How to Impact antibiotic prescribing?

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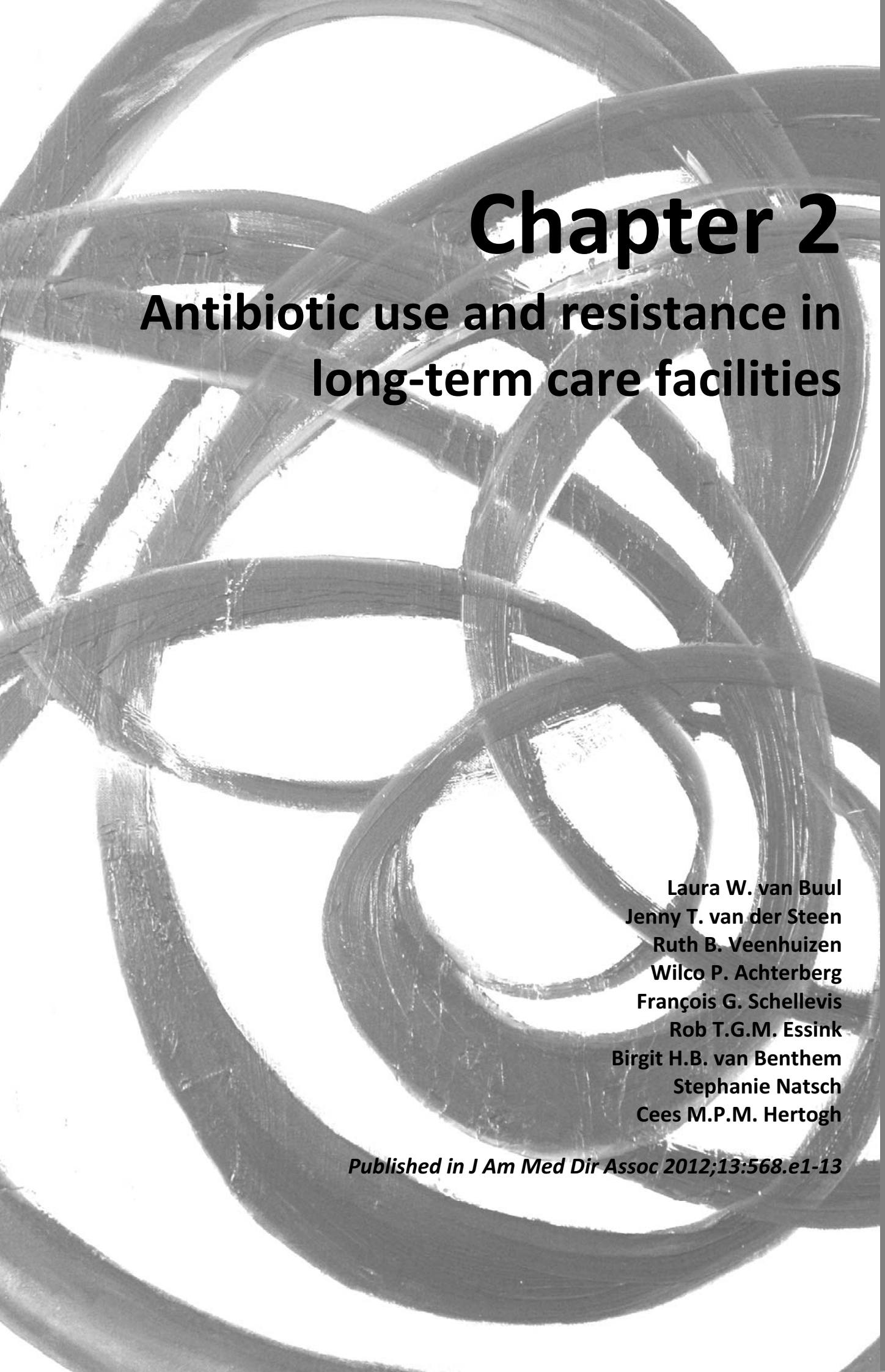

Chapter 2

Antibiotic use and resistance in long-term care facilities

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Abstract

Introduction: The common occurrence of infectious diseases in nursing homes and residential care facilities may result in substantial antibiotic use, and consequently antibiotic resistance. Focusing on these settings, this article aims to provide a comprehensive overview of the literature available on antibiotic use, antibiotic resistance, and strategies to reduce antibiotic resistance.

Methods: Relevant literature was identified by conducting a systematic search in the MEDLINE and EMBASE databases. Additional articles were identified by reviewing the reference lists of included articles, by searching Google Scholar, and by searching Web sites of relevant organizations.

Results: A total of 156 articles were included in the review. Antibiotic use in long-term care facilities is common; reported annual prevalence rates range from 47% to 79%. Part of the prescribed antibiotics is potentially inappropriate.

The occurrence of antibiotic resistance is substantial in the long-term care setting. Risk factors for the acquisition of resistant pathogens include prior antibiotic use, the presence of invasive devices, such as urinary catheters and feeding tubes, lower functional status, and a variety of other resident- and facility related factors. Infection with antibiotic-resistant pathogens is associated with increased morbidity, mortality, and health care costs.

Two general strategies to reduce antibiotic resistance in long-term care facilities are the implementation of infection control measures and antibiotic stewardship.

Conclusion: The findings of this review call for the conduction of research and the development of policies directed at reducing antibiotic resistance and its subsequent burden for long-term care facilities and their residents.

Introduction

Elderly people living in nursing homes and residential care facilities are at increased risk of acquiring infectious diseases. This is because of several age-related factors, such as pathologic alterations to the immune system, functional disability, the presence of chronic diseases, and the use of invasive devices, such as urinary catheters and feeding tubes.[1-3] In addition, several facility-related factors increase the risk of spread of infectious diseases, such as residents living in close proximity and participating in social activities, and serial close contact of dependent residents with staff and medical equipment.[1,3] Because of the presence of these biological and environmental factors, infectious diseases commonly occur in nursing homes and residential care facilities. An incidence rate ranging from 3 to 7 infections per 1000 resident-care days has been reported.[4-6] In addition, a point-prevalence rate that varies between 6.7% and 7.6% was found for infections in nursing home residents.[7] Whereas some studies report urinary tract infection (UTI) as the most common infectious disease in nursing homes and residential care facilities,[5,7-9] other studies report respiratory tract infection (RTI) as the most common infection.[4,10-12] Skin and soft tissue infections (SSTIs) also represent a frequently reported type of infection.[4,8,11]

The common occurrence of infectious diseases in nursing homes and residential care facilities may result in substantial use of antibiotics in these settings, which in turn may enhance the development of antibiotic resistance. Over the past few decades, several studies have been published with regard to antibiotic use and resistance in these facilities. In addition, strategies have been proposed to reduce antibiotic resistance. This article aimed to integrate this information by providing a comprehensive overview of the literature on antibiotic use, antibiotic resistance, and strategies to reduce antibiotic resistance, thereby focusing on long-term care facilities (nursing homes, where the main focus in on providing nursing care, and residential care facilities/assisted living facilities, where the main focus is on providing a “home” for residents). Based on this literature overview, we formulate implications for future research and policy development.

Methods

Relevant literature was identified by conducting a systematic search in the MEDLINE and EMBASE databases. We used the following key words for the search in the MEDLINE database: “residential facilities [MeSH Terms] AND (anti-bacterial agents [MeSH Terms] OR drug resistance, microbial [MeSH terms]).” For the search in the EMBASE database, the following key words were used: “(’nursing home’/exp OR ’residential home’/exp) AND (’antibiotic agent’/exp OR ’antibiotic resistance’/exp).” Only publications in English, focused on humans, and listed in the database before May 5, 2011, were considered.

Evaluating the articles resulting from the systematic search, 2 researchers (L.v.B. and J.v.d.S.) identified 3 “areas of interest”: antibiotic use, antibiotic resistance, and strategies to reduce antibiotic resistance. The same researchers developed general and “area of interest” specific inclusion and exclusion criteria, based on a set of articles they considered highly relevant (Box 1). The articles resulting from the search in the MEDLINE database were independently screened for inclusion by both researchers. In case of discrepancy in the judgment for relevance, the article was discussed until consensus was reached. Next, the articles resulting from the search in the EMBASE database were screened for relevance by the first researcher (L.v.B.); the second researcher (J.v.d.S.) screened a random sample of 10% and all articles that were included by the first researcher.

We additionally included articles by reviewing the reference lists of included articles, by hand searching Google Scholar, and by searching Web sites of relevant organizations (eg, the European Centre for Disease Prevention and Control, the American Medical Directors Association, the Society for Healthcare Epidemiology of America, the Association for Professionals in Infection Control and Epidemiology, and the World Health Organization).

Results

Figure 1 shows the flow diagram of the literature search. Of 978 articles retrieved with the systematic search in MEDLINE and EMBASE and of 18 articles identified otherwise (ie, by reviewing the reference lists of included articles, by hand searching Google Scholar, and by searching Web sites of relevant organizations), 159 met the inclusion criteria for 1 or more area(s) of interest (Box 1). Most of these 159 articles was allocated to the area of interest “antibiotic resistance” (n = 103). Fewer articles dealt with “antibiotic use” (n = 44) or “strategies to reduce antibiotic resistance” (n = 16). Three articles that met the inclusion criteria were not cited because of difficulties interpreting results owing to an inadequate description of methods. Most of the 156 included articles were original articles (n = 107). Other types of articles were reviews (n = 30), letters (n = 10), reports (n = 3), editorials (n = 3), and guidelines (n = 3).

A high number of hits (142,583) was retrieved in MEDLINE for the combination of MeSH terms: “anti-bacterial agents” OR “drug resistance, microbial.” After adding the MeSH term “residential facilities,” the number of hits decreased to 469 (0.33% of total). Similarly, a decrease from 398,900 to 699 hits (0.18% of total) was observed in the number of hits retrieved with the search in EMBASE when the key words “’nursing home’/exp OR ’residential home’/exp” were added. Overall, 0.22% (1168/541,483) of the MEDLINE and EMBASE hits on antibiotics and antibiotic resistance focus on long-term care facilities.

Box 1. Inclusion criteria for articles identified with the systematic literature search.

General inclusion criteria:
- Articles focusing on the following long-term care settings: nursing homes, assisted living and/or residential care facilities.

General exclusion criteria:
- Articles focusing on other long-term care settings, such as home care, (geriatric wards in) hospitals, and orphanages.
- Articles focusing on elderly persons in general.
- Articles focusing on subgroups of the nursing home/assisted living/residential care facility population (eg, residents with a specific condition (such as pneumonia or urinary tract infection), residents who were admitted to a hospital, and specific cases (case reports). An exception is the subarea of interest "appropriateness of antibiotic prescribing/use" (below), for which the subgroups "residents with dementia" and "residents with end-stage-disease" were eligible for inclusion.
- Articles focusing on antimicrobial agents groups other than "antibiotics" (ie, antivirals, antifungals, or antiparasitics).
- Letters, editorials and author comments, unless new empirical data were presented or a systematic literature review was provided.
- Research protocols.
- Articles not available in public domain.

For each article that met the above criteria, the area(s) of interest was/were determined. If the area of interest was one or more of those described below, the article was judged for relevance based on the criteria described for the respective area(s) of interest.

Area of interest 1: Antibiotic use

Included:
- Articles with a focus on antibiotic prescribing/use.
- Articles addressing at least one of the following subareas of interest:
    - Prevalence/incidence of antibiotic prescribing/use: Articles were included in the overview table of prevalence/incidence of antibiotic use in long-term care facilities if (1) these were primary research articles, (2) the antibiotic prescribing/use was measured on the resident level, (3) sufficient methodological information was available to interpret the findings, and (4) the prevalence/incidence was measured without or before the implementation of an intervention.
    - Appropriateness of antibiotic prescribing/use

Excluded:
- Articles focusing on the management of infectious diseases in general.
- Articles describing randomized clinical trials (RCT) that examined the effectiveness of one type of antibiotic versus another.

Area of interest 2: Antibiotic resistance

Included:
- Articles focusing on the epidemiology, prevalence/incidence, risk factors and/or consequences of antibiotic resistance.

Excluded:
- Articles focusing on the molecular biology or molecular epidemiology of resistant pathogens (eg, typing of resistant strains), with no representative data on incidence/prevalence at the facility level.
- Outbreak reports of infections with antibiotic-resistant pathogens, as these do not provide a general overview of antibiotic resistance in the long-term care setting.
- Articles focusing on community-acquired resistance (eg, by sampling residents at admission to a long-term care facility).

Area of interest 3: Strategies to reduce antibiotic resistance

Included:
- Articles providing an overview of strategies to decrease antibiotic resistance.

Excluded:
- Articles focusing on the prevention of emergence/spread of specific resistant pathogens (eg, MRSA).
- Articles focusing on specific interventions to reduce antibiotic resistance (eg, hand washing).
- Articles focusing on infection control in general, without a specific focus on the control of infections with resistant pathogens.

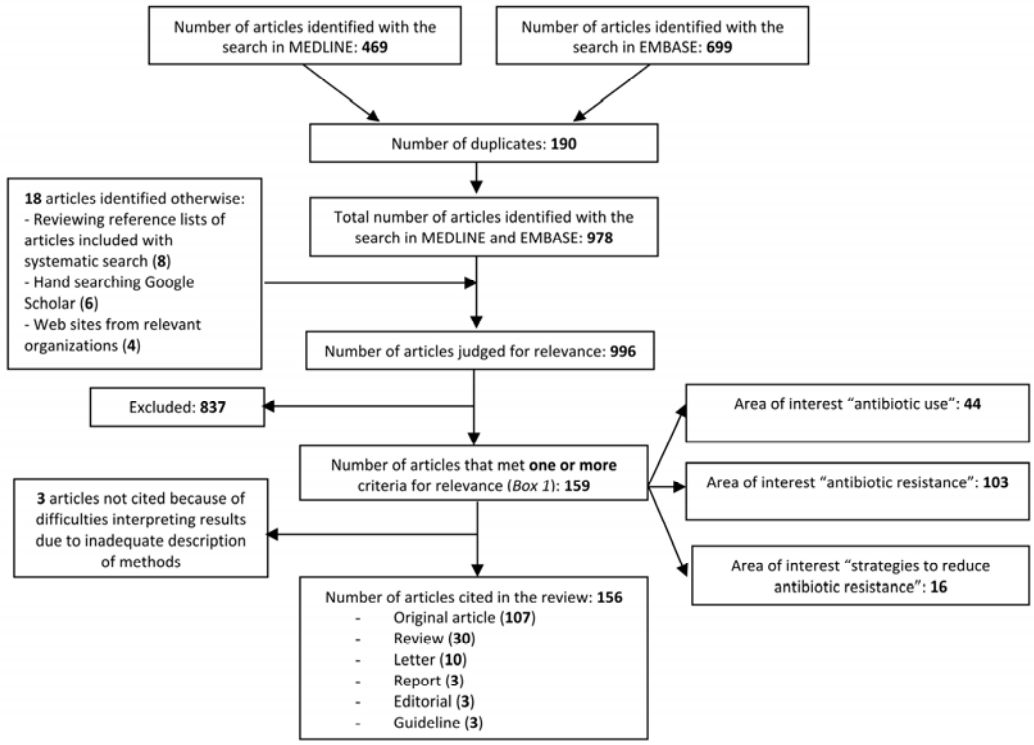

Figure 1. Flow diagram of the literature search.

Antibiotic use in nursing homes and residential care facilities

Incidence/prevalence of antibiotic use

Table 1 presents an overview of 26 studies that investigated the incidence and/or prevalence of antibiotic use among residents in long-term care settings (inclusion criteria: Box 1). Of these, 22 were identified with the systematic search and 4 were identified otherwise.

In the United States and Canada, an incidence rate of 4.0 to 7.3 antibiotic courses per 1000 resident-days has been reported between 1991 and 2008.[13-17] With regard to prevalence, between 47% and 79% of long-term care facility residents in the United States, Canada, and Italy have been reported to receive at least 1 course of antibiotics during a study period of 1 year.[14,15,17-22] In addition, 3 studies from the United States, Sweden, and Belgium reported that between 77% and 88% of nursing home residents with infectious episodes were prescribed antibiotics.[12,23,24] Further, 2 older cross-sectional studies conducted in the United States showed a point-prevalence rate of antibiotic use in nursing homes of 8.0% and 8.6%.[17,25] Studies conducted in European countries reported a point-prevalence rate between 4.8% and 15.2%.[7,8,26-28] The infectious diseases for which antibiotics are most commonly prescribed in the long-term care setting include UTIs, RTIs, and SSTIs. UTI is the most frequently reported indication for antibiotic prescribing, accounting for 32% to 66% of the prescriptions in nursing homes. RTI accounts for 15% to 36% of the prescriptions and SSTI for 13% to 18%.[5,13-15,17,19,23-26,29-33]

Table 1. Studies on the prevalence/incidence of antibiotic use in long-term care facilities.

Author / reference	Published	Study design	Study setting	Study population	Follow-up	Outcome measure	Findings
Prevalence/incidence of antibiotic use reported for residents							
Zimmer et al[25]	1986	Cross-sectional study	42 skilled nursing facilities in the United States	1748 residents	-	Prevalence of antibiotic use	• 8.6% of the residents (n = 151) received antibiotics on the day of the survey
Jacobson and Strausbaugh[33]	1990	Prospective observational study	A nursing home care unit at a Department of Veterans Affairs Medical Center in the United States	231 residents	9 months	Prevalence of antibiotic use	• 51% of the residents (n = 188) received at least 1 course of antibiotics
Warren et al[17]	1991	Retrospective study	52 nursing homes in the United States	3899 residents	12 months	Prevalence/ incidence of antibiotic use	• The prevalence of antibiotic use on the first day of study was 8% (n = 312 residents) • 54% of the residents (n = 2105) received at least 1 antibiotic course during the study period • The incidence over 12 months was 4.6 antibiotic courses per 1000 resident-days
Lee et al[32]	1992	Prospective observational study	7 nursing homes in the United States	1031 residents	3 months (3 facilities) or 4 months (4 facilities)	Prevalence of antibiotic use	• 33% of the residents (n = 340) received at least 1 course of antibiotics
Yakabowich et al[20]	1994	Quasi-experimental study	88 nursing homes in Canada	6848 residents	3 years (1 year before an intervention was implemented and 2 years thereafter)	Prevalence of antibiotic use	• 47% of the residents (n = 3219) received antibiotics in the year before the intervention was implemented (this percentage remained the same in the 2 years after the intervention was implemented)
Montgomery et al[19]	1995	Retrospective study	Approximately 100 nursing homes in a province in Canada	2093 residents	12 months (1986)	Prevalence of antibiotic use	• 57% of the residents (n = 1201) received at least 1 course of systemic antibiotics, 26% (n = 543) received at least 1 course of topical antibiotics, and 16% (n = 345) received at least 1 course of ophthalmic antibiotics. Overall, 70% of the residents (n = 1455) received at least 1 course of any antibiotic type
Lee et al[5]	1996	Prospective observational study	One private community skilled nursing facility in the United States	585 residents	20 months	Prevalence of antibiotic use	• 54% of the residents (n = 316) received 1 or more antibiotic courses
Mylotte[15]	1996	Prospective observational study	A skilled nursing facility located within a public, university-affiliated hospital in the United States	156 residents	12 months	Prevalence/ incidence of antibiotic use	• 71% of the residents (n = 111) received at least 1 course of antibiotics (in 1989) • The incidence of antibiotic use was 6.1 antibiotic courses per 1000 resident-days (in 1989)

Author / reference	Published	Study design	Study setting	Study population	Follow-up	Outcome measure	Findings
Mylotte[16]	1999	Prospective observational study	4 long-term care facilities in the United States	2 facilities with 120 beds and two facilities with 160 beds	20 to 26 months (varying per facility)	Incidence of antibiotic use	• The mean incidence of antibiotic use varied between 4.0 and 7.2 antibiotic courses per 1000 resident-days
Loeb et al[14]	2001	Prospective observational study	22 facilities in Canada (10 chronic care facilities and 12 acute care hospitals with chronic care beds)	3656 residents	12 months	Prevalence/ incidence of antibiotic use	• 66% of the residents (n = 2408) received at least 1 course of antibiotics • The mean incidence across facilities was 7.3 antibiotic courses per 1000 resident-days (facility range: 2.9 to 13.9 antibiotic courses per 1000 resident-days)
Warshaw et al[34]	2001	Retrospective study	Residents of nursing homes in the United States	A sample of 1306 elderly who spent some time in nursing homes	36 months	Prevalence of antibiotic use	• The prevalence of antibiotic use was 67% (n = 874 elderly)
Loeb et al[21,35]	2003, 2004	Prospective observational study	50 nursing homes in Canada and the United States	9156 residents	12 months	Prevalence of antibiotic use	• 79% of the residents (n = 7233) received 1 or more antibiotic courses
Moro et al[28]	2007	Point-prevalence survey	15 nursing homes and 34 residential care facilities in Italy	1926 residents (329 in nursing homes and 1597 in residential care facilities)	-	Prevalence of antibiotic use	• 12.1% of the residents (n = 234) received at least 1 course of systemic antibiotics on the day of the survey
Benoit et al[13]	2008	Retrospective study	73 nursing homes in the United States	1780 residents	6 months	Prevalence/ incidence of antibiotic use	• 42% of the residents (n = 2017) received 1 or more antibiotic courses • Overall, residents received a mean of 4.8 antibiotic courses per 1000 resident-days
Brugnaro et al[22]	2009	Retrospective study	2 long-term care facilities in Italy	551 residents	12 months	Prevalence of antibiotic use	• 63% of the residents (n = 349) received at least 1 systemic antibiotic course
Garazi et al[18]	2009	Cross-sectional study	A long-term care facility in the United States	160 residents	12 months	Prevalence of antibiotic use	• 77.7% of the residents (n = 124) received at least 1 course of antibiotics
Blix et al[26]	2010	Point-prevalence survey	44 nursing homes in Norway	1473 residents	-	Prevalence of antibiotic use	• 15.2% of the residents (n = 224) received antibiotics on the day of survey
Eikelenboom-Boskamp et al[7]	2011	Point-prevalence survey	17, 15 and 24 nursing homes (in 2007, 2008 and 2009, respectively) in the Netherlands	1275, 1323 and 1772 residents (in 2007, 2008 and 2009, respectively)	-	Prevalence of antibiotic use	• On average, 6.6% of the residents received antibiotics on the day of the survey

Author / reference	Published	Study design	Study setting	Study population	Follow-up	Outcome measure	Findings
McClean et al[27]	2011	Point-prevalence survey	Part of the European Surveillance of Antimicrobial Consumption survey: 85 nursing homes in 15 European countries and 2 UK administrations	10,388 residents in April 2009 and 9430 residents in November	-	Prevalence of antibiotic use	• 6.2% of the residents (n = 645) and 4.8% of the residents (n = 450) received antibiotics on the day of the survey in April and November, respectively • Prevalence rate range: in April from 1.4% in Germany and Latvia to 19.4% in Northern Ireland and in November from 1.2% in Latvia to 13.4% in Finland
Prevalence/incidence of antibiotic use reported for infectious episodes among residents							
Beck-Sague et al[23]	1994	Prospective observational study	13 nursing homes in the United States	1754 residents	6 months	Prevalence of antibiotic use	• Of the 835 infectious episodes that occurred during the follow-up period, 77% (n = 646) were treated with antibiotics
Moens et al[12]	1996	Retrospective study	35 nursing homes in Belgium	2595 residents	1 month	Prevalence of antibiotic use	• Of the 257 residents with an infection, 88% (n = 226) were treated with antibiotics.
Pettersson et al[24]	2008	Cross-sectional study	58 nursing homes in Sweden	3002 residents	3 months	Prevalence/ incidence of antibiotic use	• Of the 889 infectious episodes that occurred during the follow-up period, 84% (n = 769) were treated with antibiotics • The incidence of antibiotic use was 1 treatment per resident per year
Prevalence/incidence of antibiotic use reported for specific types of infectious diseases in residents							
Mott and Barker[36]	1988	Retrospective study	A skilled nursing facility in the United States	110 residents	7 years	Prevalence of antibiotic use in 3 infection types	• Of 102 residents who were treated in the nursing home for RTI, 79% (n = 81) received antibiotics • Of 66 residents who were treated in the nursing home for UTI, 89% (n = 59) received antibiotics • Of 31 residents who were treated in the nursing home for skin infections, 90% (n = 28) received antibiotics
Eriksen et al[8]	2004	2 annual point-prevalence surveys	Between 203 and 323 long-term care facilities in Norway	Between 11,465 and 17,174 residents	-	Prevalence of antibiotic use for the 4 most common infections in long-term care settings	• The prevalence rate range of antibiotic use was 5.5% - 5.9%

Factors associated with antibiotic use

We identified factors associated with antibiotic use in long-term care facilities on the resident level, facility level, and geographical level. On the resident level, the use of invasive devices, such as urinary catheters or feeding tubes, was significantly associated with antibiotic use.[13,35] Furthermore, higher rates of antibiotic use were found in residents with higher probabilities of nursing home discharge and in residents receiving extensive medical or rehabilitation services.[13] A factor on the facility level is the facility type: Moro et al[28] reported a higher prevalence of antibiotic use in residents of nursing homes (13.1%) than in residents of residential care facilities (4.9%) in Italy. In addition, Loeb et al[35] found higher rates of antibiotic use in facilities with more health care aides per 100 residents. This finding may be explained by confounding, as facilities with more health care aides may accommodate residents who require more care. On the geographical level, antibiotic use has been reported to differ within and between countries. Blix et al[29] reported large variation in antibiotic use among 133 nursing homes in Norway: from 4 to 44 defined daily doses per 100 bed days. Substantial variation in incidence of antibiotic use was also found between long-term care facilities in the United States (8.0-14.8 antibiotic courses per 1000 resident care days per month).[37] With regard to differences in antibiotic use between countries, Loeb et al[35] reported that nursing homes in the United States prescribed significantly more antibiotics than Canadian nursing homes. Furthermore, The European Centre for Disease Prevention and Control funded 2 related projects (the European Surveillance of Antimicrobial Consumption [ESAC] project and the Healthcare-Associated Infections in Long-term care Facilities [HALT] project) that reported substantial variation in antibiotic use among European nursing homes. Although their results are derived from a high number of nursing homes (304 and 117 respectively) in a high number of countries (19 and 13 respectively), drawing conclusions was complicated by the fact that a disproportionate number of cases was provided by nursing homes in only 3 countries (ie, Belgium, Italy, and Northern Ireland).[38,39] However, weighted analyses (in this case by randomly selecting 5 nursing homes per country) resulted in similar conclusions: there was large variation in antibiotic prescription rates among European countries, ranging from 1.4% in Germany and Latvia to 19.4% in Northern Ireland in April 2009 and from 1.2% in Latvia to 13.4% in Finland in November 2009.[27]

Appropriateness of antibiotic use

Diagnosing infectious diseases can be challenging in the long-term care setting for several reasons. Residents often present with atypical symptoms, have several chronic diseases (eg, diabetes or heart failure), may have hearing and speech difficulties, and may be cognitively impaired. In addition, diagnostic resources are often limited and obtaining appropriate specimens from residents may be difficult.[2,9,13,19,40-42] As a result, the prescribing of antibiotics often occurs empirically in the long-term care setting. The appropriateness of this empiric use of antibiotics, either in terms of whether antibiotics are indicated or in terms of selecting the right drug regimen,

dosage, or treatment duration, has been investigated in several studies, thereby using various criteria. Zimmer et al[25] reviewed the use of antibiotics in more than 2000 nursing home patients and judged evidence to start antibiotic treatment as adequate in 62% of cases. This judgment was based on criteria for appropriateness that had been developed by an expert panel. In another study, only 49% of 120 antibiotic prescriptions were considered appropriate. The primary reason for rating a prescription as not appropriate in this study was that a more effective antibiotic agent was recommended by infectious disease specialists and a hospital pharmacist (ie, in 71% of the cases).[30] The same percentage of appropriate antibiotic prescriptions (49%) was found by Loeb et al,[14] with the least appropriate prescriptions in UTI (28%) and more appropriate prescriptions in RTI (58%) and SSTI (65%). In the latter study, appropriateness of antibiotic prescribing was judged based on fulfillment of diagnostic criteria derived from definitions of infections in long-term care facilities, as developed by McGeer et al.[43] Clinical situations in which antibiotics are often prescribed inappropriately are viral respiratory infections and asymptomatic bacteriuria, whereas antibiotic treatment for these conditions is not recommended.[40] Warren et al[17] reported that of more than 2000 antibiotic prescriptions in nursing home residents, 13% were for viral respiratory infection and 9% for asymptomatic bacteriuria. The same percentage of inappropriate prescriptions for asymptomatic bacteriuria was found in another study.[19]

A specific domain in the determination of appropriateness of antibiotic prescribing is the use of antibiotics at the end of life. As early as 1979, it was observed that antibiotics were withheld in nursing home residents with end-stage disease who developed fever (ie, a proxy for an infectious disease).[44] There is an ongoing debate about the appropriateness of antibiotic prescribing in patients at the end of life who develop RTIs, as the effect on neither life prolongation nor discomfort relief is clear.[45-48]

Adverse effects

Even when antibiotics are prescribed appropriately, they pose a risk in terms of adverse effects. This risk has been reported to be elevated in the elderly.[49,50] As older persons often use multiple drugs, adverse effects owing to drug interactions can be an issue. In addition, elderly are more susceptible to adverse drug reactions as a result of decreased kidney and liver function and the presence of multimorbidity. Furthermore, elderly who are being treated or have recently been treated with antibiotics are at increased risk of *Clostridium difficile*-associated diarrhea.[9,45,49] Nevertheless, the greatest concern in terms of adverse consequences of antibiotic use is the development of antibiotic resistance, which potentially causes both an individual burden and a threat for public health.[9,45,49,51]

Antibiotic resistance in nursing homes and residential care facilities

Incidence and prevalence of antibiotic resistance

We identified 60 studies in 14 countries that investigated the incidence or prevalence of antibiotic-resistant pathogens in long-term care facilities.[18,22,52-109] We found that colonization or infection of residents has been studied most commonly for methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug resistant gram-negative bacteria (MDRGN), and vancomycin-resistant *Enterococci* (VRE). Trick et al[103] reported colonization with at least 1 of these resistant pathogens in 43% of the persons residing in a long-term care facility (n = 117) in the United States. Other studies from the United States reported MRSA colonization prevalence rates ranging from 8% to 82% between 1991 and 2000, and from 11% to 59% between 2001 and 2011.[18,53,54,61,73,75,76,78,81,83,86,89,91,93,98,99,102] With regard to MDRGN and VRE, prevalence rates ranging from 23% to 51%[63,86,91,96] and from 1% to 19%[60,86,91] were reported, respectively. O'Fallon et al[87] found that 31% of long-term care facility residents (n = 135) were colonized by at least 1 multidrug-resistant gram-negative organism at baseline of a cohort study. They also found that 39% of the residents acquired at least 1 of these organisms during the study period of 1 year, many of whom (62%) had not been colonized at baseline.

European studies have also addressed antibiotic resistance. The highest prevalence rate of MRSA colonization (38%) has been reported among residents (n = 109) of long-term care facilities in France,[62] and prevalence rates varying between 17% and 22% were found in nursing home residents (159 < n < 3037) in the United Kingdom.[52,65,97] A lower MRSA colonization prevalence rate has been reported in Italy (8% and 19%, n = 551 and n = 88 respectively),[22,82] Slovenia (9% and 12%, n = 107 and n = 127 respectively),[56,106] Ireland (9% and 10%, n = 743 and n = 754 respectively),[88] and Belgium (5%, n = 2857 and n = 2908).[69,100] Prevalence rates were substantially lower in studies from the Northern European countries Germany (1.1%, n = 3236),[105] Finland (0.9%, n = 213),[71] and the Netherlands (0.2%-0.8%, 204 < n < 89,573 [the sample size of 89,573 is based on the number of isolates analyzed by laboratories; the other reported sample sizes are based on the number of residents]).[59,66,67,101,107] Colonization with resistant pathogens other than MRSA during residency in long-term care facilities has been reported in France (an increase in extended-spectrum β-lactamase-producing pathogens in the period 1996-2006),[84] Ireland (prevalence of multidrug resistant Escherichia coli: 40.5% of the residents [n = 294]),[95] and Germany (prevalence of VRE: 4.3% of the residents [n = 188]).[110]

Risk factors for colonization or infection with antibiotic-resistant organisms

Table 2 presents an overview of resident and facility-related characteristics that were identified as significant risk factors for colonization or infection with antibiotic-resistant organisms in 2 or more articles. At the resident level, prior antibiotic treatment was most frequently reported as a risk factor for colonization or infection

Table 2. Risk factors* for becoming colonized or infected with antibiotic-resistant organisms in long-term care facilities.

		No. of articles in which reported, by type of analysis (+ references)		
Risk factor	**No. of articles in which reported**	**Bivariable†**	**Multivariable†**	**Review**
Resident factors				
Prior antibiotic treatment	35	13[18,21,70,96,103,105,116-122]	12[62,80,86,87,100,109,123-128]	10[2,41,42,113,115,129-133]
Presence of invasive devices (eg, urinary catheter, feeding tube)	29	7[102,103,111,118,119,121,134]	9[62,94,96,100,105,125,127,128,135]	13[2,41,42,113,115,129-133,136-138]
Lower functional status	26	8[53, 68, 77, 96, 102, 109, 111, 139]	7[86,103,105,111,121,125,140]	11[2,41,113,115,129,130,132,133,136-138]
Prior hospitalization	18	10[18,65,68,70,94,117,120-122,141]	3[100,105,123]	5[41,115,131,133,138]
Presence of decubitus ulcers	15	5[102,105,111,117,142]	5[86,100,120,126,134]	5[41,113,115,132,138]
Presence of wounds	14	5[53,62,70,102,142]	1[105]	8[2,41,113,129,131,132,136,137]
Prior colonization by antibiotic-resistant organisms‡	10	3[18,103,118]	3[96,134,143]	4[2,41,113,129]
Urinary incontinence	7	2[87,139]	1[134]	4[41,113,115,138]
Presence of comorbidities				
- Diabetes mellitus and/or peripheral vascular disease	7	2[102,120]	1[94]	4[2,41,113,115]
- 'Underlying illness'	4	-	-	4[41,42,130,138]
- Renal disease/ insufficiency	3	2[18,102]	-	1[113]
- Comorbidities in general	3	1[134]	-	2[41,129]
- Prior pneumonia	3	1[102]	-	2[41,113]
- Inflammatory bowel disease	2	1[102]	-	1[113]
Male sex	5	1[142]	3[94,120,134]	1[113]
Fecal incontinence	4	1[139]	1[86]	2[115,138]
Higher intensity of nursing care	4	-	1[109]	3[41,129,133]
Length of stay in the facility				
- 'longer'	3	-	-	3[41,42,113]
- ≥ 4 y	1	-	1[86]	-
- 1-4 y	1	-	1[100]	-
- < 6 mo	2	2[105,120]	-	-
- 'shorter' when comparing interquartile ranges	2	2[103,141]	-	-
Higher age	3	1[120]	-	2[113,115]
Lower cognitive status	2	-	1[120]	1[130]
Facility factors				
Lack of infection control policy	5	-	-	5[42,113,115,138,144]
Higher patient-to-staff ratio	5	-	-	5[42,113,115,138,144]
Frequent staff-turnover	4	-	-	4[113,115,138,144]
Staffing by nonprofessional personnel	4	-	-	4[113,115,138,144]
Facility size				
- Large	4	-	-	4[41,113,115,133]
- Medium	1	-	1[105]	-
Higher number of residents per bedroom	3	-	1[100]	2[42,113]
More frequent resident-to-resident contact	2	-	-	2[138,144]
Limited facilities for hand washing	2	-	-	2[42,113]

* Included in this overview are risk factors that were reported to be significant in articles that investigated the risk factor by bivariable (column 3) or multivariable analysis (column 4), and by systematic and nonsystematic review articles (column 5).

† Risk factors that were identified in a study by both bivariable and multivariable analysis are listed only in the column "multivariable".

‡ Either colonization/infection with an antibiotic-resistant organism is a risk factor for (another) infection or colonization with one antibiotic-resistant organism is a risk factor for colonization with another antibiotic-resistant organism.

with antibiotic-resistant organisms, followed by the presence of invasive devices, such as urinary catheters or feeding tubes. Another frequently reported risk factor is lower functional status, which may be explained by the fact that residents with a lower functional status have more frequent contact with health care workers and therefore more opportunities for acquisition of antibiotic-resistant organisms.[86,103,105] Other risk factors that are related to the physical status of residents include the presence of decubitus ulcers, the presence of wounds, urinary incontinence, the presence of comorbidities, and fecal incontinence. In addition, several articles report prior

hospitalization as a risk factor, which suggests that the hospital is a source of antibiotic-resistant organisms. Nevertheless, Hsu[111] did not find an association between prior hospitalization and MRSA carriage in nursing home residents and argued that nursing homes serve as reservoirs of antibiotic-resistant pathogens as well. This was supported by other authors, who identified nursing home stay as a risk factor for colonization with MRSA at hospital admission.[112-114] Both "longer" and "shorter" length of stay in long-term care facilities have been associated with increased risk of colonization or infection with antibiotic-resistant organisms. Prolonged duration of stay in the facility may increase the likelihood of acquisition of antibiotic-resistant organisms from other colonized residents or health care workers.[86] With regard to the risk factor "shorter length of stay in the facility," von Baum et al[105] argue that this association may be confounded by prior hospitalization of residents admitted to a long-term care facility. Other reported risk factors on the resident level include prior colonization by antibiotic-resistant organisms, male sex, higher intensity of nursing care, higher age, and lower cognitive status.

A lack of infection control policy is the most frequently reported facility-related factor that is associated with an increased risk of becoming colonized or infected with antibiotic-resistant organisms. This includes a lack of hygienic measures, such as hand washing, the use of gloves, cough etiquette, and barrier precautions.[115] Other factors on the facility level include a number of factors related to staffing (ie, higher patient-to-staff ratio, frequent staff turnover, and staffing by nonprofessional personnel), an increased number of residents per bedroom, increased resident-to-resident contact, increased facility size, and limited facilities for hand washing.

Consequences of infection with antibiotic-resistant organisms

We identified consequences of infection with antibiotic-resistant organisms for public health, long-term care facilities, and residents. Croft et al[145] describe that the general impact of antibiotic resistance on public health and its costs are unknown owing to the complexity of estimating the burden of the problem. Nevertheless, experts agree on the assumption that antibiotic resistance results in increased costs and worse outcomes through higher morbidity and mortality. For long-term care facilities, it has indeed been described that morbidity resulting from infection with antibiotic-resistant organisms results in increased costs for treatment of residents, more frequent hospitalization, and the implementation of measures to control transmission of the resistant organism within the facility (eg, because of performing isolation procedures and screening of residents and staff).[113,146,147] On the resident level, infection with antibiotic-resistant organisms has been associated with higher mortality compared with infection with antibiotic-susceptible organisms.[87] In addition, Suetens et al[147] reported a significantly higher risk of 36-month mortality in residents with MRSA colonization at baseline than in non-colonized residents, after adjustment for comorbidities and other potential confounders. This association was significant only in residents with advanced cognitive impairment, which may be explained by

different therapeutic approaches in this population, such as less frequent hospital referral and withholding of treatment in residents with severe dementia. Another consequence reported on the resident level involves quality of life. Loeb et al[148] investigated the quality of life of a small number of residents (n = 14) colonized with multiresistant organisms and found a trend toward more depressive symptoms, dysfunctional behavior, dependency in activities of daily living, and lower health-related quality of life. This trend toward worse quality of life may be related to isolation precautions, which may impede opportunities for residents to socialize or participate in group activities.[113,148]

Strategies to reduce antibiotic resistance in long-term care settings

Implementation of infection control measures

Infection control refers to measures directed at preventing or decreasing the emergence and spread of infectious diseases. This results in a lower incidence of infectious diseases and antibiotic use, and in turn to a reduced emergence and spread of antibiotic-resistant organisms. Examples of infection control measures in the long-term care facility include hand washing, the use of gloves, disinfection of surfaces, cough etiquette, appropriate ventilation, immunization of residents, and minimal use of invasive devices, such as urinary catheters and feeding tubes.[1,21,113,131,149-151] Furthermore, important components of infection control programs include the assignment of a well-trained infection control practitioner to head the program, the assignment of an infection control committee, the dissemination of an infection control plan, staff education, ensuring sufficient administrative and financial support to undertake core infection control functions, and the surveillance of antibiotic-resistant organisms and antibiotic use.[149-152] The implementation of infection control programs, however, can be challenging in long-term care settings. Lack of personnel, high workload, insufficient training, and a lack of resources are examples of factors that can impair the implementation of infection control measures.[1,6,103,113,153-155]

Policy initiatives for infection control have been developed specific to the long-term care setting. A number of guidelines on infection control in long-term care facilities have been published, such as by the American Medical Directions Association, and by the Society for Healthcare Epidemiology of America and the Association for Professionals in Infection Control and Epidemiology.[156,157] In Europe, the recently concluded HALT project investigated the distribution and characteristics of infection control programs in 117 nursing homes in 13 European countries, and found that there is room for improvement with regard to infection control policies. For example, only a minority of the nursing homes had assigned an infection control committee (30.4%) or an infection control practitioner (38.1%).[39]

Improving the rational use of antibiotics (antibiotic stewardship)
Warnings not to abuse antibiotics date back to Alexander Fleming in the 1940s.[158] More recently, several initiatives have been taken in promoting rational antibiotic use in long-term care settings. In 2000, Nicolle et al[9] published a guideline with recommendations on antibiotic prescribing for RTI, UTI, SSTI, diarrhea, and fever of unknown origin. In another guideline, published by Loeb et al,[40] minimum criteria for the initiation of antibiotics in long-term care facilities were formulated. Both guidelines represent highly cited works. In addition to adherence to guidelines on antibiotic prescribing, other elements of antibiotic stewardship programs include physician education on antibiotic prescribing, providing feedback on prescriptions (eg, antibiotic use review by a pharmacist), monitoring appropriateness of antibiotic prescribing, providing resources for obtaining cultures for diagnosis, using restricted formularies, using antibiotic order forms, and limiting the use of broad-spectrum antibiotics.[9,25,131,152,159] The involvement of nursing staff is considered important for the success of antibiotic stewardship programs, as the information on which physicians base treatment decisions is often derived from nursing assessments.[132,154] At the physician level, factors that need to be addressed in the successful implementation of antibiotic stewardship programs include knowledge and preferences regarding antibiotic use, and perceived expectations of the patient and the family of the patient with regard to antibiotic treatment.[160]

In the European setting, the availability of antibiotic stewardship resources was investigated by the ESAC project group. Data were obtained from 260 nursing homes in 17 countries. A finding that suggests room for improvement is that no specific guidelines for rational use of antibiotics in the long-term care setting were available in 50% of the nursing homes. Furthermore, a restricted antibiotic formulary was used in only 16.2% of the facilities and the same percentage of facilities did not provide regular training of physicians on appropriate antibiotic prescribing.[38]

Discussion

The aim of this article was to provide an overview of the literature for the long-term care setting (nursing homes and residential care facilities/assisted living) on each of the following topics: antibiotic use, antibiotic resistance, and strategies to reduce antibiotic resistance. This overview demonstrated that the use of antibiotics in long-term care facilities is substantial and that antibiotic resistance is common. It also suggested that antibiotic resistance has an impact on individuals, facilities, and public health in terms of quality of life, morbidity, mortality, and health care costs. In addition, this overview identified a variety of risk factors for colonization or infection with antibiotic-resistant organisms in residents of long-term care facilities. Furthermore, it described 2 general strategies to reduce antibiotic resistance in the long-term care setting: the implementation of infection control measures and improving the rational use of antibiotics (ie, antibiotic stewardship).

Remarkably, fewer than 0.3% of the MEDLINE and EMBASE publications on antibiotic use and antibiotic resistance focus on long-term care facilities. Research on these topics may be relatively underdeveloped in the long-term care setting, compared with other health care settings, such as the hospital and primary care. Of the articles identified for the long-term care setting, more were allocated to the area of interest "antibiotic resistance" (103/159) than to the area of interest "antibiotic use" (44/159), which indicates that relatively more research focuses on the former topic. A broad interest in antibiotic resistance concurs with the World Health Organization's theme of World Health Day 2011, during which the agency called on governments to undertake action with regard to the resistance problem in all health care settings under the slogan "no action today means no cure tomorrow."[161]

The ESAC project reported large variation among countries in antibiotic use for nursing home residents. The highest prevalence rates were found for northern European countries (ie, Northern Ireland and Finland).[27] This is a remarkable finding, as in primary care settings, southern European countries account for the highest antibiotic use.[162]

Interestingly, some authors report that only 49% to 62% of the antibiotics in long-term care facilities are prescribed appropriately[14,25,30]; however, these studies based their findings on different criteria for judging appropriateness of antibiotic prescribing. The lack of a universally accepted definition for diagnosing infectious diseases and subsequent appropriate prescribing of antibiotics,[163] in combination with the small number of studies conducted, complicates drawing conclusions on the appropriateness of antibiotic prescribing in long-term care facilities.

In addition to prior antibiotic treatment and presence of invasive devices, such as urinary catheters and feeding tubes, lower functional status is one of the most frequently reported risk factors for becoming colonized or infected with antibiotic resistant organisms in long-term care facilities. Some of the authors who identified this association by multivariable analysis suggest that this may be because residents with lower functional status have more frequent contact with health care workers.[86,103,105] Another explanation, which we did not encounter in the retrieved literature, may be that residents with lower functional status are more vulnerable for the acquisition of infections because of a more compromised immune system.

The hospital is commonly regarded as a source of antibiotic-resistant pathogens from which transmission to other health-care setting occurs. Nonetheless, some studies retrieved with the literature search suggested that long-term care facilities may serve as reservoirs for antibiotic-resistant pathogens as well.[112-114] These studies focused on the epidemiology of transmission (eg, by determining prior nursing home stay in colonized patients admitted to the hospital), and could not draw firm conclusions with regard to the transmission of resistant strains from one health care facility to another.

Studies focusing on molecular epidemiology, which were not addressed in this review, are better suitable to elucidate the role of the nursing home in the transmission of antibiotic-resistant pathogens. For example, a Dutch study on the distribution of MRSA isolates between 1998 and 2005 indicated nursing homes as a potential intermediate for MRSA transmission from the community to the hospital.[164]

This review addressed antibiotic use and antibiotic resistance as separate issues, because the studies on antibiotic use differ from those on antibiotic resistance in terms of study setting and design. Comparing these studies across countries provides inconsistent evidence for an association between antibiotic use and antibiotic resistance. For example, Germany, a country with a low antibiotic use point-prevalence (1.4%),[27] is reported to have a low prevalence of MRSA resistance when compared with other European countries (1.1%).[105] In Italy, with a moderate antibiotic use point-prevalence (8.4%),[28] resistance rates were also moderate (8% to 19%).[22,82] By contrast, in Northern Ireland (19.4%) and Finland (13.4%),[27] antibiotic use point-prevalence was reported to be among the highest in Europe, but reported MRSA prevalence was moderate to low in these countries (9%-10% and 0.9%, respectively).[71,88] This inconsistent evidence for an association between antibiotic use and resistance on the country level may be explained by antibiotic resistance not only being associated with antibiotic use, but also with the extent to which infection control activities are implemented in long-term care facilities.

Many articles that we retrieved through the literature search focused on specific interventions to reduce antibiotic resistance, such as hand washing and implementation of guidelines. Such articles were not included this review, as we aimed to provide a general overview of strategies to reduce antibiotic resistance rather than an overview of effectiveness of specific interventions. This explains the relatively low number of articles allocated to the area of interest “strategies to reduce antibiotic resistance” (16/159); clearly, a higher number of articles would have been allocated to this area of interest if specific interventions would have been included.

We also did not include articles that addressed antibiotic use and resistance in subgroups of long-term care facility residents (eg, residents with pneumonia or residents with invasive devices, such as urinary catheters and feeding tubes). Instead, a rather broad focus on the general long-term care facility population was chosen to ensure a comprehensive situation analysis without elaboration on subgroup details.

Another limitation is that only publications in English were considered. As a consequence, limited data on antibiotic use and resistance were included for other countries that mainly publish on patterns of antibiotic use and resistance in their native language. Other possible limitations are that only 2 databases were searched (MEDLINE and EMBASE) and that only keywords and no free text terms were used in the literature search. Therefore, additional possibly relevant articles may have been

missed. We are, however, confident that the most relevant literature is included in this review, as many articles identified with the search strategy were encountered in the reference lists of other identified articles. Furthermore, additional relevant articles were included by reviewing the reference lists of included articles, by hand searching Google Scholar, and by searching Web sites of relevant organizations.

The relatively low percentage of publications on antibiotic use and resistance that focus on long-term care facilities indicates a need for more research specific to this setting. In addition, further research is required to elucidate the extent of the problem of inappropriate antibiotic prescribing. Although it may promote comparability of results if future studies used a universal definition for appropriateness of antibiotic prescribing, it is questionable whether this is feasible. Different countries use different guidelines for diagnosis and treatment of infectious diseases in long-term care residents, which may call for definitions tailored to the specific situation in these countries. Other areas for future research include further elucidation of the role of nursing homes as a possible source of antibiotic-resistant pathogens, investigation of the association between lower functional status and becoming colonized or infected with antibiotic-resistant organisms, and possible associations between antibiotic use rates and antibiotic resistance rates within countries, also addressing the degree to which resistance is avoidable.

The serious consequences of antibiotic resistance in long-term care facilities provide a rationale for the conduction of research and the development of policies directed at reducing antibiotic resistance in these facilities. These should focus on both the implementation of infection control measures and antibiotic stewardship. With regard to infection control measures, training of health care personnel is crucial to implement hygiene practice. To establish a sustainable training program, facilities should allocate adequate resources. The assignment of an infection control committee or an infection control practitioner may facilitate the development and sustainability of such a program. With regard to antibiotic stewardship, it is important that physicians are well educated on the diagnosis and treatment of infectious diseases in residents, and that this education is based on relevant guidelines. Other measures to facilitate appropriate antibiotic prescribing include monitoring of antibiotic use, encouraging physicians and pharmacists to develop and regularly review formularies, and promoting specimen culturing in residents with suspected infection. It is important to realize that, although infection control measures and antibiotic stewardship address different aspects of the antibiotic resistance problem, they are closely interrelated. For example, the effect of rational antibiotic prescribing by physicians is abolished if no attention is paid to infection control measures by nursing staff. Therefore, strategies to combat antibiotic resistance are more likely to be successful if they are multifaceted. Hence, they require close collaboration among all disciplines involved.

Differences between types of long-term care facilities should be taken into account in research and policy development to reduce antibiotic resistance. Whereas residential care facilities or assisted living facilities generally have a main focus on providing a "home" for their residents, the focus of nursing homes is on providing nursing care. Consequently, the way in which medical care is organized often differs between these types of facilities. For example, in US nursing homes, medical care may include provision of antibiotics and intravenous fluids, whereas such services are not directly available in assisted living environments.[165] This difference in antibiotic availability may explain the finding of Moro et al[28] that the prevalence of antibiotic use was higher in nursing homes than in residential care facilities.

The organization of medical care in long-term care facilities also differs among countries, because of distinct health care systems. This may result in international variation in antibiotic use, antibiotic resistance, and opportunities to implement infection control and antibiotic stewardship measures. As a consequence, extrapolation of research and policy to other countries or other long-term care settings is frequently complicated. Therefore, research on the impact of different types of long-term care facilities and different health care systems on antibiotic use and resistance is needed (eg, collaborative cross-national studies), to explain differences in antibiotic use and resistance between countries and health care settings.

Despite the potential limitations, we believe that this review clearly points out that antibiotic use and antibiotic resistance in the long-term care setting is common and that it causes substantial burden to individuals, long-term care facilities, and public health. This calls for the conduction of research and the development of policies directed at reducing the antibiotic resistance and subsequent burden for long-term care facilities and their residents.

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