Quantitative Antibiotic Use in Hospitals: Comparison of Measurements, Literature Review, and Recommendations for a Standard of Reporting

S. P. Kuster, C. Ruef, B. Ledergerber, A. Hintermann, C. Deplazes, L. Neuber, R. Weber

Abstract

Background: Reports on antibiotic use often lack complete definitions of the units of measurement, hampering the comparison of data between hospitals or hospital units.
Methods: To compare methods of measures of in-hospital antimicrobial use, we determined aggregate in-hospital consumption data at a tertiary care university hospital using variations of nominators and denominators. Means of defined daily doses (DDD) of individual antimicrobials per 100 bed-days and per 100 admissions at each hospital and intensive care unit (ICU) were calculated. Furthermore, a literature review was performed for benchmarking purposes.
Results: Antibiotic use in different hospital units ranged from 0.105 to 323.37 DDD/100 bed-days and from 4.23 to 6737.92 DDD/100 admissions, respectively. Including the day of discharge in the denominator 'bed-days' underestimated antibiotic use in various hospital wards by up to 27.7 DDD/100 bed-days (26.0%). Equating 'numbers of patients admitted to the hospital' and 'numbers of admissions' on a hospital level resulted in a difference of 192.6 DDD/100 admissions (64%) because patients transferred between hospital units accounted for multiple admissions. Likewise, reporting antimicrobial (Anatomical Therapeutic Chemical [ATC] group 'J') instead of antibiotic (ATC group 'J01') use led to a difference of 16.5 DDD/100 bed-days (19.3%). The literature review revealed underreporting of complete definitions of antibiotic use measurements.
Conclusions: Data on in-hospital antimicrobial use vary widely not only due to different antibiotic policies at different institutions but also due to different methods of measures. Adherence to the standard of reporting the methods of measurement is warranted for benchmarking and promotion of rational antimicrobial use.

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Introduction

Antimicrobials are increasingly and often inappropriately used in human and veterinary medicine and agriculture. The quantity of antibiotic use in hospitals and the community has been shown to correlate with antimicrobial resistance, resulting in increased morbidity, mortality, and cost of health care [1–9]. The recommended standard unit of measurement of antibiotic consumption for hospitals is 'defined daily dose (DDD) per 100 bed-days', as promoted by the World Health Organization (WHO) [10]. The WHO assigned DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Definitions of DDD are updated on a yearly basis. Expressing antibiotic use by using the 'DDD per 100 bed-days' unit is thought to allow hospitals to compare their antibiotic use with other hospitals, regardless of differences in formulary composition, antibiotic potency, and hospital census. Standardized comparisons between organizations, aiming for improvement of operations, are often called benchmarking [11]. Benchmarking can be defined as the process of comparing the performance of an individual organization against a benchmark, or ideal, level of performance. For hospital antibiotic use data, benchmarks can be set across a sample of similar organizations [12].

Even though the ATC/DDD system for all drugs was available since the 1980s, it was not widely used or even misunderstood, resulting in confusion due to publications of antibiotic utilization data with only incomplete definitions and without sufficient specification. Various other measures of antibiotic use have subsequently been proposed. The most common method is direct measurement of the number of days of therapy (DOTs) [13, 14]. Advantages

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of measuring DOTs are lack of influence by changes in the recommended DDD and by discrepancies between the DDD and the preferred daily dose. Disadvantages are its difficulty to measure without computerized pharmacy records of individual patients. Other studies use prescribed daily doses (PDDs), reflecting the usually prescribed dose in adult hospitalized patients with normal renal function [15]. When compared to DDDs, PDDs might provide a better estimate of true antibiotic use. However, large differences between DDD and PDD of a substance that is used in large amounts may result in substantial over- or underestimations not only of the true use of that certain drug, but also of overall antibiotics [16]. The main disadvantage is its lack of standardization, as the usually prescribed daily dose of an antibiotic may vary in different settings.

Not only the ATC/DDD system but also the denominator 'bed-days' has been challenged. A clear description of the methods used to calculate bed-days (e.g., whether the days of admission and discharge count together as one bed-day) is only provided rarely, and additional terms such as occupied bed-days, census-days, and patient-days are used frequently without precise definitions [17]. Due to an increasing number of admissions and a decreasing length of stay over the years, numbers of 'DDD per admissions' may remain stable while numbers of 'DDD per 100 bed-days' are rising [16].

Length of stay is of high importance for benchmarking purposes. It correlates with age (older subjects have longer lengths of stay), morbidity (severely ill patients need longer hospitalization), and hospital size and hospital composition (length of stay varies depending on medical specialty) [18, 19]. Due to economical and insurance reasons, length of hospital stay varies substantially between different countries and trends point toward shorter length of hospital stay with intensified ambulatory care worldwide [19–22].

We aimed to compare different measurements of antibiotic use at our institution, to review the approaches of analyses and presentation of hospital antibiotic use in the literature for benchmark purposes, and to recommend amendments to the standard of reporting the methods of measurement. We determined antibiotic use in different hospital wards of a tertiary care hospital using various calculations of bed-days and admissions; analyzed consumption data by including or excluding different antimicrobial classes; and studied the impact of changing DDD definitions in the course of time on antibiotic use data.

Materials and Methods

Setting

The University Hospital Zurich is a 800-bed tertiary care teaching hospital. It covers all specialties except pediatrics and orthopedics. Six intensive care units are assigned to different departments (Medical ICU; Cardiac Surgery ICU; Neurosurgery ICU; Trauma ICU; Burn ICU, and Visceral, Thoracic, and Transplant Surgery ICU). Bone marrow and solid organ transplantations are performed in specialized units.

Data Collection

Aggregate in-hospital antimicrobial use data, including both deliveries and returns, for 2006 were collected from the hospital pharmacy and entered into a Microsoft® Office Access 2003 database similar to the ABC Calc developed by the Danish Statens Serum Institut [23]. Bed-days and numbers of admissions were calculated from computerized hospital administration records of each patient hospitalized for ≥ 24 h in the same hospital site, service, and defined patient care areas counting the days of admission and discharge together as one bed-day unless specified otherwise. Length of stay is calculated as numbers of bed-days divided by numbers of patients admitted. As one patient can be admitted several times during one hospitalization due to transfers between wards, the number of admissions is larger than the numbers of patients admitted. Means of DDD divided by 100 bed-days and by 100 admissions were calculated measuring means of each hospital site. Unless indicated otherwise, the 2007 version (Group 'J01' [Antibiotics for systemic use]) of the 'WHO Guidelines for ATC (Anatomical Therapeutic Chemical classification index for antibiotics) classification and DDD assignment' was used. Alterations in definitions of DDD of the past years were retrieved from the WHO website [10].

Definitions

'Antibiotics' are all substances of ATC group 'J01' (Antibiotics for systemic use). 'Antimicrobials' are all substances of ATC group 'J' (anti-infectives for systemic use, including antibiotics for systemic use, antimycotics for systemic use, antimycobacterials, antivirals for systemic use, immune sera, and immunoglobulins and vaccines) [10]. Antiparasitic products (antiprotozoals, antihelminthics, and ectoparasiticides) are assigned to ATC group 'P' and are thus not included.

Literature Review

For benchmarking purposes, a literature review of reports on hospital antibiotic use applying the ATC/DDD system was conducted. The period of January 2000 until January 2008 was covered using MEDLINE (combining the MeSH search terms '*anti-infective agents*' and '*hospital*') and PubMed (search terms used alone and in combination included 'antimicrobial', 'antibiotic', 'DDD', 'methodology' and 'hospital'). The reference lists of each publication were reviewed to identify additional reports on hospital antibiotic use.

Results

Overall Antibiotic Use at University Hospital Zurich

In 2006, 239,314 bed-days were recorded and 33,576 patients were admitted to our hospital, accounting for a total of 55,102 admissions (including transfers between units) and a mean length of stay of 7.13 days (day of hospital admission and of discharge counted as one day). Mean antibiotic use (all wards, ATC group 'J01') was 69.15 DDD/100 bed-days and 300.34 DDD/100 admissions, respectively. Mean antimicrobial use (ATC group 'J') was 85.69 DDD/100 bed-days (372.14 DDD/100 admissions) in the entire hospital and 125.88 DDD/100 bed-days (451.80 DDD/100 admissions) in the intensive care units. Includ-

Table 1
Differences in DDD/100 bed-days and DDD/100 admissions of different wards at a tertiary care university hospital in 2006.

Wards included in analysis	DDD/100 bed-days	DDD/100 admissions
All wards, including intensive care units and Bone Marrow Transplant Unit	69.15	300.34
All wards, excluding intensive care units and Bone Marrow Transplant Unit	61.50	283.17
All intensive care units, including Bone Marrow Transplant Unit	147.02	578.95
All intensive care units, excluding Bone Marrow Transplant Unit	125.88	451.80
Bone Marrow Transplant Unit	323.37	6,737.92
ICU - visceral, thoracic and transplant surgery	176.09	727.58
ICU - internal medicine	150.90	534.04
ICU - trauma	126.42	530.00
ICU - burns	106.63	610.71
ICU - neurosurgery	106.62	304.18
ICU - cardiac surgery	101.16	351.19
Internal medicine (including oncology)	110.40	559.70
Urology	95.29	343.45
Ophthalmology and ear-nose-throat	68.06	200.60
Surgery	64.32	278.09
Neurosurgery	54.33	232.28
Dermatology	38.41	264.72
Radio-oncology	33.20	258.24
Neurology	28.72	126.58
Gynecology and obstetrics	22.52	90.95
Rheumatology	20.96	241.62
Psychiatry	0.10	4.23

DDD: defined daily dose; ICU: intensive care unit

ing or excluding Intensive Care Units in aggregate antibiotic use data results in a difference of 7.65 DDD/100 bed-days (12.4%) (Table 1). Including the Bone Marrow Transplant Unit in the aggregated ICU data results in a further increase of 21.14 DDD/100 bed-days (16.8%).

Antibiotic Use in Various Hospital Wards

Antibiotic use varied markedly between different specialties or hospital wards (Table 1). The Bone Marrow Transplant Unit represented the site with the highest antibiotic use (323.37 DDD/100 bed-days or 6,737.92 DDD/100 admissions). However, 150.34 DDD/100 bed-days thereof consisted of gentamicin, an antibiotic with a remarkable difference between DDD (240 mg) and prescribed daily dose, provided that a once daily dosing regimen is used (5 mg/kg body weight once daily). If the Defined Daily Dose was adapted to this prescribed daily dose (350 mg for a person weighing 70 kg), gentamicin use would decrease from 150.34 to 103.09 DDD/100 bed-days. Depending on specialty, considerable differences within Intensive Care Units (ICUs) (101.16 DDD/100 bed-days or 351.19 DDD/100 admissions in Cardiac Surgical ICU compared to 176.09 DDD/100 bed-days or 727.58 DDD/100 admissions in Visceral, Thoracic and Transplant Surgical ICU) were observed.

Differences Depending on the Definition of the Denominator

Bed-days. Due to differences in the definition of the denominator 'bed-days', discrepancies of up to 26.0% were found for DDD/100 bed-days, depending on whether the days of admission and discharge were counted as one bed-day or as two bed-days (Table 2). A short length of stay resulted in a larger difference, playing a key role when reporting ICU antibiotic use data.

Admissions. In contrast, 'DDD/100 admissions' is thought to be a measure which is less influenced by length of stay and more likely to correlate with the risk for antimicrobial resistance. 'DDD/100 bed-days' and 'DDD/100 admissions' are contrasted in Table 1 and Figure 1. However, as observed in the Bone Marrow Transplant Unit, in wards with a long mean length of stay and a high antibiotic use (often in combination therapy), antibiotic use density measured in the DDD/100 admissions format is more likely to take extreme values. Due to transfers between wards, patients may be admitted several times during their hospital stay. Therefore, 33,576 patients who were admitted to our hospital accounted for a total of 55,102 admissions to different hospital units. Not defining the denominator 'admissions' precisely may bias the results substantially.

Differences Depending on the Definition of the Numerator

DDD definitions. Since 2000, definitions of DDD of 11 substances of group 'J01' of the 'WHO Guidelines for ATC classification and DDD assignment' have been changed [10]. Three of these substances (amoxicillin and enzyme inhibitor, cefuroxime and cefepime) were found among the five most widely used antibiotics at the Uni-

Table 2
Differences in DDD/100 bed-days of different wards depending on the definition of the denominator.

Hospital ward	Mean length of stay excluding day of discharge (days)	Antibiotic use excluding day of discharge (DDD/100 bed-days)	Antibiotic use including day of discharge (DDD/100 bed-days)	Difference (%)
ICU - neurosurgery	3.85	106.616	78.945	26.0
Ophthalmology and ear–nose–throat	3.95	68.057	50.817	25.3
ICU - cardiac surgery	4.47	101.164	78.540	22.4
ICU - internal medicine	4.54	150.896	117.652	22.0
Urology	4.60	95.292	74.595	21.7
Gynecology and obstetrics	5.04	22.524	18.053	19.8
ICU - visceral, thoracic and transplant surgery	5.13	176.088	141.776	19.5
ICU - trauma	5.19	126.423	102.075	19.3
Neurosurgery	5.28	54.329	44.030	19.0
Surgery	5.32	64.317	52.236	18.8
Neurology	5.41	28.716	23.406	18.5
Internal medicine (including oncology)	6.07	110.400	92.210	16.5
ICU - burns	6.73	106.627	90.778	14.9
Dermatology	7.89	38.407	33.540	12.7
Radio-oncology	8.78	33.202	29.420	11.4
Rheumatology	12.53	20.963	19.290	8.0
Bone Marrow Transplant Unit	21.84	323.373	308.564	4.6
Psychiatry	41.41	0.105	0.102	2.4
All wards	7.13	69.15	56.21	18.7

Mean length of stay includes only patients hospitalized > 24 h; 'Antibiotics' are all substances of ATC group 'J01 (Antibiotics for systemic use); DDD: defined daily dose; ICU: intensive care unit

versity Hospital Zurich in 2006. The DDD of amoxicillin and enzyme inhibitor was changed from 1 g (parenteral) to 3 g (parenteral) in 2005, the DDD of levofloxacin from 0.25 g (oral and parenteral) to 0.5 g (oral and parenteral) in 2004, the DDD of cefuroxime from 1 g (oral)/4 g (parenteral) to 0.5 g (oral)/3 g (parenteral), the DDD of ceftazidime from 6 g (parenteral) to 4 g (parenteral) and the DDD of cefepime from 4 g (parenteral) to 2 g (parenteral), all in 2000. Applying the 2007 version of the 'WHO Guidelines for ATC classification and DDD assignment' instead of the 2002 version resulted in a reduction of overall antibiotic use of 20.6% at our hospital (69.15 DDD/100 bed-days [2007 version] vs 87.09 DDD/100 bed-days [2002 version]), mainly due to the altered DDD of amoxicillin and enzyme inhibitor.

Drug classes. These included antimicrobials (ATC group 'J') other than antibiotics (ATC group 'J01') account for 16.5 DDD/100 bed-days (19.25%) in the entire hospital and for 30.6 DDD/100 bed-days (19.5%) in the Intensive Care Units, respectively. Differences on hospital site level are shown in Table 3.

Benchmarking

A comparison of antibiotic use data originating from various countries is shown in table 4. Several difficulties with benchmarking were noted. Many studies do not provide essential methodological information. A large proportion of the publications lack a clear definition of the

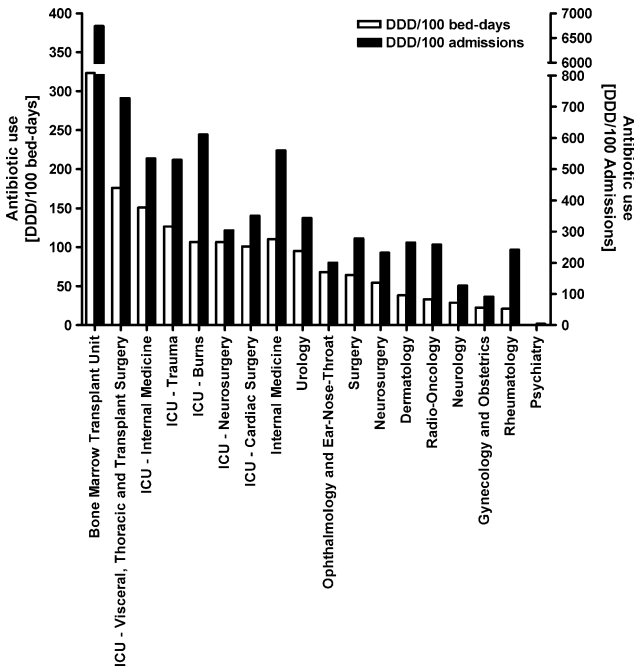

Figure 1. Comparison of antibiotic use (ATC group 'J01') between different wards of the University Hospital Zurich presented in 'DDD/100 bed-days' and 'DDD/100 admissions'. Abbreviations: DDD: defined daily dose; ICU: intensive care unit; ATC: anatomical therapeutic chemical classification index for antibiotics; 'Antibiotics' are all substances of ATC group 'J01 (antibiotics for systemic use)'.

Table 3
Differences in DDD/100 bed-days of different wards depending on the definition of the numerator.

Hospital ward	Antibiotics (ATC group 'J01') (DDD/100 bed-days)	Antimicrobials (ATC group 'J') (DDD/100 bed-days)	Difference (%)
Internal medicine	110.40	156.60	29.5
ICU - visceral, thoracic and transplant surgery	176.09	246.77	28.6
ICU - internal medicine	150.90	209.53	28.0
Bone Marrow Transplant Unit	323.37	438.25	26.2
ICU - cardiac surgery	101.16	126.84	20.2
Psychiatry	0.10	0.13	20.0
Rheumatology	20.96	25.97	19.3
Surgery	64.32	75.78	15.1
Neurology	28.72	32.75	12.3
Neurosurgery	54.33	61.26	11.3
Dermatology	38.41	43.30	11.3
ICU - neurosurgery	106.62	119.30	10.6
ICU - burns	106.63	118.15	9.7
ICU - trauma	126.42	138.43	8.7
Radio-oncology	33.20	36.22	8.3
Urology	95.29	100.37	5.1
Gynecology and obstetrics	22.52	23.65	4.7
Ophthalmology and ear–nose–throat	68.06	70.67	3.7
All wards	69.15	85.69	19.3

Antibiotics are all substances of ATC group 'J01' (antibiotics for systemic use); Antimicrobials are all substances of ATC group 'J' (anti-infectives for systemic use, including antibiotics for systemic use, antimycotics for systemic use, antimycobacterials, antivirals for systemic use, immune sera and immunoglobulins and vaccines); DDD: defined daily dose; ATC: anatomical therapeutic chemical classification index for antibiotics; ICU: intensive care unit

drugs according to the Anatomical Therapeutic Chemical classification index for antibiotics whereas some do indeed provide a complete list of all antimicrobials including DDD definitions. The version of the 'WHO Guidelines for ATC classification and DDD assignment' used is often but not always mentioned. A definition of the term 'bed-day' is only provided in four studies, all originating from The Netherlands or from Sweden. A discrimination of different wards or intensive care units is rarely provided as well as a discrimination of the hospital affiliation (e.g., primary vs secondary vs tertiary care hospital) where data from multiple hospitals are presented. Additionally, different versions of the 'WHO guidelines for ATC classification and DDD assignment' are used in varying studies.

Discussion

In-hospital antimicrobial use varies widely, which may partially be explained by differences in patients' and hospital characteristics, antibiotic policies, physicians' education, or health care systems. However, a substantial part of the differences may be the result of differences in methods to measure antimicrobial use. Exploiting original data collected in 2006 at a university-based tertiary care hospital, we demonstrate how different definitions of nominators and denominators lead to substantially different results. This effect renders valid benchmarking difficult. Consequently, we propose an improved format for reporting hospital antibiotic use.

We demonstrate that hospital structure is an important determinant for antibiotic use and should accurately be disclosed. The definition of the denominator 'bed-day' has been identified as a major obstacle to meaningful data comparison. Due to the lack of a precise definition, substantial discrepancies can result especially on wards with a short mean length of stay. We propose to count the days of admission and discharge together as one bed-day, especially when data on hospital site level are collected, to avoid duplicate counts when patients are transferred from one clinical unit to another. Not only for data comparison within a single institution, but even more important for studies involving multiple centers, a uniform denominator seems mandatory.

Antibiotic use calculated per admissions or per bed-days complement one another. DDD/100 bed-days may more appropriately reflect days of therapy and DDD/100 admissions may provide a better estimate of antibiotic selection pressure, although studies to prove this assumption are lacking [42]. Both calculations are easily available in contrast to data on prescription in individual patients. Trends in antibiotic use over time have been shown to differ when both measures are contrasted [16, 42]. Therefore, both measures should be reported when patient-level data are not available. But, also the denom-

Table 4
Reported antibiotic use in hospitals in different geographic regions between January 2000 and January 2008.

Country, hospital(s), number of hospitals, year (reference)	DDD of antibiotics*/ 100 bed-days	DDD of antibiotics/ 100 admissions	DDD of all antimicrobials/ 100 bed-days	Definition of drug classes studied	Version of WHO/ATC definition	Definition of bed-days; mean length of stay (days)	Remarks
Europe							
Switzerland, tertiary care, 1, 2007 (present study)	All wards: 69.2 Wards excl. ICU: 61.5 ICU only: 125.9	300.3 283.17 451.8	85.7 73.4 156.5	ATC groups 'J01' and 'J'	2007	Yes; 7.1	Admission and discharge days counted as 1 bed-day
Switzerland, tertiary care, 1, 2003 [24]	All wards: 40.0 Surgical ICU: 46.2 Medical ICU: 68.3	NA	NA	List of antibiotic classes in graph legend	1993	No; NA	
Switzerland, tertiary care medical wards, 1, 2004 [25]	Pre-intervention: 30.7 Post-intervention: 21.9	430 270	NA	No	NA	No; 12.4 (post)	'Pre' and 'post' relate to the interventions performed
Czech Republic, general hospital, 1, 2007 [26]	All wards: 37.1	NA	NA	List of antibiotics	NA	No; NA	Data for 2004
Denmark, public hospitals, 55, 2004 [27]	All wards: 44.82	NA	NA	ATC group 'J01'	2001	No; NA	Data for 2001
Denmark, 97.5% of DDD used in hospitals, NA, 2006 [28]	All wards: 64.93	273.76	NA	ATC group 'J01'	2006	No; NA	DDD/100 discharges instead of DDD/100 admissions
Estonia, university hospitals, 1, 2000 [29]	All wards: 62.1	NA	NA	List of antibiotic classes in graph legend	1992	No; NA	Data for 1998
France, university-based acute care hospital, 1, 2006 [30]	All wards: 71.85 ICU only: 151.77	NA	NA	ATC group 'J01'	2005	No; NA	
France, public and private hospitals including two university hospitals, 49, 2004 [31]	All wards: 40.2 ICU only: 128.5	NA	NA	List of antibiotics and DDD	2003	No; 9.99	
Germany, non-university regional hospitals, 40, 2005 [15]	All wards: 49.8 ICU only: 97.8	NA	NA	No	2001	No; NA	Data for hospital size ≥ 400 beds
Germany, university hospitals, 8, 2004 [6]	All surgical wards: 60.1 All medical wards: 79.3 Surgical wards excl. ICU: 51.6 Medical wards excl. ICU: 66 SICU: 146 MICU: 187	NA	NA	No	2001	No; NA	
Germany, acute care hospitals, 145, 2006 [32]	Non-ICU non-surgical wards: 49.3 Non-ICU surgical wards: 50.7 ICUs: 126.5	NA	NA	ATC group 'J01'	2003	No; NA	
Germany, 92 intensive care units, university and non-university, 64, 2006 [33]	ICU only: 114	NA	NA	No	2001	No; NA	Data for 2002

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Table 4
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Country, hospital(s), number of hospitals, year (reference)	DDD of antibiotics*/ 100 bed-days	DDD of antibiotics/ 100 admissions	DDD of all antimicrobials/ 100 bed-days	Definition of drug classes studied	Version of WHO/ATC definition	Definition of bed-days; mean length of stay (days)	Remarks
Germany, university hospital, 1, 2006 [16]	Medical wards: 122.2 Surgical wards: 70.7	1,051 1,033	NA	No	2001	No; NA	
Greece, university hospital, 1, 2006 [17]	All wards: 98.7 ICU only: 98.2	NA	NA	No	2002	No; NA	Editorial
Italy, university-affiliated teaching hospital, 1, 2001 [34]	Pre-intervention: 28.00 Post-intervention: 25.62	NA	NA	List of antibiotics	1995	No; 10.69 (1998)	'Pre' and 'post' relate to the interventions performed
Norway, emergency, referral and university hospitals, 13, 2005 [35]	All wards: 47.5	NA	NA	ATC group 'J01'	2001	No; NA	
Russia, university hospital, 1, 2008 [36]	All wards: 8.8	NA	NA	ATC group 'J01'	2004	No, NA	Data for 2005
Spain, general hospital, 1, 2003 [37]	All wards: 59.47 Wards excl. ICU: 54.44 ICU only: 176.16	NA	NA	No	1997	No; NA	
Sweden, 38 ICUs, NA, 2002 [38]	ICU only: 154.1	NA	NA	No	NA	No; 2.3	Data for tertiary care centers
Sweden, hospitals in Stockholm, 7, 2004 [39]	Reported according to specialty	NA	NA	ATC group 'J01'	2000	Yes; reported according to specialty	Admission and discharge days counted as 1 bed-day
Sweden, hospital care, NA, 2006 [40]	All wards: 58.9	340.1	NA	ATC group 'J01'	NA	No; NA	
The Netherlands, all hospitals, 59, 2005 [41]	All wards: 58.5	391.6	NA	ATC group 'J01'	2002	Yes; 6.7	Admission and discharge days counted as 1 bed-day; data for 2002
The Netherlands, acute care hospitals, 59, 2005 [42]	All wards: 54.7	377.2	NA	ATC group 'J01'	2002	Yes; 6.9	Admission and discharge days counted as 1 bed-day; data for 2002
The Netherlands, 60% of all hospitals, NA, 2007 [43]	All wards: 58.3	317	NA	ATC group 'J01'	2007	Yes; 6.3	Admission and discharge days counted as 1 bed-day
UK, 6.65 % of hospital activity, 12, 2004 [44]	All wards: 114.62	NA	NA	ATC group 'J01'	1999	No; NA	
UK, district general hospital, 1, 2006 [45]	NA	NA	ICU only: 311	No	NA	No; NA	
Hospitals of 15 European countries, NA, 2006 [46]	NA	NA	NA	ATC group 'J01'	2003	–;NA	Reported data in DDD/1000 inhabitants per day
European hospitals from 30 countries, 139, 2006 [47]	All wards: 49.6	NA	NA	ATC group 'J01'	2005	No; NA	
Asia							
Iran, university teaching hospital, 1, 2001 [48]	All wards: NA ICU only: 153.7	NA NA	101.9 166	ATC group 'J'	1996 and 1998	No; NA	
Thailand, tertiary care hospital, 1, 2006 [49]	Pre-intervention: 5.7 Post-intervention: 5.0	NA	NA	List of antibiotic classes	NA	No; NA	'Pre' and 'post' relate to the interventions performed

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Table 4
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Country, hospital(s), number of hospitals, year (reference)	DDD of antibiotics*/ 100 bed-days	DDD of antibiotics/ 100 admissions	DDD of all antimicrobials/ 100 bed-days	Definition of drug classes studied	Version of WHO/ATC definition	Definition of bed-days; mean length of stay (days)	Remarks
Americas							
Argentina, public teaching hospital, 1, 2003 [50]	Pre-intervention: 43.09 Post-intervention: 27.64	NA	NA	List of antibiotics	NA	No; NA	'Pre' and 'post' relate to the interventions performed
U.S. hospitals, 130, 2007 [13]	All wards: 79.2	NA	NA	List available from author	2005	No; NA	

'Antibiotics' are all substances of ATC group 'J01' (antibiotics for systemic use); 'Antimicrobials' are all substances of ATC group 'J' (anti-infectives for systemic use, including antibiotics for systemic use, antimycotics for systemic use, antimycobacterials, antivirals for systemic use, immune sera and immunoglobulins and vaccines); DDD: defined daily dose; ATC: anatomical therapeutic chemical classification index for antibiotics; ICU: intensive care unit; NA: not available; SICU: surgical intensive care unit; MICU: medical intensive care unit

inator 'admissions' must be defined properly. 'Numbers of patients admitted to the hospital' cannot be equated to 'numbers of admissions' because patients transferred between hospital units account for multiple admissions.

Several aspects concerning the numerator have to be taken into account when reporting antibiotic use data. Due to recent changes in the definitions of DDD of substances that are widely used (e.g., amoxicillin with enzyme inhibitor and levofloxacin) in hospitals, the version of the 'WHO Guidelines for ATC classification and DDD assignment' used plays an important role in benchmarking. This must be taken into account for longitudinal comparisons. The Anatomical Therapeutic Chemical Classification Index for antibiotics offers the advantage to clearly define the drug classes that are included in a study. Not defining the drugs included in a survey, using arbitrary drug selections or other definitions (e.g., providing a list of drugs included) further impedes benchmarking.

Aggregate antibiotic use of our hospital is comparable to published data originating from Europe, the United States, and Asia [6, 13, 15–17, 24–51]. However, differences in methodology limit the comparability of the results of the various studies. We particularly observed large discrepancies between the DDD of gentamicin and the usually prescribed dose in daily practice in the Bone Marrow Transplant Unit resulting in a systematic bias.

Strengths of our study are the comprehensive data set of DDD/100 bed-days and DDD/100 admissions from all wards of an entire university hospital, providing a basis for future interventions to promote rational antimicrobial use, and for further research on development and spread of antimicrobial resistance within our institution. Previous studies mainly focused on areas with high antibiotic use, e.g., hemato-oncology or intensive care units [6, 17, 33, 52]. Reporting data from all patient care areas, however, permits to unmask unexpected patterns and time-trends within individual hospital units [31, 37, 53]. Furthermore, we quantified the impact of different methodological issues that are often incompletely reported in the present literature [54].

The findings of our study are limited to a large tertiary care hospital. Our data show that differences between units of measurement are largest between ICUs and specialized units. It remains unclear whether different units of measurements would have the same impact on a smaller peripheral hospital. Other limitations are that we could not discriminate antimicrobial use among specialties of internal medicine (e.g., infectious diseases, oncology, and hemato-oncology) or surgery (e.g., traumatology, visceral surgery, and thoracic surgery) due to hospital and department structures. Future changes in hospital service structure may limit comparability of data and measurement of trends over time. The study of the relation between antimicrobial use and resistance would require data collection on the level of individual patients, e.g., through

Table 5
Recommendations for reporting methodological information in publications on hospital antibiotic use.

1. Report hospital size, composition (e.g., types of intensive care units, with/without bone marrow transplant or burn units, etc.) and affiliation
2. Report mean length of stay, total number of bed-days, numbers of patients admitted and numbers of admissions including multiple admissions of individual patients to multiple hospital sites
3. Describe in detail the hospital wards that were included in the analysis; independently summarize 'all wards' (including Intensive Care Units), 'all Intensive care units' and 'all wards, excluding intensive care units'
4. Report DDD/100 bed-days and DDD/100 admissions
5. Provide a clear definition of the term 'bed-day'; count admission and discharge day together as 1 bed-day if possible
6. Report the version of the 'WHO guidelines for ATC classification and DDD assignment' that were used; use the most recent version at time of publication
7. Select antimicrobials according to the ATC classification. Include all drugs of ATC group 'J01' (antibiotics) and/or ATC group 'J' (antimicrobials)
8. For antibiotic use data in pediatrics, use days of therapy (DOTs) instead of DDDs, if possible

Antibiotics are all substances of ATC group 'J01' (antibiotics for systemic use); Antimicrobials are all substances of ATC group 'J' (anti-infectives for systemic use, including antibiotics for systemic
use, antimycotics for systemic use, antimycobacterials, antivirals for systemic use, immune sera and immunoglobulins and vaccines); DDD: defined daily dose; ATC: anatomical therapeutic chemical classification index for antibiotics

retrieving data from applications for electronic drug prescribing [55]. Nevertheless, the use of aggregate data provided by the hospital pharmacy is a common method, because, as it is the case in our institution, prescription data on the individual patient level often are not accessible.

The recently published 'Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship' from the Infectious Disease Society of America and the Society for Healthcare Epidemiology of America recommend using the ATC/DDD system without elaborating the difficulties of this method in detail [56]. On the basis of our data, we provide more distinct and practical recommendations to circumvent the pitfalls that may emerge when using aggregate hospital antibiotic use data.

In conclusion, methodological details are a prerequisite in publications on antibiotic use to provide a basis for benchmarking of hospitals and individual hospital units. To counteract the publication of utilization studies with incomplete definitions and without sufficient specifications in medical journals, researchers should be forced to precisely report hospital composition and affiliation, wards included in the analysis, a clear definition of the terms 'bed-day', and 'admissions', the version of the WHO Guidelines for ATC classification and DDD assignment used and the drugs that were included in their publications (Table 5). Ongoing and open-access publications of hospital antibiotic use data are crucial for quality control, prevention of nosocomial infections, and the struggle against the worldwide emergence of antibiotic resistance.

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