


RESEARCH ARTICLE

Temporal and regional trends of antibiotic use in long-term aged care facilities across 39 countries, 1985-2019: Systematic review and meta-analysis

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Abstract

Background

Antibiotic misuse is a key contributor to antimicrobial resistance and a concern in long-term aged care facilities (LTCFs). Our objectives were to: i) summarise key indicators of systemic antibiotic use and appropriateness of use, and ii) examine temporal and regional variations in antibiotic use, in LTCFs (PROSPERO registration CRD42018107125).

Methods & findings

Medline and EMBASE were searched for studies published between 1990–2021 reporting antibiotic use rates in LTCFs. Random effects meta-analysis provided pooled estimates of antibiotic use rates (percentage of residents on an antibiotic on a single day [point prevalence] and over 12 months [period prevalence]; percentage of appropriate prescriptions). Meta-regression examined associations between antibiotic use, year of measurement and region. A total of 90 articles representing 78 studies from 39 countries with data between 1985–2019 were included. Pooled estimates of point prevalence and 12-month period prevalence were 5.2% (95% CI: 3.3–7.9; $n = 523,171$) and 62.0% (95% CI: 54.0–69.3; $n = 946,127$), respectively. Point prevalence varied significantly between regions ($Q = 224.1$, $df = 7$, $p < 0.001$), and ranged from 2.4% (95% CI: 1.9–2.7) in Eastern Europe to 9.0% in the British Isles (95% CI: 7.6–10.5) and Northern Europe (95% CI: 7.7–10.5). Twelve-month period prevalence varied significantly between regions ($Q = 15.1$, $df = 3$, $p = 0.002$) and ranged from 53.9% (95% CI: 48.3–59.4) in the British Isles to 68.3% (95% CI: 63.6–72.7) in Australia. Meta-regression found no association between year of measurement and antibiotic use prevalence. The pooled estimate of the percentage of appropriate antibiotic prescriptions was 28.5% (95% CI: 10.3–58.0; $n = 17,245$) as assessed by the McGeer criteria. Year of measurement was associated with decreasing appropriateness of antibiotic use over time (OR:0.78, 95% CI: 0.67–0.91). The most frequently used antibiotic classes were penicillins ($n = 44$ studies), cephalosporins ($n = 36$), sulphonamides/trimethoprim ($n = 31$), and quinolones ($n = 28$).

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Conclusions

Coordinated efforts focusing on LTCFs are required to address antibiotic misuse in LTCFs. Our analysis provides overall baseline and regional estimates for future monitoring of antibiotic use in LTCFs.

Introduction

Antibiotic use in long-term aged care facilities (LTCFs) continues to be a global concern, particularly amid rising antimicrobial resistance [1–3]. LTCF residents are at higher risk of infections due to age-related physiological changes, comorbidities, higher rates of hospitalisation, and close contact with other residents and facility staff [4]. Studies have highlighted that LTCF residents are often prescribed antibiotics inappropriately, more frequently and for longer than people in the community [4–10]. Overuse of antibiotics exposes LTCF residents to adverse events, and an increased risk for the development of antimicrobial resistance [11, 12].

The World Health Organization's (WHO) global strategy to curb antimicrobial resistance includes surveillance of antibiotic use [13]. The WHO's three tiered AWaRe classification groups antibiotics according to whether their use is preferred or should be restricted, providing a framework for stewardship programs. The classification's three tiers include: i) "Access" antibiotics of choice for each of the most common infections, ii) "Watch" antibiotics that are recommended only for specific, limited indications and are the "highest priority critically important" antibiotics; and iii) "Reserve" antibiotics that should only be used as a last resort.

Understanding patterns of antibiotic use is crucial for developing and planning policies to address inappropriate use. In response to concerns over high rates of inappropriate antibiotic use in LTCFs, survey programs have been initiated in the last decade to monitor antibiotic use in this setting. These include the Healthcare-Associated infections in Long-Term care (HALT) [14] and European Surveillance of Antimicrobial Consumption (ESAC) [15] surveys run by the European Centre for Disease Prevention and Control, and the Australian Aged Care National Antimicrobial Survey (acNAPS) [16]. Guidelines on monitoring of antibiotic use have been published [17–19], and there have been increasing efforts to develop and evaluate antimicrobial stewardship programs specifically for LTCFs [20–23]. However, a comprehensive summary of the available data on antibiotic use in LTCFs is not available. Two previous narrative international reviews on antibiotic use in LTCFs were published in 2012 [6] and 2019 [4], and reported data on antibiotic use up to 2011 and 2017, respectively. Thus, despite antibiotic surveillance being a core component of the WHO's global strategy to addressing antibiotic resistance, there is an absence of recent global estimates of antibiotic use in LTCFs. We aimed to address this gap. Our aims were to: i) undertake the first meta-analysis to quantitatively summarise key indicators of antibiotic use and appropriateness of use in LTCFs; ii) to explore temporal and regional trends and differences in antibiotic use using meta-regression; and iii) to summarise the most frequently used antibiotic classes overall and by geographic region.

Materials and methods

The protocol for this systematic review and meta-analysis was registered with PROSPERO (ID: CRD42018107125; [S1 File](#)) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA; checklist in [S2 File](#)) guideline.

Information sources and search strategy

We searched the bibliographic databases Medline (via OvidSP and PubMed) and EMBASE (via OvidSP) for original research articles reporting rates of antibiotic use in LTCFs published in English between 1990–2021. Studies could report data prior to 1990. The search strategy used a combination of keywords and subject headings on ‘long-term care facilities’ and ‘antibiotics’. The full search strategy is provided in the [S3 File](#). Reference lists of included articles were hand searched for further relevant citations. Authors of published papers were contacted for additional details when required.

Eligibility criteria and study selection

Articles reporting rates of systemic antibiotic use in LTCFs for the aged were eligible, including intervention studies. Examples of antibiotic use rates are: the percentage of residents on an antibiotic (prevalence); number of antibiotic courses per 1000 resident days; days of therapy (DOT) per 1000 resident days; and the number of defined daily doses (DDD) per 1000 resident days. Studies not providing separate estimates for systemic antibiotic use were included if it was stated that topical use was a small proportion ($\leq 10\%$) of overall use. To ensure we were including facilities predominantly for older adults, we included studies in long-term aged care facilities, skilled nursing facilities, nursing homes, residential aged care facilities and assisted living facilities; but excluded studies in specialist LTCFs described as psychiatric, palliative, rehabilitation, for physically disabled people or those in hospitals. Studies only reporting rates of antibiotic use for specific infections were excluded.

Two reviewers from a panel of three (MR, CG, PG) independently screened the title and abstracts of papers generated by the literature search, after exclusion of duplicates, and then assessed potential full-text articles to determine eligibility. Disagreements in screening were resolved through discussion between reviewers until consensus was achieved.

Data collection process and data items

Data were extracted independently by three authors (MR, PG, CG) and discrepancies were resolved through discussion. Multiple articles from the same study were grouped and data extracted for the study, rather than each article. For each study data on: the study country, sample size (number of LTCFs and residents), study design (point prevalence survey, longitudinal cohort study, intervention study), period of data collection (which could precede 1990), and the method used to measure antibiotic use (e.g. point prevalence survey, pharmacy supply databases, chart review) were extracted. Characteristics of LTCF residents recorded included their demographics (mean or median age, proportion of women) and prevalence of key conditions that may affect antibiotic use (dementia and catheter use). Data on the antibiotic use rate, appropriateness of use and most frequently used antibiotics were extracted. For studies with an intervention, the baseline antibiotic use rates were extracted. For appropriateness of antibiotic therapy, the assessment criteria used (e.g. McGeer criteria) were recorded as methods for assessing appropriateness vary, and can assess whether an antibiotic was required or whether the chosen antibiotic follows treatment guidelines. When available, the three most frequently used antibiotics and/or antibiotic classes were also recorded.

Countries were grouped into regions for analysis. Regions consisted of continents, with Europe divided further into five sub-regions broadly following European Union terminology: British Isles, Western Europe, Southern Europe, Northern Europe, Eastern Europe [24].

We grouped antibiotics into antibiotic classes using the World Health Organisation’s Anatomical Therapeutic Chemical Classification System (ATC) level 3 codes [25]. These included: tetracyclines (ATC: J01A), penicillins (J0C), other beta-lactams (including cephalosporins;

J01D), sulfonamides and trimethoprim (J01E), macrolides (J01F), quinolones (J01M), and other classes (includes only methenamine and nitrofurantoin; J01X).

Assessment of study quality

Two reviewers (MR, PG) independently assessed the quality of each study using the Joanna Briggs Institute Critical Appraisal Tool for Prevalence Studies [26]. The tool includes nine assessment criteria regarding the sampling strategy, sample description, methods of measurement, and statistical analysis. An overall rating of quality was then assigned to each study based on the number of criteria with a 'yes' score. Studies were rated as *good quality* when they met 7–9 of the criteria; *fair quality* for 5–6 of the criteria, and *poor quality* when they met <5 criteria.

Synthesis of results

The available data allowed us to conduct meta-analyses for three antibiotic use measures: point prevalence, 12-month period prevalence, and the proportion of appropriate prescriptions as assessed against the McGeer criteria. There was a lack of reporting of measures of dispersion (e.g. standard deviation) and denominator sample sizes for other outcomes (DDD/1000 days, DOT/1000 days, number of courses/1000 days, other appropriateness criteria) to allow meta-analysis. Thus, a narrative synthesis was used for these outcomes. Point prevalence was defined as the percentage of residents on an antibiotic on one day. Twelve-month period prevalence was defined as the percentage of residents who used an antibiotic over 12 months and was extracted from studies measuring use over 12-months (i.e. 12-month period prevalence was not extrapolated from studies measuring prevalence over shorter or longer periods).

We conducted sub-group meta-analyses by regions to generate pooled estimates of antibiotic use by region and overall. We used random effects models (i.e. random effects models for each region and to generate an overall estimate) with a pooled estimate of Tau^2 (T^2). Pooling Tau^2 overcomes the limitation of underestimating the variance in subgroups with fewer studies. Heterogeneity among study estimates within regions and between regions were examined by visually inspecting forest plots, the Q-statistic, Higgins' I^2 and T^2 [27]. Publication bias was assessed using funnel plots and the Egger's regression test, which is a measure of funnel plot asymmetry [28]. Duval and Tweedie's Trim and Fill method [29] was used to correct for publication bias in the meta-analyses when it was present.

We further explored the heterogeneity in estimates of antibiotic use and appropriateness using meta-regression. Meta-regression was fitted using restricted maximum likelihood estimation with a Knapp-Hartung adjustment. We examined the association between the three outcomes (point prevalence, 12-month period prevalence estimates, appropriateness), and the year of data collection and region. Since antibiotic use is higher during influenza season, we adjusted the point prevalence model for whether data collection took place during the influenza season [30]. When estimates were available for only one country in a region, we used country names. We were not able to include independent variables for resident demographics or health conditions (dementia and catheter use prevalence) in the models as they were not reported with enough consistency in the studies. However, the demographic details reported in the studies are provided in Supplementary files. An estimate of R^2 was used to estimate the proportion of between study variance explained by the model. Comprehensive Meta-Analysis 3.0 was used to perform all analyses [31] and R Studio was used to generate forest plots [32].

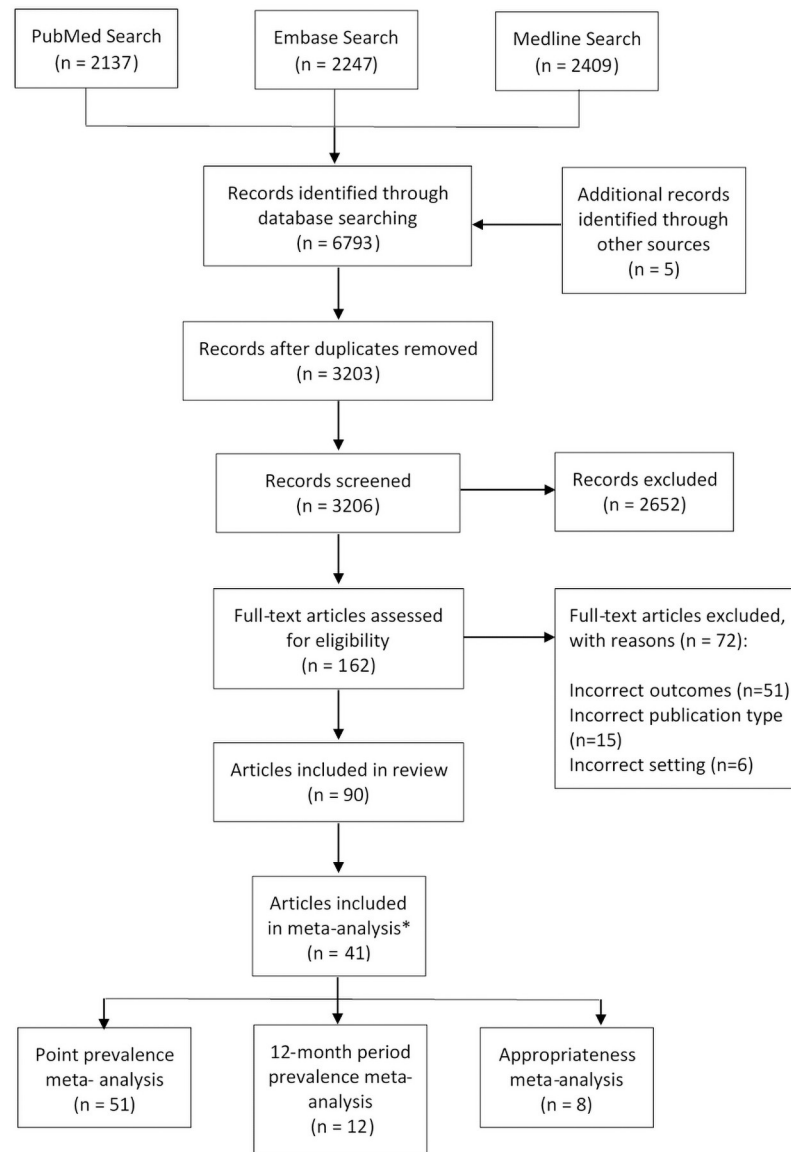


Fig 1. Flowchart of search strategy and screening results. *Some studies contributed more than one estimate to the meta-analyses.

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Results

Study characteristics

A total of 90 articles and reports were included [7–10, 15, 18, 30, 33–109], representing 78 individual studies (Fig 1). Study characteristics are presented in Table 1. There were 29 studies from Europe and the British Isles, 32 from North America (24 from the US, 9 from Canada, and one from both US and Canada), 12 from Australia, and four from Asia (two from Singapore and two from Japan); plus one study reporting data from Australia and the Netherlands. Study sample sizes had a median of 39 LTCFs (interquartile range: 9–174). The majority of studies reported the outcome percent of residents using an antibiotic (period and/or point prevalence; $n = 49$), followed by percentage of appropriate prescriptions ($n = 25$), number of

Table 1. Characteristics of included studies measuring the antibiotic use rates in long-term care facilities.

Author, year	Country	Number of facilities	Data collection year/s	Study design	Antibiotic use data source	Outcomes ^a	Overall quality rating ^b
Alberg, 2017 [33]	Norway	540	2016	Cross-sectional study	Point prevalence survey	1, 5	Poor (4/9)
acNAPS, 2016 [35]	Australia	186	2015	Cross-sectional study	Point prevalence survey	1, 5	Good (8/9)
acNAPS, 2017 [36, 121]	Australia	287	2016	Cross-sectional study	Point prevalence survey	1, 5	Good (8/9)
acNAPS, 2018 [37]	Australia	292	2017	Cross-sectional study	Point prevalence survey	1, 5	Good (8/9)
acNAPS, 2019 [38]	Australia	407	2018	Cross-sectional study	Point prevalence survey	1, 5	Good (8/9)
acNAPS, 2020 [39]	Australia	568	2019	Cross-sectional study	Point prevalence survey	1	Good (7/9)
Barney, 2019 [34]	United States	4	2016–2017	Retrospective cohort	Pharmacy database	1, 2	Good (7/9)
Benoit, 2008 [40]	United States	73	2001–2002	Retrospective cohort	Chart review	1, 3	Good (7/9)
Blix, 2007 [41]	Norway	133	2003	Retrospective cohort	Antibacterial sales database	4	Good (8/9)
Blix, 2010 [125]	Norway	44	2006	Cross-sectional study	Point prevalence survey	1	Good (7/9)
Boivin, 2013 [42]	France	18	2012	Retrospective cohort	Chart review; point prevalence survey	1, 5	Good (8/9)
Cowan, 2016 [43]	Australia	2	2014	Retrospective cohort	Chart review	1, 5	Poor (1/9)
Daneman, 2011 [116]	Canada	363	2009	Retrospective cohort	Pharmacy database	1	Good (7/9)
Daneman, 2013 [7]	Canada	630	2010	Retrospective cohort	Pharmacy database	1	Good (7/9)
Daneman, 2015 [44]	Canada	607	2010–2011	Retrospective cohort	Pharmacy database	2	Good (8/9)
Daneman, 2017 [45]	Canada	628	2014	Retrospective cohort	Pharmacy database	1	Good (7/9)
Drinka, 2004 [46]	United States	1	1996–2002	Retrospective cohort	Pharmacy database	1	Fair (6/9)
Eikelenboom-Boskamp, 2019 [47]	Netherlands	25, 44	2010–2017	Cross-sectional study	Point prevalence survey	1	Good (8/9)
ESAC-1 [15, 48–51]	21 European countries	323	2009	Cross-sectional study	Point prevalence survey	1, 4, 5 ^c	Good (8/9)
ESAC-2 [51, 52]	Northern Ireland, Finland	30 & 9	2010	Cross-sectional study	Point prevalence survey	1, 5	Good (8/9)
ESAC-3 [52]	Northern Ireland	30	2011	Cross-sectional study	Point prevalence survey	1, 5	Good (8/9)
Fagan, 2012 [53]	Norway	10	2007–2008	Retrospective Cohort	Health record data	1, 4, 5	Good (7/9)
Felsen, 2020 [54]	United States	6	2014–2018	Intervention study	Pharmacy database	2	Poor (4/9)
Fleet, 2014 [55]	England	30	2010–2011	Intervention study	Chart review	1, 4, 5	Fair (6/9)
Gillespie, 2015 [56]	Wales	10	2010–2012	Retrospective Cohort	Chart review	1, 3	Good (7/9)
HALT-1 [57–60]	28 European countries	676 ^d	2010	Cross-sectional study	Point prevalence survey	1, 5 ^e	Good (8/9)
HALT-2 [18, 63, 64]	19 European countries	1051 ^d	2013	Cross-sectional study	Point prevalence survey	1	Good (8/9)
HALT-3 [61, 62, 65]	24 European countries	1,788 ^d	2016–2017	Cross-sectional study	Point prevalence survey	1, 5	Good (8/9)
Heudorf, 2012 [66]	Germany	40	2011	Cross-sectional study	Point prevalence survey	1	Good (7/9)
Ishikane, 2020 [67]	Japan	6	2016	Retrospective cohort	Pharmacy database	4	Fair (5/9)
Jump, 2012 [68]	United States	1	2006–2010	Retrospective Cohort	Pharmacy database	2	Fair (6/9)
Kabbani, 2019 [69]	United States	12	2016	Retrospective Cohort	Pharmacy database	2	Good (8/9)
Katz, 1990 [70]	United States	2	1985	Prospective cohort	Chart review; observation	3, 5	Fair (6/9)
Lee, 1992 [71]	United States	7	1989	Prospective cohort	Chart review; point prevalence survey	1, 5	Fair (6/9)
Lee, 1996 [72]	United States	1	Not reported	Prospective cohort	Chart review; point prevalence survey	1, 5	Fair (5/9)
Loeb, 2005 [73]	United States, Canada	24	2001–2003	Intervention study	Chart review	3	Fair (6/9)
Marquet, 2015 [74]	France	52, 74	2011–2013	Retrospective Cohort	Pharmacy database	4	Fair (5/9)

(Continued)

Table 1. (Continued)

Author, year	Country	Number of facilities	Data collection year/s	Study design	Antibiotic use data source	Outcomes ^a	Overall quality rating ^b
Marra, 2017 [8]	Canada	381	2007–2014	Retrospective Cohort	Pharmacy database	3, 4	Good (8/9)
Mayne, 2018 [9]	Australia	5	2015–2016	Prospective cohort	Chart review	1	Fair (6/9)
Monette, 2007 [75]	Canada	8	2001–2003	Intervention study	Pharmacy database; chart review	1, 5	Poor (4/9)
Montgomery, 1995 [76]	Canada	100	1986	Retrospective cohort	Chart review	1, 5	Good (7/9)
Moro, 2007 [77]	Italy	49	2001	Cross-sectional study	Point prevalence survey	1	Good (7/9)
Mylotte, 1999 [78]	United States	4	1996–1998	Prospective cohort	Survey	3	Fair (5/9)
Mylotte, 2005 [111]	United States	11	2003	Retrospective cohort	Survey	2	Fair (5/9)
Natsch, 1998 [79]	Netherlands	6	1995	Retrospective Cohort	Pharmacy database	4	Fair (4/9)
Olsho, 2013 [80]	United States	12	2011	Prospective cohort	Chart review	3, 5	Good (7/9)
Pakyz, 2010 [81] ^f	United States	1174	2004	Retrospective cohort	Chart review	1	Good (8/9)
Pluss-Suard, 2020 [82]	Switzerland	23	2011–2016	Prospective cohort	Pharmacy database	4	Fair (5/9)
Raban, 2020 [30]	Australia	68	2014–2017	Retrospective cohort	Health record data	1, 2, 3	Good (9/9)
Rahme, 2016 [83]	United States	1	2012–2013	Prospective cohort	Pharmacy database	4	Fair (6/9)
Roukens, 2017 [84]	Netherlands	31	2012–2014	Point prevalence; Retrospective cohort	Survey; chart review	4	Fair (5/9)
Rummukainen, 2009 [85]	Finland	29	2004–2006	Cross-sectional study	Point prevalence survey	1	Fair (6/9)
Rummukainen, 2013 [86]	Finland	263	2011	Cross-sectional study	Point prevalence survey	1	Good (8/9)
Saxena, 2019 [87]	Canada	87,947 (residents)	2016	Retrospective cohort	Pharmacy database	1	Good (7/9)
Selcuk, 2018 [88]	Singapore	4	2008	Retrospective cohort	Chart review	1, 2, 4	Fair (5/9)
Selcuk, 2019 [89]	Singapore	9	2017	Cross-sectional study	Point prevalence survey	1, 4	Fair (5/9)
Sloane, 2014 [90]	United States	4	2010–2012	Prospective cohort	Chart review	3	Fair (5/9)
Sloane, 2019 [91]	United States	14	2015–2017	Prospective cohort	Chart review	3	Fair (6/9)
Sloane, 2020 [91]	United States	27	2015–17	Intervention study	Chart review by nursing home staff	3	Fair (5/9)
Sluggett, 2020 [92]	Australia	3218	2005–2006; 2010–2011; 2015–2016	Repeated cross-sectional study	National pharmaceutical claims data	1, 4	Good (9/9)
Smith, 2013 [94]	Australia	29	2011	Cross-sectional study	Point prevalence survey	1, 5	Good (8/9)
Smith, 2020 [93]	United Kingdom	135	2016–2017	Retrospective cohort	Pharmacy database; electronic records	3 ^g	Good (8/9)
Song, 2021 [95]	United States	29	2016	Retrospective cohort	Invoice data	2, 3	Good (9/9)
Stepan, 2018 [96]	Slovenia	80	2016	Cross-sectional study	Point prevalence survey	1	Good (7/9)
Stuart, 2012 [98]	Australia	5	2011	Cross-sectional study	Point prevalence survey	1, 5	Fair (5/9)
Stuart, 2015 [97]	Australia	2	2012	Prospective cohort	Chart review	2, 5	Poor (4/9)
Sundvall, 2015 [99]	UK	7481 (residents)	2011	Retrospective cohort	Health record data	1	Good (7/9)
Takito, 2020 [100]	Japan	1	2013–2017	Intervention study	Chart review	3 ^g	Poor (1/9)
Taxis, 2017 [101]	Australia, Netherlands	26 & 6	2009	Retrospective cohort	Pharmacy database	1	Good (7/9)
Temime, 2018 [102]	France	13	2014–2015	Intervention study	LTCF database	4	Poor (4/9)
Thompson, 2016 [103, 113]	United States	9	2013–2014	Point prevalence	Survey	1, 5	Poor (4/9)
Thompson, 2021 [104]	United States	161	2017	Point prevalence	Survey	1	Good (8/9)
Thornley, 2019a [10]	United Kingdom	341,536 (residents)	2016–2017	Retrospective cohort	Pharmacy database	1	Good (7/9)

(Continued)

Table 1. (Continued)

Author, year	Country	Number of facilities	Data collection year/s	Study design	Antibiotic use data source	Outcomes ^a	Overall quality rating ^b
Thornley, 2019b [105]	United Kingdom	644	2017	Cross-sectional study	Point prevalence survey	1	Good (7/9)
van Buul, 2015 [106]	Netherlands	10	2012–2013	Intervention study	Pharmacy database	3	Good (7/9)
Warren, 1991 [107]	United States	52	1985–1986	Prospective cohort	Chart review	1, 3, 5	Fair (5/9)
Wu, 2015 [108]	Canada	17	2011–2012	Retrospective cohort	Chart review	2	Good (7/9)
Zimmerman, 2014 [109]	United States	12	2011	Intervention study	Chart review	3	Fair (6/9)

acNAPS: Aged Care National Antimicrobial Prescribing Survey, Australia; ESAC: European Surveillance of Antimicrobial Consumption; HALT: Healthcare-Associated Infections in Long-Term Care Facilities Project, Europe.

^aOutcome 1 is percentage of residents on an antibiotic; 2 is days of therapy per 1000 residents; 3 is courses per 1000 resident days; 4 is defined daily doses per 1000 resident days; 5 is percentage of appropriate antibiotic prescriptions.

^bStudy quality assessed based on the Joanna Briggs Institute Critical Appraisal Tool for Prevalence Studies. The score in the brackets is the total number of criteria met.

^cSubset of facilities from Northern Ireland provided the percentage of appropriate antibiotic prescriptions.

^dNumber of participating general nursing homes, residential homes, and mixed long-term care facilities. Other facility types reported in the HALT surveys excluded here are psychiatric long-term care facilities, long-term care facilities for the mentally disabled, long-term care facilities for the physically disabled, rehabilitation centres, palliative care centres, and 'other' long-term care facilities.

^eSubset of facilities from Italy.

^fPakyz et al. report on results of the National Nursing Home Survey, conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics.

^gSmith reported as number of prescriptions per resident year. Takito reported as number of prescription per 100 residents per month.

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courses per 1000 resident days ($n = 17$), DDD/1000 resident days ($n = 15$), and DOT/1000 days ($n = 12$). Thirty-three studies reported multiple outcomes. Most studies ($n = 51$) used surveys or chart review to measure antibiotic use, and 27 studies used electronic records or databases of medication supply.

Assessment of study quality

We assessed 45 studies to be of good quality, 25 as fair, and only eight studies to be of poor quality (Table 1, and detailed assessment in S4 File). Criteria 4 and 8 were most frequently assessed as not being met (both scored as 'no' in 46 studies) across the studies. Criterion 4 requires descriptions of the study setting and subjects; and criterion 8 requires appropriate statistical analysis, including reporting of denominators, confidence intervals or standard errors.

Point prevalence estimates of antibiotic use in LTCFs

Meta-analysis was conducted on a total of 123 point-prevalence estimates from 37 countries between 1985 and 2019. Resident characteristics were available for 71 of the estimates, and eligibility criteria for residents were similar across these studies, primarily following those used in the HALT and ESAC programs (S5 File). The percentage of residents receiving an antibiotic on a single day ranged from 0.7% to 17.3%. The pooled estimate, taking into account subgroups, was 5.2% (95% CI: 3.3–7.9%; $n = 523,171$; $I^2 = 98.6$; $T^2 = 0.162$) with a significant test for differences between regions ($Q = 224.1$, $df = 7$, $p < 0.001$). Table 2 shows the pooled estimates for regions and detailed heterogeneity statistics are shown in S6 File. The Q-statistics for within region heterogeneity indicated significant variation between studies within regions (S6 File), for all regions except Singapore (which had only two studies). The I^2 values for each region indicated that the majority of the heterogeneity was likely due to real variation in estimates.

Table 2. Pooled estimates from meta-analysis of point prevalence of antibiotic use by region.

Region	Number of estimates	Range of point prevalence estimates	Pooled point prevalence (95% CI)	I ²	T ²
Singapore	2	2.33, 2.97	2.6 (1.4, 4.7)	0.0	0.000
Australia	7	5.47, 8.95	7.2 (5.4, 9.5)	94.6	0.026
British Isles	22	5.53, 12.7	9.0 (7.7, 10.4)	92.8	0.063
Eastern Europe	27	0.73, 11.3	2.3 (1.9, 2.7)	95.6	0.493
Northern Europe	24	2.72, 17.3	9.1 (7.8, 10.6)	97.4	0.224
Southern Europe	16	0.79, 12.2	4.9 (4.0, 6.1)	97.8	0.249
Western Europe	21	1.15, 6.10	3.2 (2.7, 3.8)	97.3	0.224
North America	4	5.86, 11.1	7.2 (4.7, 10.9)	98.1	0.055
OVERALL	123	0.73, 17.3	5.2 (3.3, 7.9)	98.6	0.077^a

^aWithin region Tau² pooled across regions.

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Sensitivity analysis removing one [103] study of poor quality gave a pooled estimate of 5.1% (95% CI: 3.3–7.8%; I²: 98.6; T²: 0.156). The Egger's test showed potential publication bias (p = 0.003) so we employed the Duval and Tweedie's trim and fill method. A total of 18 studies were trimmed, resulting in an adjusted point prevalence estimate of 6.2% (95% CI: 5.6–6.8%).

Meta-regression examined the association between point prevalence estimates of the percentage of residents on an antibiotic, and year of measurement and geographic region, while adjusting for whether measurement took place during influenza season (Table 3). There was no significant association with the year of measurement. All regions, were more likely to have LTCF residents on an antibiotic on the day of survey compared to Eastern Europe, with the exception of Singapore (Table 3). The model explained 56% of between study variance.

Period prevalence estimates of antibiotic use

There was a total of 30 period prevalence estimates from 11 countries between 1985 and 2017. Of these, 19 were estimates of the percentage of residents who used an antibiotic over 12-months (12-month period prevalence) from nine countries between the years 1985–2017.

Table 3. Meta-regression of point prevalence estimates of antibiotic use in long-term care facilities (N = 123).

Independent variable	No. of estimates	Odds ratio (95% CI)	p-value
Year	123	0.98 (0.96, 1.01)	0.284
Measured during flu season			
No	105	1.00	
Yes	18	1.01 (0.67, 1.53)	0.968
Region			
Eastern Europe	27	1.00	
Northern Europe	24	4.16 (3.04, 5.69)	<0.001
Western Europe	21	1.43 (1.03, 1.97)	0.032
Southern Europe	16	2.18 (1.52, 3.14)	<0.001
British Isles	22	4.24 (3.03, 5.94)	<0.001
Australia	7	3.53 (1.90, 6.55)	0.0001
Singapore	2	1.17 (0.50, 2.71)	0.716
North America	4	3.43 (1.76, 6.70)	0.0004

R²: 0.56 (estimate of proportion of between-study variance explained by model).

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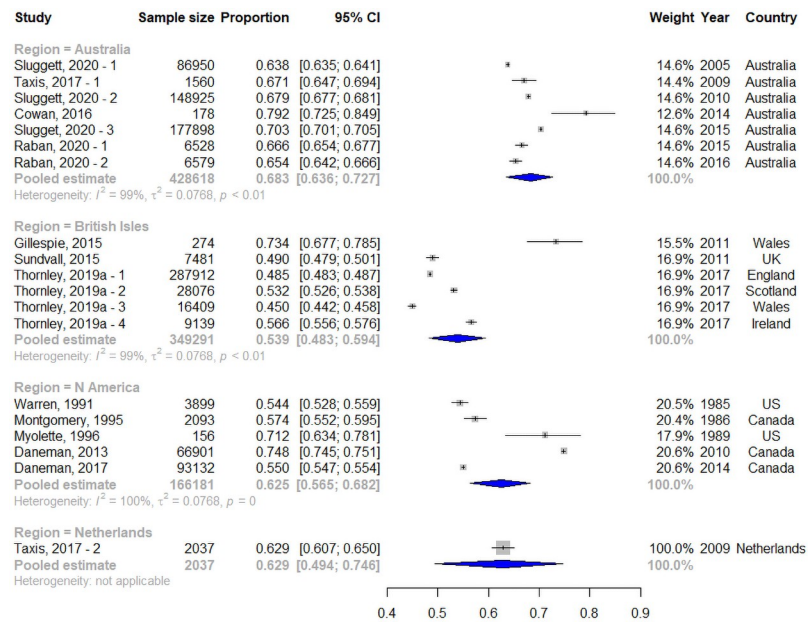


Fig 2. Meta-analysis by region of twelve-month period prevalence of antibiotic use. CI is confidence interval. Markers for individual studies are proportional to the studies' weight in generating the region estimate.

<https://doi.org/10.1371/journal.pone.0256501.g002>

Resident characteristics were available for 11 of these studies (S7 File). The 12-month period prevalence ranged from 45.0% to 79.2% of residents. Meta-analysis, taking into account sub-groups, gave a pooled estimate of 62.0% (95% CI: 54.0–69.3%; n = 946,127; I^2 : 100%; T^2 : 0.077) of residents using an antibiotic annually, with statistically significant differences between regions ($Q = 15.1$, $df = 3$, $p = 0.002$). Fig 2 shows the pooled estimates for each region. I^2 values indicated that almost all variation was likely due to real differences in estimates (S6 File).

Sensitivity analysis, removing two studies [43, 110] of poor quality, gave a pooled estimate of 61.0% (95% CI: 53.767.9%; I^2 : 100%; T^2 : 0.077). The Egger's test showed no significant publication bias ($p = 0.714$).

Meta-regression showed year of measurement was not significantly associated with 12-month period prevalence (Table 4). Of the regions, Australia had higher odds of residents being on an antibiotic over a 12-month period compared to the British Isles (Table 4). The model explained 24% of the total between study variance.

Nine other studies estimated the percentage of residents on an antibiotic over varying time periods of six months or less, and all were of fair or good quality (S8 File) [9, 34, 40, 47, 48, 71, 75, 81, 88].

Table 4. Meta-regression of 12-month prevalence estimates of antibiotic use in long-term care facilities (N = 19).

Independent variable	No. of estimates	Odds ratio (95% CI)	p-value
Year	19	1.01 (0.98, 1.03)	0.501
Region			
British Isles	6	1.00	
Netherlands	1	1.51 (0.66, 3.47)	0.300
Australia	7	1.76 (1.13, 2.75)	0.017
North America	5	1.51 (0.79, 2.86)	0.188

R^2 : 0.24 (estimate of proportion of between-study variance explained by model).

<https://doi.org/10.1371/journal.pone.0256501.t004>

Other estimates of antibiotic use

A total of 14 studies reported a range of mean antibiotic use from 2.7 to 237 DOT/1000 bed days [30, 34, 44, 54, 68, 69, 78, 88, 91, 95, 97, 106, 108, 111]. Fourteen studies reported a range from 2.1 to 13.0 antibiotic courses per 1000 resident days [8, 30, 40, 56, 70, 73, 80, 90, 93, 95, 107, 109, 111, 112]. Finally, 15 studies reported a range of 38.2 to 148 DDD/1000 bed days [8, 41, 53, 55, 67, 74, 79, 82–84, 88, 89, 92, 102, 106]. Details are provided in [S8 File](#).

Appropriateness of antibiotic therapy

Nine studies, conducted between 2010 and 2018, assessed the appropriateness of antibiotic treatment against the McGeer criteria [35–38, 55, 60, 97, 98, 113], which assess whether antibiotic treatment was warranted based on the presence of infection symptoms. Eight studies included courses for all infections [35–38, 55, 60, 97, 98], and one study assessed appropriateness for UTIs [113], which was excluded from the meta-analysis. The percentage of appropriate courses ranged between 9.5% to 60.3% in individual studies, conducted between 2010 and 2018 in three countries ([S9 File](#) shows the resident characteristics reported in seven of the studies). Meta-analysis, taking into account sub-groups by country, gave a pooled estimate of 28.5% (95% CI: 10.3–58.0; $n = 17,245$; $I^2 = 99.6\%$; $\text{Tau}^2 = 0.858$) with differences between regions not significant as assessed by the Q-statistic ($Q = 3.57$, $df = 2$, $p = 0.167$). [S6 File](#) shows the detailed heterogeneity statistics. [Fig 3](#) shows pooled estimates for each region. Sensitivity analysis removing two studies of poor quality [97, 113] yielded a pooled estimate of 28.0% (95% CI: 9.9–57.9%; $I^2 = 99.7\%$; $T^2 = 0.869$). The Egger's test showed no significant publication bias ($p = 0.352$).

Meta-regression showed the percentage of appropriate courses decreased every year and Australia and Italy had higher rates of appropriate courses compared to England ([Table 5](#)). The model explained 85% of the between study variance.

Studies also applied other methods to assess appropriateness ($n = 16$), including the Loeb Minimum Criteria; local and national algorithms and guidelines; microbiology laboratory results; urinalysis; and expert consensus. Estimates of the percentage of appropriate prescriptions ranged from 5.6% to 88.5% when assessing prescribing for all infections; 4% to 81.3% respiratory tract infections; 13% to 59.3% for skin and soft tissue infections; and 18% to 97.3% for urinary tract infections. Details are provided in [S8 File](#).

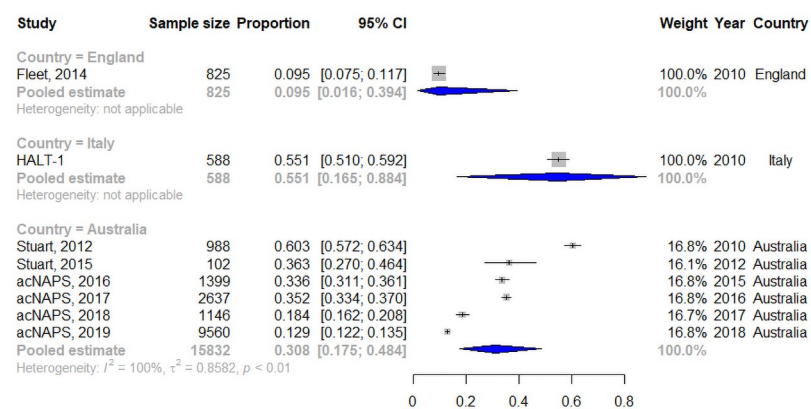


Fig 3. Meta-analysis by region of the percent of appropriate prescriptions according to McGeer criteria. CI is confidence interval. Markers for individual studies are proportional to the studies' weight in generating the region estimate.

<https://doi.org/10.1371/journal.pone.0256501.g003>

Table 5. Meta-regression of the percentage of appropriate^a antibiotic courses in long-term care facilities (N = 8).

Independent variable	No. of estimates	Odds ratio (95% CI)	p-value
Year	8	0.78 (0.67, 0.91)	0.0112
Country			
England	1	1.00	
Australia	6	13.64 (3.47, 53.52)	0.0061
Italy	1	11.75 (2.63, 52.58)	0.0103

R²: 0.85 (estimate of proportion of between-study variance explained by model).

^aAppropriateness was assessed using the McGeer criteria.

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Most frequently used antibiotics

There were 59 studies reporting on the most frequently used antibiotics or antibiotic classes. Fig 4 shows the three most frequently used classes of antibiotics reported in each study, grouped by region. Overall, the three most frequently reported antibiotic classes used were penicillins (n = 44 studies), cephalosporins (n = 36), and sulphonamides/trimethoprim (n = 31). Quinolones were among the three most common classes used in Western Europe (n = 3 studies), Southern Europe (n = 2), Eastern Europe (n = 2), North America (n = 14), and Asia (n = 4). Macrolides were among the three most common antibiotic classes in only four studies. There were nine studies that included data after 2017, the year when the WHO AWaRe classification was introduced. Quinolones, on the WHO's Watch List, were still among the top three antibiotics used in Asia, Southern Europe in North America from 2017 onwards.

Discussion

In this systematic review and meta-analysis, we compiled the international literature on rates of systemic antibiotic use, appropriateness of use, and types of antibiotics used in LTCFs. Our review spans 34 countries across eight geographic regions between 1985 and 2019. We found significant variation between geographic regions in the point prevalence (average pooled estimate: 5.2% (95% CI: 3.3–7.9%)) and 12-month period prevalence (pooled estimate: 62.0% (95% CI: 54.0%–69.3%)) estimates of residents on an antibiotic. There was no significant change in the prevalence of use across all regions over time. The percentage of appropriate prescriptions (pooled average estimated: 28.5% (95% CI: 10.3–58.0)), as assessed by the McGeer criteria, also differed between regions, and decreased over time though this result is largely based on data from Australia. There were also regional differences in the most frequently used antibiotic classes, with quinolones being a common class in five of seven regions.

Our analysis of the point prevalence estimates of antibiotic use in LTCFs indicated that use was higher in the British Isles, followed by Northern Europe, and Australia compared to other regions. Twelve-month period prevalence estimates were available for only four regions, and antibiotic use was highest in Australia. The regions we identified as having the highest antibiotic use in LTCFs are broadly consistent with the regions reported to have high national levels of antibiotic consumption. An analysis of global antibiotic consumption, based on national pharmaceutical sales data between 2000 and 2010, reported national antibiotic consumption was highest in Australia, Ireland, and the United Kingdom compared to other European countries [2]. In addition, data from the European Surveillance of Antibiotic Consumption from 2017 also show that national antibiotic consumption in Australia and the British Isles is above the Organisation for Economic Cooperation and Development (OECD) country average

Region / Study	Country	Data collection year/s	J01C	J01D	J01E	J01M	J01X	J01A	J01F
Region: Multiple European countries									
ESAC-1	21 countries	2009 (April)	■		■		■		
ESAC-1	17 countries	2009 (April)	■		■		■		
ESAC-1	17 countries	2009 (November)	■			■	■		
HALT-3*	24 countries	2016 – 2017				■			
TOTAL NUMBER OF STUDIES			4	0	2	1	4	0	0
Region: Northern Europe									
Blix, 2007	Norway	2003	■		■		■		
Blix, 2010	Norway	2006	■				■		
Fagan, 2012	Norway	2007 - 2008	■		■	■	■		
ESAC-1	Norway	2009	■		■		■		
Alberg, 2017	Norway	2016	■				■		
Rummukainen, 2009	Finland	2004 - 2005	■	■	■				
Rummukainen, 2013b	Finland	2009 - 2010	■	■	■				
Rummukainen, 2013a	Finland	2011	■				■		
van Buul, 2015b	Netherlands	2012 - 2013	■				■		
TOTAL NUMBER OF STUDIES			7	4	7	1	7	0	0
Region: British Isles									
Fleet, 2014	England	2010 - 2011	■		■				
Gillespie, 2015	Wales	2010 - 2012	■		■				
ESAC-2	Northern Ireland	2010	■				■		
ESAC-2	Northern Ireland	2011	■				■		
Roukens, 2017	Ireland	2011	■				■		
Thornley, 2019a	UK	2016	■		■		■		
Smith, 2020	UK	2016	■				■		
Thornley, 2019b*	UK	2017	■				■		
TOTAL NUMBER OF STUDIES			7	2	5	1	5	0	0
Region: Western Europe									
Heudorf, 2012	Germany	2011	■			■	■		
Marquet, 2015	France	2011 - 2013	■			■	■		■
Pluss-Suard, 2019	Switzerland	2011 - 2016	■			■	■		
TOTAL NUMBER OF STUDIES			3	2	0	3	0	0	1
Region: Southern Europe									
Moro, 2013	Italy	2010	■			■	■		
HALT-3*	Italy	2017	■			■	■		
TOTAL NUMBER OF STUDIES			2	2	0	2	0	0	0
Region: Eastern Europe									
HALT-2	Hungary	2013	■			■	■		
Stepan, 2018	Slovenia	2016	■			■	■		
TOTAL NUMBER OF STUDIES			2	2	0	2	0	0	0
Region: North America									
Drinka, 2004	US	1996 - 2002		■	■				
Benoit, 2008	US	2001 - 2002		■	■				■
Mylotte, 2005	US	2003		■	■				■
Pakyz, 2010	US	2004		■	■				■
Jump, 2012	US	2006 - 2010		■	■				■
Sloane, 2014	US	2010 & 2012		■	■				■
Rahme, 2012	US	2012		■	■				■
Felsen, 2020	US	2014		■	■				■
Kabbani, 2019	US	2016		■	■				■
Song, 2021	US	2016		■	■				■
Thompson, 2021*	US	2017		■	■				■
Marra, 2017	Canada	2007 - 2014	■			■	■		
Daneman, 2011	Canada	2009	■			■	■		
Daneman, 2013	Canada	2010	■			■	■		
Daneman, 2015	Canada	2010 - 2011	■			■	■		
Wu, 2015	Canada	2011 - 2012	■			■	■		
TOTAL NUMBER OF STUDIES			6	11	7	14	4	2	1
Region: Australia									
Sluggett, 2020	Australia	2005-2016	■						■
Smith, 2013	Australia	2011	■						■
Stuart, 2012	Australia	2011	■						■
Stuart, 2015	Australia	2012 & 2013	■						■
Cowan, 2016	Australia	2014	■						■
Raban, 2020*	Australia	2014-2017	■						■
acNAPS, 2016	Australia	2015	■						■
acNAPS, 2017	Australia	2016	■						■
acNAPS, 2018*	Australia	2017	■						■
acNAPS, 2019*	Australia	2018	■						■
acNAPS, 2020*	Australia	2019	■						■
TOTAL NUMBER OF STUDIES			11	11	9	0	0	2	0
Region: Asia									
Selcuk, 2018	Singapore	2008	■						■
Selcuk, 2019*	Singapore	2017	■						■
Takito, 2020	Japan	2010		■					■
Ishikane, 2020	Japan	2016		■					■
TOTAL NUMBER OF STUDIES			2	2	1	4	0	1	2
Total number of studies for all regions			44	36	31	28	20	5	4

Fig 4. Classes of three most frequently used antibiotics reported by studies. J01C is penicillins; J01D is cephalosporins; J01M is quinolones; J01X is other classes (includes only methenamine and nitrofurantoin); J01A is tetracyclines; J01F is macrolides. Classes J01M, J01A and J01F are on the World Health Organization’s (WHO) AWARe ‘Watch List’ and should be targeted for reduced use due to high resistance potential. Studies including data from 2017 or later are indicated with an asterisk. The WHO AWARe list was first published in 2017.

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[114]. In contrast, national antibiotic consumption in countries of Northern Europe is well below the average consumption of OECD countries [2, 114], however our analysis suggests rates of antibiotic use in Northern European LTCFs are high compared to other regions. The higher rates of antibiotic use in LTCFs, despite low national antibiotic consumption, demonstrate the importance of examining antibiotic use by health care sector to identify where targeted interventions are required.

Variation in antibiotic use between regions could be attributable to a number of factors. Firstly, LTCF resident characteristics can impact antibiotic use and may vary between countries and regions. We extracted the available data on resident characteristics reported in studies (S5, S7, and S9 Files). An examination of the available ($n = 71$) resident profiles for studies included in our point prevalence meta-analysis reveals these were generally consistent (S5 File). For example, the age of residents in studies included in our meta-analyses of point prevalence showed that between 40–60% of residents were aged >85 years. A few studies had younger populations, particularly in Eastern Europe; however these represented the minority of all studies (3 of 12 in Eastern Europe with available data). Secondly, differences in health systems and models of care could also account for between region variation in antibiotic use. By using regions in our subgroup analysis, some of these differences can be accounted for, albeit in an imperfect way. A more detailed analysis of models of care or health system factors that lead to lower antibiotic use in LTCFs was beyond the scope of this analysis; however recent systematic reviews and analyses of facility level variation in antibiotic use elucidate some of these factors and strategies that may be effective in reducing use [20, 30, 45, 115]. Finally, differences in prescribing practices and LTCF policies in infection treatment and control have an impact on antibiotic use. This has been highlighted in research examining antibiotic use differences between LTCFs within countries and states, as well as those within single aged care provider networks [7, 10, 30, 115].

There were also regional differences in the types of antibiotics used. Quinolones were one of the three most frequently prescribed classes of antibiotics in five of the eight regions, particularly in studies from North America (14 of 16 studies in that region [7, 8, 40, 44, 68, 81, 90, 108, 111, 116]). This is a concern as quinolones are antibiotics with high resistance potential and are listed on the WHO's Watch List of antibiotics that should be targeted for a reduction in use. Additionally, quinolones carry a higher risk for development of *Clostridioides difficile* colitis compared to other antibiotic classes [117]. In Australia, quinolone use is restricted in the community (and hence LTCFs) by the requirement that doctors obtain special authority at the time of prescribing. As a result of this national regulation, quinolone use in Australian LTCFs is low, despite overall antibiotic use in Australian LTCFs being high compared to other regions. A positive finding with respect to antibiotics on the WHO Watch List was that macrolides were reported to be among the three most frequently prescribed antibiotics in only four studies, one from France [74], one from the US [40], and two from Japan [67, 100].

Our findings indicate low rates of appropriate use of antibiotics in LTCFs, and, as assessed by the McGeer criteria, each year was associated with lower odds of antibiotic prescriptions being appropriate. However, this result is heavily based on estimates from Australia (six of eight studies) which show a decreasing trend in appropriateness between 2010–2018. Between 2006 and 2015 in Australia, the people entering LTCFs were older and more frail, a trend which likely contributes to increases in antibiotic use overall, as well as inappropriate use [30, 118]. However, the changes in the health and demographics of the LTCFs population would not account entirely for the decrease in antibiotic appropriateness, which requires further investigation. Furthermore, measurement of appropriateness across more countries and regions is required for a more robust estimation of regional and temporal trends.

The McGeer criteria were originally developed for infection surveillance in LTCFs [119] and to assess whether an infection is present, and thus whether treatment with an antibiotic is warranted. By way of comparison, seven studies included in our review used national or local guidelines to assess whether the type and dose of antibiotic used was appropriate (S8 File). Though we were not able to pool these results in a meta-analysis, levels of appropriate antibiotic choice were typically above 70%. This demonstrates how the choice of appropriateness algorithm or guideline affects estimates of appropriateness, and the need for studies to be clear in what features of antibiotic appropriateness they are assessing. Furthermore, based on the results of the included studies, the initiation of antibiotic treatment in LTCFs should be a key area for antimicrobial stewardship programs.

Our analysis did not find a change in antibiotic use prevalence in LTCFs over the study period (1985–2019 for point prevalence and 1985–2017 for 12-month period prevalence). This may be due to the small number of studies in earlier years (see S10 File). However, national antibiotic consumption levels are changing at varying rates between countries. For example, between 2000 and 2010, national antibiotic consumption was shown to be decreasing in the US, Canada, Spain, France, and Germany; but increasing in Australia, the United Kingdom, and several Asian countries [2]. In Australia, the first decreases in national antibiotic consumption were reported in 2015 and have persisted till now [120]. Thus, though we did not detect an overall trend in antibiotic use in LTCFs, this does not preclude changes in antibiotic use rates within regions and countries over time, which our analysis was not powered to detect. This raises the important issue of surveillance of antibiotic use in LTCFs by countries. Ideally, the data collected would allow the measurement of temporal trends. Point prevalence surveys, which are the main source of antibiotic use data in LTCFs, have limited ability to do this unless they are conducted for many years. Other data sources such as electronic databases of medication supply or electronic records from LTCFs provide the ability to monitor trends over time using multiple key indicators in addition to prevalence, such as DOT per 1000 resident days and number of courses per 1000 resident days [10, 30, 92, 116].

There are several limitations to our analysis. Firstly, we were not able to combine estimates of the DOT/1000 days, DDD/1000 days and number of courses/1000 days with meta-analysis due to differences in the reporting of these outcomes. These outcomes account for the length of treatment (DOT, DDD), the dose of treatment (DDD), and the frequency of treatment (number of courses). Thus, they are more sensitive to detecting changes over time than the prevalence of antibiotic use. Standardising the reporting of these outcomes in studies to facilitate the compilation of results is important for ongoing surveillance efforts. Secondly, there was heterogeneity in the antibiotic use rates reported in the meta-analyses. The variation in antibiotic use between facilities has been reported in previous studies and reviews [4, 6, 44, 50, 121]. A strength of our analysis was that we explored whether region and year of measurement explained this heterogeneity using meta-regression; however, we were unable to adjust for resident demographics and prevalence of key health conditions as planned due to inconsistencies in the way these were reported. We also ensured we were comparing systemic antibiotic use rates and rates of use in LTCFs for older adults. The meta-regression models for point prevalence and the prevalence of appropriate antibiotic courses explained 56% and 85% of the between study variance, respectively. Lastly, our review did not identify data from countries in the regions of Asia (aside from Singapore), South America or Africa. This is a key limitation of current surveillance efforts in LTCFs since antibiotic use is growing at rapid rates in middle-income countries [2].

Antibiotic use in LTCFs has gained substantial attention nationally and internationally in recent years as evidenced by the steady growth in the number of monitoring activities and intervention studies (see S10 File) [16, 20, 62]. However, growing concerns of inappropriate

antibiotic use are yet to be addressed by the widespread development of national antibiotic stewardship activities specific to LTCFs in many countries. The majority of antibiotic stewardship in LTCFs to date have been local initiatives involving small numbers of facilities and delivered mixed results [18, 20]. The European Centre for Disease Prevention and Control reported that of the 1043 LTCFs participating in the HALT-2 survey of 2013, 46% did not have any antibiotic stewardship elements in place, and 76.4% did not have a list of antibiotics for restricted use [18]. There was no substantial improvement in the presence of these antibiotic stewardship elements in the 2016–17 HALT survey [62]. While many countries release national strategies to combat antimicrobial resistance that address human antibiotic use, these tend to focus on strategies and targets for community and hospital antibiotic use [122–124]. Our results highlight the need for specific strategies for LTCFs, particularly since LTCFs serve a unique population with complex care needs distinct from the general population.

Conclusions

Concerted efforts are needed to tackle inappropriate use of antibiotics in LTCFs. In this review, we have summarized the body of literature on antibiotic use in LTCFs over a 35-year period (1985–2019) and compared antibiotic use among regions. We have highlighted key areas requiring action, including regions without data, regions with higher antibiotic use in LTCFs and the common use of antibiotics with high resistance potential, namely quinolones. Our analysis provides a regional and overall baseline against which to monitor progress in reducing antibiotic use in LTCFs.

Supporting information

S1 File. PROSPERO registration.

(PDF)

S2 File. PRISMA checklist.

(DOCX)

S3 File. Search strategy.

(DOCX)

S4 File. Quality assessment score for studies as assessed against Joanna Briggs Institute Critical Appraisal Tool for Prevalence Studies.

(DOCX)

S5 File. Point prevalence meta-analysis results, reported resident characteristics, and resident eligibility.

(DOCX)

S6 File. Detailed heterogeneity statistics.

(DOCX)

S7 File. Resident characteristics and inclusion criteria reported in studies included in 12-month period prevalence antibiotic use meta-analysis.

(DOCX)

S8 File. Antibiotic use in long-term aged care facilities (studies not included in meta-analyses).

(DOCX)

S9 File. Resident characteristics reported in studies included in appropriateness of antibiotic use (according to McGeer criteria) meta-analysis.

(DOCX)

S10 File. Number of studies measuring antibiotic use in LTCF included in this systematic review by year.

(DOCX)

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References

1. World Health Organization. Antibiotic resistance—a threat to global health security. WHO. 2013. http://www.who.int/antimicrobial-resistance/events/wha66_side_event/en/
2. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis*. 2014; 14(8):742–750. [https://doi.org/10.1016/S1473-3099\(14\)70780-7](https://doi.org/10.1016/S1473-3099(14)70780-7) PMID: 25022435
3. World Health Organization. WHO report on surveillance of antibiotic consumption: 2016–2018 early implementation. Geneva: WHO. 2018. <https://apps.who.int/iris/bitstream/handle/10665/277359/9789241514880-eng.pdf?ua=1>
4. Falcone M, Paul M, Yahav D, Orlando G, Tiseo G, Prendki V, et al. Antimicrobial consumption and impact of antimicrobial stewardship programmes in long-term care facilities. *Clin Microbiol Infect*. 2019; 25(5):562–569. <https://doi.org/10.1016/j.cmi.2018.07.028> PMID: 30076978
5. Brown KA, Chambers A, MacFarlane S, Langford B, Leung V, Quirk J, et al. Reducing unnecessary urine culturing and antibiotic overprescribing in long-term care: a before-and-after analysis. *CMAJ Open*. 2019; 7(1):E174–e181. <https://doi.org/10.9778/cmajo.20180064> PMID: 30926601
6. van Buul LW, van der Steen JT, Veenhuizen RB, Achterberg WP, Schellevis FG, Essink RT, et al. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc*. 2012; 13(6):568.e1–13. <https://doi.org/10.1016/j.jamda.2012.04.004> PMID: 22575772
7. Daneman N, Gruneir A, Bronskill SE, Newman A, Fischer HD, Rochon PA, et al. Prolonged antibiotic treatment in long-term care: role of the prescriber. *JAMA Intern Med*. 2013; 173(8):673–682. <https://doi.org/10.1001/jamainternmed.2013.3029> PMID: 23552741

8. Marra F, McCabe M, Sharma P, Zhao B, Mill C, Leung V, et al. Utilization of Antibiotics in Long-Term Care Facilities in British Columbia, Canada. *J Am Med Dir Asso.* 2017; 18(12):1098.e1091–1098. e1011. <https://doi.org/10.1016/j.jamda.2017.09.018> PMID: 29169741
9. Mayne S, Sundvall PD, Gunnarsson R. Confusion Strongly Associated with Antibiotic Prescribing Due to Suspected Urinary Tract Infections in Nursing Homes. *J Am Geriatr Soc.* 2018; 66(2):274–281. <https://doi.org/10.1111/jgs.15179> PMID: 29318570
10. Thornley T, Ashiru-Oredope D, Normington A, Beech E, Howard P. Antibiotic prescribing for residents in long-term-care facilities across the UK. *J Antimicrob Chemother.* 2019; 74(5):1447–1451. <https://doi.org/10.1093/jac/dkz008> PMID: 30698718
11. Donskey CJ, Sunkesula VCK, Stone ND, Gould CV, McDonald LC, Samore M, et al. Transmission of *Clostridium difficile* from asymptotically colonized or infected long-term care facility residents. *Infect Control Hosp Epidemiol.* 2018; 39(8):909–916. <https://doi.org/10.1017/ice.2018.106> PMID: 29848392
12. Kahvecioglu D, Ramiah K, McMaughan D, Garfinkel S, McSorley VE, Nguyen QN, et al. Multidrug-resistant organism infections in US nursing homes: a national study of prevalence, onset, and transmission across care settings, October 1, 2010–December 31, 2011. *Infect Control Hosp Epidemiol.* 2014; 35 Suppl 3:S48–55.
13. World Health Organization. Global antimicrobial resistance surveillance system (GLASS) report: Early implementation 2017–2018. Geneva: WHO. 2019. <https://www.who.int/glass/resources/publications/early-implementation-report-2017-2018/en/>
14. European Centre for Disease Prevention and Control. ECDC/HALT point prevalence survey of health-care-associated infections and antimicrobial use in nursing homes. 2012. www.ecdc.europa.eu/en/publications/publications/0512-ted-pps-hai-antimicrobialuse-protocol.pdf
15. McClean P, Hughes C, Tunney M, Goossens H, Jans B, European Surveillance of Antimicrobial Consumption Nursing Home Project G. Antimicrobial prescribing in European nursing homes. *J Antimicrob Chemother.* 2011; 66(7):1609–1616. <https://doi.org/10.1093/jac/dkr183> PMID: 21596722
16. Australian Commission on Safety and Quality in Health Care. 2018 Aged Care National Antimicrobial Prescribing Survey Report. 2019. <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/2018-aged-care-national-antimicrobial-prescribing-survey-report>
17. Centers for Disease Control and Prevention. The Core Elements of Antibiotic Stewardship for Nursing Homes. Atlanta, GA: US Department of Health and Human Services, CDC. 2015. <https://www.cdc.gov/longtermcare/pdfs/core-elements-antibiotic-stewardship.pdf>
18. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European long-term care facilities. April–May 2013. 2014, ECDC: Stockholm.
19. Public Health Agency of Canada. Canadian Antimicrobial Resistance Surveillance System—Update 2018. Ottawa: Public Health Agency of Canada. 2019. <https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-2018-report-executive-summary/pub1-eng.pdf>
20. Raban MZ, Gasparini C, Li L, Baysari MT, Westbrook JI. Effectiveness of interventions targeting antibiotic use in long-term aged care facilities: a systematic review and meta-analysis. *BMJ Open.* 2020; 10(1):e028494. <https://doi.org/10.1136/bmjopen-2018-028494> PMID: 31924627
21. Wu JH, Langford BJ, Daneman N, Friedrich JO, Garber G. Antimicrobial Stewardship Programs in Long-Term Care Settings: A Meta-Analysis and Systematic Review. *J Am Geriatr Soc.* 2019; 67(2):392–399. <https://doi.org/10.1111/jgs.15675> PMID: 30517765
22. Fleming A, Browne J, Byrne S. The effect of interventions to reduce potentially inappropriate antibiotic prescribing in long-term care facilities: a systematic review of randomised controlled trials. *Drugs Aging.* 2013; 30(6):401–8. <https://doi.org/10.1007/s40266-013-0066-z> PMID: 23444263
23. Nace DA, Hanlon JT, Crnich CJ, Drinka PJ, Schweon SJ, Anderson G, et al. A multifaceted antimicrobial stewardship program for the treatment of uncomplicated cystitis in nursing home residents. *JAMA Intern Med.* 2020. <https://doi.org/10.1001/jamainternmed.2020.1256> PMID: 32391862
24. Publications Office of the European Union. EuroVoc. 2020. <http://publications.europa.eu/resource/dataset/eurovoc>
25. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. ATC/DDD Index 2020. 2019. https://www.whocc.no/atc_ddd_index/
26. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. *Int J Evid Based Healthcare.* 2015; 13(3):147–153. <https://doi.org/10.1097/XEB.000000000000054> PMID: 26317388

27. Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I(2) is not an absolute measure of heterogeneity. *Res Synth Methods*. 2017; 8(1):5–18. <https://doi.org/10.1002/jrsm.1230> PMID: 28058794
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315(7109):629–34. <https://doi.org/10.1136/bmj.315.7109.629> PMID: 9310563
29. Duval S, Tweedie R. A Nonparametric “Trim and Fill” Method of Accounting for Publication Bias in Meta-Analysis. *J Am Stat Assoc*. 2000; 95(449):89–98.
30. Raban MZ, Lind KE, Day RO, Gray L, Georgiou A, Westbrook JI. Trends, determinants and differences in antibiotic use in 68 residential aged care homes in Australia, 2014–2017: a longitudinal analysis of electronic health record data. *BMC Health Serv Res*. 2020; 20(1):883. <https://doi.org/10.1186/s12913-020-05723-3> PMID: 32948168
31. Borenstien MHL.; Higgins J. P. T.; Rothstein H, *Comprehensive Meta-Analysis Version 3*. 2013, Bio-statistics, Englewood, NJ 2013.
32. RStudio Team. *RStudio: Integrated Development for R*. Boston: RStudio, PBC. 2020. <http://www.rstudio.com/>
33. Alberg T, Holen O, Blix HS, Lindbaek M, Bentele H, Eriksen HM. Antibiotic use and infections in nursing homes. *Tidsskr Nor Laegeforen*. 2017; 137(5):357–361. PMID: 28272565
34. Barney GR, Felsen CB, Dumyati GK. One-day point prevalence as a method for estimating antibiotic use in nursing homes. *Infect Control Hosp Epidemiol*. 2019; 40(2):221–223. <https://doi.org/10.1017/ice.2018.309> PMID: 30516118
35. National Centre for Antimicrobial Stewardship, Australian Commission on Safety and Quality in Health Care. *Antimicrobial prescribing and infections in Australian residential aged care facilities: results of the 2015 Aged Care National Antimicrobial Prescribing Survey pilot*. 2016. <https://www.safetyandquality.gov.au/sites/default/files/migrated/Antimicrobial-prescribing-and-infections-in-Australian-residential-aged-care-facilities-2015-acNAPS.pdf>
36. National Centre for Antimicrobial Stewardship, Australian Commission on Safety and Quality in Health Care. *Aged Care National Antimicrobial Prescribing Survey 2016*. Sydney: ACSQHC. 2017. <https://www.safetyandquality.gov.au/sites/default/files/migrated/Report-2016-acNAPS-Sep-2017.pdf>
37. National Centre for Antimicrobial Stewardship, Australian Commission on Safety and Quality in Health Care. *Antimicrobial Prescribing and Infections in Australian Aged Care Homes: Results of the 2017 Aged Care National Antimicrobial Prescribing Survey*. Sydney: ACSQHC. 2018. <https://www.safetyandquality.gov.au/sites/default/files/migrated/2017-acNAPS.pdf>
38. National Centre for Antimicrobial Stewardship, Australian Commission on Safety and Quality in Health Care. *Antimicrobial Prescribing and Infections in Australian Aged Care Homes: Results of the 2018 Aged Care National Antimicrobial Prescribing Survey*. 2019. <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/2018-aged-care-national-antimicrobial-prescribing-survey-report>
39. National Centre for Antimicrobial Stewardship, Australian Commission on Safety and Quality in Health Care. *2019 Aged Care National Antimicrobial Prescribing Survey Report*. Sydney: ACSQHC. 2020. https://www.safetyandquality.gov.au/sites/default/files/2020-11/report_-_2019_ac_naps.pdf
40. Benoit SR, Nsa W, Richards CL, Bratzler DW, Shefer AM, Steele LM, et al. Factors associated with antimicrobial use in nursing homes: a multilevel model. *J Am Geriatr Soc*. 2008; 56(11):2039–2044. <https://doi.org/10.1111/j.1532-5415.2008.01967.x> PMID: 19016937
41. Blix HS, Roed J, Sti MO. Large variation in antibacterial use among Norwegian nursing homes. *Scand J Infect Dis*. 2007; 39(6–7):536–541. <https://doi.org/10.1080/00365540601113701> PMID: 17577815
42. Boivin Y, Talon D, Leroy J, Floret N, Gbaguidi-Haore H, Bertrand X. Antibiotic prescription in nursing homes for dependent elderly people: a cross-sectional study in Franche-Comte. *Medecine et Maladies Infectieuses*. 2013; 43(4):163–169. <https://doi.org/10.1016/j.medmal.2013.03.004> PMID: 23622952
43. Cowan RU, Kishan D, Walton AL, Sneath E, Cheah T, Butwilowsky J, et al. Cleaning, resistant bacteria, and antibiotic prescribing in residential aged care facilities. *Am J Infect Control*. 2016; 44(3):e19–21. <https://doi.org/10.1016/j.ajic.2015.09.034> PMID: 26590000
44. Daneman N, Bronskill SE, Gruneir A, Newman AM, Fischer HD, Rochon PA, et al. Variability in Antibiotic Use Across Nursing Homes and the Risk of Antibiotic-Related Adverse Outcomes for Individual Residents. *JAMA Intern Med*. 2015; 175(8):1331–1339. <https://doi.org/10.1001/jamainternmed.2015.2770> PMID: 26121537
45. Daneman N, Campitelli MA, Giannakeas V, Morris AM, Bell CM, Maxwell CJ, et al. Influences on the start, selection and duration of treatment with antibiotics in long-term care facilities. *CMAJ Canadian Medical Association Journal*. 2017; 189(25):E851–E860. <https://doi.org/10.1503/cmaj.161437> PMID: 28652480

46. Drinka PJ, Gauwerke C, Le D. Antimicrobial use and methicillin-resistant *Staphylococcus aureus* in a large nursing home. *J Am Med Dir Asso*. 2004; 5(4):256–258.
47. Eikelenboom-Boskamp A, Saris K, van Loosbroek M, Drabbe MIJ, de Jongh F, de Jong JWD, et al. Prevalence of healthcare-associated infections in Dutch nursing homes: follow-up 2010–2017. *J Hosp Infect*. 2019; 101(1):49–52. <https://doi.org/10.1016/j.jhin.2018.08.011> PMID: 30149087
48. Eriksen HM, Saether AR, Viktil KK, Andberg L, Munkeud MW, Willoch K, et al. Use of antibiotics in nursing homes—surveillance with different methods. *Tidsskr Nor Laegeforen*. 2013; 133(19):2052–2056. PMID: 24129536
49. Latour K, Catry B, Broex E, Vankerckhoven V, Muller A, Stroobants R, et al. Indications for antimicrobial prescribing in European nursing homes: results from a point prevalence survey. *Pharmacoepidemiol Drug Saf*. 2012; 21(9):937–944. <https://doi.org/10.1002/pds.3196> PMID: 22271462
50. McClean P, Tunney M, Gilpin D, Parsons C, Hughes C. Antimicrobial prescribing in nursing homes in Northern Ireland: results of two point-prevalence surveys. *Drugs Aging*. 2011; 28(10):819–29. <https://doi.org/10.2165/11595050-000000000-00000> PMID: 21970309
51. Rummukainen ML, Karki T, Kanerva M, Haapasaari M, Ollgren J, Lyytikainen O. Antimicrobial prescribing in nursing homes in Finland: results of three point prevalence surveys. *Infection*. 2013; 41(2):355–360. <https://doi.org/10.1007/s15010-012-0331-9> PMID: 22983808
52. McClean P, Tunney M, Gilpin D, Parsons C, Hughes C. Antimicrobial prescribing in residential homes. *J Antimicrob Chemother*. 2012; 67(7):1781–1790. <https://doi.org/10.1093/jac/dks085> PMID: 22438433
53. Fagan M, Maehlen M, Lindbaek M, Berild D. Antibiotic prescribing in nursing homes in an area with low prevalence of antibiotic resistance: compliance with national guidelines. *Scand J Prim Health Care*. 2012; 30(1):10–15. <https://doi.org/10.3109/02813432.2011.629156> PMID: 22188479
54. Felsen CB, Dodds Ashley ES, Barney GR, Nelson DL, Nicholas JA, Yang H, et al. Reducing Fluoroquinolone Use and *Clostridioides difficile* Infections in Community Nursing Homes Through Hospital-Nursing Home Collaboration. *J Am Med Dir Assoc*. 2020; 21(1):55–61.e2. <https://doi.org/10.1016/j.jamda.2019.11.010> PMID: 31888865
55. Fleet E, Gopal Rao G, Patel B, Cookson B, Charlett A, Bowman C, et al. Impact of implementation of a novel antimicrobial stewardship tool on antibiotic use in nursing homes: a prospective cluster randomized control pilot study. *J Antimicrob Chemother*. 2014; 69(8):2265–2273. <https://doi.org/10.1093/jac/dku115> PMID: 24777901
56. Gillespie D, Hood K, Bayer A, Carter B, Duncan D, Espinasse A, et al. Antibiotic prescribing and associated diarrhoea: a prospective cohort study of care home residents. *Age Ageing*. 2015; 44(5):853–860. <https://doi.org/10.1093/ageing/afv072> PMID: 26104506
57. Eilers R, Veldman-Ariesen MJ, Haenen A, van Benthem BH. Prevalence and determinants associated with healthcare-associated infections in long-term care facilities (HALT) in the Netherlands, May to June 2010. *Euro Surveill*. 2012; 17(34). PMID: 22939212
58. European Centre for Disease Prevention and Control, Point prevalence survey of healthcare-associated infections and antimicrobial use in European long-term care facilities. May–September 2010. 2014, ECDC: Stockholm.
59. Cotter M, Donlon S, Roche F, Byrne H, Fitzpatrick F. Healthcare-associated infection in Irish long-term care facilities: results from the First National Prevalence Study. *J Hosp Infect*. 2012; 80(3):212–6. <https://doi.org/10.1016/j.jhin.2011.12.010> PMID: 22305100
60. Moro ML, Ricchizzi E, Morsillo F, Marchi M, Puro V, Zotti CM, et al. Infections and antimicrobial resistance in long term care facilities: a national prevalence study. *Ann Ig*. 2013; 25(2):109–118. <https://doi.org/10.7416/ai.2013.1912> PMID: 23471448
61. Furmenti MF, Rossello P, Bianco S, Olivero E, Thomas R, Emelurumonye IN, et al. Healthcare-associated infections and antimicrobial use in long-term care facilities (HALT3): an overview of the Italian situation. *J Hosp Infect*. 2019; 102(4):425–430. <https://doi.org/10.1016/j.jhin.2019.02.007> PMID: 30790605
62. Ricchizzi E, Latour K, Karki T, Buttazzi R, Jans B, Moro ML, et al. Antimicrobial use in European long-term care facilities: results from the third point prevalence survey of healthcare-associated infections and antimicrobial use, 2016 to 2017. *Euro Surveill*. 2018; 23(46). <https://doi.org/10.2807/1560-7917.ES.2018.23.46.1800394> PMID: 30458913
63. Szabo R, Borocz K. Antimicrobial use in Hungarian long-term care facilities: high proportion of quinolone antibacterials. *Arch Gerontol Geriatr*. 2014; 59(1):190–193. <https://doi.org/10.1016/j.archger.2014.02.011> PMID: 24679670
64. Tandan M, Burns K, Murphy H, Hennessy S, Cormican M, Vellinga A. Antimicrobial prescribing and infections in long-term care facilities (LTCF): a multilevel analysis of the HALT 2016 study, Ireland, 2017. *Euro Surveill*. 2018; 23(46).

65. Tandan M, O'Connor R, Burns K, Murphy H, Hennessy S, Roche F, et al. A comparative analysis of prophylactic antimicrobial use in long-term care facilities in Ireland, 2013 and 2016. *Euro Surveill.* 2019; 24(11).
66. Heudorf U, Boehlcke K, Schade M. Healthcare-associated infections in long-term care facilities (HALT) in Frankfurt am Main, Germany, January to March 2011. *Euro Surveill.* 2012; 17(35):30.
67. Ishikane M, Kusama Y, Tanaka C, Hayakawa K, Kuwahara T, Ohmagari N. Epidemiology of Antimicrobial Use among Nursing Homes in Japan, 2016: a Pilot Study. *Jpn J Infect Dis.* 2020; 73(4):293–295. <https://doi.org/10.7883/yoken.JJID.2019.476> PMID: 32009058
68. Jump RL, Olds DM, Seifi N, Kypriotakis G, Jury LA, Peron EP, et al. Effective antimicrobial stewardship in a long-term care facility through an infectious disease consultation service: keeping a LID on antibiotic use. *Infect Control Hosp Epidemiol.* 2012; 33(12):1185–1192. <https://doi.org/10.1086/668429> PMID: 23143354
69. Kabbani S, Palms DL, Bartoces M, Marek J, Stone ND, Hicks LA, et al. Potential utility of pharmacy data to measure antibiotic use in nursing homes. *Infect Control Hosp Epidemiol.* 2019; 40(7):819–820. <https://doi.org/10.1017/ice.2019.95> PMID: 31014405
70. Katz PR, Beam TR Jr., Brand F, Boyce K. Antibiotic use in the nursing home. Physician practice patterns. *Arch Intern Med.* 1990; 150(7):1465–1468. PMID: 2369244
71. Lee YL, Thrupp LD, Friis RH, Fine M, Maleki P, Cesario TC. Nosocomial infection and antibiotic utilization in geriatric patients: a pilot prospective surveillance program in skilled nursing facilities. *Gerontology.* 1992; 38(4):223–232. <https://doi.org/10.1159/000213332> PMID: 1427120
72. Lee YL, Thrupp LD, Lee R, Nothvogel S, Farsad N, Cesario T. Infection surveillance and antibiotic utilization in a community-based skilled nursing facility. *Aging Clin Exper Res.* 1996; 8(2):113–122.
73. Loeb M, Brazil K, Lohfeld L, McGeer A, Simor A, Stevenson K, et al. Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. *BMJ.* 2005; 331(7518):669. <https://doi.org/10.1136/bmj.38602.586343.55> PMID: 16150741
74. Marquet A, Thibaut S, LePabic E, Huon JF, Ballereau F. Three years of antibiotic consumption evaluation in French nursing homes. *Medecine et Maladies Infectieuses.* 2015; 45(8):313–317. <https://doi.org/10.1016/j.medmal.2015.05.006> PMID: 26112930
75. Monette J, Miller MA, Monette M, Laurier C, Boivin JF, Sourial N, et al. Effect of an educational intervention on optimizing antibiotic prescribing in long-term care facilities. *J Am Geriatr Soc.* 2007; 55(8):1231–1235. <https://doi.org/10.1111/j.1532-5415.2007.01250.x> PMID: 17661962
76. Montgomery P, Semenchuk M, Nicolle LE. Antimicrobial use in nursing homes in Manitoba. *J Geriatr Drug Ther.* 1995; 9(3):55–74.
77. Moro ML, Mongardi M, Marchi M, Taroni F. Prevalence of long-term care acquired infections in nursing and residential homes in the Emilia-Romagna Region. *Infection.* 2007; 35(4):250–255. <https://doi.org/10.1007/s15010-007-6200-2> PMID: 17646916
78. Mylotte JM. Antimicrobial prescribing in long-term care facilities: prospective evaluation of potential antimicrobial use and cost indicators. *Am J Infect Control.* 1999; 27(1):10–19. [https://doi.org/10.1016/S0196-6553\(99\)70069-6](https://doi.org/10.1016/S0196-6553(99)70069-6) PMID: 9949373
79. Natsch S, Hekster YA, de Jong R, Heerdink ER, Herings RM, van der Meer JW. Application of the ATC/DDD methodology to monitor antibiotic drug use. *Eur J Clin Microbiol Infect Dis.* 1998; 17(1):20–24. <https://doi.org/10.1007/BF01584358> PMID: 9512177
80. Olsho LE, Bertrand RM, Edwards AS, Hadden LS, Morefield GB, Hurd D, et al. Does adherence to the Loeb minimum criteria reduce antibiotic prescribing rates in nursing homes? *J Am Med Dir Assoc.* 2013; 14(4):309.e301–307. <https://doi.org/10.1016/j.jamda.2013.01.002> PMID: 23414914
81. Pakyz AL, Dwyer LL. Prevalence of antimicrobial use among United States nursing home residents: results from a national survey. *Infect Control Hosp Epidemiol.* 2010; 31(6):661–662. <https://doi.org/10.1086/653072> PMID: 20426578
82. Pluss-Suard C, Niquille A, Hequet D, Krahenbuhl S, Pichon R, Zanetti G, et al. Decrease in Antibacterial Use and Facility-Level Variability After the Introduction of Guidelines and Implementation of Physician-Pharmacist-Nurse Quality Circles in Swiss Long-term Care Facilities. *J Am Med Dir Assoc.* 2020; 21(1):78–83. <https://doi.org/10.1016/j.jamda.2019.05.016> PMID: 31327571
83. Rahme CL, Jacoby HM, Avery LM. Impact of a Hospital's Antibiotic Stewardship Team on Fluoroquinolone Use at a Long-Term Care Facility. *Ann Longterm Care.* 2016; 24(6):13–20.
84. Roukens M, Verhoef L, Stobberingh E, Natsch S. Surveillance of antimicrobial use in Dutch long-term care facilities. *J Antimicrob Chemother.* 2017; 72(5):1516–1520. <https://doi.org/10.1093/jac/dkw581> PMID: 28100443

85. Rummukainen M, Jakobsson A, Karppi P, Kautiainen H, Lyytikäinen O. Promoting hand hygiene and prudent use of antimicrobials in long-term care facilities. *Am J Infect Control*. 2009; 37(2):168–171. <https://doi.org/10.1016/j.ajic.2008.09.020> PMID: 19155095
86. Rummukainen ML, Makela M, Noro A, Finne-Soveri H, Lyytikäinen O. Assessing prevalence of antimicrobial use and infections using the minimal data set in Finnish long-term care facilities. *Am J Infect Control*. 2013; 41(4):e35–37. <https://doi.org/10.1016/j.ajic.2012.09.007> PMID: 23332375
87. Saxena FE, Bronskill SE, Brown KA, Campitelli MA, Garber G, Langford B, et al. The Association of Resident Communication Abilities and Antibiotic Use in Long-Term Care. *J Am Geriatr Soc*. 2019; 67(6):1164–1173. <https://doi.org/10.1111/jgs.15771> PMID: 30690721
88. Selcuk A, Teng CB, Chan SY, Yap KZ. Antimicrobial use and drug-drug interactions among nursing home residents in Singapore: a multicentre prevalence study. *Int J Clin Pharm*. 2018. <https://doi.org/10.1007/s11096-018-0683-z> PMID: 30054787
89. Selcuk A, Yap KZ, Wong CL, Yang JX, Yong PC, Chan SY, et al. A Point Prevalence Study of Antimicrobial Use and Practice Among Nursing Homes in Singapore. *Drugs Aging*. 2019; 36(6):559–570. <https://doi.org/10.1007/s40266-019-00651-2> PMID: 30972716
90. Sloane PD, Zimmerman S, Reed D, Beeber AS, Chisholm L, Kistler C, et al. Antibiotic prescribing in 4 assisted-living communities: incidence and potential for improvement. *Infect Control Hosp Epidemiol*. 2014; 35 Suppl 3:S62–68. <https://doi.org/10.1086/677821> PMID: 25222900
91. Sloane PD, Zimmerman S, Ward K, Kistler CE, Paone D, Weber DJ, et al. A 2-Year Pragmatic Trial of Antibiotic Stewardship in 27 Community Nursing Homes. *J Am Geriatr Soc*. 2020. <https://doi.org/10.1111/jgs.16059> PMID: 31317534
92. Sluggett JK, Moldovan M, Lynn DJ, Papanicolas LE, Crotty M, Whitehead C, et al. National Trends in Antibiotic Use in Australian Residential Aged Care Facilities, 2005–2016. *Clin Infect Dis*. 2020.
93. Smith CM, Williams H, Jhass A, Patel S, Crayton E, Lorenzatto F, et al. Antibiotic prescribing in UK care homes 2016–2017: retrospective cohort study of linked data. *BMC Health Serv Res*. 2020; 20(1):555. <https://doi.org/10.1186/s12913-020-05422-z> PMID: 32552886
94. Smith M, Atkins S, Worth L, Richards M, Bennett N. Infections and antimicrobial use in Australian residential aged care facilities: a comparison between local and international prevalence and practices. *Austr Health Rev*. 2013; 37(4):529–534.
95. Song S, Wilson BM, Bej T, Gravenstein S, Carter RR, Marek J, et al. Antibiotic Use Among Residents Receiving Skilled Nursing Care in 29 U.S. Nursing Homes. *J Am Geriatr Soc*. 2021; 69(2):399–406. <https://doi.org/10.1111/jgs.16856> PMID: 33037613
96. Stepan D, Usaj L, Petek Ster M, Smolinger Galun M, Smole H, Beovic B. Antimicrobial prescribing in long-term care facilities: a nationwide point-prevalence study, Slovenia, 2016. *Euro Surveill*. 2018; 23(46).
97. Stuart RL, Orr E, Kotsanas D, Gillespie EE. A nurse-led antimicrobial stewardship intervention in two residential aged care facilities. *Healthcare Infection*. 2015; 20(1):4–6.
98. Stuart RL, Wilson J, Bellaard-Smith E, Brown R, Wright L, Vandergraaf S, et al. Antibiotic use and misuse in residential aged care facilities. *Intern Med J*. 2012; 42(10):1145–1149. <https://doi.org/10.1111/j.1445-5994.2012.02796.x> PMID: 22472087
99. Sundvall PD, Stuart B, Davis M, Roderick P, Moore M. Antibiotic use in the care home setting: a retrospective cohort study analysing routine data. *BMC Geriatr*. 2015; 15:71. <https://doi.org/10.1186/s12877-015-0073-5> PMID: 26108340
100. Takito S, Kusama Y, Fukuda H, Kutsuna S. Pharmacist-supported antimicrobial stewardship in a retirement home. *J Infect Chemother*. 2020; 26(8):858–861.
101. Taxis K, Kochen S, Wouters H, Boersma F, Jan Gerard M, Mulder H, et al. Cross-national comparison of medication use in Australian and Dutch nursing homes. *Age Ageing*. 2017;320–323 LID—<https://doi.org/10.1093/ageing/afw218> PMID: 27974305
102. Temime L, Cohen N, Ait-Bouziad K, Denormandie P, Dab W, Hocine MN. Impact of a multicomponent hand hygiene-related intervention on the infectious risk in nursing homes: A cluster randomized trial. *Am J Infect Control*. 2018; 46(2):173–179. <https://doi.org/10.1016/j.ajic.2017.08.030> PMID: 28987524
103. Thompson ND, LaPlace L, Epstein L, Thompson D, Dumyati G, Concannon C, et al. Prevalence of Antimicrobial Use and Opportunities to Improve Prescribing Practices in U.S. Nursing Homes. *J Am Med Dir Asso*. 2016; 17(12):1151–1153. <https://doi.org/10.1016/j.jamda.2016.08.013> PMID: 27751803
104. Thompson ND, Stone ND, Brown CJ, Penna AR, Eure TR, Bamberg WM, et al. Antimicrobial Use in a Cohort of US Nursing Homes, 2017. *JAMA*. 2021; 325(13):1286–1295. <https://doi.org/10.1001/jama.2021.2900> PMID: 33821897

105. Thornley T, Ashiru-Oredope D, Beech E, Howard P, Kirkdale CL, Elliott H, et al. Antimicrobial use in UK long-term care facilities: Results of a point prevalence survey. *J Antimicrob Chemother.* 2019; 74(7):2083–2090. <https://doi.org/10.1093/jac/dkz135> PMID: 30993326
106. van Buul LW, van der Steen JT, Achterberg WP, Schellevis FG, Essink RT, de Greeff SC, et al. Effect of tailored antibiotic stewardship programmes on the appropriateness of antibiotic prescribing in nursing homes. *J Antimicrob Chemother.* 2015; 70(7):2153–2162. <https://doi.org/10.1093/jac/dkv051> PMID: 25745104
107. Warren JW, Palumbo FB, Fitterman L, Speedie SM. Incidence and characteristics of antibiotic use in aged nursing home patients. *J Am Geriatr Soc.* 1991; 39(10):963–972. <https://doi.org/10.1111/j.1532-5415.1991.tb04042.x> PMID: 1918783
108. Wu LDY, Walker SAN, Elligsen M, Paimay L, Simor A, Daneman N. Antibiotic use and need for antimicrobial stewardship in long-term care. *Canadian Journal of Hospital Pharmacy.* 2015; 68(6):445–449.
109. Zimmerman S, Sloane PD, Bertrand R, Olsho LE, Beeber A, Kistler C, et al. Successfully reducing antibiotic prescribing in nursing homes. *J Am Geriatr Soc.* 2014; 62(5):907–912. <https://doi.org/10.1111/jgs.12784> PMID: 24697789
110. Mylotte JM. Measuring antibiotic use in a long-term care facility. *Am J Infect Control.* 1996; 24(3):174–9. [https://doi.org/10.1016/s0196-6553\(96\)90009-7](https://doi.org/10.1016/s0196-6553(96)90009-7) PMID: 8806993
111. Mylotte JM, Keagle J. Benchmarks for antibiotic use and cost in long-term care. *J Am Geriatr Soc.* 2005; 53(7):1117–1122. <https://doi.org/10.1111/j.1532-5415.2005.53351.x> PMID: 16108927
112. Sloane PD, Zimmerman S, Ward K, Kistler CE, Paone D, Weber DJ, et al. A 2-Year Pragmatic Trial of Antibiotic Stewardship in 27 Community Nursing Homes. *Journal of the American Geriatrics Society.* 2019. <https://doi.org/10.1111/jgs.16059> PMID: 31317534
113. Eure T, LaPlace LL, Melchreit R, Maloney M, Lynfield R, Whitten T, et al. Measuring Antibiotic Appropriateness for Urinary Tract Infections in Nursing Home Residents. *Infect Control Hosp Epidemiol.* 2017; 38(8):998–1001. <https://doi.org/10.1017/ice.2017.96> PMID: 28560933
114. European Centre for Disease Prevention and Control. Antimicrobial Consumption—Annual Epidemiological Report for 2017. Stockholm: European Centre for Disease Control. 2018. https://www.ecdc.europa.eu/sites/portal/files/documents/AER_for_2017-antimicrobial-consumption.pdf
115. Sluggett JK, Moldovan M, Lang C, Lynn DJ, Papanicolas LE, Crotty M, et al. Contribution of facility level factors to variation in antibiotic use in long-term care facilities: a national cohort study. *J Antimicrob Chemother.* 2021.
116. Daneman N, Gruneir A, Newman A, Fischer HD, Bronskill SE, Rochon PA, et al. Antibiotic use in long-term care facilities. *J Antimicrob Chemother.* 2011; 66(12):2856–2863.
117. Dingle KE, Didelot X, Quan TP, Eyre DW, Stoesser N, Golubchik T, et al. Effects of control interventions on *Clostridium difficile* infection in England: an observational study. *Lancet Infect Dis.* 2017; 17(4):411–421.
118. Inacio MC, Lang CE, Bray SCE, Visvanathan R, Whitehead C, Griffith EC, et al. Health Status and Health Care Trends of Individuals Accessing Australian Aged Care Programs Over a Decade: The Registry of Senior Australians (ROSA) Historical Cohort. *Intern Med J.* 2020.
119. Stone ND, Ashraf MS, Calder J, Crnich CJ, Crossley K, Drinka PJ, et al. Surveillance definitions of infections in long-term care facilities: revisiting the McGeer criteria. *Infect Control Hosp Epidemiol.* 2012; 33(10):965–77. <https://doi.org/10.1086/667743> PMID: 22961014
120. Australian Commission on Safety and Quality in Health Care. AURA 2019: third Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC. 2019. <https://www.safetyandquality.gov.au/sites/default/files/2019-06/AURA-2019-Report.pdf>
121. Bennett N, Imam N, James R, Chen C, Bull A, Thursky K, et al. Prevalence of infections and antimicrobial prescribing in Australian aged care facilities: Evaluation of modifiable and nonmodifiable determinants. *Am J Infect Control.* 2018; 46(10):1148–1153. <https://doi.org/10.1016/j.ajic.2018.03.027> PMID: 29779689
122. Van Buul LW, Monnier AA, Sundvall PD, Ulleryd P, Godycki-Cwirko M, Kowalczyk A, et al. Antibiotic Stewardship in European Nursing Homes: Experiences From the Netherlands, Norway, Poland, and Sweden. *J Am Med Dir Assoc.* 2020; 21(1):34–40.e1. <https://doi.org/10.1016/j.jamda.2019.10.005> PMID: 31791900
123. Global and Public Health Group—Emergency Preparedness and Health Protection Policy Directorate. Tackling antimicrobial resistance 2019–2024: The UK’s five-year national action plan. Government of the United Kingdom. 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf

124. Department of Health, Department of Agriculture Water and the Environment. Australia's national antimicrobial resistance strategy: 2020 and beyond. Government of Australia. 2019. <https://www.amr.gov.au/resources/australias-national-antimicrobial-resistance-strategy-2020-and-beyond>
125. Blix HS, Bergman J, Schjott J. How are antibacterials used in nursing homes? Results from a point-prevalence prescription study in 44 Norwegian nursing homes. *Pharmacoepidemiol Drug Saf.* 2010; 19(10):1025–1030. <https://doi.org/10.1002/pds.1980> PMID: 20712026