Antibiotic Stewardship Programs in Nursing Homes: A Systematic Review

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ABSTRACT

Introduction: Antibiotic stewardship programs (ASPs) are coordinated interventions promoting the appropriate use of antibiotics to improve patient outcomes and reduce microbial resistance. These programs are now mandated in nursing homes (NHs) but it is unclear if these programs improve resident outcomes. This systematic review evaluated the current evidence regarding outcomes of ASPs in the NH.
Methods: PubMed, CINAHL, EMBASE, and the Cochrane Library were systematically searched for intervention trials of ASPs performed in NHs that evaluated final health outcomes (mortality and *Clostridium difficile* infections), healthcare utilization outcomes (emergency department visits and hospital admissions) and intermediate health outcomes (number of antibiotics prescribed, adherence to recommended guidelines).
Results: A total of 14 studies rated good or fair quality were included. Eight studies reported a reduction in antibiotic prescriptions. Ten found an increase in adherence to guidelines proposed by the studied ASP. None reported a statistically significant change in NH mortality rates, *C. difficile* infection rates, or hospitalizations.
Discussion: The limited research to date suggests that NH ASPs can affect intermediate health outcomes, but not key health outcomes or health care utilization.
Conclusion: Larger trials evaluating more intensive interventions over longer durations may be needed to determine whether ASPs in NHs improve health outcomes as they have in hospitals.

The 1.4 million older adults residing in American nursing homes (NHs)[1] are at a particularly high risk of multidrug-resistant organism (MDRO) infection due to antibiotic overuse.[2] It is estimated that 1 in 3 NH residents are colonized with an MDRO and that as many as 75% of the 3 million annual antibiotic prescriptions for presumed infections in NH residents may be inappropriate.[3–5] MDRO infections are difficult to treat and require broad-spectrum antibiotics, thereby increasing the risk of potentially fatal *C. difficile* infections (CDI).[6] The tremendous cost and risk of CDI and other adverse events associated with antibiotic overuse has led to calls for a more judicious approach to antibiotic prescribing[7–9] via antibiotic stewardship programs (ASPs)—coordinated efforts promoting the optimal use of these powerful medications throughout all healthcare settings, including NHs.[10]

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NH residents present unique challenges for antibiotic stewardship. The multiple comorbidities typical of NH residents,[11] combined with the aging immune system, lead to atypical and often subtle changes in the presentation of bacterial infections.[12] More than half of the current NH population has some degree of functional impairment and needs assistance in many or all of the activities of daily living (including bathing, toileting, dressing, ambulation, feeding).[1,13] This leads to high levels of intimate contact between staff and residents, which contributes to the spread of MDROs from person to person.[2] Furthermore, the majority of NH residents have sufficient cognitive impairment to limit their ability to communicate a coherent history,[14] and this can lead to antibiotic prescriptions for nonspecific symptoms that are not necessarily caused by bacterial infections.[15] In addition, frail NH residents are hospitalized more frequently than an age-matched cohort,[16] increasing their exposure to even more MDROs.

The typical NH has limited resources to diagnose acute bacterial infections, such as diagnostic testing or imaging.[5] NHs often have staff-to-resident ratios that are orders of magnitude lower than those of hospitals,[17] which may lower the quality of care.[18] Medical equipment is shared between caregivers and residents, also contributing to the rapid spread of MDROs in this environment.[19] Not surprisingly, then, the risk of colonization with MDROs is especially high in residents with in-dwelling devices such as urinary catheters.[20]

Recognizing these challenges, specific guidelines for infection surveillance and treatment recommendations in the NH have been published.[21,22] However, these guidelines are largely based on expert opinion, as there is limited empirical research on management of infections in the NH. Furthermore, published guidelines do not appear to be used regularly to guide NH infection management.[23–25] Rather than using these guidelines, providers appear to rely on diagnostic tests such as urinalyses or chest radiographs when an infection is suspected. Although these results may not provide evidence of an infection, they more often increase antibiotic prescribing.[24,26,27]

Hospital-based ASPs have been successful at reducing potentially inappropriate prescribing.[10] ASPs are now mandated in American NHs,[9] but it is unknown what aspects of these programs are effective in this setting. To assess the potential benefit of ASPs in NHs, we conducted a systematic review. Our main study questions involved whether these programs lead to improved health outcomes and lower rates of health care utilization.

Methods

To evaluate the impact of ASPs on health outcomes, we sought to determine if ASPs in the NH reduced mortality and/or reduced the incidence of CDI. To evaluate ASPs' impact on health care utilization, we focused on emergency department visits for a suspected bacterial infection (sepsis, pneumonia, urinary tract infection [UTI], or cellulitis) and hospitalizations (overall and for bacterial infections). We also sought to evaluate the impact of ASPs on the following intermediate health outcomes: changes in the rates of antibiotic prescriptions and the proportion of antibiotic prescriptions that were concordant with guidelines.

Data Sources and Searches

PubMed/MEDLINE, the Cochrane Library, EMBASE, and CINAHL were searched for relevant English-language articles from database inception through February 2017. Medical Subject Headings were used as search terms when available and keywords when appropriate, focusing on terms that describe relevant populations, interventions, and study designs. Complete search terms and limits are listed in Appendix A. Targeted searches were used for unpublished literature by searching ClinicalTrials.gov and the WHO International Clinical Trials Registry Data Platform. To supplement electronic searches, reference lists of pertinent review articles were examined, and studies that met the inclusion criteria were added to potentially relevant articles.

Study Selection

We included English-language randomized controlled trials, nonrandomized trials and observational studies of eligible interventions in adults age 65 years or older conducted in countries categorized as "very high" on the Human Development Index.[28] We excluded studies of patients with active cancer, HIV/AIDS, end-stage renal disease requiring hemodialysis, organ transplant recipients, and other conditions that directly cause or require immunosuppression, thereby changing antibiotic treatment and prophylaxis practices.

Cluster randomized controlled trials comparing NHs with ASPs to those without were eligible. Nonrandomized controlled trials and observational studies were also acceptable given the limited literature on this topic. Studies with a comprehensive ASP were included, but not studies assessing interventions focused on one single component of an ASP, such as hand hygiene.

Titles and abstracts of all publications identified were reviewed against prespecified inclusion criteria. All full texts of abstracts that appeared relevant were reviewed to determine final eligibility.

Quality Assessment and Data Abstraction

For each included study, we extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings and study design. We then assessed the quality of the included studies as good, fair, or poor using predefined criteria developed by the National Institutes of Health for RCTs[29] and nonrandomized interventional studies[30] as seen in Appendix B. We included only studies rated as having good or fair quality.

Data Synthesis and Analysis

We qualitatively synthesized findings by summarizing the characteristics and results of included studies in tabular and narrative format. Meta-analysis was not appropriate because of heterogeneity across studies in terms of intervention type, outcomes, and study design.

Results

We identified 592 unique titles and abstracts and assessed 29 full-text articles for eligibility (Figure 1). We excluded 15 articles for various reasons detailed in Appendix C and included 14 published studies of good or fair quality.[31–44] These included 5 cluster randomized controlled trials,[32,37,39–41] 3 controlled before-after trials,[34,36,42] 4 before-after trials without controls,[31,33,35,43] and 2 nonrandomized controlled trials.[38,44]

Characteristics of included studies are summarized in Table 1. All included studies used the individual NH as unit of intervention allocation; sample sizes ranged from 1 NH to 58 NHs. Eleven of the 14 studies reported the residents of participating NHs as study subjects, but, in reality, only 4 studies treated the individual NH resident as a study subject,[33,34,36,40] with the remainder analyzing antibiotic prescriptions as the unit of intervention. Ten studies were set in the United States and one each in the United Kingdom,[32] Sweden,[41] the Netherlands,[42] and Canada.[37]

There was significant heterogeneity in terms of intervention components and delivery personnel. Most studies included some aspect of an educational lecture to NH staff and physicians. One study included 2 arms: a physician-only arm and a multidisciplinary arm including physicians and nurses.[40] Two used an infectious disease consultant team that directed recommendations exclusively to NH prescribers; 3 used an intervention that included NH prescribers and nursing staff[37,40–43]; and 1 included residents and families as well as prescribers and nurses.[44] The comparators were generally usual care (ie, no formal ASP). The outcomes of interest included final health outcomes (mortality or CDI), healthcare utilization outcomes (emergency department visits, hospitalizations), and intermediate healthcare outcomes (decreased antibiotic use, improved guideline adherence). The longest studies were 36 months.[34,36] Quality assessments of the included studies are presented in Appendix B.

Impact of ASPs on Health Outcomes and Health Care Utilization

Four studies measured mortality following institution of ASPs in NHs.[34,35,37,40] Loeb et al did not find a significant difference in morality between intervention homes and controls (1.11 per 1000 resident days in the intervention arm compared with 1.09, weighted mean difference 0.07, −0.22 to 0.36).[37] Naughton et al similarly did not find a difference in mortality, with a mortality of 23.9% in intervention

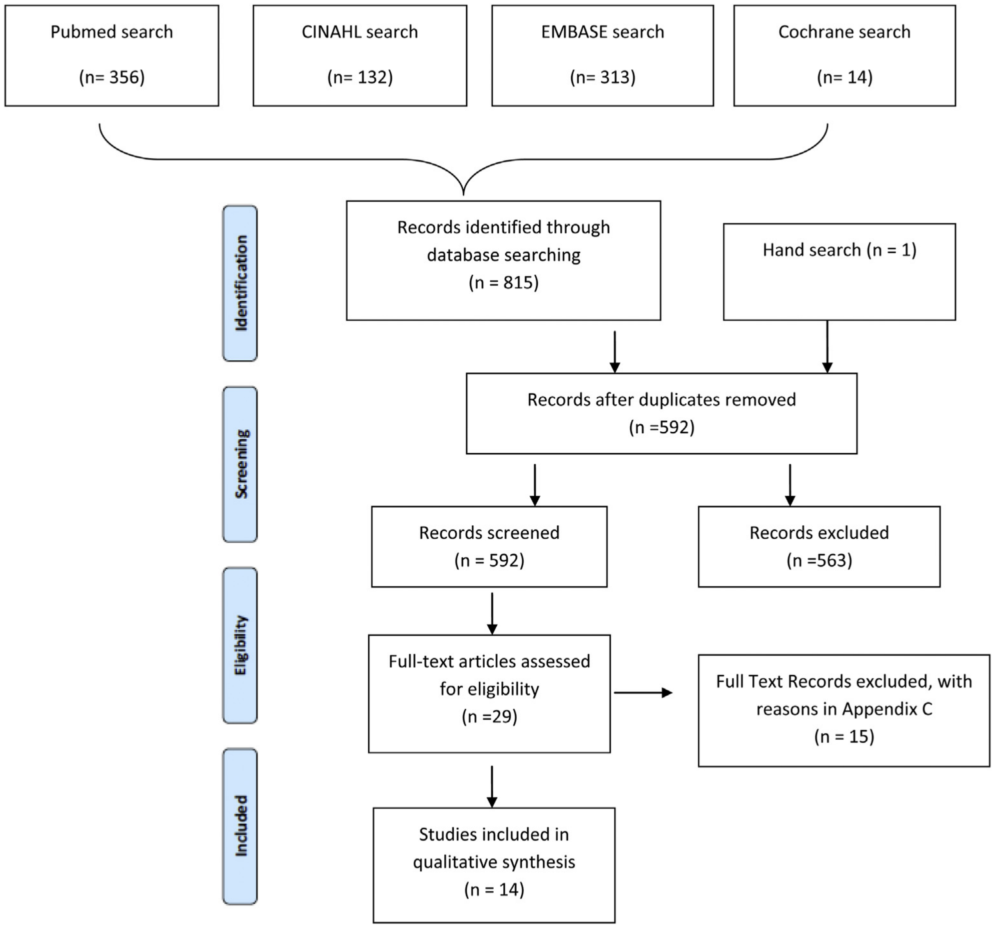

Fig. 1. PRISMA flow diagram.

homes and 18.1% (P = .27) in controls.[40] Although mortality was measured in the 2 remaining studies, it was simply reported as unchanged.[34,35] None of these studies found a difference in the overall mortality rate for residents of intervention NHs with ASPs compared to control NHs. Outcomes in these 4 studies were measured over 18 to 36 months.[34,36,37]

Two included studies reported the CDI incidence as an outcome of interest.[31,35] One was an interventional trial performed in 3 community NHs over 7 months[31]; the other was conducted in one Veterans Affairs NH over 30 months.[35] Both used an infectious diseases consult team as part of their intervention, and neither reported a statistically significant change in the incidence of CDI.

We found no eligible studies that directly addressed emergency department visits for suspected bacterial infections. Similarly, no study directly measured hospitalizations attributed to infectious etiologies. However, 4 included studies did measure the overall rates of hospitalization.[34,36,37,41] Of these, none observed a statistically significant change in hospitalizations following the studied intervention.

Table 1
Included Study Characteristics

Study	Year	Design	No. of Nursing Homes	Country	Intervention Subjects	Primary Outcome Measured	% of Total Outcomes Measured
Doernberg et al, 2015	2015	Before-after	3	US	Prescribers	Prescriptions	57%
Fleet et al, 2014	2014	cRCT	30	UK	Nurses	Guidelines	CD
Hutt et al, 2006	2006	Before-after	2	US	Multidisciplinary*	Guidelines	NR
Hutt et al, 2011	2011	Controlled before after	16	US	Multidisciplinary	Guidelines	NR
Jump et al, 2012	2012	Before-after	1	US	Prescribers	Prescriptions	NR
Linnebur et al, 2011	2011	Controlled before -after	16	US	Multidisciplinary	Guidelines	NR
Loeb et al, 2005	2007	cRCT	24	US	Multidisciplinary	Prescriptions	NR
McMaughan et al, 2016	2016	NRCT	12	US	Multidisciplinary	Guidelines	NR
Monette et al, 2007	2007	cRCT	10	Canada	Prescribers	Guidelines	97%
Naughton et al, 2001	2001	cRCT	10	US	Multidisciplinary	Guidelines	98%
Pettersson et al, 2014	2011	cRCT	58	Sweden	Multidisciplinary	Prescriptions	NR
van Buul et al, 2015	2015	Controlled before -after	10	Netherlands	Multidisciplinary	Prescriptions	84%
Zabarsky et al, 2008	2008	Before-after	1	US	Multidisciplinary	Prescriptions	NR
Zimmerman et al, 2014	2014	NRCT	12	US	Multidisciplinary†	Prescriptions	NR

CD, cannot determine; cRCT, cluster randomized controlled trial; NR, not reported; NRCT, nonrandomized controlled trial.
*Multidisciplinary interventions included prescribers and nursing staff.
†This study also included NH residents and their families.

Impact of ASPs on Intermediate Health Outcomes

Eight studies measured changes in antibiotic prescribing associated with ASPs. Results are shown in Table 2. Each of these studies reported a decrease in either overall or for indication-specific antibiotic prescriptions in NHs allocated to an ASP intervention. Doernberg et al compared intervention homes to historical controls and reported decreased antibiotic prescriptions for UTIs by 6% (95% CI 3% to 8%) and a 5% decrease in antibiotic prescriptions overall (no measures of variance reported).[31] Loeb et al found that fewer courses of antimicrobials for suspected UTIs per 1000 resident days were prescribed in intervention NHs compared with control NHs (1.17 vs 1.59 courses; weighted mean difference: −0.49, 95% CI −0.93 to −0.06) but the difference in total antimicrobial use per 1000 resident days between the intervention and control NHs was not significantly different (3.52 vs 3.93; weighted mean difference −0.37, 95% CI −1.17 to 0.44).[37] The intervention in Pettersson et al reduced the odds of any antibiotic prescription for intervention NHs compared to control NHs (odds ratio 0.124, 95% CI 0.019 to 0.228).[41] Zabarsky et al reduced the treatment for UTIs (incidence rate ratio 0.37, 95% CI 0.19 to 0.72, $P = .02$), and the total antibiotic days of therapy decreased from 167 per 1000 patient-days to 109 days of therapy per 1000 patient-days over 9 months of follow-up ($P = .001$) compared with performance prior to the intervention.[43] van Buul et al found a decreased daily drug dose (DDD) with overall antibiotic use in intervention NHs (−2.3 DDDs per 1000 resident-care days) while noting usual care NH increased antibiotic use by 1.1 DDDs per 1000 resident-care days.[42] Zimmerman et al found reduced total antibiotic prescriptions ordered between baseline and follow-up in intervention NH compared with control NHs (adjusted incidence rate ratio 0.86, 95% CI 0.79 to 0.95).[44]

Ten studies reported "guideline adherence" as an outcome, but the guidelines measured varied widely. These studies are further described in Table 3. Fleet et al found a 6.44% ($P = .004$) relative increase in adherence to the McGeer criteria[21] (used for surveillance definitions) in intervention NHs compared to controls.[32] This study also found that adherence to the Loeb minimum criterion[22] (used for antibiotic initiation) increased in intervention NHs from 11.5% prior to the intervention to 19.3% post intervention ($P = .06$). The infectious disease team evaluated in Doernberg et al made recommendations according to the Loeb minimum criteria, but guideline adherence following the intervention was not reported.[31]

The studies by Hutt et al (2006, 2011) and Linnebur et al examined adherence to the Nursing Home Acquired Pneumonia (NHAP) management guideline.[33,34,36,45] None found a meaningful change in guideline adherence associated with the intervention in their studies.[34,36] Naughton et al measured adherence to a different guideline for NHAP and found that a multidisciplinary intervention was more effective in improving adherence to the NHAP guideline than an intervention directed toward prescribers only (67% to 60% respectively, no measures of effect reported).[46] Monette et al developed a guideline formulated from expert opinion and found a reduction in the odds of nonadherent antibiotic prescriptions (OR 0.36, 95% CI 0.18 to 0.73) to the study-specific guidelines.[39] Pettersson et al also created a study-specific guideline and found lower rates of antibiotic prescription in intervention NHs compared with controls, but adherence to the guideline used was not reported.[41]

Finally, McMaughan et al developed a decision-making aid for the management of asymptomatic bacteriuria and measured adherence to the Loeb minimum criterion for antibiotic initiation and the High guidelines.[47] They found that NHs using the decision aid with low fidelity did not have a decrease in prescriptions for asymptomatic bacteriuria (70% to 69%, no measures of effect reported), whereas NHs with high fidelity to the guidelines reduced antibiotic prescribing (73% to 49%, no effect measures reported).

Table 2
ASPs' Changes in Antibiotic Prescribing

Author, Year	Study Design	Study Length (mo)	Number of NHs	Intervention	Intervention Subjects	Results, Overall Antibiotics	Results, Indication-Specific Antibiotics
Doernberg et al, 2015	Before-after, no control	7	3	ID team consult	Prescribers	Decreased prescriptions by 5% (effect measures NR)	UTI: Decreased prescribing for UTI 6% (95% CI 3% to 8%)
Fleet et al, 2014	cRCT	18	30	Nursing ASP form	Nurses	Decreased prescriptions by 4.9% (95% CI 1.0% to 8.6%)	NR
Jump et al, 2012	Before-after, no control	36	1	ID team consult	Prescribers	Decreased prescribing by 30.1% ($P < .001$)	NR
Loeb et al, 2005	cRCT	18	24	NH infection-specific algorithms for MD and nurse, Individual meetings with prescribers	Prescribers and nurses	Weighted mean difference, intervention vs control: −0.37 (95% CI −1.17 to 0.44)	UTI: weighted mean difference in prescribing −9.6% (95% CI −16.9% to −2.4%)
Pettersson et al, 2011	cRCT	9	58	Audit and feedback for MD and nurse, local resistance profiles	Prescribers and nurses	NR	UTI: Decreased prescribing by OR = 0.124 (95% CI 0.019 to 0.228)
Van Buul et al, 2015	Controlled before-after	8	10	QI process for NH MD and nurses for specific guidelines, audit, and feedback	Prescribers and nurses	NSC	UTI: OR = 0.74 (95% CI 0.39 to 1.40) RTI: 0.95 (95% CI 0.39 to 2.33)
Zabarsky et al, 2008	Before-after	30	1	MD and nursing interview and pocket cards	Prescribers and nurses	NR	ASB overtreatment: IRR 0.37 (0.19-0.72, $P = .02$)
Zimmerman et al, 2014	NRCT	8	12	Education sessions for nursing, prescribers, and families	Prescribers, nurses, residents, and their families	Decrease in 11.1 prescription per 1000 resident-days from baseline	NR

ASB, asymptomatic bacteriuria; ID, infectious disease team comprised of ID physician and pharmacist; IRR, incidence rate ratio; MD, physician; NR, not reported; NRCT, nonrandomized controlled trial; NSC, no significant change; OR, odds ratio; QI, quality improvement; RTI, respiratory tract infection.

Table 3
ASPs and Guideline Adherence

Author, Year	Study Design	Study Length (mo)	Number of NH	Intervention	Intervention Subjects	Results, Guideline Measured	Results, Treatment Adherent to Guideline?
Doernberg et al, 2015	Before-after, no control	7	3	ID team consult	Prescribers	LMC	NR
Fleet et al, 2014	cRCT	18	30	Nursing ASP form	Nurses	MCG, LMC	MCG: Relative increase in intervention NH compared to control NH 6.44 ($P = .004$) LMC: Relative increase 7.8% of preintervention to postintervention NH group, (no measure of variance reported)
Hutt et al, 2006	Controlled before- after	36	2	Nursing: conference, toolkit, pocket card MD: conference, pocket card, preprinted orders	Prescribers and nurses	NHAP management guidelines	5-point increase in overall compliance (no measure of variance reported)
Hutt et al, 2011	Controlled before-after	36	16	Nursing: conference, toolkit, pocket card MD: conference, pocket card, preprinted orders	Prescribers and nurses	NHAP Management Guidelines	NR
Linnebur et al, 2011	Controlled Before-After	36	16	Nursing: conference, toolkit, pocket card MD: NHAP conference, pocket cards, preprinted orders	Prescribers and nurses	NHAP management guidelines	Timing: 44% ($P = .0003$) increase in antibiotics administered within 4 hours of order Correct antibiotic: NSC Therapy duration: NSC
McMaughan et al, 2016	NRCT	12	12	Decision aid and IT support	Prescribers and nurses	LMC, high guidelines	Nonadherent antibiotics: High-fidelity NH OR = 0.35 (95% CI 0.16-0.76) for antibiotics Others: NR
Monette et al, 2007	cRCT	16	8	MD audit and guide	Prescribers, Pharmacist	Study Specific	Nonadherent antibiotics: OR = 0.36 (95% CI 0.18-0.73) for intervention compared to control
Naughton et al, 2001	cRCT	12	10	MD only (education, pocket cards) vs MD (education and pocket cards) and RN education	Prescribers vs prescribers *and* nurses	Study specific	Adherent antibiotics: Multidisciplinary arm increased correct antibiotics 31.8% ($P = .06$) whereas the prescriber-only arm had NSC
Pettersson et al, 2011	cRCT	9	58	Audit for MD and nurse, local resistance profiles	Prescribers and nurses	Study specific	NR
Van Buul et al, 2015	Controlled before-after	8	10	QI process for NH-specific guidelines, audit and feedback	Prescribers and nurses	Study specific	Adherence to guideline UTI with catheter: 15.9% (no measure of variance reported) UTI without catheter: 8.3% (no measure of variance reported) RTI: 0.8% (no measure of variance reported)

cRCT, cluster Randomized Controlled Trial; ID, infectious disease team comprised of ID physician and pharmacist; IT, information technology; LMC, Loeb minimum criterion; MCG, McGeer Criteria; MD, physician; NHAP, nursing home–acquired pneumonia; NR, not reported; NRCT, nonrandomized controlled trial; NSC, no significant change; QI, quality improvement; RN, registered nurse; RTI, respiratory tract infection.

Discussion

This systematic review did not find evidence that NH ASPs change the incidence of CDI, rates of hospitalizations or mortality. No study measured emergency department visits. The studies reviewed did, however, indicate that NH ASPs can change intermediate health outcomes by reducing the number of antibiotic prescriptions in the NH and improving adherence to recommended treatment guidelines. This contrasts with findings from studies assessing ASP in hospital settings; a recent Cochrane review found that ASPs in the hospital reduce both the number of days a patient receives antibiotics and length of hospital stay, without an apparent change in mortality.[48] Evidence suggests that ASPs in the hospital can also change local resistance patterns, thereby making infections more susceptible to antibiotics that are less broad spectrum,[49] but not patient mortality.[48]

Our review does not support or refute the concern that NH ASPs may increase the number of NH residents who die or experience morbidity from untreated infections. We found only one NH study that reported both the number of antibiotic prescriptions and the mortality rate[37]; this study found that an ASP reduced the number of antibiotic prescriptions without changing the overall mortality. We also found no change in CDI rates in the 2 studies measuring this outcome, one of which lasted 14 months,[31] the other 18.[35] Studies of ASPs in the hospital indicate that it may take as long as 5 years to change the incidence of CDIs,[50] so short study duration may have led to negative results in the NH studies published to date. Furthermore, both studies used an infectious disease consult team that made recommendations exclusively to prescribers. This ignores the role of caregivers in infection transmission in the NH. Because other studies in this review found positive changes in intermediate health outcomes among interventions that targeted nurses, residents, and/or families as well as prescribers,[32,37,41–44,51,52] broadening the consult team approach, as well as lengthening study length, might have achieved different outcomes.

There are significant limitations for this review, mostly related to the paucity of studies. Only 5 of the 14 studies were randomized controlled trials; other interventional trials were included because the literature in this area is scant. Many of the included studies had significant methodological limitations, as described in Appendix C. Only Naughton et al and Zimmerman et al ensured that their data abstractors were blinded to the NH allocation. The other 12 studies are at risk of selection, performance, and detection bias. Publication bias may also affect reported results. In addition, the overall heterogeneity of the studied populations, interventions, and staffing made our review challenging.

Given the importance of this topic, additional research evaluating ASPs in NH settings is clearly needed. All included studies had relatively small populations and short follow-up times when compared with research of hospital ASPs; these factors may be responsible for the lack of definitive findings on health outcomes. NH populations are generally smaller and less often acutely ill than hospital patients; so the ideal study to measure outcomes of ASPs in the NH may need to be longer in duration than hospital-based programs. To reduce risk of bias, future studies should consider using blinded data collectors and reviewers. Although our results indicate that ASP educational interventions involving the entire NH staff (prescribers, nursing staff, NH residents, and their families) can be effective in changing antibiotic prescribing practices, many studies were not so comprehensive. Further data regarding longer, comprehensive studies are, therefore, needed to establish more definitively the benefit of ASP programs on emergency department visits, hospitalizations, antibiotic resistance, and infection-specific mortality.

In conclusion, the evidence on the effectiveness of ASPs in NHs is encouraging but limited. These programs can reduce antibiotic prescriptions. This can, theoretically, improve health outcomes for NH residents, but results to date have not shown reductions in hospitalizations, emergency department visits, or CDI rates. ASPs are now mandated in the NH and more research is needed to determine whether and to what extent these complex programs will improve NH resident health and, if so, which program components are most effective.

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jamda.2017.06.019.

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