ORIGINAL ARTICLE

Systematic review of antibiotic consumption in acute care hospitals

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Abstract

Antibiotic consumption is an easily quantifiable performance measure in hospitals and might be used for monitoring. We conducted a review of published studies and online surveillance reports reporting on antibiotic consumption in acute care hospitals between the years 1997 and 2013. A pooled estimate of antibiotic consumption was calculated using a random effects meta-analysis of rates with 95% confidence intervals. Heterogeneity was assessed through subgroup analysis and metaregression. Eighty studies, comprising data from 3130 hospitals, met the inclusion criteria. The pooled rate of hospital-wide consumption was 586 (95% confidence interval 540 to 632) defined daily doses (DDD)/1000 hospital days (HD) for all antibacterials. However, consumption rates were highly heterogeneous. Antibacterial consumption was highest in intensive care units, at 1563 DDD/1000 HD (95% confidence interval 1472 to 1653). Hospital-wide antibacterial consumption was higher in Western Europe and in medium-sized, private and university-affiliated hospitals. The methods of data collection were significantly associated with consumption rates, including data sources, dispensing vs. purchase vs. usage data, counting admission and discharge days and inclusion of low-consumption departments. Heterogeneity remained in all subgroup analyses. Major heterogeneity currently precludes defining acceptable antibiotic consumption ranges in acute care hospitals. Guidelines on antibiotic consumption reporting that will account for case mix and a minimal set of hospital characteristics recommending standardized methods for monitoring and reporting are needed.
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Introduction

Numerous studies have shown the association between antimicrobial use and increasing resistance to the antimicrobial used [1,2]. Furthermore, the use of one class of antimicrobials can lead to resistance to another class, as has been the case with resistance of *Streptococcus pneumoniae* to penicillin due to the use of macrolides [3]. Antibiotic use is also associated with *Clostridium difficile* diarrhoea in hospitals. Thus, efforts must be made to implement a judicious and safe culture of antibiotic use in hospitals.

Monitoring is an accepted method for performance improvement, with experience relating mainly to device-related infection rates [4]. Surveillance *per se* reduced hospital-acquired infection rates [5,6]. Monitoring antibiotic stewardship is complex. The preferable method would be to classify individual antibiotic treatments as appropriate, inappropriate, superfluous or unnecessary both in the empirical and definitive phases of treatment. Such monitoring is labor intensive and time consuming, and it might be affected by nonuniform definitions regarding the necessity of antibiotic treatment and its appropriateness, since only about 30% of suspected episodes of infection are microbiologically documented [7]. Monitoring the

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amount of antibiotics used in hospitals, adjusted for bed-days and case mix, might provide some additional information. These data are available in most hospitals.

We reviewed reports of antibiotic consumption in the acute-care hospital setting. Our objectives were to document the antibiotic consumption rates reported overall and for specific antibiotic classes and to derive a range for the common rate. We secondarily sought to determine clinical and methodologic modifiers of the rate.

Methods

Study selection

We included prospective and retrospective studies or surveillance program reports describing antibiotic (antibacterial and antifungal) consumption in acute-care hospitals. Antibiotic consumption must have been reported as defined daily doses (DDD) per hospital day (HD). We used HDs as reported in the study. When the studies reported on consumption over time or before and after an intervention, we used data from the most recent time period. We excluded studies published before 1997 because we believe that their data are less relevant to current practice. We excluded studies performed exclusively in nursing homes, rehabilitation centres or long-term care facilities. We excluded duplicate publication of data from the same hospital or unit. We excluded studies whose data were clearly incomplete for the targeted antibiotic or antibiotics and hospital units.

The outcomes assessed were total antibacterial consumption and consumption of antibiotic classes of interest, including cephalosporins, carbapenems, glycopeptides and antifungals. Studies reporting on a single antibiotic or a single antibiotic class other than the antibiotic classes of interest were excluded. Antibiotic classes were defined as reported by the authors because reclassification by the Anatomic Therapeutic Classification (ATC)/DDD was not always possible. We evaluated hospital-wide antibiotic consumption and consumption rates in medical wards, intensive care units (ICUs) and haemato-oncologic wards.

Search strategy

We conducted a comprehensive search attempting to identify data published in medical journals, but we also assessed data published only online in surveillance reports. We searched PubMed (January 1997 to March 2013), all references of included studies and the grey literature (national and international surveillance reports). In PubMed we searched as follows: (Antibiotic OR Anti-Bacterial Agents[MESH]) AND (consumption OR consum* OR use OR usage) AND (defined daily dose OR ddd OR pdd OR prescribed daily dose) AND (hospital OR department OR ward) AND (prospective OR retrospective OR cohort OR observational OR clinical trial). In Google and Google Scholar, we searched 'antibiotic consumption hospital.' No language restrictions were applied.

Data extraction

Two reviewers independently extracted the data from included studies. In case of disagreement, a consensus was reached by discussion. We extracted data on the outcomes of interest and clinical variables that could possibly modify antibiotic consumption or the reported values. Among the clinical variables evaluated were hospital type; hospital size; study period; country; paediatric/adult ward; the number of intensive care and haemato-oncologic beds and other parameters describing the hospital's case mix; and presence and components of an antibiotic stewardship program (ASP).

Risk of bias assessment

Because the included studies were neither randomized controlled studies nor comparative studies, traditional methods for assessment of risk of bias were not applicable. We collected data on methodologic variables that we deemed relevant for the reporting of antibiotic consumption. These included the study design, DDD definitions, whether the sources of the data for consumption were reported and whether these represented purchase, dispensing or actual use, the inclusion of oral antibiotics in the numerator and the days of admission and discharge in the denominator and whether the emergency department and low consumption departments (e.g. psychiatry, maternity wards) were included in the analysis. We assessed the effect of analysis and reporting methodology on results through sensitivity analyses.

Data synthesis and analysis

We pooled consumption data by antibiotic (total or specific antibiotic use) and departments (combined as well as separate unit data) by random effects meta-analysis of rates, using consumption in DDD/1000 HD as the rate and the hospital size (number of beds) as the denominator in the hospital-wide analysis. For department-specific analysis, we used the number of units as the denominator, as data regarding number of beds were sparse. In the random effects model, the studies are weighted in the meta-analysis by the inverse of their variance, where the variance of each study is determined by its standard errors (defined by the number of beds or units in the study) and the between-study variance (heterogeneity of the meta-analysis). Heterogeneity was assessed using the I^2 test of inconsistency and a chi-square test of heterogeneity. Heterogeneity was investigated by subgroup analysis for categorical moderators and metaregression for continuous variables.

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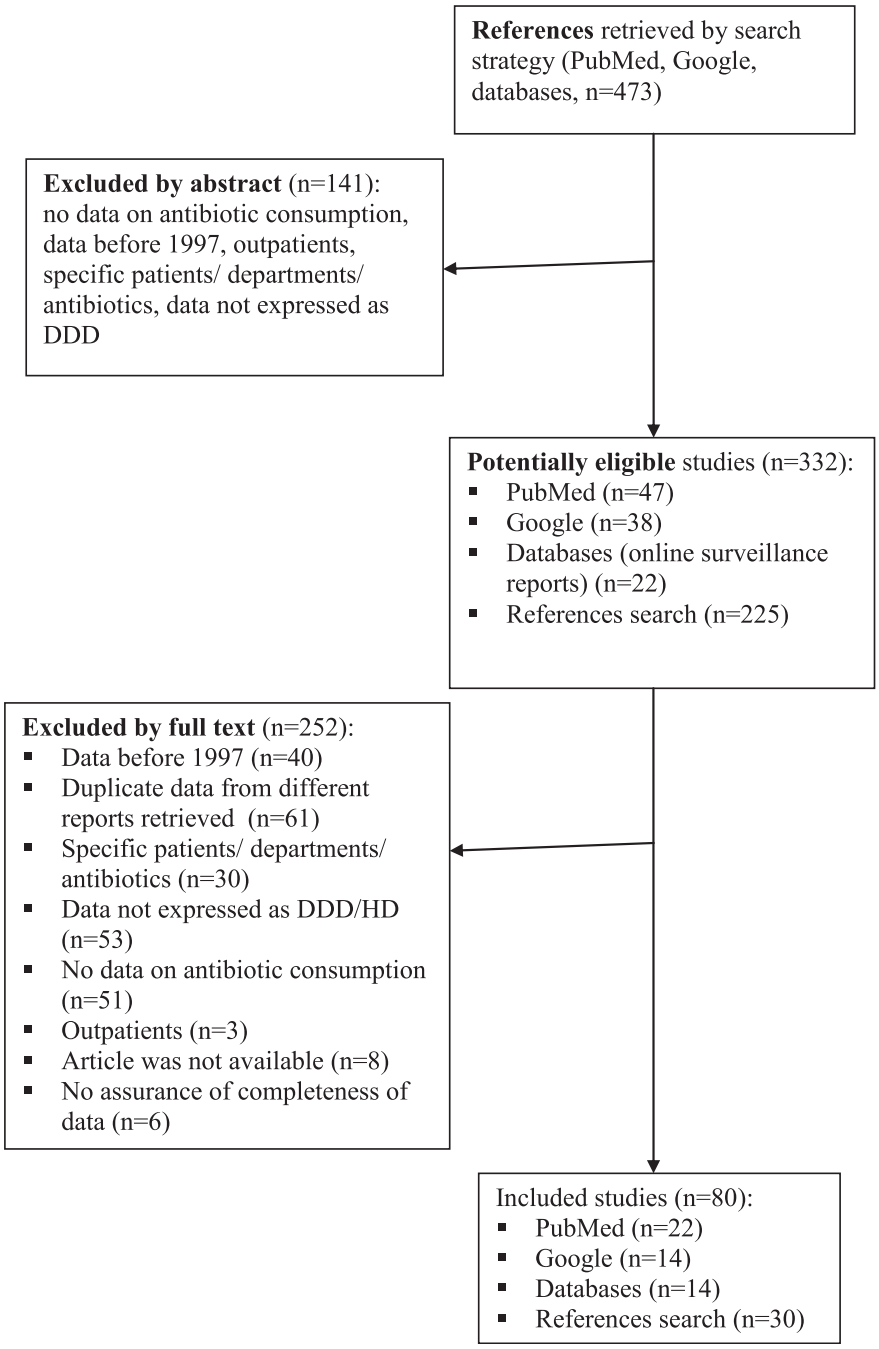

FIG. 1. Study flow.

Subgroups reported were predefined before data analysis. All analyses were conducted by Comprehensive Meta-analysis 2.2 (Biostat, Englewood, NJ, USA).

Results

The search for potentially eligible studies yielded 332 results, 80 of which fulfilled the inclusion criteria, comprising 66 published articles and 14 online databases (Fig. 1) [8–87]. The studies included data from 3130 hospitals comprising 2 471 961 beds and were conducted between 1997 and 2013. The studies were carried out worldwide but predominantly in Western Europe and in Mediterranean countries (Table 1). Sixty-one studies reported on overall or specific antibiotic class consumption across the hospital (hospital-wide), 33 studies in ICUs, 24 studies in medical departments and 14 in haemato-oncology departments, with most reporting on more than one setting.

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TABLE I. Characteristics of included studies

Study	Location	No. of hospitals	Years	Hospital type			Adults, children, or both	Departments included	Antibiotics included
				Tertiary vs. nontertiary	Teaching vs. nonteaching	Public vs. private			
Cabrera 2012 [8]	Uruguay	1	2008	NS	Teaching	NS	Adults	Medicine	Total, carbapenem, cephalosporin, glycopeptide
Al-Tawfiq 2012 [9]	Saudi Arabia	1	2008	NS	NS	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide
Yeo 2012 [10]	Singapore	1	2009–2010	Tertiary	Teaching	Public	Adults	Haemato-oncology	Carbapenem, cephalosporin, glycopeptide
Porta 2012 [11]	UK, Italy, Greece	4	2009	Tertiary	NS	NS	Children	All	Total
Vojtova 2011 [12]	Czech Republic	1	2008	NS	Teaching	NS	NS	ICU	Carbapenem, cephalosporin
Liew 2011 [13]	Singapore	5	2010	NS	NS	Public	Adults	All	Carbapenem, cephalosporin, glycopeptide
Benko 2009 [14]	Hungary	173	2005	NS	NS	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide
Bruce 2009 [15]	Europe	110	2001	NS	NS	NS	Both	All	Total, cephalosporin
Ion-Nedelcu 2009 [16]	Romania	1	2008	NS	Teaching	NS	NS	All, medicine, ICU	Total
Borg 2008 [17]	Mediterranean countries	22	2004–2005	NS	NS	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide
Zhang 2008 [18]	China	5	2006	Tertiary	Teaching	NS	Children	All	Total, cephalosporin
Pakyz 2008 [19]	USA	42	2003	NS	NS	NS	NS	All	Total, carbapenem, cephalosporin, glycopeptide
Kritsotakis 2006 [20]	Greece	1	2002	NS	Teaching	NS	NS	All, medicine, ICU, haemato-oncology	Total, carbapenem, cephalosporin, glycopeptide
Blix 2005 [21]	Norway	13	1998–1999	NS	NS	NS	Both	All	Total, carbapenem, cephalosporin
Shankar 2005 [22]	Nepal	1	2002	NS	Teaching	NS	NS	ICU	Total, cephalosporin
Curtis 2004 [23]	UK	12	2001–2002	NS	NS	NS	Both	All	Total
Ruttimann 2004 [24]	Switzerland	1	1998	Tertiary	Teaching	NS	Adults	Medicine	Total
Bergman 2004 [25]	Sweden	7	1999–2000	NS	NS	NS	Adults	Medicine	Total
Hermosilla Najera 2003 [26]	Spain	1	1996–2000	NS	NS	NS	Both	All, ICU	Total, carbapenem, cephalosporin, glycopeptide
Loeffler 2003 [27]	Switzerland	1	2000	Tertiary	Teaching	NS	Both	All, ICU	Total, carbapenem, cephalosporin, glycopeptide
Raveh 2001 [28]	Israel	1	1998	NS	Teaching	NS	Both	Medicine, ICU	Total
Akalin 2012 [29]	Turkey	1	2010	Tertiary	Teaching	NS	Both	All, medicine, ICU	Total, carbapenem, cephalosporin, glycopeptide, antifungal
Markogiannakis 2012 [30]	Greece	3	2011	NS	NS	Public	NS	Medicine, ICU	Total
Pluss-Suard 2011 [31]	Switzerland	57	2008	NS	NS	NS	Both	All, ICU	Total, carbapenem, cephalosporin, glycopeptide
Cizman 2011 [32]	Slovenia	29	2007	NS	NS	NS	Both	All, medicine, ICU	Total
Haug 2011 [33]	Norway	8	2007	NS	NS	NS	Adults	All	Total
Lai 2011 [34]	Taiwan	1	2009	Tertiary	Teaching	NS	Both	All	Carbapenem, cephalosporin
Velickovic-Radovanovic 2009 [35]	Serbia	1	2007	Tertiary	Teaching	NS	Both	All	Total
Kuster 2008 [36]	Switzerland	1	2006	Tertiary	Teaching	NS	Adults	All, medicine, ICU, haemato-oncology	Total
Shalit 2008 [37]	Israel	6	2003–2004	NS	Teaching	NS	Adults	Medicine	Total, carbapenem, cephalosporin, glycopeptide
Polk 2007 [38]	USA	130	2002–2003	NS	NS	NS	Adults	All	Total, glycopeptide
De With 2006 [39]	Germany	145	2003	NS	NS	NS	Adults	Haemato-oncology	Total
Palcevski 2004 [40]	Croatia, Russia	2	2000	NS	Teaching	NS	Children	All	Total, carbapenem, cephalosporin, glycopeptide
Bantar 2003 [41]	Argentina	1	2001	NS	Teaching	Public	Adults	All	Total, carbapenem, cephalosporin, glycopeptide
Naaber 2000 [42]	Estonia	1	1998	NS	Teaching	NS	NS	All, medicine, ICU	Total, carbapenem, cephalosporin, glycopeptide
Cheng 2009 [43]	Hong Kong	1	2007	Tertiary	Teaching	NS	Adults	All	Carbapenem
Cook 2004 [44]	USA	1	2003	Tertiary	Teaching	NS	Both	All	Total, carbapenem, glycopeptide, antifungal
Vaccheri 2008 [45]	Italy	5	2004	NS	NS	NS	Both	All, medicine, ICU, haemato-oncology	Total, carbapenem, cephalosporin, glycopeptide
Ansari 2010 [46]	Europe	18	2000–2005	NS	NS	NS	Both	All	Total
Monnet 2004 [47]	UK	1	2000	Tertiary	NS	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide
Kern 2002 [48]	Germany	1	2000	NS	Teaching	NS	Adults	Medicine, haemato-oncology	Glycopeptide
Kuster 2008 [49]	Switzerland	12	2006	Nontertiary	NS	NS	Both	All	Total
Vlahovic-Palcevski 2000 [50]	Croatia	1	1997	NS	Teaching	NS	Adults	Medicine, ICU	Total, carbapenem, cephalosporin, glycopeptide
Vlahovic-Palcevski 2004 [51]	Croatia	1	2001	NS	Teaching	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide
Vlahovic-Palcevski 2001 [52]	Croatia	1	1997	NS	NS	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide
Walther 2002 [53]	Sweden	30	1999	NS	NS	NS	Adults	ICU	Total, carbapenem, cephalosporin, glycopeptide
Sintchenko 2005 [54]	Australia	1	2002–2003	Tertiary	Teaching	NS	Adults	ICU	Total, carbapenem, glycopeptide
Hsueh 2005 [55]	Taiwan	1	2003	NS	Teaching	NS	NS	All	Glycopeptide
Hosoglu 2005 [56]	Turkey	15	2003	NS	NS	NS	Both	All	Carbapenem, glycopeptide
Ozkurt 2005 [57]	Turkey	1	2003	Tertiary	Teaching	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide, antifungal
Lang 2001 [58]	Italy	1	1998–1999	NS	NS	NS	NS	ICU, haemato-oncology	Total, carbapenem, cephalosporin, glycopeptide
Giachetto 2003 [59]	Uruguay	1	2002	NS	NS	NS	Children	All	Cephalosporin
Hanberger 2009 [60]	Europe	8	2005	NS	NS	NS	Adults	ICU	Total, carbapenem, cephalosporin

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Jacoby 2010 [61]	Brazil	1	2004–2006	Tertiary	Teaching	Public	Both	All, ICU	Total, cephalosporin
Mach 2007 [62]	Czech Republic	1	2004	NS	NS	NS	NS	All	Total, carbapenem, cephalosporin, glycopeptide
Bassetti 2001 [63]	Italy	1	1998	Tertiary	Teaching	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide
Goryachkina 2008 [64]	Russia	1	2005 (all) 2003 (ICU)	NS	Teaching	NS	Both	All, ICU	Total
Dancer 2006 [65]	Scotland	1	NS	Tertiary	NS	NS	NS	ICU	Total, carbapenem
Ansari 2001 [66]	Iran	1	1997	NS	Teaching	NS	Both	All, medicine, ICU	Total, cephalosporin
Apisarnthanarak 2006 [67]	Thailand	1	2004–2005	Tertiary	Teaching	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide
Shetka 2005 [68]	USA	1	2003	Tertiary	Teaching	NS	NS	All	Glycopeptide
Arnold 2006 [69]	USA	1	2003–2004	NS	NS	NS	NS	All	Glycopeptide
Wattal 2005 [70]	India	1	2001	Tertiary	NS	NS	NS	All	Total, cephalosporin, glycopeptide
Evans 1999 [71]	USA	1	1997–1998	Tertiary	Teaching	NS	NS	All	Glycopeptide
Kitzes Cohen 2004 [72]	Israel	1	1998–2000	Tertiary	Teaching	NS	Adults	All	Total
DANMAP [73]	Denmark	66	2011	NS	NS	Public	Both	All	Total, carbapenem, cephalosporin, glycopeptide
SWAB/NETHMAP [74]	Netherland	78	2011	NS	NS	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide, antifungal
SARI [75]	Germany	NS	2012	NS	NS	NS	Adults	ICU	Total, carbapenem, cephalosporin, glycopeptide, antifungal
GERMAP [76]	Germany	184	2004 and 2009	NS	Teaching and nonteaching	NS	Adults	All, medicine, haemato-oncology	Total, glycopeptide, antifungal
STRAMA/SWEDRES [77]	Sweden	41	2011	NS	NS	NS	Both	All	Total, carbapenem, cephalosporin, glycopeptide
NNIS/ICARE/AUR [78]	USA	300	1998–2004	NS	NS	NS	Adults	ICU, haemato-oncology	Total, carbapenem, cephalosporin, glycopeptide
CCLIN Paris North [79]	France	346	2012	NS	NS	NS	Both	All, medicine, ICU, haemato-oncology	Total, carbapenem, cephalosporin, glycopeptide, antifungal
CCLIN South West [80]	France	283	2012	NS	Teaching and nonteaching	Public and private	Both	All, medicine, ICU, haemato-oncology	Total, carbapenem, cephalosporin, glycopeptide
CCLIN South East [81]	France	310	2012	NS	Teaching and nonteaching	Public and private	Both	All, medicine, ICU, haemato-oncology	Total, carbapenem, cephalosporin, glycopeptide, antifungal
CCLIN West [82]	France	262	2012	NS	Teaching and nonteaching	Public and private	Both	All, medicine, ICU	Total, carbapenem, cephalosporin, glycopeptide
CCLIN East [83]	France	210	2012	NS	Teaching and nonteaching	Public and private	Both	All, medicine, ICU, haemato-oncology	Total, carbapenem, cephalosporin, glycopeptide
VINCat [84]	Spain	54	2011	NS	NS	NS	Adults	All, medicine, ICU	Total, carbapenem, cephalosporin, antifungal
NAUSP [85]	Australia	52	2012–2013	Tertiary	NS	NS	Adults	All, ICU	Total, carbapenem, cephalosporin, glycopeptide
HPSC [86]	Ireland	41	2012	Tertiary and nontertiary	NS	NS	Both	All	Total
Our hospital [87]	Israel	1	2011–2013	Tertiary	Teaching	Public	Both	All, medicine, ICU, haemato-oncology	Total, carbapenem, cephalosporin, glycopeptide, antifungal

NS, not specified.

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Most studies reported on antibiotic consumption among adults or both adults and children (n = 23 and 38, respectively). When hospital characteristics were described, most studies were done in tertiary, teaching or public hospitals; only two studies were done in nontertiary, five in nonteaching and four in private hospitals. Most studies reported on antibacterials alone; consumption of antivirals and antiparasitics was negligible. We therefore focus our analysis on antibacterials and antifungals.

Antibiotic consumption

Random effect meta-analysis yielded a pooled estimate of hospital wide antibacterial consumption of 586 DDD/1000 HD (95% confidence interval (CI) 540 to 632) with significant heterogeneity (I^2 = 99.9%, p <0.001). Out of 50 studies evaluating hospital-wide overall antibacterial consumption, only six fell within the 95% confidence limits of the pooled estimate. Antibacterial consumption in medical wards was higher than the hospital-wide consumption, with 677 DDD/1000 HD (95% CI 634 to 720). Antibacterial consumption was highest in ICUs (1563 DDD/1000 HD, 95% CI 1472 to 1653) and in haemato-oncology departments (1535 DDD/1000 HD, 95% CI 1363 to 1707).

Among the specific antibiotic classes, cephalosporin consumption was highest (115 DDD/1000 HD, 95% CI 105 to 124 in the hospital-wide analysis). Carbapenem consumption was highest in the haemato-oncology department (113 DDD/1000 HD, 95% CI 84 to 141) and lowest in medical departments (16 DDD/1000 HD, 95% CI 13 to 19). Glycopeptide consumption presented a similar pattern, with 146 DDD/1000 HD (95% CI 116 to 176) in the haemato-oncology department and 13 DDD/1000 HD (95% CI 10 to 16) in the medical department. Consumption of other specific antibiotic classes is shown in Table 2. All analyses remained highly heterogeneous.

Analysis of effect modifiers

Demographic and clinical variables. Significant between-group heterogeneity was present in an analysis stratified by country, with Western Europe, Mediterranean countries and the Middle East having the highest rates. Antibacterial consumption was significantly higher in Western than in Eastern Europe for hospital-wide total and specific antibiotic data (total 617 vs. 366 DDD/1000 HD, p 0.001). Hospital size (comparing <400 beds to 400–800 beds to >800 beds) did not usually affect antibiotic consumption. However, in some analyses (hospital-wide total

TABLE 2. Pooled rates of antibiotic consumption

Variable	No. of studies [references]	Random effect model pooled rates (DDD/1000 HD)			
		Point estimate	Lower 95% CI	Upper 95% CI	I^2
Hospital-wide all antibacterial	50 [9,11,14–21,23,26,27,29, 31–33,35,36,38,40–42,44–47, 49,51,52,57,61–64,66,67,70, 72–74,76,79–87]	586	540	632	99.9%
Hospital-wide carbapenem	34 [9,13,14,19–21,26,27,29,31, 34,40,41,43–45,47,51,52,56, 57,62,63,67,73,74,77,79–81, 83–85,87]	17	15	19	99.5%
Hospital-wide cephalosporin	38 [9,13–15,17–21,26,27,29,31, 34,40,41,47,51,52,57,59, 61–63,66,67,70,73,74,77,79–85,87]	115	105	124	99.8%
Hospital-wide glycopeptide	37 [9,13,14,19,20,26,27,29,31, 38,40,41,44,45,47,51,52, 55–57,62,63,67–71,73,74, 77,79–83,85,87]	16	14	18	99.5%
Hospital-wide antifungal	8 [29,44,57,74,76,81,84,87]	36	25	46	99.8%
Medicine all antibacterial	23 [8,16,20,24,25,28–30,32,36, 37,42,45,50,66,76,79–84,87]	677	634	720	99.8%
Medicine carbapenem	13 [8,20,29,37,45,50,79–84,87]	16	13	19	99.8%
Medicine cephalosporin	14 [8,20,29,37,45,50,66,79–84,87]	118	104	131	99.7%
Medicine glycopeptide	14 [8,20,29,37,45,48,50,76,79–83,87]	13	10	16	99.5%
Medicine antifungal	4 [29,76,84,87]	27	7	47	99.7%
ICU all antibacterial	32 [16,20,22,26–32,36,42,45,50,53, 54,58,60,61,64–66,75,78–85,87]	1563	1472	1653	99.9%
ICU carbapenem	24 [12,20,26,27,29,31,42,45,50,53, 54,58,60,65,75,78–85,87]	109	86	132	99.9%
ICU cephalosporin	23 [12,20,22,26,27,29,42,45,50,53, 58,60,66,75,78–85,87]	275	255	295	99.5%
ICU glycopeptide	20 [20,26,27,29,31,42,45,50,53,54, 58,75,78–83,85,87]	80	68	92	99.7%
ICU antifungal	6 [29,75,79,81,84,87]	145	125	164	99.3%
Haemato-oncology all antibacterial	10 [20,36,39,58,78–81,83,87]	1535	1363	1707	99.9%
Haemato-oncology carbapenem	9 [10,20,58,78–81,83,87]	113	84	141	99.4%
Haemato-oncology cephalosporin	9 [10,20,58,78–81,83,87]	213	153	274	99.5%
Haemato-oncology glycopeptide	10 [10,20,48,58,78–81,83,87]	146	116	176	99%
Haemato-oncology antifungal	4 [76,79,81,87]	418	292	543	99.9%

CI, confidence interval; DDD, defined daily dose; HD, hospital days; ICU, intensive care unit.

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antibacterial, hospital-wide cephalosporin and ICU glycopeptide), consumption was significantly higher in medium-sized hospitals compared to large hospitals (p <0.01 for all comparisons). Hospital-wide antibacterial consumption significantly decreased when comparing the period 1997–2002 to 2009–2013 (666 vs. 528 DDD/1000 HD, p 0.02), but the effect was nonsignificant using time as a continuous variable. Hospital-wide carbapenem consumption increased with time (increase of 1.12 DDD/1000 HD, 95% CI 0.68 to 1.57; for each year, p <0.001), whereas hospital-wide cephalosporin use decreased (decrease of 2.5DDD/1000 HD, 95% CI −4.3 to −0.7; for each year, p 0.006). There was also a significant decrease with time in ICU for total antibacterial (1737 vs. 1438 DDD/1000 HD), cephalosporin (334 vs. 246 DDD/1000 HD) and glycopeptide (130 vs. 74 DDD/1000 HD) consumption (p <0.01 for all comparisons).

Teaching hospitals demonstrated significantly higher hospital-wide carbapenem (14 vs. 5 DDD/1000 HD), cephalosporin (105 vs. 47 DDD/1000 HD) and glycopeptide (16 vs. 5 DDD/1000 HD) consumption than other hospitals (p <0.01 for all comparisons), but with no difference in total antibacterial consumption. Public hospitals had significantly increased hospital-wide consumption of carbapenems (21 vs. 6 DDD/1000 HD) and glycopeptides (13 vs. 7 DDD/1000 HD) compared to private hospitals (p <0.05 for all comparisons). There was a nonsignificant trend for higher antibiotic consumption in tertiary compared to nontertiary hospitals.

Antibiotic stewardship programs. Among the 80 studies included, 35 reported having an ASP. Of these, 25 evaluated the effect of implementing an ASP and 21 noted a positive effect on antibiotic consumption.

The ASP interventions evaluated included automatic stop orders for antibiotics, need for approval by antibiotic advisor, guidelines and performing audits and educational activities. There was a significant association between program intensity (comparing one to three ASP interventions) and lower hospital-wide consumption of cephalosporins (137 vs. 55 DDD/1000 HD) and glycopeptides (23 vs. 5 DDD/1000 HD; p <0.05 for both). ASPs reported as successful in the primary publications were associated with lower hospital-wide total antibacterial (458 vs. 588 DDD/1000 HD), carbapenem (12 vs. 19 DDD/1000 HD) and cephalosporin (80 vs. 125 DDD/1000 HD) consumption (p <0.05 for all), but there was no association between ASP success and hospital-wide glycopeptide use, antibiotic consumption in ICUs or in medical wards.

Study methods and risk of bias assessment

Nearly all studies evaluated antibiotic consumption over time; only two were point prevalence studies. Sixty-three studies were retrospective and 15 were prospective (Table 3). Only 34 of 80 studies clearly reported whether dispensing, use or purchase data were used to calculate antibiotic consumption, and 63 studies defined data sources (most commonly pharmacy records). Most studies (51/80) clearly reported which antibiotics were included. Eleven studies counted the day of admission and the day of discharge as 1 day, while other studies did not address the issue. Eleven studies excluded low-consumption departments, usually psychiatry and rehabilitation, and only three studies referred to antibiotic consumption in the emergency department. Most studies did not note whether the antibiotics included in the numerator were oral, intravenous (iv) or both. When noted, consumption of both oral and iv antibiotics was the most common (29/34 studies).

Antibiotic consumption was not usually affected by whether the study was retrospective or prospective. When comparing the data sources for DDD calculation (purchase, dispensing or actual use), dispensing data were associated with increased antibiotic consumption compared to other forms of data collection (p <0.01 for all comparisons except for glycopeptides). For instance, total antibacterial consumption in ICUs was highest using dispensing data (1644 DDD/1000 HD) compared to purchase or actual use (1143 and 1081 DDD/1000 HD, respectively, p <0.01). An ASP was described more frequently in studies reporting on actual antibiotic use (3/5) than in studies reporting on purchase or dispensing (12/47) (p 0.1). Reporting of data collection methods and of the data source were associated with significantly lower antibiotic consumption, both in the different departments and for the different antibiotic classes (p <0.05 for all comparisons). For example, total antibacterial consumption in medical departments was significantly lower when data collection methods were reported clearly, with 593 DDD/1000 HD compared to 754 DDD/1000 HD among studies where data collection methods were described vaguely (p <0.001). As expected, counting the day of admission and discharge as 1 day and exclusion of low-consumption departments from the analysis were both associated with significantly increased antibiotic consumption (p <0.05 for all comparisons). We found no significant difference in antibiotic consumption between single-centre studies and multicentre studies. We performed a sensitivity analysis comparing high-quality studies (those with clear reporting of source of data and antibiotics included) to those with inferior methodology. High-quality studies were found to have significantly lower hospital-wide antibacterial consumption (559 vs. 619 DDD/1000 HD, p <0.001).

Discussion

In the current review, we aimed to define benchmark values for antibiotic consumption in acute care hospitals and specific

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TABLE 3. Methodology of included studies

Study	Retrospective or prospective	Purchase, dispensing, use data for calculating DDD	ATC classification and DDD assignment version (year)	Addressed admission and discharge day	Excluded departments with low antibiotic consumption	Clear reporting of antibiotics included
Cabrera 2012 [8]	Prospective	Use	2010	NS	NR	No
Al-Tawfiq 2012 [9]	Retrospective	Dispensing	2001	NS	No	Yes
Yeo 2012 [10]	Prospective	Dispensing	2009	NS	NR	Yes
Porta 2012 [11]	Retrospective	Dispensing	2011	NS	No	Yes
Vojtova 2011 [12]	Retrospective	Dispensing	2009	NS	NR	Yes
Liew 2011 [13]	Retrospective	Dispensing	2011	NS	No	Yes
Benko 2009 [14]	Retrospective	Purchase	2005	NS	No	Yes
Bruce 2009 [15]	Retrospective	NS	2005	NS	No	Yes
Ion-Nedelcu 2009 [16]	Retrospective	Dispensing	NS	NS	No	No
Borg 2008 [17]	Prospective	Use	2005	NS	No	Yes
Zhang 2008 [18]	Retrospective	NS	2006	NS	No	Yes
Pakyz 2008 [19]	Retrospective	Dispensing	NS	NS	No	Yes
Kritsotakis 2006 [20]	Retrospective	Dispensing	2002	NS	Yes	Yes
Blix 2005 [21]	Retrospective	NS	2001	NS	No	Yes
Shankar 2005 [22]	Retrospective	Use	2002	Day of admission and day of discharge counted as 1 day	NR	No
Curtis 2004 [23]	Retrospective	NS	1999	NS	No	Yes
Ruttimann 2004 [24]	Prospective	Use	NS	NS	NR	No
Bergman 2004 [25]	Prospective	Dispensing	2000	Day of admission and day of discharge counted as 1 day	NR	Yes
Hermosilla Najera 2003 [26]	Retrospective	Dispensing	1997	NS	No	No
Loeffler 2003 [27]	Retrospective	Use	1993	NS	No	No
Raveh 2001 [28]	Prospective	Use	NS	NS	Yes	No
Akalin 2012 [29]	Prospective	Use	2010	NS	No	Yes
Markogiannakis 2012 [30]	Retrospective	Dispensing	NS	NS	NR	Yes
Pluss-Suard 2011 [31]	Retrospective	Purchase	2009	NS	No	Yes
Cizman 2011 [32]	Retrospective	NS	2007	NS	No	Yes
Haug 2011 [33]	Retrospective	Dispensing	2007	NS	Yes	Yes
Lai 2011 [34]	Retrospective	Dispensing	NS	NS	No	Yes
Velickovic-Radovanovic 2009 [35]	Retrospective	Dispensing	NS	NS	No	No
Kuster 2008 [36]	Retrospective	Dispensing	2007	Day of admission and day of discharge counted as 1 day	No	Yes
Shalit 2008 [37]	Retrospective	NS	2003	NS	NR	Yes
Polk 2007 [38]	Retrospective	Use	2005	NS	No	No
De With 2006 [39]	Retrospective	Dispensing	2003	NS	Yes	Yes
Palcevski 2004 [40]	Retrospective	Dispensing	2001	NS	No	Yes
Bantar 2003 [41]	Prospective	Dispensing	NS	NS	No	No
Naaber 2000 [42]	Retrospective	NS	NS	NS	No	No
Cheng 2009 [43]	Retrospective	Use	NS	NS	No	Yes
Cook 2004 [44]	Retrospective	Dispensing	2003	NS	No	Yes
Vaccheri 2008 [45]	Retrospective	Dispensing	2005	NS	No	Yes
Ansari 2010 [46]	Retrospective	Dispensing	2006	Day of admission and day of discharge counted as 1 day	No	Yes
Monnet 2004 [47]	Retrospective	Dispensing	2001	NS	No	No
Kern 2002 [48]	Prospective	Dispensing	Defined internally	NS	NR	Yes
Kuster 2008 [49]	Retrospective	Dispensing	2007	Day of admission and day of discharge counted as 1 day	Yes	Yes
Vlahovic-Palcevski 2000 [50]	Retrospective	Dispensing	1997	NS	NR	No
Vlahovic-Palcevski 2004 [51]	Retrospective	Dispensing	2001	Day of admission and day of discharge counted as 1 day	No	Yes
Vlahovic-Palcevski 2001 [52]	Retrospective	Dispensing	1997	NS	No	Yes
Walther 2002 [53]	Retrospective	Dispensing	NS	NS	NR	No
Sintchenko 2005 [54]	Prospective	Dispensing	NS	NS	NR	No
Hsueh 2005 [55]	Retrospective	Dispensing	NS	NS	No	Yes
Hosoglu 2005 [56]	Prospective	Use	2003	NS	Yes	No
Ozkurt 2005 [57]	Retrospective	Dispensing	NS	NS	No	No
Lang 2001 [58]	Retrospective	NS	Defined internally	NS	NR	No
Giachetto 2003 [59]	Retrospective	Dispensing	NS	NS	No	Yes
Hanberger 2009 [60]	Retrospective	NS	2008	NS	NR	No
Jacoby 2010 [61]	Retrospective	NS	2005	NS	No	No
Mach 2007 [62]	Retrospective	Use	NS	NS	No	No
Bassetti 2001 [63]	Retrospective	Dispensing	1995	NS	No	No
Goryachkina 2008 [64]	Retrospective	Dispensing	2003–2005 (yearly updated)	NS	No	Yes
Dancer 2006 [65]	Retrospective	NS	NS	NS	No	No
Ansari 2001 [66]	Retrospective	Dispensing	1996	NS	No	Yes
Apisarnthanarak 2006 [67]	Prospective	Dispensing	NS	NS	No	No
Shetka 2005 [68]	Retrospective	Dispensing	2005	NS	No	Yes
Arnold 2006 [69]	Prospective	NS	NS	NS	NS	Yes
Wattal 2005 [70]	Retrospective	NS	NS	NS	No	No
Evans 1999 [71]	Prospective	Dispensing	Defined internally	NS	No	Yes
Kitzes-Cohen 2004 [72]	NS	NS	NS	NS	No	No
DANMAP [73]	Retrospective	Dispensing	2011	Day of admission and day of discharge counted as 1 day	Yes	Yes

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TABLE 3. Continued

Study	Retrospective or prospective	Purchase, dispensing, use data for calculating DDD	ATC classification and DDD assignment version (year)	Addressed admission and discharge day	Excluded departments with low antibiotic consumption	Clear reporting of antibiotics included
SWAB/NETHMAP [74]	Retrospective	Purchase	2011	Day of admission and day of discharge counted as 1 day	Yes	Yes
SARI [75]	Retrospective	Dispensing	NS	NS	NR	Yes
GERMAP [76]	Retrospective	Dispensing	NS	NS	Yes	No
STRAMA/SWEDRES [77]	Retrospective	Dispensing	2011	Day of admission and day of discharge counted as 1 day	No	Yes
NNIS/ICARE/AUR [78]	Retrospective	NS	2004	NS	NR	No
CCLIN Paris North [79]	Retrospective	Dispensing	2012	NS	No	Yes
CCLIN South West [80]	Retrospective	Dispensing	2012	NS	No	Yes
CCLIN South East [81]	Retrospective	Dispensing	2012	NS	No	Yes
CCLIN West [82]	Retrospective	Dispensing	2012	NS	No	Yes
CCLIN East [83]	Retrospective	Dispensing	2012	NS	No	Yes
VINCat [84]	NS	Dispensing	NS	Day of admission and day of discharge counted as 1 day	Yes	Yes
NAUSP [85]	Prospective	Dispensing	2013	NS	Yes	Yes
HPSC [86]	Retrospective	Dispensing	NS	NS	No	No
Our hospital [87]	Retrospective	Dispensing	2013	Day of admission and day of discharge counted as 1 day	No	Yes

ATC, Anatomic Therapeutic Classification; DDD, defined daily dose; NR, not relevant; NS, not specified.

hospital wards. The pooled estimate of hospital-wide antibacterial consumption was 586 DDD/1000 HD (95% CI 540 to 632) but varied up to 40-fold between studies, and only six of 50 studies fell within the 95% confidence limits. Moderators partially explaining the heterogeneity for this analysis included the country, hospital size and characteristics, study years and the intensity of ASPs. Methodologic characteristics of data collection and reporting also affected results.

We found increased antibiotic consumption in Western Europe, Mediterranean countries and the Middle East compared to Eastern Europe. Study location might have been correlated with prevalence of resistance that was not reported in the studies. Few previous studies compared antibiotic consumption in hospitals across borders. The ARPAC project [15] collected data from 32 European countries, and the ARMed project [17] collected data from seven Mediterranean countries. However, even in these projects antibiotic consumption was not compared between the different regions. The European Surveillance of Antimicrobial Consumption (ESAC) Network [88] was originally founded for monitoring antibiotic consumption in the outpatient setting. In-hospital antibiotic consumption was added more recently; however, data are still expressed as DDD/1000 inhabitants.

In the last study period (2009–2013), we observed a decrease in total antibacterial and cephalosporin consumption alongside an increase in carbapenem consumption compared to the first study period. Surprisingly, antibiotic consumption was largely unrelated to hospital size, except for a few subgroups that demonstrated higher use in medium-sized hospitals (400–800 beds). This analysis might be affected by use of hospital size to determine studies' weight in the meta-analysis, although subgroup analyses are still valid. Previous studies have usually shown increased antibiotic consumption in larger hospitals [39,89], but not all [90]. As expected, there was higher antibiotic consumption in teaching and public hospitals compared to private hospitals. In our analysis, tertiary hospitals did not have higher antibiotic consumption compared to

TABLE 4. Minimal data set for antibiotic consumption reports

Item to be reported	Explanation
Methods	
Data source	Purchase, dispensing or actual usage
Antibiotic spectrum	Define which antibiotic classes (or ATC groups) are included in the report
ATC/DDD version	Define the version (year) of ATC/DDD definitions used
Departments included	Report on inclusion or exclusion of high and low consumption departments
Hospital days calculation	Describe the methods used including counting of admission and discharge day
Hospital characteristics and case mix	
Hospital type and size	Primary/secondary or tertiary care hospital; public/private; teaching/nonteaching
Inclusion of children	Percentage of antibiotics prescribed for children, if included in analysis
ASP	Existence of an ASP and types of its activities
Overall no. of beds	Overall no. of beds included in report
No. of ICU beds	
No. of haemato-oncologic beds	
Prevalence of resistance	Percentage of multidrug-resistant bacteria (ESBL, MRSA, CRE)

ASP, antibiotic stewardship program; ATC, Anatomic Therapeutic Classification; CRE, carbapenem-resistant *Enterobacteriaceae*; DDD, defined daily dose; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

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primary care hospitals, but that could be due to the paucity of data in nontertiary hospitals.

Adequate study methodology (i.e. clear reporting of whether purchase, dispensing or usage data were used; data sources; and ATC version) was associated with lower antibiotic use. The use of dispensing data for calculating the DDD, which was the most common method, was associated with a report of higher antibiotic consumption than actual usage. This could be correlated with the existence of ASPs in hospitals reporting on actual usage. Importantly, very few studies reported on how the denominator of HDs was calculated, addressing admission and discharge days, time spent in the emergency department and whether all departments were included. Exclusion of low-consumption departments or counting the day of admission and the day of discharge as 1 day causes an artificial increase in DDD/1000 HD. We observed no significant difference between iv only, combined iv and oral hospital-wide antibacterial consumption or whether or not this measure was reported. This is probably due to the paucity of studies reporting on the consumption of iv antibiotics only.

There are also several possible modifiers that we did not or could not evaluate for various reasons. Firstly, not all studies reported on the same antibacterial agents in the analysis of 'all antibacterials.' We also believe that the estimate of cephalosporin consumption is a slight underestimate, as several of the included studies reported only on third- and fourth-generation cephalosporins. The ATC and DDD definitions change on a yearly basis by the World Health Organization, but we could not separate the contribution of the DDD definitions and the actual changes of antibiotic consumption with time. The DDD method for evaluating drug consumption has several inherent limitations: it does not necessarily reflect recommended or prescribed daily dose; it is defined irrespective of age, weight, pharmacokinetic consideration or genetic polymorphism; and it does not take into account variation in the antibiotic regimens between various countries. Lastly, although we attempted to extract data on the case mix of patients included in the analyses, we could not obtain such data. These include, for example, the number of ICUs, bone marrow transplantation and burn unit beds or percentage of patient days in these settings, data regarding catheter usage, infection rates and prevalence of multidrug-resistant bacteria in the hospital. These have been proposed in other studies as modifiers of antibiotic consumption [91]. Obviously the inclusion of children affected the results; the percentage of children was not reported in most studies.

There are other limitations related to the review process. We did not conduct a formal systematic search, acknowledging in advance that we could not identify each and every study reporting on antibiotic consumption. However, the set of identified studies allowed an appreciation of the range of consumption patterns, methods of reporting and modifiers of consumption rates. When studies reported on consumption over time or before and after an intervention, we included only the last time period. This could have introduced bias towards lower consumption because the last time period usually follows an intervention or is shown as proof of a successful ASP. Most of our analyses are based on univariate associations. It might be that the associations identified or unidentified are confounded by ignoring association between effect modifiers. Finally, risk of bias assessment has not been previously defined for surveillance reports of this type. On the basis of the methodologic modifiers of effects, we propose a set of items related to study's risk of bias that can be used for assessment of future surveillance reports (Table 4).

In summary, the total antibacterial consumption rate hospital-wide was about 590 DDD/1000 HD, and 10% of hospitals ranged between 540 and 632. Other than the case mix, the methods of data collection, computing rates and reporting significantly affected results. Our results provide general estimates of antibiotic consumption in hospitals and specific wards. However, to enable benchmarking of antibiotic consumption, there is a need to standardize reporting methodology of studies on antibiotic consumption. On the basis of the variables identified as underlying the heterogeneity between studies, we propose a set of variables that should probably be defined in antibiotic consumption reports. A multidisciplinary expert group should define the appropriate standards for antibiotic consumption reporting.

Transparency Declaration

All authors report no conflicts of interest relevant to this article.

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