ANTIBIOTIC STEWARDSHIP IN AMERICAN NURSING HOMES

by

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Antibiotic Use in American Nursing Homes

Abstract

by

REBECCA ROSALY CARTER

Antibiotic resistance is a public health crisis. Infections caused by antibiotic resistant bacteria lead to over 2.5 million infections and 23,000 deaths annually in the United States (US). Non-judicious use of antibiotics can accelerate what should be avoidable selective pressure, accelerating the evolution of antibiotic resistant bacteria.

Although any antibiotic exposure, whether appropriate or not, may contribute to the selection of antibiotic resistant bacteria, failure to follow clinical prescribing guidelines make the problem worse. In American Long-Term Care Facilities (LTCFs) up to 75% of antibiotic prescriptions do not meet these guidelines. Antibiotic stewardship, which seeks to minimize inappropriate or unnecessary antibiotic use, is one solution to combating antibiotic-resistant bacteria. Antibiotic stewardship is urgently needed in LTCFs to improve resident outcomes and to reduce selection for antibiotic-resistant bacteria.

Driven by both the increasing prevalence of antibiotic-resistant bacteria and recent federal mandate from the Centers for Medicare and Medicaid Services, LTCFs across the US are rapidly implementing antibiotic stewardship programs (ASPs). ASPs are coordinated approaches for harmonizing competing concerns of adequate spectrum of coverage, adverse events, and resistance. The CMS mandate will be enforced through a range of sanctions ranging from civil fines to closure of the facility. To date, LTCFs have been slow

to adopt stewardship measures. Studies of US LTCFs are limited and there is also a paucity of well-validated strategies specific to these healthcare settings. Despite emerging evidence of successful stewardship in a selection of US LTCF settings, adoption may be bottlenecked due to personnel who may lack training or experience in data collection and analysis, funding or logistical constraints, prescriber's decision-making autonomy, or few electronic resources.

The objective of this dissertation is to examine the patterns of antibiotic use in LTCFs, as well as views of LTCF providers about that use. Such knowledge should provide critical information necessary to design strategies for improving antibiotic stewardship in LTCFs. Our goal is to identify actionable, pragmatic targets to support specific strategies for responsible antibiotic use with the intent of improving care of LTCF residents.

Chapter 1

Introduction

1.1 The problem of antibiotic resistant bacteria

Antibiotics are powerful drugs that treat bacterial infections. At the time of their discovery the first half of the 20^{th} century, researchers and clinicians alike assumed that the evolution of antibiotic resistance was unlikely [1]. The widely held assumption was that the frequency of mutations generating resistant bacteria was both trivial and inconsequential [2]. However, the same year that clinical evidence of the first commercially available antibiotic penicillin G was reported, another publication observed that penicillin G could be rendered inactive by enzymatic degradation [3], [4]. The scientist who discovered penicillin G, Alexander Fleming, stated in a 1945 New York Times interview shortly after winning the Nobel prize for his discovery, “the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out…. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted” [5].

New antibiotic agents will always be needed in modern medicine, however antibiotic drug development has not kept pace with antibiotic resistance [6]. More than 2.5 million infections and 23,000 deaths caused by antibiotic resistant bacteria occur each year in the United States (US) [7], [8]. Infections caused by antibiotic resistant bacteria generate higher medical costs ($6,000 - $30,000/per patient), resulting in direct costs of $20 billion per year coupled with productivity losses of $35 billion [7], [9]–[11]. The public health crisis caused by antibiotic resistant organisms spurred the World Health Organization to warn that the world is on the cusp of an era in which antibiotics will become less effective. The United Nations declared that antibiotic resistance represents one of the most important threats to global health [12], [13]. Antibiotic resistance is a natural process, where bacteria are under selective pressure to pass on favorable characteristics either by mutation or by exchange of genetic material that make them more likely to survive and reproduce [14]–[17]. Non-judicious use of antibiotics can accelerate avoidable selective pressure, hastening the accumulation of antibiotic resistant bacteria [8], [18].

Infection by antibiotic resistant bacteria limits the antibiotics available for effective treatment. Additionally, people may become colonized with antibiotic resistant bacteria, rendering subsequent infections more difficult to treat. Once colonized, individuals may harbor resistant bacteria for years [19], [20]. People infected or colonized with antibiotic resistant bacteria become reservoirs for those pathogens, contributing to their prevalence. Antibiotic resistance cannot be eliminated but its emergence and spread can be mitigated. The limitations of the antibiotic drug development pipeline has precipitated the need for other solutions, including antibiotic stewardship [6].

1.2 Reducing antibiotic resistant bacteria through stewardship

Antibiotic stewardship is defined as “the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance" [21]. This approach is one of the fundamental actions recommended by the Centers for Disease Control and Prevention (CDC) for reducing antibiotic resistant infections [8]. Stewardship strategies can include selection of narrow-spectrum agents, staff and provider education, or shortened treatment durations [22]. Inappropriate and/or unnecessary antibiotic prescribing contributes to the burden of antibiotic resistant bacteria and exacerbates the emergence and spread of antibiotic resistant infections. Inappropriate and/or unnecessary antibiotic prescribing encompasses several domains: (1) Antibiotic prescribing for a condition where an antibiotic is not indicated, such as for a viral infection; (2) Antibiotic selection for a condition that does not warrant treatment; (3) Prolonged duration of therapy when shorter duration of therapy is equally effective; (4) Choice of antibiotic route of administration, such as use of intravenous agents when oral agents are likely to be equally effective [23]. Antibiotic stewardship programs (ASPs) are coordinated approaches for harmonizing competing concerns of adequate spectrum of coverage, adverse events, and resistance, can be a solution in preserving the efficacy of antibiotics for the future [24]. In a joint position statement from the Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Disease Society (PIDS), stewardship was declared a "fiduciary responsibility for all healthcare institutions" and mandatory implementation was recommended [25]. Given the importance of ASPs in reducing the proliferation of antibiotic-resistant bacteria, this dissertation will examine influences that promote inappropriate and/or unnecessary antibiotic prescribing decisions with the goal of improving implementation of such programs.

Since their inception, ASPs have proven highly successful in improving judicious use of antibiotics [26]. A systematic review of 32 studies by Baur *et al*. concluded that ASP implementation was associated with a reduction in incidence of infections (*i.e.* the patient shows signs and symptoms in the presence of bacteria) and colonization (*i.e.* the patient has no signs or symptoms in the presence of bacteria) of antibiotic-resistant bacteria for hospital patients [27], [28]. Notably, ASP interventions became more effective over time, with a 10% reduction of antibiotic resistance from 1980-2000 to a 32% reduction from 2006-2013 [27]. Substitution of one antibiotic to a comparable antibiotic in terms of spectrum of activity was found to be the most effective ASP intervention strategy, followed by audit and feedback [29], [30]. However, the vast majority of our current knowledge about successful ASPs comes from hospital settings [31]–[33]. Studies by Cooper *et al.* and Huang *et al.* demonstrated that the reduction of infection and colonization in hospitals provide evidence for the need to have ASPs beyond this setting [34]–[36]. For example, the prevalence of asymptomatic individuals colonized with particular strains of antibiotic-resistant bacteria in hospitals reached estimates of up to 10% [34]. In long-term care facilities (LTCFs) this prevalence is approximately 50%, suggesting ASPs can be relevant and necessary for this healthcare environment [34], [37], [38].

1.3 The need for antibiotic stewardship in long-term care facilities

Long-term care facilities (LTCFs) are an important setting for antibiotic stewardship. Hospital-tested ASPs have been successful at reducing potentially inappropriate prescribing, but applying those ASPs directly to the LTCF setting may be unrealistic. Like hospitals, LTCFs provide some healthcare services, including rehabilitation. Unlike hospitals, LTCFs are residential settings with a mandate of care for the social, emotional and spiritual well-being of their residents. Most LTCFs are resource limited settings without ready access to infrastructure or organizational supports necessary for robust ASPs. LTCF residency is the strongest known risk factor for residents to be colonized with and develop infections with antibiotic resistant bacteria [39]. Colonized residents can spread antibiotic resistant bacteria to other LTCF residents, as well as to individuals in other health care settings through transitions of care [40]. In US LTCFs up to 75% of antibiotic prescriptions do not meet clinical prescribing guidelines, suggesting LTCFs are a major site of inappropriate and/or unnecessary antibiotic use [41], [42]. Studies of American LTCFs are limited and there is also a paucity of well-validated strategies specific to those healthcare settings [43], [44].

To address the prevalence of antibiotic resistant bacteria in LTCFs driven by inappropriate and/or unnecessary antibiotic use, in 2016 The Centers for Medicare and Medicaid services (CMS) finalized their mandate for comprehensive implementation of an antibiotic stewardship program (ASP) and a system for monitoring antibiotic use in all US nursing homes as a condition of participation [45]. This mandate will be enforced through a range of sanctions, including civil fines or closure of the facility [46]. Given that funding of most US nursing homes is highly dependent on CMS reimbursement, this mandate will likely have large consequences [47].

In 2017 the CDC released their Core Elements for Antibiotic Stewardship in Nursing Homes to provide guidance for LTCF antibiotic stewardship program development [48],

[49]. Seven core elements associated with successful ASPs were identified: (1) Leadership commitment; (2) Accountability; (3) Drug expertise; (4) Action-oriented policies and practices (including clinical guidelines and communication guides); (5) Tracking antibiotic use and outcomes, (6) Reporting regular feedback on antibiotic use and resistance outcomes to providers and staff; and (7) Education of providers, staff, residents, and families. [48]. The goal of the Core Elements was to provide a framework for implementing an antibiotic stewardship program, regardless of facility size or resources [50]. Yet when the top academic centers and hospitals with established and successful ASP programs were surveyed, researchers found that although there was a general agreement that good stewardship programs were essential, there was little consensus on the best approach [51]. To date, LTCFs have been slow to adopt stewardship measures. Despite emerging evidence of successful stewardship in a selection of US LTCF settings, adoption may be impeded by funding or logistical constraints, personnel who may lack training or experience in data collection and analysis, a prescriber's decision-making autonomy, or few electronic resources [22], [43], [52]–[55]. The goal of this dissertation is to examine antibiotic prescribing patterns in LTCFs, along with LTCF providers sharing their perception of influences on those patterns, to help to identify opportunities to achieve effective antibiotic stewardship practices in LTCFs.

1.4 Background on Long-Term Care Facilities (LTCFs)

LTCFs house a clinically distinct and vulnerable population of the US, where infections represent a prevalent and potentially modifiable cause of death [8], [18], [56]–[60]. Approximately 1.4 million people reside in these facilities, accounting for 3.6% of the US population over the age of 65 [61]. Co-morbid conditions and immunosenescence (*i.e.* functional decline in the immune response with age) increases the vulnerability of older adults to infections [62]. The CDC estimates approximately 1 to 3 million serious infections occur in LTCF residents annually and that as many as 380,000 succumb to these infections per year [63], [64]. Infections account for almost one-quarter of hospitalizations among LTCF residents, making them the primary cause for hospital admission [59], [65]. The high risk of infection among frail older adults contributes to antibiotics being the most commonly prescribed medications in American LTCFs, where up to 15% of residents have an active prescription for an antibiotic at any given time [66], [67]. The majority of antibiotic prescriptions in an LTCF are considered inappropriate and/or unnecessary [67]. For example, instances of asymptomatic bacteriuria are often inappropriately treated in the LTCF setting [22], [68]. Despite there being no evidence of clinical benefit from treatment antibiotic therapy for asymptomatic bacteriuria remains common in practice [69]. LTCFs represent a challenging environment for introducing and sustaining stewardship strategies in the unique context of their frail population, communal setting, and provider practices.

1.5 Decision making and antibiotic prescribing in LTCFs

In order to improve antibiotic prescribing practices in LTCFs it is important to recognize the decision-making process involved. Ideally, the decision to prescribe an antibiotic in a LTCF can begin with a diagnosis of an infection, subsequent sensitivity testing of the infecting pathogens, followed by the decision of whether or not to prescribe an antibiotic [42]. In practice, however, the decision to prescribe starts with a clinical concern or change in status of a resident. The subsequent evaluation process may be governed by interpretation of clinical signs and symptoms, or incorporation of accessory investigations such as a test, culture, or use of guidelines to support the decision to prescribe an antibiotic [70], [71]. LTCFs have a number of compelling subjective considerations when adopting stewardship measures that can vary from a case to case and facility to facility that depend on an interplay of influences (**Figure 1**) [72], [73].

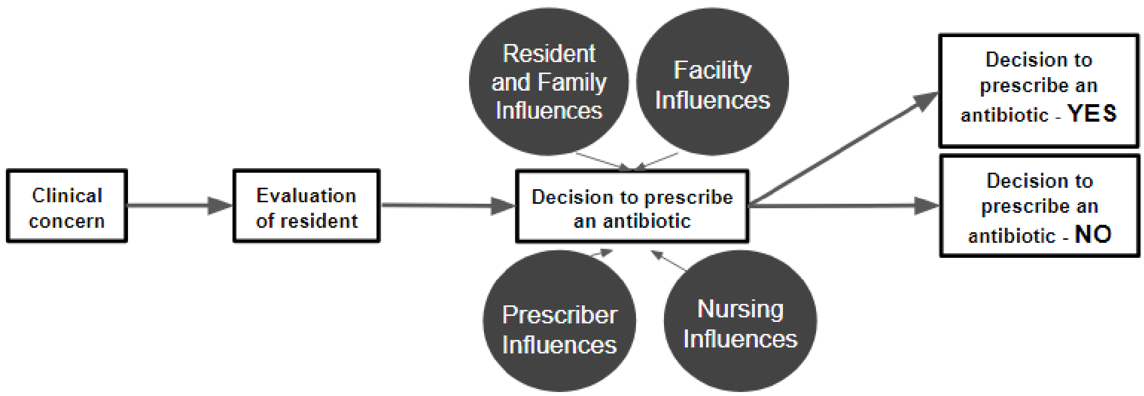


Figure 1. Concept map of factors influencing the decision to prescribe an antibiotic in LTCFs

An initial step in the assessment of LTCF antibiotic use involves understanding the context in which the decision to prescribe an antibiotic in an LTCF occurs. This includes the influence of prescribers, residents and family members, nursing staff, and the facility [74], [75].

Provider factors can include fear of withholding or adjusting treatment, resistance to change, lack of agreement or awareness of guidelines, and a prescriber's decision-making autonomy [76]. Additional factors can include constraints on time, information, and organizational culture considerations such as hierarchical roles among LTCF staff [77].

Studies show most antibiotic stewardship strategies fail to consider these factors in their approach which may lead to suboptimal intervention effectiveness or impede implementation [78].

1.5.1 Prescriber influences related to antibiotic prescribing decisions in LTCFs

Previous research suggests that prescriber practice patterns, rather than the clinical needs of the residents, drive antibiotic use in LTCFs [73], [79], [80]. For example, LTCF residents are frequently treated with broad-spectrum antibiotics [81]–[83]. There is considerable variation in broad-spectrum antibiotic prescribing in LTCFs, particularly for fluoroquinolones, that cannot be accounted for by any context of facility, demographic factors, or variation in the incidence of infections [84]. Prolonged duration of antibiotic therapy in LTCFs has also been indicated as a function of prescriber preference rather than resident characteristics [85]. In a study by Daneman *et al*., researchers sought to describe the variability in the duration of antibiotic courses from a cohort of LTCFs from the Canadian province of Ontario. The mode of antibiotic treatment course was 7 days (41.0%), but 44.9% of courses exceeded 7 days [85]. Broad-spectrum antibiotic therapy or duration of therapy may indicate prescribing patterns of interest among US LTCFs.

Provider knowledge, attitudes, and behavior can take precedent in dictating resident care. The vast majority (85%) of medical providers who prescribe antibiotics in LTCFs are community-based physicians with training in family or internal medicine but not geriatrics [72], [86]. Population-based studies of LTCF prescribers showed a tendency describe the choice of broad-spectrum fluoroquinolones as a “socially responsible” decision that would expedite resolution of the infection and avoid hospital admission of their residents [87]. Studies suggest LTCF prescribers are biased toward being risk averse, tending to treat potential infections more aggressively than clinical guidelines dictate or recommending unnecessary hospital transfers [88]. Other related factors that may influence the decision to prescribe are medical provider's rejection of clinical guidelines and policies that they may perceive to encroach on their professional autonomy [79], [89]. Specifically, some LTCF prescribers may hold the belief that facility residents are "outside" evidence-based policies and guidelines, which has been previously reported as a key influential factor of their antibiotic prescribing behavior [76], [90]. Prescribers may also believe that antibiotics can only help and not harm the resident or lack of awareness of the problem of resistance and the effects of antibiotic prescribing on resistance [91], [92]. Deciding who benefits from antibiotics is challenging, and a prescribers' perception of a resident's severity with nonspecific symptoms will compel them to prescribe antibiotics in order to err on the side of caution [70] [93].

1.5.2 Resident and family influences related to antibiotic prescribing decisions in LTCFs

Resident and family preferences are a common influential factor, where LTCF providers (*i.e.* medical providers and nurses) cited both perceived or real resident and family expectations for an antibiotic as a barrier to stewardship [54], [94]**.** Expectations by residents and families can strongly influence antibiotic prescribing but are mediated by their knowledge, beliefs, and experience with antibiotics [95]. Prescribers within an LTCF may anticipate that failing to prescribe may induce resident or family dissatisfaction or that attempts to dissuade the family from requesting an antibiotic may impact consultation time constraints [96], [97].

The use of antibiotics at the end of life can be a particularly illustrative domain of the interplay of influences on the decision to prescribe. Studies show the use of antibiotic therapy in this domain can be highly emotional [98]. The role of antibiotics for end-of-life care in geriatric population is an evolving area, where providers making care decisions must consider not only clinical guidelines for starting treatment with antibiotic therapy but also whether such treatment aligns with the goals of care such as extending life or providing relief [99], [100]. As early as 1979 providers made the conscious choice to withhold treatment of antibiotics among debilitated end-of-life LTCF residents that presented with fever, a typical proxy for infection [71], [101]. Almost 30 years later, the interaction between resident, family, and provider became more elaborate, as demonstrated from a cohort study of 214 residents with advanced dementia from 21 Boston-area LTCFs [102]. Results of the 18-month prospective study showed the proportion of residents prescribed antibiotic therapy was 7 times greater in the last 2 weeks of life compared with 6 to 8 weeks before death [102]. The decision to prescribe for end-of-life decisions is complex, given the influence of resident and family preferences, presenting an additional need for successful implementation of antibiotic stewardship in any given LTCF setting [103].

1.5.3 Nursing influences related to antibiotic prescribing decisions in LTCFs

Medical providers may not be onsite in the case of a clinical event that requires the decision prescribe an antibiotic [43]. Therefore these providers must often rely on clinical information gathered by LTCF nursing staff. LTCF nursing staff may not be trained to evaluate residents with a possible infection. LTCF nurses may hold misconceptions about resident infections, including the belief that the presence of bacteria in urine is reason enough to prescribe an antibiotic [104]. Nursing staff may also face time or logistical constraints that can affect the quality of their evaluation [105]. Some LTCF programs use clinical guidelines such as the Loeb Minimum Criteria for antibiotic initiation, but nurses and medical providers reported difficulty in reducing antibiotic prescribing despite incorporating these guidelines into practice [96].

Beyond antibiotic prescribing, communication among LTCF providers can impact resident care. In a LTCF, prescribing decisions often rely on telephone communication to off-site medical providers. As decisions are often based on limited diagnostic or clinical information, nurses and their aides must communicate their assessments and findings to the medical provider on-call who may not know the resident and may not be well-versed in LTCF care [70]. The quality of communication between nurses and medical providers is an important influence on the decision to prescribe. Nurses may perceive medical providers to rush communication or ignore their views [105]. Nurses also may face logistical challenges such as a lack of privacy or have personal barriers in organizing and communicating resident information [105]. The nurses' workload, hierarchical roles and relationships, and heterogeneous priorities can also complicate communication [106]. One communication protocol used in healthcare is the SBAR (Situation, Background, Assessment, and Recommendation). This approach has been found useful to organize information and cue nurses on what information to communicate to off-site providers.

While useful, the SBAR tool has not yet become firmly entrenched into routine clinical communication between LTCF nursing staff and providers [107].

1.5.4 Facility influences related to antibiotic prescribing decisions in LTCFs

The LTCF setting can also influence antibiotic prescribing practices. LTCFs settings often lack the electronic infrastructure to support measurement of antibiotic use [108]. LTCFs may also be impeded by financial barriers or limited resources for diagnostic testing from a microbiology laboratory [109]. Additional barriers may include a lack of access to infectious disease experts or appropriate staff training to interpret results from diagnostic testing [110]. This lack of access to diagnostic equipment, specialists, or may delay the opportunity for LTCF medical providers to reduce antibiotic use or narrow the therapeutic spectrum [111]. This promotes an environment in an LTCF where prescribers may opt for a "treat first then diagnose" approach to address potential infections [22].

Diagnosing and treating infections among LTCF residents can present challenges even to experienced providers. Access to rapid diagnostic methods are often not available, delayed, or used insufficiently due to difficulties with interpretation or correlation with other medical data [73]. This array of challenges fall under the collective term of "diagnostic uncertainty," which studies show contributes to inappropriate and/or unnecessary antibiotic use in LTCFs.

1.6 Specific aims and hypothesis

Our research question is: Can an examination of influences that promote inappropriate and/or unnecessary antibiotic prescribing decisions in LTCFs support identification of specific characteristics that may advance effective LTCF antibiotic stewardship? I hypothesize that assessing antibiotic prescribing patterns in LTCFs, along with LTCF providers sharing their perception of influences on those patterns, will help to identify opportunities to achieve effective antibiotic stewardship practices in LTCFs. To address this complex issue, this study has been divided into two components: (1) Demonstrating the utility of existing data to characterize patterns of antibiotic use, thereby supporting identification of possible targets for change that are specific to individual LTCFs, and (2) Identifying features of LTCFs associated with judicious antibiotic use. We will test our hypothesis via the following specific aims:

Specific Aim 1: To use pharmaceutical invoices to describe patterns of antibiotic use within US LTCFs.

Hypothesis 1: Existing pharmaceutical invoice data can adequately characterize patterns of antibiotic use in LTCFs and suggest facility-tailored targets for evaluation and possible reduction.

Specific Aim 2: To identify features of US LTCF environments associated with lower rates of overall antibiotic use by exploring the qualitative views by LTCF leadership concerning antibiotic stewardship, within the context of comparative quantitative reports of the LTCF's antibiotic use data.

Hypothesis 2: LTCFs with more judicious antibiotic use will have an environment more favorable to antibiotic stewardship than LTCFs with less-judicious antibiotic use.

This dissertation is organized into 4 chapters. The first chapter provides the background on inappropriate antibiotic use, antibiotic resistance, and the crisis of antibiotic use in nursing homes. Chapter 2 and 3 address each aim of this dissertation. Chapter 4 provides a general discussion and conclusion for the body of this work.

1.7 References:

[1] A. Van Hoek, D. Mevius, B. Guerra, P. Mullany, A. Roberts, and H. Aarts, “Acquired antibiotic resistance genes: An overview,” *Front. Microbiol.*, vol. 2, no. SEP, pp. 1–27, 2011.

[2] J. Davies, “Inactivation of antibiotics and the dissemination of resistance genes,” *Science*, vol. 264, no. 5157, pp. 375–382, 1994.

[3] E. Chain, H. Florey, A. Gardner, N. Heatley, M. Jennings, J. Orr-Ewing, and A. Sanders, “Penicillin as a chemotherapeutic agent,” *Lancet*, vol. 236, no. 6104, pp. 226–228, 1940.

[4] E. Abraham and E. Chain, “An enzyme from bacteria able to destroy penicillin,” *Nature*, vol. 3713, pp. 146–837, 1940.

[5] T. Parker-Pope, “Free antibiotics may contribute to drug resistance, officials say,” *New York Times*, p. A22.

[6] R. J. Fair and Y. Tor, “Perspectives in Medicinal Chemistry Antibiotics and Bacterial Resistance in the 21st Century,” *Perspect. Medicin. Chem.*, pp. 25–64, 2014.

[7] L. L. Maragakis, E. N. Perencevich, and S. E. Cosgrove, “Clinical and economic burden of antimicrobial resistance,” *Expert Rev. Anti. Infect. Ther.*, vol. 6, no. 5, pp. 751–763, 2008.

[8] Centers for Disease Control and Prevention, “Antibiotic Resistance Threats in the United States,” 2013. [Online]. Available: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar- threats-2013-508.pdf.

[9] R. R. Roberts, B. Hota, I. Ahmad, R. D. Scott, S. D. Foster, F. Abbasi, S. Schabowski, L. M. Kampe, G. G. Ciavarella, M. Supino, J. Naples, R. Cordell, S. B. Levy,

and R. A. Weinstein, "Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship," *Clin. Infect. Dis.*, vol. 49, no. 8, pp. 1175–1184, 2009.

[10] World Health Organization, "Antimicrobial resistance: global report on surveillance," 2014. [Online]. Available: http://www.who.int/drugresistance/documents/surveillancereport/en/.

[11] H. Gelband, "The State of the World's Antibiotics 2015," *Wound Heal. South. Africa*, vol. 8, no. 2, pp. 30–34, 2015.

[12] S. Reardon, "Antibiotic resistance sweeping developing world: bacteria are increasingly dodging extermination as drug availability outpaces regulation," *Nature*, vol. 509, no. 7499, pp. 141–143, 2014.

[13] United Nations, "High-Level Meeting on Antimicrobial Resistance." [Online]. Available: http://www.un.org/pga/71/2016/09/21/press-release-hl-meeting-on-antimicrobial-resistance/. [Accessed: 10-Dec-2016].

[14] P. Sarkar and I. M. Gould, "Antimicrobial agents are societal drugs: How should this influence prescribing?," *Drugs*, vol. 66, no. 7, pp. 893–901, 2006.

[15] J. Davies and D. Davies, "Origins and Evolution of Antibiotic Resistance," *Microbiol. Mol. Biol. Rev.*, vol. 74, no. 3, pp. 417–433, 2010.

[16] B. Spellberg, R. Guidos, D. Gilbert, J. Bradley, H. Boucher, and W. Scheld, "The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America," *Clin. Infect. Dis. An Off. Publ. Infect. Dis. Soc. Am.*, vol. 46, pp. 155–64, 2008.

[17] T. Van Schooneveld, "Antimicrobial stewardship: attempting to preserve a

strategic resource," *J. Community Hosp. Intern. Med. Perspect.*, vol. 1, no. 2, pp. 1–7, 2011.

[18] C. L. Ventola, "The antibiotic resistance crisis: part 1: causes and threats," *Pharm. Ther.*, vol. 40, no. 4, pp. 277–283, 2015.

[19] R. B. Slayton, D. Toth, B. Y. Lee, W. Tanner, S. M. Bartsch, K. Khader, K. Wong, K., Brown, J. A. McKinnell, W. Ray, and L. G. Miller, "Vital signs: estimated effects of a coordinated approach for action to reduce antibiotic-resistant infections in health care facilities—United States," *MMWR. Morb. Mortal. Wkly. Rep.*, vol. 64, no. 30, p. 826, 2015.

[20] S. A. Smith, D. L., Dushoff, J., Perencevich, E. N., Harris, A. D., & Levin, "Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: resistance is a regional problem," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 101, no. 10, pp. 3709–3714, 2004.

[21] D. Gerding, "The Search for Good Antimicrobial Stewardship," *J. Qual. Improv.*, vol. 27, no. 8, pp. 403–404, 2001.

[22] R. Jump, D. Olds, N. Seifi, K. Georgios, L. Jury, E. Peron, A. Hirsch, P. Drawz, B. Watts, R. Bonomo, and C. Donskey, "Effective Antimicrobial Stewardship in a Long-Term Care Facility through an Infectious Disease Consultation Service: Keeping a LID on Antibiotic Use," *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 12, pp. 1185–1192, 2012.

[23] A. L. Hersh and M. P. Kronman, "Inappropriate Antibiotic Prescribing: Wind at Our Backs or Flapping in the Breeze?," *Pediatrics*, vol. 139, no. 4, p. e20170027, 2017.

[24] C. M. Katsios, L. Burry, S. Nelson, T. Jivraj, S. E. Lapinsky, R. S. Wax, M. Christian, S. Mehta, C. M. Bell, and A. M. Morris, "An antimicrobial stewardship program improves antimicrobial treatment by culture site and the quality of antimicrobial

prescribing in critically ill patients.,” *Crit. Care*, vol. 16, no. 6, p. R216, 2012.

[25] N. Fishman, “Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS),” *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 4, pp. 322–327, 2012.

[26] T. M. File Jr, A. Srinivasan, and J. G. Bartlett, “Antimicrobial Stewardship: Importance for Patient and Public Health,” *Clin. Infect. Dis.*, vol. 59, no. Suppl 3, pp. S93–S96, 2014.

[27] D. Baur, B. P. Gladstone, F. Burkert, E. Carrara, F. Foschi, S. Döbele, and E. Tacconelli, “Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis,” *Lancet Infect. Dis.*, vol. 17, no. 9, pp. 990–1001, 2017.

[28] A. Dani, “Colonization and infection,” *Cent. Eur. J. Urol.*, vol. 67, no. 1, pp. 86–87, 2014.

[29] N. Cobos-Trigueros, M. Solé, P. Castro, J. L. Torres, M. Rinaudo, E. De Lazzari, L. Morata, C. Hernández, S. Fernández, A. Soriano, and J. M. Nicolás, “Evaluation of a mixing versus a cycling strategy of antibiotic use in critically-ill medical patients: Impact on acquisition of resistant microorganisms and clinical outcomes,” *PLoS One*, vol. 11, no. 3, p. e0150274, 2016.

[30] S. J. Patel, L. Saiman, J. M. Duchon, D. Evans, Y. H. Ferng, and E. Larson, “Development of an antimicrobial stewardship intervention using a model of actionable feedback,” *Interdiscip. Perspect. Infect. Dis.*, p. 150367, 2012.

[31] S. K. Fridkin and A. Srinivasan, “Implementing a strategy for monitoring inpatient

antimicrobial use among hospitals in the United States," *Clin. Infect. Dis.*, vol. 58, no. 3, pp. 401–406, 2014.

[32] M. K. Yong, K. L. Buising, A. C. Cheng, and K. A. Thursky, "Improved susceptibility of Gram-negative bacteria in an intensive care unit following implementation of a computerized antibiotic decision support system," *J. Antimicrob. Chemother.*, vol. 65, no. 5, pp. 1062–1069, 2010.

[33] T. R. Pasquale, T. L. Trienski, D. E. Olexia, J. P. Myers, M. J. Tan, A. K. Leung, J. E. Poblete, and T. M. File, "Impact of an antimicrobial stewardship program on patients with acute bacterial skin and skin structure infections," *Am. J. Heal. Pharm.*, vol. 71, no. 13, pp. 1136–1139, 2014.

[34] C. C. Cooper, R. L. P. Jump, and T. Chopra, "Prevention of Infection Due to Clostridium difficile," *Infect. Dis. Clin. North Am.*, vol. 30, no. 4, pp. 999–1012, 2016.

[35] S. S. Huang, R. Datta, and R. Platt, "Risk of Acquiring Antibiotic-Resistant Bacteria From Prior Room Occupants," *Arch. Intern. Med. Intern. Med.*, vol. 166, no. 18, pp. 1945–1951, 2006.

[36] S. S. Huang and R. Platt, "Risk of methicillin-resistant Staphylococcus aureus infection after previous infection or colonization," *Clin. Infect. Dis.*, vol. 36, no. 3, pp. 281–285, 2003.

[37] M. Riggs, M. Michelle, A. Sethi, T. Zabarsky, E. Eckstein, R. Jump, and C. Donskey, "Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic Clostridium difficile strains among long-term care facility residents," *Clin. Infect. Dis.*, vol. 45, no. 8, pp. 992–998, 2007.

[38] A. Pop-Vicas, "Multidrug-resistant Gram-negative bacteria in a long-term care

facility: Prevalence and risk factors," *J. Am. Geratric Soc.*, vol. 56, pp. 1276–1280, 2008.

[39] A. March, "Colonization of residents and staff of a long-term care facility and adjacent acute-care hospital geriatric unit by multiresistant bacteria," *J. Antimicrob. Infect.*, vol. 16, pp. 934–944, 2010.

[40] B. Y. Lee, Y. Song, S. M. Bartsch, D. S. Kim, A. Singh, T. R. Avery, S. T. Brown, S. L. Yilmaz, K. F. Wong, M. A. Potter, D. S. Burke, R. Platt, and S. S. Huang, "Long-Term care facilities: Important participants of the acute care facility social network?," *PLoS One*, vol. 6, no. 12, pp. 1–7, 2011.

[41] L. E. Nicolle, D. W. Bentley, R. Garibaldi, G. Ellen, P. W. Smith, T. Care, and E. G. Neuhaus, "Antimicrobial Use in Long-Term – Care Facilities," *Infect. Control Hosp. Epidemiol.*, vol. 21, no. 8, pp. 537–545, 2000.

[42] N. Daneman, S. E. Bronskill, A. Gruneir, A. M. Newman, H. D. Fischer, P. A. Rochon, G. M. Anderson, and C. M. Bell, "Variability in antibiotic use across nursing homes and the risk of antibiotic-related adverse outcomes for individual residents," *JAMA Intern. Med.*, vol. 175, no. 8, pp. 1331–1339, 2015.

[43] G. Dumyati, N. D. Stone, D. A. Nace, C. J. Crnich, and R. L. P. Jump, "Challenges and Strategies for Prevention of Multidrug-Resistant Organism Transmission in Nursing Homes," *Curr. Infect. Dis. Rep.*, vol. 19, no. 18, pp. 1–9, 2017.

[44] M. J. Katz, A. P. Gurses, P. D. Tamma, S. E. Cosgrove, M. A. Miller, and R. L. P. Jump, "Implementing Antimicrobial Stewardship in Long-term Care Settings: An Integrative Review Using a Human Factors Approach," *Clin. Infect. Dis.*, vol. 65, no. 11, pp. 1943–1951, 2017.

[45] Centers for Medicare & Medicaid Services, "CMS issues proposed rule that

prohibits discrimination, reduces hospital-acquired conditions, and promotes antibiotic stewardship in hospitals," 2016.

[46] J. E. Bostick, M. J. Rantz, M. K. Flesner, and C. J. Riggs, "Systematic Review of Studies of Staffing and Quality in Nursing Homes," *J. Am. Med. Dir. Assoc.*, vol. 7, no. 6, pp. 366–376, 2006.

[47] L. S. Johnson, C. MacDougall, and K. K. Trivedi, "The Legislative Momentum of Antimicrobial Stewardship: the US Perspective," *Curr. Treat. Options Infect. Dis.*, vol. 8, no. 2, pp. 93–101, 2016.

[48] L. A. Pollack and A. Srinivasan, "Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention," *Clin. Infect. Dis.*, vol. 59, no. May, pp. S97–S100, 2014.

[49] R. Kaki, M. Elligsen, S. Walker, A. Simor, L. Palmay, and N. Daneman, "Impact of antimicrobial stewardship in critical care: A systematic review," *J. Antimicrob. Chemother.*, vol. 66, no. 6, pp. 1223–1230, 2011.

[50] S. Fridkin, J. Baggs, R. Fagan, S. Magill, L. a Pollack, P. Malpiedi, R. Slayton, K. Khader, M. a Rubin, M. Jones, M. H. Samore, G. Dumyati, E. Dodds-Ashley, J. Meek, K. Yousey-Hindes, J. Jernigan, N. Shehab, R. Herrera, C. L. McDonald, A. Schneider, and A. Srinivasan, "Vital signs: improving antibiotic use among hospitalized patients," *MMWR. Morb. Mortal. Wkly. Rep.*, vol. 63, no. 9, pp. 194–200, 2014.

[51] T. F. Barlam and M. DiVall, "Antibiotic-stewardship practices at top academic centers throughout the United States and at hospitals throughout Massachusetts," *Infect. Control Hosp. Epidemiol.*, vol. 27, no. 7, pp. 695–703, 2006.

[52] T. H. Dellit, R. C. Owens, J. E. McGowan, D. N. Gerding, R. A. Weinstein, J. P.

Burke, W. C. Huskins, D. L. Paterson, N. O. Fishman, C. F. Carpenter, P. J. Brennan, M. Billeter, and T. M. Hooton, "Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship," *Clin. Infect. Dis.*, vol. 44, no. 2, pp. 159–177, 2007.

[53] A. N. Malani, B. M. Brennan, C. D. Collins, J. Finks, J. M. Pogue, and K. S. Kaye, "Antimicrobial Stewardship Practices in Michigan Long-Term Care Facilities," *Infect. Control Hosp. Epidemiol.*, vol. 37, no. 2, pp. 236–237, 2016.

[54] T. Van Schooneveld, H. Miller, H. Sayles, K. Watkins, and P. Smith, "Survey of antimicrobial stewardship practices in Nebraska long-term care facilities," *Infect. Control Hosp. Epidemiol.*, vol. 32, no. 7, pp. 732–734, 2011.

[55] Z. M. Tun, M. Moorthy, M. Linster, Y. C. F. Su, R. J. Coker, E. E. Ooi, J. G.-H. Low, G. J. D. Smith, and C. C. Tam, "Patterns of medication use and factors associated with antibiotic use among adult fever patients at Singapore primary care clinics.," *Antimicrob. Resist. Infect. Control*, vol. 5, p. 47, 2016.

[56] L. J. Strausbaugh and C. L. Joseph, "The burden of infection in long-term care.," *Infect. Control Hosp. Epidemiol.*, vol. 21, no. 10, pp. 674–9, Oct. 2000.

[57] W. S. Aronow, "Clinical causes of death of 2372 older persons in a nursing home during 15-year follow-up," *J. Am. Med. Dir. Assoc.*, vol. 1, no. 3, pp. 95–96, 2000.

[58] N. D. Stone, M. S. Ashraf, J. Calder, C. J. Crnich, K. Crossley, P. J. Drinka, C. V Gould, M. Juthani-Mehta, E. Lautenbach, M. Loeb, T. Maccannell, P. N. Malani, L. Mody, J. M. Mylotte, L. E. Nicolle, M.-C. Roghmann, S. J. Schweon, A. E. Simor, P. W. Smith, K. B. Stevenson, and S. F. Bradley, "Surveillance definitions of infections in long-term

care facilities: revisiting the McGeer criteria.," *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 10, pp. 965–77, Oct. 2012.

[59] S. Zimmerman, A. L. Gruber-Baldini, J. R. Hebel, P. D. Sloane, and J. Magaziner, "Nursing home facility risk factors for infection and hospitalization: Importance of registered nurse turnover, administration, and social factors," *J. Am. Geriatr. Soc.*, vol. 50, no. 12, pp. 1987–1995, 2002.

[60] R. K. Flamm, M. K. Weaver, C. Thornsberry, M. E. Jones, J. a. Karlowsky, and D. F. Sahm, "Factors Associated with Relative Rates of Antibiotic Resistance in Pseudomonas aeruginosa Isolates Tested in Clinical Laboratories in the United States from 1999 to 2002," *Antimicrob. Agents Chemother.*, vol. 48, no. 7, p. 2431, 2004.

[61] L. Harris-Kojetin, M. Sengupta, E. E. Park-Lee, and R. Valverde, "Long-Term Care Services in the United States: 2013 Overview.," *Vital Health Stat. 3.*, no. 37, p. 1, Dec. 2013.

[62] C. M. Faulkner, H. L. Cox, and J. C. Williamson, "Unique aspects of antimicrobial use in older adults," *Clin. Infect. Dis.*, vol. 40, no. 7, pp. 997–1004, 2005.

[63] P. D. Sloane, K. Huslage, C. E. Kistler, and S. Zimmerman, "Optimizing Antibiotic Use in Nursing Homes Through Antibiotic Stewardship," *N. C. Med. J.*, vol. 77, no. 5, pp. 324–329, 2016.

[64] Centers for Disease Control and Prevention, "Long Term Care," 2016. [Online]. Available: https://www.cdc.gov/longtermcare/.

[65] P. W. Irvine, N. Buren, and K. Crossley, "Causes for hospitalization of nursing home residents: the role of infection," *J. Am. Geriatr. Soc.*, vol. 32, no. 2, pp. 103–107, 1984.

[66] L. E. W. Olsho, R. M. Bertrand, A. S. Edwards, L. S. Hadden, G. B. Morefield, D. Hurd, C. M. Mitchell, P. D. Sloane, and S. Zimmerman, "Does Adherence to the Loeb Minimum Criteria Reduce Antibiotic Prescribing Rates in Nursing Homes?," *J. Am. Med. Dir. Assoc.*, vol. 14, no. 4, pp. 2–8, 2013.

[67] L. E. Nicolle, D. W. Bentley, R. Garibaldi, E. G. Neuhaus, and P. W. Smith, "Antimicrobial use in long-term-care facilities. SHEA Long-Term-Care Committee.," *Infect. Control Hosp. Epidemiol.*, vol. 21, no. 8, pp. 537–45, 2000.

[68] R. Jump, D. Olds, L. Jury, B. Sitzlar, E. Saade, B. Watts, R. Bonomo, and C. Donskey, "Specialty Care Delivery: Bringing Infectious Disease Expertise to the Residents of a Veterans Affairs Long-Term Care Facility," *J. Am. Geriatr. Soc.*, vol. 61, no. 5, pp. 782–787, 2013.

[69] T. F. Zabarsky, A. K. Sethi, and C. J. Donskey, "Sustained reduction in inappropriate treatment of asymptomatic bacteriuria in a long-term care facility through an educational intervention," *Am. J. Infect. Control*, vol. 36, no. 7, pp. 476–480, 2008.

[70] C. J. Crnich, R. L. Jump, B. Trautner, P. D. Sloane, and L. Mody, "Optimizing Antibiotic Stewardship in Nursing Homes: A Narrative Review and Recommendations for Improvement," *Drugs and Aging*, vol. 32, no. 9, pp. 699–716, 2015.

[71] K. P. High, S. F. Bradley, S. Gravenstein, D. R. Mehr, V. J. Quagliarello, C. Richards, and T. T. Yoshikawa, "Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America," *Clin. Infect. Dis. An Off. Publ. Infect. Dis. Soc. Am.*, vol. 48, no. 2, pp. 149–171, Jan. 2009.

[72] M. D. Cabana, C. S. Rand, N. R. Powe, A. W. Wu, M. H. Wilson, P.-A. C. Abboud,

and H. R. Rubin, “Why don’t physicians follow clinical practice guidelines?: A framework for improvement,” *Jama*, vol. 282, no. 15, pp. 1458–1465, 1999.

[73] L. E. Nicolle, “Antimicrobial stewardship in long term care facilities: what is effective?,” *Antimicrob. Resist. Infect. Control*, vol. 3, no. 1, p. 6, Feb. 2014.

[74] J. P. Spradley and D. W. McCurdy, *Anthropology, the cultural perspective*. John Wiley & Sons, 1980.

[75] Scott, T.I.M., R. Mannion, H. T. Davies, and M. N. Marshall, “Implementing culture change in health care: theory and practice,” *Int. J. Qual. Heal. Care*, vol. 15, no. 2, pp. 111–118, 2003.

[76] E. Charani, E. Castro-Sanchez, N. Sevdalis, Y. Kyratsis, L. Drumright, N. Shah, and A. Holmes, “Understanding the determinants of antimicrobial prescribing within hospitals: The role of ‘prescribing etiquette,’” *Clin. Infect. Dis.*, vol. 57, no. 2, pp. 188–196, 2013.

[77] R. H. Thaler and C. R. Sunstein, *Nudge: Improving decisions about health, wealth, and happiness*. New Haven, CT: Yales University Press, 1999.

[78] E. Charani, E. R, and S. N, “Behavior change strategies to influence antimicrobial prescribing in acute care: A systematic review,” *Clin. Infect. Dis. An Off. Publ. Infect. Dis. Soc. Am.*, vol. 53, no. 7, pp. 651–652, 2011.

[79] A. Fleming, C. Bradley, S. Cullinan, and S. Byrne, “Antibiotic prescribing in long-term care facilities: a qualitative, multidisciplinary investigation.,” *BMJ Open*, vol. 4, no. 11, p. e006442, 2014.

[80] S. R. Benoit, W. Nsa, C. L. Richards, D. W. Bratzler, A. M. Shefer, L. M. Steele, and J. A. Jernigan, “Factors associated with antimicrobial use in nursing homes: A

multilevel model," *J. Am. Geriatr. Soc.*, vol. 56, no. 11, pp. 2039–2044, 2008.

[81] R. A. Bonomo, "Multiple antibiotic-resistant bacteria in long-term-care facilities: an emerging problem in the practice of infectious diseases," *Clin. Infect. Dis.*, vol. 31, no. 6, pp. 1414–1422, 2000.

[82] M. Viray, D. Linkin, J. N. Maslow, D. Donald, L. S. Carson, W. B. Bilker, E. Lautenbach, and R. Esistance, "Longitudinal trends in antimicrobial susceptibilities across long-term–care facilities: emergence of fluoroquinolone resistance," *Infect. Control Hosp. Epidemiol.*, vol. 26, no. 1, pp. 56–62, 2005.

[83] S. PW and P. Rusnak, "Infection prevention and control in the long-term-care facility," *Infect. Control Hosp. Epidemiol.*, vol. 18, no. 12, pp. 831–849, 1997.

[84] A. Majeed and K. Moser, "Age- and sex-specific antibiotic prescribing patterns in general practice in England and Wales in 1996," *Br. J. Gen. Pract.*, vol. 49, no. 446, pp. 735–736, 1999.

[85] N. Daneman, A. Gruneir, S. E. Bronskill, A. Newman, H. D. Fischer, P. A. Rochon, G. M. Anderson, and C. M. Bell, "Prolonged Antibiotic Treatment in Long-term Care: Role of the Prescriber," *JAMA Intern. Med.*, vol. 173, no. 8, p. 673, 2013.

[86] A. L. Jones, L. L. Dwyer, A. R. Bercovitz, and G. W. Strahan, "The National Nursing Home Survey: 2004 overview," *Vital Heal. Stat.*, pp. 1–155, 2009.

[87] N. Daneman, M. A. Campitelli, V. Giannakeas, A. M. Morris, C. M. Bell, C. J. Maxwell, L. Jeffs, P. C. Austin, and S. E. Bronskill, "Influences on the start, selection and duration of treatment with antibiotics in long-term care facilities," *Cmaj*, vol. 189, no. 25, pp. E851–E860, 2017.

[88] H. J. Morrill, A. R. Caffrey, R. L. P. Jump, D. Dosa, and K. L. LaPlante,

"Antimicrobial Stewardship in Long-Term Care Facilities: A Call to Action," *J. Am. Med. Dir. Assoc.*, vol. 17, no. 2, p. 183.e1-183.e16, 2016.

[89] T. Bridget Giblin, R. L. Sinkowitz-Cochran, P. L. Harris, S. Jacobs, K. Liberatore, M. A. Palfreyman, E. I. Harrison, and D. M. Cardo, "Clinicians' Perceptions of the Problem of Antimicrobial Resistance in Health Care Facilities for the CDC Campaign to Prevent Antimicrobial Resistance Team," vol. 164, pp. 1662–1668, 2004.

[90] B. W. Trautner, N. J. Petersen, S. J. Hysong, D. Horwitz, P. A. Kelly, and A. D. Naik, "Overtreatment of asymptomatic bacteriuria: Identifying provider barriers to evidence-based care," *Am. J. Infect. Control*, vol. 42, no. 6, pp. 653–658, 2014.

[91] C. C. Butler, S. Rollnick, R. Pill, F. Maggs-Rapport, and N. Stott, "Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats.," *BMJ*, vol. 317, no. 7159, pp. 637–42, 1998.

[92] S. A. Simpson, F. Wood, and C. C. Butler, "General practitioners' perceptions of antimicrobial resistance: A qualitative study," *J. Antimicrob. Chemother.*, vol. 59, no. 2, pp. 292–296, 2007.

[93] C. E. Kistler, P. D. Sloane, T. F. Platts-Mills, A. S. Beeber, C. Khandelwal, D. J. Weber, C. M. Mitchell, D. Reed, L. Chisholm, and S. Zimmerman, "Challenges of antibiotic prescribing for assisted living residents: perspectives of providers, staff, residents, and family members.," *J. Am. Geriatr. Soc.*, vol. 61, no. 4, pp. 565–570, 2013.

[94] E. K. Vladar, Y. L. Lee, T. Stearns, and J. D. Axelrod, "Multisite Exploration of Clinical Decision-Making for Antibiotic Use by Emergency Medicine Providers Using Quantitative and Qualitative Methods Larissa," *Infect. Control Hosp. Epidemiol.*, vol. 35, no. 9, pp. 1114–1125, 2014.

[95] J. L. Cosby, N. Francis, and C. C. Butler, “The role of evidence in the decline of antibiotic use for common respiratory infections in primary care,” *Lancet Infect. Dis.*, vol. 7, no. 11, pp. 749–756, 2007.

[96] S. Duane, C. Domegan, A. Callan, S. Galvin, M. Cormican, K. Bennett, A. W. Murphy, and A. Vellinga, “Using qualitative insights to change practice: exploring the culture of antibiotic prescribing and consumption for urinary tract infections.,” *BMJ Open*, vol. 6, no. 1, p. e008894, 2016.

[97] R. McKay, A. Mah, M. R. Law, K. McGrail, and D. M. Patrick, “Systematic review of factors associated with antibiotic prescribing for respiratory tract infections,” *Antimicrob. Agents Chemother.*, vol. 60, no. 7, pp. 4106–4118, 2016.

[98] C. D. Caron, J. Griffith, and M. Arcand, “Decision making at the end of life in dementia: How family caregivers perceive their interactions with health care providers in long-term-care settings,” *J. Appl. Gerontol.*, vol. 24, no. 3, pp. 231–247, 2005.

[99] L. W. van Buul, J. T. van der Steen, R. B. Veenhuizen, W. P. Achterberg, F. G. Schellevis, R. T. G. M. Essink, B. H. B. van Benthem, S. Natsch, and C. M. P. M. Hertogh, “Antibiotic Use and Resistance in Long Term Care Facilities,” *J. Am. Med. Dir. Assoc.*, vol. 13, no. 6, p. 568.e1-568.e13, 2012.

[100] S. Mitchell, M. Shaffer, M. Loeb, J. Givens, D. Habtemariam, D. Kiely, and E. D’Agata, “Infection management and multidrug-resistant organisms in nursing home residents with advanced dementia,” *JAMA Intern. Med.*, vol. 174, no. 10, pp. 1660–1667, 2014.

[101] D. J. Brown, N. K., & Thompson, “Nontreatment of fever in extended-care facilities,” *N. Engl. J. Med.*, vol. 300, no. 22, pp. 1246–1250, 1979.

[102] E. D’Agata and S. L. Mitchell, “Patterns of Antimicrobial Use Among Nursing Home Residents With Advanced Dementia,” *Arch. Intern. Med.*, vol. 168, no. 4, pp. 357–362, 2008.

[103] M. Juthani-mehta, P. N. Malani, A. Arbor, A. Editor, and S. L. Mitchell, “Antimicrobials at the End of Life: An Opportunity to Improve Palliative Care and Infection Management,” *JAMA*, vol. 314, no. 19, pp. 2017–2018, 2015.

[104] J. Scott-Cawiezell, M. Schenkman, L. Moore, C. Vojir, R. P. Connoly, M. Pratt, and L. Palmer, “Exploring nursing home staff’s perceptions of communication and leadership to facilitate quality improvement.,” *J. Nurs. Care Qual.*, vol. 19, no. 3, pp. 242–252, 2004.

[105] S. Renz, M. Boltz, L. Wagner, E. Capezuti, and T. Lawrence, “Examining the feasibility and utility of an SBAR protocol in long-term care,” *Geriatr. Nurs. (Minneap).*, vol. 34, no. 4, pp. 295–301, 2013.

[106] S. N. Hastings, H. E. Whitson, H. K. White, R. Sloane, H. MacDonald, D. A. Lekan, and E. S. McConnell, “After-hours calls from long-term care facilities in a geriatric medicine training program,” *J. Am. Geriatr. Soc.*, vol. 55, no. 12, pp. 1989–1994, 2007.

[107] A. Ashcraft and D. Owen, “Comparison of standardized and customized SBAR communication tools to prevent nursing home resident transfer,” *Appl. Nurs. Res.*, vol. 38, no. July, pp. 64–69, 2017.

[108] L. Gravatt and A. Pakyz, “Challenges in measuring antibiotic consumption,” *Curr. Infect. Dis. Rep.*, vol. 15, no. 6, pp. 559–563, 2013.

[109] E. Stenehjem, A. L. Hersh, X. Sheng, P. Jones, W. R. Buckel, J. F. Lloyd, S. Howe, R. S. Evans, T. Greene, and A. T. Pavia, “Antibiotic Use in Small Community Hospitals,”

Clin. Infect. Dis., vol. 63, no. 10, pp. 1273–1280, 2016.

[110] E. O'Fallon, J. Harper, S. Shaw, and R. Lynfield, "Antibiotic and infection tracking in Minnesota long-term care facilities," *J. Am. Geriatr. Soc.*, vol. 55, no. 8, pp. 1243–1247, 2007.

[111] S. M. Rhee and N. D. Stone, "Antimicrobial stewardship in long-term care facilities," *Infect. Dis. Clin. North Am.*, vol. 28, no. 2, pp. 237–246, 2014.

Chapter 2

Use of Pharmaceutical Invoices to Characterize Antibiotic Patterns in American LTCFs

2.1 Introduction

When the decision to prescribe an antibiotic is made in a long-term care facility (LTCF), one of the most important barriers to stewardship is the paucity of information [1]. Factors affecting the decision to prescribe include the challenges of diagnosing infections that occur among LTCF residents with non-specific symptoms [2]. This includes pneumonia in elderly LTCF residents, where typically defined fever is absent in more than one-half of LTCF residents with serious infection [3]. Clinical diagnosis is further impeded by difficulties in obtaining an accurate history from the resident, as the LTCF population may suffer from dementia or have hearing or speech difficulties [4]. Such challenges can promote antibiotic selections that are often not in accordance with clinical guidelines [5]. Particularly problematic is the tendency of providers to overuse fluoroquinolone antibiotics for suspected urinary and skin infections [1]. These broad spectrum antibiotics can lead to the selection of antibiotic-resistant bacteria and increase the risk of individuals becoming infected with *C. difficile* [6]. Overall, with limited information to support the decision to initiate antibiotic therapy in LTCFs, prescriptions can be excessively broad coverage [7]. Hence, insufficient clinical information prior to the decision to prescribe contributes to inappropriate and/or unnecessary prescriptions for LTCF residents [8], [9].

Research is needed to determine patterns of antibiotic use within an LTCF setting [10]. In the context of factors influencing antibiotic prescribing decisions, it is important that prescribers in LTCF are aware that their individual prescribing patterns can influence the overall antibiotic usage in their LTCF [11]. Studies show that antibiotic treatment duration in LTCFs more of a product of prescriber preference rather than resident characteristics [12]. Historically, duration of antibiotic courses of therapy were driven by a fear of under treating [13], [14]. Despite clinical evidence of the safety and benefits of short-courses (≤ 7 days) of antibiotic therapy for most infections, Daneman *et al.* showed nearly two-thirds of LTCF residents received long-courses of antibiotic therapy (>7 days), with nearly a third treated for ≥ 10 days [15]–[17]. Organizational characteristics may be an important area for investigation. Studies by Banaszak-Holl *et al.* and Harrington *et al.* suggest that LTCF facility size (*i.e.* number of beds) may be an important factor influencing deficiencies in resident outcome. The authors suggest that regardless of services required for a resident population, managing the distribution of staffing hours within an LTCF may be more difficult with increasing number of LTCF beds [18], [19]. However, a 2014 National Healthcare and Safety Network (NHSN) annual survey reported that increasing hospital size is a major predictor for meeting all of the CDC’s core elements of stewardship, but it is unknown if this still holds for LTCFs [20]. Identifying patterns of LTCF use is a key step toward a better understanding of how to implement effective ASPs tailored to each facility setting.

Examining patterns of antibiotic use can facilitate identification and monitoring of targets for improvement, as well as permit evaluation the size of improvement over time. As

LTCFs are now mandated to incorporate stewardship strategies in their facilities, one approach is for LTCFs to track and report patterns of their antibiotic use [21], [22]. According to Crnich *et. al*, the capacity to measure and track process and outcomes is a fundamental characteristic of successful quality improvement [16]. However, there are challenges to obtaining antibiotic use data in LTCFs. Many estimates of LTCF antibiotic use almost exclusively rely on proprietary measurement systems that are not necessarily available to all LTCFs [23]. Although electronic health data might be a viable option in other healthcare settings, there can be difficulties in acquiring specific usage measures within LTCFs. This is due to their limited information technology support and funding constraints [24], [25]. Accordingly, selection of a data source to examine patterns of antibiotic use will need to take into consideration the paucity of resources available to this setting.

Our understanding of patterns of antibiotic use in American LTCFs is limited, but use of existing data may serve as a valuable resource for results generalizable to LTCF residents [26]–[31]. Insight from existing data can have high impact when drawn from a combination of data sources, as opposed to a single data source. This technique is called data linkage, defined as large-scale integration and analysis of heterogeneous data sources [32]. However, gaining utility from existing data and linking it is extraordinarily challenging [33], [34]. Capturing useful information requires data access permissions, standardization of data elements, and developing epidemiologic methods to use the data [35]. Therefore, systematic and detailed methodologies are required in order to reduce the effort necessary for processing the data and subsequently evaluate patterns of antibiotic use.

We sought to capitalize on pharmaceutical invoice data as a means to characterize antibiotic use in American LTCFs. Prior retrospective studies with access to pharmaceutical and administrative data for the purpose of evaluating antibiotic use patterns have been established for hospitals, although the data were extracted exclusively from major existing data warehouses and for large academic medical centers [36]–[39]. An advantage of using pharmaceutical invoice data is that it does not require additional data collection or rely on self-reported outcomes by facilities or providers [40]. Because invoice data is carefully audited they are highly accurate [41]. However, an important limitation of invoice data is that treatment indication is not recorded, and must be inferred from other sources of information such as agent and length of therapy [40]. We hypothesized that LTCFs that prescribe longer courses of antibiotics (>7 days) will have a greater number of beds and fewer daily nursing hours per resident compared to LTCFs that use shorter courses (≤7 days) of antibiotics. To test our hypothesis, we conducted a retrospective cohort study of 29 LTCFs with pharmaceutical invoice data to assess the rates and length of therapy of antibiotics.

2.2 Methods

2.2.1 Study cohort: Data source

The Louis Stokes Cleveland Veterans Affairs Medical Center institutional review board approved the research protocol. This study was a retrospective study of 29 community-based LTCFs located in the Midwest from the same for-profit network that shared a common pharmacy. The network provided census data and occupancy rates for each facility as well as pharmaceutical invoice data. We used two data sources to determine nursing home characteristics, the Minimum Data Set (MDS) and Nursing Home Compare, a website developed by the Center for Medicare and Medicaid Services (CMS). The variables included are defined in **Supplementary Table 2.1** and **Supplementary Table 2.2** [42]–[44].

2.2.2 Prescription trends: Pharmaceutical invoice data

We extracted invoice data for transactions that occurred 1/1/2015 through 12/31/2015. Some invoices appeared weeks to months after the date of prescription. To account for this, we extracted invoice records from a dataset that extended through 3/25/2017. Each invoice record contained a prescription number, medication description, dose, days supply, start date, route of administration, financial expenditure or reimbursement, and LTCF affiliation.

The invoice data required preparation prior to analysis. Medication refills used the same prescription number, which permitted tracking of intended courses and identification of duplicate records. We began by removing non-systemic medications including topical, otic, ophthalmologic preparations as well as suppositories. Vaccines, nutritional supplements and vitamins were also excluded. We excluded insulin as the frequency and dose could not be reliably assessed from the invoice data. Exclusions were implemented by an iterative computational script of pattern matching regular expressions that scanned each record's drug descriptions for text-matching keywords.

A multi-step algorithm was applied to each individual LTCF's dataset to remove duplicate records of pharmaceutical invoices. Some of these duplicate records represented reimbursement while others were for overlapping courses, most commonly noted with analgesics and other medications prescribed as needed rather than as scheduled doses. Each invoice record contained an identification number assigned to each distinct prescription type. Records with unique identification numbers were identified and reserved from additional processing. Records with identification numbers that occurred more than twice were considered candidate duplicate records. Briefly, the candidate duplicates were grouped and sequenced by their identification number, and the days between each grouped and sequenced record was calculated. Duplication identification needed multiple passes by group and start dates and ranking of a prescription's cost and supply, as some prescription types (*e.g.* intravenous prescriptions or opiates) required different approaches. The algorithm is delineated in **Supplementary Table 2.3**.

We categorized antibiotics by route of administration (*i.e.* oral administration or intravenous (IV) administration) and class. Antibiotic classes included aminoglycosides, β-lactams/β-lactamase inhibitors, carbapenems, cephalosporins, clindamycin, fluoroquinolones, linezolid, macrolides, metronidazole, nitrofurantoin, penicillins/aminopenicillins, sulfonamides tetracyclines and vancomycin. β-lactams/β-lactamase inhibitors included ampicillin/sulbactam, amoxicillin/clavulanic acid, and piperacillin/tazobactam. Penicillins/aminopenicillins included amoxicillin, ampicillin, nafcillin, and oxacillin. Cephalosporins were classified as 1st and 2nd generation or extended spectrum (3rd generation or later). We considered the intravenous vancomycin and oral vancomycin to be distinct agents.

2.2.3 Antibiotic use metrics: Intended course, Rates of therapy, Length of therapy

Metrics to describe antibiotic use in LTCFs included: number of systemic prescriptions per LTCF; the proportion of antibiotic prescriptions to systemic prescriptions, the number of antibiotic starts, the rate of antibiotic use and the length of therapy in days. Rates of antibiotic use were calculated as the number of days of therapy (DOT) per 1000 resident days of care (DOC). One DOT represented the administration of a single agent on a given day regardless of the number of doses administered or dosage strength. To accurately determine the length of antibiotic therapy in days, we linked prescription numbers and determine the first and last day of consecutive therapy (**Figure 2.1**). These were grouped into 2 categories: short-course (≤7 days) and long-course (>7 days).

2015 MM/DD	Rx	Agent	Type	Supply	Rate
08/13	1119490	Vancomycin	IV	4	0.12
08/17	1119490	Vancomycin	IV	2	0.06
08/19	1119490	Vancomycin	IV	5	0.15
08/24	1119490	Vancomycin	IV	4	0.12
08/28	1119490	Vancomycin	IV	3	0.09
08/31	1119490	Vancomycin	IV	1	0.03
09/01	1119490	Vancomycin	IV	3	0.09
09/04	1119490	Vancomycin	IV	4	0.12
09/08	1119490	Vancomycin	IV	1	0.03
09/09	1119490	Vancomycin	IV	7	0.21
09/16	1119490	Vancomycin	IV	2	0.06

Rx	Agent	Type	Supply	Rate
1119490	Vancomycin	IV	36	1.08

Figure 2.1 Overview of collapsing individual records into intended course of therapy.

2.2.4 Statistical analysis

We compared MDS assessments of our study's LTCFs compared to a national cohort of for-profit LTCFs with nonparametric methods. Continuous variables were summarized using mean and standard deviation (SD), and categorical variables were summarized using frequencies and percentages. Occupancy rates were calculated as the proportion of residents to number of beds per facility [45]. The association between rates of therapy and length of therapy was tested with a simple linear regression and validated with Pearson correlation. In a secondary analysis, a logistic regression was performed to test the association between length of therapy (short-course vs. long-course) and facility size. LTCF groups were dictated by natural breaks (*e.g.,* small: ≤100 beds; medium: 101-150 beds; large: >150 beds). These groupings were relatively comparable to nationwide LTCF size categories from CMS, with differences of an additional stratification for facilities with fewer than 50 beds and large facilities classified as 200 or more beds [46]–[48]. Using the standard approach for covariate selection we applied the stepwise selection procedure to evaluate candidate predictor variables, highlighted in bold in **Supplementary Table 2.1** and **Supplementary Table 2.2**, and the Akaike Information Criterion (AIC) was used to select which variables to retain in the model [49], [50]. Our final model assessed length of therapy (*i.e.* short-course vs. long-course) as the dependent variable, and facility size, activities of daily living (ADL), average resident age, proportion of admissions from acute care hospitals, and total nurse staffing hours per resident per day as independent variables. We considered two-sided $\alpha < 0.05$ to be statistically significant. Analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.3 Results

2.3.1 Study cohort

We compared our community-based resident population to a representative national population of for-profit NH residents with MDS assessments from 2015 (**Table 2.1**). The only significant differences observed were for average age, facility size, and median length of stay. Compared to other for-profit LTCFs, our cohort's residents were younger (74 vs. 78 years, P<0.0001), moderately larger facilities (133 vs. 111 beds, P<0.001), and were less dependent on LTCF staff for personal care tasks as indicated by a lower ADL score (15.1 vs. 17.1, P<0.0001).

2.3.2 Prescription trends and patterns: Systemic drugs, Antibiotics

Between 1/1/15-12/31/15, 190,251 systemic drug courses written at 29 LTCFs. The average rate of systemic therapy per LTCF was 2427.6 DOT/1000 DOC (SD=1133.7). During the study period, an average of 11.7% of all systemic prescriptions were written for an antibiotic (SD=3.4%), and the average rate of therapy for antibiotics was 70.3 DOT/1000 DOC (SD=39.9) (**Table 2.2**). When stratified by route of administration, the average rate of therapy for oral and intravenous antibiotics was 58.0 (SD=32.5) and 16.7 (SD=10.3) DOT/1000 DOC, respectively. For duration of therapy, nearly 1 in 4 antibiotics (19.7%, SD=7.3) were written for a long-course of therapy (>7 days) and over 1 in 6 antibiotics (17.5%, SD=6.7) orally administrated were written for a long course of therapy (>7 days) (**Table 2.2**).

We ranked the antibiotic classes with the highest rates of therapy across all LTCFs in 2015, subsequently grouped by agent. The top classes and their respective groupings by agent resulted in eight classes total: fluoroquinolones, cephalosporins (grouped by 1st and 2nd generation; extended spectrum [*i.e.* 3rd generation and greater]), penicillins (grouped by β-lactams/β-lactamase inhibitors; pencilllins/aminopenicillins), tetracyclines, and glycopeptides (grouped by oral vancomycin; IV vancomycin).

Figure 2.2A reflects the total rates of therapy among the cohort of LTCFs in 2015, ordered by highest rates of therapy and grouped by agent. The most commonly prescribed antibiotics were fluoroquinolones, which are broad-spectrum agents predominantly used for community-acquired infections [51].

When the top classes were grouped by agent and summarized among the LTCF cohort the average rates of therapy were: fluoroquinolones, 14.2 DOT/1000 DOC (SD=7.9), 1st and 2nd generation cephalosporins (7.3, SD=5.5), β-lactams/β-lactamase inhibitors (7.2, SD=3.6), tetracycline (5.3, SD=3.6), IV vancomycin (4.6, SD=3.4), extended spectrum cephalosporins (4.6, SD=3.4), oral vancomycin (3.6, SD=3.7), and pencilllins/aminopenicillins (2.7, SD=2.8).

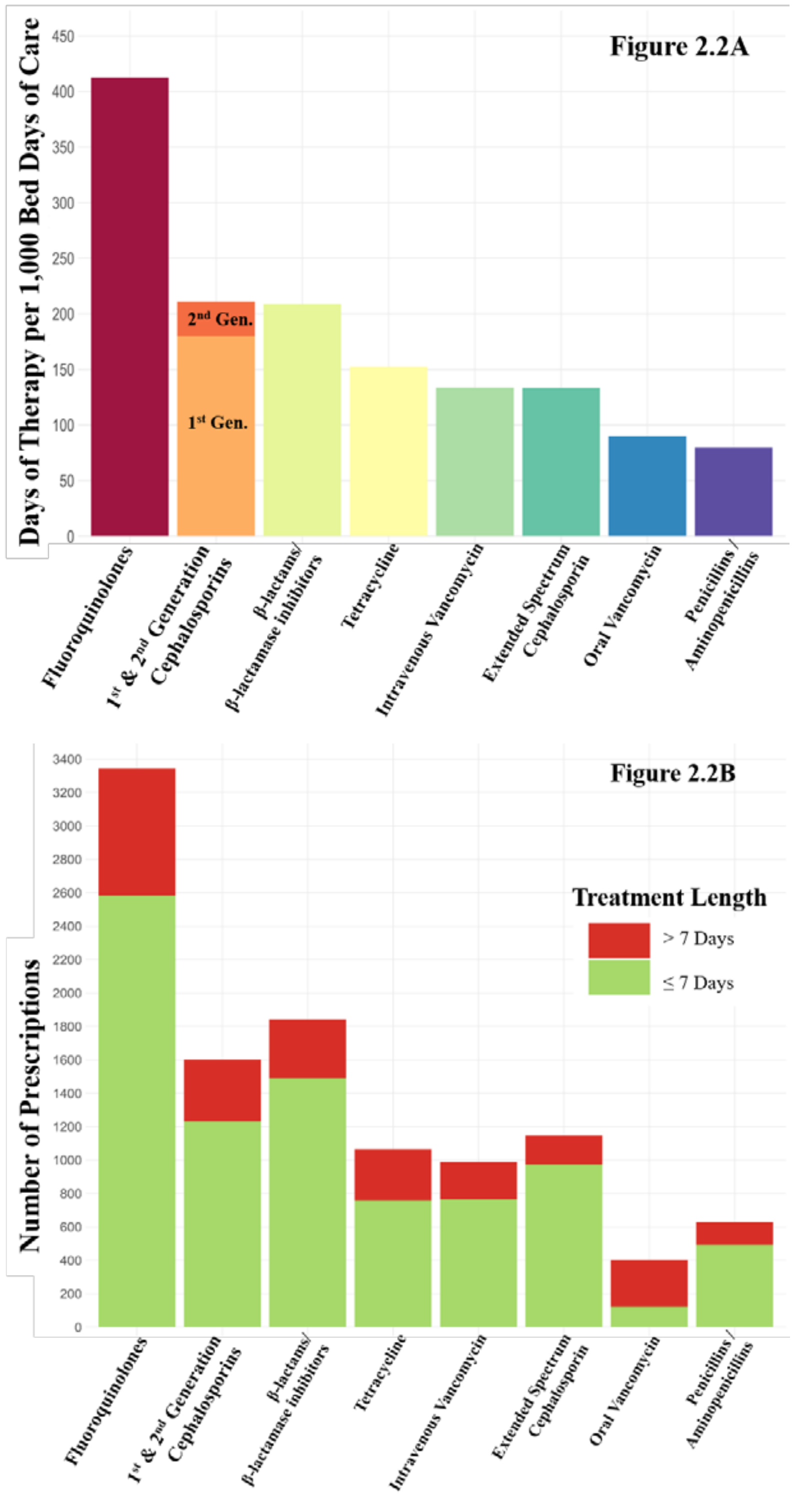


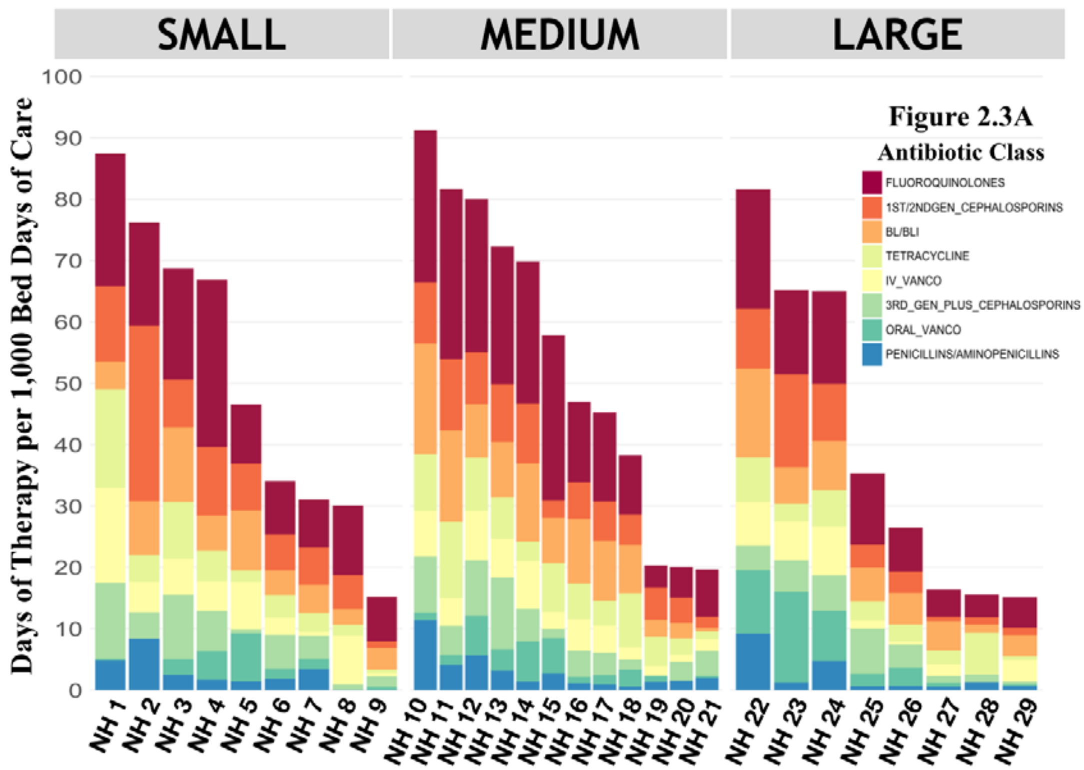
Figure 2.2: Rates and length of therapy in 2015 among the top five antibiotic classes across all community-based LTCFs, ordered by highest rates of therapy and grouped by

mechanism and agent. **A.** Rate of therapy in 2015 grouped by mechanism and agent. **B.** Length of therapy in 2015 grouped by short-course (≤7 days) and long-course (>7 days).

We stratified rates of therapy by course length, ordered by highest rates of therapy and grouped by agent (**Figure 2.2B**). On average, nearly 1 in 5 antibiotics were written for a fluoroquinolone (19.4%, SD=5.8), with over 1 in 4 fluoroquinolones were prescribed for more than 7 days (22.9%, SD=10.6) (**Table 2.3)**. On average 65.7% of courses written for oral vancomycin were prescribed for more than 7 days (SD=27.0), which are often used for treatment of *C.difficile*, an infection that LTCF residents are at high risk for acquiring [52].

2.3.3 Comparison of antibiotic prescribing patterns by small, medium, and large facilities

We compared prescribing characteristics of LTCFs in 2015 (**Table 2.4)**. Small and medium facilities prescribed 23%-24% higher normalized days of therapy, respectively, in comparison to large facilities. Small facilities prescribe 14-17% higher proportion of antibiotics to systemic prescriptions in comparison to medium and large facilities. **Figure 2.3A** displays results ordered by highest rates of therapy grouped by agent within each facility size strata. The antibiotic class with the highest average rate of therapy for small, medium, and large facilities was fluoroquinolones, escribed for 14.3 DOT/1000 DOC (SD=7.0), 17.0 DOT/1000 DOC (SD=9.0), and 10.0 DOT/1000 DOC (SD=5.8), respectively (**Table 2.5**). Length of therapy was not found to be significantly different based on facility size (**Figure 2.3B, Table 2.4).** Among small and medium sized facilities, nearly 1 in 5 antibiotics were written for a fluoroquinolone (21.0%, SD=7.6 and 20.2%, SD=5.5 respectively), and 1 in 6 antibiotics in a large facility were written for floroquinolones (17.0, SD=3.2) **(Table 2.5)**. When grouped by agent, the largest proportion of antibiotics written as a long course of therapy were for tetracyclines (47.0%, SD=29.10) among small facilities. The largest proportion of antibiotics written as a long course of therapy at medium and large facilities were for oral vancomycin (67.8%, SD=28.2; 60.6%, SD=30.7), respectively. Between 4 to 8 percent of intravenous vancomycin was written as for more than 7 days, which is predominantly used to manage methicillin-resistant *Staphylcoccus aureus* (MRSA) [53].


SMALL
MEDIUM
LARGE
Figure 2.3A
Antibiotic Class
FLUOROQUINOLONES
1ST/2NDGEN_CEPHALOSPORINS
BL/BLI
TETRACYCLINE
IV_VANCO
3RD_GEN_PLUS_CEPHALOSPORINS
ORAL_VANCO
PENICILLINS/AMINOPENICILLINS
Days of Therapy per 1,000 Bed Days of Care
0
10
20
30
40
50
60
70
80
90
100
NH 1
NH 2
NH 3
NH 4
NH 5
NH 6
NH 7
NH 8
NH 9
NH 10
NH 11
NH 12
NH 13
NH 14
NH 15
NH 16
NH 17
NH 18
NH 19
NH 20
NH 21
NH 22
NH 23
NH 24
NH 25
NH 26
NH 27
NH 28
NH 29

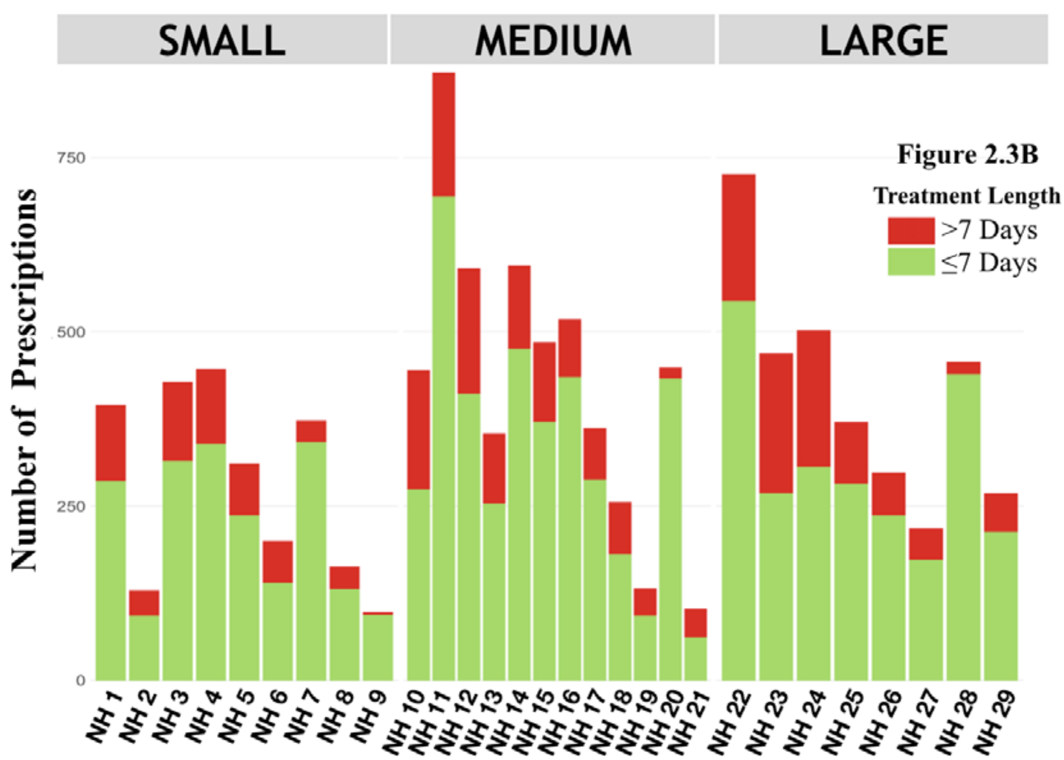

SMALL
MEDIUM
LARGE
Figure 2.3B
Treatment Length
>7 Days
≤7 Days
Number of Prescriptions
0
250
500
750
NH 1
NH 2
NH 3
NH 4
NH 5
NH 6
NH 7
NH 8
NH 9
NH 10
NH 11
NH 12
NH 13
NH 14
NH 15
NH 16
NH 17
NH 18
NH 19
NH 20
NH 21
NH 22
NH 23
NH 24
NH 25
NH 26
NH 27
NH 28
NH 29

Figure 2.3 Rates and length of therapy in 2015 ordered by highest rates of therapy and grouped by agent and stratified by facility size group. A. Rate of therapy in 2015, stratified by facility size. B. Length of therapy in 2015 grouped by short-course (≤7 days) and long-course (>7 days), stratified by facility size.

The variation in the rates of therapy explained almost half of the variation in length of antibiotic therapy written as long- or short- courses (R^2 = 42%, Pearson correlation = 0.65, $p<0.001$). The significant correlation between rates and duration of therapy does not imply causation, therefore a multivariate regression was used to assess this relationship while controlling for resident-based and organizational factors [19], [54]. **Table 2.6** shows results from a multivariate model that a long-course of antibiotic therapy (>7 days) was not associated with facility size, average resident age, Activities of Daily Living Score. Each one-unit increase in admissions from acute-care hospitals was associated with a 3.5% increase in the odds of an antibiotic prescribed as a long-course of therapy (adjusted odds ratio [aOR], 1.035; 95% confidence interval [CI], 1.03-1.04, $p<0.0001$). Results show that the relationship between nurse staffing time and long-course of antibiotic therapy (>7 days) is significant, where for each hour increase of total nurse staffing per resident per day, an antibiotic prescription was associated with an 36% decrease in the odds of being written as a long-course of therapy (aOR, 0.64; 95% CI, 0.57-0.72, $p<0.0001$).

2.4 Discussion

We conducted a longitudinal retrospective analysis using pharmaceutical invoices derived from a cohort of 29 LTCFs for a 12-month period to evaluate their antibiotic prescribing patterns. Our findings show that measures of antibiotic utilization can be derived from pharmaceutical invoice data, which can be further enriched with publicly available data to build a repository of adequate information for providers to consult in their decision making process. Studies show that decision making in an LTCF can be impacted by provider preference, defined as a tendency to treat with antibiotics, prescribing for antibiotic therapy for periods exceeding 7 days, and tendency to prescribe for fluoroquinolones [5]. This may be partly due to the LTCF setting, where a limited-number of prescribers may write many prescriptions for a large population of residents. Therefore when presented a paucity of adequate information these prescribers may refer to a limited list of therapeutic options that benefited previous residents [55]. Our study results show that evaluating patterns of antibiotic use may provide opportunities for feedback on prescriber contributions to antibiotic use patterns within an LTCF facility and supporting modification of provider antibiotic choices.

Results suggest that overall LTCFs demonstrate prescribing tendencies for fluoroquinolones. According to the CDC, these agents are effective in the treatment selected community-acquired infections [56]. However, LTCFs have reported outbreaks of antibiotic resistance to fluoroquinolones, and research Kupronis *et. al*. demonstrate patterns of resistance to fluoroquinolones are more than five times greater among older LTCF residents [57]. Systematic reviews of antibiotic resistant bacteria in LTCFs suggest that the problem of fluoroquinolone resistance may be driven by inappropriate and/or unnecessary use of this agent [58]. In a retrospective analysis of the appropriate use of fluoroquinolones, only 25% of the treatment orders were considered appropriate [59]. The therapeutic preference for fluoroquinolones have remained relatively unchanged in US LTCFs, which may raise the possibility of persistent selective pressure favoring fluoroquinolone resistant bacteria [52]. In the outpatient setting, fluoroquinolones prescriptions among older adults in the US have been consistent from 2000 to 2010 [52], [60]. A 2008 study of 73 LTCFs described fluoroquinolones as the most prescribed class of antibiotic (38%) followed by first-generation cephalosporins (11%) [61]. A 2012 study of a single 160-bed LTCF showed that fluoroquinolones accounted for 30%-44% of antimicrobial prescriptions written for that facility [62]. More recently, a 2014 study by Furuno *et al.* reviewed 839 resident charts of Maryland-based LTCFs, and determined that fluoroquinolones were the most frequently used broad-spectrum antibiotics, accounting for 39.8% of all broad-spectrum antibiotic prescribed [63]. The widespread use of fluoroquinolones in LTCFs for respiratory and urinary tract infections is likely to increase risk for development of fluoroquinolone-resistant bacteria [57]. Unfortunately, preference for fluoroquinolone therapy remains despite a FDA warning in effect since 2011 on all drugs within this class [64], [65]. In a study by Linden *et al.*, this drug class was independently associated with increased risk of Achilles tendon rupture and demonstrated only in persons aged 60 years or older [66], [67]. Concurrent use of steroids increased the risk of rupture substantially in the elderly [68]. Although fluoroquinolones are useful as they are typically active against a wide range of pathogens common to an LTCF resident, our study results suggest that fluoroquinolones remain important target for evaluation and possible reduction in this healthcare setting [69]–[71].

Particularly alarming in LTCFs is the rise of gram-negative bacteria rapidly acquiring resistance to several major classes of antibiotics [72]. Among these major classes reflected in our cohort were fluoroquinolones and extended-spectrum cephalosporins. Residents with infections resistant to these classes of antibiotics are reported to have longer hospital stays, increased readmission rates, and present significant financial burden to their respective facility than patients with infections susceptible to these classes [73], [74]. One in twelve antibiotics were prescribed for extended generation cephalosporins among our study cohort, which present a high risk of promoting emergence of bacterial resistance (*i.e.* MRSA) and C. *difficile* infections [75], [76]. Further, gram-negative bacteria resistant to extended-spectrum cephalosporins are emerging in LTCF settings, producing pathogens that can spread rapidly given the nature of the residential setting [77].

Our study findings point to hospitalization as an important association with antibiotic course written for >7 days. Although transfers between acute-care hospitals to LTCFs are frequent, according to Mor *et al.* these hospitalizations can cost an estimated $17.4 billion to CMS Medicare services [78]. Our study findings indicated that an antibiotic prescription was more likely to be written as a long-course of therapy (>7 days) with each unit increase of admissions from acute-care hospitals. These findings are consistent with previous research where antibiotic use was substantially higher among post-acute residents [79].

Although many antibiotic prescriptions are a continuation from an acute care hospitalization, they are also initiated because of a presumed infection developing in the LTCF [79]. To reduce the length of acute care hospital stay, LTCFs are accepting more residents who are sicker and have more severe illnesses [80]. This change in case mix of the resident population has led to increased care transitions between hospitals and LTCFs, which can lead to increased risk of pathogen transmission between the two settings [80], [81]. For example, in a study assessing transfer of residents between health care settings, more than half of individuals identified with an antibiotic resistant bacteria during a hospitalization were discharged to LTCFs [82], [83]. These hospital-acquired infections can influence healthcare costs to an LTCF [84]. Improving resident care through use of automatic stop orders or de-escalation of acute care hospital initiated therapy may be a meaningful ASP approach for an LTCF [62]. In the hospital setting, a 2016 nationwide survey of ASP practices among 130 Veterans Affairs facilities found that although 75% of facilities had automatic-stop orders only 15% of facilities had a policy for de-escalation [85]. Studies show that automatic stop orders and de-escalation strategies are unlikely to pose a substantial risk of denying necessary antibiotic therapy to individuals and therefore may present beneficial financial and clinical impact to resident care [86]–[88].

There may be an additional relationship antibiotic prescribing patterns and for-profit status of facilities among our study cohort. A 2002 study by Zimmerman *et al.* described the relationship between hospitalizations and LTCF proprietary status, where for-profit LTCFs had three times the number of hospitalizations per year and chain affiliated facilities had two times the number of hospitalizations [89]. Previous studies have hypothesized that these differences may be related to reinvestments that not-for-profit facilities make into resident care that for-profit facilities collect as profit [90]. Further, not-for-profit facilities have also been hypothesized to more closely associated with acute care facilities and provide more specialized care [91]. In part to address concerns of the disconnect between LTCF revenue and quality of resident care, CMS has implemented a series of pay-for-performance measures that promote better outcomes and experiences for post-acute LTCF residents. The approach, termed "The Skilled Nursing Facility Value-Based Purchasing Program", will start in 2019 [92]. Future studies will be needed to assess the consequences on antibiotic prescribing by this policy implementation for-profit LTCFs in the US.

The association between antibiotic patterns of use and nurse staffing can be an important area for stewardship. Although differences in staffing among facilities does not directly imply differences in quality of resident care, an extensive body of research in the US connects higher staffing levels in LTCFs to beneficiary resident health outcomes [19], [70], [93]. Nurse staffing hours of care as a resource has been linked to fewer pressure ulcers, urinary tract infections, and reduced urinary catheter use [93]. A study commissioned by the US Congress evaluated over 5,000 LTCFs in 10 states and determined that higher staffing predicted improved care outcomes including reduced hospital transfer and incidence of pressure sores, up to thresholds of 2.8 hours per resident DOC for CNAs and 1.3 hours per resident DOC for RNs and LPN hours combined [94]. The report found that Implementation of these thresholds as requirements would find 97 percent of all nursing homes failing to meet one or more of these standards [94]. RNs, LPNs, and CNAs can impact antibiotic use in LTCFs by administering and monitoring response to antibiotics

[16], [95]. Therefore LTCF ASPs must consider both the importance of and challenges related to staffing in this setting, where instances of understaffing in an LTCF may impact patterns of antibiotic use and adherence to infection control procedures [96], [97]. Future studies may be warranted to examine if inappropriate and/or unnecessary antibiotic prescribing in an LTCF be mitigated by investment in education of nursing staff and subsequent improvement in resident outcomes [45], [98].

This study has several limitations. First, our analysis does not include resident-level data such as indications or diagnostic test results, which prevented us from evaluating the appropriateness of each antibiotic prescribed or the comorbidities of patients who received antibiotics. There could be unmeasured aspects of resident case-mix (*i.e.* the distribution of resident conditions and services required for their care) to the facility and unmeasured variability of strains of antibiotic resistant bacteria unique to a given facility that impacts the decision to prescribe. Second, our primary data source of pharmaceutical invoices can be considered a major limitation, as prescriptions were captured only when claims were processed. Our data likely underestimates antibiotic utilization of our cohort, as pharmaceutical invoice data cannot capture prescribing behavior such as canceled orders, polypharmacy, or adjustments to a residents' therapy [99].

Third, antibiotics that were initiated in the LTCF or continued from post-acute care could not be directly determined from our prescription invoice data. Courses continued from post-acute care may inflate the rates of antibiotic therapy reported by an LTCF [79]. Fourth, our cohort is not a random sample of US LTCFs. Although we obtained data on resident case-mix characteristics via 2015 MDS assessments to facilitate comparison to a profile of for-profit LTCFs nationwide, we cannot be certain that the LTCFs in our sample are representative of US in terms of the volume of antibacterial use or resident demographic characteristics.

In spite of these limitations, this study presents important new findings relevant to understanding prescription patterns in US LTCFs and may suggest focused clinical targets for reduction of fluoroquinolones.

2.5 References

[1] P. D. Sloane, K. Huslage, C. E. Kistler, and S. Zimmerman, "Optimizing Antibiotic Use in Nursing Homes Through Antibiotic Stewardship," *N. C. Med. J.*, vol. 77, no. 5, pp. 324–329, 2016.

[2] P. K. Peterson, D. Stein, D. R. Guay, G. Logan, S. Obaid, R. Gruninger, S. Davies, and R. Breitenbucher, "Prospective study of lower respiratory tract infections in an extended-care nursing home program: potential role of oral ciprofloxacin," *Am. J. Med.*, vol. 85, no. 2, pp. 164–171, 1988.

[3] K. P. High, S. F. Bradley, S. Gravenstein, D. R. Mehr, V. J. Quagliarello, C. Richards, and T. T. Yoshikawa, "Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America," *Clin. Infect. Dis. An Off. Publ. Infect. Dis. Soc. Am.*, vol. 48, no. 2, pp. 149–171, 2009.

[4] L. E. Nicolle, D. Bentley, R. Garibaldi, E. Neuhaus, P. Smith, and S. L.-T. Committee, "Antimicrobial use in long-term–care facilities," *Infect. Control Hosp. Epidemiol.*, vol. 17, no. 2, pp. 119–128, 1996.

[5] N. Daneman, M. A. Campitelli, V. Giannakeas, A. M. Morris, C. M. Bell, C. J. Maxwell, L. Jeffs, P. C. Austin, and S. E. Bronskill, "Influences on the start, selection and duration of treatment with antibiotics in long-term care facilities," *CMAJ*, vol. 189, no. 25, pp. E851–E860, 2017.

[6] A. J. Kallen, A. Thompson, P. Ristaino, L. Chapman, A. Nicholson, F. Sim, B.T., Lessa, U. Sharapov, E. Fadden, R. Boehler, and C. Gould, "Complete restriction of

fluoroquinolone use to control an outbreak of Clostridium difficile infection at a community hospital," *Infect. Control Hosp. Epidemiol.*, vol. 30, no. 3, pp. 264–272, 2009.

[7] R. H. Drew, K. Kawamoto, and M. B. Adams, "Information technology for optimizing the management of infectious diseases," *Am. J. Heal. Pharm.*, vol. 63, no. 10, pp. 957–965, 2006.

[8] L. E. Nicolle, D. W. Bentley, R. Garibaldi, E. G. Neuhaus, and P. W. Smith, "Antimicrobial use in long-term-care facilities. SHEA Long-Term-Care Committee.," *Infect. Control Hosp. Epidemiol.*, vol. 21, no. 8, pp. 537–45, 2000.

[9] L. E. Nicolle, D. W. Bentley, R. Garibaldi, G. Ellen, P. W. Smith, T. Care, and E. G. Neuhaus, "Antimicrobial Use in Long-Term – Care Facilities," *Infect. Control Hosp. Epidemiol.*, vol. 21, no. 8, pp. 537–545, 2000.

[10] Infectious Diseases Society of America, "Combating antimicrobial resistance: Policy recommendations to save lives," *Clin. Infect. Dis.*, vol. 52, no. SUPPL. 5, pp. S397–S428, 2011.

[11] A. Fleming and S. Byrne, "Prescriber preference may influence prolonged antibiotic usage more than patient characteristics in long-term care facilities," *Evid. Based. Nurs.*, vol. 17, no. 2, pp. 61–62, 2014.

[12] N. Daneman, A. Gruneir, S. E. Bronskill, A. Newman, H. D. Fischer, P. A. Rochon, G. M. Anderson, and C. M. Bell, "Prolonged Antibiotic Treatment in Long-term Care: Role of the Prescriber," *JAMA Intern. Med.*, vol. 173, no. 8, p. 673, 2013.

[13] B. Spellberg, R. Guidos, D. Gilbert, J. Bradley, H. Boucher, and W. Scheld, “The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America,” *Clin. Infect. Dis. An Off. Publ. Infect. Dis. Soc. Am.*, vol. 46, pp. 155–64, 2008.

[14] B. Spellberg, “The Maturing Antibiotic Mantra: ‘Shorter Is Still Better,’” *J. Hosp. Med.*, vol. 176, no. 9, pp. 1254–1255, 2018.

[15] G. Dimopoulos, D. K. Matthaiou, D. E. Karageorgopoulos, A. P. Grammatikos, Z. Athanassa, and M. E. Falagas, “Short- versus long-course antibacterial therapy for community-acquired pneumonia : a meta-analysis.,” *Drugs*, vol. 68, no. 13, pp. 1841–1854, 2008.

[16] C. J. Crnich, R. L. Jump, B. Trautner, P. D. Sloane, and L. Mody, “Optimizing Antibiotic Stewardship in Nursing Homes: A Narrative Review and Recommendations for Improvement,” *Drugs and Aging*, vol. 32, no. 9, pp. 699–716, 2015.

[17] N. Daneman, A. Gruneir, A. Newman, H. D. Fischer, S. E. Bronskill, P. A. Rochon, G. M. Anderson, and C. M. Bell, “Antibiotic use in long-term care facilities,” *J. Antimicrob. Chemother.*, vol. 66, no. 12, pp. 2856–2863, 2011.

[18] J. Banaszak-Holl, J. S. Zinn, and V. Mor, “The Impact of Market and Organizational Characteristics on Nursing Care Facility Service Innovation: A Resource Dependency Perspective,” *Health Serv. Res.*, vol. 31, no. 1, pp. 97–117, 1996.

[19] C. Harrington, D. Zimmerman, S. L. Karon, J. Robinson, and P. Beutel, “Nursing home staffing and its relationship to deficiencies,” *Journals Gerontol. - Ser. B Psychol. Sci. Soc. Sci.*, vol. 55, no. 5, pp. S278–S287, 2000.

[20] L. A. Pollack, K. L. Van Santen, L. M. Weiner, M. A. Dudeck, J. R. Edwards, and A. Srinivasan, “Antibiotic stewardship programs in U.S. acute care hospitals: Findings from the 2014 national healthcare safety network annual hospital survey,” *Clin. Infect. Dis.*, vol. 63, no. 4, pp. 443–449, 2016.

[21] Centers for Disease Control and Prevention, “Core Elements of Antibiotic Stewardship for Nursing Homes,” pp. 1–21, 2015.

[22] Centers for Medicare and Medicaid Services Office of Minority Health, “The CMS Equity Plan for Improving Quality in Medicare,” 2015.

[23] S. K. Fridkin and A. Srinivasan, “Implementing a strategy for monitoring inpatient antimicrobial use among hospitals in the United States,” *Clin. Infect. Dis.*, vol. 58, no. 3, pp. 401–406, 2014.

[24] M. B. Jha, A.K., Burke, M.F., DesRoches, C., Joshi, M.S., Kralovec, P.D., Campbell, E.G. and Buntin, A. K. Jha, M. F. Burke, C. DesRoches, M. S. Joshi, P. D. Kralovec, E. G. Campbell, and M. B. Buntin, “Progress toward meaningful use: hospitals’ adoption of electronic health records,” *Am. J. Manag. Care*, vol. 17, no. 12 Spec No, pp. 117–24, 2011.

[25] L. Gravatt and A. Pakyz, “Challenges in measuring antibiotic consumption,” *Curr. Infect. Dis. Rep.*, vol. 15, no. 6, pp. 559–563, 2013.

[26] R. E. Polk, S. F. Hohmann, S. Medvedev, and O. Ibrahim, “Benchmarking risk-adjusted adult antibacterial drug use in 70 US academic medical center hospitals,” *Clin. Infect. Dis.*, vol. 53, no. 11, pp. 1100–1110, 2011.

[27] H. C. Standiford, S. Chan, M. Tripoli, E. Weekes, and G. N. Forrest, "Antimicrobial Stewardship at a Large Tertiary Care Academic Medical Center: Cost Analysis Before, During, and After a 7-Year Program," *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 04, pp. 338–345, 2012.

[28] T. D. Bennett, M. C. Spaeder, R. I. Matos, R. S. Watson, K. V Typpo, R. G. Khemani, S. Crow, B. D. Benneyworth, R. R. Thiagarajan, J. M. Dean, and B. P. Markovitz, "Existing data analysis in pediatric critical care research," *Front. Pediatr.*, vol. 2, p. 79, 2014.

[29] C. R. Cooke and J. I. Theodore, "Using existing data to address important clinical questions in critical care," *Crit. Care Med.*, vol. 41, no. 3, pp. 886–896, 2013.

[30] T. D. Wade, "Refining gold from existing data," *Curr. Opin. Allergy Clin. Immunol.*, vol. 14, no. 3, pp. 181–5, 2014.

[31] S. Monteith, T. Glenn, J. Geddes, and M. Bauer, "Big data are coming to psychiatry: a general introduction.," *Int. J. bipolar Disord.*, vol. 3, no. 1, p. 21, 2015.

[32] G. M. Weber, K. D. Mandl, and I. S. Kohane, "Finding the Missing Link for Big Biomedical Data," *JAMA*, vol. 311, no. 24, pp. 2479–2480, 2014.

[33] C. Safran, M. Bloomrosen, W. E. Hammond, S. Labkoff, S. Markel-Fox, P. C. Tang, and D. E. Detmer, "Toward a National Framework for the Secondary Use of Health Data: An American Medical Informatics Association White Paper," *J. Am. Med. Informatics Assoc.*, vol. 14, no. 1, pp. 1–9, 2007.

[34] G. Hripcsak, S. Bakken, P. D. Stetson, and V. L. Patel, "Mining complex clinical

data for patient safety research: A framework for event discovery," *J. Biomed. Inform.*, vol. 36, no. 1–2, pp. 120–130, 2003.

[35] J. I. Tokars, C. Richards, M. Andrus, M. Klevens, A. Curtis, T. Horan, J. Jernigan, and D. Cardo, "The changing face of surveillance for health care-associated infections.," *Clin. Infect. Dis.*, vol. 39, no. 9, pp. 1347–1352, 2004.

[36] Ö. O. Gundeslioglu, R. Tekin, S. Cevik, Y. Y. Palanci, and A. Yazicioglu, "The effects of nosocomial rotavirus gastroenteritis on the length of hospital stay and cost," *J. Infect. Dev. Ctries.*, vol. 10, no. 2, pp. 163–167, 2016.

[37] M. J. Durkin, S. R. Jafarzadeh, K. Hsueh, Y. H. Sallah, K. D. Munshi, R. R. Henderson, and V. J. Fraser, "Outpatient Antibiotic Prescription Trends in the United States: A National Cohort Study.," *Infect. Control Hosp. Epidemiol.*, no. 1, pp. 1–6, 2018.

[38] J. Whittle, M. Fine, D. Z. Joyce, J. R. Lave, W. W. Young, L. J. Hough, and W. N. Kapoor, "Community-acquired pneumonia: can it be identified with claims data?," *Am. J. Med. Qual.*, vol. 12, no. 4, pp. 187–193, 1997.

[39] T. Schwarz, S., Kehrenberg, C., Walsh, "Use of antimicrobial agents in veterinary medicine and food animal production," *Int. J. Antimicrob. Agents*, vol. 17, no. 6, pp. 431–437, 2001.

[40] G. Cadieux and R. Tamblyn, "Accuracy of physician billing claims for identifying acute respiratory infections in primary care," *Health Serv. Res.*, vol. 43, no. 6, pp. 2223–2238, 2008.

[41] R. Tamblyn, G. Lavoie, L. Petrella, and J. Monette, "The use of prescription

claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec," *J. Clin. Epidemiol.*, vol. 48, no. 8, pp. 999–1009, 1995.

[42] Brown University, "Shaping Long Term Care in America Project: Funded in part by the National Institute on Aging (1P01AG027296)," 2009. [Online]. Available: http://ltcfocus.org/. [Accessed: 01-Apr-2018].

[43] C. Bizer, P. Boncz, M. L. Brodie, and O. Erling, "The meaningful use of big data: four perspectives--four challenges," *Acm Sigmod Rec.*, vol. 40, no. 4, pp. 56–60, 2012.

[44] U.S. Centers for Medicare and Medicaid Services, "Nursing Home Compare," 2015. [Online]. Available: http://www.medicare.gov/nursinghomecompare/search.html. [Accessed: 01-Jan-2018].

[45] J. E. Bostick, M. J. Rantz, M. K. Flesner, and C. J. Riggs, "Systematic Review of Studies of Staffing and Quality in Nursing Homes," *J. Am. Med. Dir. Assoc.*, vol. 7, no. 6, pp. 366–376, 2006.

[46] L. Harris-Kojetin, M. Sengupta, E. Park-Lee, R. Valverde, C. Caffrey, V. Rome, and J. Lendon, *Long-term care providers and services users in the United States: Data from the National Study of Long-Term Care Providers , 2013 – 2014*, vol. 3, no. 38. 2016.

[47] L. Harris-Kojetin, M. Sengupta, E. E. Park-Lee, and R. Valverde, "Long-Term Care Services in the United States: 2013 Overview.," *Vital Health Stat. 3.*, no. 37, p. 1, Dec. 2013.

[48] Centers for Medicare & Medicaid Services, “Nursing Home Data Compendium, 2015,” 2015.

[49] C. LM and S. Lanza, *Latent class and latent transition analysis: With applications in the social, behavioral, and health sciences*. New York: Wiley, 2010.

[50] M. Vallin, M. Polyzoi, G. Marrone, S. Rosales-Klintz, K. T. Wisell, and C. S. Lundborg, “Knowledge and attitudes towards antibiotic use and resistance - A latent class analysis of a Swedish population-based sample,” *PLoS One*, vol. 11, no. 4, pp. 1–18, 2016.

[51] Centers for Disease Control and Prevention, “Antimicrobial use and resistance (AUR) option,” 2011.

[52] R. Jump and C. J. Donskey, “Clostridium difficile in the Long-Term Care Facility: Prevention and Management,” *Curr. Geriatr. Reports*, vol. 4, no. 1, pp. 60–69, 2015.

[53] S. F. Bradley, “Methicillin-resistant Staphylococcus aureus: Long-term care concerns,” *Am. J. Med.*, vol. 106, no. 5, pp. 2–10, 1999.

[54] J. M. Mylotte and J. Keagle, “Benchmarks for Antibiotic Use and Cost in Long-Term Care,” *J. Am. Geriatr. Soc.*, vol. 53, no. 7, pp. 1117–1122, 2005.

[55] J. D. de Jong, P. Groenewegen, P.P. Spreeuwenberg, G. P. Westert, and D. H. de Bakker, “Do decision support systems influence variation in prescription?,” *BMC Health Serv. Res.*, vol. 9, no. 1, p. 20, 2009.

[56] U.S. Centers for Medicare and Medicaid Services, “Quinolones and the Clinical

Laboratory,” *Healthcare-associated Infections (HAI)*, 2010. [Online]. Available: https://www.cdc.gov/hai/settings/lab/quinolones-clinical-laboratory.html. [Accessed: 07-Jan-2018].

[57] B. Kupronis, C. Richards, C. Whitney, and Active Bacterial Core Surveillance Team, “Invasive pneumococcal disease in older adults residing in long-term care facilities and in the community.,” *J. Am. Geriatr. Soc.*, vol. 51, no. 11, pp. 1520–1525, 2003.

[58] R. A. Bonomo, “Multiple antibiotic-resistant bacteria in long-term-care facilities: an emerging problem in the practice of infectious diseases,” *Clin. Infect. Dis.*, vol. 31, no. 6, pp. 1414–1422, 2000.

[59] T. D. Pickering, J. H. Gurwitz, D. Zaleznik, J. P. Noonan, and J. Avorn, “The appropriateness of oral fluoroquinolone-prescribing in the long-term care setting,” *J. Am. Geriatr. Soc.*, vol. 42, no. 1, pp. 28–32, 1994.

[60] G. C. Lee, K. R. Reveles, R. T. Attridge, K. A. Lawson, I. A. Mansi, J. S. Lewis, and C. . Frei, “Outpatient antibiotic prescribing in the United States: 2000 to 2010,” *BMC Med.*, vol. 12, no. 1, p. 96, 2014.

[61] S. R. Benoit, W. Nsa, C. L. Richards, D. W. Bratzler, A. M. Shefer, L. M. Steele, and J. A. Jernigan, “Factors associated with antimicrobial use in nursing homes: A multilevel model,” *J. Am. Geriatr. Soc.*, vol. 56, no. 11, pp. 2039–2044, Nov. 2008.

[62] R. Jump, D. Olds, N. Seifi, K. Georgios, L. Jury, E. Peron, A. Hirsch, P. Drawz, B. Watts, R. Bonomo, and C. Donskey, “Effective Antimicrobial Stewardship in a Long-Term Care Facility through an Infectious Disease Consultation Service: Keeping a LID

on Antibiotic Use," *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 12, pp. 1185–1192, 2012.

[63] J. P. Furuno, A. C. Comer, J. K. Johnson, J. H. Rosenberg, S. L. Moore, T. D. MacKenzie, K. K. Hall, and J. M. Hirshon, "Using Antibiograms to Improve Antibiotic Prescribing in Skilled Nursing Facilities," *Infect. Control Hosp. Epidemiol.*, vol. 35, no. S3, pp. S56–S61, 2014.

[64] A. Altiner, S. Wilm, K. Wegscheider, M. Sielk, S. Brockmann, A. Fuchs, H. H. Abholz, and J. in der Schmitten, "Fluoroquinolones to treat uncomplicated acute cough in primary care: Predictors for unjustified prescribing of antibiotics," *J. Antimicrob. Chemother.*, vol. 65, no. 7, pp. 1521–1525, 2010.

[65] FDA, "Information for Healthcare Professionals: Fluoroquinolone Antimicrobial Drugs," 2017. [Online]. Available: https://www.fda.gov/Drugs/DrugSafety/ucm511530.htm. [Accessed: 31-Mar-2018].

[66] S. R. McEwan and P. G. Davey, "Ciprofloxacin and tenosynovitis," *Lancet*, vol. 332, no. 8616, p. 900, 1988.

[67] P. D. Van der Linden, M. C. J. M. Sturkenboom, R. M. C. Herings, H. M. G. Leufkens, S. Rowlands, and B. H. C. Stricker, "Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids," *Arch. Intern. Med.*, vol. 163, no. 15, pp. 1801–1807, 2003.

[68] T. Rowe and G. Iyer, "Challenges to Diagnosis and Management of Infections in Older Adults," in *New Directions in Geriatric Medicine*, Springer, Cham, 2016, pp. 31–47.

[69] H. Von Baum, C. Schmidt, D. Svoboda, O. Bock-Hensley, and C. Wendt, “Risk factors for methicillin-resistant Staphylococcus aureus carriage in residents of German nursing homes,” *Infect. Control Hosp. Epidemiol.*, vol. 23, no. 9, pp. 511–515, 2002.

[70] W. D. Spector and H. A. Takada, “Characteristics of nursing homes that affect resident outcomes,” *J. Aging Health*, vol. 3, no. 4, pp. 427–454, 1991.

[71] W. D. Spector and D. B. Mukamel, “Using outcomes to make inferences about nursing home quality,” *Eval. Health Prof.*, vol. 21, no. 3, pp. 291–315, 1998.

[72] M. Exner, S. Bhattacharya, B. Christiansen, J. Gebel, P. Goroncy-Bermes, P. Hartemann, P. Heeg, C. Ilschner, A. Kramer, E. Larson, W. Merkens, M. Mielke, P. Oltmanns, B. Ross, M. Rotter, R. M. Schmithausen, H.-G. Sonntag, and M. Trautmann, “Antibiotic resistance: What is so special about multidrug-resistant Gram-negative bacteria?,” *GMS Hyg. Infect. Control*, vol. 12, p. Doc05, 2017.

[73] S. E. Cosgrove, K. S. Kaye, G. M. Eliopoulous, and Y. Carmeli, “Health and economic outcomes of the emergence of third-generation cephalosporin resistance in Enterobacter species,” *Arch. Intern. Med.*, vol. 162, no. 2, pp. 185–190, 2002.

[74] M. A. Cataldo, G. Granata, and N. Petrosillo, “Antibacterial Prophylaxis for Surgical Site Infection in the Elderly: Practical Application,” *Drugs Aging*, vol. 34, no. 7, pp. 489–498, 2017.

[75] B. Warshawsky, Z. Hussain, D. B. Gregson, R. Alder, M. Austin, D. Bruckschwaiger, A. H. Chagla, J. Daley, C. Duhaime, K. Mcghie, G. Pollett, H. Potters, and L. Schiedel, “Hospital-and community-based surveillance of methicillin-resistant Staphylococcus aureus: previous hospitalization is the major risk factor,” *Infect. Control*

Hosp. Epidemiol., vol. 21, no. 11, pp. 724–727, 2000.

[76] S. S. Huang and R. Platt, “Risk of methicillin-resistant Staphylococcus aureus infection after previous infection or colonization,” *Clin. Infect. Dis.*, vol. 36, no. 3, pp. 281–285, 2003.

[77] C. Sandoval, S. D. Walter, A. McGeer, A. E. Simor, S. F. Bradley, L. M. Moss, and M. B. Loeb, “Nursing home residents and Enterobacteriaceae resistant to third-generation cephalosporins,” *Emerg. Infect. Dis.*, vol. 10, no. 6, pp. 1050–1055, 2004.

[78] V. Mor, O. Intrator, Z. Feng, and D. C. Grabowski, “The revolving door of rehospitalization from skilled nursing facilities,” *Health Aff.*, vol. 29, no. 1, pp. 57–64, 2010.

[79] C. L. Richards, M. Darradji, A. Weinberg, and J. G. Ouslander, “Antimicrobial use in post-acute care: A retrospective descriptive analysis in seven long-term care facilities in Georgia,” *J. Am. Med. Dir. Assoc.*, vol. 6, no. 2, pp. 109–112, 2005.

[80] L. Mody, “Infection Control Issues in Older Adults,” *Clin. Geriatr. Med.*, vol. 23, no. 3, pp. 499–514, 2007.

[81] S. J. Schweon, S. L. Edmonds, J. Kirk, D. Y. Rowland, and C. Acosta, “Effectiveness of a comprehensive hand hygiene program for reduction of infection rates in a long-term care facility,” *Am. J. Infect. Control*, vol. 41, no. 1, pp. 39–44, 2013.

[82] S. M. Rhee and N. D. Stone, “Antimicrobial stewardship in long-term care facilities,” *Infect. Dis. Clin. North Am.*, vol. 28, no. 2, pp. 237–246, 2014.

[83] F. Perez, A. Endimiani, A. J. Ray, B. K. Decker, C. J. Wallace, K. M. Hujer, D. J.

Ecker, M. D. Adams, P. Toltzis, M. J. Dul, A. Windau, S. Bajaksouzian, M. R. Jacobs, R. A. Salata, and R. A. Bonomo, “Carbapenem-resistant acinetobacter baumannii and klebsiella pneumoniae across a hospital system: Impact of post-acute care facilities on dissemination,” *J. Antimicrob. Chemother.*, vol. 65, no. 8, pp. 1807–1818, 2010.

[84] P. Tanuseputro, M. Chalifoux, C. Bennett, A. Gruneir, S. E. Bronskill, P. Walker, and D. Manuel, “Hospitalization and Mortality Rates in Long-Term Care Facilities: Does For-Profit Status Matter?,” *J. Am. Med. Dir. Assoc.*, vol. 16, no. 10, pp. 874–883, 2015.

[85] A. F. Chou, C. J. Graber, M. Jones, Y. Zhang, M. B. Goetz, K. Madaras-Kelly, A. Kelly, and P. A. Glassman, “Characteristics of Antimicrobial Stewardship Programs at Veterans Affairs Hospitals: Results of a Nationwide Survey,” *Infect. Control Hosp. Epidemiol.*, vol. 37, no. 6, pp. 647–654, 2016.

[86] D. M. Connor, S. Binkley, N. O. Fishman, L. B. Gasink, D. Linkin, and E. Lautenbach, “Impact of Automatic Orders to Discontinue Vancomycin Therapy on Vancomycin Use in an Antimicrobial Stewardship Program,” *Infect. Control Hosp. Epidemiol.*, vol. 28, no. 12, pp. 1408–1410, 2007.

[87] J. Carlet, V. Jarlier, S. Harbarth, A. Voss, H. Goossens, and D. Pittet, “Ready for a world without antibiotics? The Pensières Antibiotic Resistance Call to Action,” *Antimicrob. Resist. Infect. Control*, vol. 1, pp. 1–13, 2012.

[88] R. Jump, D. Olds, L. Jury, B. Sitzlar, E. Saade, B. Watts, R. Bonomo, and C. Donskey, “Specialty Care Delivery: Bringing Infectious Disease Expertise to the Residents of a Veterans Affairs Long-Term Care Facility,” *J. Am. Geriatr. Soc.*, vol. 61, no. 5, pp. 782–787, 2013.

[89] S. Zimmerman, A. L. Gruber-Baldini, J. R. Hebel, P. D. Sloane, and J. Magaziner, "Nursing home facility risk factors for infection and hospitalization: Importance of registered nurse turnover, administration, and social factors," *J. Am. Geriatr. Soc.*, vol. 50, no. 12, pp. 1987–1995, 2002.

[90] M. J. McGregor, R. B. Tate, K. M. McGrail, L. A. Ronald, A. M. Broemeling, and M. Cohen, "Care outcomes in long-term care facilities in British Columbia, Canada: Does ownership matter?," *Med. Care*, pp. 929–935, 2006.

[91] M. J. McGregor, M. Cohen, K. McGrail, A. M. Broemeling, R. N. Adler, M. Schulzer, L. Ronald, Y. Cvitkovich, and M. Beck, "Staffing levels in not-for-profit and for-profit long-term care facilities: Does type of ownership matter?," *Cmaj*, vol. 172, no. 5, pp. 645–649, 2005.

[92] U.S. Centers for Medicare and Medicaid Services, "The Skilled Nursing Facility Value-Based Purchasing Program," 2016.

[93] B. M. Schnelle, J.F., Simmons, S.F., Harrington, M.C., Garcia, E., Bates-Jensen, "Relationship of Nursing Home Staffing and Quality of Care," *Health Serv. Res.*, vol. 39, no. 2, pp. 225–255, 2004.

[94] U.S. Centers for Medicare and Medicaid Services, "Report to Congress: Appropriateness of minimum nurse staffing ratios in nursing homes phase II final report," Baltimore, 2001.

[95] R. N. Olans, R. D. Olans, and A. DeMaria Jr, "The critical role of the staff nurse in antimicrobial stewardship—unrecognized, but already there," *Clin. Infect. Dis.*, vol. 62, no. 1, pp. 84–89, 2015.

[96] S. Zimmerman, P. D. Sloane, R. Bertrand, L. E. W. Olsho, A. Beeber, C. Kistler, L. Hadden, A. Edwards, D. J. Weber, and C. M. Mitchell, "Successfully reducing antibiotic prescribing in nursing homes," *J. Am. Geriatr. Soc.*, vol. 62, no. 5, pp. 907–912, 2014.

[97] F. J. Silverblatt, C. Tibert, D. Mikolich, J. Blazek-D'Arezzo, J. Alves, M. Tack, and P. Agatiello, "Preventing the spread of vancomycin-resistant enterococci in a long-term care facility," *J. Am. Geriatr. Soc.*, vol. 48, no. 10, pp. 1211–1215, 2000.

[98] R. . Anderson, R.A., Issel, L.M. and McDaniel Jr, "Nursing homes as complex adaptive systems: relationship between management practice and resident outcomes," *Nurs. Res.*, vol. 52, no. 1, p. 12, 2003.

[99] V. Laliberté, L. Joseph, and I. Gold, "A bayesian approach to latent class modeling for estimating the prevalence of schizophrenia using administrative databases," *Front. Psychiatry*, vol. 6, p. 99, 2015.

[100] Z. Feng, D. Grabowski, O. Intrator, and V. Mor, "The effect of state medicaid case-mix payment on nursing home resident acuity," *Health Serv. Res.*, vol. 41, no. 4, pp. 1317–1336, 2006.

Table 2.1. Community-based LTCFs compared to national cohort of for-profit LTCFs in 2015

Variable	Community Based LTCFs (N=29)	U.S. For Profit[a] LTCFs (N = 10583)	Significance
	Mean (SD)		
Resident Characteristics			
Average age (years)	74 (7)	78 (7)	*P<0.0001*
Activities of Daily Living Score[b]	15.1 (2.5)	17.1 (2.6)	*P<0.0001*
Acuity index[c]	11.84 (1.1)	12.19 (1.5)	
Proportion of admissions to LTCF from acute care hospitals	83.1% (13.4)	85% (12.7)	
Facility Characteristics			
Number of beds	133 (39)	111 (53)	*P<0.001*
Proportion of full time RNs to total full time nursing staff	32.0% (9.2)	34.0% (19.2)	
Ratio of admissions to number of beds per facility	1.9 (0.9)	2.3 (2.1)	
Hospitalizations per resident year[d]	1.2 (0.5)	1.2 (0.6)	

Abbreviations: RUG, Resource Utilization Group; LOS, Length of Stay; RN, Registered Nurse
[a]Met criteria of "For-Profit" facility in 2015.
[b]Score range is from 0 to 28. 0 indicates completely independent and 28 completely dependent.
[c]Defined as the measurement of the intensity of nursing care required by an individual resident. Acuity index is calculated by the number of residents needing levels of activities of daily living (ADL) assistance and special treatment measures over the total number of residents per facility, as detailed by [100]. Mean acuity index of long-term care facilities nationwide: 0.95 (SD=0.13) [100].
[d]Rate of LTCF residents admitted to acute-care hospitalization per resident year, adjusted by MDS-determined facility census days and divided by 365 to establish the number of resident years.

Table 2.2. Prescription characteristics (N=29)

	2015 Jan 1 – Dec 31	
	Mean (SD)	
Systemic Prescriptions		
Number of prescriptions	5693.9	(3398.2)
Rate of therapy (DOT/1000 DOC)	2427.6	(1133.7)
Antibiotics[a]		
Number of antibiotic prescriptions	621	(308.6)
Proportion of antibiotics to systemic prescriptions	11.7%	(3.4)
Rate of therapy (DOT/1000 DOC): Antibiotics	70.3	(39.9)
Proportion of antibiotic courses written for a length of therapy >7 days	19.7%	(7.3)
Number of oral antibiotic prescriptions	410	(218.1)
Proportion of oral antibiotics to systemic prescriptions	7.8%	(3.2)
Rate of therapy (DOT/1000 DOC): oral antibiotics	58.0	(32.5)
Proportion of oral antibiotic courses written for a length of therapy >7 days	17.5%	(6.6)
Number of IV antibiotic prescriptions	210	(130.8)
Proportion of IV antibiotics to systemic prescriptions	3.9%	(1.6)
Rate of Therapy (DOT/1000 DOC): IV antibiotics	16.7	(10.3)
Proportion of IV antibiotic courses written for a length of therapy >7 days	2.2%	(2.3)

[a] Defined as antimicrobials that do not include antifungals, antivirals, or anti-tuberculosis agents.
[*] Mean value per year reported among cohort of 29 LTCFs.

Table 2.3: Top antibiotic classes, grouped by agent and evaluated by long-course of therapy$ in 2015% (N=29).

Antibiotics	Average Rate of Therapy (DOT/ 1000 DOC)	Average proportion of antibiotic courses by class to total number of antibiotics (per facility)	Proportion of antibiotic courses by class written for a length of therapy >7 days to total number of antibiotics by class: All	Intravenous	Oral
	Mean (SD)				
Fluoroquinolones	14.2 (7.9)	19.4% (5.8)	22.9% (10.6)	0.3%	22.6%
1st and 2nd generation cephalosporins	7.3 (5.5)	10.1% (3.8)	18.7% (9.1)	1.4%	17.3%
β-lactams/β-lactamase inhibitors	7.2 (4.3)	11.9% (4.7)	15.6% (7.5)	1.6%	14.0%
Tetracycline	5.3 (3.6)	6.0% (5.1)	37.9% (20.7)		37.9%
IV vancomycin	4.6 (3.4)	9.0% (3.8)	6.2% (5.5)	6.2%	
Extended spectrum cephalosporins	4.6 (3.4)	8.3% (4.4)	8.5% (9.1)	4.8%	3.6%
Oral vancomycin	3.6 (3.7)	2.3% (2.0)	65.7% (27.0)		65.7%
Pencillins/aminopenicillins	2.7 (2.8)	3.8% (2.4)	18.7% (15.4)	1.4%	17.3%

* Mean value per year reported among cohort of 29 LTCFs.

$(>7 days)

% Stratified by route of administration and proportion of long-course of therapy when appropriate. Note: Among this cohort in 2015, intravenous tetracyclines were prescribed as short-courses of therapy (≤7 days)

Table 2.4. Summary of LTCF characteristics in 2015 stratified by facility size.

	Small[a] (N=9)		Medium[b] (N=12)		Large[c] (N=8)	
	Mean (SD)					
LTCF facility characteristics						
Number of beds	87	(22.5)	135	(14.7)	180	(13.0)
Occupancy rate^	85.0%	(9.8)	84.7%	(15.5)	87.2%	(10.5)
Total nurse staffing time (hours)	3.5	(0.2)	3.7	(0.5)	3.6	(0.2)
Activities of Daily Living score	15.8	(1.3)	16.2	(2.2)	14.9	(2.4)
Hospitalizations per resident year	1.13	(0.4)	1.38	(0.57)	1.08	(0.59)
Proportion of admissions from acute care hospitals	80.8%	(11.0)	84.3%	(14.1)	83.7%	(16.0)
Antibiotic Characteristics						
Proportion of antibiotics to systemic prescriptions	13.0%	(3.7)	11.3%	(3.6)	11.0%	(2.7)
Rate of therapy (DOT/1000 DOC)	78.5	(41.2)	79.0	(37.3)	63.7	(45.1)
Proportion of antibiotic courses written for a length of therapy >7 days	18.4%	(7.4)	21.0%	(7.0)	19.2%	(8.4)
Proportion of oral antibiotics to systemic prescriptions	9.0%	(3.3)	7.7%	(3.4)	6.8%	(2.9)
Rates of therapy (DOT/1000 DOC): oral antibiotics	62.0	(36.0)	62.0	(29.4)	47.3	(34.6)
Proportion of oral antibiotic courses written for a length of >7 days	16.7%	(7.4)	18.6%	(6.1)	16.6%	(7.1)
Proportion of IV antibiotics to systemic prescriptions	4.0%	(2.1)	3.6%	(1.3)	4.2%	(1.4)
Rates of therapy (DOT/1000 DOC): IV antibiotics	16.5	(10.2)	17.0	(10.1)	16.4	(12.0)
Proportion of IV antibiotic courses written for a length of >7 days	1.7%	(1.1)	2.4%	(3.2)	2.6%	(1.9)

Abbreviations: DOT/1000 DOC, Days of Therapy normalized by 1,000 resident-days of care; IV, Intravenous administration

[a] Small (≤100 beds) | [b] Medium (101-150 beds) | [c] Large (>150 beds)

^ Proportion of residents to number of beds per facility.

Table 2.5: Top antibiotic classes grouped by agent and stratified by facility size and evaluated by long-course of therapy$ in in 2015%.

				Proportion of antibiotic courses by class written for a length of therapy >7 days to total number of antibiotics by class		
		Average Rate of Therapy (DOT/ 1000 DOC)	Average proportion of antibiotic courses by class to total number of antibiotics (per facility)	All	Intravenous	Oral
Facility Size	Antibiotics	*Mean (SD)*				
Small (N=9)						
	Fluoroquinolones	14.3 (7.0)	21.0% (7.6)	20.4% (10.4)	0.3% (0.6)	20.1% (10.6)
	1st and 2nd generation cephalosporins	9.6 (7.8)	11.3% (3.0)	19.2% (9.6)	0.8% (1.5)	18.4% (9.7)
	β-lactams/β-lactamase inhibitors	6.2 (3.3)	10.4% (3.5)	15.0% (8.9)	0.8% (1.6)	14.2% (8.5)
	Tetracycline	5.1 (4.8)	4.8% (3.2)	47.0% (29.1)		47.0% (29.1)
	IV vancomycin	5.7 (4.6)	9.8% (6.9)	4.4% (3.0)	4.4% (3.0)	
	Extended spectrum cephalosporins	5.1 (4.1)	8.3% (3.9)	8.7% (11.7)	3.1% (4.0)	5.6% (11.3)
	Oral vancomycin	2.7 (2.7)	1.8% (1.4)	38.3% (39.3)		38.3% (39.3)
	Pencillins/aminopenicillins	2.7 (2.6)	4.0% (2.9)	12.7% (12.3)	0.3% (1.0)	12.4% (12.3)

Medium (N=12)						
	Fluoroquinolones	17.0 (9.0)	20.2% (5.5)	25.0% (11.5)	0.1% (0.2)	24.9% (11.5)
	1st and 2nd generation cephalosporins	6.7 (3.1)	10.5% (4.1)	20.5% (9.0)	1.9% (3.4)	18.6% (10.4)
	β-lactams/β-lactamase inhibitors	8.7 (5.1)	12.0% (4.1)	16.4% (8.2)	1.0% (1.2)	
	Tetracycline	6.3 (3.3)	6.1% (1.8)	35.1% (12.4)		35.1% (12.4)
	IV vancomycin	4.4 (2.5)	8.7% (3.1)	7.7% (6.4)	7.7% (6.4)	
	Extended spectrum cephalosporins	4.8 (3.5)	8.3% (5.3)	8.8% (9.3)	5.7% (8.2)	3.1% (4.7)
	Oral vancomycin	2.9 (2.3)	1.8% (1.3)	67.8% (28.2)		67.8% (28.2)
	Pencillins/aminopenicillins	3.0 (3.0)	3.9% (2.5)	20.7% (17.6)	2.6% (7.9)	18.1% (14.0)
Large (N=8)						
	Fluoroquinolones	10.0 (5.8)	17.0% (3.2)	22.7% (10.0)	0.5% (0.8)	22.2% (9.8)
	1st and 2nd generation cephalosporins	5.6 (5.2)	8.5% (4.1)	15.7% (9.2)	2.7% (3.3)	13.0% (7.7)
	β-lactams/β-lactamase inhibitors	6.1 (3.9)	13.3% (6.4)	14.8% (4.8)	3.3% (3.7)	11.5% (5.6)
	Tetracycline	3.9 (2.4)	7.2% (9.2)	31.9% (18.6)		31.9% (18.6)
	IV vancomycin	3.6 (3.1)	8.7% (5.2)	5.9% (6.2)	5.9% (6.2)	
	Extended spectrum cephalosporins	3.6 (2.5)	8.4% (4.2)	7.8% (6.3)	5.5% (5.5)	2.3% (2.6)
	Oral vancomycin	5.6 (5.6)	3.5% (2.9)	60.6% (30.7)		60.6% (30.7)
	Pencillins/aminopenicillins	2.4 (3.1)	3.5% (2.0)	22.3% (15.1)	0.8% (2.4)	

$(>7 days)

% Stratified by route of administration and proportion of long-course of therapy when appropriate. Note: Among this cohort in 2015, intravenous tetracyclines were prescribed as short-courses of therapy (≤7 days)

Table 2.6: Effect of facility size on short-course vs. long-course of antibiotic therapy in LTCFs, after accounting for resident and facility characteristics.

Duration of Antibiotic Therapy: [1 = Long-Course (>7 days), 0 = Short-Course (≤ 7 Days)]	Odds Ratio	95% CI	*p*-value
Average age (years)	0.99	0.98-1.00	0.23
Total nurse staffing time (hours)[a]	0.64	0.57-0.72	**0.0001**
Activities of Daily Living score[b]	0.97	0.94-1.00	0.16
Proportion of admissions from acute care hospitals	1.035	1.03-1.04	**0.0001**
Facility Size			
Small	Reference	Reference	Reference
Medium	1.10	1.0-1.2	0.63
Large	0.92	0.83-1.0	0.14
Constant	0.14	0.07-0.30	**0.0001**

[a]Reported total nurse staffing hours per resident per day: Registered Nurse (RN) + Licensed Practical Nurse (LPN) + Certified Nursing Assistant (CNA)
[b]Range is from 0 to 28. 0 indicates completely independent and 28 completely dependent.
Bold type indicates $p<0.05$

Supplementary Table 2.1: Variables Derived from Minimum Data Set (MDS) assessments from the Shaping Long-Term Care in America Project

Variable Name	Definition
PROV0475	Facility Name
state	State of facility
totbeds	Number of beds
profit	Status: Profit or non-profit
acuindex	Acuity index
rn2nrs	Proportion of full time RNs to total full time nursing staff
avgrugcmi_2011p	Average RUG nursing case mix index. The RUG III Grouper places residents into 44 resource utilization groups (RUGs), based on their medical conditions. Each group is assigned a case mix weight. The weights are based on the average number of minutes of time of the caregivers that a resident in each group requires. The RUG with the lowest number of minutes is assigned a case mix weight of 1.000. The case mix weight for each RUG is determined by dividing the lowest group's total weighted minutes into the total weighted minutes for each other group, rounding to the third decimal place. Groups demanding higher levels of care will have correspondingly higher case mix weights.
aggadl_2011p	The average Activities of Daily Living (ADL) score for all residents admitted during the calendar year. Range is from 0 to 28. 0 indicates completely independent and 28 completely dependent.
agg_hosp	Proportion of admissions from acute care hospitals

Supplementary Table 2.2: Variables Derived from CMS Nursing Home Compare

Variable Name	Definition
BEDCERT	Number of federally certified beds
RESTOT	Number of residents in federally certified beds
RESFAMCOUNCIL	Facilities with a resident and family council (Resident Council, Family Council, Both, or None)
AIDHRD	Reported certified nursing assistant (CNA) staffing hours per resident per day
VOCHRD	Reported licensed practical nurse (LPN) staffing hours per resident per day
RNHRD	Reported registered nurse (RN) staffing hours per resident per day
TOTLICHRD	Reported licensed staffing hours per resident per day (RN + LPN)
TOTHRD	Reported total nurse staffing hours per resident per day (RN + LPN + CNA)

Supplementary Table 2.3: Outline of duplicate removal algorithm

<table>
<tr><th>Description</th><th>Example pseudo-code</th></tr>
<tr><td>Extract data of one LTCF (B) and apply a function that generates a unique alphanumeric row ID (A) to each record of that LTCF.</td><td>(A) rawdata[rawdata$FACILITY == “LTCF_NAME”,]

(B) LTCF_NAME$UNIQUE_ID <-
MAKE_RANDOM_STRINGS(nrow(LTCF_NAME), 12)</td></tr>
<tr><td>Initialize a flag column which permits each record to be tagged.</td><td>LTCF_NAME$FLAG <- NA</td></tr>
<tr><td>Identify if record is a reimbursement or not a reimbursement by pattern matching for invoice amount in parentheses. If a reimbursement, flag as “-1”. If not a reimbursement, flag of “0”.</td><td>ifelse(grepl(“//(”,LTCF_NAME), -1, 0)</td></tr>
<tr><td>Select for duplicates (B) using duplicate function (A) that evaluates extracted dataset forwards and backwards looking for duplicate prescription identification numbers, and (C) extract the unique row IDs.</td><td>(A) allDup <- function (Rx) {
duplicated(RX_ID) | duplicated(RX_ID, fromLast =
TRUE) }

(B) <- LTCF_DUPES
LTCF_NAME[allDup(LTCF_NAME$RX_ID),]
LTCF_DUPE_IDS <-
as.vector(LTCF_NAME[,c(“UNIQUE_IDS”)])</td></tr>
<tr><td>Identify non-duplicates with a flag of “1” and duplicates with a flag of “2” among records that are not reimbursements (i.e. flag of “0”)</td><td>LTCF_NAME[!LTCF_NAME$UNIQUE_ID %in%
LTCF_DUPE_IDS & LTCF_NAME$FLAG != -
1,][,c(“FLAG”)] <- 1 or
LTCF_NAME[LTCF_NAME$UNIQUE_ID %in%
LTCF_DUPE_IDS & LTCF_NAME$FLAG != -
1,][,c(“FLAG”)] <- 2</td></tr>
<tr><td>Among duplicate records, A) sort by date and order by prescription ID, B) identify the first and last in the sequence</td><td>LTCF_ DUPES %>%
group_by(RX_ID) %>%
arrange(desc(RX_ID), DATE) %>%
mutate(before.date = lead(DATE, order_by=RX_ID),
next.date = DATE,</td></tr>
</table>

of records with the same prescription ID, C) create a new column that computes the difference in time between records with the same prescription ID.	difference = as.numeric (next.date – before.date), flag = if_else(is.na(difference), 1, -1))
Extract unique IDs of just the first and last records in a sequence and apply a flag of “3”	LTCF_NAME[!LTCF_NAME$UNIQUE_ID %in% LTCF_FIRSTLAST_IDS & !LTCF_NAME$FLAG %in% c(1,-1),][,c(“FLAG”)] <- 3
Among records that had been flagged by first and last record, force rank the highest prescription cost within each prescription ID sequence to identify either A) a day’s supply that is less than or equal to the interval leading to the next record in the same prescription ID sequence, or B) a day’s supply that is greater than the interval leading to the next record and apply a flag of “2”	LTCF_FIRSTLAST %>% group_by(RX_ID, DATES) %>% arrange(desc(RX_ID), DATES) %>% mutate(amount.c = as.numeric(gsub(‘[$,]’,’’, Amount)), rank = dense_rank(desc(amount.c)), flag = if_else(SUPPLY <= difference & rank ==1 | SUPPLY >= difference & rank==1, 2, flag))
Select those intra-sequence prescriptions that were ranked again to break ties of remaining duplicate records by prescription cost and apply a flag of “22”	
Check remaining duplicates, distinguish them, and apply a flag of “23”	LTCF_NAME %>% group_by(RX_ID, Dates) %>% filter(allDup(DATES) == TRUE & allDup(RX_ID) == TRUE & max(row_number(UNIQUE_ID) == 2) %>% mutate(amount.c = as.numeric(gsub(‘[$,]’,’’, Amount)), rank_1 = rank(desc(amount.c), ties.method=”first”), flag_nu = if_else(rank_1 > 1, 23, FLAG))
We exclude all records with flags of “-1” (reimbursements), “2”	

(duplicates), “22” (intrasequence duplicates identified by force rank) and “23” (intrasequence duplicates identified by force rank and ties)	
Apply duplication removal protocol to each LTCF dataset separately, then recombine back to common data model.	

Chapter 3

Mixed-Methods Pilot Study to Assess Perceptions of Antibiotic Stewardship in Long-Term Care Facilities

3.1 Introduction

Antibiotic stewardship is a critical part of preventing illness caused by antibiotic-resistant and healthcare-associated pathogens. The goals of antibiotic stewardship are to ensure that patients receive the right dose, of the right antibiotic, by the right route, for the right amount of time and only when necessary [1]. There are a number of studies that describe successful antibiotic stewardship in long-term care facilities (LTCFs) [2]. However, little is known about antibiotic use patterns in LTCFs or how that use corresponds with current engagement in antibiotic stewardship practices. We hypothesized that LTCFs with more judicious antibiotic use would have an environment more favorable towards antibiotic stewardship compared to LTCFs with less judicious antibiotic use. To test this hypothesis, we conducted a pilot study using a mixed methods approach to explore the qualitative views of LTCF leadership about antibiotic stewardship in the context of quantitative data that compared antibiotic use among the LTCFs.

3.2 Methods

3.2.1 Study design

We used a mixed-methods explanatory sequential design. The design was chosen to explain and interpret quantitative results by collecting analyzing follow-up qualitative data, and is useful for examining quantitative results in more detail [3]. Our study began with a quantitative stage measuring LTCF antibiotic use, followed by a qualitative stage consisting of semi-structured interviews of LTCF leadership that included comparative feedback about antibiotic use (**Figure 3.1**) [3]. The final components were a triangulation stage that evaluated the emergent themes from the semi-structured interviews, followed by an interpretation stage for analyzing the emergent themes within the context of each LTCFs antibiotic use [7]. **Figure 3.2** shows each stage of the study's explanatory sequential design in the context of the data preparation stages required for the quantitative and qualitative stages.

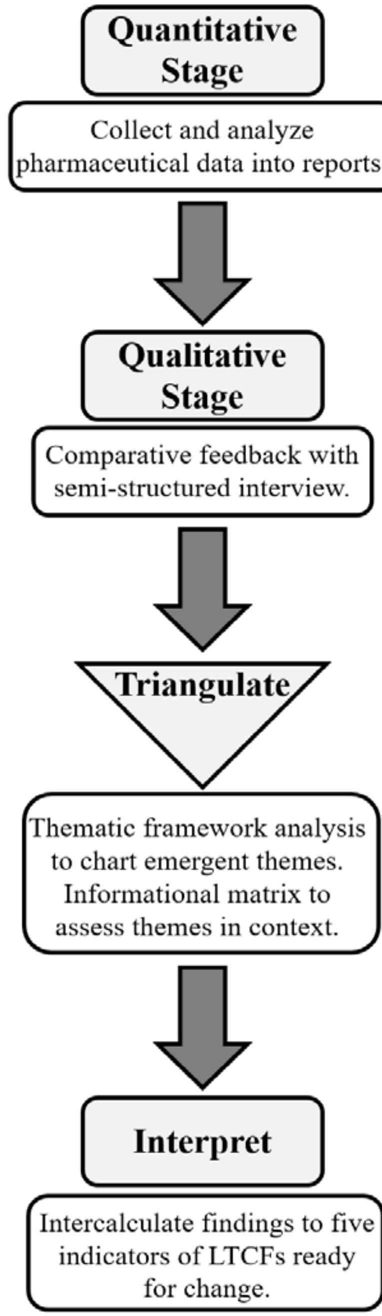


Figure 3.1: Overview of explanatory sequential design. The explanatory approach is characterized by the collection and analysis of quantitative data in the first phase of research followed by the collection of and analyses of qualitative data in the second phase which build on the initial quantitative results. These two forms of data are separate but connected by the triangulation and interpretation phases.

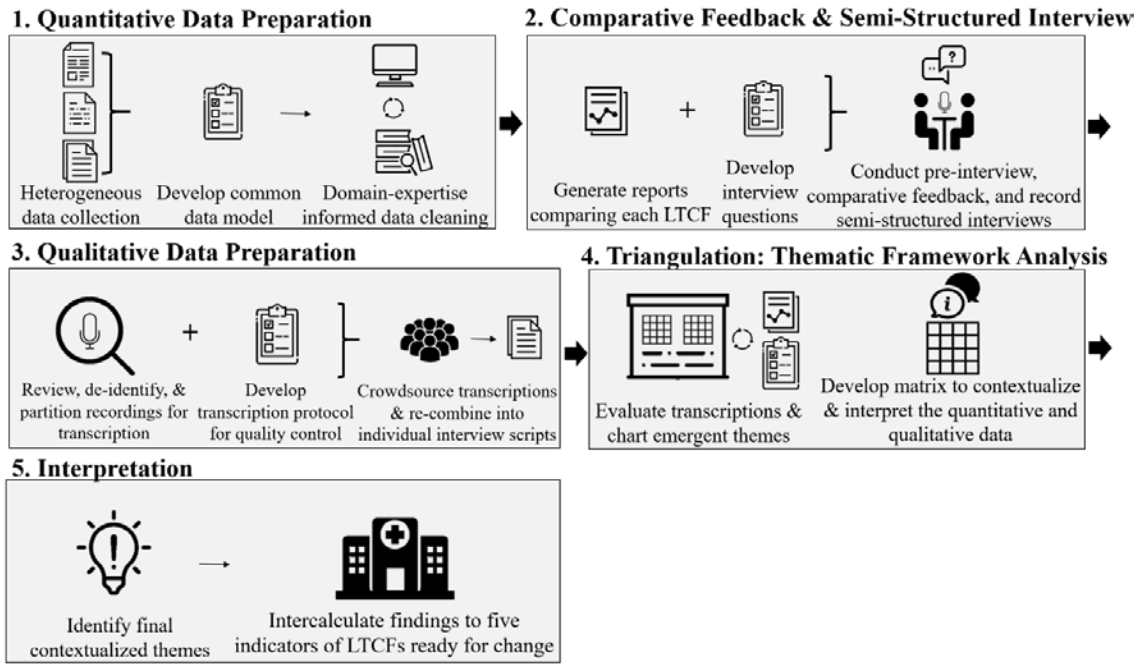


Figure 3.4: Overview of the stages of data preparation and/or analytic components that supported the quantitative and qualitative phases of the explanatory sequential design.

LTCFs were recruited from the Association for Professionals in Infection Control and Epidemiology member list and personal contacts from individual facilities. The initial research plan called for recruiting at least two interview participants from four LTCFs with the intent of testing the feasibility of collecting prescription data, transforming it into standardized metrics and using it to offer comparative feedback to LTCFs. For the purposes of this pilot study, following recruitment the PI (RJ) identified 12 facilities for possible enrollment. Eight LTCFs expressed interest in participating in the research study. Ultimately, six of the LTCFs provided prescription data and five had staff that participated in the semi-structured interviews.

The LTCFs that agreed to participate supplied their antibiotic prescriptions and census data for 2013. We obtained additional information on LTCF characteristics from CMS's Nursing Home Compare [4]. The Louis Stokes Cleveland Veterans Affairs Medical Center institutional review board approved the research protocol.

3.2.2 Quantitative data preparation

Each LTCF-supplied antibiotic prescription data obtained through its pharmaceutical vendor in a unique, unstructured format. The datasets were processed and transformed into a common data model with the open source software OpenRefine (formally Google Refine) [5]. We retrieved antibiotic utilization values from the free-text prescription directions, including days of therapy (DOT) and length of therapy (LOT), although some datasets did not consistently provide both values. To build a consistent data model, we applied the domain expertise of the study infectious disease expert to determine length of therapy from the provided days' supply values to facilitate calculation of utilization metrics [6]. Census data from each facility permitted calculations of days of therapy (DOT) per 1000 resident days of care.

After cleaning and transforming the data into a standard and consistent dataset, we determined the number of prescriptions and length of therapy for systemic antibiotics. Antibiotics were grouped based on their pharmacological class or subclass. The major classes were penicillins, β-lactam and β-lactam inhibitor combinations, 1st generation cephalosporins, 2nd or later generation cephalosporins, fluoroquinolones, macrolides, tetracyclines, nitrofurantoin, and sulfamethoxazole and/or trimethoprim. The oral and intravenous forms of vancomycin have clinically distinct indications and therefore were considered separately. The following classes (or agents) were used infrequently and were grouped together as “other”: aminoglycosides, monobactam (aztreonam), carbapenems, lipopeptide (daptomycin), macrocyclic (fidaxomycin), fosfomycin, and rifamycins.

3.2.3 Comparative feedback & semi-structured interview

We developed antibiotic utilization reports to facilitate comparative feedback and the semi-structured interviews that were tailored to each participating LTCF (**Appendix 3.1**: Example interviewer version with questions; **Appendix 3.2**: Example participant version with graphs). Before each session, participants gave informed consent and permission for audio recordings of the session. Each session began with a pre-interview followed by a semi-structured interview. The pre-interview, grounded in the cognitive interview approach, familiarized participants with all the survey components and primed them to respond with feelings [7]. This technique elicits information that is less constrained by interviewer-imposed bias or the dynamics of the interview itself [8]. The semi-structured interview asked participants to respond to de-identified tables and figures ranking antibiotic use from six participating LTCFs. During the interview, interviewers and participants promoted anonymity by deliberately avoiding identifiers of their facility. However, any unintentional identifiers were timestamped for removal by interviewers in anticipation of the subsequent transcription stage. The infectious disease expert and co-interviewer gave comparative feedback during the semi-structured interview with the intent of providing clinical information and education unique to each LTCFs antibiotic utilization. Participants knew only of the identity of their facility. The interviewers (RJ, RC), who were not blinded to the identity of the LTCFs, used an appreciative inquiry (AI) to ask participants pre-determined open-ended questions and would immediately follow up on new, unanticipated ideas that emerged within the dynamic of the interview. The AI approach is an affirmative interview technique that engages participants on a solution-focused rather than problem-focused level [9]. Researchers selected this solution-focused approach because AI is grounded in the theory developed by Case Western Reserve University faculty Cooperrider and Srivastva on the premise that focusing on problems reduces the possibility of generating new ideas that may induce change [10], [11]. The comparative feedback and semi-structured interview sessions generated 45 minutes to 1 hour of recordings per session, with a combined 8 sessions total (*i.e.* two facilities required two sessions to interview participants from that LTCF).

3.2.4 Qualitative data preparation

Researchers recruited anonymous individuals from the web-based crowdsourcing platform Amazon Mechanical Turk (*http://mturk.com*) to expedite transcription of the semi-structured interview recordings. To ensure standardized transcriptions, researchers developed a protocol to guide recruited individuals (*https://sites.google.com/site/mturkworkhits/*). The guidelines facilitated validation of the transcriptions and the subsequent triangulation step. Notable components to the guidelines included: 1) a list of possible antibiotic-related vocabulary that might be novel to the recruited transcribers, 2) indicators for guessing words and speaker changes, and 3) a request to retain repeated words in the transcript to serve as a possible signal of concept importance in anticipation of the following thematic framework analysis step. To ensure anonymity of participants in the interviews, the following precautions were taken by reviewing, de-identifying, and portioning the recordings with the software SoundForge. Each interview audio file was: 1) reviewed, cleaned (*i.e.* pre-interview responses, loud noises), and de-identified. 2) partitioned into approximately 5 minute segments and uploaded on a secure university server, 3) designated a unique URL that contained a link to the transcription guidelines. Researchers provided a blank webpage with an embedded javascript audio player (*http://kolber.github.io/audiojs/*) instead of a direct download link. The advantage to using the javascript audioplayer was that it could support a wide range of browsers. Furthermore, the embedded MP3 file served as a barrier to downloading the de-identified file for an additional privacy consideration, although it would not restrict the most motivated of MTurk transcribers. Fifteen transcribers were recruited from the MTurk platform, seven of whom were identified as high-quality transcribers and given additional opportunities to transcribe with payment bonus.

The last step in qualitative data preparation was transcription of the interview recordings. Processing all transcriptions took less than two weeks and for minimal total cost (<$50). Payment for transcriptions was higher than the average rate of a $0.5 per minute to $1.5 per minute to ensure quality transcriptions and in recognition of the tasks specific format requirements and the clinical topics [12], [13]. Each segment was transcribed by two workers. This redundancy ensured accuracy of transcription for the final output given that the workers were not necessarily professionals nor possessed a clinical background [24]. All administration typically conducted within the MTurk online platform such as payments, messaging, and task approval were implemented within R programming environment using the package MTurkR [25]. Typically, MTurk users manually download individual .csv files of their results to evaluate their quality and determine which workers to pay for work completed. Using the MTurkR package, researchers implemented quality control and worker payments entirely within the R programming environment. Workers who produced high quality transcriptions were identified and contacted through their MTurk identifier for an opportunity to do more transcriptions for an additional bonus of $0.6 cents per transcription segment. MTurkR permitted messaging these workers and sending payment bonuses by running one line of R code. After all transcriptions were completed, researchers merged the transcriptions from each respective LTCF. Following comparison of transcriptions to the original recordings, researchers verified the precision of the final transcription output in anticipation of the triangulation stage.

3.2.5 Triangulation & Interpretation

We analyzed the interviews with a thematic framework approach designed to identify and triangulate emergent themes [14]. The approach, detailed by Thomas and Harden, guided systematic evaluation of the qualitative data to identify emergent themes [15]. These themes are the key outcomes of a mixed method study [3], [15]. First, researchers became familiarized with the qualitative results to achieve immersion and determined initial themes. Two raters independently coded and grouped the interview content and then collaboratively charted their findings (RC, MM). Discrepancies were discussed and the framework revised until there was a shared understanding of theme definitions and interrater agreement. Finally, we considered the responses from each emergent qualitative theme through use of several triangulation strategies [16]. We sought perspectives from participants with different roles for resident care about their LTCF's reports of antibiotic data (*i.e.* data triangulation), discussed organizational workflow and documentation related to antibiotic prescribing with the participants (*i.e.* methodological triangulation), and considered the views of participants from LTCFs in different locations (*i.e.* environmental triangulation) to delineate themes that were more supportive or less supportive of stewardship (RC, RJ) [17]–[19]. For interpretation, we intercalated the study findings to five indicators of LTCFs ready for change. These outcomes are described in the discussion section.

3.3 Results

Of the eight LTCFs that expressed interest in participating, six provided antibiotic prescription data (**Table 3.1**). The LTCFs were free-standing facilities and accepted both Medicare and Medicaid, with the exception of LTCF E which only accepted Medicare. **Figure 3.3A** shows the total number of antibiotic prescriptions, categorized according to length of therapy, and rates of antibiotic use at each LTCF. The majority of the antibiotic prescriptions were for 7 days or fewer (50-83%). **Figure 3.3B** shows rates of antibiotic use at each LTCF. Fluoroquinolones were the most frequently administered antibiotic, ranging from 27-32% of total DOT per 1,000 resident days of care per facility, followed by sulfonamides, ranging from 7-17% of DOT per 1,000 resident days of care per facility.

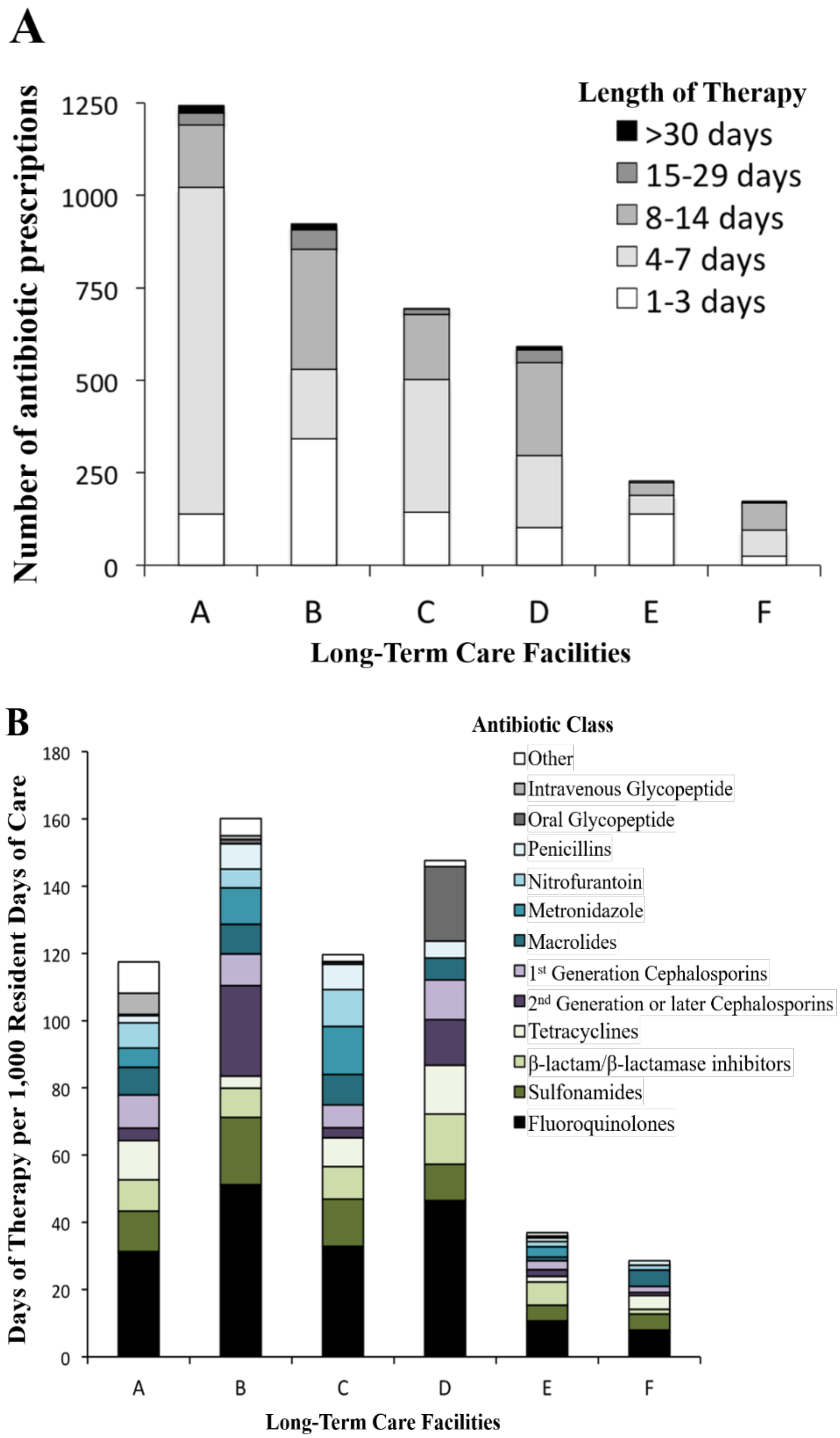


Figure 3.3*:* Antibiotic use at six community nursing homes in 2013. (A) Total number of antibiotic prescriptions, stratified according to length of therapy. (B) Rates of antibiotic

use, grouped according to pharmacological class. Antibiotics grouped as other include the following classes (or agents): aminoglycosides, monobactam (aztreonam), carbapenems, lipopeptide (daptomycin), macrocyclic (fidaxomicin), fosfomycin, and rifamycins.

For the qualitative phase, at least one staff member from each facility participated in a semi-structured interview, with the exception of LTCF A. Roles of participants included five infection control nurses, two directors of nursing, two medical directors, and one attending physician, and nurse manager (**Table 3.1**). The participants' comments portrayed their LTCFs along a spectrum of less to more supportive of antibiotic stewardship principles.

The interviews revealed 6 themes describing antibiotic stewardship in LTCFs. We expand on these themes in a matrix, by providing quotes to illustrate each theme classified as either more or less supportive of antibiotic stewardship. Each illustrative quote is followed with the alphabetical code (A-F) by its respective LTCF (**Table 3.2**).

Theme 1: Practice Patterns

We defined practice patterns as responses to changes in a resident's clinical status, including decisions about ordering diagnostic tests and medical treatments such as antibiotics. Practice patterns less supportive of antibiotic stewardship included little use of established criteria to order diagnostic studies or to start antibiotics (LTCFs B, C, D), starting antibiotics based on urinalysis or urine culture rather than on symptoms (LTCF D), no trial of watchful waiting or hydration in residents with nonspecific symptoms (LTCF B), no post-prescription reassessment based on culture results or response to treatment (LTCFs B, E), greater likelihood of prescribing antibiotics for cultures growing multi-drug-resistant organisms (LTCF C), and use of antibiotics for months to prevent or suppress urinary tract infections (LTCF D.)

Practice patterns more supportive of antibiotic stewardship took the form of those applicable to LTCFs and to general practice. LTCF-specific practice patterns included education of nurses leading to practice changes (LTCF C), nurse- or pharmacist-initiated review of antibiotic prescriptions for longer than 30 days (LTCF C), having only LTCF-experienced providers provide night, weekend or holiday coverage (LTCF E), awareness of LTCF medical providers' residents and their expectations for care (LTCF F), and established communication between the LTCF and the hospital, such as a shared electronic medical record and a collegial relationship among providers (LTCF E). Generalized practice patterns included using established criteria to assess for symptoms of infection (LTCF E), responding to non-specific symptoms with supportive measures such as hydration or cough syrup (LTCFs B, D), writing shorter antibiotic courses (LTCFs C, E), using the results of diagnostic tests to adjust antibiotics (LTCFs D, F), and offering feedback to providers about their antibiotic use (LTCF C)[20][21].

Theme 2: External Influences

We defined external influences as factors and people outside the LTCF that directly affected residents' care. As LTCFs B to F described, pressure from family members to prescribe antibiotics was the most notable external influence. Participants from LTCF F indicated that specialists and emergency department physicians also faced pressure from family members. Participants from LTCFs C, E, and F indicated that their LTCF staff could at times influence family members to avoid unnecessary antibiotics. LTCF F gave a specific example of teaching families that a negative urinalysis excluded infection.

Theme 3: Infection Control & Prevention

We defined infection control and prevention as systematic efforts of the LTCF to minimize transmission of pathogens by residents and LTCF staff. Infection control and prevention strategies less supportive of antibiotic stewardship included lack of routine surveillance practices to monitor rates of healthcare-acquired infections (LTCFs C, D) and, as interview participants described, slow responses to viral outbreaks (LTCF D) and lack of experience and education about fundamental infection control practices (LTCFs B, D).

Infection control and prevention strategies more supportive of antibiotic stewardship involved proactive approaches, including protocols for initiating contact precautions (LTCFs C, F) and active surveillance for multi-drug resistant organisms and *C. difficile* (LTCFs D, E, F). LTCF F reported placing its residents in isolation as soon as *C. difficile* infection was suspected rather than waiting for laboratory results. LTCF F also developed a protocol such that residents under contact precautions received physical and occupational therapy at the end of the day, permitting thorough disinfection of shared equipment. LTCF E stressed resident hand hygiene and restricted visitors during influenza season and a norovirus outbreak to minimize the risk of visitors becoming sick.

Theme 4: Leadership

We defined leadership as the priority given to and the dedication of resources to activities supportive of antibiotic stewardship. Most of these activities were about providing resources to support infection control and prevention. Leadership less supportive of antibiotic stewardship provided the minimum federally mandated education for staff (upon hire and annually) and did not set institutional expectations for standards of care regarding hand hygiene or documentation of changes in clinical status (LTCFs B, D). Participants reported that leadership at LTCFs B and D did not support development of protocols to use during outbreaks of infection, largely because other needs were perceived as having a higher priority. Leadership more supportive of antibiotic stewardship promoted frequent education for nurses and nurse aides (LTCFs E, F), using monthly in-service sessions to review important topics such as hand washing (LTCFs E, F), and addressing new concerns (LTCFs D, E, F). In addition, leadership at LTCFs E and F stressed the importance of staff longevity and reducing aide turnover as a way to maintain an institutional culture supportive of antibiotic stewardship.

Theme 5: Communication

Communication was defined as the process of sharing and receiving information between LTCF staff. Communication less supportive of antibiotic stewardship relied upon clinical notes to convey information between staff. In LTCFs B, C, and D, use of forms, including handwritten notes and templates in an electronic medical record, led to breakdowns and gaps in communication. In addition, the absence of feedback to staff about facility measures such as antibiotic use (LTCF C and D), infection rates, or changes in policies pertaining to infection control (LTCFs D and F) did not support antibiotic stewardship. Participants who described communication more supportive of antibiotic stewardship highlighted scheduled interdisciplinary meetings. The frequency varied from monthly (LTCF B) to daily reports (LTCFs D, E, and F) to discuss residents and develop plans to address symptoms as a way to forestall initiating antibiotics. Furthermore, communication was multimodal, involving forms, telephone calls, faxes, email, and texting when providers were not available in person (LTCFs E and F).

Theme 6: Facility Culture

We defined facility culture as interconnectedness of providers, nurses, nurse aides, family members, and other staff. Facility cultures less supportive of antibiotic stewardship suggested a staff hierarchy characterized by a lack of rapport among personnel at different seniority levels, perpetuated by a desire to avoid conflict. At LTCFs B, C, and D, participants reported considerable reluctance of nurses to question physicians and nurse practitioners. At LTCF D, this reluctance sometimes manifested as nurses being reluctant to educate families about potentially inappropriate antibiotic use, most commonly for asymptomatic bacteriuria. Facility cultures more supportive of antibiotic stewardship revealed a less-hierarchal organizational structure (LTCFs E and F) characterized by a strong voice for nurses to share their views about resident care and providers who were receptive to discussion. This extended to providers and nurses providing consistent information to family members about risks associated with antibiotics.

3.4 Discussion

This pilot study used comparative feedback, an effective means of improving healthcare practice, to inform a qualitative assessment of barriers and facilitators to antibiotic stewardship perceived by LTCF staff members [22], [23]. Comparative feedback about antibiotic use combined with thematic analysis was an important and, to our knowledge, novel component of this pilot study. Findings suggest that LTCFs with lower rates of antibiotic use have a different culture than those with higher rates of antibiotic use. Features of LTCFs that appear supportive of antibiotic stewardship include practice patterns grounded in established diagnostic criteria, proactive infection control, communication between team members, and interconnectedness among staff.

In **Table 3.3** study findings are intercalated with five indicators of LTCFs ready for change, categorized into philosophy of care or task oriented [24], [25]. These echo the Centers for Disease Control and Prevention's Core Elements for Antibiotic Stewardship in Nursing Homes [26]. Task-oriented activities, such as recording the attendance and frequency of in-service training about signs and symptoms of infection or determining rates of antibiotics prescribed for infections that do not meet the Loeb minimum criteria, lend themselves to quantitative measures and are likely to lead to positive outcomes [21], [25]. Such activities may support the efforts of LTCFs to demonstrate their compliance with CMS' Condition of Participation mandate [27].

A metasynthesis of qualitative studies reported that external pressure from family members can drive antibiotic prescriptions in a LTCF [28]. The current study expands upon these findings in two ways. First, the interview participants reported that outside providers, including specialists and emergency department providers, may prescribe antibiotics for LTCF residents in the absence of signs and symptoms suggestive of infection or give in to pressure to treat from well-intentioned family members. These actions may impede LTCFs' attempts to avoid antibiotic prescriptions for nonspecific criteria, such as confusion or cloudy or foul-smelling urine [29], [30]. Second, LTCFs with lower rates of antibiotic use detailed their often successful and united efforts of nursing and providers to educate family members about asymptomatic bacteriuria.

All of the interview participants introduced the topic of infection control and prevention as an aspect of antibiotic stewardship [19]. LTCFs with lower rates of antibiotic use reported using surveillance criteria to monitor their rates of infection and improve care. LTCFs more supportive of antibiotic stewardship communicated a more-proactive approach balanced with a concern for maintaining a home-like environment than LTCFs with higher rates of antibiotic use, in which the discussion of infection prevention and control efforts focused on regulatory concerns [31].

Furthermore, the themes of communication, facility culture, and leadership presented here expand upon previous findings that nurses strongly influence antibiotic prescribing and infection management [28]. A previous study noted that the quality of the communication between nurses and physicians may affect the quality of residents' care [28]. The current study found that LTCFs with a more hierarchical culture, in which nurses avoided conflict, had higher rates of antibiotic use than LTCFs that encouraged routine communication among a multidisciplinary team.

Last, crowdsourcing is a relatively recent approach for surveying the public about healthcare related matters. Use of MTurk workers to transcribe interviews as a part of a larger healthcare-related mixed-methods investigation is, to our knowledge, also novel. The approach minimized the rate of cost and time for conducting the study. For optimal accuracy and complete data-protection the researchers could have composed the transcriptions directly. However, the MTurk platform offers benefits such as minimal risk of experimenter effects in study implementation, and the data-protection and embedded quality control components offered researchers an acceptable cost-benefit ratio of expedited study results in comparison to traditional studies [16].

This study has several limitations. First, the sample size was small, with antibiotic data from six LTCFs and 11 interview participants from the clinical leadership of five LTCFs. The constraint of a small number of participants and narrow spectrum of roles may limit the generalizability of the findings. Second, the participating LTCFs varied in size, location and population. Although dissimilar in some respects, the LTCFs were all community-based and did not have academic affiliates. The in-depth examination of the interview participants' portrayal of their LTCFs allowed detection of emergent themes common to the 5 participating facilities. Third, the LTCFs provided antibiotic data using different formats. Most of the prescription data did not include indications for the antibiotics, precluding interpretations about the appropriate selection, indication, and dosage of agents. Furthermore, the data did not permit identification of consecutive antibiotic prescriptions for the same individual. This may have led to an inconsistent underestimation of length of therapy between the LTCFs.

Despite these limitations, the outcomes suggest specific features of LTCFs that favor antibiotic stewardship. The emergent themes merit further exploration because they may suggest targets for interventions to augment antibiotic stewardship practices at LTCFs. Finally, comparative feedback using objective quantitative data about antibiotic use in LTCFs has the potential to validate ongoing antibiotic stewardship efforts and to identify LTCFs in need of improvement.

3.5 References

[1] N. Fishman, “Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS),” *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 4, pp. 322–327, 2012.

[2] M. J. Katz, A. P. Gurses, P. D. Tamma, S. E. Cosgrove, M. A. Miller, and R. L. P. Jump, “Implementing Antimicrobial Stewardship in Long-term Care Settings: An Integrative Review Using a Human Factors Approach,” *Clin. Infect. Dis.*, vol. 65, no. 11, pp. 1943–1951, 2017.

[3] J. Creswell and V. Clark, *Designing and conducting mixed methods research*. Thousand Oaks, CA: SAGE Publications, 2010.

[4] U.S. Centers for Medicare and Medicaid Services, “Nursing Home Compare,” 2015. [Online]. Available: http://www.medicare.gov/nursinghomecompare/search.html. [Accessed: 01-Jan-2018].

[5] K. Ham, “Open Refine (version 2.5). http://openrefine. org. Free, open-source tool for cleaning and transforming data,” *J. Med. Libr. Assoc.*, vol. 101, no. 3, p. 233, 2013.

[6] N. Daneman, A. Gruneir, S. E. Bronskill, A. Newman, H. D. Fischer, P. A. Rochon, G. M. Anderson, and C. M. Bell, “Prolonged Antibiotic Treatment in Long-term Care: Role of the Prescriber,” *JAMA Intern. Med.*, vol. 173, no. 8, p. 673, 2013.

[7] G. B. Willis, *Cognitive interviewing: A tool for improving questionnaire design*. SAGE Publications, 2004.

[8] S. Daugherty, L. Harris-Kojetin, C. Squire, and E. Jael, "Maximizing the quality of cognitive interviewing data: An exploration of three approaches and their informational contributions," in *Proceedings of the Annual Meeting of the American Statistical Association*, 2001.

[9] G. Bushe, "Advances in Appreciative Inquiry as an Organization Development Intervention," *Organ. Dev. J.*, vol. 13, no. 3, pp. 14–22, 1995.

[10] D. L. Cooperrider and S. Srivastva, "Appreciative inquiry in organizational life," *Res. Organ. Chang. Dev.*, vol. 1, no. 1, pp. 129–169, 1987.

[11] D. Cooperrider, D. Whitney, and J. Stavros, *Appreciative inquiry handbook*. Berrett-Koehler Publishers, 2003.

[12] R. R. Carter, A. DiFeo, K. Bogie, G. Q. Zhang, and J. Sun, "Crowdsourcing awareness: Exploration of the ovarian cancer knowledge gap through amazon mechanical turk," *PLoS One*, vol. 9, no. 1, p. e85508, 2014.

[13] J. Sun, K. Bogie, J. Teagno, Y.-H. Sun, R. Carter, L. Cui, and G.-Q. Zhang, "Design and Implementation of a Comprehensive Web-based Survey for Ovarian Cancer Survivorship with an Analysis of Prediagnosis Symptoms via Text Mining," *Cancer Inform.*, vol. 14, no. Suppl 3, pp. 113–123, 2014.

[14] J. Ritchie and L. Spencer, "Qualitative data analysis for applied policy research," in *The qualitative researcher's companion,* 1st ed., SAGE Publications, 2002, pp. 305–329.

[15] J. Thomas and A. Harden, "Methods for the thematic synthesis of qualitative

research in systematic reviews," *BMC Med. Res. Methodol.*, vol. 8, no. 1, pp. 1–10, 2008.

[16] M. Q. Patton, *Qualitative Research & Evaluation Methods*, 3rd ed. SAGE Publications, Inc, 2001.

[17] M. R. Boland, A. Rusanov, Y. So, C. Lopez-Jimenez, L. Busacca, R. C. Steinman, S. Bakken, J. T. Bigger, and C. Weng, "From expert-derived user needs to user-perceived ease of use and usefulness: A two-phase mixed-methods evaluation framework," *J. Biomed. Inform.*, vol. 52, pp. 141–150, 2014.

[18] D. M. Mertens and S. Hesse-biber, "Triangulation and Mixed Methods Research : Provocative Positions," *J. Mix. Methods Res.*, vol. 6, no. 2, pp. 75–79, 2012.

[19] C. J. Lim, M. Kwong, R. L. Stuart, K. L. Buising, N. D. Friedman, N. Bennett, A. C. Cheng, A. Y. Peleg, C. Marshall, and D. C. M. Kong, "Antimicrobial stewardship in residential aged care facilities: need and readiness assessment.," *BMC Infect. Dis.*, vol. 14, no. 1, p. 410, 2014.

[20] N. Stone, M. Ashraf, J. Calder, C. Crnich, K. Crossley, P. Drinka, C. Gould, M. Juthani-Mehta, E. Lautenbach, M. Loeb, T. Maccannell, P. Malani, L. Mody, J. Mylotte, L. Nicolle, M.-C. Roghmann, S. Schweon, A. Simor, P. Smith, K. Stevenson, and S. Bradley, "Surveillance definitions of infections in long-term care facilities: revisiting the McGeer criteria.," *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 10, pp. 965–77, 2012.

[21] M. Loeb, D. Bentley, S. Bradley, K. Crossley, R. Garibaldi, N. Gantz, A. McGeer, R. Muder, J. Mylotte, L. Nicolle, B. Nurse, S. Paton, A. Simor, P. Smith, and L. Strausbaugh, "Development of Minimum Criteria for the Initiation of Antibiotics in Residents of Long-Term–Care Facilities: Results of a Consensus Conference," *Infect.*

Control Hosp. Epidemiol., vol. 22, no. 2, pp. 120–124, 2001.

[22] A. C. Tricco, N. M. Ivers, J. M. Grimshaw, D. Moher, L. Turner, J. Galipeau, I. Halperin, B. Vachon, T. Ramsay, B. Manns, M. Tonelli, and K. Shojania, "Effectiveness of quality improvement strategies on the management of diabetes: A systematic review and meta-analysis," *Lancet*, vol. 379, no. 9833, pp. 2252–2261, 2012.

[23] D. Meeker, J. A. Linder, C. R. Fox, M. W. Friedberg, S. D. Persell, N. J. Goldstein, T. K. Knight, J. W. Hay, and J. N. Doctor, "Effect of Behavioral Interventions on Inappropriate Antibiotic Prescribing Among Primary Care Practices: A Randomized Clinical Trial.," *J. Am. Med. Assoc.*, vol. 315, no. 6, pp. 562–70, 2016.

[24] M. J. Rantz, M. Zwygart-Stauffacher, M. Flesner, L. Hicks, D. Mehr, T. Russell, and D. Minner, "Challenges of Using Quality Improvement Methods in Nursing Homes that 'Need Improvement,'" *J. Am. Med. Dir. Assoc.*, vol. 40, no. 6, pp. 1301–1315, 2012.

[25] L-F. F. Low, J. Fletcher, B. Goodenough, Y.-H. H. Jeon, C. Etherton-Beer, M. MacAndrew, E. Beattie, C. Etherton-Beer, M. MacAndrew, and E. Beattie, "A systematic review of interventions to change staff care practices in order to improve resident outcomes in nursing homes," *PLoS One*, vol. 10, no. 11, p. e0140711, 2015.

[26] Centers for Disease Control and Prevention, "Core Elements of Antibiotic Stewardship for Nursing Homes," pp. 1–21, 2015.

[27] D. Feldstein, P. D. Sloane, and C. Feltner, "Antibiotic Stewardship Programs in Nursing Homes: A Systematic Review," *J. Am. Med. Dir. Assoc.*, vol. 19, no. 2, pp. 110–116, 2018.

[28] A. Fleming, C. Bradley, S. Cullinan, and S. Byrne, "Antibiotic Prescribing in Long-Term Care Facilities : A Meta-synthesis of Qualitative Research," *Drugs Aging*, vol. 32, no. 4, pp. 295–303, 2015.

[29] L. E. Nicolle, S. Bradley, R. Colgan, J. C. Rice, A. Schaeffer, and T. M. Hooton, "Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults," *Clin. Infect. Dis.*, vol. 40, no. 5, pp. 643–654, 2005.

[30] D. A. Nace, P. J. Drinka, and C. J. Crnich, "Clinical uncertainties in the approach to long term care residents with possible urinary tract infection," *J. Am. Med. Dir. Assoc.*, vol. 15, no. 2, pp. 133–139, 2014.

[31] "Keeping the 'home' in nursing home: Implications for infection prevention," *JAMA Intern. Med.*, vol. 173, no. 10, pp. 853–854, 2013.

Table 3.1: LTCF Characteristics

Characteristics	Participating LTCFs A	B	C	D	E	F
Location	IL	VA	IL	OH	OH	OH
Ownership[a]	For profit, corporation	For profit, corporation	Non-profit, Church related	Non-profit, corporation	Non-profit, corporation	Non-profit, corporation
Number of beds[a]	251-300	101-150	51-100	101-150	51-100	101-150
Bed days of care per month[b]	7001-7500	3001-3500	3001-3500	3001-3500	2001-2500	3501-4000
Staff hours per resident per day						
(Hours:Minutes)[a]	Registered Nurse	1:00	1:10	1:40	0:40	0:40
	Licensed Practical or Vocational Nurse	0:10	1:10	1:20	1:10	1:10
	Certified nursing assisttant	2:00	3:00	4:30	2:10	2:30
Roles and number (#) of staff who participated in semi-structured interviews		Infection control nurse (1)	Infection control nurse (1)	Infection control nurse (1), Attending Physician (1)	Infection control nurse (1), Director of Nursing (1)	Infection control nurse (1), Nurse Manager (1)

[a]Data obtained from Nursing Home Compare at Medicare.gov on 06/27/14. To preserve the anonymity of the participating nursing homes, bed numbers and bed-days of care are reported in 50-bed increments and 500-day increments, respectively. Time are rounded to the nearest 10-minute increment.
[b]Average for 2013

Table 3.2: Matrix of Themes and Illustrative Quotations from Semi-Structured Interviews of LTCF Leadership

Theme	Illustrative Quotations[a] Less Supportive of Antibiotic Stewardship	More Supportive of Antibiotic Stewardship
Practice Patterns		
	"I feel like I often don't have enough documentation on the nursing side or the provider side. [It makes me] wonder if it's just a knee jerk response anytime someone says this resident's more confused today and they just automatically start antibiotics for a UTI. I'm not sure that we're always treating appropriately." (LTCF B)	"We went to the McGeer criteria, hung them up everywhere in the nursing station, so the nurses weren't calling about inappropriate things, especially the UTIs. That made a huge drop in our UTIs." (LTCF E)
	"We were retesting every UTI that we treated. There were some that were just ten thousand CFU's. Did we even need to treat that?" (LTCF C)	"[Covering doctors] know what we do and they pretty much follow the pattern. They are physicians that we've worked with for a long time, so they know our style. They tend to do things in the way that they would anticipate [the LTCF staff] would do them." (LTCF F)
External Influences		
	"It's very frustrating. I'll send someone out who's been perfectly fine for us to the emergency department for chest pains. They get a diagnosis of UTI. I think it feeds the family problem because every time they go to the ED because of whatever… the ED says they're diagnosed with a UTI." (LTCF F)	"The big thing for most of us is families—convincing families that we don't need to put [the resident] on an antibiotic. Sometimes you have to go through ten family members and explain it to them." (LTCF E)
	"Unfortunately, I think being a physician in a long-term care facility, you get a lot of calls [from families and the emergency department to prescribe antibiotics].	"I've seen eventually the family builds trust in the physicians here" (LTCF F)

	Sometimes I think maybe they should know better, but it's just easier to just say get a urine and put them on an antibiotic.” (LTCF D)	
Infection Control		
	“I'm not happy going and making my rounds in this facility that has all these germs running around and they don't seem to be trying to track it or see who's developing it or trying to contain it in any way. They haven't isolated people. They do put *C. diff* patients in their own room. They didn't do that up until the last year. (LTCF D)	“We are kind of strict with isolation. The state isn't always very happy with it, but once someone is coughing and has a fever, they don't leave their room. When the flu season starts, we're very strict on visiting and that, not to visit when you're sick.” (LTCF F)
	“Generally [the nurse practitioners] always say if it's the first time [a resident has MRSA], we're going to treat them, even if they're not symptomatic. They're probably colonized. [If] there's no symptoms there, I'm not sure what we're treating.” (LTCF C)	“We all work hard at getting the residents to wash their hands and they do. And with having the hand sanitizer as they walk out the door, having the residents use it each time, I think that cuts down on a lot.” (LTCF E)
Leadership		
	“One thing I'd like to do is take the McGeer criteria and say these are the things that you should be looking for if someone has an infection [but] it always seems like there's something else [the staff] needs to be learning before that.” (LTCF B)	“We do at least 1 to 2 [training sessions] a month on all different topics for the STNAs. If we have something unusual develop, we will in-service the staff. If we bring something into the building that the staff isn't familiar with, we in-service the staff on that as well.” (LTCF F).
	“We do all online training now. There are a couple on there about infection control and antibiotic use. [There is] some stuff in there for the STNAs too that they're required to take every year.” (LTCF D)	If we see that we have an issue, we'll do additional training for that unit. We recently did that. We were having several UTIs, so we did a peri-care refresher with all the staff on that unit.” (LTCF D)

Communication		
	"We have a little document that the nurse's aide can write on and give to the nurse and also give to the manager. They don't always use that." (LTCF B)	"We talk a lot about [patient care]. There's actually communication on what's happening with this resident and what else could we possibly do." (LTCF E).
	"We send emails [to communicate about patient care], we talk about it at our staff meetings. [There is] not a whole lot [of feedback for nurses and staff], other than talking with them one on one when things are going on, letting them know...." (LTCF C)	"If we weren't on call for the weekend, we hear what happened first thing on Monday mornings. This person got sick. The on-call doctor got called. This got started. This is what we're doing. We did check this. There is a chest X-ray out." (LTCF F)
Facility Culture		
	"We do have a fair number of nurses who are perfectly comfortable talking to the provider about that [antibiotics]. I think the providers always listen, but do they respond in the way that maybe we were hoping for?" (LTCF B)	"In the beginning it was kind of a scary step. I'm questioning a doctor, but, but backing it up. I tell them, 'The CDC's recommendation isn't that we treat for 14 days every time now. Can we cut it down a few?' " (LTCF C)
	"Are we doing what's best for our patients or are we just following orders because somebody said this is what you need to do?" (LTCF C)	"Our regular doctors are great. Sometimes the on-call doctors, just because they don't know the residents and they don't know the staff, it's not that good relationship. But the doctors that we have here, the nurses aren't afraid to talk to them." (LTCF E)

[a]UTI, urinary tract infection; CFU, colony forming units; ED, emergency department; MRSA. methicillin-resistance *Staphylococcus aureus*; STNA, state tested nursing assistant; CDC, Centers for Disease Control and Prevention.

Table 3.3: Activities at LTCFs Supportive of Antibiotic Stewardship

Category	Indicators[a]	Activities
Philosophy of Care		
	Leadership engagement and commitment	
		• Set a facility-wide expectation for evidence-based clinical and diagnostic criteria before starting antibiotics. • Engage covering providers familiar with the care of nursing home residents. • Foster longevity among staff to support "institutional memory" and consistent practice patterns.
	Ownership and sense of responsibility by all staff	
		• Minimize hierarchy among staff. • Cultivate opportunities for nurses, nurses aides and providers to work as teams. • Schedule daily to weekly meetings by a multidisciplinary team to discuss residents with changes in clinical status. • Develop and communicate strategies to address requests for antibiotics by family members and to review antibiotics prescribed by external providers.
Task Oriented		
	Ongoing education activities for all staff	
		• Frequent (*i.e.*, quarterly) and recurring in-service training on a range of infection control and prevention topics, such as hand hygiene to use of personal protective equipment. • Training in the use of standardized assessment tools to facilitate communication between nursing staff and providers. • Support antibiotic stewardship education for providers.
	Regularly share process measures with all staff	
		• Share the LTCF's rate of infections over time and, if appropriate, by unit. • Share the rate of antibiotic prescriptions that did and did not meet established surveillance criteria for infections.

Compare outcomes to that of other LTCFs[b]

- Comparative feedback common infections, prevention measures and surveillance outcomes for drug-resistant pathogens and *C. difficile*s.
- Comparative feedback about antibiotic use within a region, chain or network of LTCFs.

[a]As detailed in reference [24].

[b]While comparative feedback about antibiotic use is not yet feasible for most LTCFs, the CDC's National Healthcare Safety Network has a long-term care component to help assess progress towards national healthcare-associated infection goals.

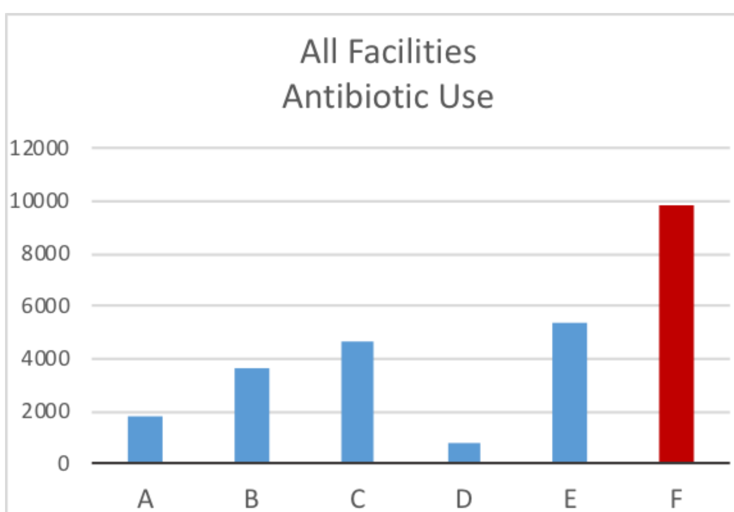
Appendix 3.1: Example semi-structured interview report, Interviewer version with follow up questions.

Self-Assessment

1) How would you summarize your facility's approach to antibiotics?
2) What are the strengths of your facility's approach to antibiotics?
3) How are you currently documenting antibiotic use?

Antibiotic Graphs

1) What are your initial impressions of these graphs?
2) What information stands out to you from these graphs?
3) Do you believe there are any special characteristics of your facility that would explain certain patterns of antibiotic use? If so what are they?
4) Do you think these antibiotic utilization graphs might prompt changes within your facility?
a. Use of narrow spectrum agents over broad-spectrum agents
b. Encourage oral antibiotics over IV antibiotics



c. Formulary restriction on specific antibiotics (based on cost or overuse or …?)

5) How will you share these ABLE antibiotic use data and graphs with your facility staff?

Facility level resources available over the previous 12 months

1) What resources do you have available to support antibiotic stewardship?
ie:
a. Administration support
b. Infection Control Committee
c. Audit/Review from Pharmacy
d. Education for providers
e. Education for nursing staff
f. Education for patients/families

2) What are possible barriers to antibiotic stewardship at your facility?
ie:
a. Time
b. Communication
c. Lack of Technology
d. Staff Commitment
e. Fear of direct reporting
f. System issues within institution
g. Compliance
h. Physician Practice

Measures currently in place to support antibiotic stewardship

1) Are you using any of the following methods for antimicrobial stewardship?
a. Intravenous to oral conversion of antibiotics
b. Order sets or protocols for specific conditions (like urinary tract infection or pneumonia)
c. Recommendations for length of antibiotic treatment for specific conditions
d. Automatic stop orders
e. Narrowing antibiotics in response to culture data or a changing clinical picture (ie someone in whom it's clear after a couple of days has heart failure compared to an initial concern for heart failure or pneumonia)
f. An antibiotic "time-out" after 48-96 hours of therapy

How are you doing it?

1) If yes to any of the above, how are you carrying out the procedure?
a. How are you measuring outcomes?
b. How are you sharing outcomes?

c. Do you feel policy/procedure has been effective?
d. Why or why not?
2) Of the interventions mentioned above, which would you like to try?
a. How would you implement it?
b. What resources do you have?
c. What resources do you need?

What resources do you need to achieve that goal/outcome?

1) What tools are you using/could you use to facilitate antibiotic stewardship for clinical staff? For families?
a. Laminated pocket cards
b. Slide shows
c. Didactic education, meaning formal lecture series
d. On-demanding teaching through YouTube or other online platforms
e. Order sets
f. Small group
g. Recommendations from the infection control committee
h. Audit and feedback to prescribers
i. Educational materials for patients and families

Appendix 3.2 Example semi-structured interview report, participant version.

Thank you for participating in this interview about antibiotic use and antibiotic stewardship at your facility. Your answers will be recorded and the tapes will be stored in a locked cabinet in a locked office. **Once we begin the recording process, we ask that you do not state your name or the name of your facility. Any inadvertent identifying information (other than your role) that might identify you or your facility will be removed from the recorded interviews prior to transcription and analysis.**

We will ask you questions about on-going antibiotic stewardship efforts and related infection control efforts. **You may choose not to answer questions or stop the interview at any time. There are no consequences or penalties for skipping questions or stopping the interview.**

The interviewer has a general script to provide structure to the interview, as a means to offer some consistency when talking to different providers. We can discuss relevant topics not addressed by our questions.

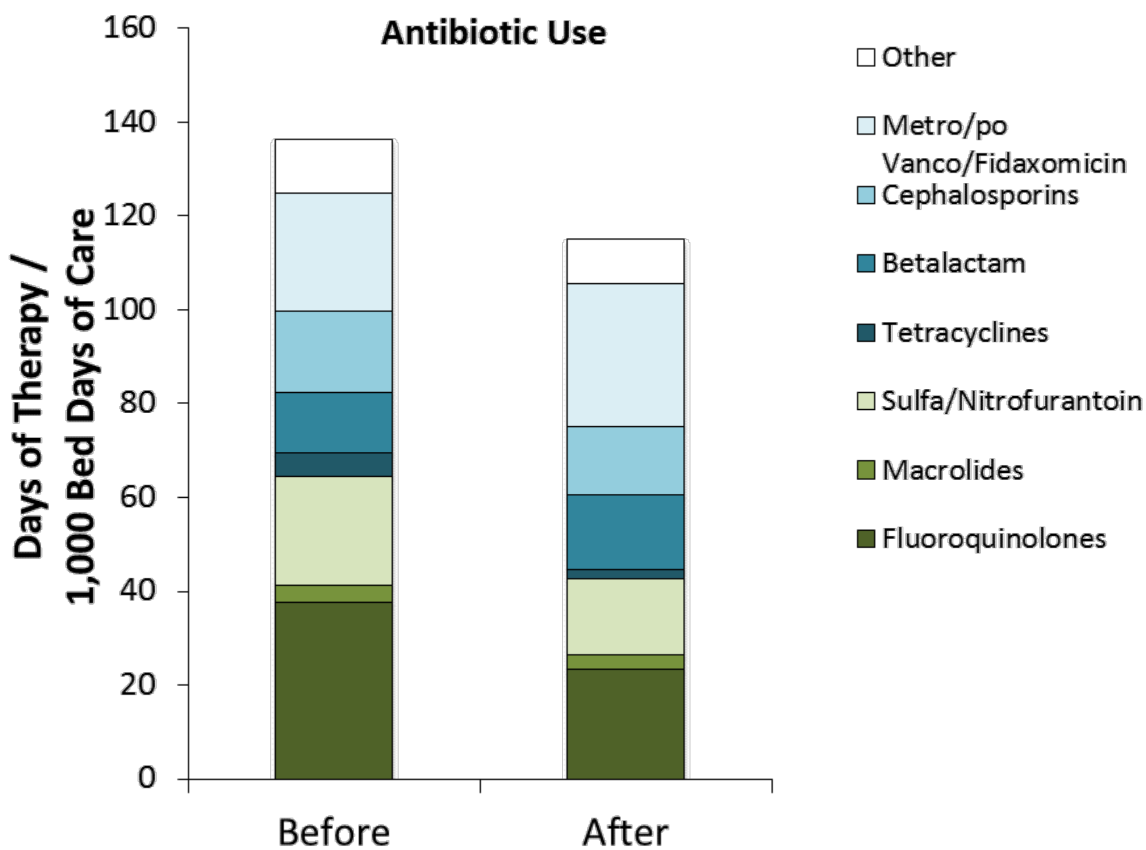
The following information compares your facility to others participating in our study. The only information shared about your facility is that what you see here. Only you and your staff know the random 3-letter code for your facility.

We will start with a few warm-up questions to get you used to the interview process, which includes talking out loud about your thoughts.

What are your initial impressions about this graph?

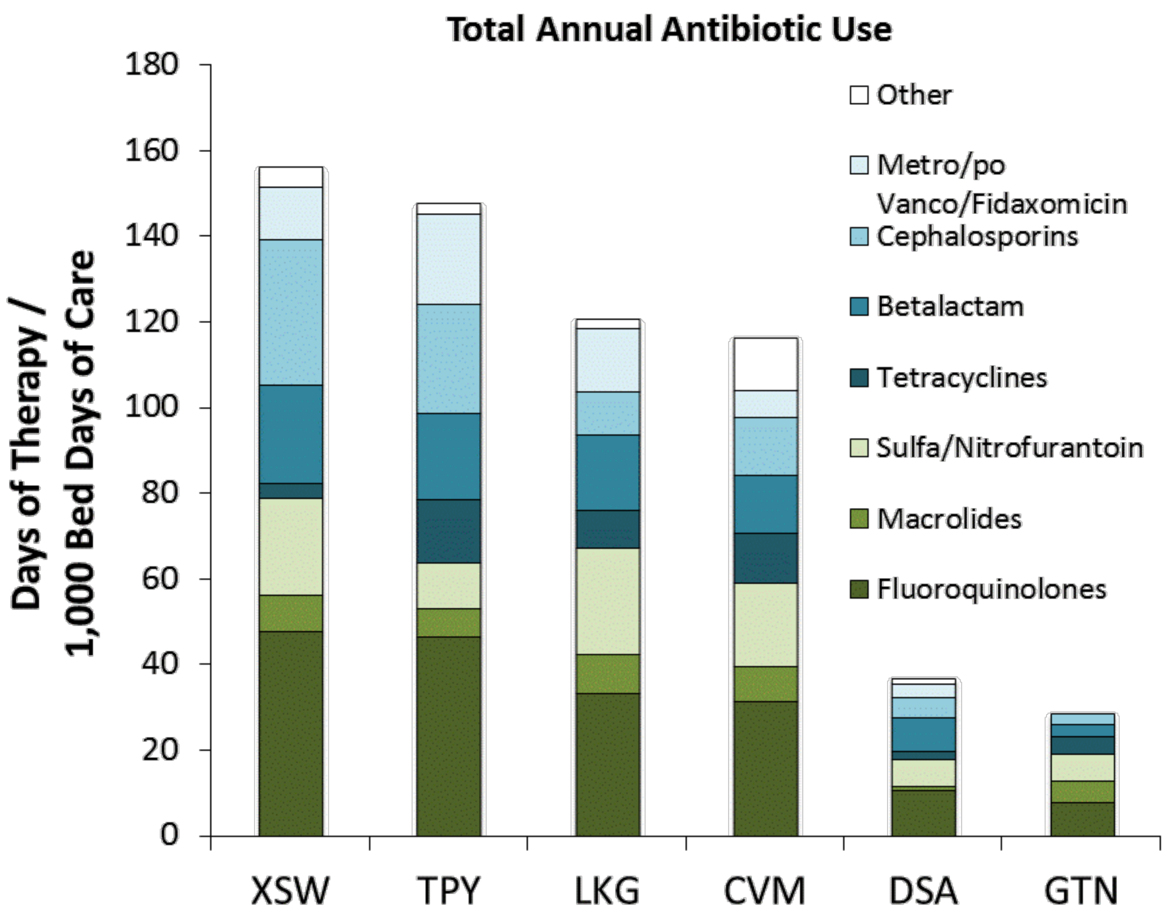
What information stands out?

What are your impressions of the different antibiotic classes?



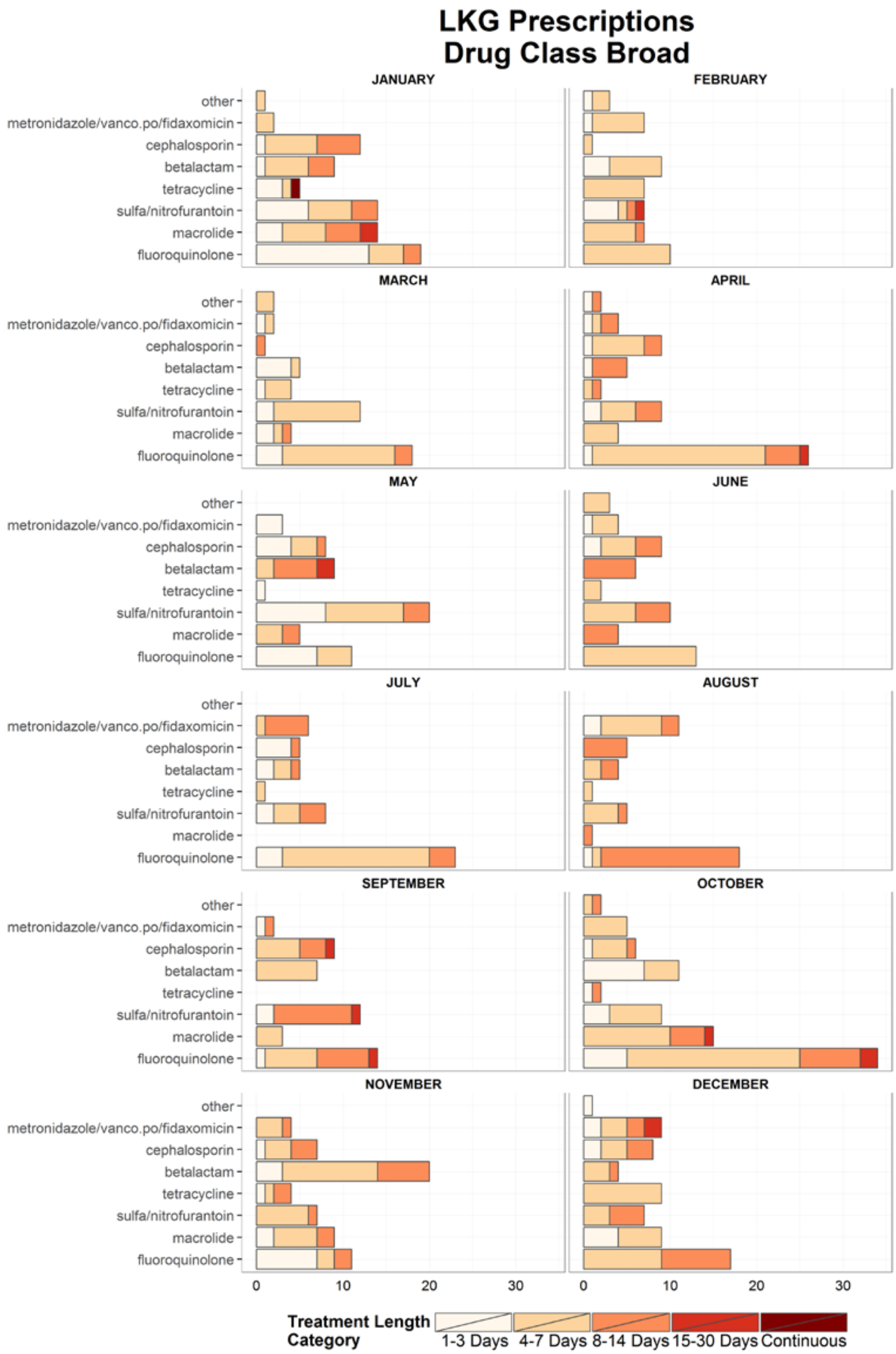
Now we will officially begin and ask some questions about on-going practices at your facility.

Let's start with the first graph. This graph compares total antibiotic use for your facility compares to other long-term care facilities.



Location	Virginia	Ohio	Illinois	Illinois	Ohio	Ohio
Beds	100-150	100-150	<100	>250	<100	100-150
Average Bed Days of Care/Month	3000-4000	3000-4000	3000-4000	>7000	2000-3000	3000-4000
RN Hours per Resident per Day	61 - 75m	30-45m	90-120m	46-60m	30-45m	NA
For Profit	Yes	No	No	Yes	No	No
Continuing Care Retirement Community	Yes	Yes	No	No	Yes	No

Let's move onto the second graph, shown on the next page. The second graph shows monthly antibiotic use at your facility.



Lets discuss the table, which describes the length of therapy (ie: number of days of treatment) for antibiotics.

Antibiotic Prescriptions at each Facility by Length

	XSW		TPY		LKG		CVM		DSA		GTN	
Prescription Length	n	%	n	%	n	%	n	%	n	%	n	%
1-3 days	342	38%	101	17%	140	20%	138	11%	139	61%	24	14%
4-7 days	188	21%	196	33%	363	52%	883	71%	49	22%	69	41%
8-14 days	325	36%	250	42%	176	25%	170	14%	36	16%	73	43%
15-29 days	51	6%	36	6%	14	2%	31	2%	3	1%	3	2%
≥ 30 days	0	0%	8	1%	1	0%	22	2%	0	0%	1	1%
Total Prescriptions	**906**		**591**		**694**		**1244**		**227**		**170**	

Additional Questions:

1) Do you think this data about antibiotic use at your facility will prompt changes at your facility?
2) Do you plan to share these antibiotic use data and graphs with your facility staff?
3) Finally, we would like to ask you a series of questions about ongoing antibiotic stewardship practices at your facility.

Chapter 4

Discussion

4.1 Background

Antibiotic resistant bacteria cause over 2.5 million infections and 23,000 deaths annually [1]. Long-term care facilities (LTCFs), where experts estimate that 25% to 75% of antibiotic prescriptions are inappropriate and/or unnecessary, contribute to the burden of antibiotic resistant bacteria [2-4]. Antibiotic stewardship, which seeks to minimize inappropriate or unnecessary antibiotic use, is critical to combating antibiotic resistant bacteria. Antibiotic stewardship programs (ASPs) are coordinated strategies that promote responsible use of antibiotics to slow emergence of antibiotic resistant bacteria and increase resident benefit [5]. Stewardship strategies can include selection of narrow-spectrum agents over broad spectrum agents, education for LTCF staff and medical providers, or shortened treatment durations [6]. ASPs are urgently needed in LTCFs to improve resident outcomes and reduce selection for antibiotic-resistant bacteria in this setting.

The decision to prescribe an antibiotic in a LTCF is complex, with a number of diverse and critical contextual influences that may help or hinder ASPs in these settings [7]. These influences can be generated by factors such provider attitudes and knowledge hindered by lack of awareness of guidelines and provider autonomy. Facility-related factors influencing the decision to prescribe can include constraints on logistical resources and funding, which may shape hierarchical roles and communication within an LTCF as well foster diagnostic uncertainty of providers [8]–[10]. In the context of factors influencing antibiotic prescribing decisions, it is important that providers are aware that their individual prescribing patterns can impact the overall antibiotic usage in their LTCF [11].

LTCFs are now federally mandated to incorporate ASPs, and one approach is for these healthcare settings to track and report patterns of their antibiotic use [12], [13]. However, there are challenges to obtaining antibiotic use data in LTCFs. Estimates of LTCF antibiotic use almost exclusively rely on proprietary measurement systems or electronic health data sources that are not necessarily available to all LTCFs [14]. These limitations are due to a lack of information technology support and funding constraints [15], [16]. Use of existing data such as pharmaceutical invoice data may serve as a valuable resource for results generalizable to LTCF residents [17]–[22]. There is emerging evidence of successful stewardship in US LTCF settings, but little is known about antibiotic use patterns in LTCFs or how that use corresponds with engagement in antibiotic stewardship practices [23].

4.2 Study findings

LTCFs have been slow to adopt stewardship measures. Adoption may be impeded due to financial and technological resource constraints or personnel who may lack training or experience in data collection and analysis [6], [24]–[28]. Our central research question is: Can an examination of influences that promote inappropriate and/or unnecessary antibiotic prescribing decisions in LTCFs support identification of specific characteristics that may advance effective LTCF antibiotic stewardship? We hypothesized that assessing antibiotic prescribing patterns in LTCFs, along with LTCF providers' sharing their perceptions of influences on those patterns, will help to identify opportunities to achieve effective antibiotic stewardship practices in LTCFs.

4.2.1 Use of Pharmaceutical Invoices to Characterize Antibiotic Patterns in American LTCFs

Our primary motivation was to evaluate if existing invoice data can reasonably capture antibiotic prescribing patterns in LTCFs. Our findings show that derivation of antibiotic use from a sample cohort of LTCFs is feasible. Our analytic approach addressed two challenges posed by the invoice data: duplicate records and intended course of therapy. We found that in the absence of patient-level data, linking individual records by prescription ID was an important first step towards obtaining valid metrics and filtering out duplicate records. Specifically, removal of reimbursements and identifying duplicate records by cost and date within their prescription ID group were the most important characteristics towards extracting valid use measures from LTCF invoice data.

Another important challenge addressed by our analytic approach was intended course of therapy. When the individual course records were linked and subsequently collapsed by total rates of therapy, we could estimate the LTCF medical provider's intended course of therapy. The rates of therapy were unaffected by intended as they were normalized per

1,000 resident days of care. However, when we estimated the proportion of length of therapy stratified by route of administration, we found that individual records tend to underestimate the intended length of therapy for antibiotics administered intravenously (IV) more than orally (**Table 4.1**). This

differences in estimation may be a limitation of use of pharmaceutical invoice data, where treatment indication is not available [29]. Specifically, invoice data does not permit evaluation of the complete dynamics of the decision to prescribe. These dynamics can include

canceled orders, polypharmacy, therapy changes for the same resident, or if therapy originated in the LTCF or prior acute-care hospitalization [30].

Table 4.2 Comparison of proportion of long-course of therapy (>7 Days) when summarized by intended course vs. individual records.

		2015
		Mean (SD)
Intended Course		
	Proportion of length of IV therapy >7 days	2.2% (2.3)
	Proportion of length of oral therapy >7 days	17.5% (6.6)
Individual Records		
	Proportion of length of IV therapy >7 days	0.3% (0.3)
	Proportion of length of oral therapy >7 days	16.8% (6.7)

Our secondary motivation was to characterize antibiotic prescribing patterns among a cohort of American LTCFs. The invoice data illustrated patterns of use among a cohort of 29 LTCFs over a 12-month study period. Results suggest that LTCFs from this cohort favor the class of fluoroquinolones for treatment, as nearly 1 in 5 antibiotics were written for a fluoroquinolone. In addition, nearly 2/3rds of antibiotics written for a long course of therapy were written for oral vancomycin. When stratified by facility size, study results showed that small and medium facilities prescribed 23%-24% higher normalized days of therapy, respectively, in comparison to large facilities. Results indicated each one-unit increase in admissions from acute-care hospitals was associated with a 3.5% increase in the odds of an antibiotic prescribed as a long-course of therapy. Further, results show that the relationship between nurse staffing time and long-course of antibiotic therapy (>7 days) is significant, where for each hour increase of total nurse staffing per resident per day, an antibiotic prescription was associated with an 36% decrease in odds of being written as a long-course of therapy.

4.2.2 Study findings: Mixed-Methods pilot study to assess perceptions of antibiotic stewardship in LTCFs

Our motivation was to examine providers' view of their patterns of antibiotic use in order to better understand how to improve stewardship strategies for LTCFs through comparative feedback and semi-structured interviews. Our study identified several LTCF features supportive of antibiotic stewardship, including practice patterns grounded in established diagnostic criteria; proactive infection control and prevention; and open communication and interconnectedness among staff. For example, practice patterns more supportive of antibiotic stewardship included use of diagnostic tests to adjust antibiotic course of therapy, writing shorter antibiotic courses, and nurse-initiated review of antibiotic prescriptions for longer than 30 days. These practice patterns supportive of stewardship may include use of study guidelines to offset inappropriate and/or unnecessarily aggressive antibiotic treatment and provider awareness of outliers in their patterns of use.

Our study described infection control and communication approaches that illustrate factors influencing the decision to prescribe. This included LTCFs with proactive approaches to infection control and prevention, including select facilities restricting residents to their rooms as soon as a *C. difficile* infection was suspected rather than waiting for diagnostic test results. Communication was an important factor and LTCF feature supportive of antibiotic stewardship. Communication supportive of stewardship was distinguished by interdisciplinary staff meetings and daily reports, which can facilitate interconnectedness and knowledge sharing within a LTCF organization.

4.3 Implications for LTCF stewardship

4.3.1. Use of Pharmaceutical Invoices to Characterize Antibiotic Patterns in American LTCFs

Health services and infectious disease researchers have previously recognized the enormous potential of using pharmaceutical invoice data to evaluate patterns of antibiotic use due to the accuracy embedded in the raw data [31], [32]. However, the same studies note that extraction of antibiotic use metrics from existing data can be labor-intensive and error-prone. These challenges may compromise the efficiency and efficacy of this resource [29], [31]–[33]. However, our study offers a manageable approach for deriving usable metrics from this resource by linking individual records by prescription ID, removing reimbursements, and identifying duplicate records by cost and date within their prescription ID group. This collection of approaches derived from our complex multi-step model may invite other researchers to use invoice data as a resource.

Another challenge for researchers to pursue this type of resource can be intended course of therapy. Without linking and collapsing records by total rates of therapy, intravenous antibiotics may be underestimated. Reasons for this may be that intravenous antibiotics have a shorter shelf-life compared to orally administered antibiotics, particularly for those reconstituted by the dispensing pharmacy [34]–[36]. Studies show this underestimation may be related to a LTCF's limited access to an on-site dispensing pharmacy. Residents may continue a long-course (>7 days) of antibiotic therapy post-hospital discharge for infections with symptoms that may take several weeks to resolve [37]. To counteract underestimation, careful linking and evaluation of intravenous antibiotic therapy and review with a multi-disciplinary team may be required.

Our study findings reflect important patterns of broad-spectrum antibiotic use in LTCFs. The prevalence of antibiotic resistant gram-negative bacteria is high among LTCFs of which 50% of LTCF residents are colonized with antibiotic resistant gram-negative bacteria [45]–[47]. Several classes of antibiotics used to combat gram-negative bacteria had the highest rates and duration of therapy in our cohort including fluoroquinolones and extended-spectrum cephalosporins. These antibiotics often treat infections that can emerge due to the residential setting or from hospital transfer [48]. Our study findings warrant further attention for these classes of antibiotics as targets for responsible use in an LTCF facility.

We had expected facility size to be an important factor in determining patterns of use of antibiotics. In a study of 3,236 LTCF residents from Southern Germany, small facilities (<100 beds) were found to be significant risk factors for MRSA colonization [49]. Related, our study results showed that half intravenous antibiotic prescriptions written as a long-course of therapy (>7 days) among small facilities were written for vancomycin, which is predominantly used to treat MRSA [50]. Therefore, our study results offer additional opportunities for investigation of facility characteristics beyond resident frailty or number of beds. These characteristics may include an assessment of differences in payer mix (*i.e.* Medicare Part A vs. Medicare Part D), as a study by Stenehjem *et al*. indicated that healthcare settings with fewer resources may be distinguished by their financial incentives as opposed to resident clinical indication [51].

Interestingly, although not surprisingly, a dynamic between nurse staffing hours and proportion of residents admitted from acute-care hospitals emerged as an important association with antibiotics written as a long-course of therapy. Antibiotics prescribed as a long-course of therapy may be prescriptions continued from a resident's acute-care hospital stay [52]. However, it is unknown what proportion of antibiotic prescriptions written for a long-course of therapy within our study cohort had originated outside of the LTCF given the limitations of our invoice data. Our study findings can support nurse staffing as having a meaningful impact in resident care. For an LTCF, nurse staffing hours serve as an indicator of quality that improves resident health outcomes, including fewer pressure ulcers and fewer urinary tract infections [53]. To support staffing quality as a part of the decision to prescribe, studies show education should be targeted and tailored to nursing assistants, nursing staff [54]. Targeted education is endorsed by the CDC core elements of stewardship for LTCFs, and may offer an additional benefit of reducing acute-care hospitalization costs to LTCFs [12], [55].

4.3.2 Implications for the field: Mixed-Methods Pilot Study to Assess Perceptions of Antibiotic Stewardship in Long-Term Care Facilities

Our results expand upon previous discussions of influences on antibiotic prescribing in two important directions. First, outside providers, including specialists and emergency department providers, may prescribe antibiotics for LTCF residents in the absence of signs and symptoms suggestive of infection or give in to pressure to well-intentioned family members. Studies have indicated a need for a greater understanding of residents' and family members' preferences in support of stewardship in LTCFs [56]. LTCF providers and nurses report that residents and families both want antibiotics and exercise influence over treatment decisions [57]–[59]. In a sample drawn from 31 LTCFs in North Carolina, open-ended responses by providers underscored the role of individuals and families in decision-making, particularly by nurses [60]. Second, findings from our mixed-methods study showcases the unique role of nurses in an LTCF setting, as they can strongly influence antibiotic prescribing. Our findings point to the importance of empowering nurses in this healthcare setting [54], [61]. Specifically, our study results showed higher rates of antibiotic use in LTCFs where there was a more hierarchical culture and nurses tended to avoid conflict, compared to LTCFs that encouraged routine communication among a multidisciplinary team. Nurses affect multiple aspects of resident care, including administering and monitoring response to antibiotics, as well as navigating pressure by families on a provider's decision to prescribe an antibiotic for a resident [62]. Studies indicate that addressing nurse's educational needs can motivate their involvement in ASPs [22]. A 2017 integrative review by Katz *et al.* underscored the importance of nurses on the antibiotic prescribing process, indicating that engaging nursing staff with structured education measures may represent a feasible, pragmatic, and cost-effective strategy for LTCFs [23]. Our mixed-methods study emphasizes the need to empower nurses for the purpose of advancing stewardship in LTCFs.

Our approach offered a critical opportunity for comparative feedback to evaluate stewardship in context of a clinician's perceptions, particularly nurses. The mixed-methods approach has significant limitations to implementation, due to the time required for the qualitative semi-structured interviews and thematic framework analysis. Additional limitations to the mixed-methods approach included challenges in analyzing the unstructured quantitative data [63]. We overcame important aspects of this limitation with our use of crowdsourced transcribers for generating transcriptions at a minimized the rate of cost and time while implementing data protection and de-identification measures. Studies show that Amazon Mechanical Turk can be used as a reliable method of transcribing spoken language data with an accuracy that rivals conventional transcription methods [64], [65]. The utility of our methods may reduce the time and labor investment for a typical mixed-methods approach, where traditionally researchers either pay for their transcriptions or manually transcribe themselves at ratio of six to seven hours of transcription labor per hour of recorded interview [66].

4.4 Additional questions and future directions

We provide important key considerations and process strategies for systematically extracting antibiotic use metrics from raw invoice data. Our approach demonstrates that pharmaceutical invoice data is useful for deriving patterns of antibiotic use in a facility. Our approach may invite other researchers to use invoice data for examining use patterns for results generalizable to their underlying study population [21].

We indicated specific, actionable targets for review or adjustment of antibiotic class and duration. Targets include evaluation of antibiotic agents of fluoroquinolones and extended generation cephalosporins and prescriptions written for a long-course of therapy (>7 Days). Employing antibiotic use targets for review or implementing adjustment from broad to narrow spectrum (*i.e.* de-escalation) are shown to improve antibiotic use in hospitals [67]. There is emerging evidence that de-escalation can also improve antibiotic use in LTCFs [68]. However, studies show that prescribers rarely switch to agents with a more narrow spectrum even when culture results indicate the opportunity make the switch [69]. Therefore, specific targets of agent and duration present an important opportunity for LTCFs to improve antibiotic use within their facilities.

We used a two-stage sequential design to identify features of LTCFs supportive of antibiotic stewardship. Advantages to this design include opportunities to explore the patterns of antibiotic use in more detail through comparative feedback and semi-structured interviews. This design was especially useful for the opportunity to explore emergent themes and discuss barriers to stewardship with LTCF leadership using the guiding context of antibiotic use rankings among our limited cohort [70]. Rather than considering patterns of antibiotic use data or surveys of provider perceptions of stewardship as independent silos of information, our approach demonstrates the value of LTCFs introducing an integrated approach to their local setting.

Finally, providers' perceptions of influential factors on patterns of antibiotic prescribing revealed specific opportunities to change and support an LTCF to be actively engaged in judicious use of antibiotics such as the importance of communication between providers and nurses and reduction of hierarchy at an organizational level. Study findings support future opportunities to explore comparative feedback with objective quantitative data about antibiotic use in LTCFs. More importantly, the combination of feedback in the context of utilization may be used as an opportunity to validate ongoing antibiotic stewardship efforts as well as identify LTCFs in need of improvement.

A possible future direction of research would be an assessment of the prescribing tendencies of LTCF prescribers by leveraging the pharmaceutical invoice data. Studies by Daneman *et al.* suggest that antibiotic patterns of use is more dependent on who prescribes the drug than the characteristics of the resident receiving the drug [3], [71]. Understanding antibiotic patterns of behavior specific to individual prescribers within a facility can provide an avenue for reducing inappropriate and/or unnecessary use of antibiotics tailored to that LTCF. With our data, each pharmaceutical invoice record includes its prescribers' first and last name, lending to the feasibility of this future research. Possible patterns of use that reflect the decision to prescribe an antibiotic can include the tendency to select a specific class of antibiotics and the tendency to use antibiotics for a long-course of therapy (>7 Days)). In a study of 1,869 LTCF providers in Ontario, Canadian prescribers wrote for an interquartile range of 19%–46% of antibiotic prescriptions with a long-course of therapy (median: 30%), and among antibiotic prescriptions selected for an interquartile range of 18%–37% of fluoroquinolones (median 27%) [72]. We can anticipate there will be a wide range of individual provider patterns of use within an American LTCF and illustrate the need for a behavioral intervention.

Study findings from our future research could be further expanded through provision of feedback to prescribers about their antibiotic patterns of use by means of comparison to other antibiotic prescribers within their facility. Building on our pilot mixed-methods study that discussed patterns of use among LTCFs, a peer comparison approach could be incorporated within an LTCF to expand beyond describing patterns of use by individual prescribers in a facility. Using metrics derived from the pharmaceutical invoice data, antibiotic prescribers could be ranked from highest to lowest by a reduction target of interest chosen by an individual facility such as selection for fluoroquinolones or proportion of courses written as a long-course of therapy (>7 days). Prescribers with the lowest rates of target antibiotic use would be informed via a monthly email that they are a "Top Performer." The remaining prescribers would be informed they are "Not a Top Performer" in an email that includes the number and proportion of antibiotic prescriptions the prescriber wrote for either the target antibiotic class or duration of therapy compared to the proportion written by top performers. Meeker *et al.* evaluated this approach in an 18-month study of 47 primary care practices randomized to one of three behavioral interventions: peer comparison, an automatic prompt suggesting antibiotic prescribing alternatives, or a mandatory record of justification for prescribing an antibiotic. The study found that peer comparison resulted in statistically significant reductions in inappropriate and/or unnecessary antibiotic prescribing in a hospital setting [73]. Peer comparison is distinct from traditional audit-and-feedback interventions on the grounds of direct comparison with top-performing peers as opposed comparison to a facility or regional average, in conjunction with its positive reinforcement of top performers. The strategy of peer comparison is shown to sustain performance of antibiotic stewardship in a hospital setting [74]–[76]. The approach of addressing the highest prescribers in an LTCF may reduce inappropriate and/or unnecessary antibiotic prescribing, thereby reducing the pressure for selection of antibiotic resistant bacteria within an LTCF. Given the administrative nature of the pharmaceutical invoice data used for this future research, we would be unable to evaluate the appropriateness of the antibiotics prescribed or explicitly determine if a prescriber was a designated LTCF medical provider as opposed to a specialist (*e.g.* a surgeon). However, the approach could introduce a dimension of accountability directly to prescribers whose antibiotic decision making tendencies that contribute to inappropriate and/or unnecessary prescribing in an LTCF either by selection for an antibiotic class or long-course of therapy.

Incorporating accountability into antibiotic prescribing patterns of individual prescribers within an LTCF may have the following beneficial effects. First, the feedback provides positive reinforcement of prescribers that employ responsible use as a desired social norm, while other prescribers will be exposed to their colleagues' patterns of use that meet their facility's intended targets for reduction. This exposure may encourage the prescribers identified as poor performers to shift away from contributing to inappropriate and/or unnecessary antibiotic use in their facility. Second, the approach could relieve a prescriber's possible fears about medical malpractice liability, as the feedback presents a safe harbor for prescribers who follow the standard of care recommended by antibiotic stewardship guidelines and their facility's expectations [77]. Therefore, incorporating this dimension of accountability could incentivize appropriate antibiotic prescribing both socially and legally.

4.5 References:

[1] Centers for Disease Control and Prevention, “Antibiotic Resistance Threats in the United States,” 2013. [Online]. Available: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar- threats-2013-508.pdf.

[2] L. E. Nicolle, D. W. Bentley, R. Garibaldi, G. Ellen, P. W. Smith, T. Care, and E. G. Neuhaus, “Antimicrobial Use in Long-Term – Care Facilities,” *Infect. Control Hosp. Epidemiol.*, vol. 21, no. 8, pp. 537–545, 2000.

[3] N. Daneman, S. E. Bronskill, A. Gruneir, A. M. Newman, H. D. Fischer, P. A. Rochon, G. M. Anderson, and C. M. Bell, “Variability in antibiotic use across nursing homes and the risk of antibiotic-related adverse outcomes for individual residents,” *JAMA Intern. Med.*, vol. 175, no. 8, pp. 1331–1339, 2015.

[4] E. Peron, A. Hirsch, L. Jury, R. L. Jump, and C. Donskey, “Another setting for stewardship: High rate of unnecessary antimicrobial use in a veterans affairs long-term care facility,” *J. Am. Geriatr. Soc.*, vol. 61, no. September 2010, pp. 289–290, 2015.

[5] D. Feldstein, P. D. Sloane, and C. Feltner, “Antibiotic Stewardship Programs in Nursing Homes: A Systematic Review,” *J. Am. Med. Dir. Assoc.*, vol. 19, no. 2, pp. 110–116, 2018.

[6] R. Jump, D. Olds, N. Seifi, K. Georgios, L. Jury, E. Peron, A. Hirsch, P. Drawz, B. Watts, R. Bonomo, and C. Donskey, “Effective Antimicrobial Stewardship in a Long-Term Care Facility through an Infectious Disease Consultation Service: Keeping a LID on Antibiotic Use,” *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 12, pp. 1185–1192, 2012.

[7] S. Duane, C. Domegan, A. Callan, S. Galvin, M. Cormican, K. Bennett, A. W. Murphy, and A. Vellinga, "Using qualitative insights to change practice: exploring the culture of antibiotic prescribing and consumption for urinary tract infections.," *BMJ Open*, vol. 6, no. 1, p. e008894, 2016.

[8] A. Fleming, C. Bradley, S. Cullinan, and S. Byrne, "Antibiotic prescribing in long-term care facilities: a qualitative, multidisciplinary investigation.," *BMJ Open*, vol. 4, no. 11, p. e006442, 2014.

[9] S. R. Benoit, W. Nsa, C. L. Richards, D. W. Bratzler, A. M. Shefer, L. M. Steele, and J. A. Jernigan, "Factors associated with antimicrobial use in nursing homes: A multilevel model," *J. Am. Geriatr. Soc.*, vol. 56, no. 11, pp. 2039–2044, Nov. 2008.

[10] L. Nicolle, "Antimicrobial stewardship in long term care facilities: what is effective?," *Antimicrob. Resist. Infect. Control*, vol. 3, no. 1, p. 6, 2014.

[11] A. Fleming and S. Byrne, "Prescriber preference may influence prolonged antibiotic usage more than patient characteristics in long-term care facilities," *Evid. Based. Nurs.*, vol. 17, no. 2, pp. 61–62, 2014.

[12] Centers for Disease Control and Prevention, "Core Elements of Antibiotic Stewardship for Nursing Homes," pp. 1–21, 2015.

[13] Centers for Medicare and Medicaid Services Office of Minority Health, "The CMS Equity Plan for Improving Quality in Medicare," 2015.

[14] S. K. Fridkin and A. Srinivasan, "Implementing a strategy for monitoring inpatient antimicrobial use among hospitals in the United States," *Clin. Infect. Dis.*, vol. 58, no. 3,

pp. 401–406, 2014.

[15] M. B. Jha, A.K., Burke, M.F., DesRoches, C., Joshi, M.S., Kralovec, P.D., Campbell, E.G. and Buntin, A. K. Jha, M. F. Burke, C. DesRoches, M. S. Joshi, P. D. Kralovec, E. G. Campbell, and M. B. Buntin, "Progress toward meaningful use: hospitals' adoption of electronic health records," *Am. J. Manag. Care*, vol. 17, no. 12 Spec No, pp. 117–24, 2011.

[16] L. Gravatt and A. Pakyz, "Challenges in measuring antibiotic consumption," *Curr. Infect. Dis. Rep.*, vol. 15, no. 6, pp. 559–563, 2013.

[17] R. E. Polk, S. F. Hohmann, S. Medvedev, and O. Ibrahim, "Benchmarking risk-adjusted adult antibacterial drug use in 70 US academic medical center hospitals," *Clin. Infect. Dis.*, vol. 53, no. 11, pp. 1100–1110, 2011.

[18] H. C. Standiford, S. Chan, M. Tripoli, E. Weekes, and G. N. Forrest, "Antimicrobial Stewardship at a Large Tertiary Care Academic Medical Center: Cost Analysis Before, During, and After a 7-Year Program," *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 04, pp. 338–345, 2012.

[19] T. D. Bennett, M. C. Spaeder, R. I. Matos, R. S. Watson, K. V Typpo, R. G. Khemani, S. Crow, B. D. Benneyworth, R. R. Thiagarajan, J. M. Dean, and B. P. Markovitz, "Existing data analysis in pediatric critical care research," *Front. Pediatr.*, vol. 2, p. 79, 2014.

[20] C. R. Cooke and J. I. Theodore, "Using existing data to address important clinical questions in critical care," *Crit. Care Med.*, vol. 41, no. 3, pp. 886–896, 2013.

[21] T. D. Wade, “Refining gold from existing data,” *Curr. Opin. Allergy Clin. Immunol.*, vol. 14, no. 3, pp. 181–5, 2014.

[22] S. Monteith, T. Glenn, J. Geddes, and M. Bauer, “Big data are coming to psychiatry: a general introduction.,” *Int. J. bipolar Disord.*, vol. 3, no. 1, p. 21, 2015.

[23] M. J. Katz, A. P. Gurses, P. D. Tamma, S. E. Cosgrove, M. A. Miller, and R. L. P. Jump, “Implementing Antimicrobial Stewardship in Long-term Care Settings: An Integrative Review Using a Human Factors Approach,” *Clin. Infect. Dis.*, vol. 65, no. 11, pp. 1943–1951, 2017.

[24] T. H. Dellit, R. C. Owens, J. E. McGowan, D. N. Gerding, R. A. Weinstein, J. P. Burke, W. C. Huskins, D. L. Paterson, N. O. Fishman, C. F. Carpenter, P. J. Brennan, M. Billeter, and T. M. Hooton, “Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship,” *Clin. Infect. Dis.*, vol. 44, no. 2, pp. 159–177, 2007.

[25] A. N. Malani, B. M. Brennan, C. D. Collins, J. Finks, J. M. Pogue, and K. S. Kaye, “Antimicrobial Stewardship Practices in Michigan Long-Term Care Facilities,” *Infect. Control Hosp. Epidemiol.*, vol. 37, no. 2, pp. 236–237, 2016.

[26] T. Van Schooneveld, H. Miller, H. Sayles, K. Watkins, and P. Smith, “Survey of antimicrobial stewardship practices in Nebraska long-term care facilities,” *Infect. Control Hosp. Epidemiol.*, vol. 32, no. 7, pp. 732–734, Jul. 2011.

[27] Z. M. Tun, M. Moorthy, M. Linster, Y. C. F. Su, R. J. Coker, E. E. Ooi, J. G.-H.

Low, G. J. D. Smith, and C. C. Tam, “Patterns of medication use and factors associated with antibiotic use among adult fever patients at Singapore primary care clinics.,” *Antimicrob. Resist. Infect. Control*, vol. 5, p. 47, 2016.

[28] G. Dumyati, N. D. Stone, D. A. Nace, C. J. Crnich, and R. L. P. Jump, “Challenges and Strategies for Prevention of Multidrug-Resistant Organism Transmission in Nursing Homes,” *Curr. Infect. Dis. Rep.*, vol. 19, no. 18, pp. 1–9, 2017.

[29] G. Cadieux and R. Tamblyn, “Accuracy of physician billing claims for identifying acute respiratory infections in primary care,” *Health Serv. Res.*, vol. 43, no. 6, pp. 2223–2238, 2008.

[30] V. Laliberté, L. Joseph, and I. Gold, “A bayesian approach to latent class modeling for estimating the prevalence of schizophrenia using administrative databases,” *Front. Psychiatry*, vol. 6, p. 99, 2015.

[31] R. Tamblyn, G. Lavoie, L. Petrella, and J. Monette, “The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec,” *J. Clin. Epidemiol.*, vol. 48, no. 8, pp. 999–1009, 1995.

[32] K. Schwartz, D. N., Evans, R. S., Camins, B. C., Khan, Y. M., Lloyd, J. F., Shehab, N., & Stevenson, “Deriving measures of intensive care unit antimicrobial use from computerized pharmacy data: methods, validation, and overcoming barriers,” *Infect. Control Hosp. Epidemiol.*, vol. 32, no. 5, pp. 472–480, 2011.

[33] J. M. Overhage, J. Suico, and C. J. McDonald, “Electronic laboratory reporting:

barriers, solutions and findings,” *J. public Heal. Manag. Pract.*, vol. 7, no. 6, pp. 60–66, 2001.

[34] R. C. Lyon, J. S. Taylor, D. A. Porter, H. R. Prasanna, and A. S. Hussain, “Stability profiles of drug products extended beyond labeled expiration dates,” *J. Pharm. Sci.*, vol. 95, no. 7, pp. 1549–1560, 2006.

[35] L. P. Cohen, “Many Medicines Are Potent Years Past Expiration Dates,” *The Wall Street Journal*, 28-Mar-2000.

[36] R. N. Davidson and R. a Wall, “Prevention and management of infections in patients without a spleen.,” *Clin. Microbiol. Infect.*, vol. 7, no. 12, pp. 657–60, 2001.

[37] J. Le, M. Castanheira, D. S. Burgess, B. McKee, R. Iqbal, and R. N. Jones, “Clonal dissemination of Klebsiella pneumoniae carbapenemase KPC-3 in Long Beach, California,” *J. Clin. Microbiol.*, vol. 48, no. 2, pp. 623–625, 2010.

[38] M. Jones, B. Huttner, K. Madaras-Kelly, K. Nechodom, C. Nielson, M. B. Goetz, M. M. Neuhauser, M. H. Samore, and M. A. Rubin, “Parenteral to Oral Conversion of Fluoroquinolones: Low-Hanging Fruit for Antimicrobial Stewardship Programs?,” *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 04, pp. 362–367, 2012.

[39] D. Mertz, M. Koller, P. Haller, M. L. Lampert, H. Plagge, B. Hug, G. Koch, M. Battegay, U. Flückiger, and S. Bassetti, “Outcomes of early switching from intravenous to oral antibiotics on medical wards,” *J. Antimicrob. Chemother.*, vol. 64, no. 1, pp. 188–199, 2009.

[40] M.-E. T. Horntvedt, M. Romøren, and B.-A. Solvoll, “Ethical problems related to

intravenous fluids in nursing homes," *Nurs. Ethics*, vol. 21, no. 8, pp. 890–901, 2014.

[41] N. P. Vogtländer, M. E. van Kasteren, S. Natsch, B. J. Kullberg, Y. A. Hekster, and J. . van der Meer, "Improving the process of antibiotic therapy in daily practice: interventions to optimize timing, dosage adjustment to renal function, and switch therapy," *Arch. Intern. Med.*, vol. 164, no. 11, pp. 1206–1212, 2004.

[42] D. J. Funk and A. Kumar, "Antimicrobial Therapy for Life-threatening Infections: Speed is Life," *Crit. Care Clin.*, vol. 27, no. 1, pp. 53–76, 2011.

[43] J. A. Schouten, M. E. J. L. Hulscher, S. Natsch, B. J. Kullberg, J. W. M. Van Der Meer, and R. P. T. M. Grol, "Barriers to optimal antibiotic use for community-acquired pneumonia at hospitals: A qualitative study," *Qual. Saf. Heal. Care*, vol. 16, no. 2, pp. 143–149, 2007.

[44] E. Reeve, J. To, I. Hendrix, S. Shakib, M. Roberts, and M. Wiese, "Patient barriers to and enablers of deprescribing: A systematic review," *Drugs and Aging*, vol. 30, no. 10, pp. 793–807, 2013.

[45] E. O'Fallon, R. Kandel, R. Schreiber, E. M. C. D'Agata, R. Kandell, R. Schreiber, and E. M. C. D'Agata, "Acquisition of multidrug-resistant gram-negative bacteria: incidence and risk factors within a long-term care population," *Infect Control Hosp Epidemiol*, vol. 31, no. 11, pp. 1148–53, 2010.

[46] E. O'Fallon, E., Pop-Vicas, A. and D'Agata, "The emerging threat of multidrug-resistant gram-negative organisms in long-term care facilities," *Journals Gerontol. Ser. A Biomed. Sci. Med. Sci.*, vol. 64, no. 1, pp. 138–141, 2009.

[47] D. M. Rooney, P.J., O'leary, M.C., Loughrey, A.C., McCalmont, M., Smyth, B., Donaghy, P., Badri, M., Woodford, N., Karisik, E. and Livermore, "Nursing homes as a reservoir of extended-spectrum β-lactamase (ESBL)-producing ciprofloxacin-resistant Escherichia coli," *J. Antimicrob. Chemother.*, vol. 64, no. 3, pp. 635–641, 2009.

[48] M. Exner, S. Bhattacharya, B. Christiansen, J. Gebel, P. Goroncy-Bermes, P. Hartemann, P. Heeg, C. Ilschner, A. Kramer, E. Larson, W. Merkens, M. Mielke, P. Oltmanns, B. Ross, M. Rotter, R. M. Schmithausen, H.-G. Sonntag, and M. Trautmann, "Antibiotic resistance: What is so special about multidrug-resistant Gram-negative bacteria?," *GMS Hyg. Infect. Control*, vol. 12, p. Doc05, 2017.

[49] H. Von Baum, C. Schmidt, D. Svoboda, O. Bock-Hensley, and C. Wendt, "Risk factors for methicillin-resistant Staphylococcus aureus carriage in residents of German nursing homes," *Infect. Control Hosp. Epidemiol.*, vol. 23, no. 9, pp. 511–515, 2002.

[50] S. F. Bradley, "Methicillin-resistant Staphylococcus aureus: Long-term care concerns," *Am. J. Med.*, vol. 106, no. 5, pp. 2–10, 1999.

[51] E. Stenehjem, A. L. Hersh, X. Sheng, P. Jones, W. R. Buckel, J. F. Lloyd, S. Howe, R. S. Evans, T. Greene, and A. T. Pavia, "Antibiotic Use in Small Community Hospitals," *Clin. Infect. Dis.*, vol. 63, no. 10, pp. 1273–1280, 2016.

[52] H. J. Morrill, A. R. Caffrey, R. L. P. Jump, D. Dosa, and K. L. LaPlante, "Antimicrobial Stewardship in Long-Term Care Facilities: A Call to Action," *J. Am. Med. Dir. Assoc.*, vol. 17, no. 2, p. 183.e1-183.e16, 2016.

[53] B. M. Schnelle, J.F., Simmons, S.F., Harrington, M.C., Garcia, E., Bates-Jensen,

"Relationship of Nursing Home Staffing and Quality of Care," *Health Serv. Res.*, vol. 39, no. 2, pp. 225–255, 2004.

[54] C. J. Crnich, R. L. Jump, B. Trautner, P. D. Sloane, and L. Mody, "Optimizing Antibiotic Stewardship in Nursing Homes: A Narrative Review and Recommendations for Improvement," *Drugs and Aging*, vol. 32, no. 9, pp. 699–716, 2015.

[55] V. Mor, O. Intrator, Z. Feng, and D. C. Grabowski, "The revolving door of rehospitalization from skilled nursing facilities," *Health Aff.*, vol. 29, no. 1, pp. 57–64, 2010.

[56] R. Shield, M. Rosenthal, T. Wetle, D. Tyler, M. Clark, and O. Intrator, "Medical Staff Involvement in Nursing Homes: Development of a Conceptual Model and Research Agenda," *J. Appl. Gerontol.*, vol. 33, no. 1, pp. 75–96, 2014.

[57] K. Scales, S. Zimmerman, D. Reed, A. S. Beeber, C. E. Kistler, J. S. Preisser, B. J. Weiner, K. Ward, A. Fann, and P. D. Sloane, "Nurse and Medical Provider Perspectives on Antibiotic Stewardship in Nursing Homes," *J. Am. Geriatr. Soc.*, vol. 65, no. 1, pp. 165–171, 2017.

[58] E. D'Agata and S. L. Mitchell, "Patterns of Antimicrobial Use Among Nursing Home Residents With Advanced Dementia," *Arch. Intern. Med.*, vol. 168, no. 4, pp. 357–362, 2008.

[59] C. D. Caron, J. Griffith, and M. Arcand, "Decision making at the end of life in dementia: How family caregivers perceive their interactions with health care providers in long-term-care settings," *J. Appl. Gerontol.*, vol. 24, no. 3, pp. 231–247, 2005.

[60] P. D. Sloane, K. Huslage, C. E. Kistler, and S. Zimmerman, “Optimizing Antibiotic Use in Nursing Homes Through Antibiotic Stewardship,” *N. C. Med. J.*, vol. 77, no. 5, pp. 324–329, 2016.

[61] B. Wilson, S. Shick, R. Carter, B. Heath, P. Higgins, B. Sychla, D. Olds, and R. Jump, “An Online Course Improves Nurses’ Awareness of their Role as Antimicrobial Stewards in Nursing Home,” *Am. J. Infect. Control*, 2017.

[62] R. N. Olans, R. D. Olans, and A. DeMaria Jr, “The critical role of the staff nurse in antimicrobial stewardship—unrecognized, but already there,” *Clin. Infect. Dis.*, vol. 62, no. 1, pp. 84–89, 2015.

[63] N. V. Ivankova, J. W. Creswell, and S. L. Stick, “Using mixed-methods sequential explanatory design: From theory to practice,” *Field methods*, vol. 18, no. 1, pp. 3–20, 2006.

[64] W. Mason and S. Suri, “Conducting behavioral research on Amazon’s Mechanical Turk.,” *Behav. Res. Methods*, vol. 44, no. 1, pp. 1–23, 2012.

[65] M. Marge, S. Banerjee, and A. I. Rudnicky, “Using the Amazon Mechanical Turk for transcription of spoken language,” in *Proceedings of the 2010 IEEE Conference on Acoustics, Speech and Signal Processing*, J. Hansen, Ed. IEEE, 2010, pp. 5270–5273.

[66] N. Britten, “Qualitative research: qualitative interviews in medical research,” *Bmj*, vol. 311, no. 6999, pp. 251–253, 1995.

[67] A. L. Pakyz, L. R. Moczygemba, H. Wang, M. P. Stevens, and M. B. Edmond, “An evaluation of the association between an antimicrobial stewardship score and antimicrobial usage,” *J. Antimicrob. Chemother.*, vol. 70, no. 5, pp. 1588–1591, 2015.

[68] R. L. Jump, C. J. Crnich, L. Mody, S. F. Bradley, L. E. Nicolle, and T. T. Yoshikawa, “Infectious Diseases in Older Adults of Long-Term Care Facilities: Update on Approach to Diagnosis and Management,” *J. Am. Geriatr. Soc.*, vol. 66, no. 4, pp. 789–803, 2018.

[69] P. Rotjanapan, D. Dosa, and K. S. Thomas, “Potentially Inappropriate Treatment of Urinary Tract Infections in Two Rhode Island Nursing Homes,” *Arch. Intern. Med.*, vol. 171, no. 5, pp. 438–443, 2011.

[70] J. M. Morse, “Approaches to qualitative-quantitative methodological triangulation,” *Nurs. Res.*, vol. 40, no. 2, pp. 120–123, 1991.

[71] N. Daneman, A. Gruneir, S. E. Bronskill, A. Newman, H. D. Fischer, P. A. Rochon, G. M. Anderson, and C. M. Bell, “Prolonged Antibiotic Treatment in Long-term Care: Role of the Prescriber,” *JAMA Intern. Med.*, vol. 173, no. 8, p. 673, 2013.

[72] N. Daneman, M. A. Campitelli, V. Giannakeas, A. M. Morris, C. M. Bell, C. J. Maxwell, L. Jeffs, P. C. Austin, and S. E. Bronskill, “Influences on the start, selection and duration of treatment with antibiotics in long-term care facilities,” *CMAJ*, vol. 189, no. 25, pp. E851–E860, 2017.

[73] D. Meeker, J. A. Linder, C. R. Fox, M. W. Friedberg, S. D. Persell, N. J. Goldstein, T. K. Knight, J. W. Hay, and J. N. Doctor, “Effect of Behavioral Interventions on Inappropriate Antibiotic Prescribing Among Primary Care Practices: A Randomized Clinical Trial.,” *J. Am. Med. Assoc.*, vol. 315, no. 6, pp. 562–70, Feb. 2016.

[74] C. I. Kiefe, J. J. Allison, O. D. Williams, S. D. Person, M. T. Weaver, and N. W.

Weissman, “Improving quality improvement using achievable benchmarks for physician feedback: a randomized controlled trial,” *JAMA*, vol. 285, no. 22, pp. 2871–2879, 2001.

[75] P. W. Schultz, J. M. Nolan, R. B. Cialdini, N. J. Goldstein, and V. Griskevicius, “The constructive, destructive, and reconstructive power of social norms,” *Psychol. Sci.*, vol. 18, no. 5, pp. 429–434, 2007.

[76] M. Hallsworth, T. Chadborn, A. Sallis, M. Sanders, D. Berry, F. Greaves, L. Clements, and S. C. Davies, “Provision of social norm feedback to high prescribers of antibiotics in general practice: A pragmatic national randomised controlled trial,” *Lancet*, vol. 387, no. 10029, pp. 1743–1752, 2016.

[77] C. Llor and L. Bjerrum, “Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem.,” *Ther. Adv. drug Saf.*, vol. 5, no. 6, pp. 229–41, 2014.