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

Jacob Anhøj,1 Jonas Boel,2 Birthe Riis Olesen,3 Helle Boelsmand Bak,1 Anne-Marie Blok Hellesøe,1 Kim Thomsen,1 Jenny Dahl Knudsen1

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. 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.

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 healthcare. 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 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.6–13
Some studies report temporal trends in AWaRe data using point-to-point comparisons or linear regression analysis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{18} an organisation owned by the Danish Regions\textsuperscript{19} 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.
from the period January 2015 to July 2021. Somatic public hospitals account for approximately 98% of the total hospital consumption of antibiotics in Denmark. 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.4.1.1 with functions from the add-on package dplyr V.1.0.7. 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.

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.

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(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.
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

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

<table>
<thead>
<tr>
<th>ATC</th>
<th>Drug</th>
<th>DDD</th>
<th>WHO</th>
<th>DK</th>
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<td>85844</td>
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Continued
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, 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, which have proven reliable and robust over many years of use and have recently been thoroughly validated.

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 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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Contributors

JA designed the study, wrote the draft manuscript, performed the statistical analyses, and contributed to the development of the software package. JB contributed to the writing of the manuscript and contributed to the development of the software package. All other authors contributed to the writing of the manuscript.

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ORCID iDs

Jacob Anhøj http://orcid.org/0000-0002-7701-1774
Jonas Boel http://orcid.org/0000-0003-3085-0930

REFERENCES