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Haley J. Morrill
University of Rhode Island

Aisling R. Caffrey
University of Rhode Island, aisling_caffrey@uri.edu

Robin L. P. Jump

David Dosa

Kerry L. LaPlante
University of Rhode Island, kerrylaplante@uri.edu

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Antimicrobial Stewardship in Long-Term Care Facilities: A Call to Action

Haley J. Morrill, PharmD[a,b,c], Aisling R. Caffrey, PhD, MS[a,b,c], Robin L. P. Jump, MD, PhD[d,e], David Dosa, MD, MPH[a,f], and Kerry L. LaPlante, PharmD[a,b,c,f]

a. Veterans Affairs Medical Center, Center of Innovation for Long-term Services and Supports, Providence, RI, United States
b. Veterans Affairs Medical Center, Infectious Diseases Research Program, Providence, RI, United States
c. University of Rhode Island, Department of Pharmacy Practice, College of Pharmacy, Kingston, RI, United States
d. Louis Stokes Cleveland VA Medical Center, Geriatric Research Education and Clinical Center (GRECC) and Infectious Diseases Section, Cleveland, OH, United States
e. Case Western Reserve University, Division of Infectious Disease & HIV Medicine, Department of Medicine, Cleveland, OH, United States
f. Warren Alpert Medical School of Brown University, Division of Infectious Diseases, Providence, RI, United States

Corresponding author. Haley J. Morrill, Pharm.D., Research Health Science Specialist, Providence Veterans Affairs Medical Center, 830 Chalkstone Ave, Providence, RI 02908, 401-273-7100 ext 4150 (office); haley.morrill@va.gov

Alternate Corresponding author. Kerry L. LaPlante, Pharm.D., FCCP Professor, University of Rhode Island, College of Pharmacy, 7 Greenhouse Rd, Suite 295A, Kingston, RI 02881, 401-874-5560 (office); KerryLaPlante@uri.edu

Running Title. Antimicrobial Stewardship in Long-Term Care Facilities

Abstract

Antimicrobial resistance is a global public health crisis and a national security threat to the United States, as stated in an Executive Order signed by the President in September 2014. This crisis is a result of indiscriminant antimicrobial use, which promotes selection for resistant organisms, increases the risk of adverse drug events and renders patients vulnerable to drug-resistant infections. Antimicrobial stewardship is a key measure to combat antimicrobial resistance and specifically seeks to do this by improving antimicrobial use. Antimicrobial stewardship compliments infection control practices and it is important to note that these two disciplines are distinct and cannot be discussed interchangeably. Antimicrobial stewardship promotes the appropriate diagnosis, drug, dose, and duration of treatment. The appropriate diagnosis falls into the hands of the prescriber and clinical staff. Optimal antimicrobial drug selection, dosing strategy, and duration of treatment, however, often require expertise in antimicrobial therapy, such as an infectious disease trained physician or pharmacist. Therefore, successful antimicrobial stewardship programs must be comprehensive and interdisciplinary. Most antimicrobial stewardship programs focus on hospitals yet, in long-term care, up to 75% of antimicrobial use is inappropriate or unnecessary. Therefore, one of the most pressing areas in need for antimicrobial stewardship is in long-term care facilities. Unfortunately, there is little evidence that describes effective antimicrobial stewardship interventions in this setting. This review discusses the need for and barriers to antimicrobial stewardship in long-term care facilities. Additionally, this review describes prior interventions that have been implemented and tested to improve antimicrobial use in long-term care facilities.

Keywords. antimicrobial stewardship program; antimicrobial resistance; long-term care; nursing home; antibiotic use

Introduction

Antimicrobial resistance is one of the greatest public health threats in the United States, prompting the President of the United States, the enters for Disease Control and Prevention (CDC) and the World Health Organization to spearhead initiatives seeking effective solutions.[1-3] The prevalence of antimicrobial-resistant organisms is increasing throughout the United States (US), as is the use of "last line" and toxic antibiotics to treat infections caused by resistant bacteria.[4] The driving force that selects for antimicrobial-resistant bacteria and promotes *Clostridium difficile (C. difficile)* infection is antimicrobial use.[1] Approximately 50% of antimicrobial use in hospitals and up to 75% of antibiotic use in long-term care facilities may be inappropriate or unnecessary.[5,6] As such, it is critically important to the safety of patients that antimicrobial use is improved throughout the entire healthcare system. Antimicrobial stewardship is typically defined as any activity to improve the drug, dose, duration or route of an antimicrobial.[7] However, stewardship should also focus on an appropriate diagnosis. The primary goal of antibiotic stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use.

Implementation of new antimicrobial stewardship programs is challenging, requiring increased resources and time. Despite this, implementation of antimicrobial stewardship programs has been recommended for all healthcare settings in the US, including long-term care facilities.[7,8] According to the CDC, over the next five years, approximately 619,000 infections due to resistant pathogens and *C. difficile* could be prevented with the immediate and national implementation of antibiotic stewardship and infection control interventions,.[9] In acute care facilities, comprehensive antimicrobial stewardship programs have been shown to improve the quality of patient care and safety. Through reduction of inappropriate antibiotic use and optimization of antimicrobial therapy, antimicrobial stewardship programs can reduce rates of *C. difficile* infection and slow the emergence of antimicrobial resistance.[10-12] However, applying the evidence-based principles of antimicrobial stewardship developed in acute care facilities to long-term care facilities, presents significant challenges.[7]

In an effort to support improved antimicrobial use, the Obama administration recently released an Executive Order (September 2014) and a National Action Plan (March 2015) for combating antibiotic-resistant bacteria.[3,13] This plan specifically calls for strengthening antibiotic stewardship in long-term care settings “by

expanding existing programs, developing new ones, and monitoring progress and efficacy".[3] Additionally, for the first time since 1991, Centers for Medicare and Medicaid service (CMS) has now opened for comments their new proposed rules for long-term care facilities. Proposed recommendations include: 1) a required infection prevention and control officer, and 2) an antibiotic stewardship program that includes antibiotic use protocols and a system to monitor antibiotic use. Additionally, the CDC recently released seven Core Elements of antimicrobial stewardship in long-term care facilities, including 1) facility leadership commitment, 2) accountability, 3) drug expertise, 4) actions to improve use, 5) education, 6) tracking and 7) reporting.[14] While progressive, these recommendations face many challenges, particularly due to the paucity of evidence on effective antimicrobial stewardship practices in long-term care. Here, to help advance these efforts, we review the literature describing antimicrobial stewardship efforts in long-term care. Specifically, we discuss the need for and barriers to antimicrobial stewardship in long-term care facilities as well as prior strategies that have been implemented to improve antimicrobial use in this unique setting.

Methods

We conducted a structured review of existing literature related to antimicrobial stewardship in long-term care facilities. This review was conducted to identify: 1) the need for antimicrobial stewardship in long-term care facilities, 2) barriers to antimicrobial stewardship in long-term care facilities, and 3) prior studies related to implementation of antimicrobial stewardship interventions in long-term care facilities. We used Medline to perform the structured search using the following relevant key words: antimicrobial stewardship, antimicrobial use, long-term care facility and nursing home. References in English dated between 1966 and June 2015 were considered. We also conducted a follow up Internet Search and search of reference lists from relevant studies. Based on a review of titles and abstracts, documents were selected for full text review if they fell in to one of the three categories above. All documents selected for full-text review were included in our review article. In order to describe and synthesize intervention literature, the following were collected from each article: year of publication, infection type, study design, study setting, intervention, unit of analysis, and major findings.

Results

We selected 67 articles for inclusion based on full text review. Of these, 30 (44.8%) articles were categorized as needs for antimicrobial stewardship, 26 (38.8%) as barriers to antimicrobial stewardship, and 15 (22.4%) as prior studies related to implementation of antimicrobial stewardship interventions in long-term care facilities. Four (6.0%) articles addressed more than one category. Needs for antimicrobial stewardship in long-term care can be found in Table 1. These articles included 23 (76.7%) observational studies, 5 (16.7%) review articles, and 2 (6.7%) professional society guidelines. Barriers to antimicrobial stewardship in long-term care can be found in Table 2. These articles included 9 (34.6%) review articles, 5 (19.2%) professional society guidelines/recommendations, and 4 (15.4%) observational studies.

Prior studies related to implementation of antimicrobial stewardship interventions in long-term care facilities can be found in Tables 3 and 4. These articles include 8 (53.3%) quasi-experimental studies, 5 (33.3%) randomized controlled trials, 1 (6.7%) pre- vs. post-intervention survey, and 1 (6.7%) systematic review. Of the articles that tested an intervention (n=14), 78.6% were multifaceted educational interventions. Studies that assessed the impact of interventions on general antibiotic use were most common (n=7, 50.0%), followed by interventions that target a specific syndrome (n = 7, 50.0%).

Discussion

Need for Antimicrobial Stewardship in Long-Term Care Facilities.

In 2013, approximately 1.4 million adults received nursing home care at one of the over 15,700 facilities in the United States.[15] As a group, the residents of long-term care facilities represent some of the oldest and frailest members in our communities.[16] Based on results from the 2004 National Nursing Home Survey, 45% of nursing homes residents were aged 85 years and older, with an average length of stay 2.3 years.[17] Nearly 80% were dependent for assistance with at least 4 of the 5 activities of daily living: toileting, bathing, transfer, dressing and eating. Increasing age, frailty, immune senescence, and comorbid conditions render long-term care facility residents vulnerable to infection. Even for experienced clinicians, determining whether a long-term care resident has an infection presents significant challenges. This may contribute to the high prevalence of antibiotic use in this population.[18,19]

Inappropriate and Unnecessary Antibiotic Use in Long-Term Care Facilities

Antimicrobials account for almost half of all prescriptions in long-term care facilities.[20,21] It is estimated that 50-75% of residents receive at least one course of an antibiotic each year.[22-24] Unfortunately, many of these prescriptions represent overuse or inappropriate use.[25] A study of 2 community-based nursing homes in Rhode Island found several types of inappropriate antibiotic prescribing patterns related to urinalyses ordered on 172 case residents. Antibiotic treatment was initiated in 70 case residents (41%) that did not meet the McGeer criteria. Additionally, 72% of case residents received an inappropriate drug based on Infectious Diseases Society of American criteria, 46% were dosed inappropriately based on creatinine clearance, and 67% received treatment for longer than recommended.[26] A study which reviewed antimicrobial orders from 42 skilled nursing facilities found that 38% of orders were inappropriate.[27] Similarly, in a retrospective chart review of systemic antimicrobial regimens administered to residents of a 160-bed Veterans Affairs (VA) skilled nursing facility, 43% of the 1,351 days of antimicrobial therapy were deemed unnecessary and 49% of residents received at least one day of unnecessary antimicrobial therapy.[6] The most common reasons for entirely and partially unnecessary regimens were asymptomatic bacteriuria and longer than recommended treatment durations, respectively.

Inappropriate antibiotic prescriptions not only originate in the long-term care facility, but also in other settings where residents receive care. For example, a resident may be sent to the emergency department for a potentially non-infectious cause such as delirium or agitation, and be sent back to the nursing home with an inappropriate antimicrobial prescription. Additionally, a resident may be discharged from the hospital with an antimicrobial prescription that was not indicated, was the wrong drug or dose, or was continued for too long a duration.[26] A resident may also be prescribed an inappropriate antibiotic at a specialist visit, such as urology, rheumatology, dermatology, or even through an infectious diseases consult, all of which may contribute to the high prevalence of inappropriate use among long-term care facilities.

Increased Risk for Colonization with Resistant Bacteria

On average, at least 30-50% of long-term care residents are colonized with one or more resistant organisms and colonization can lead to subsequent infection, particularly in older, frail residents.[28-34] The primary mode of

introduction of resistant organisms into this setting is the transfer of infected or colonized residents from acute care hospitals to long-term care facilities.[35] Acute care facilities and long-term care facilities are connected through shared residents. A recent study using the Long-Term Care Minimum Data Set revealed a high volume of bidirectional flow between long-term care facilities and acute care hospitals.[36] During the 15-month study period, there were over two million discharges from long-term care facilities to acute care hospitals and over four million admissions to long-term care facilities from acute care hospitals.[36] As an example, long-term care residents in a regional health system in Iowa colonized with vancomycin-resistant enterococci (VRE) were significantly more likely than non-colonized residents to have been hospitalized at an acute care facility (19/30 vs. 12/66; odds ratio [OR], 8.0; 95% confidence interval [CI], 2.7 - 23.8).[37] However, long-term care facilities residents may be seen as reservoirs of resistant bacteria, and can also transport resistant organisms to the acute care setting or into the community.[35,38]

Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization among long-term care residents can be as high as 60%, as identified in one study among 412 residents at three separate long-term care facilities.[31] A point prevalence survey of long and short-term acute care facilities in Chicago found the prevalence of those colonized with carbapenem-resistant *Enterobacteriaceae* (CRE) was much higher among residents in long-term care facilities compared to patients in acute care facilities (30.4% vs. 3.3%).[39] Factors that increase the risk of colonization with multi-drug resistant organisms relate both to residents health and their environment. Exposure to multiple courses of antibiotics select for resistant bacteria. Other factors that increase the risk of colonization by resistant bacteria for long-term care facility residents include poor nutritional status, skin and soft-tissue breakdown, and the presence of multiple devices, including gastrostomy tubes and/or indwelling catheters.[35] In an effort to support a home-like environment, long-term care facilities encourage social interaction in shared spaces. Unfortunately, these practices may increase opportunities for residents to disseminate and acquire resistant organisms through shared dining rooms, rehabilitation equipment and recreation areas. Among long-term care residents, independent risk factors found to be associated with colonization for multi-drug resistant organisms include, prior colonization or infection by multi-drug resistant organisms, hospitalization in the past three months, recurrent urinary tract infections, peripheral arterial

disease, current wound management, medical devices *in situ*, pressure ulcers, advanced dementia, and prolonged antibiotic use.[32,33]

Increased Risk of C. difficile Infections

C. difficile infections are another major concern in the long-term care environment.[40] *C. difficile* infections are endemic in many facilities, despite efforts to manage the burden of *C. difficile* infections in this setting.[41] Up to 30% of residents treated with antibiotics in long-term care facilities acquire *C. difficile*.[42] Residents in two Rhode Island nursing homes who received inappropriate antimicrobials for asymptomatic bacteriuria were 8.5 times more likely to develop *C. difficile* infections compared to the rest of the nursing home population (95% CI 1.7 - 42).[26] Though exposure to systemic antibiotics and to *C. difficile* spores often occurs in acute care hospitals, symptom onset may not develop until after the resident is transferred to the nursing home.[43] Importantly, older residents who develop *C. difficile* infections are more likely to develop severe complications.[44,45]

Older adults, including long-term care residents, are also at increased risk for recurrent disease.[46] In 2006, the Ohio Department of Public Health mandated reporting of healthcare-onset *C. difficile* infection, using standardized case definitions.[46] While the incidence rate of first time *C. difficile* infection in 2006 was lower in long-term care facilities than hospitals (up to 2.9 vs. 7.9 cases per 10,000 patient days), the absolute number of *C. difficile* infections was higher in long-term care facilities (11,200 vs. 7,000 cases). For recurrent cases, the mean number of cases per month was higher in long-term care facilities (358 vs. 108).[46] The incidence of recurrent cases for long-term care facilities and hospitals was as high as 2.4 cases and 2.0 cases per 10,000 patient days, respectively, for the reporting period.

Barriers to Antimicrobial Stewardship in Long-Term Care Facilities.

The prevalence of antimicrobial stewardship (various definitions used) among long-term care facilities varied greatly in three large statewide/regional surveys from approximately 25% to 60%.[47-49] In our literature review, we identified several barriers to formalizing antimicrobial stewardship programs in long-term care (Table 2). These barriers are notable and can impede the implementation and success of these programs. One of the

main challenges includes a paucity of well-validated strategies specific to long-term care facilities, as evidenced by limited finding of studies to improve antimicrobial use in long-term care facilities (Tables 3 and 4).

In general, in long-term care facilities, a clinical event suggestive of infection, such as a fever, prompts an evaluation of the affected resident followed by an antimicrobial prescription., Unfortunately, few people that work at nursing homes possess specialized knowledge or access to educational resources on antimicrobial use and infection management.[50-54] Nurses usually conduct the initial evaluations of residents.[50] In many facilities, nurses are the only licensed healthcare professionals available on-site 24 hours a day.[55] Less than 20% of nursing homes employ full-time staff physicians.[56] Providers are most often off-site, splitting their time between other long-term care facilities and office-based practice. A survey of medical directors found that they provide primary care at an average of four facilities, where they spend eight to twelve hours a week providing care to residents, while also serving as a medical director to two facilities.[56] Therefore, providers must rely on nursing staff to assess changes in a resident's status and then communicate their findings via phone or fax.[18] The timing and quality of these communications, as well as professional practice patterns, often favor antimicrobial prescriptions as the "safest", and often most expedient, course of action. Physicians at one hospital reported that they often prescribe treatment for urinary tract infections without seeing the residents and rely on nurses to provide information regarding the signs and symptoms of urinary tract infection.[57] Another study found that only 44% of residents who received antibiotics had an associated claim for a bedside visit by a physician within one day of their prescription.[58]

Resource Limitations

Additional barriers include lack of funding and facility resources,.[7,19,48] For example, tools to measure antibiotic utilization or to develop antibiograms in long-term care have thus far been limited. Another barrier is that many long-term care facilities do not have on-site laboratories, which may delay reporting of organism identification and susceptibility results, and any resultant stewardship interventions.[59] Additionally, few facilities have on-site laboratories or radiologic equipment, thus hindering ready access to many diagnostic tests, such as complete blood counts or chest films. The delays inherent to arranging for these tests may significantly delay the clinician's ability to make a prompt and accurate diagnosis.

Need for Diagnostic Criteria and Treatment Pathways: Focus on Urinary Tract Infections

The proper diagnosis and treatment of infection in residents, is itself a barrier to antimicrobial stewardship. Diagnosing infections in older residents can be exceedingly challenging due to many factors, such as comorbid disease states, blunted immune response, vague symptoms, cognitive impairment, and high rates of colonization with drug-resistant bacteria.[50] Suspected urinary tract infections in this population are particularly challenging.

In long-term care settings, the most common reason residents receive antimicrobials is concern for a urinary tract infection (UTI).[60-63] Diagnostic criteria for UTIs includes acute dysuria, fever, leukocytosis, and symptoms that localize to the urinary tract along with bacterial growth from an appropriately collected urine sample.[64] Distinct from UTI is *asymptomatic bacteriuria*, in which older adults have positive urinalyses and urine cultures without any systemic signs or symptoms of illness (also referred to as "dirty urine").[65] The prevalence of asymptomatic bacteriuria is high in this population, affecting 15% of community-dwelling older adults and 50% of long-term care facility residents.[65] Some healthcare providers respond to any positive urine culture from an older adult by prescribing antimicrobials, regardless of whether symptoms of a UTI are present, even though treatment has not been shown to decrease the incidence of symptomatic urinary tract infections, nor has it been associated with a decrease in morbidity or mortality.[65] This is concerning because there is a strong association between the treatment of asymptomatic bacteriuria and the subsequent emergence of resistant organisms.[66,67]

Treatment of asymptomatic bacteriuria is especially problematic in residents with indwelling urinary catheters. In a cross-sectional study of antibiotic prescription data for residents from four nursing homes in Texas, the strongest predictor of antibiotic treatment for asymptomatic bacteriuria was the presence of an indwelling urinary catheter.[68] For residents with urinary catheters, more than 80% of the antibiotics prescribed were for asymptomatic bacteriuria. In residents without a catheter, approximately 50% of prescriptions were for residents with no documented UTI symptoms. Alarmingly, multivariate analyses demonstrated that resident characteristics did not affect whether an antibiotic was prescribed for asymptomatic bacteriuria. Moreover, the

only significant factor identified was the nursing home itself. This evidence suggests that the practices of providers may drive treatment for suspected urinary tract infections, rather than the clinical characteristics and symptoms of the resident. Thus, efforts to improve prescriber practices in regards to the treatment of suspected urinary tract infections may be an important focus of antimicrobial stewardship interventions in long-term care facilities.

Lack of trained infectious diseases physicians and pharmacists

Formal training in infectious diseases and/or antibiotic stewardship is recommended for antimicrobial stewardship program leaders.[7,69] However, few formal residency and fellowship programs provide specialized training in antimicrobial stewardship for physicians and pharmacists.[53,54] A recent survey of long-term care facilities in Rhode Island demonstrated that approximately 80% of facilities did not have any full-time equivalent infectious diseases physicians or pharmacist facility-wide.[49]

Resident and Family Expectations

Efforts to promote the judicious use of antibiotics in long-term care may also be hampered by expectations from residents and family members. In a recent prospective cohort study, in 35 Boston-area nursing homes on healthcare proxy involvement in decisions on residents with advanced dementia, involvement was associated with both increased antibiotic use (adjusted OR 3.43, 95% CI 1.94 - 6.05) and hospital transfer (adjusted OR 3.00, 95% CI 1.19 - 7.53).[73] This trend is likely influenced by a general fear of litigation on the part of the provider. Studies suggest that long-term care physicians often operate in a state of high legal anxiety that may prompt more aggressive care and unnecessary transfers out of the nursing home.[74] When notified about a complex medical resident with nonspecific symptoms, nursing home providers often err on the side of caution.[75]

What works to Improve Appropriate Antimicrobial Use in Long-term Care Facilities?

Few randomized controlled trials have evaluated interventions to reduce inappropriate antimicrobial use in long-term care facilities (Table 3). A recent systematic review identified only four randomized controlled trials designed to reduce inappropriate antimicrobial use in this setting.[76] All of these studies provided educational

material to physicians and nurses[77-79] or to physicians only,[80] with two studies also incorporating prescribing feedback.[79,80] As Table 3 shows, all four studies produced either a decrease in antibiotic utilization or an increase in the prevalence of appropriate antibiotic utilization.[77-80] However, overall, the quality of evidence was weak, the results were mixed and the interventions implemented varied greatly. Nonetheless, these findings support multifaceted interventions, which include educational strategies, as well as locally developed guidelines, and prescribing feedback to improve antimicrobial prescribing in the long-term care setting.[76] However, there has been no standardization of programs and multiple components designed to improve antimicrobial use are often implemented simultaneously, so the efficacy or effectiveness of any one program component is largely unknown.[19]

Multifaceted Educational Interventions Targeting General Antibiotic Use for All Infection Types

Antimicrobial stewardship programs that utilize multiple educational modalities have generally been effective at improving antimicrobial use for the treatment of both infections in general and specific infection types (discussed below)[57,81-84] The types of educational interventions and the combinations of stewardship interventions assessed to date have varied greatly in the literature (Table 4). Examples of strategies studied include educational sessions, academic detailing, prescribing feedback, and/or dissemination of written materials, such as guidelines, algorithms, pocket cards, posters, and toolkits.

Multifaceted educational intervention studies that only target providers have yielded modest results (Table 4).[80,84] The impact of an educational intervention for physicians was assessed in a cluster randomized controlled trial among long-term care facilities in Montreal, Canada.[80] In intervention facilities, physicians were mailed an antibiotic guide and feedback on their prescribing practices over the previous three months. This intervention was then repeated four months later. By the end of the study, there was a greater decrease in antibiotic orders which did not adhere with the guide in the intervention homes versus control (usual care) homes (-20.5% vs. -5.1%). After the second mailing, physicians were 64% less likely to prescribe non-adherent antibiotics (OR 0.36, 95% CI 0.18 - 0.73), but this effect was not sustained 15 months later (OR 0.48, 95% CI 0.23 - 1.02). Similarly, an uncontrolled single-center quasi-experimental study at a public hospital with 340 long-term care beds assessed the impact of educational sessions with feedback and guidelines on

antibiotic use for physicians.[84] Post-intervention, 39% of antibiotic use was compliant with guidelines as compared to 11% pre-intervention ($p<0.001$). During the intervention antimicrobial use and antimicrobial starts decreased 29.7% and 25.9%, respectively. Notably, an interrupted time-series analysis indicated that the overall decrease in antimicrobial use persisted for 2 years following the intervention period. The availability of infectious diseases consultations at this long-term care facility may have contributed to the longevity of the success of this intervention.

Due to the significant role nurses play in recognizing, assessing and monitoring residents with infections, nurses may be an important target for educational interventions aimed at improving antimicrobial use in long-term care facilities. The impact of a multifaceted educational intervention for nurses and physicians was tested in a cluster randomized controlled trial among 58 nursing homes in Sweden.[79] The main components of the intervention included small group educational sessions for nurses and physicians, feedback on prescribing, presentation of guidelines and written materials. While there was no significant impact on the primary outcome, proportion of quinolones prescribed for lower urinary tract infection, the intervention did achieve a significant reduction in the proportion of infections treated with antibiotics (absolute risk reduction [ARR] -0.124, 95% CI -0.228 - -0.019) and a significant increase in the proportion of infections handled by physicians as "wait and see" (ARR 0.143, 95% CI 0.047 - 0.240). Similarly, a quality improvement program which included educational sessions to providers and nurses, a medical care referral form, prescriber feedback, and education for staff, residents and families was associated with a significant reduction in antibiotic prescribing rates for all indications assessed.[83]

Educational and Academic Detailing Interventions Targeting Pneumonia

Multifaceted educational interventions targeting pneumonia have had only a limited impact on improving antibiotic use (Table 4). Three studies have assessed the impact of implementing nursing home-acquired pneumonia (NHAP) guidelines through educational programs.[78,85,86] Two of these studies, which both assessed the impact of educational sessions for nurses and academic detailing to physicians failed to demonstrate improvement in antimicrobial use.[85,86] A controlled, quasi-experimental study in two state Veterans Homes found guideline adherence with respect to choice and timing of antibiotics did not improve significantly post-

intervention at the intervention facility.[85] However, this study did find guideline adherence for these measures was higher at the intervention facility as compared to the control facility, during the intervention period.

The second study used a controlled quasi-experimental design among 16 nursing homes in Colorado and Kansas to assess the impact of a multifaceted intervention to improve adherence to the NHAP guidelines.[86] The intervention included educational sessions for nurses to improve recognition of pneumonia symptoms and timing of antibiotics and academic detailing to prescribers by pharmacists regarding diagnostic and treatment practices over the influenza seasons (October to April) of 2005/2006 and 2006/2007. This study found no significant impact on guideline adherence for choice of antibiotic or duration; however improvements in adherence to timely antibiotics were significantly higher in intervention homes compared to control homes. Neither study found improvements in clinical outcomes, such as mortality and hospitalization rates, post-intervention. The impact of these interventions may have been higher if: 1) education had also been provided to nurses, (2) academic detailing had been facilitated by a multidisciplinary team, (3) the intervention period had been longer in duration, or 4) education had been provided to residents and family members or caregivers.

The third study, a randomized controlled study among ten skilled nursing facilities, assessed the impact of small-group education for providers only versus providers and nurses.[78] The proportion of antibiotic use meeting guidelines (pre- 50% vs. post- 81.8%, p=0.06) improved with the multidisciplinary intervention which targeted both providers and nurses, while the physician-only intervention did not have a significant effect (pre- 64.5% vs. post- 69%, p=0.73). However, in multivariate analysis, treatment according to the guidelines was not significantly different between the multidisciplinary and physician-only intervention groups. This study similarly found no significant differences in overall antibiotic use, mortality or hospitalization rates.

Education to Prevent Misdiagnosis and Overtreatment of Presumed Urinary Tract Infections

Interventions to improve antimicrobial use for presumed urinary tract infections have generally demonstrated greater success than those targeting pneumonia (Table 4). A cluster randomized controlled trial assessed the impact of a multifaceted intervention targeting suspected urinary tract infections on intervention and control nursing homes in Ontario, Canada.[77] A diagnostic and treatment algorithm for urinary tract infections was

implemented using multiple modalities including, small group educational sessions for nurses, videotapes, written materials, outreach visits and interviews with physicians. This intervention was associated with significant improvements in antimicrobial prescriptions for suspected urinary tract infections (pre- 1.59 vs. post- 1.17 courses per 1,000 resident days; weighted mean difference -0.49, 95% CI -0.93 - -0.06) and a non-significant reduction in urine cultures obtained (pre- 2.48 vs. post- 2.03 cultures per 1,000 resident days; weighted mean difference -0.51, 95% CI -1.38 – 0.35). Unfortunately, the effect on antimicrobial prescriptions was not sustained during a 12-month post-intervention observation period. Additionally, the study did not report significant differences in mortality or hospital admissions.

An uncontrolled quasi-experimental study assessed the effect of a multifaceted educational intervention, which included individualized direct feedback for nurses and providers, to reduce inappropriate treatment of asymptomatic bacteriuria.[57] The rate of treatment of asymptomatic bacteriuria (pre- 1.7 to post- 0.6 asymptomatic bacteriuria treated per 1,000 resident days; incidence rate ratio [IRR] 0.37, 95% CI 0.19 - 0.72, p=0.002) and inappropriate submission of urine cultures (pre- 2.6 to post- 0.9 cultures per 1,000 resident days; IRR 0.36, 95% CI 0.21 - 0.62, p<0.001) decreased significantly six months post-intervention and these reductions were sustained for 30 months.

A multidisciplinary team, including an infectious diseases consultant, an infection control nurse and a geriatrician, provided academic detailing concerning the diagnosis and treatment of urinary tract infections to head practitioners and head nurses at all long-term care facilities for older persons in Finland during 2004 to 2005.[81] After the visits, regional guidelines were developed and published and an annual questionnaire was mailed to the head nurse of each unit. This multifaceted intervention was associated with a significant reduction in the proportion of residents on antibiotic prophylaxis for urinary tract infections (14.5% in 2005 vs. 7.8% in 2008, p<0.001). Most recently, a controlled, quasi-experimental study among two Veterans Affairs Healthcare System Medical Centers, both of which included long-term care and general medicine wards, found a multifaceted educational program, which included individualized feedback to clinicians, was associated with significant reductions in overtreatment of asymptomatic bacteriuria in intervention vs. comparison sites (long-term care residents only; intervention period: 20% vs. 40%, maintenance period: 10% vs. 19.2%).[82]

Antimicrobial Stewardship Tool

An antimicrobial stewardship tool for nurses in long-term care facilities was associated with significant decreases in total antibiotic use.[55] This tool to promote appropriate use of antibiotics was a pre-printed form with two parts to be completed by nurses at treatment initiation and 48-72 hours after starting treatment. Other educational interventions implemented included a support pack, a dedicated telephone number for the project, follow-up visits, posters, and promotional material. The support pack included signs and symptoms of infections in elderly, obtaining clinical cultures, and information on resistance. Post-intervention there was a significant 4.9% decrease (95% CI 1.0% - 8.6%, p=0.02) in total antibiotic consumption in the intervention group (3.25 less defined daily doses per 1,000 resident days) and a 5.1% increase (95% CI 0.2%-10.2%, p=0.04) increase in the control group (2.42 more defined daily doses per 1,000 resident days). Total antibiotic consumption for prophylaxis of infection, and appropriateness of prescribing (measured by proportion of residents that fully met McGreer Criteria and also by proportion of residents that fully met the minimum Loeb Criteria) improved post-intervention. Additionally, no adverse events related to the tool were identified.

Infectious Diseases Consult Services

A recent quasi-experimental study assessed the impact of an infectious diseases consult service implemented as a 160-bed Veterans Affairs long-term care facility.[87] This consult service included an infectious diseases physician and nurse practitioner that provided on-site weekly rounds. The remainder of the week they were available for remote consultation. This service was associated with a reduction in total antimicrobial use by 30% ($p<0.001$), fluoroquinolones by 38% ($p<0.001$), and β-lactam/β-lactamase inhibitor combinations by 28% ($p<0.001$). Additionally, the rate of positive *C. difficile* tests declined significantly post-intervention as compared to pre-intervention ($p=0.04$). Since this was a VA facility, these findings may be not easily translated to community based facilities.

Antibiograms

The utility of antibiograms in improving antimicrobial use in acute care facilities is well recognized, however their use in long-term care facilities is relatively unknown. Antibiograms are cumulative summaries of

antimicrobial susceptibilities of local bacterial isolates over a period of time, usually six months or a year.[88] Clinicians typically use antibiograms to assess local susceptibility rates, which aids in the selection of appropriate empiric antibiotic therapy. One study specifically evaluated the impact of an antibiogram in a community-based skilled nursing facility.[89] Appropriate antibiotic empiric prescribing, defined in this study as an antibiotic choice that sufficiently covered the infecting organism based on antibiotic susceptibilities (i.e., facility specific antibiogram), increased from 32% to 45% after implementing the facility-specific antibiogram (p=0.32).

Measuring Outcomes and Metrics in Long-term Care.

Based upon our experience with antimicrobial stewardship and our review of the literature, we have additional ideas on how to advance antimicrobial stewardship in long-term care, which will be discussed throughout the remainder of our article. The studies conducted to date have mostly focused on the impact of antimicrobial stewardship programs on antimicrobial utilization. Though this is often the easiest outcome to measure, overall antibiotic use alone is not the strongest surrogate endpoint for improving resident safety and clinical outcomes. Declines in antibiotic use may not capture appropriate use since appropriate use means not only non-prescribing when an indication is absent but also proper prescribing when indicated. Instead, change in use should be targeted based on areas of high resistance or overuse. Additionally, a standard definition of appropriate use is needed since it varies greatly in the literature.

More research is needed using metrics that capture hard endpoints of resident safety and clinical outcomes rather than surrogate measures. However, doing this type of research is challenging. The studies conducted to date provide important foundation needed to begin to conduct this type of research in the future. At this time, none of the studies reviewed assessed the impact of their intervention on antimicrobial resistance or total costs of care. Few studies attempted to measure clinical outcomes, such as reductions in mortality or adverse events, or healthcare utilization, such as reductions in rates of emergency department visits and hospitalizations, as a result of improvements in appropriate antibiotic use. Moreover, no single study was able to provide a comprehensive assessment of their intervention on all the important outcomes of such a program, including antimicrobial utilization, healthcare utilization, costs, resistance, and clinical outcomes, including

relevant adverse outcomes such as *C. difficile* infection and adverse drug events. Finally, assessing the sustainability of implemented strategies is a worthy future research endeavor.

Future of Antimicrobial Stewardship in Long-term Care.

Continued research must be done to broaden the arsenal of stewardship interventions in long-term care and to identify the most effective strategies. Antimicrobial stewardship guidelines for the acute care setting recommend a multidisciplinary approach and support from hospital leadership.[7] These principles may also be important in the long-term care setting, but require further investigation. Due to important differences between acute care hospitals and long-term care facilities, the ability to obtain financial support from leadership for antimicrobial stewardship multidisciplinary personnel and other resources may be challenging. However, as the CDC has recently recommended, leadership should at least demonstrate their support for antimicrobial stewardship through written statements.[14] Leadership should sign and support a written antimicrobial stewardship policy that should be shared with staff, residents, and families. Additionally, leadership can include stewardship-related duties in position descriptions and create a culture that promotes antimicrobial stewardship.[14] Additionally, for now, there is a call for the infection prevention control officer to work together with a physician or pharmacist to champion antimicrobial stewardship needs.

Support and collaboration of administration and clinicians are essential to the success of any antimicrobial stewardship program.[7] This support can be obtained through effective and local champions or leaders.[72] Champions are individuals who take ownership over the mission of the program and advocate for and support antimicrobial stewardship interventions.[72] Champions can help empower both leadership and staff to support antimicrobial stewardship efforts. The CDC recently recommended that nursing homes identify individuals accountable for antimicrobial stewardship to empower and engage leadership and staff.[14] For facilities where stewardship is one of several competing priorities, an administrative champion such as the medical director can argue the case for antimicrobial stewardship to other medical staff leadership. Peer clinical champion or champions are also critically important. Well-respected clinicians, such as physicians, pharmacists, or nurses, with training in antimicrobial stewardship are ideally suited to act as peer champions. Peer champions should be committed to spearheading the program, and educating and gaining acceptance of other clinicians and staff

on the program. Without written polices "championing" for antimicrobial stewardship action may be difficult, therefore the champion should consider developing policies that promote optimal antibiotic use.

Many long-term care facilities across the country utilize central fill pharmacies and automated medication and supply systems. A central fill pharmacy is a one that processes and fills prescriptions for several local long-term care facilities. Therefore, the central fill pharmacy and pharmacists at those sites can play a unique role in promoting appropriate antimicrobial use within the local long-term care facilities they serves. Pharmacists are ideally suited to ensure that for each antimicrobial order an infectious diagnosis is documented, and can make recommendations on appropriate drug choice, dose and duration using a facility's local antibiogram and treatment pathways.[69] A clinically trained ID pharmacist's specialized knowledge of pathogenic microbiology, drug-resistance, pharmacotherapy, drug-drug interactions, pharmacokinetics (i.e., absorption, metabolism, distribution and excretion of antibiotics) and pharmacodynamics (i.e., maximizing antimicrobial killing / activity profiles) allows them to meaningfully contribute to antimicrobial stewardship. They can provide educational "in services", assist in treatment pathway development, and recommend alternative antimicrobial choices at time of prescribing. However, busy pharmacists at central fill locations may not have protected workload time for antimicrobial stewardship activities, and thus other daily responsibilities may take precedence over stewardship. Additionally, the central fill pharmacy may not have access to clinically trained ID pharmacists. Therefore, training staff through antimicrobial stewardship certification programs may be a helpful option. Fortunately, there are antimicrobial stewardship certificate training programs among other informal training opportunities available for interested pharmacists and providers.[70,71]

Other strategies to advance stewardship include bringing staff with antibiotic expertise to long-term care facilities. Several facilities could share an infectious diseases consultant or a facility could share an infectious diseases consultant with a local acute care hospital to mitigate the cost of obtaining these individuals. Federal agencies are likely to continue to increase antimicrobial stewardship demands on long-term facilities to improve the safety of residents, however resources are not likely to increase. As such, there is a critical need to develop minimally sufficient and direct antimicrobial-focused interventions, which can effect significant reductions in inappropriate antimicrobial use with the least amount of resources.

Conclusion

Antimicrobial resistance is a global public health crisis, one that has been accelerated through indiscriminant antimicrobial use. Antimicrobial stewardship programs have been recommended across all facets of healthcare to improve antimicrobial use and combat antimicrobial resistance, however in the long-term care setting; effective antimicrobial stewardship interventions are largely unknown. High prevalence of antimicrobial use and resistant bacteria, coupled with limited resources, plague effective antimicrobial stewardship in this setting. Our review only identified fourteen studies of antimicrobial stewardship interventions in long-term care. Overall, the quality of evidence was weak, the results were mixed, the interventions varied greatly, as did study definitions and outcomes measures, such as “appropriate use”. Several studies suggest that multifaceted educational interventions may be effective in increasing appropriate antimicrobial use in long-term care facilities. However, there is a critical need for future well-designed studies to develop tailored interventions to improve the care of the 1.4 million residents of long-term care facilities across the United States.

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Table 1: Needs for Antimicrobial Stewardship in Long-Term Care Facilities

Needs Identified
High prevalence of inappropriate and unnecessary antibiotic use
Increased risk for colonization with resistant bacteria
Increased risk of *Clostridium difficile* Infections and potential complications

Table 2: Barriers to Antimicrobial Stewardship in Long-Term Care Facilities

Barriers Identified
Paucity of well-validated strategies specific to long-term care facilities
Lack of funding and facility resources, such as lack of on-site microbiology laboratories
Challenges associated with proper diagnosis and treatment of infection in residents
Lack of trained infectious diseases physicians and pharmacists
Resident and family expectations

Table 3: Randomized Controlled Trials to Improve Antimicrobial Use in Long-Term Care Facilities

Study (Primary Author Year of Publication)	Infection of Interest	Design	Setting	Intervention	Unit of Analysis	Main Outcomes/Results
Naughton 2001 **Overall findings:** *Education targeting pneumonia did not significantly change antibiotic use (PO or IV) or resident outcomes.*	Pneumonia (focus of education on national nursing home-acquired pneumonia guidelines)	RCT (Pre-Intervention period: Nov 1997- April 1998; Post-Intervention period: Nov 1998- April 1999); *Unit of Randomization:* - SNFs *Allocation of randomization:* - Physician-only intervention group - Multidisciplinary intervention group	Ten SNFs from Buffalo, New York, United States (total of 2,375 beds)	*Physician-only group:* - Small-group consensus process for guideline development limited to physicians and nurse practitioners by two study physicians - Laminated pocket cards *Multidisciplinary group:* - 1-hour training session on the guidelines for nurses (RNs and LPNs) by two study nurses (similar to the small-group consensus conference) - Laminated pocket cards - Laminated posters	- Episodes of pneumonia acquired more than 3 days after admission to SNF - 226 episodes of pneumonia pre-Intervention -116 episodes of pneumonia post-Intervention	*Pre- vs. Post-*Intervention *treatment in accordance with guidelines:* - IV: 62.2% (79/127) vs. 73.4% (47/64), p = 0.15 -Multivariate analysis found significantly more IV use in accordance with guidelines post-Intervention (p < 0.02) PO: 57.6% (57/99) vs. 59.6% (31/52), p = 0.86 *Pre- vs. Post-Intervention IV use in accordance with guidelines by group:* - Physician-only group: 64.5% (69/107) vs. 69% (29/42), p=0.73 - Multidisciplinary group: 50% (10/20) vs. 81.8% (18/22), p=0.06 -Multivariate analysis found no significant difference in IV use in

						accordance with guidelines between groups (*P* =0.13) *Physician vs. multidisciplinary PO use in accordance with guidelines:* No difference (p = 0.27) -Multivariate analysis found no significant difference in PO use in accordance with guidelines between groups (p =0.27) No differences in 30-day mortality or hospitalization rates between pre- and post-intervention groups.
Loeb 2005 **Overall findings:** *Educational interventions targeting UTIs significantly decreased overall antimicrobial use*	UTI	Cluster RCT (NHs enrolled from Sept 2001 – Feb 2002; last follow-up Mar 2003); *Unit of Randomization:* - NHs *Allocation of randomization:* -Multifaceted AMS intervention group (Intervention group) - Usual care group	24 NHs in Ontario, Canada, and Idaho, United States (12 intervention homes, 12 control homes; mean beds 183 +/- 64.7)	- Diagnostic and treatment algorithm for physicians and nurses -Small group interactive sessions for nurses -Videotapes -Written explanatory materials for physicians	20 NHs that completed the study -Included 1,896 residents in intervention group -Included 1,858 residents in control group	*Intervention vs. control homes:* -Antimicrobials for suspected UTIs/ 1,000 RD: 1.17 vs. 1.59 (weighted mean difference -0.49, 95% CI -0.93 - -0.06) - Monthly rates of antimicrobial prescriptions for UTIs were lower in the intervention homes, however non-significant trend

		(Control group)		-Large posters -Pocket cards -NH staff member assigned to remind nurses to use algorithm -Outreach visits every three months -One on one interviews with physicians		towards a reduced effect over 12 months (regression coefficient -0.017, 95% CI -0.056 – 0.02) - Proportion of total antimicrobials for suspected UTIs: 28.4% vs. 38.6% (weighted mean difference -9.6%, 95% CI -16.9% - -2.4%). -DDD/1,000 RD for suspected UTIs: 6.9 vs. 10.9 (weighted mean difference -3.85, 95% CI -7.37—0.34) -Total antimicrobial use/ 1,000 RD: 3.52 courses vs. 3.93 (weighted mean difference -0.37, 95% CI -1.17 - 0.44). - Urine cultures obtained/1,000 RD: 2.03 vs. 2.48 (weighted mean difference -0.51, 95% CI -1.38-0.35) No significant differences in mortality or hospital admissions between intervention and control NHs.
Monette 2007	UTI, SSTI, lower respiratory tract	Cluster RCT (Pre-Intervention period:	8 public LTCFs in Montreal,	- Antibiotic guide with feedback on	1,539 initial antibiotic	*Change in non-adherent antibiotics*

Overall findings: *When provided with an antibiotic guide and feedback physicians were less likely to prescribe non-adherent antibiotics.*	infection, and septicemia of unknown origin	Dec 2001- Feb 2002; Intervention 1: Mar – April 2002; Post- Intervention period 1: May-July 2002; Intervention 2: Aug 2002; Post-Intervention period 2: Sept-Nov 2002; Follow-up period: Dec 2002 – February 2003) *Unit of Randomization:* LTCFs *Allocation of randomization:* - Physicians who received the intervention (Intervention group) - Physicians who provided usual care (Control group)	Canada (4 intervention LTCFs; 4 control LTCFs)	prescribing practices over the previous 3 months mailed to 36 physicians - Intervention repeated 4 months apart	prescriptions (1,003 intervention; 590 control)	*pre- to post-intervention between intervention vs. control homes:* 20.5% decrease vs. 5.1% decrease *Effect of the intervention on the physicians' likelihood of prescribing non-adherent antibiotics with the pre-intervention period as reference:* - Post- Intervention period 1: Intervention physicians 53% less likely to prescribe non-adherent antibiotics (OR=0.47, 95% CI=0.21-1.05) -Post- Intervention period 2: Intervention physicians 64% less likely to prescribe non-adherent antibiotics (OR=0.36, 95% CI =0.18-0.73) -15 months follow-up: Intervention physicians 52% less likely to prescribe non-adherent antibiotics (OR=0.48, 95% CI= 0.23=1.02)
Pettersson 2011	All infections	- Cluster RCT (Pre-Intervention period:	58 NHs in Sweden (26	- Small educational group	46 nursing homes	*Effect of the intervention (95% CI)*

Overall findings: *Educational group sessions with feedback decreased the overall prescribing of antibiotics.*		Sep- Dec 2003; Intervention Oct 2004 – Jan 2005; Post- Intervention: Feb – May 2005) *Unit of Randomization:* NHs *Allocation of randomization:* -Multifaceted AMS intervention group (Intervention group) - Usual care group (Control group)	intervention NHs; 20 control NHs)	sessions with nurses and physicians - Feedback - Presentation of guidelines -Written materials	completed the study -Included 1,373 residents in intervention group -Included 1,138 residents in control group	*at 2 years (difference):* -Proportion of quinolones prescribed for lower urinary tract infection: 0.028 (-0.193 - 0.249). -Proportion of infections treated with antibiotics: -0.124 (-0.228, -0.019) - Proportion of infections handled by physicians as 'wait and see: 0.143 (0.047, 0.240) - UTIs per resident: 0.038 (-0.013-0.089) No differences in hospital admissions for intervention or control groups.

ADE= adverse drug event; AMS= antimicrobial stewardship intervention; ASB= asymptomatic bacteriuria; CAUTI= catheter-associated urinary tract infection; CI= confidence interval; DDD= days daily dose; DOC= resident days of care; DOT= days of therapy; IC= infection control; ID= infectious diseases; IRR= incidence rate ratio; ITS= Interrupted time series analysis; IV: Intravenous antibiotic; LPN=licensed practical nurse; LTC= long-term care; LTCF= long-term care facility; NH=nursing home; OR= odds ratio; PA= parenteral antibiotics; PD= patient days; PO= oral antibiotics; QI= quality improvement; RCT=randomized, controlled trial; RD= resident days; RN= registered nurse; SNF= skilled nursing facility; SSTI=skin and soft structure infection; UTI= urinary tract infection; VA= Veterans Affairs

Table 4: Studies to Improve Antimicrobial Use in Long-Term Care Facilities by Type of Intervention

Study (Primary Author Year of Publication)	Infection of Interest	Design	Setting	Intervention	Unit of Analysis	Main Outcomes/Results
Multifaceted Educational Interventions Targeting General Antibiotic Use for All Infection Types.						
Interventions Targeting Providers Only.						
Monette 2007	*See Table 3*					
Schwartz 2007 **Overall findings:** *Educational sessions with feedback improved appropriate treatment and decreased antimicrobial use.*	All infections	Uncontrolled Quasi-experimental Study (Pre-Intervention period: Jan – Oct 2000; Post-Intervention period: May– Sept 2002)	Public LTC and acute care hospital (340 LTC beds) in Illinois, United States	- Four educational sessions to 20 internists given by ID specialists (included national guidelines, hospital resistance data, and physician feedback) - Pocket-sized booklets, algorithms, guidelines	- 200 randomly selected residents treated with antimicrobials (100 pre-Intervention; 100 post-Intervention)	*Antibiotic use compliant with guidelines pre- vs post-Intervention:* -Initial treatment agreed with guidelines: 11% vs. 39%, p<0.001 -Clinical criteria agreed with guideline diagnostic criteria: 62% vs. 32%, p = 0.006 *Interrupted time series analysis of the effect of the interventions on antimicrobial use during the 1.5 year intervention period and 2 year post-intervention.* Antimicrobial use: Decreased 29.7%; sustained during the post-intervention period (ITS demonstrated reduced level and slope during intervention period was significant,

						p<0.001) - Antimicrobial starts: Decreased 25.9%; sustained during the post-intervention period (ITS demonstrated reduced level and slope during intervention period but this was not significant) No significant differences in all-cause and infection related mortality.
Interventions Targeting Providers and Nurses.						
Pettersson 2011	*See Table 3*					
Zimmerman 2014 **Overall findings:** *A QI program with educational sessions and feedback decreased overall antimicrobial prescribing rates and prescribing rates for respiratory tract infections.*	UTI, SSTI, respiratory infections, and non-infectious vomiting/diarrhea	Controlled Quasi-experimental Study (Pre- Intervention Period: Mar – May 2011, Post-Intervention period: June – Nov 2011)	12 NHs in North Carolina, United States (6 intervention NHs [mean beds 146 +/- 37.1]; 6 control NHs [mean beds 124 +/- 22.2])	*QI program:* - Educational sessions to providers and nurses by a physician, nurse, ID specialist, ands experts in LTC - Medical care referral form and pocket card -Monthly feedback on prescribing to prescribers and nurses - Informational brochure and meetings for nursing home	All residents, including 1,497 residents treated with antibiotics	*Effect of intervention on antibiotic prescribing rates between pre- and post-Intervention periods for intervention vs. control NHs:* -Total antibiotics for all infections: IRR 0.86, 95% CI 0.79-0.95, p<0.05 - Antibiotics for respiratory infections: IRR 0.71, 95% CI 0.56-0.90, p<0.05 - Antibiotics for UTIs: IRR 0.84, 95% CI 0.66-1.05, p>0.05 - Antibiotics for SSTI:

				staff, residents, and families		IRR 0.89, 95% CI 0.62-1.28, p>0.05
Multifaceted Educational Interventions Targeting Antibiotic Use for Pneumonia.						
Naughton 2001	*See Table 3*					
Hutt 2006 **Overall findings:** *Educational sessions and academic detailing for pneumonia not associated with significant improvements in antibiotic choice or timing in intervention homes.*	Pneumonia (focus of education on national nursing home-acquired pneumonia guidelines)	Controlled Quasi-experimental Study (Pre- Intervention Period: Nov 2003-Apr 2004, Post-Intervention Period: Nov 2004 - Apr 2005)	Two State Veterans Home in Colorado, United States (1 intervention NH [134-beds]; 1 control NH [120-beds])	- Interactive educational sessions for nurses - Toolkit (Annotated copy of guidelines, case studies, preprinted orders, pocket card with guidelines reminders, and posters) disseminated throughout facility - Academic detailing to physicians and providers	86 residents with two or more signs of lower respiratory tract infections (46 intervention group; 40 control group)	*Change in guideline compliant antibiotics pre- to post-Intervention in intervention homes:* - Antibiotic choice: 63% vs. 81%, p >0.05 - Timely antibiotic: 88% vs. 79%, p >0.05 *Guideline compliant antibiotics in intervention homes vs control homes during Post*-Intervention *Period:* - Antibiotic choice: 81% vs. 33%, p <0.05 - Timely antibiotic: 79% vs. 17%, p <0.05 No significant differences in mortality or hospitalization rates between intervention and control groups. No significant differences in mortality or hospitalization rates between pre- and post- periods.
Linnebur 2011	Pneumonia	Controlled Quasi-	Sixteen NHs in	- Educational	1,123 episodes	*Difference in change*

Overall findings: *Educational sessions and academic detailing or pneumonia improved timing but not choice of antibiotics.*	(focus of education on national nursing home-acquired pneumonia guidelines)	experimental Study (Pre- Intervention Period: Oct 2004 – Apr 2005, Post-Intervention Period: Oct 2005- Apr 2006 and Oct 2006- Apr 2007)	Colorado (8 intervention NHs [mean beds 134]) and Kansas, United States (8 control NHs [mean beds 128])	sessions for nurses - Academic detailing to prescribers by pharmacists regarding diagnostic and prescribing practices	of pneumonia evaluated (549 intervention group; 574 control group)	*pre- and post-intervention of antibiotic use compliant with guidelines between intervention vs. control homes:* Antibiotic choice: 6% increase vs 7% increase, p=0.3 Antibiotic duration: 14% decrease vs. 5% increase, p>0.05 Timely antibiotic: 18% increase vs. 7% decrease, p=0.0003 No significant differences in mortality between intervention and control groups.
Multifaceted Educational Interventions Targeting Antibiotic Use for Suspected Urinary Tract Infections.						
Loeb 2005	*See Table 3*					
Zabarsky 2008 **Overall findings:** *Educational sessions with feedback for ASB decreased treatment for ASB and inappropriate urine cultures.*	ASB	Uncontrolled Quasi-experimental Study (Pre-Intervention period: 3 months, Post- Intervention period 30 months; Feb 2002 – Oct 2004)	VA Medical Center in Cleveland, Ohio, United States (190 LTC beds)	- Educational sessions to nurses and providers conducted by an IC nurse and ID physician -Pocket-sized reference cards, larger cards at each computer station -Semi-annual		*Pre-Intervention vs. 6 months post and vs. 30 months post:* Antibiotic regimens for ASB: 68% vs. 69%, p=0.90 vs. 44%, p=0.022 ASB treated/1,000 PD days: 1.7 → 0.6 (IRR 0.37, 95% CI 0.19-0.72, p=0.002) → 0.3

				follow up educational sessions - Individualized direct feedback for nurses and providers		Total antibiotic days DOT/1,000 PD: 167.7 → 117.4 (p<0.001) → 109 (p<0.001) Inappropriate cultures: 69% vs. 61% vs. 46% Inappropriate cultures sent/1,000 PD: 2.6 → 0.9 (IRR 0.36, 95% CI 0.21-0.62, p<0.001) → 0.6
Rummukainen 2013 **Overall findings:** *Academic detailing decreased proportion of residents on antibiotic prophylaxis for UTI.*	UTI prophylaxis	Uncontrolled Pre- (2005 baseline visit) vs. Post (2006, 2007, 2008) surveys	25 primary care hospitals and 39 NHs in Finland	- Academic detailing to head practitioners and head nurses (by an ID consultant, IC nurse, and geriatrician) - Regional guidelines - Annual surveys to reinforce guidelines	68 units visited and responded to surveys	*The proportion of residents on antibiotic prophylaxis for UTI:* 14.5% in 2005 to 7.8% 2008, p<0.001
Trautner 2015 **Overall findings:** *Educational sessions, feedback, and a diagnostic algorithm targeting ASB*	ASB	Controlled Quasi-experimental Study (Pre-Intervention period: July 2010 – June 2011; Intervention Period: July 2011- June 2012; Maintenance Period: July 2012 – June 2013)	Two VA Health Care System Medical Centers in Texas, United Sates (1intervention center in Houston [5 general medicine and 5 LTC wards	- CAUTI vs. ASB diagnostic algorithm - Case-based individualized audit and feedback to train clinicians to use algorithm		*LTC Residents Only:* Overtreatment of ASB lower during the intervention (OR 0.23, 95% CI 0.08-0.65) and maintenance (OR 0.10, 95% CI 0.01-0.84) periods at the intervention facility.

reduced overtreatment of ASB.			included], 1 control center in San Antonio [3 general medicine and 2 LTC wards included]); United States	- Educational sessions to practitioners and nurses by Principal investigator (MD, PhD)		Overtreatment of ASB higher during the intervention (OR 9.67, 95% CI 1.43-65.38) and similar for the maintenance (OR 3.45, 95% CI 0.61-19.53) periods at the control facility. *All subjects:* Significant decrease in the number of urine cultures ordered per month over time when comparing 2 sites (p<0.001)
Implementation of a Novel Antimicrobial Stewardship Tool.						
Fleet 2014 **Overall findings:** *Antimicrobial stewardship tool decreased antibiotic use and improved appropriate treatment.*	All infections	Cluster RCT (Pre-Intervention period: Jan– May 2010; Post- Intervention period: Jan– May 2011 Post) *Unit of Randomization:* - NHs *Allocation of randomization:* - AMS Tool group (Intervention group) - Usual care group (Control group)	30 NHs in London, England (15 intervention NHs,15 control homes [total of 1,832 beds in both groups])	- Antimicrobial stewardship tool (pre-printed form) for nurses -Support pack for nursing staff and managers -Dedicated telephone number for the project -Follow-up visits - Posters and promotional material	3,328 residents (1,663 intervention, 1,575 control)	*Intervention vs. control homes:* Change in total antibiotic consumption pre. vs. post: I4.9% decrease (3.25 DDD/1,000 RD, 95% CI 1.0% - 8.6%, p=0.02, intervention group) 5.1% increase (2.42 DDD/1,000 RD, 95% CI 0.2% - 10.2%, p=0.04, control group) Change in total antibiotic consumption for prophylaxis pre. vs. post: 2.72 DDD/1,000 RD

						decrease (intervention group) 0.83 DDD/1,000 RD increase (control group) *Proportion of residents that fully met "McGreer Criteria' post-intervention between intervention vs. control homes:* 11.1% vs. 2.6%, p=0.004 (estimated relative increase 6.44) *Proportion of residents that fully met "Loeb minimum Criteria' post- intervention between intervention vs. control homes:* 19.3% vs. 5.1%, p=0.001 No ADEs due to tool.
Implementation of an Infectious Diseases Consultation Service.						
Jump 2012 **Overall findings:** *ID consult service decreased antibiotic use and* of rate of positive *C. difficile* tests	All infections	Uncontrolled Quasi-experimental Study (Pre-ID Service Period: July 2006–June 2009, Post-ID Service Period: July 2009–Dec 2010)	VA LTCF in United States (160-beds)	ID consult service that consisted of an ID physician and a nurse practitioner who examined residents at the LTCF once each weekly and the remainder of the week were available for remote	Antibiotic DOT/ 1,000 DOC *C. difficile* tests/ 1,000 DOC	*Pre-vs. Post-ID Consult:* - Total systemic antibiotic mean DOT/1,000 DOC: 175.1 vs.122.3, $p<0.001$ (30.1% decrease) - Rate of positive *C. difficile* tests declined in the post-period

				consultation (via telephone and the electronic medical record)		relative to pre-period rates, p=0.04 - Hospital Transfers Per Month: 19.0 vs. 17.6, p=0.27
Implementation of an Antibiogram.						
Furuno 2014 **Overall findings:** *Antibiogram non-significantly increased appropriate empiric prescribing.*	All infections	Uncontrolled Quasi-experimental Study (Pre-antibiogram Period: 6 months, Post-antibiogram Period: 6 months)	Three SNFs in Maryland, United States (Antibiogram effectiveness assessed a single SNF [118-beds])	-Antibiogram -Educational in-services (introduction of the antibiogram and explanation of how to use to use the tool) to nursing staff, administrators, nurse managers, and physicians by study staff	839 resident charts reviewed to inform the antibiograms	*Pre- vs. Post-antibiogram prevalence of appropriate empiric antibiotic prescribing:* 32% vs. 45%, p=0.32

ADE= adverse drug event; AMS= antimicrobial stewardship intervention; ASB= asymptomatic bacteriuria; CAUTI= catheter-associated urinary tract infection; CI= confidence interval; DDD= days daily dose; DOC= resident days of care; DOT= days of therapy; IC= infection control; ID= infectious diseases; IRR= incidence rate ratio; ITS= Interrupted time series analysis; IV: Intravenous antibiotic; LPN=licensed practical nurse; LTC= long-term care; LTCF= long-term care facility; NH=nursing home; OR= odds ratio; PA= parenteral antibiotics; PD= patient days; PO= oral antibiotics; QI= quality improvement; RCT=randomized, controlled trial; RD= resident days; RN= registered nurse; SNF= skilled nursing facility; SSTI=skin and soft structure infection; UTI= urinary tract infection; VA= Veterans Affairs