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ORIGINAL PAPER

Antibiotic use varies substantially among adults: a cross-national study from five European Countries in the ARITMO project

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Abstract
Purpose To examine patterns of outpatient and community antibiotic use among adults in five European countries.
Methods We used healthcare data of 28.8 million adults from six population-based ARITMO project databases to ascertain information on systemic antibiotic use in Denmark (2000–2008), the Netherlands (1999–2010), Italy (2000–2010), the UK (1996–2009), and Germany (2004–2008). We estimated overall, and age-group and sex specific antibiotic use as defined daily doses (DDD) per 1000 inhabitants per day. We computed annual age- and sex-standardized population prevalence of antibiotic use per 1000 persons-years (p-y) and the mean duration (in days) of antibiotic use.
Results The overall antibiotic use varied from 8.7 DDD per 1000 inhabitants per day in the UK to 18.1 DDD in Denmark, representing a 2.1-fold geographical variation. In all countries, prescribing was relatively high among individuals aged 15–19 years; lower in those aged 20–50 years; and then increased steadily reaching 41.8 DDD per 1000 inhabitants per day in individuals ≥85 years in Denmark. After age- and sex-standardization, prevalence of antibiotic use varied threefold from 160.2/1000 p-y in the UK to 421.1/1000 p-y in Italy. The ratio of broad- to narrow-spectrum penicillin, cephalosporin, and macrolide use varied from 0.6 in Denmark to 120.2 in Italy. Women used more antibiotics than men did in all countries. Across countries, the mean duration of antibiotic use varied 1.3 to 21.1-fold for different antibiotics.
Conclusions Antibiotic use is high in women and the elderly. Prescribing patterns vary substantially across European countries, both according to overall consumption, user prevalence, duration, and narrow- versus broad-spectrum antibiotics.

Keywords Antibiotic resistance · Drug utilization · Prescription · Europe · Electronic health records

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Introduction

Antibiotic resistance driven by selective pressure from both appropriate and inappropriate use of antibiotics is an evolving public health crisis and a potential threat to future healthcare delivery [1, 2]. The European Centre for Disease Control (ECDC) recently estimated that 25,000 deaths per year within Europe are directly related to antibiotic resistance [3]. Therefore, data on antibiotic use is vital to identify priority areas for interventions to optimize antibiotic use.

The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) program has documented a 3.1-fold variation in antibiotic use between countries with the highest use [35.1 defined daily doses (DDD) per 1000 inhabitants per day in Greece] and the country with the lowest use (11.4 DDD per 1000 inhabitants per day in the Netherlands) in 2011 [4]. Striking geographical variation was observed not only for overall prescription but also for use of various specific antibiotic subgroups including quinolones, macrolides, penicillins, and cephalosporins [5, 6]. ESAC-net presents aggregated measures on antibiotic use according to DDD per 1000 inhabitants per day and as packages per 1000 inhabitants per day (PID) that are based on DDDs, which is a parameter that does not necessarily reflect the prescribed daily dose. Additionally, ESAC-net does not provide patient-level information, such as number of patients treated in the population, age and sex distribution, and duration of treatment, which is necessary to identify target groups for intervention to improve prudent use of antibiotics. Therefore, to fill this gap, we utilized data from the EU funded "Arrhythmogenic potential of drugs (ARITMO)" project (www.aritmo-project.org). For the overall antibiotics and for each antibiotic subgroup and chemical substance, separately, we measured and compared across five European Countries: (1) the volume (expressed as DDD per 1000 inhabitants per day) of antibiotics used in the community, (2) the annual population prevalence of antibiotic use; and (3) the mean duration of antibiotic use.

Methods

Data sources and setting

ARITMO is a collaborative project started in 2010 and funded by the European Commission under the VII Framework Programme (Grant agreement number: HEALTH 241679). The overall objective of ARITMO was to analyze the arrhythmogenic potential of antihistamines, antipsychotics and anti-infectives, including antibiotics. The ARITMO project combines anonymized electronic healthcare records data of about 30 million individuals from six population-based databases of five European countries. The databases included in the project are, the PHARMO research database from the Netherlands; Aarhus University Hospital (AUH) database from Denmark; the German Pharmacoepidemiological Research Database (GePaRD) from Germany; the health improvement network (THIN) database from the United Kingdom (UK); and the Health Search/Longitudinal Patients Database (HSD) and Emilia-Romagna regional database (ERD) from Italy. The HSD [7, 8] and THIN databases [9, 10] are general practice databases documenting clinical information and drug prescriptions. The information is gathered and transferred by selected and trained practitioners from all over Italy and the UK. The PHARMO and GePaRD are claims and record linkage databases collecting information on drug dispensing. The PHARMO database collects information from the entire population of 65 municipalities in the Netherlands, whereas GePaRD gathers information from four national statutory health insurance providers. The AUH and ERD are population-based record linkage registries and cover the entire population of the respective geographical regions of Denmark and Italy. Table 1 shows an overview of the contributing databases. Data from the individual databases were extracted locally using a common pre-specified data model and thereafter elaborated using a dedicated software Jerboa which allowed anonymization and aggregation of data [11]. Data were ultimately sent in encrypted format, for data protection reasons, to a central repository managed by the Department of Medical Informatics at Erasmus Medical Center in the Netherlands for further evaluation and analyses. All databases obeyed the European Union guidelines on the usage of medical data for research. The study was given approval by regulatory agencies or by scientific and ethical advisory boards of the databases where

Table 1 Characteristics of healthcare databases involved in the study

	Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
Study population	1.6 million	4 million	1.2 million	17 million	2.4 million	2.6 million
Source of study population	North and Central Denmark region	Emilia-Romagna region	Nationwide	Nationwide	65 municipalities throughout the Netherlands	Nationwide
Type of coverage	Population-based	Population-based	Patient-centered	Population-based	Population-based	Patient-centered
Follow-up period	2000–2008	2006–2010	2000–2010	2004–2008	1999–2010	1996–2009
Type of database	Record linkage	Administrative	GP database	Administrative	Record linkage	GP database
Drug coding system	ATC	ATC	ATC	ATC	ATC	BNF

AUH Aarhus University Hospital, *ERD* Emilia-Romagna regional database, *HSD* Health Search Database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network, *ATC* Anatomical therapeutic classification, *BNF* British national formulary

applicable. The whole process of data extraction, quality check and analyses when combining multiple databases has been in depth described elsewhere [12].

Study population and study period

We included all persons aged 15 years or above from the source population who were registered in the databases during the study period. The study duration varied across databases and ranged from 1996 through 2010, as summarized in Table 1. We defined the eligibility period for each patient as starting 1 year after the date of registration in the database and ending on the date of last supply of data, death, or December 31, 2010, whichever came first.

Data on antibiotic use

Data on outpatient and community antibiotic prescription and dispensation were collected from different databases and used as a proxy for antibiotic use. Data on antibiotic use were aggregated at the level of the active chemical substance, using the Anatomical Therapeutic Chemical (ATC) classification and the DDD measurement unit (WHO, version 2011) [13]. From each database we retrieved information on date of prescription or dispensing (if both dates were available we used the date of dispensing), total quantity of the active principle in each prescription, DDD-value, number of units per prescription, strength per unit, number of prescribed units per day (if available), and total number of DDD for each prescription/dispensing.

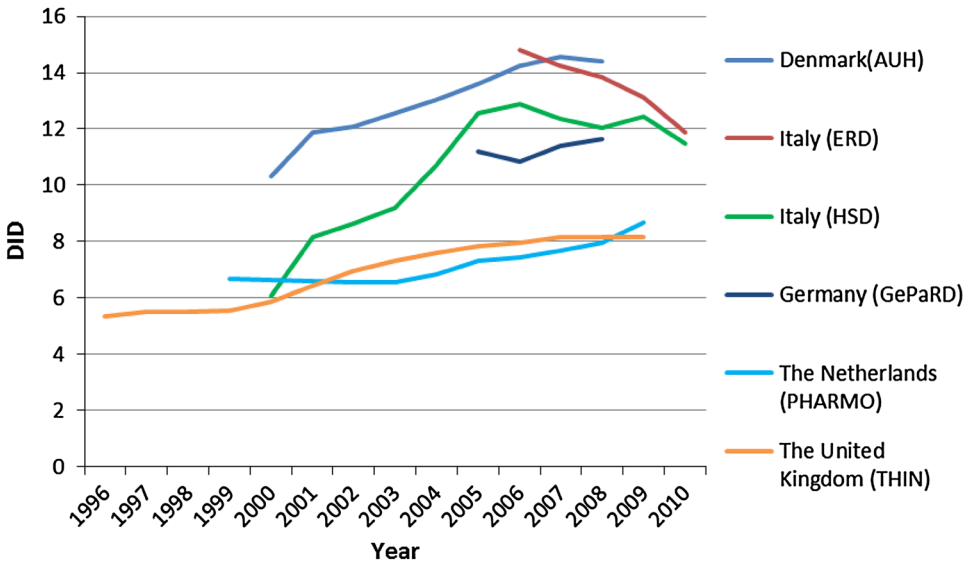

Fig. 1 Annual trends in the age- and sex-standardized antibiotic use as DDDs per 1000 inhabitants per day among participating countries. *DDDs* defined daily doses, *DID* DDD per 1000 inhabitants per day, *AUH* Aarhus University Hospital, *ERD* Emilia-Romagna regional database, *HSD* Health Search Database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

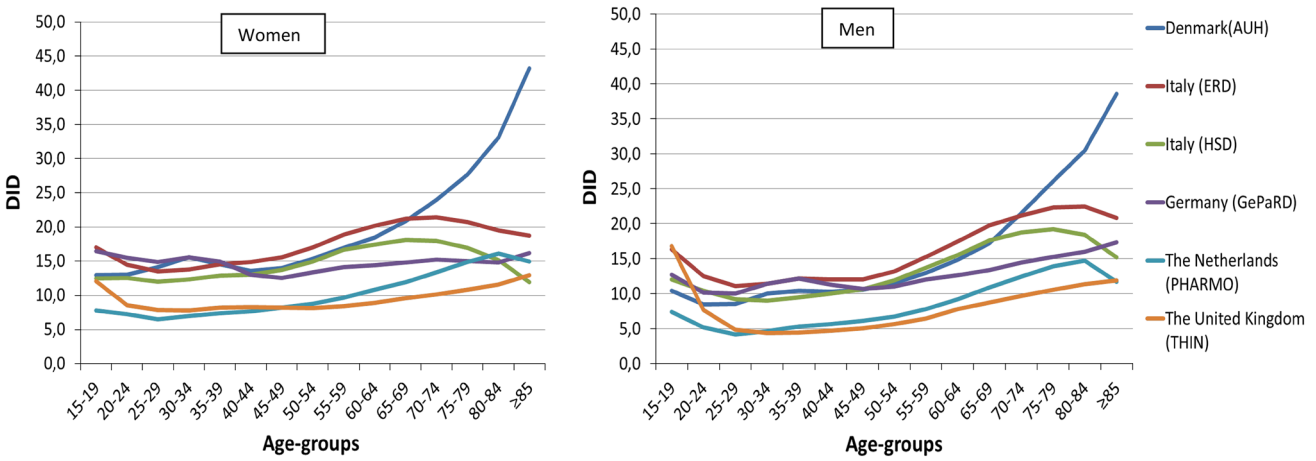

Fig. 2 Volume of antibiotic use as DDDs per 1000 inhabitants per day by country and age-groups in women (*left*) and men (*right*). *DDDs* defined daily doses, *DID* DDD per 1000 inhabitants per day, *AUH* Aarhus University Hospital, *ERD* Emilia-Romagna regional database, *HSD* Health Search Database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

Statistical analysis

We computed volume of antibiotic use as DDDs per 1000 inhabitants per day. Inhabitants per day were calculated as: total person-days observed in each database divided by 1000. We computed sex and age-group stratified volume of antibiotic use for each database. To compare antibiotic use across the participating countries, we standardized the estimates to age and sex according to the EUR27 standard population for the year 2004 (http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database).

Furthermore, we computed the annual age- and sex-standardized population prevalence of antibiotic use according to ATC 4th level (antibiotic subgroup) and ATC 5th level (antibiotic chemical substance). We presented annual prevalence per 1000 person-years calculated as the number of individuals who received at least one antibiotic prescription/dispensing divided by the total cumulated person time in the observation year and multiplied by 1000. We then repeated the analyses for broad- and narrow-spectrum antibiotics, separately. Broad spectrum antibiotics included broad-spectrum penicillins (ATC code: J01CR+J01CA), cephalosporins (ATC code: J01DC+J01DD), and macrolides (ATC code: all J01F except J01FA01). Narrow spectrum antibiotics included narrow-spectrum penicillins (ATC code: J01CE+J01CF), cephalosporins (ATC code: J01DB), and macrolides (ATC code: J01FA01). We also computed sex and age-group stratified annual prevalence of antibiotic use per 1000 person-years for each database. Additionally, we calculated the mean duration of antibiotic use per prescription/dispensing at the ATC 4th level and ATC 5th level. We calculated mean days of antibiotic use per prescription/dispensing by adding the total days of antibiotic exposure (ATC 4th level and ATC 5th level) divided by the total number of prescriptions retrieved.

Results

Volume of antibiotic use in the community

Antibiotic use ranged from 8.7 DDD per 1000 inhabitants per day in the UK to 18.1 DDD per 1000 inhabitants per day in Denmark, representing a 2.1-fold variation. The consumption was 9.4 DDD per 1000 inhabitants per day in the Netherlands, 13.7 DDD per 1000 inhabitants per day in Germany, and 13.9–16.7 DDD per 1000 inhabitants per day in Italy. The age- and sex-standardized annual use of antibiotics increased steadily over time in Denmark (from 10.3 to 14.4 DDD per 1000 inhabitants per day), the Netherlands (from 6.7 to 8.6 DDD per 1000 inhabitants per day), the UK (from 5.3 to 8.1 DDD per 1000 inhabitants per day), and Germany (from 11.2 to 11.6 DDD per 1000 inhabitants per day). In Italy antibiotic use increased up to 2006 (from 6.1 to 11.5 DDD per 1000 inhabitants per day) followed by a decrease (from 14.8 to 11.9 DDD per 1000 inhabitants per day in the ERD database, and from 12.9 to 11.5 DDD per 1000 inhabitants per day in the HSD database) (Fig. 1). In all countries, antibiotic use was relatively high among individuals aged 15–19 years, lower at a stable level among individuals aged 20–50 years, and then increased steadily with age (Table 4 in the "Appendix"). In particular, there was more than a 3.1-fold increase with age in Denmark, from 13.5 DDD per 1000 inhabitants per day in individuals aged 50–54 years to 41.8 DDD per 1000 inhabitants per day in individuals ≥85 years. The antibiotic use was substantially lower among the elderly in the other countries. Stratifying by sex revealed a higher antibiotic use among women compared to men in all age-groups, except among individuals older than 70 years in Italy where use was higher in men compared with women (Fig. 2).

Population prevalence of antibiotic use

The age- and sex-standardized annual prevalence of antibiotic use varied from 160.2/1000 person-years in the UK to 421.1/1000 person-years in the Emilia-Romagna region of Italy, equivalent to a threefold variation (Table 2). The most frequently used subgroups were beta lactamase sensitive penicillins in Denmark (161.9/1000 person-years), penicillin combinations including beta lactamase inhibitors in Italy (77.1–94.7/1000 person-years), tetracycline in the Netherlands (52.9/1000 person-years), beta-lactamase resistant penicillins in the UK (34.2/1000 person-years), and macrolides in Germany (72.3/1000 person-years) (Fig. 3). Antibiotics used for intestinal infections (ATC code: A07AA) were relatively frequent in Italy (24.2–25.6/1000 person-years) while the prevalence accounted for less than 4/1000 person-years in the other countries.

The annual prevalence of individual chemical substances also varied widely among participating countries (Table 5 in the "Appendix"). Highest age- and sex-standardized prevalences were found for phenoxymethylpenicillin in Denmark (161.9/1000 person-years), amoxicillin with clavulanic acid in Italy (75.9–94.3/1000 person-years), doxycycline in the Netherlands (49.3/1000 person-years), amoxicillin in Germany (47.8/1000 person-years), and flucloxacillin in the UK (34.2/1000 person-years) (Table 5 in the "Appendix"). Dicloxacillin, sufamethizole, pivmecillinam, and pivampicillin were widely used in Denmark but not in the other countries or with a very low prevalence in the UK, respectively.

In Denmark and the UK narrow-spectrum penicillin, cephalosporin, and macrolides were more commonly prescribed than broad-spectrum penicillin, cephalosporin, and macrolides. Whereas in Germany, Italy and the Netherlands broad-spectrum penicillin, cephalosporin, and macrolides were more frequently prescribed than narrow-spectrum

Table 2 Age- and sex-standardized annual prevalence of antibiotic use per 1000 person-years by antibiotic subgroups

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
Overall		384.8	421.1	377.6	390.4	229.2	160.2
A07AA	Antibiotics against intestinal infections	4.1	25.6	24.2	1.0	<0.1	<0.1
J01AA	Tetracyclines	0.8	4.6	4.8	47.3	52.9	27.7
J01CA	Penicillins with extended spectrum	71.2	51.8	54.8	48.4	35.2	3.6
J01CE	Beta-lactamase sensitive penicillins	161.9	0.3	0.3	32.5	11.1	<0.1
J01CF	Beta-lactamase resistant penicillins	30.2	<0.1	0.2	0.6	9.1	34.2
J01CR	Combinations of penicillins incl. beta-lactamase inhibitors	1.2	94.7	77.1	10.1	27.1	21.6
J01DB	First-generation cephalosporins	<0.1	1.5	1.8	2.6	0.1	23.5
J01DC	Second-generation cephalosporins	<0.1	7.1	7.6	22.7	0.2	5.7
J01DD	Third-generation cephalosporins	<0.1	40.0	27.5	13.3	0.1	0.3
J01DE	Fourth-generation cephalosporins	–	0.1	0.3	<0.0	–	–
J01DH	Carbapenems	<0.1	<0.1	<0.1	<0.0	<0.1	<0.1
J01EA	Trimethoprim and derivatives	6.9	–	<0.1	1.9	12.6	–
J01EB	Short-acting sulfonamides	36.3	–	–	–	<0.1	<0.1
J01EE	Combinations of sulfonamides and trimethoprim. incl. derivatives	0.1	6.9	8.3	31.5	7.2	0.2
J01FA	Macrolides	63.9	84.6	71.3	72.3	27.9	12.8
J01FF	Lincosamides	<0.1	0.5	4.7	27.4	1.4	0.2
J01GB	Aminoglycosides other than streptomycin	<0.1	0.7	1.4	0.2	0.1	<0.1
J01MA	Fluoroquinolones	0.4	78.9	66.6	68.9	19.5	13.7
J01MB	Other quinolones	–	1.8	2.9	<0.1	0.5	0.1
J01XA	Glycopeptide antibacterials	<0.1	0.1	0.1	0.1	<0.1	<0.1
J01XB	Polymyxins	<0.1	<0.1	<0.0	<0.1	<0.1	0.1
J01XD	Imidazole derivatives	<0.1	<0.1	<0.1	<0.1	0.1	9.7
J01XE	Nitrofuran derivatives	7.0	0.1	1.1	3.7	21.7	4.6
J01XX	Other antibacterials	0.1	20.8	18.7	2.5	0.4	<0.1
J04AB	Antibiotics against tuberculosis	0.1	0.4	0.7	0.2	0.2	0.2
J04AK	Other anti-tuberculosis drugs	<0.1	<0.1	0.1	0.1	0.1	<0.1

Annual prevalence is expressed per 1000 person-years and is calculated by adding the number of individuals exposed to the antibiotic subgroup for at least 1 day divided by the total person-time in the observation window in 1000 person-years

AUH Aarhus University Hospital, *ERD* Emilia-Romagna regional database, *HSD* Health Search Database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

counterparts (Fig. 4). The ratio of broad- to narrow-spectrum penicillin, cephalosporin, and macrolides varied from 0.60 in Denmark to 102.18 in Italy (HSD). The ratio was 4.94 in Germany, 69.78 in the Emilia-Romagna region of Italy (ERD), and 3.99 in the Netherlands.

After stratifying by age and sex, we observed a relatively higher prevalence of antibiotic use in individuals aged 15–19 years. The annual prevalence was lower at a stable level in individuals aged 20–44 years and increased steadily with age in individuals over 45 years of age until 79 years in all countries, and varied thereafter (Fig. 5 in the "Appendix"). This pattern was similar for men and women, but annual prevalence was highest for women in all countries (Fig. 6 in the "Appendix").

Duration of antibiotic treatment

Mean duration of antibiotic use varied for all antibiotic subgroups among the five countries (Table 3). The lowest variation in duration was observed for macrolides (J01FA) with a 1.3-fold variation between countries with the shortest and longest duration of use, respectively, (6.7 days in Germany versus 8.8 days in Denmark). In comparison, the greatest variation was a 21.1-fold variation in the duration of use of aminoglycosides other than streptomycin (J01GB) [2.3 days in Italy (HSD) versus 47.7 days in Denmark]. The duration of antibiotic use also varied greatly for individual antibiotic substances across the five participating countries (Table 6 in the "Appendix").

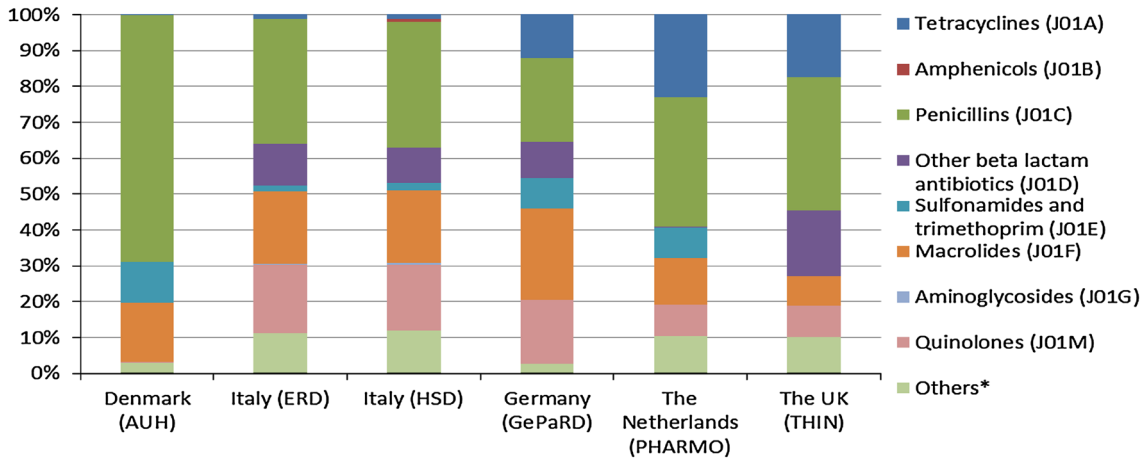

Fig. 3 Distribution of mean annual prevalence of antibiotic use at ATC group level 3 in the five participating countries. *Others: other J01 codes, A07AA, A02BD, J04AB, J04AC, J04AD, J04AK, J04AM, G01AA, R02AB. *AUH* Aarhus University Hospital, *ERD* Emilia-Romagna regional database, *HSD* Health Search Database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network, *UK* the United Kingdom

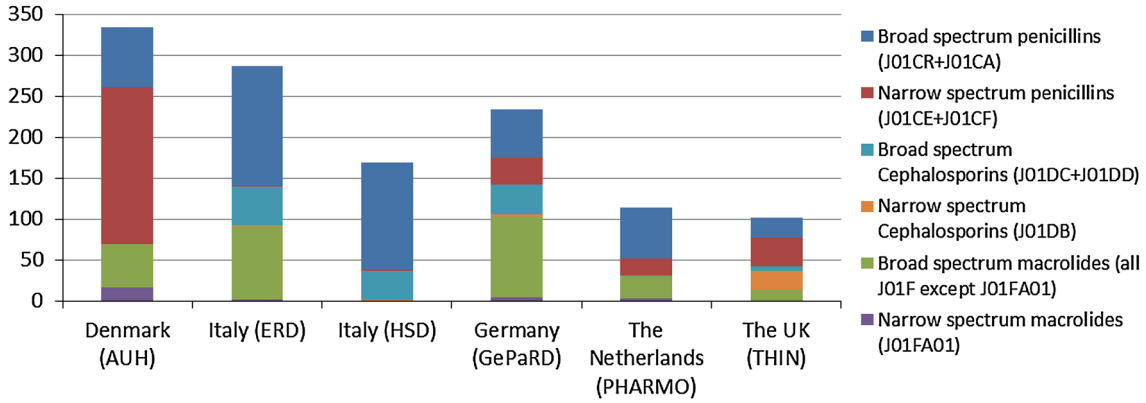

Fig. 4 Annual prevalence of broad- and narrow-spectrum penicillin, cephalosporin, and macrolides use at ATC group level 3 in the five participating countries. *AUH* Aarhus University Hospital, *ERD* Emilia-Romagna regional database, *HSD* Health Search Database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network, *UK* the United Kingdom

Discussion

This population-based study of 28.8 million people covered by six databases of five European countries identified substantial variations in the use of antibiotics from 8.7 DDD per 1000 inhabitants per day in the UK to 18.1 DDD per 1000 inhabitants per day in Denmark. The overall use increased with age over 20 years in all countries but most markedly in Denmark. The overall age- and sex-standardized prevalence of antibiotic use varied from 160/1000 person-years in the UK to 421/1000 person-years in the Emilia-Romagna region of Italy with large variations in the use of individual antibiotic subgroups. Denmark and the UK prescribed more narrow-spectrum antibiotics whereas broad-spectrum penicillin, cephalosporin, and macrolides were used more frequently than narrow-spectrum counterparts in the Netherlands, Germany and mostly in Italy. Antibiotic use was relatively higher among women compared with men. Additionally, we observed substantial variation in the mean duration of antibiotic use among the participating countries.

The ESAC-Net project recently documented a 3.5 fold variation in antibiotic use among 26 European countries [14]. Our study extends these findings by including results for antibiotic subgroups and individual chemical substances and enhances comparability by providing age and sex standardized results. Additionally, we provide information on demographic characteristics of antibiotic users in the participating countries. Our finding of an increasing use with age in Denmark and the UK are of the same magnitude as

Table 3 Mean duration of antibiotic use (in days) per subgroup in each database

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
A07AA	Antibiotics against intestinal infections	5.3	6.1	4.3	5.0	17.9	8.4
J01AA	Tetracyclines	29.4	12.5	10.5	16.0	12.2	24.1
J01BA	Amphenicols	–	1.8	1.3	3.0	37.1	8.5
J01CA	Penicillins with extended spectrum	9.5	11.9	12.2	13.6	10.5	7.1
J01CE	Beta-lactamase sensitive penicillins	8.0	1.0	1.3	8.4	10.1	6.3
J01CF	Beta-lactamase resistant penicillins	8.5	7.1	7.2	3.6	9.2	7.2
J01CR	Combinations of penicillins incl. beta-lactamase inhibitors	11.7	11.4	10.1	5.8	9.6	7.2
J01DB	First-generation cephalosporins	14.2	4.8	4.5	6.4	12.1	8.0
J01DC	Second-generation cephalosporins	24.3	7.1	6.0	8.0	12.1	7.2
J01DD	Third-generation cephalosporins	10.6	4.9	4.1	5.8	9.7	7.9
J01DE	Fourth-generation cephalosporins	–	3.4	2.9	10.8	–	–
J01DF	Monobactams	20.2	1.9	1.1	3.6	1.0	5.5
J01DH	Carbapenems	15.7	2.3	1.4	4.2	7.1	6.4
J01EA	Trimethoprim and derivatives	14.6	–	3.0	6.6	9.7	–
J01EB	Short-acting sulfonamides	3.0	–	–	–	19.3	28.4
J01EC	Intermediate-acting sulfonamides	–	29.9	24.8	48.5	41.7	21.3
J01ED	Long-acting sulfonamides	–	–	4.2	–	–	11.7
J01EE	Combinations of sulfonamides and trimethoprim. incl. derivatives	24.4	9.2	8.4	6.2	17.3	16.0
J01FA	Macrolides	8.8	8.2	7.2	6.7	8.5	7.5
J01FF	Lincosamides	16.7	2.6	2.2	6.5	14.5	11.6
J01GA	Streptomycins	–	6.5	5.8	11.1	.	3.6
J01GB	Aminoglycosides other than streptomycin	47.7	2.9	2.3	13.0	20.4	9.8
J01MA	Fluoroquinolones	15.9	6.0	5.1	5.2	9.8	8.0
J01MB	Other quinolones	–	11.7	9.9	7.2	14.0	12.1
J01RA	Combinations of antibacterials	–	–	–	7.9	–	–
J01XA	Glycopeptide antibacterials	5.9	3.5	3.0	2.6	7.5	6.6
J01XB	Polymyxins	13.2		3.5	24.9	45.5	11.8
J01XD	Imidazole derivatives	4.0	2.2	2.3	3.1	22.5	7.2
J01XE	Nitrofuran derivatives	14.2	8.4	7.8	18.1	8.9	12.7
J01XX	Other antibacterials	43.5	2.6	2.3	4.3	13.2	22.2
J04AB	Aantibiotics against tuberculosis	42.5	11.6	8.5	31.7	29.1	14.3
J04AD	Thiocarbamide derivatives	–	–	–	25.2	–	7.0
J04AK	Other anti-tuberculosis drugs	30.7	21.3	15.1	19.9	24.2	15.3
J04AM	Combinations of drugs for treatment of tuberculosis	–	22.3	16.3	33.5	38.6	22.8

Mean duration of antibiotic exposure was calculated by adding the total days of exposure to the specific antibiotic divided by the total number of prescriptions

AUH Aarhus University Hospital, *ERD* Emilia-Romagna regional database, *HSD* Health Search Database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

observed in a previous study comparing antibiotic utilization in Denmark and Italy [15]. Additionally, a recent Swedish study reported higher antibiotic use among individuals aged ≥65 years old (556/1000 inhabitants) compared with individuals aged 40–65 years (339/1000 inhabitants) [16]. Other prior studies have also shown wide variations in community antibiotic use both between [14] and within [17] countries.

Higher antibiotic use in some settings does not necessarily indicate inappropriate prescribing but may relate to differences in disease occurrence. Differences in healthcare systems including the number of GPs in a country [18], antibiotic dosage regimens, guidelines, patient expectation and attitude toward taking medications, cultural and social factors, source of information available to

the GPs, and knowledge of the GPs [19, 20] also play a role. For example, the longer duration of aminoglycosides use observed in Denmark despite its low overall consumption is likely because it is it is indicated for haematological cases for longer duration and as a prophylactic drug after intra-abdominal surgeries and prescribed for weeks [21]. The Social and Cultural Planning Office of The Netherlands have reported that countries with a more egalitarian society (The Netherlands, the UK, Scandinavia) have a much lower level of medication use than countries with a hierarchical society (France, Italy, Spain, Portugal, etc.) [22]. Thus, it is possible to reduce community antibiotic use, as the observed variations are explained by multiple factors rather than mere differences in disease incidence, severity, etiology, or different demographics [23–26]. For example, implementation of antibiotic stewardship program in Sweden significantly reduced the outpatient antibiotic use [27]. Similarly, the marked decrease in the antibiotic use in the Emilia-Romagna region of Italy as reported in our results might be the result of informative campaigns and adoption of effective treatment guidelines by the region.

Our study is a sub-study of the ARITMO project that combined electronic health records from five European countries to build a unique dataset to study several outcomes. The databases included in ARITMO are compliant with the anonymity, European directives, national data regulations and database governance rules. Local experts from each of the participating countries were involved in the project to maximize the efficiency and to deal effectively with methodological, cultural, ethical, governance and political issues of sharing data out of the country.

Our study extends prior studies by providing information on prescription prevalence and duration of antibiotic use. We used the ATC classification system and DDD measurement units, developed by the WHO collaborating center for drug statistics methodology. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults [13] and only gives a rough estimate of the drug used. Thus, actual doses of drug may differ from DDD and are usually based on patient factors (age, weight, severity of disease etc.). This might have contributed to the observed variation across the countries. However, as Monnet et al. [28] reported the number of DDD may indicate the number of prescriptions for outpatients at the national level. We used reimbursement data, thereby excluding drugs that were sold over-the-counter, which may underestimate the actual use of drugs. However, a questionnaire survey among EU member states found that only 2–3 % of survey participants obtained antibiotics without a prescription [29], so we believe any underestimation is likely to be negligible. Caution should be taken when interpreting our findings because the results are based on sections of a population. However, we believe that the source population of most databases is representative of the whole population, except for the data from the Emilia-Romagna region of Italy. Results for Italy cannot be directly generalized due to substantial differences in regional prescribing patterns, and we assume that the results for Italy are underestimated due to the sale of antibiotics without prescription [30]. Finally, the slightly different time-frames of our available data should be kept in mind when comparing countries. To address this we provide the time-trends for each database and report standardized estimates.

In conclusion, this study observed considerable differences in the amount of antibiotic use and the user prevalence across Europe. Antibiotics are mostly prescribed to people younger than 20 years or older than 50 years, and to women. The ratio of broad- to narrow-spectrum penicillin, cephalosporin, and macrolides seems to be lowest in Denmark and the UK, and was high for Germany, the Netherlands, and to a much greater extent in Italy. Further population-based studies are warranted to understand the mechanism behind the differences in antibiotic use pattern. Understanding the determinants of antibiotic use may help to frame a targeted approach to reduce antibiotic use, which is urgently needed to halt the emerging antibiotic resistance.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Appendix

See Tables 4, 5, 6, 7 and Figs. 5, 6, 7.

Table 4 Antibiotic use as DDDs per 1000 inhabitants per day in countries according to age groups

	Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
Overall	18.1	16.7	13.9	13.7	9.4	8.7
15–19	11.7	16.7	12.2	14.5	7.6	14.6
20–24	10.8	13.5	11.5	12.9	6.3	8.1
25–29	11.5	12.4	10.6	12.5	5.5	6.4
30–34	13.0	12.7	10.7	13.6	5.9	6.1
35–39	12.6	13.4	11.2	13.6	6.4	6.3
40–44	12.0	13.5	11.6	12.1	6.7	6.5
45–49	12.4	13.8	12.2	11.6	7.2	6.6
50–54	13.5	15.1	13.5	12.1	7.8	6.9
55–59	15.0	17.1	15.2	13.0	8.8	7.4
60–64	16.7	18.9	16.5	13.4	10.1	8.4
65–69	19.2	20.5	17.9	14.0	11.4	9.2
70–74	22.8	21.3	18.3	14.8	13.0	9.9
75–79	27.0	21.4	17.9	15.2	14.5	10.7
80–84	32.1	20.6	16.3	15.3	15.6	11.5
85+	41.8	19.4	12.9	16.6	14.0	12.6

Antibiotic use is calculated by adding the person-days for each antibiotic in each month and year and dividing it by the annual mean of patients exposed and expressed in DDD/1000 inhabitants per day

DDDs defined daily doses, *DID* DDD per 1000 inhabitants per day, *AUH* Aarhus University Hospital, *ERD* Emilia-Romagnia regional database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

Table 5 Age- and sex-standardized annual prevalence of antibiotic use per 1000 person-years according to antibiotic chemical substances

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
Overall		396.2	442.0	198.4	401.8	210.0	138.5
A07AA	Antibiotics-intestinal	4.1	25.6	24.2	1.0	<0.1	<0.1
J01GB06	Amikacin	–	0.2	–	<0.1	<0.1	<0.1
J01CA04	Amoxicillin	20.2	489.4	478.1	478.1	352.4	–
J01CR02	Amoxicillin and enzyme inhibitor	1.2	943.5	759.1	72.8	270.9	216.1
J01CA01	Ampicillin	0.1	13.5	31.9	0.6	<0.1	0.7
J01CR01	Ampicillin and enzyme inhibitor	–	0.2	13.7	<0.1	–	–
J01CA51	Ampicillin. Combinations	–	–	–	–	–	28.5
J01CE04	Azidocillin	–	–	–	<0.1	–	–
J01FA10	Azithromycin	22.6	350.6	–	213.2	127.9	13.3
J01DF01	Aztreonam	<0.1	<0.1	–	<0.1	<0.1	<0.1
J01CA06	Bacampicillin	<0.1	17.5	45.8	–	–	<0.1
J01CE08	Benzathine benzylpenicillin	–	0.3	0.3	0.1	0.4	–
J01CE10	Benzathine phenoxymethylpenicillin	–	–	–	<0.1	–	–
J01CE01	Benzylpenicillin	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
J01CA03	Carbenicillin	–	–	<0.1	–	–	<0.1
J01DC04	Cefaclor	–	14.9	14.0	75.3	0.1	52.2
J01DB05	Cefadroxil	–	0.1	<0.1	16.0	–	10.3
J01DB01	Cefalexin	<0.1	10.7	13.9	1.0	0.1	196.1
J01DB03	Cefalotin	–	–	<0.1	–	<0.1	–
J01DC03	Cefamandole	–	<0.1	<0.1	–	<0.1	–
J01DB07	Cefatrizine	–	–	<0.1	–	–	–
J01DB04	Cefazolin	–	0.4	0.4	<0.1	<0.1	<0.1
J01DD16	Cefditoren	–	0.9	–	–	–	–
J01DE01	Cefepime	–	0.1	–	<0.1	–	–
J01DD10	Cefetamet	–	<0.1	–	–	–	–
J01DD08	Cefixime	–	200.4	116.9	65.1	–	0.2
J01DC09	Cefmetazole	–	–	<0.1	–	–	–
J01DD09	Cefodizime	–	0.2	–	–	–	–
J01DC06	Cefonicide	–	0.8	18.3	–	–	–
J01DD12	Cefoperazone	–	<0.1	–	–	–	–
J01DD01	Cefotaxime	–	0.3	0.5	<0.1	<0.1	<0.1
J01DC07	Cefotiam	–	–	–	<0.1	–	–
J01DC01	Cefoxitin	–	<0.1	–	<0.1	–	–
J01DD13	Cefpodoxime	–	42.9	–	40.5	<0.1	<0.1
J01DC10	Cefprozil	–	18.0	19.4	–	–	<0.1
J01DB09	Cefradine	–	–	<0.1	–	<0.1	30.7
J01DD02	Ceftazidime	<0.1	0.6	12.7	<0.1	<0.1	<0.1
J01DB12	Ceftezole	–	<0.1	<0.1	–	–	–
J01DD14	Ceftibuten	–	63.4	–	26.1	0.1	<0.1
J01DD07	Ceftizoxime	–	<0.1	0.1	–	–	–
J01DD04	Ceftriaxone	<0.1	103.7	87.7	0.3	<0.1	<0.1
J01DC02	Cefuroxime	<0.1	31.3	25.5	147.6	0.2	0.5
G01AA05	Chloramphenicol	–	<0.1	0.1	–	–	–
J01BA01	Chloramphenicol	–	–	0.1	<0.1	<0.1	<0.1
J01AA03	Chlortetracycline	–	–	<0.1	–	–	<0.1
J01MB06	Cinoxacin	–	0.3	–	<0.1	–	–
J01MA02	Ciprofloxacin	0.4	337.5	–	359.1	89.5	44.3

Table 5 continued

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
J01FA09	Clarithromycin	9.6	416.9	–	235.0	129.4	115.3
G01AA10	Clindamicin	<0.1	<0.1	0.2	0.8	<0.1	0.5
J01FF01	Clindamycin	<0.1	0.1	–	273.9	14.0	0.2
J01AA11	Clomocycline	–	–	–	–	–	<0.1
J01CF02	Cloxacillin	–	–	–	–	<0.1	<0.1
J01XB01	Colistin	<0.1	<0.1	–	<0.1	<0.1	–
A07AA10	Colistin	–	–	<0.1	<0.1	<0.1	<0.1
J01CE30	Combinations	–	–	<0.1	0.1	0.1	<0.1
J01CA20	Combinations	–	–	–	–	–	<0.1
J01CR50	Combinations of penicillins	–	–	<0.1	0.5	–	–
J01AA20	Combinations of tetracyclines	–	–	–	–	–	0.3
J01XX09	Daptomycin	–	–	–	<0.1	–	–
J01AA01	Demeclocycline	–	–	<0.1	–	<0.1	<0.1
J01CF01	Dicloxacillin	30.1	–	–	<0.1	<0.1	–
J01AA02	Doxycycline	0.1	23.3	23.9	387.0	493.3	124.6
J01MA04	Enoxacin	–	<0.1	–	13.7	–	–
J01DH03	Ertapenem	–	–	–	<0.1	<0.1	<0.1
J01FA01	Erythromycin	16.8	0.9	–	36.0	24.0	–
J04AK02	Ethambutol	<0.1	<0.1	–	0.1	–	–
J04AM03	Ethambutol and isoniazid	–	<0.1	–	–	–	–
J01MA08	Fleroxacin	–	–	–	<0.1	–	–
J01CF05	Flucloxacillin	0.2	<0.1	0.2	0.6	91.4	341.9
J01FA14	Flurithromycin	–	0.1	–	–	–	–
J01XX01	Fosfomycin	–	207.7	–	15.2	–	–
J01XC01	Fusidic acid	0.3	–	–	–	<0.1	–
J01MA16	Gatifloxacin	–	–	–	<0.1	–	–
J01GB03	Gentamicin	<0.1	0.3	–	0.2	<0.1	<0.1
J01MA11	Grepafloxacin	–	–	–	–	<0.1	–
J01DH51	Imipenem and enzyme inhibitor	–	<0.1	–	<0.1	<0.1	<0.1
J04AC01	Isoniazid	<0.1	0.1	–	<0.1	–	–
J04AC51	Isoniazid. Combinations	–	–	–	0.1	–	–
J01FA07	Josamycin	–	0.4	–	<0.1	–	–
J01GB04	Kanamycin	–	–	–	–	<0.1	–
A02BD07	Lansoprazole amoxicillin and clarithromycin	–	–	–	–	–	10.1
J01MA12	Levofloxacin	–	324.7	–	124.2	16.2	–
J01FF02	Lincomycin	–	0.4	–	<0.1	<0.1	–
J01XX08	Linezolid	<0.1	–	–	<0.1	–	–
J01MA07	Lomefloxacin	–	24.8	–	–	–	–
J01DC08	Loracarbef	–	–	–	0.7	<0.1	–
J01AA04	Lymecycline	0.1	0.8	0.3	–	–	18.0
J01CA11	Mecillinam	<0.1	–	–	–	–	–
G01AA09	Mepartricin	–	–	<0.1	–	–	–
J01DH02	Meropenem	<0.1	–	–	<0.1	<0.1	<0.1
J01AA05	Metacycline	–	<0.1	<0.1	–	–	–
J01XX05	Methenamine	0.1	–	–	<0.1	–	–
J01XD01	Metronidazole	<0.1	<0.1	–	<0.1	–	–
J01CA10	Mezlocillin	–	<0.1	<0.1	<0.1	–	–
J01FA03	Midecamycin	–	<0.1	–	–	–	–

Table 5 continued

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
J01AA08	Minocycline	–	18.3	20.6	36.7	30.4	30.3
J01FA11	Miocamycin	–	0.8	–	–	–	–
J01MA14	Moxifloxacin	0.1	70.0	–	111.5	13.7	–
G01AA02	Natamycin	–	–	–	–	–	<0.1
J01GB05	Neomycin	–	–	–	–	<0.1	<0.1
A07AA01	Neomycin	–	–	–	–	<0.1	<0.1
A07AA51	Neomycin. Combinations	–	<0.1	0.8	–	–	–
J01GB07	Netilmicin	<0.1	0.1	–	<0.1	<0.1	<0.1
J01XE01	Nitrofurantoin	7.0	0.1	–	37.1	–	–
J01XX07	Nitroxoline	–	–	–	0.9	–	–
J01MA06	Norfloxacin	<0.1	48.7	–	76.3	72.0	–
A07AA02	Nystatin	4.1	26.3	32.7	0.9	–	–
J01MA01	Ofloxacin	<0.1	0.2	–	68.1	21.0	0.8
J01CF04	Oxacillin	–	<0.1	<0.1	<0.1	–	–
J01AA06	Oxytetracycline	0.1	–	–	–	<0.1	102.9
J01AA56	Oxytetracycline. Combinations	–	–	–	49.5	–	–
A02BD04	Pantoprazole. Amoxicillin and clarithromycin	–	–	–	21.1	12.5	–
A07AA06	Paromomycin	–	1.0	12.4	<0.1	<0.1	–
J01MA03	Pefloxacin	–	0.9	–	–	–	–
J01CE06	Penamecillin	–	–	–	–	–	<0.1
J01CE05	Pheneticillin	–	–	–	–	83.8	–
J01CE02	Phenoxymethylpenicillin	161.9	–	0.1	308.2	23.8	–
J01MB04	Pipemidic acid	–	15.5	–	<0.1	0.5	–
J01CA12	Piperacillin	<0.1	0.1	0.1	<0.1	<0.1	<0.1
J01CR05	Piperacillin and enzyme inhibitor	<0.1	0.4	0.2	<0.1	<0.1	<0.1
J01CA02	Pivampicillin	24.2	–	–	–	–	0.2
J01CA08	Pivmecillinam	33.3	–	–	–	–	0.1
J01XB02	Polymyxin B	–	–	–	–	<0.1	–
J01CE09	Procaine benzylpenicillin	<0.1	–	–	–	–	<0.1
J01CE03	Propicillin	–	–	–	15.4	–	–
J04AD01	Protionamide	–	–	–	<0.1	–	–
J01MA17	Prulifloxacin	–	71.7	–	–	–	–
J04AK01	Pyrazinamide	<0.1	<0.1	–	<0.1	–	–
J04AB04	Rifabutin	<0.1	<0.1	–	<0.1	–	–
J04AB02	Rifampicin	0.1	0.4	–	0.2	–	–
J04AM02	Rifampicin and isoniazid	–	<0.1	–	<0.1	–	–
J04AM05	Rifampicin. Pyrazinamide and isoniazid	–	<0.1	–	–	–	–
J04AM06	Rifampicin. Pyrazinamide. Ethambutol and isoniazid	–	<0.1	–	–	–	–
J04AB03	Rifamycin	–	<0.1	–	–	–	–
A07AA11	Rifaximin	–	224.2	194.2	<0.1	–	–
J01FA12	Rokitamycin	–	17.3	–	–	–	–
J01FA06	Roxithromycin	19.7	45.0	–	264.2	0.7	–
J01MA10	Rufloxacin	–	0.5	–	–	–	–
J01XX04	Spectinomycin	–	<0.1	–	<0.1	–	–
J01FA02	Spiramycin	<0.1	42.4	–	0.2	0.1	<0.1
J01GA01	Streptomycin	–	<0.1	–	<0.1	–	<0.1
J01EC02	Sulfadiazine	–	<0.1	–	<0.1	<0.1	<0.1
J01EE06	Sulfadiazine and tetroxoprim	–	–	–	<0.1	–	–

Table 5 continued

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
J01EE02	Sulfadiazine and trimethoprim	<0.1	–	–	–	–	–
J01ED01	Sulfadimethoxine	–	–	–	–	–	<0.1
J01EB05	Sulfafurazole	–	–	–	–	<0.1	–
J01ED02	Sulfalene	–	–	–	–	–	<0.1
J01EE07	Sulfamerazine and trimethoprim	–	–	–	0.1	–	–
J01EB02	Sulfamethizole	36.3	–	–	–	<0.1	–
J01EC01	Sulfamethoxazole	–	–	–	–	<0.1	–
J01EE01	Sulfamethoxazole and trimethoprim	0.1	69.3	–	314.9	71.9	0.2
J01ED05	Sulfamethoxypyridazine	–	–	–	–	–	<0.1
J01EE04	Sulfamoxole and trimethoprim	–	–	–	–	–	<0.1
J01EB04	Sulfapyridine	–	–	–	–	<0.1	<0.1
J01EB07	Sulfathiazole	–	–	–	–	<0.1	–
J01RA02	Sulfonamides. Combinations with other antibacterials (excl. Trimethoprim)	–	–	–	<0.1	–	–
J01CR04	Sultamicillin	–	<0.1	<0.1	23.6	–	–
J01CA15	Talampicillin	–	–	–	–	–	<0.1
J01XA02	Teicoplanin	<0.1	0.1	–	<0.1	<0.1	–
J01FA15	Telithromycin	–	10.9	–	0.7	–	<0.1
J01MA05	Temafloxacin	–	<0.1	–	–	–	–
J01CA17	Temocillin	–	–	–	–	–	<0.1
J04AK03	Terizidone	–	–	–	<0.1	–	–
J01AA07	Tetracycline	0.6	<0.1	0.1	0.7	0.9	10.2
J01BA02	Thiamphenicol	–	<0.1	25.0	–	–	–
J01CA13	Ticarcillin	–	–	–	–	–	<0.1
J01CR03	Ticarcillin and enzyme inhibitor	–	–	<0.1	–	–	<0.1
J01AA12	Tigecycline	–	–	<0.1	<0.1	<0.1	–
J01GB01	Tobramycin	<0.1	0.1	–	<0.1	<0.1	<0.1
J01EA01	Trimethoprim	6.9	–	–	19.4	125.8	–
J01MA13	Trovafloxacin	–	–	–	–	<0.1	–
A07AA09	Vancomycin	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
J01XA01	Vancomycin	<0.1	–	–	0.1	<0.1	–

Annual prevalence is expressed per 1000 person-years and is calculated by adding the number of individuals exposed to the antibiotic compound for at least 1 day divided by the total persons in the study and divided by the number of years of observation

AUH Aarhus University Hospital, *ERD* Emilia-Romagnia regional database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

Table 6 Mean duration of antibiotic chemical substances use (in days) per prescription according to country

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
J01GB06	Amikacin	–	4.1	3.0	4.9	13.3	8.7
J01CA04	Amoxicillin	8.0	12.0	12.7	13.7	10.5	–
J01CR02	Amoxicillin and enzyme inhibitor	11.7	11.5	10.3	6.2	9.6	7.2
J01CA01	Ampicillin	1.5	7.1	6.1	8.1	5.4	7.5
J01CR01	Ampicillin and enzyme inhibitor	–	3.2	2.9	5.0	–	–
J01CA51	Ampicillin. Combinations	–	–	–	–	–	7.0
J01CE04	Azidocillin	–	–	–	8.1	–	–
J01FA10	Azithromycin	5.0	5.9	5.4	4.8	5.1	7.3
J01DF01	Aztreonam	20.2	1.9	1.1	3.6	1.0	5.5
J01CA06	Bacampicillin	–	13.3	12.3	–	–	38.0
J01CE08	Benzathine benzylpenicillin	–	1.0	0.9	1.0	2.3	–
J01CE10	Benzathine phenoxymethylpenicillin	–	–	–	8.3	–	–
J01CE01	Benzylpenicillin	2.9	1.3	1.1	8.5	6.6	6.3
J01EA02	Brodimoprim	–	–	1-	–	–	–
J01CA03	Carbenicillin	–	–	1.0	–	–	14.7
J01DC04	Cefaclor	–	7.2	6.3	6.8	12.2	7.1
J01DB05	Cefadroxil	–	5.3	6.0	6.3	–	8.2
J01DB01	Cefalexin	14.2	5.9	5.3	6.8	13.1	7.9
J01DB03	Cefalotin	–	–	1.3	–	14.8	–
J01DC03	Cefamandole	–	1.1	1.3	–	2.7	–
J01DB07	Cefatrizine	–	–	4.9	–	–	–
J01DB04	Cefazolin	–	2.2	1.9	3.5	6.7	6.9
J01DD16	Cefditoren	–	10.4	9.8	–	–	–
J01DE01	Cefepime	–	3.4	2.9	10.8	–	–
J01DD10	Cefetamet	–	–	4.5	–	–	–
J01DD08	Cefixime	–	6.0	5.5	6.2	–	8.0
J01DC09	Cefmetazole	–	–	1.4	–	–	–
J01DD09	Cefodizime	–	2.9	2.6	–	–	–
J01DC06	Cefonicide	–	5.5	5.1	–	–	–
J01DD12	Cefoperazone	–	2.2	1.2	–	–	–
J01DD01	Cefotaxime	–	2.1	1.3	3.4	1.5	6.5
J01DC07	Cefotiam	–	–	–	1.2	–	–
J01DC01	Cefoxitin	–	1.4	–	2.0	–	–
J01DD13	Cefpodoxime	–	4.0	4.5	5.1	8.6	7.6
J01DC10	Cefprozil	–	4.4	3.8	–	–	8.3
J01DB09	Cefradine	–	.	6.6	–	12.2	8.8
J01DD02	Ceftazidime	12.2	2.0	1.2	3.0	6.3	7.7
J01DB12	Ceftezole	–	–	2.4	–	–	–
J01DD14	Ceftibuten	–	6.6	6.3	6.2	15.5	9.5
J01DD07	Ceftizoxime	–	1.9	1.2	–	–	–
J01DD04	Ceftriaxone	7.8	2.8	2.5	7.2	5.7	6.4
J01DC02	Cefuroxime	24.3	8.9	8.2	9.7	12.0	8.9
G01AA05	Chloramphenicol	–	4.0	3.1	–	–	–
J01BA01	Chloramphenicol	–	–	1.4	3.0	37.1	8.5
J01AA03	Chlortetracycline	–	–	4.7	–	–	6.6
J01MB06	Cinoxacin	–	12.1	10.5	–	–	23.4
J01MA02	Ciprofloxacin	16.6	4.8	4.0	4.7	10.7	7.9

Table 6 continued

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
J01FA09	Clarithromycin	9.7	11.0	1-	8.2	10.2	7.5
G01AA10	Clindamicin	8.1	8.0	5.3	8.0	39.0	7.1
J01FF01	Clindamycin	16.7	3.1	2.2	6.5	14.5	11.6
J04BA01	Clofazimine	–	–	–	–	50.7	22.0
J01XX03	Clofoctol	–	–	4.6	–	–	–
J01AA11	Clomocycline	–	–	–	–	–	–
J01CF02	Cloxacillin	–	–	–	–	8.6	6.7
A07AA10	Colistin	–	–	2.1	5.0	15.9	10.1
J01XB01	Colistin	13.2	–	3.5	24.9	45.9	11.8
J01CA20	Combinations	–	–	–	–	–	7.0
J01CE30	Combinations	–	–	35.8	8.1	2.2	6.2
J01CR50	Combinations of penicillins	–	–	3.2	7.6	–	–
J01AA20	Combinations of tetracyclines	–	–	–	–	–	13.2
J04AB01	Cycloserine	–	–	–	–	–	49.9
J04BA02	Dapsone	83.0	–	–	60.6	45.8	26.8
J01XX09	Daptomycin	–	–	–	6.3	6.9	6.6
J01AA01	Demeclocycline	–	–	12.0	–	25.5	15.1
J01CF01	Dicloxacillin	8.5	–	–	4.4	1-	–
J01AA02	Doxycycline	41.3	15.1	14.0	17.7	9.6	13.3
J01MA04	Enoxacin	–	6.6	5.6	3.5	–	–
J01DH03	Ertapenem	–	–	7.0	3.9	21.0	6.4
J01FA01	Erythromycin	11.7	5.2	4.1	6.8	15.8	–
J04AK02	Ethambutol	34.9	25.8	17.0	26.8	36.5	15.4
J04AM03	Ethambutol and isoniazid	–	25.0	19.5	–	–	–
J01MA08	Fleroxacin	–	–	–	–	–	–
J01CF05	Flucloxacillin	11.7	7.3	7.3	3.6	9.2	7.2
J01FA14	Flurithromycin	–	7.1	5.7	–	–	–
J01XX01	Fosfomycin	–	2.6	2.3	1.0	1.2	6.9
R02AB03	Fusafungine	–	11.5	28.6	21.1	–	–
J01XC01	Fusidic acid	7.2	–	–	–	29.2	12.8
J01MA16	Gatifloxacin	–	–	–	5.7	–	–
J01GB03	Gentamicin	9.4	2.3	1.9	2.9	8.5	9.4
R02AB30	Gramicidin	–	–	–	–	5.0	–
J01MA11	Grepafloxacin	–	–	–	–	7.4	–
J01DH51	Imipenem and enzyme inhibitor	–	2.3	1.3	2.5	7.5	6.5
J04AC01	Isoniazid	55.9	48.7	29.5	23.2	45.0	18.7
J04AC51	Isoniazid. Combinations	–	–	–	67.4	–	18.6
J01FA07	Josamycin	–	5.9	5.5	3.9	–	–
J01GB04	Kanamycin	–	–	–	–	–	–
A02BD07	Lansoprazole amoxicillin and clarithromycin	–	–	–	–	–	6.8
J01MA12	Levofloxacin	–	6.4	5.5	6.1	11.1	7.7
J01FF02	Lincomycin	–	2.4	2.2	2.2	3.7	–
J01XX08	Linezolid	16.6	–	7.0	9.4	15.3	10.9
J01MA07	Lomefloxacin	–	6.4	5.8	–	–	–
J01DC08	Loracarbef	–	–	–	5.6	9.7	–
J01AA04	Lymecycline	42.1	2-	14.7	–	–	33.1
J01XX06	Mandelic acid	–	–	–	–	32.6	–

Table 6 continued

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
J01CA11	Mecillinam	3.3	–	–	–	–	–
G01AA09	Mepartricin	–	–	14.1	–	–	–
J01DH02	Meropenem	15.7	–	11.3	10.3	7.0	6.4
J01AA05	Metacycline	–	14.0	8.7	–	–	–
J01XX05	Methenamine	44.2	–	–	48.2	30.8	22.9
J01XD01	Metronidazole	4.0	2.2	2.3	3.1	22.5	7.2
J01CA10	Mezlocillin	–	1.3	1.0	3.2	–	–
J01FA03	Midecamycin	–	6.5	5.2	–	–	–
J01AA08	Minocycline	–	8.1	7.0	14.1	35.5	41.2
J01FA11	Miocamycin	–	7.3	6.9	–	–	–
J01MA14	Moxifloxacin	14.0	6.6	5.9	6.4	7.9	7.8
J01MB02	Nalidixic acid	–	–	4.3	–	–	11.8
G01AA02	Natamycin	–	–	–	–	–	–
A07AA01	Neomycin	–	–	–	–	27.9	7.0
J01GB05	Neomycin	–	–	–	–	21.1	11.6
A07AA51	Neomycin. Combinations	–	4.3	2.0	–	–	–
J01GB07	Netilmicin	–	3.1	2.8	5.2	1.0	8.3
J01XE01	Nitrofurantoin	14.2	8.4	7.8	18.1	8.9	12.7
J01XX07	Nitroxoline	–	–	–	9.0	–	–
J01MA06	Norfloxacin	2-	8.0	7.4	5.4	8.9	9.0
A07AA02	Nystatin	5.3	9.3	7.3	5.1	–	–
J01MA01	Ofloxacin	11.6	8.5	7.4	4.9	9.4	9.3
J01CF04	Oxacillin	–	3.7	3.2	3.5	–	–
J01MB05	Oxolinic acid	–	–	–	–	–	–
J01AA06	Oxytetracycline	24.7	–	–	–	81.0	25.8
J01AA56	Oxytetracycline. Combinations	–	–	–	5.8	–	–
A02BD04	Pantoprazole. Amoxicillin and clarithromycin	–	–	–	7.0	9.1	–
A07AA06	Paromomycin	–	2.3	1.7	3.6	9.1	–
J01MA03	Pefloxacin	–	1.4	1.3	–	–	–
J01CE06	Penamecillin	–	–	–	–	–	7.0
J01RA01	Penicillins. Combinations with other antibacterials	–	–	–	–	–	–
J01CE05	Pheneticillin	–	–	–	–	10.8	7.0
J01CE02	Phenoxymethylpenicillin	8.0	–	5.5	8.3	10.6	–
J01MB04	Pipemidic acid	–	11.6	9.8	7.2	14.0	–
J01CA12	Piperacillin	5.0	1.2	1.0	2.0	11.9	11.2
J01CR05	Piperacillin and enzyme inhibitor	6.2	1.3	1.0	3.2	6.0	6.8
J01MB03	Piromidic acid	–	–	5.8	–	–	–
J01CA02	Pivampicillin	10.9	–	–	–	–	7.1
J01CA08	Pivmecillinam	10.8	–	–	–	–	7.0
J01XB02	Polymyxin b	–	–	–	–	39.5	–
J01CE09	Procaine benzylpenicillin	–	–	–	–	–	7.0
J01CE03	Propicillin	–	–	–	11.6	–	–
J04AD01	Protionamide	–	–	–	25.2	–	7.0
J01MA17	Prulifloxacin	–	8.3	5.7	–	–	–
J04AK01	Pyrazinamide	38.0	25.8	18.6	26.5	3	21.0
J01FG02	Quinupristin/dalfopristin	–	–	–	–	54.0	–
J04AB04	Rifabutin	38.3	34.7	24.6	37.9	38.7	20.8

Table 6 continued

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
J04AB02	Rifampicin	42.7	11.1	9.9	31.2	28.9	13.8
J04AM02	Rifampicin and isoniazid	–	21.5	17.9	39.5	38.7	22.8
J04AM05	Rifampicin. Pyrazinamide and isoniazid	–	15.3	12.3	14.9	–	–
J04AM06	Rifampicin. Pyrazinamide. Ethambutol and isoniazid	–	15.0	15.6	–	17.9	–
J04AB03	Rifamycin	–	1.5	1.0	–	–	–
A07AA11	Rifaximin	–	6.0	4.3	5.5	–	–
J01FA12	Rokitamycin	–	6.9	6.2	–	–	–
J01FA06	Roxithromycin	9.7	6.8	6.3	7.1	7.0	–
J01MA10	Rufloxacin	–	7.5	7.4	–	–	–
J01XX04	Spectinomycin	–	1.2	1.5	1.0	–	–
J01FA02	Spiramycin	–	4.9	3.5	1.5	7.3	16.3
J01GA01	Streptomycin	–	6.5	5.8	11.1	–	3.6
J01CG01	Sulbactam	–	–	–	12.8	–	–
J01EC02	Sulfadiazine	–	29.9	24.8	48.5	43.5	21.3
J01EE06	Sulfadiazine and tetroxoprim	–	–	1-	8.4	–	–
J01EE02	Sulfadiazine and trimethoprim	8.0	–	1-	–	–	–
J01ED01	Sulfadimethoxine	–	–	–	–	–	–
J01EB03	Sulfadimidine	–	–	–	–	–	7.0
J01EB05	Sulfafurazole	–	–	–	–	3-	–
J01ED02	Sulfalene	–	–	–	–	–	11.6
J01ED09	Sulfamazone	–	–	4.2	–	–	–
J01EE07	Sulfamerazine and trimethoprim	–	–	–	7.7	–	–
J01EB02	Sulfamethizole	3.0	–	–	–	13.3	–
J01EC01	Sulfamethoxazole	–	–	–	–	8.2	–
J01EE01	Sulfamethoxazole and trimethoprim	24.4	9.2	8.4	6.2	17.3	16.0
J01ED05	Sulfamethoxypyridazine	–	–	–	–	–	22.3
J01EE04	Sulfamoxole and trimethoprim	–	–	–	–	–	7.0
J01EB04	Sulfapyridine	–	–	–	–	27.0	28.7
J01EB07	Sulfathiazole	–	–	–	–	–	–
J01RA02	Sulfonamides. Combinations with other antibacterials (excl. Trimethoprim)	–	–	–	7.9	–	–
J01CR04	Sultamicillin	–	4.3	5.2	4.1	–	–
J01CA15	Talampicillin	–	–	–	–	–	7.0
J01XA02	Teicoplanin	4.9	3.5	3.0	5.2	7.2	6.6
J01FA15	Telithromycin	–	6.0	5.2	6.0	–	9.0
J01MA05	Temafloxacin	–	5.0	5.7	–	–	–
J01CA17	Temocillin	–	–	–	–	–	7.0
J04AK03	Terizidone	–	–	–	12.7	–	–
J01AA07	Tetracycline	27.0	5.5	5.2	12.0	23.9	21.2
J01BA02	Thiamphenicol	–	1.8	1.3	–	–	–
J01CA13	Ticarcillin	–	–	–	–	–	7.0
J01CR03	Ticarcillin and enzyme inhibitor	–	–	1.0	–	–	6.8
J01AA12	Tigecycline	–	–	29.0	7.0	57.5	–
J01XD02	Tinidazole	–	–	–	–	–	7.5
J01GB01	Tobramycin	48.2	3.2	2.2	28.0	22.3	11.5
J01EA01	Trimethoprim	14.6	–	0.7	6.6	9.7	–
J01MA13	Trovafloxacin	–	–	–	–	9.4	–

Table 6 continued

		Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
R02AB02	Tyrothricin	–	3.0	5.6	2.5	–	–
A07AA09	Vancomycin	6.8	3.1	1.3	3.2	13.6	8.3
J01XA01	Vancomycin	6.1	–	3.6	2.4	7.6	7.3

Mean duration of antibiotic exposure is calculated by adding the total days of exposure to the specific antibiotic divided by the total number of prescriptions

AUH Aarhus University Hospital, *ERD* Emilia-Romagnia regional database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

Table 7 Annual prevalence of broad- and narrow-spectrum penicillin, cephalosporin, and macrolides use per 1000 person-years

	Denmark (AUH)	Italy (ERD)	Italy (HSD)	Germany (GePaRD)	The Netherlands (PHARMO)	The United Kingdom (THIN)
Broad spectrum penicillins (J01CR+J01CA)	72.468	146.525	131.878	58.4707	62.3311	25.2597
Narrow spectrum penicillins (J01CE+J01CF)	192.152	0.347	0.561	33.0764	20.2282	34.2284
Broad spectrum macrolides (all J01F except J01FA01)	51.874	90.157	–	99.5462	27.9073	13.0930
Narrow spectrum macrolides (J01FA01)	16.773	0.916	–	3.6012	2.4016	–
Broad spectrum Cephalosporins (J01DC+J01DD)	0.034	47.166	35.103	35.9969	0.3372	5.9544
Narrow spectrum Cephalosporins (J01DB)	0.026	1.515	1.832	2.5751	0.1027	23.4853

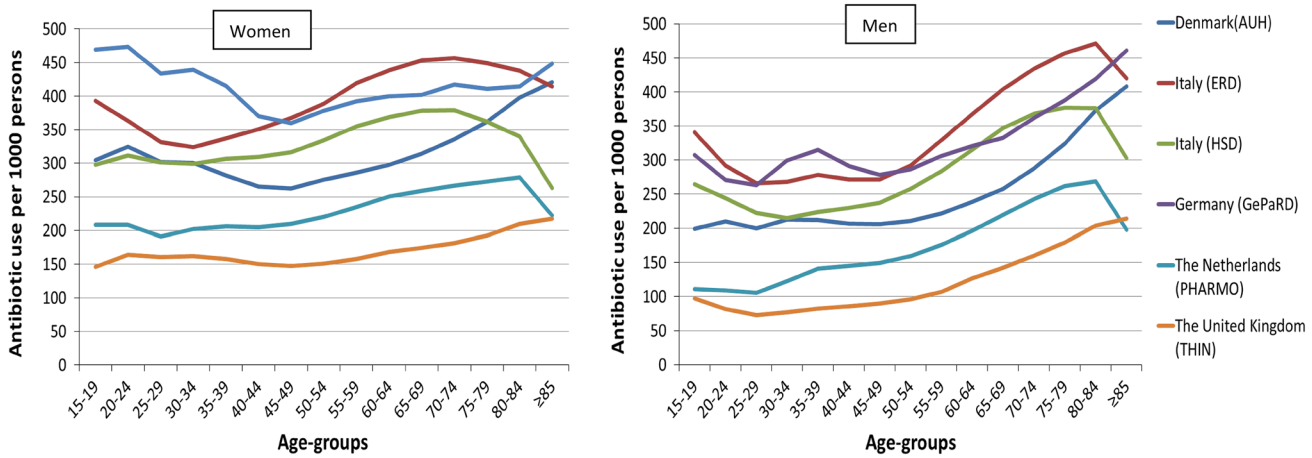

Fig. 5 Mean annual prevalence of antibiotic use per 1000 person-years by country and age-groups in women (*left*) and men (*right*). *AUH* Aarhus University Hospital, *ERD* Emilia-Romagnia regional database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

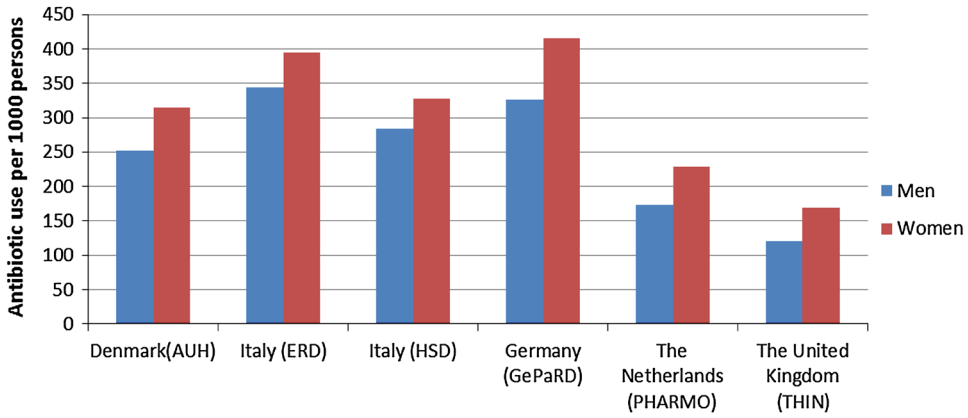

Fig. 6 Mean annual prevalence of antibiotic use per 1000 person-years by country and sex. *AUH* Aarhus University Hospital, *ERD* Emilia-Romagnia regional database, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

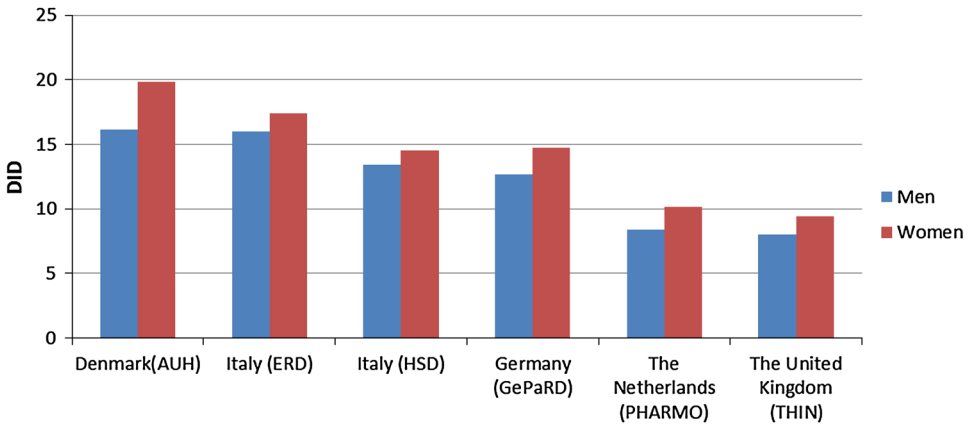

Fig. 7 Overall volume of antibiotics as DDDs per 1000 inhabitants per day by country and sex. *DDDs* defined daily doses, *DID* DDD per 1000 inhabitants per day, *AUH* Aarhus University Hospital, *ERD* Emilia-Romagnia regionaldatabase, *GePaRD* German Pharmacoepidemiological Research Database, *THIN* The Health improvement network

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