



Analysis of antibiotic use patterns in Danish hospitals 2015–2021 using an adapted version of the who aware classification

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ABSTRACT

Background AWaRe is a tool to categorise and guide antibiotic use. Antibiotics are classified in three groups: Access, Watch and Reserve. The Access group contains first choice antibiotics for 25 of the most common infections. Antibiotics in the Watch and Reserve groups should be restricted to cases that cannot be effectively treated with drugs from the Access group.

Objectives The primary aim of this study was to evaluate and adapt the WHO 2019 AWaRe classification for use with antibiotic usage data in Danish hospitals. The secondary aim was to study the usefulness of the abxaware; software package for visualisation and analysis of temporal trends in antibiotic use patterns.

Methods We obtained data on purchases of antibiotics in Danish hospitals from January 2015 to July 2021. Sixty-seven unique drugs had been purchased. To better correspond with Danish guidelines, we moved two drugs one AWaRe level upwards. To help aggregate antibiotics according to AWaRe and visualise use patterns, we developed an R package, abxaware.

Results After adding two drugs that were not included in the original AWaRe classification nearly all antibiotics (>99%) used in Danish hospitals were covered. The abxaware software package for R is a useful tool to help aggregate, visualise and analyse antibiotic use patterns.

Conclusions With minor modifications, we adapted the AWaRe classification to cover most antibiotics used in Danish hospitals and to reflect Danish treatment guidelines. The abxaware package is a useful tool to aggregate and plot antibiotic usage data according to the AWaRe classification and to test for non-random variation in the percentage use of Access antibiotics.

INTRODUCTION

Antimicrobial resistance is a major and increasing problem worldwide. A key driver is inappropriate use of antibiotics in health-care. This connection is important because antimicrobial resistance in turn leads to insufficient treatment options for patients with severe infections. For this reason, antimicrobial resistance is considered ‘one of the biggest threats to global health, food security and development today’.¹

From experience, we know that monitoring and reporting antibiotic use may help the implementation of treatment guidelines. Frequent reporting of antibiotic usage data to clinicians, infection control personnel, pharmacists and managers helps to discover inappropriate use of antibiotics and to document the effect of antibiotic stewardship programmes. However, little agreement exists on how to best categorise, aggregate and report antibiotic usage data for surveillance purposes.

AWaRe is a tool developed by the WHO ‘to help countries improve antibiotic treatment, increase access and reduce resistance’.² AWaRe was introduced in 2017 as a new categorisation of antibiotics to guide prescriptions and treatment while monitoring consumption.³ The current (as of September 2021) version was published in 2019.^{4,5} The three categories are:

1. Access which indicates the antibiotic of choice for each of the 25 most common infections. These antibiotics should be available at all times, affordable and quality-assured.
2. Watch which includes most of the highest-priority critically important antimicrobials for human medicine and veterinary use. These antibiotics are recommended only for specific, limited indications.
3. Reserve antibiotics that should only be used as a last resort when all other antibiotics have failed.

It is a general recommendation to use narrow spectrum antibiotics whenever possible. WHO suggests that countries should increase the proportion of Access antibiotics to correspond to at least 60% of total national consumption (primary and secondary care).

Several studies have published AWaRe data comparing antibiotic use between and within countries.^{3,6–13}



Some studies report temporal trends in AWaRe data using point-to-point comparisons or linear regression analysis.^{7-9 11-14} However, these methods assume that data are trending linearly over time, which is unknowable in advance. Changing trends, cyclic patterns and transient shifts will likely be overlooked while sudden shifts risk being interpreted as gradual changes.¹⁵ For these reasons, point-to-point comparisons and regression analysis are unsuitable for the study of temporal patterns in time series data.

Runs analysis comprise tests for non-random variation in data sequences and has been described in detail previously.¹⁶ Runs analysis is a suitable method for detection of any type of non-random pattern in data over time.

We identified the need for simple tools to visualise not only the proportional use of antibiotics but also temporal trends in antibiotic use patterns and to help discriminate between random fluctuations and significant, non-random shifts and trends in data over time. For this purpose, we developed an R package, *abxaware*, to aggregate, visualise and analyse AWaRe data.¹⁷

The primary aim of this study was to evaluate and adapt the WHO 2019 AWaRe classification for use with antibiotic usage data in Danish hospitals.

The secondary aim was to study the usefulness of the *abxaware* software package for visualisation and analysis of temporal trends in antibiotic use patterns.

MATERIALS AND METHODS

Since no reliable common source for the actual use of antibiotics in Danish hospitals exists, we used data on antibiotic purchase as a proxy for use.

Data source and manipulation

Data on drugs purchased by Danish hospital pharmacies are continuously collected by Amgros I/S,¹⁸ an organisation owned by the Danish Regions¹⁹ and responsible for ensuring supplies of medicines to public Danish hospitals.

For the purpose of this study, Amgros supplied data on purchase of medicines with an Anatomical Therapeutic Chemical (ATC) code starting with 'J01' (antibacterials for systemic use) from somatic public hospitals in Denmark

Table 1 Hospital names, abbreviations and key characteristics of public Danish hospitals 2020

Region	Hospital	Abbreviation	Beds	Onkology/haematology	Notes
Hovedstaden	Amager og Hvidovre Hospital	AHH	640		
Hovedstaden	Bispebjerg og Frederiksberg Hospitaler	BFH	463		
Hovedstaden	Bornholms Hospital	BoH	89		
Hovedstaden	Herlev og Gentofte Hospital	HGH	947	X	
Hovedstaden	Hospitalerne i Nordsjælland	NoH	606	X	
Hovedstaden	Rigshospitalet	RH	1271	X	National referral hospital
Midtjylland	Aarhus Universitetshospital	AaU	855	X	Regional referral hospital
Midtjylland	Hospitalsenhed Midt	HeM	482		
Midtjylland	Hospitalsenheden Vest	HeV	393	X	
Midtjylland	Regionshospitalet Horsens	RgH	210		
Midtjylland	Regionshospitalet Randers	RgR	217		
Nordjylland	Aalborg Universitetshospital	AUH	682	X	Regional referral hospital
Nordjylland	Aalborg Universitetshospital, Thisted	AUT	65		
Nordjylland	Regionshospital Nordjylland Ven	RgN	240		
Sjælland	Region Sjællands Sygehusvæsen	SjS	2011	X	One managerial hospital unit covers all regional hospital sub-units
Syddanmark	Kolding Sygehus	KoS	312		
Syddanmark	OUH Odense Universitetshospital	OUH	972	X	Regional referral hospital
Syddanmark	Sydvestjysk Sygehus	SvJ	366	X	
Syddanmark	Sygehus Sønderjylland	Ssoe	318	X	
Syddanmark	Vejle Sygehus	VejS	274	X	



Figure 1 Relative use of antibiotics 2015–2021 in Danish hospitals by AWARe group. DK, AWARe adapted to Danish guidelines; WHO, original WHO AWARe classification.

from the period January 2015 to July 2021. Somatic public hospitals account for approximately 98% of the total hospital consumption of antibiotics in Denmark.²⁰ Data were structured with one row per purchase with variables identifying: date, hospital/department, drug name, ATC code and amount in defined daily doses (DDD).

Data were cleaned and aggregated using the R programming language V.4.1.1²¹ with functions from the add-on package dplyr V.1.0.7.²² The resulting dataset contained monthly DDDs of 67 unique antibiotics from 20 hospitals from January 2015 to July 2021. No patient identifiable data were collected. Select information on the hospitals is presented in table 1.

The AWARe classification

We made two adaptations to the WHO AWARe classification to correspond better to Danish treatment guidelines:

1. Two drugs were moved up one level: amoxicillin and beta-lactamase inhibitor from Access to Watch and meropenem from Watch to Reserve.
2. We added two drugs, sulfapyridine and sulfadiazine that are unclassified by WHO to the the Access group in order to cover almost all antibiotics used in Danish hospitals.

To make data management as simple and transparent as possible, we picked the ‘highest’ AWARe class (Reserve) for two drugs, minocycline and fosfomycin, where the WHO AWARe category depends on the route of administration. A complete list of antibiotics and their corresponding AWARe classification (including unclassified drugs) is available as online supplemental file 1.

Visualising AWARe usage data and testing for non-random patterns in data over time

By default, the plot function in abxaware produces a horizontal bar chart of the proportional use of antibiotics in the three AWARe groups (figure 1). If a time variable is supplied, a time series graph is produced (figure 2). And with a unit variable, the plot is split into facets to facilitate comparison between organisational units (figure 3).

In addition, with time series plots, the median Access group proportion is plotted as a horizontal line. The line will be dashed if non-random—variation suggesting significant changes—in the proportion of Access antibiotics over time is present. Non-random variation is identified by runs analysis.

Runs analysis checks for patterns (runs) in data that are unlikely to result from random variation alone. abxaware uses two tests for (1) unusually long runs of data points on the same side of the median and (2) unusually few crossings of the median. If either of these tests is positive, it is indicative of non-random variation. The limits for ‘unusually’ long and few depend on the number of available data points and can be calculated or looked up in a statistical table as explained by Anhøj and Olesen.¹⁶

RESULTS

After adding two drugs to the WHO AWARe classification, all antibiotics purchased for Danish hospitals were covered except for two drugs with incomplete ATC codes

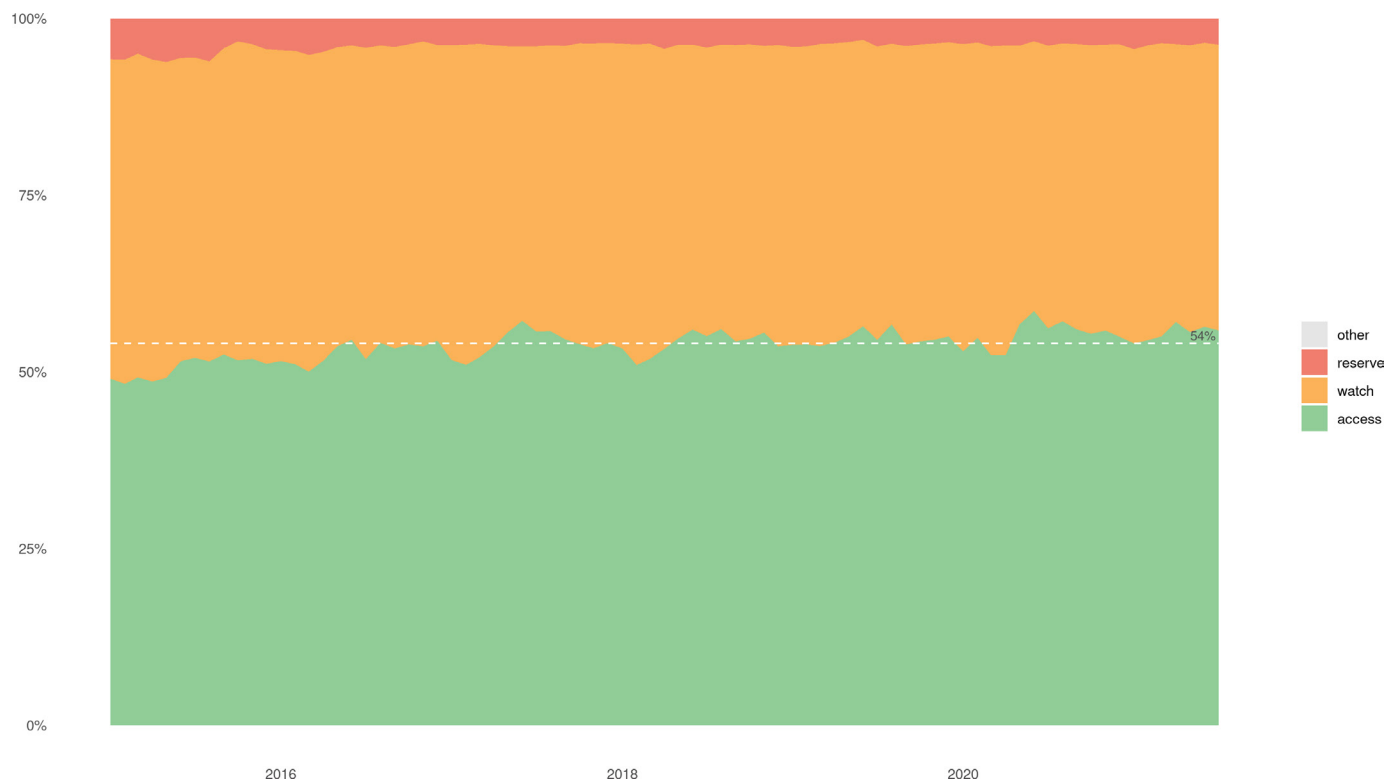


Figure 2 Antibiotic use in Danish hospitals by adapted AWARe group and month.

(J01R: combinations of antibacterials and J01DI: other cephalosporins and penems), which had been used very little.

In total, 67 unique antibiotics had been used in Danish hospitals in the period January 2015 to July 2021 (table 2).

Figure 1 shows antibiotic use data aggregated for all public hospitals in Denmark during the period January 2015 to July 2021. The upper figure shows data aggregated by AWARe adapted to Danish guidelines, while the lower figure shows data aggregated by the original WHO classification. As expected, our adaptation is stricter than the original having fewer drug classified in the Access group and more in the Watch and Reserve groups. Also, in our classification, fewer drugs are classified as ‘other’ leaving less than 0.01% in the other group.

In figure 2, a time variable, month, has been added to produce a time series plot. The white horizontal line indicates the median use of Access antibiotics over time. The line is dashed because the runs analysis suggests that there is non-random variation in data over time. As judged by eye, the Access proportion has been trending steadily over time from below 50% to around 55%. This is offset mainly by decreased use of Reserve antibiotics.

DISCUSSION

We adapted and applied the WHO AWARe classification of antibiotics to purchase data from public Danish hospitals.

After adding two drugs that are missing from the current WHO classification, our classification covered all antibiotics used in Danish hospitals in the period January 2015 to July 2021 (except drugs with incomplete ATC codes).

To better reflect Danish treatment guidelines, we moved two drugs up one level, which resulted in a more ‘stricter’ classification with less use of Access antibiotics compared with the WHO classification.

Overall, at the national level, we found a steady increase in use of Access antibiotics over time. The same pattern was present in hospital data, although more variation in use patterns was observed at the hospital level (figure 3).

In addition, we found that the abxaware package for R is a useful tool to aggregate and plot antibiotic usage data according to the AWARe classification and to test for non-random variation in the percentage use of Access antibiotics. We refer to the abxaware package vignette for detailed instructions and examples of its use.²³

It is outside the scope of this study to try to explain and interpret the observed trends in antibiotic use patterns at the national and hospital level. But we consider the overall increased use of Access antibiotics a positive thing and a deliberate result of many national and regional initiatives to optimise antibiotic use patterns in Danish hospitals over the years.²⁴

Our study has several strengths:

First, data from hospitals and departments across Denmark had been collected by the same automated processes over many years, which ensured a high degree of completeness, comparability and reproducibility.

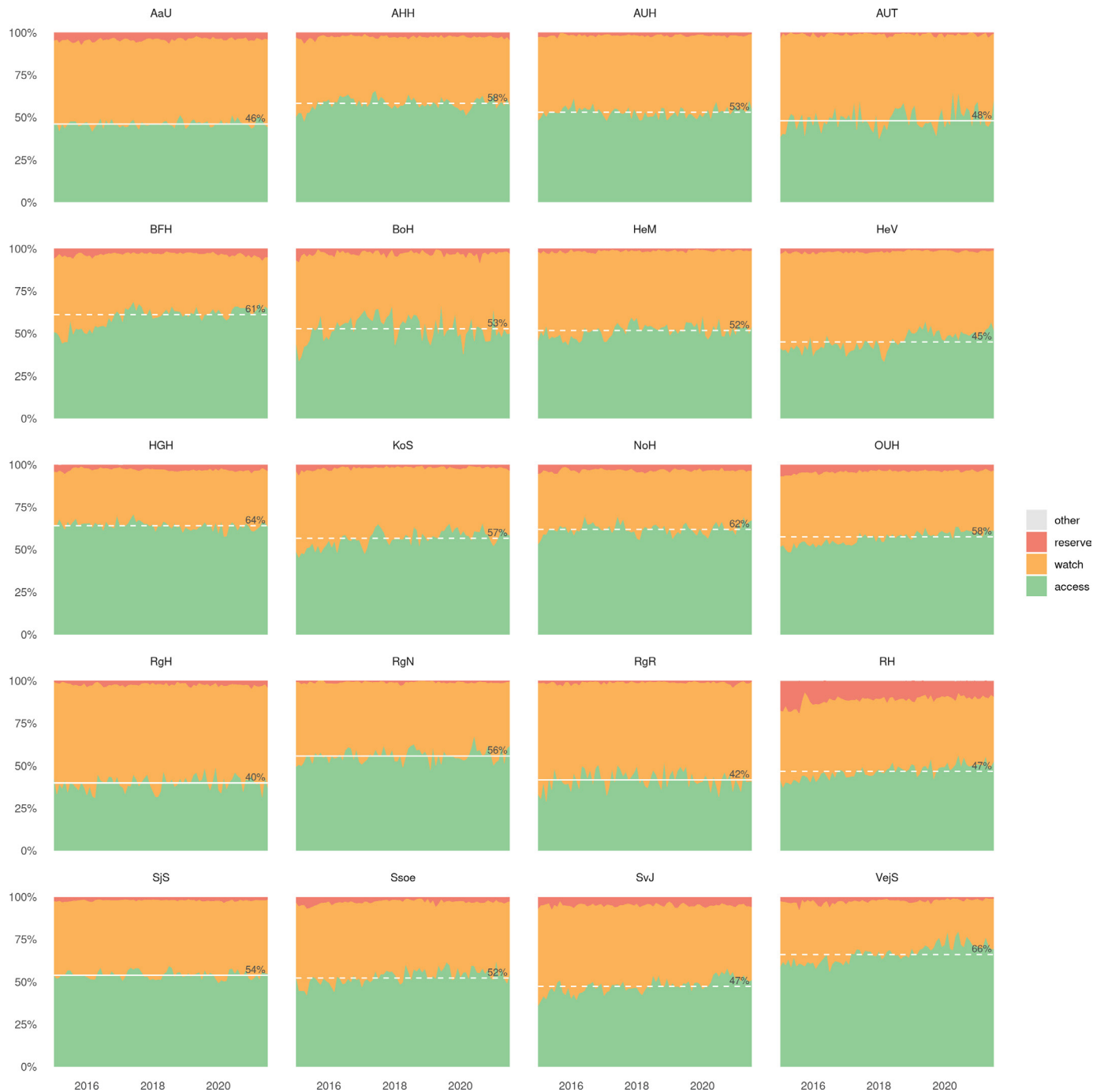


Figure 3 Shows data over time split by hospital. See table 1 for hospital characteristics and abbreviations. In most hospitals, there is non-random variation in the Access proportion mostly in the form of a relatively steady upwards trend. But in some hospitals (eg, VejS) data seem to shift in a stepwise fashion. In a few hospitals (eg, BoH) data seem to exhibit a cyclic pattern. BoH, Bornholms Hospital; VejS, Vejle Sygehus.

Second, the abxaware package makes data aggregation and visualisation easy, provided structured data are available. And the visualisation includes visual clues to the presence or absence of non-random variation in Access proportion over time, which helps to avoid overinterpretation of insignificant fluctuations in data when only random variation is present or overlooking non-random variation caused by significant trends or shifts in data over time.

Finally, data keep coming, which makes establishing continuous, real-time surveillance feasible, should someone want this. Source data are updated at the beginning of each month, and data cleaning, aggregation and visualisation can be automated using R (or any other programming language) and the abxaware package.

Some limitations should be noted:

First, we used purchase data as a proxy for antibiotic consumption. Two problems may arise from purchase

**Table 2** Total use of antibiotics in public Danish hospitals August 2020–July 2021 and the corresponding WHO and DK AWaRe classification

ATC	Drug	DDD	WHO	DK
J01AA02	Doxycycline	85 844	Access	Access
J01AA04	Lymecycline	395	Watch	Watch
J01AA07	Tetracycline	6210	Access	Access
J01AA08	Minocycline	700	Reserve	Reserve
J01AA12	Tigecycline	928	Reserve	Reserve
J01CA01	Ampicillin	37 742	Access	Access
J01CA02	Pivampicillin	9855	Access	Access
J01CA04	Amoxicillin	99 582	Access	Access
J01CA08	Pivmecillinam	483 330	Access	Access
J01CA11	Mecillinam	16 910	Access	Access
J01CE01	Benzylpenicillin	148 482	Access	Access
J01CE02	Phenoxymethylpenicillin	195 004	Access	Access
J01CE08	Benzathine benzylpenicillin	569	Access	Access
J01CF01	Dicloxacillin	207 289	Access	Access
J01CF02	Cloxacillin	232 923	Access	Access
J01CF05	Flucloxacillin	3168	Access	Access
J01CR02	Amoxicillin and beta-lactamase inhibitor	238 147	Access	Watch
J01CR05	Piperacillin and beta-lactamase inhibitor	466 319	Watch	Watch
J01DB01	Cefalexin	1230	Access	Access
J01DB04	Cefazolin	73	Access	Access
J01DC01	Cefoxitin	276	Watch	Watch
J01DC02	Cefuroxime	279 656	Watch	Watch
J01DD01	Cefotaxime	3664	Watch	Watch
J01DD02	Ceftazidime	5171	Watch	Watch
J01DD04	Ceftriaxone	33 713	Watch	Watch
J01DD52	Ceftazidime and beta-lactamase inhibitor	956	Reserve	Reserve
J01DE01	Cefepime	552	Watch	Watch
J01DF01	Aztreonam	240	Reserve	Reserve
J01DH02	Meropenem	104 524	Watch	Reserve
J01DH03	Ertapenem	2285	Watch	Watch
J01DH51	Imipenem and cilastatin	1027	Watch	Watch
J01DI	Other cephalosporins and penems in atc	63		
J01DI54	Ceftolozane and beta-lactamase inhibitor	509	Reserve	Reserve
J01EA01	Trimethoprim	16 528	Access	Access
J01EB02	Sulfamethizole	2373	Access	Access
J01EB04	Sulfapyridine	18		Access
J01EC02	Sulfadiazine	12 292		Access
J01EE01	Sulfamethoxazole and trimethoprim	268 430	Access	Access
J01FA01	Erythromycin	12 237	Watch	Watch
J01FA02	Spiramycin	50	Watch	Watch
J01FA06	Roxithromycin	13 200	Watch	Watch
J01FA09	Clarithromycin	94 990	Watch	Watch
J01FA10	Azithromycin	52 113	Watch	Watch
J01FF01	Clindamycin	23 576	Access	Access

Continued

Table 2 Continued

ATC	Drug	DDD	WHO	DK
J01FG01	Pristinamycin	345	Watch	Watch
J01GB01	Tobramycin	13 359	Watch	Watch
J01GB03	Gentamicin	73 477	Access	Access
J01GB06	Amikacin	2084	Access	Access
J01MA02	Ciprofloxacin	169 410	Watch	Watch
J01MA12	Levofloxacin	39 746	Watch	Watch
J01MA14	Moxifloxacin	42 318	Watch	Watch
J01R	Combinations of antibacterials	185		
J01XA01	Vancomycin	51 385	Watch	Watch
J01XA02	Teicoplanin	1127	Watch	Watch
J01XA04	Dalbavancin	33	Reserve	Reserve
J01XB01	Colistin	7719	Reserve	Reserve
J01XC01	Fusidic acid	1370	Watch	Watch
J01XD01	Metronidazole	144 814	Access	Access
J01XE01	Nitrofurantoin	12 249	Access	Access
J01X×01	Fosfomycin	148	Reserve	Reserve
J01X×08	Linezolid	17 340	Reserve	Reserve
J01X×09	Daptomycin	4655	Reserve	Reserve

ATC, Anatomical Therapeutic Chemical; DDD, defined daily doses.

data: First, data may be ‘chunky’. If, for example, one buys a large amount of a specific drug, this may last for longer than the inventory period creating peaks and valleys in time series plots that are not related to actual consumption. Second, the amount purchased will, due to spillage and partial use of packages, inevitably be larger than what is actually used.

However, from experience and previous studies,²⁵ we knew that as long as the organisational units of interest are big enough and the inventory periods long enough, purchase and consumption are tightly coupled, and since we did not aggregate below hospital and AWaRe level, chunky data were not a concern. Also, since we were only looking at the proportional use of antibiotics, accurate consumption data were not important as long as use patterns were preserved.

Second, our modifications to the AWaRe classification are entirely our own and should be considered suggestions for future discussion between subject matter experts in Danish healthcare.

It should also be noted that runs analysis for detection of non-random variation in time series data is a vast area and several approaches exist. They are, however, all based on the same core principles for the detection of non-random patterns in data sequences. We chose to apply the tests suggested by Anhøj and Olesen,¹⁶ which have proven reliable and robust over many years of use and have recently been thoroughly validated.^{26 27}

It is also important to stress that runs analysis in itself is unable to determine the causes, direction and

significance of non-random variation. The presence of non-random variation is simply a signal that the process in question is changing over time—for better or worse—and that further analysis including visual inspection and interpretation by subject matter experts is needed.

Finally, one should keep in mind that while the AWaRe classification is well suited for high-level aggregation and surveillance of antibiotic usage data it does not suffice as a basis for targeted interventions at the local level. For this purpose, one must apply a much more detailed look at specific antibiotic use patterns (preferably consumption) at the site of intervention. However, this is not a limitation of our study in particular but applies to the AWaRe principle in general.

It is also important to stress that while surveillance of antibiotic use is an important prerequisite for antibiotic stewardship, surveillance in itself does not ensure optimal use of antibiotics. The optimal antibiotic use pattern depends on local context and must be tailored to the patient casemix and microbial environment.

In conclusion, we have demonstrated that, with minor modifications, the WHO AWaRe classification of antibiotics is useful for monitoring antibiotic use patterns in Danish hospitals and that runs analysis of Access proportion is useful for detection of non-random variation in use patterns over time.

In addition, we developed and tested a freely available open source software package that makes aggregating, plotting and analysing antibiotic usage data easy and reproducible.



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