Received: 4 May 2021 | Revised: 8 June 2021 | Accepted: 22 June 2021

DOI: 10.1111/jcpt.13479

COMMENTARY

Journal of Clinical Pharmacy and Therapeutics WILEY

# Application of the anatomical chemical system/defined daily doses: Challenges and way forward for resource-limited countries

Hanifah Nantongo MSN[1,2] | Vincent Batwaala PhD[3,4] | Victoria Nambasa MSc[5] | Jackson K. Mukonzo PhD[1]

[1]Department of Pharmacology & Therapeutics, Makerere University College of Health Sciences, Kampala, Uganda

[2]Department of Nursing, Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

[3]Community Health Department, Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

[4]Directorate of Research & Graduate Training, Mbarara University of Science & Technology, Mbarara, Uganda

[5]Pharmacovigilance Unit, National Drug Authority, Kampala, Uganda

**Correspondence**
Jackson K. Mukonzo, Department of Pharmacology & Therapeutics, Makerere University College of Health Sciences, Kampala, Uganda.
Email: mukojack@yahoo.co.uk; jk.mukonzo@chs.mak.ac.ug

**Funding information**
SIDA -SAREC

## Abstract

**What is known and objective:** The Anatomical Therapeutic Chemical Classification/Defined Daily Doses (ATC/DDD) methodology is a WHO gold standard for ensuring systematic Drug Utilization Research (DUR) and has been mainly used in the developed world. This article examines the challenges and way forward for using this methodology in resource-limited countries.

**Content:** The ATC/DDD is superior over other methods employed in DUR as it offers a unified medicines regulation and management system at all care levels. The ATC/DDD allows access to standardized and validated information on DUR by: assessing patterns of utilization, defining optimal use levels, identification of gaps, aggregating and analysing statistics for reporting adverse drug reactions, as well as assisting in developing rational medicines use interventions and monitoring their outcomes.

**What is new and conclusion:** Application of the ATC/DDD methodology is crucial for improved patient management, optimal consumption of national pharmaceutical budgets and policy formulation in resource-limited countries.

KEYWORDS
antibiotics, ATC/DDD tool, challenges, low income settings, way forward

## 1 | WHAT IS KNOWN AND THE OBJECTIVE

Drug utilization Research (DUR) is important for improvement of patient management, optimal utilization of national pharmaceutical budgets and policy formulation.[1] As a result, DUR is strongly encouraged.[2] It includes studies on: marketing, distribution, prescription and use of drugs in a society, with special emphasis on social and economic benefits.

Unfortunately, due to lack of coordinated actions for systematic DUR,[3] many resource-limited countries lack data on production, expenditure and consumption of pharmaceuticals. Conversely, this makes it difficult for policymakers and healthcare leaders to identify optimal entry points for targeted rational drug use interventions; depriving poor countries the opportunity to optimally utilize their national pharmaceutical budgets.

The World Health Organization (WHO) and The International Network for Rational Use of Drugs (INRUD), in the early 1990s, developed and published a standard method for selected drug use indicators at health care facilities. These are given as: prescribing indicators, patient care indicators, facility indicators and complementary drug use indicators. The core prescribing indicators consist of the average number of drugs per prescription, proportion of patients prescribed antibiotics, proportion of patients prescribed injections, proportion of medicines prescribed by generic names and proportion of prescribed drugs from essential medicines list.[4]

  

These, however, can only be used to identify problems in general prescribing and the quality of care. Indeed, these interventions were the basis for prescribing guidelines but clearly fall short of drug utilization statistics.

In response to the quest for suitable tools for DUR, the Anatomical Therapeutic Chemical Classification/ Defined Daily Doses (ATC/DDD) methodology was developed for presenting drug consumption data. Whereas earlier reports have indicated that the ATC/DDD methodology is reliable,[5] it has been mainly tested and used in developed countries where the healthcare structure is well organized and utilizes advanced technology in tracking patients.[6–8] This article, therefore, examines the applications of the ATC/DDD in low-resource countries; implications, challenges and the way forward for its use.

## 2 | CONTENT

The ATC/DDD methodology is the WHO gold standard initially recommended in 1981 to monitor and study drug utilization.[9] The ATC/DDD methodology divides drugs into five different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics. Each bottom-level *ATC code* stands for a pharmaceutically used substance, or a combination of substances, in a single indication or use, and is unique to that given medicinal product,[10,11] as illustrated in Table 1.

The Defined Daily Dose (DDD) is a technical unit for the ATC/DDD methodology.[12] The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults and is independent of price, currencies, package size and strength of a medicinal product. Doses for individual patients and patient groups will often differ from the DDD as they must be based on individual patients' characteristics and pharmacokinetic considerations. Thus, drug utilization figures should ideally be presented as numbers of DDDs per 1000 inhabitants per day for outpatients or, as DDDs per 100 beds per day when the drug is used by inpatients. For anti-infectives or other drugs normally used for short periods, it is presented as numbers of DDDs per inhabitant per year. These provide a rough estimate of the proportion of the study population treated with a particular drug or group of drugs. The DDDs can also be used quantitatively to demonstrate ecological relationships between antimicrobial use and resistance in hospitals.[13] With the increasing antibiotic resistance in the low-resource settings, the use of DDD metric is essential for healthcare leaders to study such ecological relationships and develop appropriate interventions.

The Prescribed Daily Doses (PDD) is a metric, defined as the average dose prescribed according to a representative sample of prescriptions. The PDD gives the average daily amount of a drug that is actually prescribed. The PDD can be determined from studies of prescriptions/medical/pharmacy records. Using both the PDD and DDD, the cost and volume of use of a given drug can be calculated by application of different formulae provided in the ATC/DDD methodology guidelines that are updated annually.[5]

In general, the ATC/DDD metrics can be used to evaluate healthcare system performance in the following ways: to analyse in-hospital medicines use, with routine measurement being useful in defining levels of optimal use and benchmarking between hospitals, countries and regions; to describe health services to individual communities; and to indicate disease profiles across the different weather seasons, as well as the performance of health facilities, groups of health care providers or individual health providers. In addition, the WHO Programme for International Drug Monitoring (PIDM), in more than 120 countries, is currently using the WHO Drug Dictionary consisting of the ATC classification to report adverse drug reactions (ADRs) to the WHO global database of Individual Case Safety Reports (ICSRs), called VigiBase®. In pharmacovigilance studies using VigiBase® or other databases, disproportionality analysis is an acknowledged tool to support signal detection. Disproportionality metrics like the Proportional Reporting Ratio (PRR) can be calculated based on the ATC classification. When PRR is applied at the level of ATC codes, the reporting rate of one specific event is calculated for a given ATC code and compared to the reporting rate of the event in all ICSRs of the database except those that contain one or more drugs from the ATC code of interest.

However, the application of the ATC/DDD methodology comes with challenges in resource-limited countries. These can be classified into challenges relating to the existing ATC/DDD and those of the healthcare system structure.

### 2.1 | Challenges relating to the existing tool

For a country to introduce and use the ATC/DDD methodology, it has to ensure that each pharmaceutical product is linked to the appropriate ATC code and DDD. Thus, there is need to develop national registries of medicines linked to the ATC codes and DDDs as

**TABLE 1** Amoxicillin as coded in the ATC/DDD tool

| | ATC level | ATC code | ATC text |
|---|---|---|---|
| 1 | Anatomical main group (one letter) | J | Anti-infectives for systemic use |
| 2 | Therapeutic sub-group (two digits) | J01 | Antibacterial for systemic use |
| 3 | Pharmacological sub-group (one letter) | J01C | Beta lactam antibacterial (Penicillin) |
| 4 | Chemical sub-group (one letter) | J01CA | Penicillin with extended spectrum |
| 5 | Chemical substance (two digits) | J01CA04 | Amoxicillin |

Adopted from: http://www.whocc.no/atc_ddd_index

a first step, which is often very time consuming and expensive[14] to undertake given the meagre resources. Monitoring of DUR outputs internationally also requires that the data is comparable between countries and regions; thus, the need for harmonization of ATC groups and drug codes.

The ATC/DDD methodology is poorly adapted for young populations, since the DDD metric are adult-based, and in populations where dose adjustments are warranted like in renal conditions. Furthermore, drugs may be used for two or more equally important indications, and the main therapeutic use of a drug may differ from one country to another. This will often result in several possible alternatives for classification, and a decision has to be made regarding the main use.[14,15]

The difference in the classification of the bed-day measure when using the DDDs per 100 bed-day metric could make comparative studies more difficult. For example, some health workers/researchers define the bed-day measure as including patients admitted for a medical procedure or surgery in the morning and released before the evening on the same day, while others consider them as outpatients.[16] There is need to standardize this measure so as to allow effective comparisons of drug utilities when using this metric. Furthermore, the demographic differences in resource-limited countries offer a challenge of applying the ATC/DDD methodology. The annual updates of the ATC /DDD methodology warrant additional trainings for the users every year, making it very expensive for resource-poor settings. Yet again, there is need to avail the healthcare workers at the facility level with internet connectivity and the requisite infrastructure, such computers.

Nonetheless, national benefits need to be weighed against the opportunity for pharmaceutical surveillance, appropriate budgetary allocations and DUR at facilities, country and regional levels. Resource-limited countries need to solicit for funds from within and from the international community to facilitate the application of the ATC/DDD methodology.

### 2.2 | Healthcare system challenges

Many resource-limited countries lack national structures to coordinate usage of medicines that will foster consistent usage of ATC/DDD methodology.[17] These countries often have inadequacies in the data sources mainly due to poor documentation of healthcare records.[16] Moreover, the calculation of DDDs requires much more data collection as opposed to the commonly used antimicrobial prescription analysis in the community studies.[18] Thus, the available prescription data make the DDD calculations for antimicrobials prone to errors. This is worsened by the high-patient loads against a thin healthcare work force. In addition, there is no adherence to guidelines that enforce controls in both prescribing and dispensing practices, often evidenced by a big difference in actual consumption data and patient drug use.[19–21] Yet again, the healthcare work force in these settings lack knowledge of the ATC/DDD and its application despite its availability.

### 2.3 | Way forward for resource-limited countries

Access to standardized and validated information on medicines use is essential for assessing patterns of drug utilization, defining optimal use levels, identifying problems, accessibility and development of educational or other interventions aimed at rational usage of medicines and monitoring their outcomes. The ATC/DDD offers effective DUR statistics, important for policy formulation at the national level as well as for individual patient management. In addition, DUR is very important to study the growing antimicrobial resistance threat worldwide, which is worrying because of the scarcity of new medicines being developed such as antibiotics.[22] Thus, there is need for rapid action by all countries to urgently deter this crisis, particularly the developing countries, that have huge burdens of irrational medicines usage[19] with potential to propagate antimicrobial drug resistance.

The ATC/DDD methodology application in resource-limited countries will lead to improved overall healthcare outcomes of communities as it enables the implementation of specific studies or educational interventions to foster rational usage of medicines and provide appropriate budgetary allocations to pharmaceutical products. The ATC methodology also offers an aggregation of statistics and analysis in reporting drug safety particularly ADRs for a given country and across regions. In addition, drug resistance studies can be initiated using this methodology as evidenced by the ecological studies conducted in Europe that revealed a positive correlation between out-patient medicines use and resistance.[13]

Recent hospital-based studies in resource-limited countries have used the ATC/DDD methodology with the available data to report patterns of drug consumption.[22,23] This is an indication that the implementation of the ATC/DDD methodology as a national surveillance strategy for medicines use is possible if validated/adapted in these settings.[2]

The ATC/DDD methodology is valuable when aggregating costs for drug groups or therapeutic areas overtime. Resource-limited countries can utilize this indicator for proper budgetary allocation of funds and appropriate usage of the meagre resources. Costing drug usage in the treatment of any condition is very crucial as it reflects the cost of health care in general.[21]

The use of the ATC/DDD methodology in resource-limited countries will also ensure the availability of adequate data on drug utilization that has been often lacking on even the broadest measures of drug use such as the overall volume of use and total expenditure on drugs.[3]

## 3 | WHAT IS NEW AND CONCLUSION

The ATC/DDD is superior over other methods employed in studying drug utilization as it allows quantifications and comparisons at facility, national, regional and international levels.[24–26] This consequently aids appropriate formulation of policies that ensure a unified medicines regulation and management system. To facilitate its

adoption and implementation, we suggest that annual updates ought to be extended to at least every 5 years due to the cost implications. Resource-limited countries should also have a deliberate strategy of establishing structures to enable the utilization of the ATC/DDD.

## DATA AVAILABILITY STATEMENT

All data used for this manuscript may be availed for review on request.

## ORCID

*Jackson K. Mukonzo* https://orcid.org/0000-0002-0573-1908

## REFERENCES

1. WHO. Introduction to Drug Utilisation Research; 2003 01/01/2020]; https://apps.who.int/iris/bitstream/handle/10665/42627/924156234X.pdf?sequence=1&isAllowed=y
2. Rønning M. Coding and classification in drug statistics–From national to global application. *Norsk epidemiologi*. 2001;11(1):37-40.
3. WHO. ATC/DDD classification: drug utilization data constrains in developing countries. 2002 June 29, 2013; http://apps.int/medicinedocs/pdf/s4951e/s4951e.pdf
4. WHO. How to Investigate Drug Use in Health Facilities: Selected Drug Use Indicators in EDM Research Series. No. 007. 1993. p. 92.
5. WHO. Guidelines for ATC/DDD classification and assignment. 2016.
6. Natsch S, et al. Application of the ATC/DDD methodology to monitor antibiotic drug use. *Eur J Clin Microbiol Infect Dis*. 1998;17(1):20-24.
7. van de Sande-Bruinsma N, Grundmann H, Verloo D, et al. Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis*. 2008;14(11):1722.
8. Adriaenssens N, Coenen S, Versporten A, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe (1997–2009). *J Antimicrob Chemother*. 2011;66(suppl_6):vi3-vi12.
9. WHO. ATC/DDD methodolog history. 2018 17/07/2019; https://www.whocc.no/atc_ddd_methodology/history/
10. *WHO, Introduction to Drug Utilization studies*. Oslo: World Health Organization; 2003:33-38.
11. *WHO, Guidelines for ATC/DDD Classification and Assignment*. Oslo, Norway: World Health Organization; 2016.
12. WHO. ATC/DDD methodology history. 2009 2009 14/09/2017; https://www.whocc.no/atcdddmethodology/history/
13. Goossens H, et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *The Lancet*. 2005;365(9459):579-587.
14. WHO. Use of ATC/DDD methodology. 2018 15/02/2018 17/07/2019; https://www.whocc.no/useofatcddd/
15. Irwin A, Sharland M. Measuring antibiotic prescribing in hospitalised children in resource-poor countries: a systematic review. *J Paediatr Child Health*. 2013;49(3):185-192.
16. Bachhav SS, Kshirsagar NA. Systematic review of drug utilization studies & the use of the drug classification system in the WHO-SEARO Region. *Indian J Med Res*. 2015;142(2):120.
17. WHO. Antimicrobial resistance: Global report on surveillance. 2014 12/05/2020; https://apps.int/iris/bitstream/handle/10665/112642/9789241564748_eng.pdf?sequence=1
18. Holloway K, et al. Surveillance of community antimicrobial use in resource-constrained settings–experience from five pilot projects. *Tropical Med Int Health*. 2011;16(2):152-161.
19. WHO. Antimicrobial resistance: global report on surveillance. 2014 09/10/2019; https://www.int/drugresistance/documents/surveillancereport/en/
20. WHO. Global Antimicrobial Resistance Surveillance System (GLASS) Report Early implementation. 2017-2018 12/05/2020; https://apps.int/iris/bitstream/handle/10665/279656/9789241515061-eng.pdf?ua=1
21. Kumar A, Sattigeri B, Chauhan S. Drug utilization in clinical conditions: an update on its essentials. *Int J Res Med Sci*. 2013;1(4):320.
22. Kotwani A, Holloway K. Antibiotic prescribing practice for acute, uncomplicated respiratory tract infections in primary care settings in New Delhi, India. *Tropical Med Int Health*. 2014;19(7):761-768.
23. Kiguba R, Karamagi C, Bird SM. Extensive antibiotic prescription rate among hospitalized patients in Uganda: but with frequent missed-dose days. *J Antimicrob Chemother*. 2016;71(6):1697-1706.
24. Monnet DL, Mölstad S, Cars O. Defined daily doses of antimicrobials reflect antimicrobial prescriptions in ambulatory care. *J Antimicrob Chemother*. 2004;53(6):1109-1111.
25. Westh H, et al. An international multicenter study of antimicrobial consumption and resistance in *Staphylococcus aureus* isolates from 15 hospitals in 14 countries. *Microbial Drug Resistance*. 2004;10(2):169-176.
26. WHO. Applications of the ATC/DDD methodology. 2019 17/07/2019; https://www.int/medicines/regulation/medicines-safety/toolkit_application/en/

**How to cite this article:** Nantongo H, Batwaala V, Nambasa V, Mukonzo J. Application of the anatomical chemical system/defined daily doses: Challenges and way forward for resource-limited countries. *J Clin Pharm Ther*. 2021;00:1–4. https://doi.org/10.1111/jcpt.13479