called isolation (123). Cohorting has been used as an isolation strategy in suc-

cessful interventions which limited the spread of CRE in Israel and Chicago. Together, these infection prevention policies can act as institutional factors limiting the spread of CRE.

In the 1990s, nursing homes continued to be identified as an important reservoir for antibiotic resistant bacteria entering hospitals. A study of hospitalized patients admitted over two years between 1990 and 1992 found that, among patients with ESBL-producing E. coli and K. pneumoniae, 64% were admitted from nursing homes and, among these, 89% carried EBSL-producing bacteria upon admission (124). This type of patient movement between facilities creates connections between hospital and nursing home factors contributing to CRE emergence. This inter-facility patient sharing can be thought of as occupying the fourth nested level of McLeroys social ecological model of health, community factors, or the relationships among institutions.

1.9 Social Ecology of MDRO Spread: The Nursing Home Level

As with hospitals, nursing home factors occupy the institutional level of the McLeroys model. Nursing homes and their characteristics play an important role in the epidemiology of MDRO emergence. Once resistant bacteria enter a nursing home, they often spread widely among other residents (125). One of the earliest studies reporting infection surveillance in nursing homes found that 12% of nursing home residents had an infection and that half of these were acquired after the resident was admitted to the facility (126).

The first published hospital outbreak of antibiotic resistant bacteria that was attributed to the spread of bacteria within nursing homes occurred with MRSA in 1969, raising the possibility that nursing homes served as an MDRO reservoir (127). A study of VRE colonization in a hospital and its affiliated nursing home found that while colonization rates increased

from 9% to 22% in the nursing home over one year, while levels of colonization in the hospital remained consistent over this period (128). In particular, long term and post-acute care facilities serve as important reservoirs of CRE, with one study showing more than half of CRE positive isolates coming from these facilities (129) and another showing a high rate of fecal carriage of CRE in long term care (50).

In the 1980s, a review of nursing home infection surveillance reported rates of infection between 3.4 and 6.7 infections/ 1000 patient (130) and in 2012 a national survey of nursing homes found that MRSA carrier prevalence was 4.04% with an infection prevalence of 0.71% (131). Antimicrobial use in nursing homes combined with inter-facility transfer between hospitals and nursing homes has created a reservoir of antimicrobial-resistant bacteria in nursing homes (132). Once antibiotic resistant bacteria arrive in nursing homes, many nursing home level factors affect the extent of MDRO spread.

The ecological model proposed above considers facility size, case mix, and length of stay as key characteristics affecting CRE carriage. The association of MDROs and facility size is shown by modeling studies demonstrating that small nursing homes with low resident turnover are most at risk for increasing MRSA prevalence levels once MRSA is introduced from patient transfer from a hospital (133). When MDROs are introduced into nursing homes via transfer of colonized or infected patients, and when exposure occurs through frequent contact between nursing home residents both directly and through staff, large MDRO burdens result in nursing homes (80). This effect is particularly strong in settings with low patient turn-over (134). Some types of diagnoses are more associated with outbreaks and transmission in nursing homes than others, suggesting that nursing home case mix also plays an important role. A study of infection prevalence in 7 nursing homes in 1981 found that rates of urinary and lower respiratory infection rates were similar to those reported from hospitals, but rates of skin infections, conjunctivitis, and diarrhea were higher and clustered, indicating that they were likely the result of outbreaks and potentially preventable (135).

Another study found that nursing home MRSA transmission was associated with the percent of patients with diabetes among all patients in the nursing home (134).

Infection control policies act at the nursing home institutional level as well as the hospital level to impact the spread of CRE. Isolation of patients with antibiotic resistant infections in private rooms can help control infections in nursing homes, but not all nursing homes have such facilities available (136). CRE screening policy, decreased prevalence of CRE in facility, and not sharing a room with a known carrier decreased risk of CRE carriage in a study of long term care facilities (103). In a study which screened patients in Israel in 2009, 2/3 of patients screening positive for CRE had no known history of CRE carriage (103), indicating that screening can help identify patients who should be placed in contact precautions.

Policies and characteristics at the level of institutions such as nursing homes and hospitals can greatly affect patients risk of being exposed to and subsequently becoming carriers of MDROs such as CRE. At the community level, policies and characteristics of institutions affect other institutions within the region. However, studies in one large county have shown that more than 90% of patient sharing occurs indirectly, limiting communication between facilities about patients MDRO status and thus their ability to create consistent infection control policies (137). Inter-facility patient sharing must be considered in order to understand the interaction of patient, institution, and community level factors in the epidemiology of CRE emergence.

1.10 Social Ecology of MDRO Spread: Inter-facility Patient Sharing

Once patients acquire MDROs, they spread these pathogens to other patients as they move via inter-facility patient sharing, which represents a community level factor contributing to

CRE emergence. In the United States, where private decision making has long been prized in health policy (84) to the extent that patient choice has been shown to increase patient satisfaction within HMOs, independent of the satisfaction ratings of individual physicians chosen (138). This high cultural value placed on free choice of provider drives inter-facility patient sharing in the United States, in contrast with the United Kingdom and the Netherlands, where the majority of patients visit their local provider despite newer choice options. Many factors affect patient choices of providers and movement between institutions via inter-facility patient sharing. Cost plays a major role in patient choice of hospital, with the probability of a patient choosing a particular hospital declining with increasing costs (139).Quality, wait times, gate-keeping, facility location, and patient mobility are all believed to affect patient choice of healthcare providers when costs are fixed (140) .

When patients with MDROs arrive in healthcare facilities, they increase the facilitys colonization pressure, or the prevalence of patients with MDROs. Because patients with HAI often have functional disabilities (141; 142) or are bedridden (99; 143), they require high levels of nursing care (142; 144) and often have longer lengths of hospital stay (97; 102). After interacting with patients harboring MDROs, healthcare workers unknowingly spread these pathogens to other patients. This is likely why, in healthcare facilities, colonization pressure is a risk factor for MDRO spread (145). As a result, previous patient exposure to healthcare facilities whether through hospitalization (146; 147; 144) or nursing home residency (143) is associated with higher risk of HAI.

Inter-facility patient sharing in the regional healthcare community constitutes a major and material connection among the three levels of analysis in this model and plays an important role in transmission of emerging pathogens, particularly those which are healthcare associated (148). A study of direct inter-hospital Medicare patient transfers between ICUs in 2005 found that patient sharing among U.S. hospitals meant that 65% of the 3,306 hospitals accepting Medicare could receive pathogens from any starting hospital (149). Depending

on the transmissibility of the pathogen, modeling performed in this study showed that the median time for spread between any two hospitals in the country was 3 years for a highly infectious pathogen (149). Within one county, modeling has shown that an outbreak from one hospital will have the majority of its effect on hospitals county-wide within six months (150). In countries where hospitals share more patients diseases can spread more quickly and the odds that an emerging organism will stop spreading without intervention is lower (151).

Empirical studies strengthen the case for the importance of inter-facility patient sharing in increasing patients exposure to pathogens demonstrated by modeling. Firstly, such studies show that patient sharing is common. Prior research regarding endemic MDROs has shown that patient sharing among hospitals and nursing homes is extensive (152). In one study, among the 29% of patients who were admitted to a hospital more than once in a year have been shown to move to a different hospital for the subsequent admission 75% of the time, with 90% of inter-hospital patient sharing occurring indirectly, i.e. the patient was not directly transferred from the first hospital to the second (153). Further, when hospitalized Medicare patients are discharged from the hospital to skilled nursing facilities, more than 20% were re-hospitalized within 30 days (154). Secondly, patient-sharing does result in pathogen-sharing. Inter-facility patient sharing has been shown to allow endemic MDROs to spread across California (155). Empirical study of nosocomial bacteria strains (MRSA) throughout healthcare facilities in one large county demonstrated that greater inter-hospital patient sharing is associated with greater genetic similarity between strains (156).

When very ill patients enter hospitals from nursing homes, they can bring with them CRE infections which are spread to other patients, causing hospital outbreaks (157). From hospitals, these outbreaks of CRE can then spread when patients carrying the organism are discharged to nursing homes (158). In order to stop the spread of dangerous pathogens such as CRE, it is critical to examine how they spread during their first emergence within a

region. However, while free choice of provider and a lack of a centralized payer for healthcare drives inter-facility patient sharing in the United States, it also makes patient sharing difficult to track. Unlike countries such as the U.K and the Netherlands, where patient referral information is readily available for research (151), tracking inter-facility patient transfer in the United States requires piecing together data from multiple databases from different sources. While the divided healthcare system drives inter-facility patient transfer and may contribute to the spread of MDROs, it also makes these areas more difficult to study. Using data from two large databases and seven hospitals to track inter-facility patient transfer, this study examined CRE emergence in California guided by an ecological model with the aim of identifying key sites for intervention at the patient, hospital, and nursing home levels.

Chapter 2

Research Objectives

In order to address the public health concern of CRE, this project examined containment targets guided by a multi-level ecological model of CRE epidemiology. This model is designed to investigate interplay of the patient, the hospital, and the nursing home characteristics resulting in pathogen carriage during the emergence of CRE in California. Specifically, I evaluated the practice of patient sharing, taking into consideration patient characteristics, including demographics, comorbidities, and insurance, and healthcare institution characteristics, including facility type, size, and mean length of stay of patients. By examining factors at multiple levels of influence in the epidemiology of CRE emergence in California, this project sough to identify key leverage points for preventing the spread of CRE in newly emerging settings through describing CRE epidemiology and exposure characteristics at one tertiary care hospital; performance of case-control and cohort studies to identify factors at the patient and institutional levels; testing generalizability by expanding the analyses to all UC hospitals; testing the relevance of CDC-mandated changes in CRE surveillance definition; and finally, testing the efficacy of contact precaution policies at healthcare facilities.

Chapter 3

Specific Aims

3.1 Aim 1: CRE Risk Factors and Healthcare Facility Exposure of CRE Carriers at an Academic Medical Center

3.1.1 Introduction

This section focuses on assessment of risk factors for CRE carriage by comparing CRE+ and CRE- patients in order to identify population targets for containing this pathogen, and, second, quantitative evaluation of the spread of CRE as patients harboring CRE move via inter-facility patient sharing between hospitals and nursing homes within a region.

Because inter-facility patient sharing plays such a major role in the spread of MDROs, infectious disease surveillance is important for understanding their social ecology. While factors involved the spread of endemic MDROs have been described extensively in the literature, the ecology of emerging MDROs such as CRE is poorly understood.

Given the high morbidity associated with ESBLs and CRE, the speed of their spread is concerning. Between 2001, when the first case of CRE was identified in the United States, and 2010, the number of HAI caused by CRE increased to 9,000 per year (78). In 2006, carbapenem resistance in Enterobacteriaceae was still rare in the United States (78). However, now CRE infections have been reported in 44 states (78). During 2009-2010, only about 71% of Klebsiella spp., 66% of E. coli, and 73% of Enterobacter spp. reported to the NHSN were tested for resistance to carbapenems (11). Of those that were tested, 12% of Klebsiella spp., 2% of E. coli, and 4% of Enterobacter spp. were resistant to carbapenems (11). To decrease the rate of CRE, surveillance in regions in which it is still emerging is necessary to both quantify the current prevalence of CRE and identify targets for intervention.

One region where CRE is currently emerging is California, where it was first identified in 2010. As an example of CRE emergence in California, data from Gohil et al. show that CRE presents a growing problem within Orange County, CA, with the number of new cases increasing rapidly. Prior to 2012, the data from Gohil et al. show that no hospital had more than ten newly positive CRE patients per year, but by 2013, two hospitals had identified more than 30 each (159). However, while this survey of clinical culture results in one large county found a rapidly increasing prevalence of CRE, cases were concentrated in a few facilities, suggesting that it is still possible to prevent establishment of endemic CRE (160).

While CRE colonization and infection incidence appear to be growing within California, most CRE cases identified in the Orange County hospitals are found within two days of hospital admission, meaning that transmission likely did not occur in the diagnosing hospital (159). Because of their timing, these CRE cases are designated as community-onset, but researchers believe that these cases are still likely to be healthcare-associated from transmission within nursing homes (161). The current project hopes to illuminate the degree of prior healthcare exposure among these cases during the epidemic phase of an emerging pathogen in a large region.

Given the uncertainty about how CRE spreads between healthcare facilities so rapidly and its mortality rates of up to 50% (76; 77), CRE is alarming to public health officials and the general public (162). Despite this concern, CRE emergence is poorly understood and few proactive infection control interventions have been implemented to prevent CRE from gaining a foothold in non-endemic areas. This is because hospitals, nursing homes, and public health departments most commonly wait until an emerging MDRO such as CRE becomes an overt problem (e.g. widely endemic or producing outbreaks) before taking action to reduce transmission. The current reactive responses to MDRO emergence avoid taking costly measures to prevent infections which only affect small numbers of patients at a particular point in time. However, such delays allow for dangerous pathogens like CRE to take root within communities and become difficult to eradicate or even control.

The studies under Aim-1 evaluate empirical support for a paradigm shift to a more proactive response by quantifying CRE burden and evaluating exposure pathways. If successful in identifying targeted opportunities for early prevention, the results would strengthen the argument for early intervention, with the goal of containing CRE before it becomes endemic. According to the CDC, an early, coordinated approach may be needed with facilities working together to prevent patient infection and prevent the spread of deadly MDROs such as CRE (163). If identified and undertaken, appropriate containment strategies as part of a coordinated response could prevent an estimated 74% of CRE infections in the next five years (163).

The study of exposure pathways described here is grounded in an ecological framework to examine factors at the patient, or intrapersonal, and institutional, nursing home and hospital, levels. This study identified specific types of facilities and patients at high risk for CRE exposure and acquisition. Identification of risk factors at the intrapersonal and institutional levels highlights key targets for intervention in order to maximize the impact of limited infection prevention resources are available for preventing an emerging pathogen.

Given that the CDC is actively looking to re-evaluate its CRE toolkit recommendations, the results presented in this chapter can provide guidance for a more pragmatic approach to CRE containment. For example, identification of facilities at high risk of CRE could allow the CDC to recommend that only these facilities screen their patients or that only high risk patients be screened for CRE, making the recommendation more feasible for and more acceptable to healthcare facilities. If CRE exposure is concentrated in select high risk facilities, then focused early intervention efforts for CRE may become more feasible and provide insight into activities that can benefit health departments and healthcare facilities when faced with other novel emerging MDROs in the future. Thus, the theoretical findings of this chapter also have direct pragmatic applications in MDRO containment.

3.1.2 Hypotheses

1. Prior healthcare facility exposure, particularly in nursing homes, will be strongly associated with a patient being a CRE carrier. This hypothesis is based on prior studies, described in the introduction, which showed that long term care facilities were major drivers of CRE spread in Chicago and Israel.

2. The small number of individual CRE cases in California access multiple healthcare facilities, resulting in substantial exposure and risk of spreading CRE in this region. This hypothesis is based on prior studies of patient sharing in Southern California among patients with MRSA and other MDROs.

3. CRE carriage will be strongly associated with future nursing home exposure days. This hypothesis is based on prior studies showing that patients with endemic MDROs have a high degree of healthcare facility exposure.

3.1.3 Materials and Methods

CRE Epidemiology and Factors Associated with CRE Carriage

For Aim 1 Question 1, I conducted two case control studies to identify predictors of CRE carriage. The study population was all patients admitted to UC Irvine Medical Center (UCIMC) between January 1, 2010 and December 31, 2013. Cases were defined as patients with a positive CRE culture (inpatient or outpatient) and at least one inpatient admission at UCI Medical Center between January 1, 2010 and December 31, 2013. Positive CRE cultures and their associated index admissions were identified as the admission which contained, or was closest to, the date that a patient had a microbiology culture testing positive for CRE according to the CDC 2015 surveillance definition: Enterobacteriaceae which are found to be resistant to imipenem, meropenem, doripenem, or ertapenem by standard susceptibility testing methods (i.e., minimum inhibitory concentrations of 4 mcg/mL for doripenem, imipenem and meropenem or 2 mcg/mL for ertapenem). Three date-matched controls were selected for each case by choosing the three admissions immediately following the case admission. Three comorbidity-matched controls were selected for each case and were patients with admissions with the same total Elixhauser Comorbidity Index (164) and major diagnostic category of the primary diagnosis as cases.

CRE Exposure due to Inter-facility Patient Sharing

For Aim 1 Question 2, in order to describe the CRE exposure to healthcare facilities caused by their movement, I conducted a descriptive cohort study to identify the frequency of healthcare exposure days one year before and after the date of known CRE carriage. The study population was all patients admitted to UC Irvine Medical Center (UCIMC) between January 1, 2010 and December 31, 2013 who were known to be CRE carriers. The only

patient exclusion criterion was lack of a unique patient identifier which would preclude them from being linked into the California Hospital Discharge Database for assessment of addition healthcare utilization. The identifier is missing from the database in cases in which the patient did not have a social security number. Follow up time was truncated if patients died prior to one year of follow up.

Factors Associated with Healthcare Facility Exposure

For Aim 1 Question 3, I conducted a case cohort study to identify predictors of the frequency of healthcare exposure days one year after the date of first known CRE carriage. The base study population was all patients admitted to UC Irvine Medical Center (UCIMC) between January 1, 2010 and December 31, 2013. In this population, I evaluated healthcare utilization in hospitals and nursing homes for 365 days beyond hospital, or through December 31, 2013 (end of dataset), whichever came first. Cases were defined as patients with a positive CRE culture (inpatient or outpatient) and at least one inpatient admission at UCI Medical Center between January 1, 2010 and December 31, 2013. Positive CRE cultures and their associated index admissions were identified as the admission which contained, or was closest to, the date that a patient had a microbiology culture testing positive for CRE according to the CDC 2015 surveillance definition: Enterobacteriaceae which are found to be resistant to imipenem, meropenem, doripenem, or ertapenem by standard susceptibility testing methods (i.e., minimum inhibitory concentrations of 4 mcg/mL for doripenem, imipenem and meropenem or 2 mcg/mL for ertapenem). The full UCIMC cohort was comprised of all index admissions of patients with unique database identifiers admitted to UCIMC between 2010 and 2013. Control patients could be represented in the cohort more than once, provided that each subsequent admission was at least 365 days after the discharge from the prior admission included in the cohort. Similarly, case patients could serve as controls in the

cohort as long as they had an admission at least 365 days prior to their first positive CRE culture.

Data Sources

In order to identify healthcare facility exposure days for patients with and without CRE carriage, I had to link three data sets. These were: (1) line list of UCIMC patients with CRE identified in a microbiology laboratory cultures according to the 2015 CDC surveillance definition, (2) a line item hospitalization dataset from all hospitals in California, and (3) a line item nursing home dataset from all nursing homes in California who receive any Medicare/Medicaid funding (essentially all nursing homes). Each of these datasets has patients identified by a different unique patient study ID; thus programming logic was needed to link study IDs across all three datasets.

Data for CRE carrier case patients were obtained from UCIMCs Clinical Microbiology Laboratory and from the Epidemiology and Infection Prevention program and included the following data elements: CRE and other MDRO test dates and results, microbiologic data including date of culture, antimicrobial sensitivity testing, plus the patients medical record number, gender, birthdate, and admission and discharge dates from all UCIMC hospitalizations within the defined study period. Similarly, gender, birthdate, admission and discharge dates are also available from the hospitalization and nursing home datasets.

Line item hospitalization data from California was obtained from the Office of Statewide Health Planning and Development and referred to as the Hospitalization dataset. Use of this dataset was approved by the University of California, Irvine Institutional Review Board (UCI IRB) and the California Health and Human Services Agencys Committee for the Protection of Human Subjects (CPHS). The OSHPD dataset identified each patient with a unique, irreversibly encrypted identifier and, for each inpatient admission in the state, in-

cluded patient level information such as hospitalization dates, demographic information, birth date, ICD-9 diagnostic and procedure codes, and location category before and after hospital admission (e.g., home, rehabilitation center, nursing home, assisted living facility, jail, homeless).

The UCIMC laboratory and Hospitalization data set was also linked with nursing home data for the study population. The Centers for Medicare and Medicaid Services (CMS) Research Data Assistance Center provides line item nursing home data for all residents residing in nursing homes that receive any CMS reimbursement. This dataset will be referred to as the Nursing Home dataset, which was used under a data use agreement with Centers for Medicare and Medicaid Services with approval from the UCI IRB. The nursing home dataset included information from each nursing home visit in the state, such as gender, birth date, admission and discharge dates, demographic information, residential zip code, ICD-9 diagnostic and procedure codes, antibiotic use, activities of daily living, and other descriptors of social interaction and mobility.

Algorithmic Linking Methods

While the hospitalization and nursing home datasets each have unique patient identifiers to allow tracking of patients within hospitals or within nursing homes, I needed to link the two datasets to identify CRE carriers in the nursing home data set and to track patients as they moved between hospitals and nursing homes. Without this linkage, it would not have been possible to find the nursing home patient identifiers for CRE carriers or to detect direct transfers from hospitals to nursing homes or vice versa.

A similar dataset linking methodology for the study of exposure to multiple healthcare facilities was successfully used by Datta et al. to examine exposure from inter-facility patient sharing of patients harboring endemic pathogens which cause HAI (111). In their method-

ology, matches between hospital and nursing home identifiers were assigned when a patient with the same date of birth and gender had a hospital discharge date within seven days of a hospital admission. In their study population, 85% of patients who were recorded in the hospital dataset as being discharged to a nursing home were successfully matched to a nursing home admission in the nursing home dataset (113). While this method of matching has good sensitivity, it is not necessarily specific and can result in multiple matches, in which one hospital identifier is matched to more than one nursing home identifier. These multiple matches were previously resolved for hospitalized cases by manually assessing whether co-morbidities listed for the potential nursing home match were consistent with those given for the patient in the hospital dataset.

Modifications to the linking method of Datta et al. were necessary for this study because manual review to resolve multiple matches was not feasible for the more than 35,000 patients in the studies described here. Because manual review was not used to assess the quality of hospital-nursing home identifier pairs, an algorithm was created to broadly identify all possible matching identifier pairs, assign them an initial rank score, eliminate implausible matches, and finally choose the best match.

Identifying Putative Identifier Pair Matches and Assigning the Initial Match Score

In order to track patient healthcare utilization and movement between facilities over the study period, it was necessary to link each patient identifier from the hospital dataset with the corresponding identifier for the same patient in the nursing home dataset. A linking algorithm was used to test several putative identifier pair matches to find the correct matching pair of corresponding identifiers. While Datta et al. selected putative matches only among patients with a transfer from a hospital to a nursing home, in the updated version, initial putative matches were found by matching on at least one potential transfer in either

direction. The transfer could occur in either direction, either a hospital discharge date with a nursing home admission date within seven days or a nursing home discharge date with a hospital admission date within seven days.

I used gender, birthdate, and facility admission and discharge dates to perform the initial putative linkage. For example, a patient who left a hospital would be matched to a resident with the same gender, date of birth and nursing home admission date within seven days of the hospital discharge. The rationale for the 7 day gap is that patients might not have moved directly between hospitals and nursing homes upon hospital discharge. For example, a patient with high care needs might have attempted to return home initially but their caregivers soon realized that the level of care needed was beyond what could be provided at home and the patient instead went to a nursing home.

Once putative matches (hospital-nursing home patient identifier pairs) were identified, a match score was assigned for each pair. The match score was the number of potential transfers identified based on admission and discharge dates. While Datta et al. considered any putative pair with at least one match, this algorithm counted how many times each pair matched. For example, a putative identifier pair consisting of one hospital discharge followed closely by a nursing home admission was given a match score of 1, while a hospital discharge followed closely by a nursing home admission and then a discharge from the nursing home followed closely by a hospital admission with the original hospital identifier was given a match score of 2. This scoring scheme was based on the assumption that a putative match identifiers linked by larger numbers of potential transfers were less likely to be spurious than a pair linked by only one transfer, and, thus, more likely to truly represent the same patient.

Although this initial match score was able to rank and thus automatically resolve most multiple matches, occasionally, often in cases where a hospital identifier had multiple putative nursing home identifier matches based on only one transfer each, there were ties that could not be resolved by the match score alone. In these cases, a date difference score was used to

resolve ties. The date difference score was calculated by counting the sum of the number of days between the discharge and admission dates for every transfer identified for the putative match. This was based on the assumption that, all else being equal, fewer days of difference in between a discharge and admission was mostly likely to represent a true transfer of the same patient and thus a true match. For example, a putative pair is more likely to be a true match when a hospital discharge and nursing home admission occur on the same day, rather than seven days later. Initial matching and calculation of match scores and date difference scores were performed using the statistical analytic software suite SAS 9.3.

To evaluate the algorithm iteratively as new versions were created, difficult test cases were selected and manually reviewed to determine the correct hospital-nursing home identifier pair matches. Difficult test cases were those in which a hospital identifier had a large number of possible nursing home matches; typically these were patients with common dates of birth and frequent hospitalization. At each phase, the algorithms assigned matches were compared against the manually assigned goal standard matches and any failures were reviewed to identify areas for improvement of the algorithm. Ultimately, the algorithm was able to automatically eliminate multiple matches and perform as well as manual review on test cases, eliminating the need for manually resolution of multiple matches.

Match Scoring Challenges and Eliminating Double Counting

Once the match score algorithm was created, testing was performed to validate the identifier pair matches assigned. While the matching score and date difference tie-breaker score successfully identified most matched pairs correctly, review of cases in which the algorithm selected the incorrect match for difficult test cases showed that anomalies occasionally occurred in calculation of the match score, resulting in an inflating match score. Further investigation showed that this inflation arose when a patient had numerous very short hospitalizations and nursing home stays during a short time period. In these cases, the algorithm

would increment the match score for all admissions within seven days of discharge, rather than just the nearest one. Thus, one discharge could result in multiple putative transfers and thus gain multiple match score points for a putative pair.

To eliminate this double-counting, it was necessary to track which discharges had already contributed to the match score by identification of a putative transfer. Additionally, to ensure that the nearest possible admission to each discharge was selected as the putative transfer, the date difference for each possible admission discharge pair had to be minimized. Thus, the algorithm was modified so that every time a putative discharge-admission transfer was identified, a check was performed to see whether a putative transfer had already been identified using that discharge date. If it had not been previously used, the match score was incremented and the difference between the admission and discharge dates was added to the total date difference score. If the discharge date had previously been used, the date difference score of the previous putative transfer and the current one were compared. If the date difference score of the previous putative transfer was lower, the algorithm would not count the current putative transfer and would move on. If the date difference score of the previous putative transfer was higher, the algorithm would not change the match score (since a point had already been added for the discharge being used), but it would subtract the date difference score of the previous putative transfer from the total date difference score for the identifier pair and add the lower date difference score of the current putative transfer instead.

While these changes increased the complexity of the matching algorithm, they ensured that the match scores were accurate and that the date difference scores reflected transfers with the fewest days between admission and discharge. As before, match scores and date difference scores were calculated using SAS 9.3, and the algorithms assigned matches were validated against manually evaluated matches.

Eliminating Implausible Matches and Choosing the Best Match

Allowing transfers to be identified within a seven day range increased sensitivity by ensuring that a larger fraction of the true hospital-nursing home identifier pairs could be identified. It allowed for capture of linkages in cases in which a patient leaving a hospital initially went home before moving to nursing care and in cases where there were slight discrepancies between hospital and nursing home records. However, the cost of this increased sensitivity was decreased specificity caused by an increase in spurious matches.

Review of test cases showed that the initial match score alone was not sufficient to exclude these matches which appeared spurious on manual review due to a high degree of overlap between hospital and nursing home visits. The algorithm was modified to eliminate putative matches with a high degree of overlap and modify the match score of putative matches with smaller degrees of overlap to allow for more accurate ranking. All potential matches in which the overlap between hospital and nursing home stays exceeded 20% of the possible overlap time were eliminated. This cut-off was selected based on empirical testing which showed that this successfully segregated pairs manually determined to be true matches from those deemed spurious and was verified on a second set of test cases. The match score for each remaining potential pair was pro-rated to account for overlap by multiplying the match score by (1-overlap %). Because of the limitations of SAS, days of overlap and total possible overlap were calculated using Python 3.4, a programming language often used in scientific research and commercial software development.

Finally, potential pairs were ranked on their match score, with ties broken by date difference scores, selecting the pairs with the most putative transitions in which the transitions had the fewest days between discharge from one facility and admission to another. Ranking was performed using SAS 9.3, and the results were compared against manual review of matches as described previously. Ultimately, the algorithm was able to automatically eliminate mul-

tiple matches via this ranking system and perform as well as manual review on test cases, eliminating the need for manually resolution of multiple matches.

Once the best match was selected for a particular hospital identifier, the unique nursing home identifiers allowed for selection of all nursing home visits for the matching patient during the study period. This final linkage of the hospitalization and nursing home identifiers allowed all hospitalizations and nursing home visits for that linked identifier pair within the hospital and nursing home datasets to be assigned to one patient.

3.1.4 Data Analyses and Outcomes

CRE Epidemiology and Factors Associated with CRE Carriage

In order to answer question 1, I sought to examine the risk factors associated with the outcome of CRE carriage. When evaluating variables associated with CRE carriage for Aim 1 Question 3, I considered the following variables: age, gender, race, insurance type, CMS major diagnostic category of the primary diagnosis, surgical procedures during the index visit, length of stay for the index visit, and Elixhauser comorbidity classifications. Surgical procedures were classified using the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Projects Clinical Classifications Software (165). For categorical variables I used chi squared tests, and for continuous variables, I used logistic regression to evaluate factors described above as independent variables for association with CRE carriage, and independent variables meeting a cutoff of p 0.1 were advanced to the final model. Logistic regression was performed using SAS 9.3 to test the association between the dependent variable (outcome) of CRE carriage and independent variables, including age at admission, sex, race, ethnicity, insurance type, length of stay in the admission in which the patient tests positive for CRE, prior healthcare exposure, CMS MDC of the primary diagnosis, comorbidities, and whether the patient had a surgical procedure.

CRE Exposure due to Inter-facility Patient Sharing

To evaluate the outcome of CRE spread from CRE carriers from one academic medical center in terms of patient days of exposure, number of hospitals and nursing homes exposed, and number of counties exposed, the exposure due to CRE carriers in healthcare facilities across a region was calculated with the number of days a patient is in healthcare facilities following their first positive CRE culture as the numerator and the days of follow up until the patients death or the end of the dataset. Following dataset linkages as described above, the movement of patients known to harbor CRE pathogens from an academic medical center to regional healthcare facilities and counties throughout California was evaluated to quantify the burden of CRE emergence. For Aim 1 Question 2, descriptive statistics were used to assess the number of hospitals and nursing homes in which UCIMC CRE carrier patients stayed and their lengths of stay, stratifying exposures prior to and following the index visit (the visit in which each case patient had their first positive CRE culture). The extent of CRE spread was also examined at the county level.

In order to better understand the types of healthcare facilities visited by CRE carriers, facility characteristics for hospitals and nursing homes with CRE exposure were described, including facility type (short stay acute care hospital, long-term acute care hospitals, which are the facility type implicated in outbreaks in areas of endemic CRE spread, nursing home), facility size and average LOS, and measures of facility case mix (% of common comorbidities, % with major surgery). For each discharged patient, all hospital admissions and nursing home stays in any California healthcare facility for one year prior to and one year following the patients initial positive CRE culture were assessed. Healthcare exposure days were assessed according to a patients CRE status.

CRE Epidemiology and Factors Associated with Healthcare Facility Exposure

To evaluate the modifiable and non-modifiable risk factors associated with healthcare facility exposure, I examined the association between the outcome of post-discharge days spent in healthcare facilities and intra-personal level and institutional level characteristics. When evaluating variables associated with future healthcare exposure days in hospitals and nursing homes following index admission for Aim 1 Question 3, I compared the fraction of patients with each characteristic using t-tests for binary variables and the fractions of the patients in each category using ANOVA testing for categorical variables. I tested for associations between the outcome of post-discharge healthcare facility exposure and continuous independent variables described above using simple linear regression. Independent variables meeting a cutoff of p 0.1 were advanced to the final model. Poisson regression was performed using SAS 9.3 to test the association between the dependent variable (outcome) of post-discharge days per day of follow up spent in healthcare facilities and independent variables, including whether the patient was a CRE carrier, age at admission, sex, race, ethnicity, insurance type, primary diagnosis, surgery, prior healthcare exposure stratified by facility type, length of stay, and comorbidity score.

3.1.5 Results

CRE Epidemiology and Factors Associated with CRE Carriage

UCI had 13,977 admissions per year during the study period for patients with valid unique identifiers. Of these UCI patients with identifiers, 4.5% were children and 95.5% were adults. Prior work has shown that in the hospital admissions database used, 75% of hospitalizations in Orange County, where UCI is located, had valid unique identifiers, or record linking numbers (166). The majority of admissions without record linking numbers were for children,

with 63% of such admissions being for infants under 6 months of age; among admissions of adults, 92% had record linking numbers (166).

Among all patients admitted to UCIMC between January 1, 2010 and December 31, 2013, 74 patients were determined to be CRE carriers based on microbiology laboratory results interpreted using the 2015 CDC definition for CRE. Of these patients, 61 had valid unique identifiers in the OSHPD data and were examined in the remaining analysis. Of the 13 patients without identifiers 62% were female, 69% were white, 54% were Hispanic, and 31% had private insurance coverage. The mean age of these patients without identifiers was 46 years old.

The 61 cases with identifiers were identified as cases for the case-control studies. Comparative statistics were calculated for factors at patient level among CRE carriers along with their admission date-matched, non-CRE carrier controls (the 3 non-CRE carriers admitted immediately after the CRE carrier) and comorbidity-matched controls for comparison (Table 3.1). Compared to date-matched controls, CRE cases had higher mean age and number of comorbid conditions (Elixhauser Comorbidity Index). They were more likely to be female, black, and insured by Medicare. CRE cases were more likely to have a primary diagnosis classified as infectious, respiratory, or renal/urinary and to have undergone a surgical procedure, especially those on the respiratory or musculoskeletal systems. Of the 61 case patients with identifiers, 19 died within 365 days of discharge from their index admission, a mortality rate of 31%.

Table 3.1: Characteristics of Inpatients by CRE Status, California 2010-13

Characteristic	CRE +	Date matched Controls	Comorbidity matched Controls
Age (mean (SD))	63 (17)	50 (21)	60 (18)
Female gender	52%	48%	49%

Race			
White	67%	74%	72%
Asian	16%	13%	15%
Black	5%	2%	1%
Other	11%	10%	9%
Hispanic ethnicity	23%	28%	31%
Insurance type			
Medicare	51%	35%	40%
Medicaid	20%	24%	23%
Private	18%	27%	15%
Indigent Programs	3%	9%	14%
Self Pay	3%	3%	4%
All Other	5%	3%	4%
Length of Stay (mean (sd))	29 (34)	9 (15)	12 (22)
Primary diagnosis type			
Infectious	23%	1%	24%
Respiratory	13%	5%	14%
Renal/Urinary	11%	4%	12%
Circulatory	8%	11%	8%
Hepatobiliary	8%	3%	8%
Burns	7%	2%	5%
Nervous	5%	14%	5%
Digestive	5%	13%	5%
Trauma	5%	3%	5%
Musculoskeletal	3%	5%	2%
Other	11%	38%*	13%
Surgery			

Respiratory	18%	2%	9%
Cardiovascular	10%	7%	7%
Digestive	8%	10%	8%
Musculoskeletal	7%	3%	3%
Integumentary	5%	3%	3%
Total Elixhauser Groups (mean (sd))	4 (2)	2 (2)	4 (2)
Elixhauser Comorbidity Groups			
Hypertension Uncomplicated	33%	28%	38%
Renal Failure	28%	8%	19%
Cardiac Arrhythmia	26%	16%	25%
Weight Loss	26%	11%	16%
Hypertension Complicated	25%	7%	18%
Congestive Heart Failure	23%	7%	17%
Diabetes Uncomplicated	18%	15%	19%
Coagulopathy	16%	5%	9%
Obesity	16%	6%	13%
Other Neurological Disorders	15%	9%	14%

*Primarily mental disorders, pregnancy, and endocrine disorders

Two case-control analyses were performed to test for an association between prior healthcare facility exposure and CRE carrier status, when controlling for other potential CRE risk factors. In the first case-control study, cases were compared to their admission date-matched controls. Bivariate testing showed significant associations between a positive CRE carrier status and the following variables: age at admission, prior hospital exposure (days of stay at hospitals prior to index admission), length of stay in the admission in which the patient tests

positive for CRE, Elixhauser comorbidity score, CMS MDC, and whether the patient had a surgical procedure involving the cardiovascular or respiratory systems. Procedures classified as cardiovascular included heart valve procedures, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), coronary thrombolysis, cardiac catheterization, coronary arteriography, cardiac pacemaker, vascular catheterization, bypass, or shunt, and embolectomy or endarterectomy. Procedures classified as respiratory included tracheostomy, tracheoscopy and laryngoscopy with biopsy, lobectomy or pneumonectomy, lung or bronchus biopsy, incision of pleura, thoracentesis, and chest drainage. Time spent in nursing homes prior to the index admission was not significantly associated with CRE carrier status. The significantly associated independent variables were advanced to a multivariable logistic regression model, and the final model showed that age in decades ($p < 0.001$), length of index admission per ten days ($p = 0.007$), cardiovascular surgery ($p = 0.007$), respiratory surgery ($p = 0.004$), and days in the hospital per ten days in the 180 days prior to index admission ($p = 0.001$) were significantly associated with a positive CRE carrier status.

The second case-control study examined the independent variables associated with CRE when cases to controls matched on admitting diagnosis and comorbidity score. Bivariate testing showed significant associations between a positive CRE carrier status and the following variables: age at admission, prior hospital exposure, length of index admission, and whether the patient had surgery on the musculoskeletal, respiratory, or cardiovascular systems during the index admission. These independent variables were advanced to the final analysis using a multivariable logistic regression model, which showed that length of stay during the index admission was significantly associated with a patient being a CRE carrier (OR 1.16-2.04, $p = 0.003$, per 10 day increase in length of stay).

CRE Exposure due to Inter-facility Patient Sharing

Tracking the movement of the 61 case patients known to harbor CRE pathogens from the academic medical center to regional healthcare facilities and counties throughout California showed that these 61 patients spent 1907 days in 18 hospitals and 16 nursing homes in 5 counties in the year following their index admission. Case exposure to healthcare facilities in the 90, 180, and 365 days prior to and following positive CRE culture is shown in Table 3.2.

Table 3.2: Extent of CRE Patient Exposure by Facility Type, Stratified by Timing Relative to First CRE+ Culture

	Prior	**to**	**CRE +**	**After**	**CRE**	**+**
	181-365d	**91-180d**	**90d**	**90d**	**91-180d**	**181-365d**
Rate of facility visits (per 100 days of follow up)	0.16	0.35	1.54	1.80	0.39	0.19
Distinct healthcare facilities	17	20	35	26	12	11
Distinct hospitals	12	13	25	14	8	5
Distinct nursing homes	5	7	10	12	4	6
Healthcare facility visits	33	37	83	70	29	25
Hospital visits	26	28	70	44	23	16
Nursing home visits	7	9	13	26	6	9
Hospital LOS* (mean)	11.92	13.28	11.81	11.27	9.69	9.84
Hospital LOS (sd)	12.17	13.05	13.17	9.86	8.82	10.58
Nursing home LOS (mean)	29.38	24.68	20.62	10.31	16.50	26.59
Nursing home LOS (sd)	31.10	22.77	15.73	10.52	22.34	49.66
Hospital exposure days	1478	1301	827	496	649	817

Nursing home exposure days	852	543	268	268	528	1,090
Days of follow up**	20,296	10,676	5,399	3,892	7,500	13,420

*LOS = length of stay, raw exposure days, not accounting for patient deaths or loss to follow up

**Limited by death in 19 patients.

Altogether, in the year prior to and following their index visit with CRE, CRE carriers visited 39 acute care hospitals, 7 long term acute care hospitals (LTACHs), and 51 nursing homes. Institutional level descriptors for these facility types are shown in Table 3.3. As would be expected based on the facility types, hospitals had shorter lengths of stay than LTACHs and nursing homes. The case-mix descriptors (percent of patients with certain surgery and comorbidity types) showed that a larger percent of acute care hospital patients underwent surgery, while LTACHs had a larger fraction of patients with diabetes, renal failure, and congestive heart failure. At the facility level, stratifying exposures prior to and following positive CRE culture are shown in Table 3.2. The evaluation of the extent of CRE spread at the county level showed that 5 California counties were exposed to CRE by the movement of patients from one academic medical center to hospitals in those counties (Table 3.4).

Table 3.3: Characteristics of Hospitals and Nursing Homes Visited by CRE Carriers

	Hospital	**LTACH**	**Nursing Home**
Facilities Visited	39	7	61
Mean Facility Size (distinct patients/year)	7,215	817	385
Mean LOS*	4.7	27.0	57.7
% with Surgery	31%	9%	5%

Comorbidities			
Hypertension	35%	38%	31%
Diabetes	17%	32%	27%
Renal Failure	15%	34%	1%
Congestive Heart Failure	14%	35%	9%

*Raw exposure days, not accounting for patient deaths or loss to follow up

Table 3.4: Extent of CRE Exposure by County and Time Relative to Index Admission (In Patient-Days) and Hospital County

	Los Angeles	**Orange**	**Riverside**	**Sutter**	**Yuba**
365 days prior	482	888	104	4	.
180 days prior	414	801	82	4	.
90 days prior	285	481	61	.	.
90 days following	91	379	23	.	3
180 days following	112	500	29	.	8
360 days following	112	666	31	.	8

Factors Associated with Healthcare Facility Exposure

Comparisons of factors at patient level among CRE carriers and the full cohort are shown in Table 3.5. Compared to CRE negative patients, cases had significantly higher mean age, length of stay, and number of comorbid conditions (Elixhauser Comorbidity Index). Cases were more likely to have a primary diagnosis classified as infectious, respiratory, or renal/urinary and to have undergone a surgical procedure, particularly those involving respiratory system.

Table 3.5: Characteristics of UCI Inpatients by CRE Status, 2010-2013

Characteristic	**CRE Positive (%)**	**CRE Negative (%)**
Age (mean (SD))	63 (17)	50 (21)
Female gender	52%	52%
Race		
White	67%	73%
Asian	16%	13%
Black	5%	3%
Other	11%	10%
Hispanic ethnicity	23%	27%
Insurance type		
Medicare	51%	31%
Medicaid	20%	22%
Private	18%	28%
Indigent Programs	3%	11%
Self Pay	3%	3%
All Other	5%	3%
Length of Stay (mean (sd))	29 (34)	5 (9)
Primary diagnosis type		
Infectious	23%	4%
Respiratory	13%	5%
Renal/Urinary	11%	5%
Circulatory	8%	9%
Hepatobiliary	8%	5%
Burns	7%	2%
Nervous	5%	11%

Digestive	5%	9%
Trauma	5%	2%
Musculoskeletal	3%	9%
Other	11%	39%*
Surgery		
Respiratory	18%	2%
Cardiovascular	10%	6%
Digestive	8%	8%
Musculoskeletal	7%	5%
Integumentary	5%	2%
Total Elixhauser Groups (mean (sd))	4 (2)	2 (2)
Elixhauser Comorbidity Groups		
Fluid and Electrolyte Disorders	41%	16%
Hypertension Uncomplicated	33%	32%
Renal Failure	28%	7%
Cardiac Arrhythmia	26%	14%
Weight Loss	26%	6%
Hypertension Complicated	25%	6%
Congestive Heart Failure	23%	7%
Diabetes Uncomplicated	18%	15%
Coagulopathy	16%	5%
Obesity	16%	8%

*Primarily pregnancy and mental disorders.

The healthcare facility exposure of the CRE cases and cohort were also compared. The fraction of time spent in healthcare facilities is shown in Figure 3.1 for both cases and the

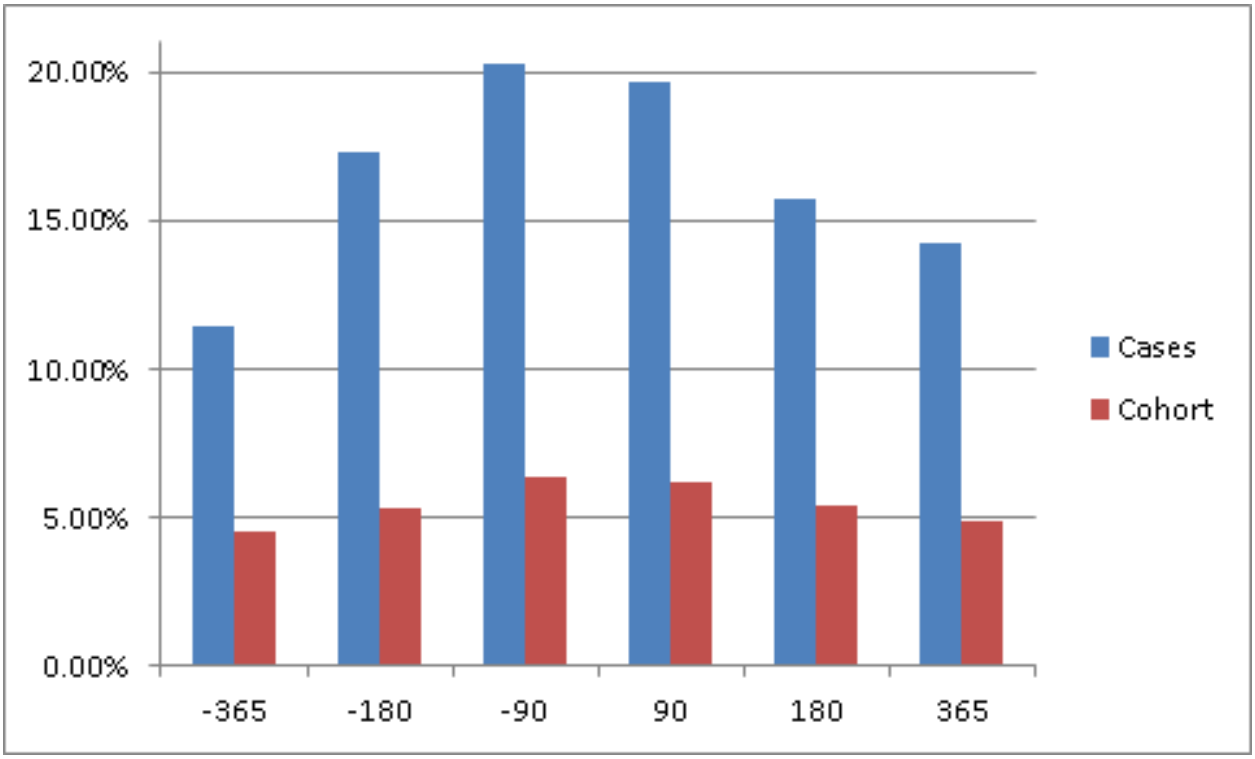


Figure 3.1: Percent of Days Spent in Healthcare Facilities Relative to Index Admission

full UCIMC cohort. The exposure due to CRE carriers in healthcare facilities across a region was calculated as the number of days patients are in healthcare facilities over the denominator of the number of days of follow up (truncated for patients who die in the year following their first positive CRE culture).

In the case cohort study of UCI patients, I found that cases compared to the population cohort of UCI inpatients were more likely to have the following characteristics on bivariate testing. For continuous variables, I found that higher patient age at index admission, higher total Elixhauser Comorbidity Index, longer length of index admission, and more time spent in both hospitals and nursing homes prior to the index admission were associated with a greater length of time spent in healthcare facilities following index admission (all $p < 0.001$). For dichotomous variables, I found CRE carriage ($p=0.03$), female gender, non-Hispanic ethnicity, respiratory surgery, or cardiovascular surgery (all $p < 0.001$) spent significantly more time in healthcare facilities following index admission. For categorical variables, the

number of days spent in healthcare facilities following index admission differed significantly with race, insurance type, and major diagnostic category of the patients primary diagnosis at the index admission (all p <0.001). The final multivariable Poisson regression model showed that number of follow up days in healthcare facilities post-discharge per day of follow up was significantly associated with whether the patient was a CRE carrier, age at admission, prior healthcare exposure in hospitals and in nursing homes, length of index admission, and comorbidity score (Table 3.6).

Table 3.6: Patient and Prior Facility Characteristics Associated with Percentage of Follow-up Spent in Healthcare Facilities

Characteristic	**Model Estimate***	**P-value**
CRE Carriage	0.32	<0.001
Hospital Visit 1 Year Prior	0.31	<0.001
Nursing Home Stay 1 Year Prior	0.83	<0.001
Age (per 10 year)	0.18	<0.001
Elixhauser Comorbidity Index	0.10	<0.001
Length of Index Admission (per 10 days)	0.15	<0.001

*For example, for each 10-year increase in patient age, the patients rate of healthcare visits (days in healthcare facilities per day of follow-up time after index admission) would increase by a factor of 1.20 (i.e., $e^{0.18}$)

A case-control study was conducted in order to assess whether the burden of healthcare exposure of CRE carrier patients following index admission remained significantly higher than that of the cohort when matching cases with controls on comorbidity score and prior healthcare exposure. In bivariate testing, simple linear regression showed that longer length of index admission was associated with a greater length of time spent in healthcare facilities

following index admission (p = 0.007). No other independent variables were significantly associated with healthcare facility exposure following index admission.

3.1.6 Discussion

These studies began necessary surveillance in a region in which CRE is still emerging to both quantify the current prevalence of CRE and identify targets for intervention. Specifically, these studies performed retrospective surveillance for CRE among clinical microbiology cultures from one academic medical center in a region where CRE is emerging with the goal of understanding the social ecology of emerging MDROs. The results confirm the importance of CRE containment by demonstrating its high mortality and extensive spread, while suggesting targets for intervention at the intra-personal and institutional levels by identifying factors associated with both CRE carriage and with future healthcare facility exposure.

The emergence of CRE places a high burden of infectious spread on the healthcare system, putting many patients at risk of contracting a pathogen associated with high mortality. The 31% overall mortality rate among CRE cases in this study, which likely underestimates the true mortality because it only includes deaths occurring in hospitals or nursing homes, demonstrates the threat CRE poses. A mortality rate of 31% or more, as found in prior studies, is the human burden that would come with allowing this dangerous pathogen to become endemic.

Because of their high exposure to healthcare facilities, a small number of CRE cases can expose many healthcare facilities and contribute to the rapid emergence of CRE. Despite the fact that many more cases than controls died in the year following admission, resulting in shorter follow up periods for cases, cases still spent more than three times as many days in healthcare facilities follow admission than controls. Results from the cohort study described here showed that CRE carrier patients spend a significantly greater percentage of

their time following hospitalization in healthcare facilities, even with controlling for other factors, resulting in a high burden of CRE exposure to facilities. The 61 CRE cases produced an average of 52 days of healthcare facility CRE exposure in the year following their index admission, bringing CRE to 18 hospitals and 16 nursing homes in four counties. Although the total number of CRE carriers identified in the study was 61, these patients generated a tremendous amount of CRE exposure in healthcare facilities despite high mortality rates, indicating the importance of early action toward CRE containment.

These results show that CRE is emerging and rapidly gaining a foothold in Southern California. Southern California is currently in a period of potential for containment of CRE. Given the high mortality of and rapid exposure to CRE seen in these data, public health officials should consider whether to take proactive steps and take deliberate action. Whether it is ultimately decided that containment efforts should be pursued or that the benefits of preventing CRE from becoming endemic do not justify the costs, the decision deserves serious consideration.

Faced with this evidence of concrete consequences of inaction on CRE emergence, public health departments and healthcare facilities may decide to contain the spread of CRE. However, even with high levels of motivation and impetus to act based on this quantification of the burden of CRE, health departments and healthcare facilities are unlikely to be able to muster a great deal of funding for a novel, proactive approach to a disease which is, as yet, uncommon. For example, currently, the CDC recommends screening all patients for CRE as a method for infection prevention; however, given the limited resources for CRE prevention mentioned above, facilities do not robustly adhere to these CDC CRE toolkit recommendations. Therefore, given that limited resources are available for this change in the public health response to MDROs, more targeted, cost-effective interventions must be identified.

To better direct the effort to identify key sites for intervention, the studies described here relied on a multi-level ecological model. Results of the examination of CRE epidemiology

showed how the intrapersonal level factor of CRE carriage can result in large institutional level exposures to CRE via the community level phenomenon of inter-facility patient sharing. Hospitals are the facilities where patients are more likely to have clinical or screening cultures that reveal their CRE status, so currently they are the sites on which current CRE containment efforts are focused. However, nursing homes, which generally do not screen patients, have an uncounted burden. More than half (57%) of the facility exposure days found in this study were in nursing homes. Thus, any CRE containment intervention must include nursing homes, rather than focusing solely on hospitals.

Prior studies of CRE emergence in this region found that most CRE cases were community-onset, i.e. occurring within two days of hospital admission, despite the belief of researchers that these cases were, in fact, healthcare associated. This study showed that, prior to testing positive for CRE, CRE carrier patients were exposed to a large number of healthcare facilities. On average, each CRE carrier spent over one month of the year prior to their positive culture in healthcare facilities. This study showed that there was a high degree of prior healthcare exposure among these cases during the epidemic phase of an emerging pathogen in a large region.

Risk factors for CRE at the intrapersonal, or patient, and institutional, or hospital and nursing home, levels were assessed, and patient primary diagnosis, comorbidity score, age, length of index admission, surgery, and prior stay in hospitals, but not in nursing homes, were found to have a significant association with being a CRE carrier. These findings should be used to assess which types of public health interventions might be best suited to prevent the spread of CRE. In particular, interventions should likely be targeted to patients with long lengths of hospital inpatient stay and high comorbidity.

This study had several limitations. First, it was not possible to determine the exact time at which patients first became CRE carriers due to a lack of CRE screening. However, even if screening were conducted on all patients, patients may carry CRE for some time and even

be able to transmit it to other patients before a rectal screening culture would test positive. The limitations posed by a lack of screening and an unknown time between exposure and positive screening tests lead to the choice of a case-control study rather than a hazards or survival analysis study to identify CRE risk factors. Healthcare exposure was stratified by facility type rather than more detailed facility characteristics because the number of CRE carriers at UCIMC was too small to power such analyses.

The emergence of CRE poses an increasing threat to public health given the large magnitude of healthcare exposure to CRE caused by inter-facility patient sharing of CRE carriers and the high mortality rate among patients with CRE. Guided by a multi-level ecological model of CRE emergence, these studies of patients admitted to one academic medical center revealed that both the patient characteristics of comorbidity and length of stay and facility characteristics such as nursing home or hospital facility type are associated with CRE carriage. These findings can both help to guide pragmatic recommendations by focusing interventions on patients with high comorbidity and lengths of stay within hospital facilities as well as to highlight key areas within the ecological model which could be further refined through study of larger CRE carrier populations, for example by identifying key hospital characteristics and patient comorbidities which are associated with CRE.

3.2 Aim 2: Evaluating the Extent to Which CRE Carriers Expose Other Healthcare Facilities in a Multi-Center Study

The work under this Aim builds upon the work of Aim-1 by examining the epidemiology of CRE across UC hospitals in the state in a larger dataset, not only to assess the generalizability of the recommendation to focus containment interventions on patients with long

lengths of hospital stay and high co-morbidity in both hospitals and nursing homes, as was found in the prior study of patients from a single center, but also to expand and refine our understanding of CRE risk beyond these general risk factors.

Efforts to understand the spread of CRE have been complicated by the fact that CRE is difficult to measure. As discussed in section 2.4, CRE are not just one type of bacteria, but instead are a group with at least five major species found in healthcare facilities. Additionally, there are several genetic mechanisms that allow carbapenem resistance, so phenotypic testing of bacterial cultures to demonstrate resistance to carbapenems in the hospital microbiology laboratory is required. However, the interpretation of phenotypic tests depends on the resistant breakpoints used, that is, how well the bacteria must grow in the presence of an antibiotic before they are said to be resistant to that antibiotic. Because of these challenges and the discovery of a novel carbapenem-resistance gene, OXA-48, which was present in strains not detected by the CDC 2012 CRE definition, the CDC revised its CRE definition in 2015.

In the second section of the chapter, the impact of changes in the surveillance definition of CRE on public health response was examined. Revisiting the recommendations from the previous chapter using a larger dataset was important to ensure that the risk factors described in Aim 1 are true of CRE more generally, rather than anomalous factors that are important among patients from one hospital. Using the larger, UC-wide dataset and considering the impact of surveillance definitions, it was possible to refine the suggested targets of intervention from prior work and more specifically direct limited resources toward the particular settings and patients most at risk of CRE.

3.2.1 State-wide Risk Factors for CRE

Rationale

To truly understand the spread of CRE throughout California, it was important to evaluate whether exposure for patients with CRE from UCIMC are representative of those of CRE patients state-wide. Thus, the study described in this section included the entire UC healthcare system. The seven UC hospitals participating in this study are all tertiary care facilities in geographically separate portions of the state. Because of their geographic distance, the facilities do not compete for patients with one another. Instead, each facility has its own unique connections to regional healthcare facilities and reach within the state. Using the exposure of CRE carriers from the entire UC system, I quantified the spread of CRE in and out of multiple counties and facilities over time in order to highlight regional differences in CRE burden.

Hypotheses

1. The prevalence of CRE carriage will be higher in Southern California than in Northern California, but that per-person exposure days will be the same in both regions. As described in the introduction, CRE first arrived in California in the Southern region, making it more likely that CRE has spread further within this region.

2. CRE carriage will be strongly associated with future healthcare exposure days in this multi-center study. Rationale for this hypothesis was similar to that in Aim 1.

Materials and Method

Study Population The study population was all patients admitted to seven UC hospitals in California between January 1, 2010 and December 31, 2013. The only patient exclusion criterion was lack of a unique patient identifier in the California Hospital Discharge Database, as described in the single-center UCI study in section 4.1.3 The seven hospitals were UCIMC; Ronald Reagan UCLA Medical Center; UCLA Medical Center, Santa Monica; UCSF Medical Center; UC Davis Medical Center; UC San Diego Thornton Hospital; and UC San Diego Medical Center, Hillcrest Hospital. For each research question, the study design was the same as those described in section 4.1.3 using patients from all seven of these hospitals rather than only UCIMC.

Data Sources, Linking Methodology, Data Analyses, and Outcomes As in section 4.1, three data sets were linked in order to carry out the study. Two of these, the nursing home (RESDAC) and hospital (OSHPD) databases, remained the same as described in Aim 1. The third was limited line list data from all seven UC hospitals describing positive microbiology laboratory cultures for CRE. Infection prevention departments at each UC (UC Irvine, UC Los Angeles, UC San Francisco, UC Davis, and UC San Diego) submitted limited line list data for positive CRE cultures for analysis.

Data from the seven sites throughout the UC system were collected under the UC Reliance IRB system. The studies conducted under this aim were important both for their individual knowledge-generating potential and because they were among the first studies to be conducted under a new system, the UC Reliance Registry, which was begun to facilitate data sharing between the UCs. This new system was designed to allow for the study of rare diseases for which relatively few cases occur at each institution.

Infection prevention departments at each UC hospital requested laboratory data for cultures meeting a broad CRE definition which included all cultures that would fall under the 2015 CDC definition of CRE. Chart review was performed as necessary at each UC in order to gather any demographic or admission data not reported in microbiology results. The following data items were collected for each positive CRE microbiology test result: CRE and other MDRO test dates and results, microbiologic data including date of culture, antimicrobial sensitivity testing, plus the patients gender, birthdate, and admission and discharge dates from each of these hospitalizations as the limited line item data, along with a study identification number unique to the patient. Additional data sources and the linking methodology used in this section were the same as those used in section 4.1.3.

The studies conducted in this aim for each research question used the same analysis methods described in Aim 1. To evaluate the outcome of CRE exposure days and demographic characteristics, I repeated the analyses for Aim 1, Question 1 using the larger group of CRE carrier patients, who tested positive for CRE according to the 2015 CDC surveillance definition, at all seven UC hospitals. To assess how CRE carriage impacts future healthcare facility readmissions state-wide, I conducted a cohort study as described in Aim 1, Question 2 using patients from all seven UC hospitals in order.

Finally, I repeated the previous case-control regression analyses described in Aim 1, Question 3, with this larger group in order to determine factors associated with CRE carriage throughout the state in a manner similar to that in Orange County. Cases were defined as patients with a positive CRE culture according to the CDC 2015 definition and at least one inpatient admission at a UC hospital. Three date-matched controls were selected for each case by choosing the three admissions immediately following the case admission at the same hospital. Three comorbidity-matched controls were selected for each case and were patients with admissions with the same total Elixhauser Comorbidity Index (7) and major diagnostic category of the primary diagnosis as cases admitted to the same hospital.

Results

CRE Epidemiology and Factors Associated with CRE Carriage The UC hospitals together had 122,137 an average of admissions with unique patient identifiers per year during the study period. Of the total UC patients with unique identifiers, 6% were children and 94% were adults. 40.4% of the total admissions occurred in Northern California and the remainder occurred in Southern California. Of the patients without unique identifiers (record linking numbers), 51% were female, 62% were white, 45% were Hispanic, and 45% had private insurance coverage. More than 50% of these patients without identifiers were less than 2 years old.

The number of CRE carrier patients at the seven UC hospitals between January 1, 2010 and December 31, 2013 was 489. Of these, 62 patients did not have unique identifiers. These patients without identifiers were 47% female, 63% white, and 29% Hispanic. Their mean age was 26, with 40% under age 2 years. Of these admissions, 40% were insured by Medicaid and 44% by private insurance coverage.

Among the 489 CRE carrier patients, 427 patients had valid unique identifier numbers in the hospital admissions database. These patients were identified as cases for the case-control studies. Comparative statistics are shown in Table 3.7 for factors at patient level among CRE carriers along with their admission date-matched, non-CRE carrier controls (the subsequent 3 admissions) and comorbidity-matched, non-CRE carrier controls for comparison. As in the single center study, compared to date-matched controls, cases had higher mean age and number of comorbid conditions (Elixhauser). They were more likely to be black and less likely to have private health insurance. Cases were more likely to have a primary diagnosis classified as infectious, respiratory, or renal/urinary and to have undergone a surgical procedure, especially those on the respiratory or cardiovascular systems.

Table 3.7: Characteristics of CRE Cases and Controls, California 2010-2013

Characteristic	**CRE+ (%)**	**Date Matched Controls (%)**	**Comorbidity Matched Controls (%)**
Age (mean (SD))	61 (20)	53 (22)	64 (19)
Female gender	47%	48%	51%
Race			
White	63%	71%	70%
Asian	8%	9%	9%
Black	16%	10%	11%
Other	12%	11%	12%
Hispanic ethnicity	19%	22	19%
Insurance type			
Medicare	56%	40%	56%
Medicaid	19%	16%	16%
Private	20%	34%	21%
Indigent Programs	1%	3%	3%
Self Pay	1%	3%	2%
All Other	2%	4%	2%
Length of Stay (mean (sd))	32 (43)	15 (25)	11 (20)
Primary diagnosis type			
Infectious	24%	5%	24%
Respiratory	12%	7%	12%
Renal/Urinary	12%	6%	12%
Hepatobiliary	11%	7%	11%
Circulatory	9%	15%	9%

Digestive	8%	10%	8%
Nervous	6%	11%	6%
Musculoskeletal	4%	7%	4%
Myeloproliferative	3%	6%	3%
Skin/Breast	2%	2%	2%
All Other	8%	25%*	8%
Surgery			
Cardiovascular	16%	11%	9%
Digestive	12%	8%	8%
Respiratory	12%	3%	4%
Nervous	4%	3%	1%
Musculoskeletal	4%	3%	3%
Total Elixhauser Groups (mean (sd))	4 (2)	3 (2)	4 (2)
Elixhauser Comorbidity Groups			
Fluid and Electrolyte Disorders	46%	26%	42%
Cardiac Arrhythmia	37%	23%	30%
Hypertension Uncomplicated	31%	31%	37%
Renal Failure	25%	15%	26%
Weight Loss	25%	9%	14%
Diabetes Uncomplicated	25%	14%	23%
Other Neurological Disorders	23%	9%	15%
Liver Disease	22%	11%	17%
Hypertension Complicated	22%	12%	22%
Chronic Pulmonary Disease	20%	14%	27%

* Primarily pregnancy, mental disorders, and endocrine disorders.

As in Aim-1, two case-control analyses were performed to identify potential CRE risk factors. In the first case-control study, cases were compared to their admission date-matched controls. Significant associations were found between a positive CRE carriage and the following variables: age at admission, prior hospital and prior nursing home exposure (days of stay in the respective health care facility type prior to index admission), length of stay in the index admission, Elixhauser comorbidity score, CMS MDC, insurance type, and whether the patient had a surgical procedure involving the musculoskeletal, respiratory, cardiovascular or integumentary system using bivariate testing. Unlike in the single center study, time spent in nursing homes prior to the index admission and insurance type were significantly associated with CRE carriage.

Regression analyses from Aim-1 were repeated to test the multi-variable association of patient age at admission, length of index hospitalization, time spent in hospitals in the three months prior to hospitalization, and cardiac and respiratory surgery with the outcome of CRE carriage. As in Aim-1, these variables were all found to be significantly associated with CRE carriage ($p < 0.001$ for age, prior hospitalization, and surgeries, and $p = 0.007$ for length of index admission).

Independent variables significantly associated with CRE carriage in bivariate testing using the UC wide data were advanced to a multivariable logistic regression model, and the final model showed that older age in decades ($p < 0.001$), longer length of index admission per 10 days ($p = 0.019$), race ($p = 0.011$), cardiovascular surgery ($p = 0.005$), respiratory surgery ($p = 0.001$), and days in hospitals ($p = 0.001$) and in nursing homes ($p < 0.001$) in the 180 days prior to index admission were significantly associated with being a CRE carrier. While the total comorbidity score was not significantly associated with being a CRE carrier, two particular comorbidities, liver disease ($p = 0.028$) and neurological disorders ($p = 0.004$) were.

The second case-control study, in which cases were compared to controls matched on admitting diagnosis and comorbidity score, examined the independent variables associated with CRE carriage when cases to. Bivariate testing showed significant associations between CRE carriage and the following variables: age at admission, race, prior hospital and nursing home exposure, length of index admission, and whether the patient had surgery on the musculoskeletal, integumentary, respiratory, or cardiovascular systems during the index admission. These independent variables were advanced to the final analysis using a multivariable logistic regression model, which showed that length of stay during the index admission, nursing home and hospital exposures during the 180 days preceding index admission, and cardiovascular and respiratory surgeries were significantly associated with being a CRE carrier (Table 3.8).

Table 3.8: Risk Factors Associated with CRE Carriage

Characteristic	**Odds Ratio**	**95% Confidence**	**Limit**	**P-value**
Length of index admission (per 10 days)	1.20	1.13	1.27	<0.001
Prior hospitalization (per 10 days)	1.14	1.10	1.18	<0.001
Prior nursing home visits (per 10 days)	1.05	1.01	1.08	0.009
Respiratory surgical procedures	1.62	1.17	2.25	0.004
Cardiovascular surgical procedures	1.78	1.36	2.31	<0.001

CRE Exposure due to Inter-facility Patient Sharing throughout California Among the 427 case patients that had valid unique identifiers in the hospital discharge dataset, 148 (35%) died within 365 days of discharge from their index admission (versus 31% for the previous single center study). Over the entire study period, there were 51,821 days of follow up, which led to admissions at 90 hospitals, 113 nursing homes, and 20 LTACHs. Tracking

the movement of these CRE carriers (cases) from the academic medical center to regional healthcare facilities throughout California showed that cases spent 80 days in healthcare facilities per 365 days of follow-up. The rate of case exposure to healthcare facilities in the 90, 180, and 365 days prior to and in the 180 and 365 days following positive CRE culture was greater than that found in the single center study, while the rate of facility visits was slightly lower for the 90 days immediately following the admission in which CRE carriage was identified (Table 3.9).

Table 3.9: Extent of CRE Carrier Patient Exposure by Facility Type, Stratified by Timing Relative to First CRE+ Culture

	Prior	**to**	**CRE +**	**After**		**CRE +**
	181-365d	**91-180d**	**90d**	**90d**	**91-180d**	**181-365d**
Rate of facility visits (per 100 days of follow up)	0.38	0.56	2.25	1.68	0.52	0.32
Distinct healthcare facilities	156	141	212	133	93	107
Distinct hospitals	84	78	122	68	56	57
Distinct nursing homes	72	63	90	65	37	50
Healthcare facility visits	543	415	845	470	272	299
Hospital visits	408	308	667	341	195	205
Nursing home visits	135	107	178	129	77	94
Hospital LOS* (mean)	14.3	15.2	13.9	13.4	14.1	13.9
Hospital LOS (sd)	20.0	19.4	15.1	13.5	17.1	17.7
Nursing home LOS (mean)	30.2	25.2	20.6	17.9	25.3	33.3
Nursing home LOS (sd)	46.4	32.7	21.2	19.4	33.5	48.2
Hospital exposure days	19,771	14,844	9,253	4,584	7,576	10,286

Nursing home exposure days	12,684	7,194	3,662	2,306	5,209	9,976
Days of follow up**	143,386	73,881	37,473	27,929	52,568	92,831

*Length of Stay (LOS), raw exposure days, not accounting for patient deaths or loss to follow up. **Limited by death in 148 patients.

Characteristics of cases were compared to those of inpatients in the full UC cohort. These comparative statistics for factors at patient level among CRE carriers and the full cohort are shown in Table 3.10. As in the single center study, compared to CRE UC cohort patients, cases had significantly higher mean age, length of stay, and number of comorbid conditions (Elixhauser). Cases were more likely to have a primary diagnosis classified as infectious, respiratory, or renal/urinary and to have undergone a surgical procedure, particularly those involving respiratory system. Compared to the single center study, a larger fraction of cases in the UC-wide study were black, had diabetes, had cardiac arrhythmia, and had cardiovascular surgery while fewer were Asian and had respiratory surgery.

Table 3.10: Characteristics of UC-wide Cohort Inpatients by CRE Status, 2010-2013

Characteristic	**CRE positive (%)**	**CRE negative (%)**
Age (mean (SD))	61 (20)	51 (22)
Female gender	47%	54%
Race		
White	63%	70%
Asian	8%	9%
Black	16%	8%

Other	12%	13%
Hispanic ethnicity	19%	26%
Insurance type		
Medicare	56%	34%
Medicaid	19%	18%
Private	20%	37%
Indigent Programs	1%	6%
Self Pay	1%	3%
All Other	2%	3%
Length of Stay (mean (sd))	32 (43)	5 (10)
Primary diagnosis type		
Infectious	24%	4%
Respiratory	12%	6%
Renal/Urinary	12%	6%
Hepatobiliary	11%	4%
Circulatory	9%	11%
Digestive	8%	9%
Nervous	6%	11%
Musculoskeletal	4%	12%
Myeloproliferative	3%	2%
Skin/Breast	2%	3%
All Other	8%	32%*
Surgery		
Cardiovascular	16%	8%
Digestive	12%	6%
Respiratory	12%	2%
Nervous	4%	4%

Musculoskeletal	4%	5%
Total Elixhauser Groups (mean (sd))	4 (2)	2 (2)
Elixhauser Comorbidity Groups		
Fluid and Electrolyte Disorders	46%	16%
Cardiac Arrhythmia	37%	15%
Hypertension Uncomplicated	31%	30%
Renal Failure	25%	9%
Weight Loss	25%	4%
Diabetes Uncomplicated	25%	13%
Other Neurological Disorders	23%	8%
Liver Disease	22%	7%
Hypertension Complicated	22%	8%
Chronic Pulmonary Disease	20%	14%

*Primarily pregnancy, endocrine and mental disorders

The healthcare facility exposure of the CRE cases and cohort were also compared. The fraction of time spent in healthcare facilities is shown in Figure 3.2 for both cases and the full UC cohort. The fraction of time spent in healthcare facilities by cases was approximately five times that of the cohort prior to the index admission and nine times that of the cohort following the index admission. While the UC-wide cohort spent a similar fraction of days in healthcare facilities following index admission as the UCI cohort, among cases, the fraction was much higher, peaking at 43% versus 20% for UCI cases during the first 90 days following discharge from the index admission.

Factors Associated with Healthcare Facility Exposure A cohort study was conducted in order to assess whether the burden of healthcare exposure of CRE patients follow

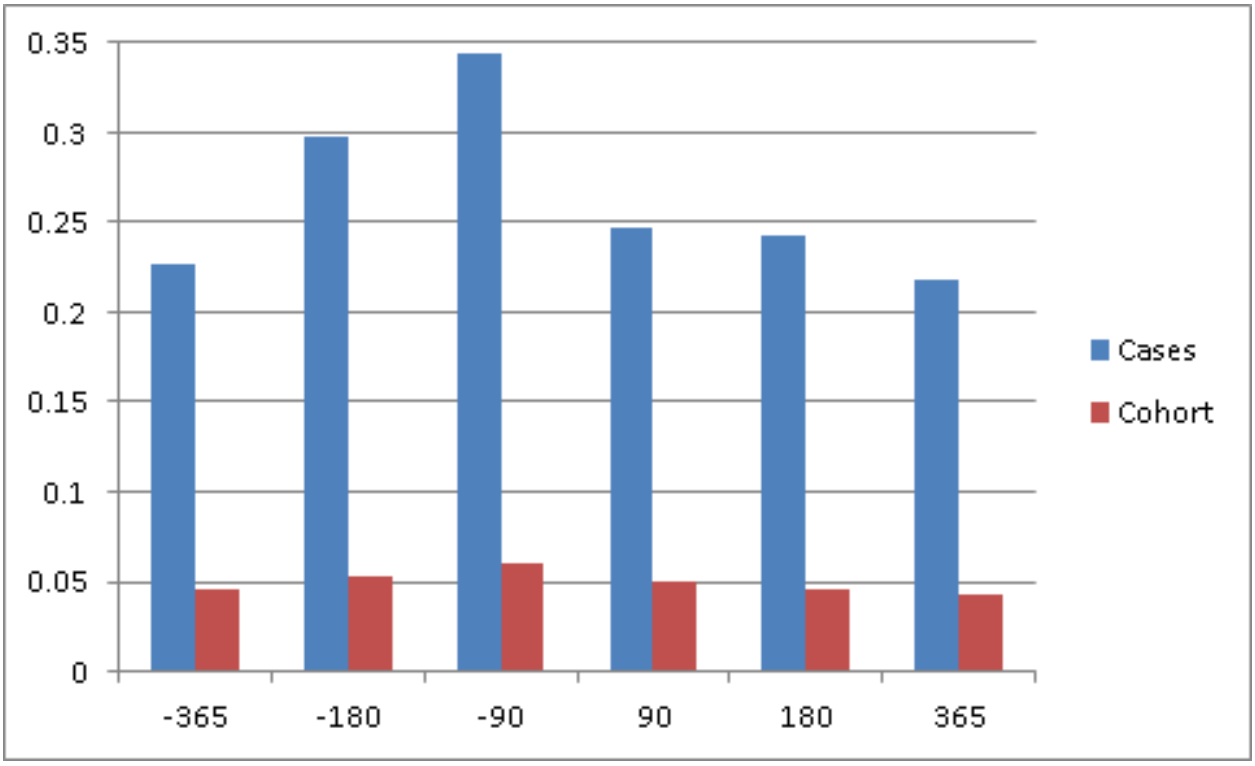


Figure 3.2: Fraction of Days Spent in Healthcare Facilities Relative to Index Admission

index admission remained significantly higher than that of the cohort when controlling for other factors. For dichotomous variables, patients with prior positive CRE culture, male gender (the opposite finding from the single center study), non-Hispanic ethnicity, respiratory surgery, or cardiovascular surgery (all p <0.001) spent significantly more time in healthcare facilities following index admission. For categorical variables, days spent in healthcare facilities following index admission differed significantly with race, insurance type, and major diagnostic category of the patients primary diagnosis at the index admission (all p <0.001). For continuous variables, higher patient age at index admission, higher total Elixhauser Comorbidity Index, longer length of index admission, and more time spent in both hospitals and nursing homes prior to the index admission were associated with a greater length of time spent in healthcare facilities following index admission (all p <0.001). Table 3.11 shows the results of the same regression as performed in the single-center study. The direction and significance of the effects were the same for all independent variables; however, the magni-

tude of the effect was greater for CRE carriage and nursing home stay in the prior year and smaller for hospital stay in the prior year and length of index admission.

Table 3.11: UC-wide Patient and Prior Facility Characteristics Associated with Rate of Healthcare Facility Days per day of Follow Up, for Comparison to Single Center

Characteristic	**Model Estimate***	**P-value**
CRE Carriage	0.67	<0.001
Hospital Visit 1 Year Prior	0.16	<0.001
Nursing Home Stay 1 Year Prior	0.98	<0.001
Age (per 10 year)	0.17	<0.001
Elixhauser Comorbidity Index	0.10	<0.001
Length of Index Admission (per 10 days)	0.07	<0.001

*For example, for each 10-year increase in patient age, the patients rate of healthcare visits (days in healthcare facilities per day of follow-up time after index admission) would increase by a factor of 1.19 (i.e., $e^{0.17}$).

The final multivariable regression model showed that number of follow up days in healthcare facilities post-discharge was significantly associated with prior CRE carriage, age at admission, prior healthcare exposure in hospitals and in nursing homes, length of index admission, and comorbidities (Table 3.12).

Table 3.12: Patient and Prior Facility Characteristics Associated with Rate of Healthcare Facility Days per day of Follow Up

Characteristic	**Model Estimate***	**P-value**
CRE carriage (prior positive CRE clinical culture)	0.63	<0.001
Hospital Visit 1 Year Prior	0.14	<0.001

Nursing Home Visit 1 Year Prior	0.98	<0.001
Age (per 10 years)	0.16	<0.001
Elixhauser Comorbidity Score	0.08	<0.001
Length of Index Admission (per 10 days)	0.07	<0.001
Respiratory Surgery	0.16	<0.001
Cardiovascular Surgery	0.11	<0.001
Insurance Type (self-pay as reference)		<0.001
Medicare	0.14	
Medicaid	0.23	
Private	-0.14	
Indigent	0.11	
All Other	-0.06	
Female	-0.16	<0.001
Hispanic	-0.06	<0.001
Race (white as reference)		<0.001
Asian	-0.07	
Black	0.19	
Other	-0.01	

*For example, for each 10-year increase in patient age, the patients rate of healthcare visits (days in healthcare facilities per day of follow-up time after index admission) would increase by a factor of 1.17 (i.e., $e^{0.16}$).

Discussion

Together, Aim 1 and Aim 2.1 demonstrate the spread of CRE across California and the rapidity of exposure of healthcare facilities, and patients within them, to CRE carriers. However, the result described in this section showed that CRE carriage (as measured by positive clinical culture) in the Northern California hospitals was far lower than that in Southern California hospitals. Northern California UC hospitals had only 21 cases per 100,000 patients whereas Southern California UC hospitals had 217 cases per 100,000 patients. This discrepancy demonstrates that CRE is still emerging in California, with the bulk of spread occurring in Southern California. Containment efforts focused on Southern California could help prevent the spread of CRE throughout the state.

Results from Aim 2.1 provide further evidence of the high burden of CRE infectious spread on the healthcare system. A 35% overall mortality rate was observed among CRE cases in the UC Hospitals, compared to 31% in the single center study. Healthcare facility exposure to CRE also remained high. Despite the fact that many more cases than controls died in the year following admission, resulting in shorter follow up periods for cases, cases spent 1.8 times as many days in healthcare facilities following index admission than controls (compared to more than three times in the single-center study), and CRE carriage was associated with this increased healthcare facility exposure even when controlling for primary diagnosis, comorbidity, and other factors. In total, the 427 CRE cases produced nearly 20,000 days of healthcare facility CRE exposure in the year following their index admission, despite the deaths of 35% of the cases.

In addition to providing further evidence that CRE remains in an emerging phase, in which it could be potentially contained, and motivating of containment efforts by reiterating the consequences of inaction on CRE and emergence, results of this aim suggest targets for the public health action. As in the single center study, about half of the facility exposure days

found in this study were in nursing homes, reenforcing the importance of their inclusion in containment efforts. In addition to the risk factors for CRE identified in the single-center study, this larger study was able to identify nursing home exposures during the 180 days preceding index admission as a risk factor, underlining the importance of nursing homes in preventing the spread of CRE. Furthermore, the study was able to provide results that can refine the previous recommendation that interventions focus on patients with high co-morbidity to specifically highlight patients who have received cardiovascular and respiratory surgeries.

This study had several limitations. First, policies for performing clinical cultures, culture techniques, and microbiology database search methods differed among the UCs under study. However, use of a consistent case definition and data collection instructions should have minimized these disparities as much as possible for these analyses. This study also possesses the same limitations posed by a lack of screening and an unknown time between exposure and positive screening tests as in Aim 1.

This study quantifies the threat posed by the emergence of CRE, both in terms of mortality and exposure to healthcare facilities. However, it also provides evidence that CRE is still emerging and could potentially be contained if action were taken. The multi-level ecological model of CRE emergence was able to guide more detailed analysis of CRE risk factors using the larger, state-wide dataset. These findings can help to further refine the pragmatic recommendations given by Aim 1, by focusing on patients with high comorbidity, particularly those who have received respiratory and cardiovascular surgery, with long lengths of stay in hospitals and nursing homes.

3.2.2 Impact of Changing CRE Surveillance Definitions

Introduction

In this section, the impact of surveillance definition choice on the epidemiology of CRE will be examined. The epidemiologist Mervyn Susser is credited with distinguishing between illness, the patients subjective experience; sickness, the cultural and societal implications; and disease, the pathobiology (167). CDC definitions of CRE can be thought of as defining CRE as both a disease and a sickness because they define the disease of CRE as the presence of certain species of bacteria possessing certain antibiotic susceptibilities but also give a distinct cultural meaning (e.g. through use of the term nightmare bacteria (168)) to the sickness of CRE as the carriage of these bacteria versus those just slightly below the resistance cutoff. The CDCs definitions of CRE disease and sickness play a major role in eliciting public health response and interventions toward CRE bacteria while deprioritizing other, similar bacteria.

Unlike recognized strains of CRE, other Enterobacteriaceae not recognized as CRE at the time of laboratory microbiology culture do not typically trigger an order placing the patient in contact precautions. As a result, healthcare workers are more likely to carry these strains to other patients on their bodies or clothing even after the microbiology report is finalized. Therefore, these strains may spread faster than strains which are recognized and contained using contact precautions.

The CDC released an initial, narrower definition of CRE in 2012 (169) and then subsequently broadened this definition by releasing a less restrictive surveillance definition in 2015 to ensure detection of the OXA-48 strain of CRE (170). Tension exists between these two definitions because some infectious disease physicians believe that the 2012 definition allows exposures to go unnoticed, allowing the outbreak to escalate, while others believe that a

broader definition increases attention to the problem, but may divert limited resources from the most important cases.

Although it was only added to the CDC CRE definition in 2015, the OXA-48 strain of CRE was first identified in Turkey in 2001 (171) and by 2010 had spread to France and Belgium where it caused healthcare associated outbreaks (172; 173; 174). Thus, by the time the CDCs initial CRE definition was written in 2012, OXA-48 was known to be spreading throughout Europe, presaging its spread to the United States, and its pattern of antimicrobial sensitivity was known. Thus, it could have been included in the definition. The first cases of OXA-48 CRE were reported in the United States in 2012 (175), shortly after the CDCs initial CRE definition was released. However, because these strains were excluded from the 2012 definition due to the requirement for resistance to all third generation cephalosporins, they were able to spread unchecked until 2015. Still, the expanded 2015 definition represents a tradeoff since it may allow some false positives and divert resources away from the most critical CRE strains. The studies described in this section aimed to quantify the impact of CDCs changing definitions of CRE.

Hypotheses

1. CRE carriage prevalence will be greater using the CDC 2015 definition. This hypothesis was based on the fact that the 2015 definition was designed to capture OXA-48, an additional strain of CRE.

2. CRE cases identified using the 2015 definition will have lower Elixhauser comorbidity scores (i.e. be healthier) than those detected using the 2012 definition. This hypothesis was based on the 2015 definition being a broader definition of CRE, potentially allowing the identification of CRE patients who were less severely affected.

3. Bacteria defined as CRE by the CDC 2015 definition, but not initially recognized as CRE under the 2012 definition, will have a faster increase in detection rate over the study period than CRE recognized under the 2012 definition. This was proposed because it was thought that failure of early identification of CRE strains would lead to greater spread.

Materials and Methods

The study population, data sources, and linking methodology used were the same as those described in section 5.1. After receipt of the data sets describing positive cultures from all seven UC hospitals, the cases were classified by each of the two definitions. The 2012 CDC interim definition of CRE described CRE as Enterobacteriaceae that are non-susceptible to one of the following carbapenems: doripenem, meropenem, or imipenem and resistant to all of the following third-generation cephalosporins that were tested: ceftriaxone, cefotaxime, and ceftazidime (176). The 2015 CDC surveillance definition of CRE is Any Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, or Enterobacter spp. testing resistant to imipenem, meropenem, doripenem, or ertapenem by standard susceptibility testing methods (177).

Data Analyses

CRE Prevalence by Surveillance Definition First, the number of CRE carriers testing positive for CRE according to the two definitions will be calculated. The overlap of two groups of patients testing positive for CRE according to the 2012 and 2015 definitions was evaluated. Exposures and demographic characteristics of patients testing positive according to the two definitions were measured using descriptive statistics.

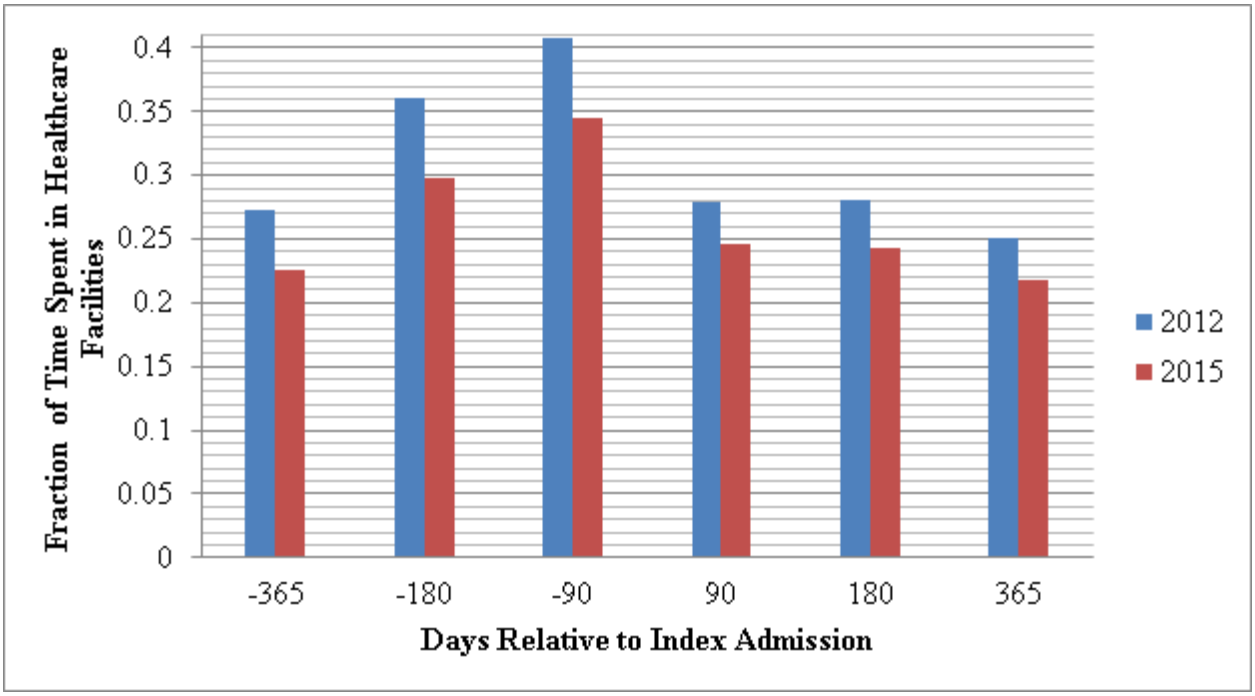
CRE Epidemiology by Surveillance Definition Patient characteristics among carriers of CRE according to the two definitions were described, including demographics, insurance status, diagnostic and procedure codes, length of stay, and recent and subsequent healthcare exposure. Using ANOVA and chi squared tests as appropriate, the exposures and demographic characteristics of the patients defined as having CRE according to two definitions were compared. I will compare the CRE exposures under these two definitions in terms of days of exposure at each type of facility before and after CRE diagnosis and the number of affected counties. Finally, I will repeat the previous case-control regression analyses described in Aim 1 with the two additional definitions in order to determine whether prior healthcare facility exposure is more closely associated with some definitions, or types, of CRE.

Rate of CRE Spread by Surveillance Definition To evaluate potential differential spread of CRE strains qualifying under the two different definitions, the incidence of positive CRE cultures according to each definition was compared among all hospital patients. Changes in the incidence of positive cultures according to each definition were examined over time for trends within the definition groups and these changes were compared between the two definitions.

Results

CRE Prevalence by Surveillance Definition The number of CRE carriers was 427 according to the 2015 definition and 303 according to the 2012 definition. Of these, 271 cases were classified as CRE by both definitions, 156 by the 2015 definition only, and 32 by the 2012 definition only. Healthcare facility exposures of patients testing positive according to the two definitions are shown in Figure 3.3. Cases classified as CRE according to the

Figure 3.3: Rate of Healthcare Facility Visits for CRE+ Cases by 2012 and 2015 CDC Definitions



2012 definition spent a greater fraction of their time both prior to and following the index admission in healthcare facilities than those classified as CRE by the 2015 definition.

CRE Epidemiology by Surveillance Definition A comparison of patient characteristics among carriers of CRE according to the two definitions is shown in Table 3.13. Patients in the two groups did not differ significantly in the categories measured, including demographics, insurance status, diagnostic and procedure codes, and length of stay. However, when comparing comorbidities, the rate of neurological comorbidities was higher in the 2012 definition group ($p = 0.02$).

Table 3.13: Characteristics of UC-wide CRE Cases by CDC definition, 2010-2013

Characteristic	**2015 Definition (%)**	**2012 Definition (%)**
Age (mean (SD))	61 (20)	62 (20)
Female gender	47%	46%

Race		
White	63%	64%
Asian	8%	8%
Black	16%	16%
Other	12%	11%
Hispanic ethnicity	19%	18%
Insurance type		
Medicare	56%	58%
Medicaid	19%	20%
Private	20%	19%
Indigent Programs	1%	1%
Self Pay	1%	1%
All Other	2%	1%
Length of Stay (mean (sd))	32 (43)	35 (46)
Primary diagnosis type		
Infectious	24%	29%
Respiratory	12%	13%
Renal/Urinary	12%	9%
Hepatobiliary	11%	10%
Circulatory	9%	9%
Digestive	8%	9%
Nervous	6%	5%
Musculoskeletal	4%	4%
Myeloproliferative	3%	4%
Skin/Breast	2%	2%
All Other	8%	6%
Surgery		

Cardiovascular	16%	15%
Digestive	12%	15%
Respiratory	12%	14%
Nervous	4%	3%
Musculoskeletal	4%	3%
Total Elixhauser Groups (mean (sd))	4 (2)	4 (2)
Elixhauser Comorbidity Groups		
Fluid and Electrolyte Disorders	46%	49%
Cardiac Arrhythmia	37%	39%
Hypertension Uncomplicated	31%	28%
Renal Failure	25%	26%
Weight Loss	25%	30%
Diabetes Uncomplicated	25%	28%
Other Neurological Disorders	23%	31%
Liver Disease	22%	20%
Hypertension Complicated	22%	24%
Chronic Pulmonary Disease	20%	20%

CRE exposures under the 2012 definition are shown in Table 3.14 (for comparison to the 2015 definition group see Table 3.9). Patients with CRE classified by the 2012 definition had a greater rate of facilities visits both before and after the index visit in which they were first identified as CRE carriers, compared to the 2015 definition group.

Table 3.14: Extent of 2012 CDC Definition CRE Carrier Patient Exposure by Facility Type, Stratified by Timing Relative to First CRE+ Culture (Compare to Table 3.9 for 2015)

	Prior	**to**	**CRE +**	**After**		**CRE +**
	181-365d	**91-180d**	**90d**	**90d**	**91-180d**	**181-365d**
Rate of facility visits (per 100 days of follow up)	0.58	0.83	3.09	2.37	0.75	0.46
Distinct healthcare facilities	218	180	234	164	123	131
Distinct hospitals	78	74	102	56	53	50
Distinct nursing homes	140	106	132	108	70	81
Healthcare facility visits	581	430	809	451	271	289
Hospital visits	346	247	543	247	149	156
Nursing home visits	235	183	266	204	122	133
Hospital LOS* (mean)	15.37	16.69	14.93	13.81	14.84	14.65
Hospital LOS (sd)	21.72	21.21	16.03	15.00	18.61	18.82
Nursing home LOS (mean)	26.58	21.06	16.52	19.04	24.84	32.37
Nursing home LOS (sd)	42.67	27.93	17.81	19.31	29.73	41.94
Hospital exposure days	17455	13182	8105	3411	5878	8088
Nursing home exposure days	18177	9455	4394	3884	8097	14859
Days of follow up**	99612	51638	26206	19045	36016	63149

*Length of Stay (LOS), in raw exposure days, not accounting for patient deaths or loss to follow up **Limited by death in 125/303 patients.

In a study comparing CRE carriers according to the 2012 CDC definition to their date-matched controls, age, prior stay in hospitals and nursing homes, respiratory and cardiovascular surgery, the patients primary diagnosis, and comorbid neurological disorders were significantly associated with CRE carriage (Table 3.15). Unlike a similar study using the 2015 CDC CRE definition, this study did not find the length of the index admission, the patients race, or comorbid liver disease to be significantly associated with CRE carriage. The odds ratios for prior nursing home exposure days, respiratory surgery, digestive and hepatobiliary primary diagnoses, and comorbid neurological disorders in this 2012 definition study were above the 95% confidence intervals found in the 2015 definition study.

Table 3.15: Comparison between Factors Associated with CRE Carriage According to the 2012 and 2015 CRE Definitions

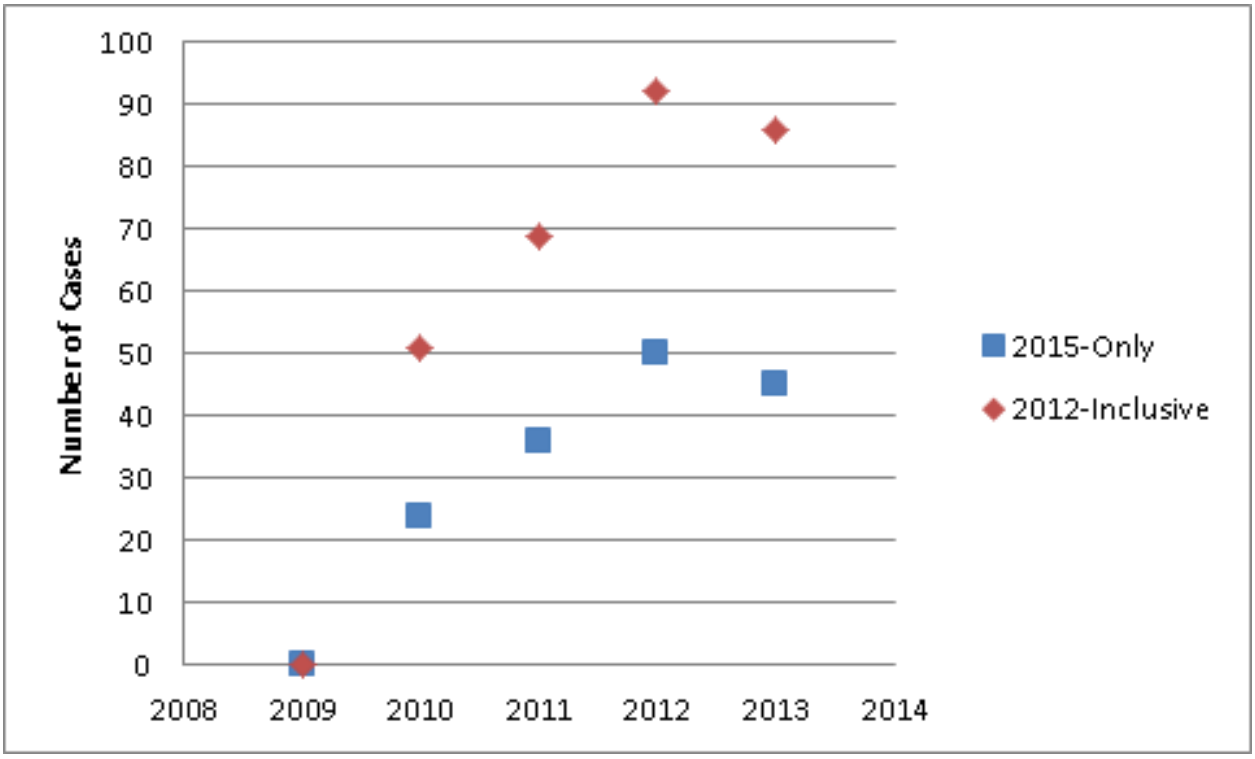
Characteristic	**Odds Ratio**	**95% Confidence**	**Limit**	**P-value**
Patient Age (per decade)	1.127	1.035	1.227	0.0058
Length of Index Admission (per 10 days)	1.009	0.964	1.055	0.7016
Prior Hospitalization Days (per 10 days)	1.209	1.152	1.269	<.0001
Prior Nursing Home Days (per 10 days)	1.16	1.103	1.22	<.0001
Respiratory Surgery	3.502	2.266	5.41	<.0001
Cardiovascular Surgery	1.849	1.247	2.743	0.0022
Race (White as reference)				0.5662
Asian	0.878	0.475	1.623	0.3595
Black	1.189	0.701	2.017	0.6929
Other	1.372	0.816	2.305	0.2796

Major Diagnostic Category (Nervous System as Reference)				<.0001
Circulatory	1.18	0.519	2.681	0.0101
Digestive	3.538	1.504	8.322	0.0918
Hepatobiliary	2.838	1.119	7.196	0.4661
Infectious	7.293	3.244	16.397	<.0001
Musculoskeletal	2.054	0.735	5.738	0.7939
Myeloproliferative	1.232	0.455	3.331	0.0926
Pregnancy	0.972	0.135	6.975	0.3324
Renal/Urinary	7.779	3.204	18.888	<.0001
Respiratory	2.718	1.17	6.317	0.5028
Skin/Breast	2.29	0.628	8.355	0.9839
Other	1.784	0.768	4.142	0.3607
Liver Disease	1.471	0.885	2.447	0.1366
Neurological Disorders	3.272	2.087	5.13	<.0001

Rate of CRE Spread by Surveillance Definition To evaluate potential differential spread of CRE strains qualifying under the two different definitions, the incidence of positive CRE cultures according to each definition was compared among all hospital patients. Examination of the changes in the incidence of positive cultures according to each definition showed similar trends for the two groups, likely owing to the large overlap of cases meeting both definitions (Figure 3.4).

*2015 group includes cultures which only qualify as CRE by the 2015 definition (i.e. they do not qualify under the 2012 definition). 2012-Inclusive group includes cultures which qualify under the 2012 CDC CRE definition regardless of whether they also qualify under the 2015 definition.

Figure 3.4: Positive CRE Cultures by Definition, California 2010-2013*



Discussion

Surveillance definitions impact the ability of healthcare facilities and public health systems to track and prevent the spread of dangerous pathogens. This comparison of the 2012 and 2015 CDC definitions of CRE found that the number of CRE carriers identified differed between the two definitions. Use of the 2012 definition of CRE resulted in failure to identify 37% of carriers identified by the 2015 definition, while use of the new 2015 definition excludes 11% of the carriers identified by the 2012 definition.

The rate of healthcare facility exposure from these carriers (in patient-days of exposure per day of follow-up) also differed between the 2012 and 2015 CRE definitions. Compared to rates of facility exposure to CRE by the 2012 definition, exposure by the 2015 definition was slightly lower in the 90, 180, and 365 days following the admission in which carriers were first identified. Thus, use of the more restrictive 2012 definition resulted in decreased identi-

fication of CRE carriers as compared to the 2015 definition, and this failure to identify 2015 definition CRE cases resulted in a rate of healthcare facility exposure following identification of the CRE carrier status that was much higher than control patients, although it was lower than that of 2012 definition cases. As a result, opportunities for intervention, such as use of contact precautions, were missed when the restrictive surveillance definition was used.

Given that the 2012 definition missed over a third of cases identified by the 2015 definition and the higher healthcare facility exposure of the missed cases, I anticipated that this failure to recognize CRE carriers would result in greater spread of the 2015 definition strains which were not identified by the 2012 definition. However, I found that strains meeting the 2015 definition, but undetected under the 2012 definition, did not appear to spread at a faster rate based on the rate of incidence of cultures newly positive for these strains over time. Nor did the undetected strains result in worse illness, as measured by greater hospital lengths of stay, due to this failure of detection.

Despite the fact that CRE strains with resistance caused by the OXA-48 gene had already been identified as causative in European outbreaks in 2010, the CDC did not incorporate this strains known sensitivity patterns when creating the 2012 surveillance definition for CRE. By highlighting differences in the rise of CRE strains included and excluded from the 2012 definition and showing the large number of additional CRE carriers only detected using the 2015 definition, this study demonstrated the results of failure to consider MDRO trends abroad when creating surveillance definitions for MDROs in the United States. A more proactive approach is needed when establishing MDRO surveillance definitions, analyzing MDRO trends abroad for clues to future MDRO spread in the United States.

3.3 Aim 3: Co-colonization of CRE Carriers with Other MDROs and Implications for CRE Containment via Contact Precautions Policies

3.3.1 Introduction

The studies under this aim sought to evaluate how the co-colonization of CRE carriers affects the potential efficacy of contact precautions policies in preventing the spread of CRE through three steps: first, assessing the rate of co-colonization of patients with CRE and other MDROs then comparing the length of time from admission to precautions for CRE patients based on their co-colonization status and timing of co-colonization to determine whether precautions policies for endemic MDROs can help prevent the spread of CRE. In this aim I examined how the interaction of institutional level infection control policies with intrapersonal level patient factors can be leveraged to limit the spread of CRE.

Because CRE is an infectious agent, institutional level policies are necessary to address safety beyond the individual CRE carriers. I focused on the potential efficacy of one institutional policy intervention, contact precautions, to help contain CRE among the high risk patients, those with high comorbidity and prior healthcare facility exposure, in light of the intrapersonal, patient level characteristic of co-colonization, i.e. the situation in which patients are carriers of one or more other pathogens in addition to CRE. The importance of organizational policies such as these in understanding a patients ecological environment was highlighted by Bronfenbrenner as part of his mesosystem level of ecological systems theory (88). In applying McLeroy and colleagues model of the multiple levels of influence over health concerns to CRE, these policies constitute the institutional factors impacting CRE emergence and spread (90).

Institutional or organization-level influences are crucial to human health and interventions at this level have been used successfully in a wide range of areas including childrens mental health treatment (178), HIV prevention (179), and work site health-promotion programs (180). For example, in the area of childrens mental health, an institutional level intervention to implement an evidence-based therapy program for delinquent youth in rural Appalachia showed improved outcomes over neighboring counties without such interventions (178). In another domain, a review of worksite nutrition and physical activity promotion programs found that these programs successfully achieved the goals of decreased employee weight and BMI in randomized control trials (181). Institutional-level interventions have also been successful in the domain of infection control, in which healthcare worker influenza vaccination programs have also been successful in reducing patient mortality and influenza (182).

The goal of studying the institutional and intrapersonal level risk factors for CRE and for healthcare facility exposure to CRE is to identify ways to interrupt the spread of this dangerous pathogen and prevent it from becoming endemic in California. An institutional level policy commonly used by hospitals to prevent the spread of multi-drug resistant HAIs is the use of contact precautions (183). Contact precautions involves placing a patient in a single room, if available, and requiring that healthcare personnel who enter the patients room clean their hands and don a gown and gloves for all in-room activity, followed by removal and re-cleaning of hands. Contact precautions are commonly used for patients known to harbor MRSA, VRE, ESBL, and multiple drug-resistant gram negative rods (MDR GNR) in order to prevent the spread of these organisms to other patients (183).

Thus, one way to prevent CRE from taking root in California may be for hospitals and nursing homes to implement institutional-level contact precautions policies for CRE. Such policies have established efficacy in controlling the spread of other MDROs. Implementation of contact precautions policies for MRSA has been shown to stop MRSA outbreaks (184) and decrease the rate of healthcare-associated MRSA infection (185; 186). Contact precautions

policies were also a component of the Israeli intervention to control CRE, as described in the introduction, suggesting that they may offer benefit for CRE specifically (66). In fact, in a recent survey of Orange County hospitals, the use of contact precautions appears to be the singular common response to CRE if a case becomes known to the hospital, contact precautions are instituted.

Several additional steps are required for contact precautions to be effective. First, there must be good communication between healthcare facilities. Next, proper attention must be given to culturing to determine the cause of infections. Finally, facilities must determine whether they will perform screening to accelerate contact precautions, an unlikely prospect given the costs and low prevalence of CRE. Unfortunately, even if facilities were to implement CRE screening, significant lags between collection of clinical cultures and laboratory report finalization would delay the application of contact precautions. First a submitted specimen is incubated for growth (1-5 days), then the organism is set up for susceptibility testing (1-2 days), and, finally, CRE confirmation steps require another day. In total, the time from culture collection to the knowledge that it harbors CRE could be a week or longer, time during which the patient is not in contact precautions. Thus, the study described in this chapter aimed to understand the extent to which contact precautions could limit the spread of CRE by quantifying patient-days of healthcare facility exposure to CRE carriers which could have been prevented had contact precautions been implemented immediately upon receipt of laboratory results confirming a patient's carriage of CRE and by contact precautions policies for endemic MDROs.

As an emerging MDRO, CRE currently has a low prevalence in California. Without knowledge of healthcare utilization patterns in the United States, one might conclude that the impact of contact precautions for CRE might be correspondingly small. However, as shown in Aims 1 and 2, patients harboring CRE are high utilizers of healthcare, with significantly higher rates of healthcare exposure prior to and following identification of the patients CRE

carrier status compared to the exposure of other hospital inpatients. In 2013, the top 1% of healthcare utilizers in the United States accounted for 21.5 percent of the healthcare expenditures (the top 5% account for roughly half of the expenditures), while the bottom 50% of healthcare utilizers accounted for only 2.7% of expenditures (111). Analyses of hospital inpatient stay days have shown trends similar to those for healthcare expenditures, meaning that a very small percentage of the population accounts for the majority of hospital inpatient days (112). These high utilizers are of great interest to insurers, including Medicare and Medicaid, for financial reasons, but also to public health because of their ability to expose large numbers of other patients to healthcare associated infections. Given these general known healthcare utilization patterns in the U.S. and the results of Aims 1 and 2, the risk of CRE exposure to others from the small group of CRE carrier patients is disproportionately large. However, the small number of CRE carriers also means that contact precautions policies for CRE could have a large infection prevention impact despite affecting relatively few patients and thus requiring few resources.

Given that the risk factors, such as high exposure to healthcare facilities, are similar for the endemic MDROs which have been studied to date, patients with these risk factors can become co-colonized with multiple MDROs, including CRE. Co-colonization has been shown to be common among carriers of the most prevalent MDROs. A study of VRE co-colonization found that 36% of VRE carriers had MRSA and 15% had Clostridium difficile (187). Other studies have found the rate of MRSA co-colonization among VRE carriers to be 23-26% (188; 189). Among carriers of ESBL-producing bacteria, of which most CRE are a subset, 47% have been found to colonized with VRE (190). A previous study of co-colonization among CRE carriers found that 40% were also colonized with carbapenem-resistant Acinetobacter baumannii or Pseudomonas aeruginosa (191). Therefore, patients newly identified as CRE carriers already may have been known to carry other MDROs and, as a result, already be on contact precautions prior to identification of their CRE status, preventing seven or more days of CRE exposure.

If most patients testing positive for CRE have not already been diagnosed with other MDROs and therefore are not on contact precautions, CRE precautions could be of great benefit. However, if many CRE carriers are already known to carry an endemic MDRO prior to laboratory results revealing their CRE carrier status, then precautions policies for those endemic MDROs could further limit the spread of CRE by placing CRE carriers into precautions before their CRE status is even known.

Given that some healthcare systems are beginning to discontinue the use of contact precautions for endemic MDROs with high prevalence (192; 193), it is important to understand the unintended impacts these policy changes may have on the spread of emerging MDROs. This aim will provide information on both co-colonization rates of CRE with other MDROs, the extent to which instutional contact precautions policies for CRE carriers could reduce healthcare facility exposure to CRE, and the frequency with which CRE carriers are placed in contact precautions for carriage of other MDROs prior to microbiology reports confirming their CRE status.

3.3.2 Hypotheses

1. A high proportion of CRE carriers will be known to also be carriers of MDROs compared to patients with similar levels of comorbidity. This was proposed because the risk factors for MDROs are similar across many groups of organisms and prior studies have shown substantial co-colonization of patients with other groups of MDROs.

2. CRE-specific contact precautions policies would result in significantly lower patient-days of CRE exposure to healthcare facilities. This hypothesis is based on prior studies of contact precautions for other MDROs.

3. CRE carriers who have co-colonization with at least one other MDRO will have a shorter time from admission to precautions than those who are not co-colonized. This hypothesis is based on both co-colonization rates and effect of contact precautions in prior studies.

3.3.3 Materials and Methods

Study Population

The study population was all patients testing positive for CRE by the 2015 CDC definition at UC Irvine Medical Center (UCIMC) between January 1, 2010 and December 31, 2013 who also had an inpatient visit at UCIMC during the study period. While the positive CRE culture may have been taken during an inpatient or outpatient visit, the patient must have had at least one inpatient visit so that the time to precautions could be assessed. Because this study was intended to describe co-colonization of all CRE carrier patients admitted to UCIMC between 2010-2013, no exclusions were used other than the requirement for a unique identifier in the hospital admissions database, as described in Aim 1. The age and gender distribution reflected the distribution across CRE carrier patients at UCIMC without bias.

When CRE carriers were compared to controls, three comorbidity-matched controls for each case were selected from among UCI inpatients hospitalized during the study period to match cases on total Elixhauser Comorbidity Index and major diagnostic category of the primary diagnosis, as described in Aim 1.

Data Sources

Data on CRE positive patients were obtained from the UCIMC limited line list data set described in Aim 1. Data regarding whether the patient had tested positive for other MDROs (MRSA, VRE, ESBL, MDR GNR, C. difficile) and the date of the first positive test were

included for each CRE positive patient. These co-colonization data for CRE carriers were obtained from the Infection Prevention Program at UCIMC, which provided detailed records of positive MDRO microbiology reports and the dates on which contact precautions were ordered for CRE carrier patients.

For the comparison of MDRO carriage among CRE carriers and controls, information regarding MRSA colonization for cases and their comorbidity-matched controls was obtained from line item hospitalization data obtained from the California Office of Statewide Health Planning and Development, referred to as the hospitalization dataset.

3.3.4 Data Analyses

MDRO Co-colonization among CRE Carriers

I identified the rate of co-colonization of CRE carriers with other MDROs using data provided by UCIMC Infection Prevention in the UCIMC limited data set. These data contained information about each patients other MDRO diagnoses and date of the first positive cultures resulting in these diagnoses for MRSA, VRE, ESBL, MDR GNR, and C. difficile. I compared the prevalence of co-colonization among the MDROs within the CRE carrier patient group.

Comparing MDRO Carriage among CRE Carriers and Controls

I then compared the rate of MRSA co-colonization of the CRE carrier cases with the rate of MRSA co-colonization for their comorbidity-matched controls (described in Aim 1) as reported in the hospital admissions database. I chose MRSA as the MDRO for comparison in this study because it is the dominant superbug in healthcare settings, representing the majority of healthcare associated MDROs. Additionally, it is the organism which is most ac-

curately and representatively captured in administrative data due to Californias mandatory MRSA screening laws.

A patient was classified as having MRSA if they had a diagnosis code field which contained one or more of the following ICD9 codes: 038.12 Methicillin-resistant Staphylococcus aureus septicemia, 041.12 Methicillin-resistant Staphylococcus aureus in conditions classified elsewhere and of unspecified site, 482.42 Methicillin-resistant pneumonia due to Staphylococcus aureus, V02.54 Carrier or suspected carrier of Methicillin-resistant Staphylococcus aureus, or V12.04 Personal history of methicillin resistant Staphylococcus aureus. To ensure fair comparison between the cases and controls, I counted a CRE case as being co-colonized with MRSA only if this information was recorded in the hospital admissions database without including any additional cases with MRSA available in the clinical data from Infection Prevention because only the administrative hospital admissions data were available for controls.

Impact of CRE Precautions Policies in Limiting CRE Exposure

I determined the number of inpatient days of CRE exposure which could have been prevented by the implementation of a CRE contact precautions policy by calculating the difference between the date on which each CRE carrier's first positive CRE culture report was finalized and their discharge from hospitalization. I stratified the CRE exposure days by those that could only have been prevented by the implementation of a CRE contact precautions policy and those which also could have been prevented by contact precautions policies for other, endemic MDROs (MRSA, VRE, ESBL, MDR GNR, and C. difficile). The lag time between CRE culture collection and finalization of the microbiology culture report was also calculated for each CRE carrier.

Additional Benefit of Endemic MDRO Precautions Policies on Time to Precautions and CRE Exposure

For each CRE carrier patient, I used the dates of the first positive MDRO culture for each of the patients MDRO diagnoses in order to determine whether and when carrier patients tested positive for other MDROs. In order to determine whether the co-colonized patients were placed on precautions as a result of carrying other MDROs, I surveyed UCIMC Infection Prevention regarding the history of their MDRO precaution policies, which were implemented through automated orders following positive microbiology cultures during the study period, 2010-2013 (194). This allowed me to determine whether and when a patient was placed on contact precautions during the index admission, the admission in which they were found to carry CRE, and to calculate the time in days between the admission and the application of precautions. Time to contact precautions during the index admission was used to quantify the number of days of CRE exposure to hospitals which would result from the discontinuation of contact precautions policies for endemic MDROs. Mean time to contact precautions was compared between CRE carriers who were co-colonized with other MDROs and those who were not co-colonized using a t-test.

3.3.5 Results

MDRO Co-colonization among CRE Carriers

Of the 61 CRE carrier patients with unique identifiers in the hospitalization database, 29 (48%) were co-colonized with at least one other MDRO. Of these, 13 had MRSA (21%), 14 had VRE (23%), 15 had ESBL (25%), 5 had other MDR GNR (8%), and 2 had C. difficile (3%). Of the 29 patients colonized with other MDROs in addition to CRE, 14 had more than one additional MDRO.

Comparing MDRO Carriage among CRE Carriers and Controls

When using only MRSA as reported in the hospital admissions database administrative data, 12 of the 61 (20%) CRE cases were co-colonized with MRSA as compared to 28 of 183 comorbidity-matched controls (15%). The difference in percent co-colonized with MRSA was not significant ($p = 0.43$).

Impact of CRE Precautions Policies in Limiting CRE Exposure

The total number of inpatient days of CRE exposure during CRE carriers index admissions which could have been prevented by the implementation of a CRE contact precautions policy was 803 (out of 1,748 possible days of CRE exposure, or 46%). The number of days of CRE exposure to healthcare facilities that could have been prevented by CRE contact precautions policies in addition to policies for other MDROs was not significantly greater than the number of exposure days which were prevented by policies for other MDROs only ($p = 0.17$). There was an average lag time of 4.9 days ($SD = 2.2$) between CRE culture collection and microbiology report finalization.

Additional Benefit of Endemic MDRO Precautions Policies on Time to Precautions and CRE Exposure

In 14 of the 29 co-colonized patients, the patient was identified as a carrier of another MDRO prior to their identification as a CRE carrier. The mean time to contact precautions for patients co-colonized with CRE and at least one other MDRO was 6.6 days, while the mean time to contact precautions for CRE carriers without other MDROs was 15.8 days. The time to precautions for co-colonized patients was significantly shorter than that of CRE carriers without other MDROs ($p = 0.01$). Presuming CRE carriers were positive for CRE

from the first day of their index admission, the number of days of CRE exposure to UCIMC during the index admission which were prevented by contact precautions policies for the other, endemic MDROs was 539 out of a total of 1,748 possible days of CRE exposure (31%). Of these days, 290 would have been prevented by contact precautions policies for CRE while 249 (14% of the 1,748 total exposure days) could only have been prevented by contact precautions policies for endemic MDROs.

3.3.6 Discussion

In this aim, I examined how institutional use of contact precautions policies for other MDROs may be advantageous in isolating patients who are eventually found to harbor CRE and containing the spread of this dangerous pathogen within healthcare facilities. The first step in examining this interaction between institutional level policies and the intrapersonal factor of co-colonization was to examine rates of co-colonization among CRE carriers. Given my finding in Aims 1 and 2 that CRE carriers possess common risk factors, such as high comorbidity and exposure to healthcare facilities, which are similar for many MDROs, I expected to find a high rate of co-colonization. However, the 48% rate of MDRO co-colonization among CRE carriers found in this study was deeply concerning given the minimal treatment options for both CRE and other MDROs.

Further examination of co-colonization with MRSA showed that both the CRE cases and their comorbidity matched controls had at least double the rate of colonization with MRSA reported in the general inpatient population, which was found to be 6.6% in 2010 (21).While the rate of MRSA co-colonization was higher among CRE carriers than among their comorbidity-matched controls, this difference was not statistically significant, which may either mean that high comorbidity, rather than any factors more specific to CRE carriers, explains much of co-colonization or simply that the sample size was too small to detect a significant difference.

In addition to being extremely high, MDRO colonization among CRE carriers had an unusual distribution compared to what in typically seen in the general hospital inpatient population. The proportions of CRE carriers with ESBL and VRE, which are gut bacteria like CRE, were slightly higher than the proportion with MRSA, which is typically found on the skin and in the nose. In the general inpatient population, MRSA is far more common than VRE and ESBL. For example, one study of MDRO incidence at hospitals in the same county as the study hospital found that mean MRSA incidence was twice that of VRE and more than ten times that of ESBL (195). These data show that CRE carriers are at an unusually high risk of co-colonization with VRE and ESBL gut bacteria, likely due to common routes of acquisition, while also at an elevated risk for MDROs such as MRSA that spread via very different routes. While these results are troubling for CRE carriers themselves, the bacterial shedding from carriers represents a major safety risk in healthcare facilities, where they can be passed to other patients.

The large overlap of CRE carriage with carriage of endemic MDROs found in this study demonstrated that contact precaution policies for endemic MDROs could have a large impact in prevention of emerging MDROs such as CRE, and this finding was supported by the impact of co-colonization on time to contact precautions and CRE exposure days. This analysis showed that the use of precautions for other MDROs results in an average ten fewer days per patient from admission to contact precautions for CRE carriers who are co-colonized compared with those who are not. Furthermore, by use of contact precautions for endemic MDROs and, therefore, on co-colonized CRE carriers even prior to microbiology results indicating their CRE status, the healthcare facility studied here decreased the time during which other patients might have inadvertently been exposed to CRE by 14%. These data used the broader 2015 CDC CRE surveillance definition. Given that the study period was 2010-2013, the 2012 CRE definition and earlier, even more stringent hospital definitions were used, so the decrease in healthcare facility exposure to CRE from endemic MDRO precautions policies would have been even greater.

These findings indicate that, currently, the spread of CRE is likely slowed by hospital contact precautions policies for other established MDROs, such as methicillin-resistant Staphylococcus aureus, which has a prevalence of nearly 7% in hospitals (196). Despite potential CRE prevention benefits, many facilities have begun to discontinue precautions for endemic MDROs, such as MRSA (192; 193). Contact precaution policies for endemic MDROs are currently threatened due to the perceived high costs and few short term benefits of using precautions for MDROs with high prevalence (193; 197; 198). However, this policy change would eliminate precautions for CRE prior to a CRE positive culture report in these co-colonized patients, which would result in large exposures of other patients to CRE due to the disproportionate healthcare facility exposure of CRE carriers.

The use of social ecological models can help reveal potential unintended consequences of health-related policy changes (199; 200), such as the impact of discontinuation of contact precautions policies for endemic MDROs on the control of emerging MDROs, including CRE. Consideration and minimization of such unpredicted side effects and their impact on those impacted by a program or policy, in this case, patients and their communities, is necessary and helps to ensure that the policy is socially valid (201). The need to examine and anticipate unintended higher order effects of changes in small systems has been deemed a central lesson of ecology in health promotion and public health (202). Consideration of inadvertent effects on the spread of infectious disease has proven important in a wide range of programs. In syringe exchange programs inadvertent impacts may have resulted in injection drug users accessing the programs having higher rates of HIV than those who did not use the program (203). In development programs, new construction has had side effects in the social ecology of disease, such as the construction of dams in Ghana and elsewhere which lead to increased rates of schistosomiasis, a parasitic infection (204). In considering the infectious impact of discontinuing contact precautions for endemic MDROs, this study drew from the emphases within social ecology theory on both examination of multiple levels of influence over health in intervention design and prospective consideration of social validity.

The study described in this chapter showed that hospital infection prevention policies intended to prevent the spread of endemic MDROs also act to contain other, emerging MDROs for which no policy yet exists. By identifying the 48% rate of co-colonization of patients with CRE and endemic MDROs, this study demonstrated how efforts to prevent endemic MDROs also work to prevent the spread of emerging MDROs. By quantifying the 249 additional patient days of potential CRE exposures from 61 CRE carriers, this study clarified the true costs of discontinuation of contact precautions for endemic MDROs, altering the cost/benefit analysis for precautions, and provides justification for reinstituting discontinued precautions policies.

This study was limited in that it only evaluated the potential impacts of contact precautions, not the methods by which contact precautions may be enhanced. Future studies could build upon this work by also examining communication and screening policies as adjuncts to contact precautions. Still, given that contact precautions are the most common policy hospitals are willing to adopt to contain CRE spread, this study presents important evidence to support policy implementation.

The results of this study demonstrate the inter-dependence of infection prevention policies targeting different pathogens and the need to consider the interactions of these institutional level policies with patient intrapersonal factors, such as co-colonization, in infection prevention. For example, because contact precautions policies for endemic MDROs could have prevented 14% of healthcare facility exposure to CRE during the CRE carriers index admissions, CDCs CRE toolkit recommendations might consider urging hospitals to not only isolate those who are identified as CRE carriers, but to also continue to use contact precautions for the endemic MDROs which are often co-carried with CRE. Future infection prevention policies must work towards a more ecological, less disease-specific approach that considers the potential implications of policy changes on all MDROs, rather than simply those the policy was originally intended to combat.

Chapter 4

Conclusion

The infectious spread of emerging MDROs such as CRE places high morbidity and mortality burdens on patients within the healthcare system. In this study, one-third of CRE carriers died within a year of their first positive microbiology study. Given the high mortality rate, lack of antibiotic treatment options, and rapid spread within California, CRE represents a key target for infection prevention containment efforts. Transmission of pathogens between people drives the emergent spread of CRE. Recognizing the importance of this social ecological component in the spread of CRE, the studies described here showed how factors at three levels - the patient, the hospital, and the nursing home - interact through inter-facility patient sharing to influence individual patient carriage of CRE and future visits to healthcare facilities that could further spread this dangerous pathogen. After identifying how these factors interact, I then considered the effects of two different surveillance definitions. Surveillance definitions are critical for identifying and then containing CRE. Finally, I used the social ecological principle of multiple levels of influence to examine how the interaction of factors at the institutional and intrapersonal levels impacts the social validity and unintended effects of contact precautions policies used to control MDROs.

These studies began necessary CRE surveillance in a region in which CRE is still emerging to understand the current extent of CRE spread and identify targets for intervention. The results demonstrate that CRE is spreading rapidly across California, exposing healthcare facilities, and patients within them, as CRE carriers move via inter-facility patient sharing. However, the order of magnitude difference in CRE prevalence between the Northern and Southern California regions (21 northern cases vs. 217 southern per 100,000 patients) found in this study confirms that CRE is still emerging in California, with the bulk of spread occurring in Southern California. Containment efforts should focus on Southern California to help prevent the spread of CRE throughout the state.

The results of these studies confirm the importance of CRE containment by demonstrating its high mortality, which was 35

Definitions of sickness and disease are culturally specific and control social response to illness. Changes in CRE surveillance definitions directly impact the ability of healthcare facilities to identify CRE carriers and prevent the spread of CRE using infection control practices such as contact precautions policies. The results of this study showed that the use of the more restrictive 2012 CDC surveillance definition for CRE resulted in decreased identification of CRE carriers as compared to the 2015 definition. The undetected carriers had a high rate of healthcare facility exposure following identification of their CRE carrier status. These unrealized opportunities for CRE carrier identification may have caused even greater, uncontrolled spread of strains missed by the 2012 definition. Because these missed strains were already circulating abroad in 2012, at the time of the original CDC CRE definition, this study demonstrates the importance of taking a global perspective and acknowledging the tight epidemiological links which exist across geopolitical boundaries when defining MDROs in the United States. In addition to earlier application of targeted infection control policies, a more proactive approach to MDRO control includes broader thinking in the creation of surveillance definitions, including consideration of world-wide epidemiological trends.

Because CRE is currently rare, proactive approaches to controlling emerging MDROs are uncommon, and funding for such measures is extremely limited, active surveillance for CRE via screening is not typically performed, despite CDC recommendations. However, patients are routinely screened for endemic MDROs. For example, in California, hospitals are required by law to screen patients for MRSA, the most common MDRO. Endemic MDROs share many risk factors with emerging MDROs, and co-colonization is common. Given that nearly half of the CRE carriers in this study were found to be co-colonized with endemic MDROs, institutional contact precautions policies for endemic MDROs can be leveraged to decrease time to contact precautions for CRE carriers in healthcare facilities. Contact precautions policies for endemic MDROs can improve institutional level safety for all patients by isolating patients who are eventually found to harbor CRE an average of ten days before their CRE carrier status is known.

More generally, this study showed that hospital infection prevention policies intended to prevent the spread of endemic MDROs also act to contain other, emerging MDROs for which no policy yet exists. As healthcare facilities consider policy changes, such as discontinuing contact precautions policies for endemic MDROs, it is important to consider how multiple levels of influence control health outcomes at the patient level in order to prospectively avoid undesirable policy impacts. Such considerations illuminate the true costs of discontinuation of contact precautions for endemic MDROs by highlighting their effects on emerging MDROs. By quantifying these effects, this study provides justification for reinstituting discontinued precautions policies. Future infection prevention policies must work towards a more ecological, less disease-specific approach that recognizes the inter-dependence of infection prevention policies and considers the potential implications of policy changes on all MDROs, endemic and emerging.

As the population in the United States ages, it becomes increasingly important to understand how factors at multiple levels of influence, including institutional infection prevention policies

and patient level comorbidity, contribute to the population burden of infectious disease. CRE can serve as one indicator to help understand the threat posed by MDROs to public health in an aging population and to provide a social ecological model of emerging MDRO epidemiology to assess regional strategies for controlling pathogen spread. The high mortality and risk of CRE exposure across healthcare facilities due to inter-facility patient sharing measured in this study should motivate collaborative, proactive work among healthcare facilities in regional networks to limit the spread of CRE. Through use of an ecological model of emerging MDRO epidemiology, proactive interventions, such as contact precautions, can be targeted to reduce the burden of emerging MDROs.

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