

## Review Article



# Defined Daily Dose (DDD): An Essential Metric in the Antimicrobial Stewardship Programmes (AMSPs) in the Healthcare Sector

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## ABSTRACT

Antimicrobial stewardship programmes (AMSPs) decrease antimicrobial resistance, optimize usage of antimicrobials, and enhance patient outcomes. The Anatomical Therapeutic Chemical (ATC) is the foundation of the World Health Organization (WHO) global methodology, which groups the pharmacologically active substances of antimicrobials according to their therapeutic, pharmacological, and chemical characteristics and the organ or system on which they work. Since varied unit doses of daily administration of antimicrobials are prescribed, it is best to utilize a standard approach to measure antimicrobial intake. The Defined Daily Dose (DDD) is awarded to active ingredients with an active ingredient code currently in effect. It is the anticipated average daily maintenance dose of an antimicrobial drug or substances used for their primary indication in adults. The ATC/DDD approach was created to enhance patient care by tracking antimicrobial usage and conducting research. Healthcare facilities would benefit immensely from establishing an antimicrobial stewardship programme, and more research is required to determine the baseline of antimicrobial consumption in the country.

**KEYWORDS:** Antimicrobials; Defined daily dose; DDD; Anatomical therapeutic chemical; ATC; Antimicrobial stewardship program; Antimicrobial resistance

## INTRODUCTION

Globally, antimicrobial resistance (AMR) is on the rise. According to recent estimates, the disease burden of AMR is predicted to have caused 4.95 million deaths in 2019, which is as high as the combined burden of HIV and malaria. It is feared that AMR might kill 10 million people annually and cost the world economy up to \$100 trillion by 2050 if it is not effectively tackled.<sup>1</sup> Antimicrobial stewardship programmes (AMSPs) have been implemented in many contexts to use

antimicrobials and postpone the emergence of resistance, while maintaining patient safety and preventing unneeded medical expenses.<sup>2-5</sup> AMSPs can lower hospital usage of limited antimicrobial medications by 27% and overall antimicrobial consumption by 19%.<sup>2</sup> Depending on the prevalence of resistant infections across the varied clinical settings and geographic regions, as well as the available resources, the effect of the ASPs on antimicrobial use may vary.<sup>3</sup> Despite antimicrobial use being

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significantly higher in low- and middle-income countries (LMICs) than in high-income countries (HICs), more comprehensive data about the efficacy of AMSPs in these settings is needed.<sup>6,7</sup> AMR drives up healthcare costs, puts Sustainable Development Goals in jeopardy, and disproportionately impacts LMICs. The Centers for Disease Control and Prevention (CDC) in the United States estimated that the total annual cost of antimicrobial resistance (AMR) in the United States is \$55 billion. This amount includes \$20 billion more than direct healthcare expenses and an additional \$35 billion in societal costs due to lost productivity. In the United States, healthcare providers prescribed 258.0 million antibiotic courses in 2010 (or 833 prescriptions per 1000 inhabitants). The two most often prescribed categories were macrolides (22%) and penicillin (23%). Azithromycin and amoxicillin were the antibiotics that were prescribed the most.<sup>8,9</sup>

Antimicrobials are among the most often prescribed drugs,<sup>10</sup> with 20 to 50 percent of these prescriptions being unnecessary.<sup>11</sup> Studies have shown that incorrect antibiotic selection or duration occurs in 25% to 75% of instances. Prescription of antimicrobials for viral infections, wrong antimicrobial type, dosage, duration, or administration method, increased use of antimicrobials in agriculture, and frequent use of broad-spectrum and last-resort antimicrobials are examples of the irrational use of antimicrobials. The prudent use of antimicrobials is crucial in mitigating the development of antimicrobial resistance in bacteria and prolonging the life of these essential life-saving medicines.<sup>12</sup> AMSP tracks adherence to interventions meant to optimize antimicrobial therapy and spot patterns of use that call for additional research.<sup>13,14</sup> Their ecological and therapeutic benefits have been proven in hospitals and the community.<sup>15-17</sup> Since consumption of antimicrobials is linked to the rise of resistant bacteria.<sup>18-20</sup> Cutting the overuse of antimicrobials would decrease the rate of emerging antimicrobial resistance and lower the increased healthcare expenditures linked to drug-resistant infections.<sup>21-24</sup>

There are various metrics for assessing antimicrobial consumption, which is a crucial parameter in the research of antimicrobial use. The World Health Organization's (WHO) Collaborating Centre for Drug Statistics Methodology has updated and approved the most widely used approach.<sup>25</sup> The idea of specified daily doses (DDD) is its foundation. The Anatomical Therapeutic Chemical (ATC), based on the WHO global methodology, is used to classify the pharmacologically

active component of antimicrobials according to their therapeutic, pharmacological, and chemical qualities and the organ or system on which they work. Since varied unit doses of daily administration of antimicrobials are prescribed, it is best to utilize a standard approach to measure antimicrobial intake. The DDD is assigned to active ingredients with an active ingredient code already in place. It is the anticipated average daily maintenance dose of an antimicrobial drug or substances used for their primary indication in adults. The ATC/DDD technique aims to monitor antimicrobial consumption and conduct research to enhance the quality of patient treatment.<sup>26-28</sup>

## ATC CLASSIFICATION SYSTEM

A global standard under WHO supervision is the ATC/DDD system.<sup>29</sup> Often known as the active ingredient(s) of a medication, active medicinal substances are categorised based on the body system (e.g., central nervous system) or organ (e.g., heart, kidney) that they affect. In its most basic form, the ATC classification is a numerical and alphabetical description of an active ingredient's characteristics that places it into one of five tiers, generally referred to as a "drug" or "medicine." One of the fourteen anatomical or bodily systems—the circulatory system [C], the gastrointestinal tract and metabolism [A], blood and blood-forming organs [B], etc. are covered in the first level. The drug's chemical name and a description of its pharmacological and therapeutic properties can be found in the second, third, and fourth levels. This technique makes it possible to communicate about this drug (or active ingredient or medicine) internationally without dealing with language and spelling issues. In pharmacoepidemiological investigations, coding is crucial because it increases precision by precisely identifying the medication; yet, since ATC and DDD are linked to a drug's dosage form, multiple ATCs (and DDDs) may exist for a single drug.<sup>30</sup>

## DEFINED DAILY DOSE

When used in conjunction with ATC, the DDD is defined as the average daily maintenance dose for the drug's major indication in adults. It is expressed in different units, such as milligrams or grams, and may vary depending on the mode of administration.<sup>31</sup> The DDD was created to address issues with dosage forms and is also a practical means of tracking usage variations over time, mainly when the composition of formulations varies or pack sizes alter, as happens frequently in hospitals. The prescribed daily dosage (PDD), the average dose prescribed based on a

representative sample of prescriptions, should be distinct from the DDD. It is critical to consider the ailment for which the dosage was recommended. It's crucial to understand the many ATC/DDDs, for instance, while figuring out PDD/DDD.

The DDD, like many average computations, may not always correspond to an advised dosage, particularly in cases where a patient's dose needs to be modified, as in the case of elderly patients. The DDD will only accurately reflect the drug's intended use when it closely aligns with the PDD, which takes into account the patient's age, sex, weight, ethnicity, and pharmacokinetics, in addition to the severity of the disease.

The quantity (by weight or count), cost, and frequency of prescriptions (and repetitions) for a given medication are some variables linked to its consumption. The variations in prescribing patterns are overcome by the DDD measure, which is also occasionally referred to as "consumption" and yields an estimate of medication use. Only one DDD is awarded for each ATC code and mode of administration by the WHO Collaborating Centre in collaboration with the WHO International Working Group on Drug Statistics Methodology.<sup>31</sup> Although most substances have an assigned ATC code, some do not have a DDD assigned, including topical products and antineoplastic agents, vaccines and sera, as well as allergen extracts and contrast media.<sup>31</sup>

## SELECTION OF UNITS

When describing DDDs for simple items, the following units are used, whenever possible: g (gram), mg (milligram), mcg (microgram), ml (millilitre), mmol (millimole), U (unit), TU (thousand units), and MU (million units). In addition to other units, the abbreviation U is used internationally.

## INDICATORS OF DDD

Data on drug use expressed in DDDs are typically presented in units that account for variations in population size. This allows for comparisons across different periods and population groupings by measuring exposure or therapy intensity in a given population. Drug use statistics should preferably be displayed using a denominator appropriate for the health setting, such as the number of DDDs per 1000 people per day, the number of DDDs per resident per year, or the number of DDDs per 100 bed days. Some of them are as follows:

**DDD per 1000 inhabitants per day:** The prescription data expressed as DDDs per 1000 people per day might give a ballpark approximation of the percentage of the study population that takes a given medicine or class of drugs daily. The statistic of 10 DDDs per 1000 residents per day can be understood as follows: on any given day of the year under analysis, 10 DDDs of the medicine are used on average in a representative sample of 1000 inhabitants. Another way to put this would be that 1% of the population, or 10/1000, would be prescribed this medication daily for that year.<sup>31</sup>

**DDD per 100 bed days:** When taking into account drug use by inpatients, the DDDs per 100 bed days may be applied. A bed day is generally defined as any day a patient is confined to bed and spends the night in a hospital. An estimate of the treatment intensity and the probability that 80% of the inpatients will receive one DDD of a hypnotic per day is given by the figure 80 DDDs per 100 bed days of hypnotics. This metric is utilised in drug use analyses conducted within hospitals.

**DDD/patient:** This indicator, which indicates the treatment intensity/total exposure by a specified research period, is frequently computed in pharmacoepidemiological databases. The DDD or patient would also specify the number of treatment days in a certain time frame if the actual dose utilised were equal to the DDD.

**DDDs per inhabitant per year:** This indicator is frequently thought to help present the data for anti-infectives or other medications typically taken for brief periods. It will provide an approximation of the average number of treatment days per resident per year. For instance, 5 DDDs/inhabitant/year means that for a given year, the consumption is equal to treating each inhabitant for five days. Alternatively, if the standard treatment time is known, the total number of DDDs can be determined as the number of treatment courses. The number of treatment courses can then be connected to the total population.

When DDD and PDD come near, this kind of information is beneficial for medications that are administered over an extended period to treat chronic diseases.<sup>32</sup> To represent inpatient use, medication use in a facility like a hospital is sometimes expressed as DDD per bed day or DDD per 100 bed days. Drug utilisation data provided in DDDs provides a general estimate of consumption rather than an exact picture of the actual drug use.

## INTERPRETATIONS OF DDD

DDD use is not the same as a dose but is a metric. The overall population's medicine use is typically represented as DDD per 1000 people per day or year. For example, several 10 DDD/1000/day indicates that, on any given day of the year, an average of 10 DDD are used per 1000 inhabitants; that is, 1% of the population takes the standard dose (DDD) daily, or 2% of the population takes 0.5 DDD daily. When it comes to medications that are administered on a long-term basis to treat chronic diseases and when the DDD is near the PDD, this kind of information is beneficial.<sup>31,32</sup>

## ATC/DDD METHODOLOGY APPLICATION IN THE AMSPS

The technique is a generally applicable instrument that supports essential information regarding the use of medications. To promote improved outcomes and high-quality medicine use, pharmacoepidemiological research employing the ATC/DDD approach offers reliable and consistent comparisons of medication use within and between nations.<sup>33</sup> Indiscriminate prescribing may be the cause if an antimicrobial is widely used in region X without a good therapeutic rationale. Use in medical institutions, including clinics and hospitals, can also be compared. Calculating comparative antimicrobial use is essential on a regional, national, and international level because of the threat of antimicrobial resistance. A recent example is a drug utilisation study that investigated the usage of quinolones for COVID-19 treatment and prophylaxis.<sup>34</sup> Research on medications directly affects policy and resource allocation, and it is used to inform the creation of standard treatment guidelines (STG) and essential medicine lists (EML).<sup>35,36</sup> Purchasing and payers are better informed about the availability and economical use of medications when they know how they are used. Studies on drug utilisation are supported by the methods employed to assess medication use. For instance, a study from the United Kingdom created indicators for tracking antimicrobial use, while a study from an Indian tertiary care hospital established a system for carrying out antimicrobial stewardship with a mechanism for prospective audit.<sup>37,38</sup> Especially regarding health and medication regulations, the usage of medications is a crucial metric for assessing the effectiveness of programmes, regulatory actions, and policy changes. Because the ATC/DDD classification can be consistently used by all parties involved in the pharmaceutical chain, including producers, distributors, insurers, pharmacies, and regulators, more

nations are incorporating the ATC into their medical product classification systems.<sup>32</sup>

Antibiograms depict the antimicrobial resistance patterns of microbes encountered in a hospital or a particular ward/unit. They can guide empiric antimicrobial choices as per the prevailing susceptibility pattern. This idea can be further developed to include syndromic and unit-specific antibiotic recommendations for various infections.<sup>39</sup> Further, the WHO has classified antimicrobials into three groups, i.e., "Access," "Watch," and "Reserve" (AWaRe), to promote rational use. The usage of antibiotics captured with ATC/DDD metric and correlated with antibiograms can help curb the irrational use of antimicrobials. These tools can be integrated to evaluate the effectiveness of the AMSPs at the institutional level and draw comparisons at regional, national, and international levels.<sup>40</sup>

## PEDIATRIC DDD

Adult DDDs are often assigned based on use. The dose recommendations for medications approved for use in children will vary depending on the patient's age and body weight. Many medications used in children aren't even licensed for that use, and there isn't any information available about dosage schedules. Therefore, the WHO International Working Group for Drug Statistics Methodology has determined that pediatric DDDs are challenging to give and that using this approach will not be able to answer issues about drug use research in children.<sup>28</sup>

It is not feasible to estimate the prevalence of drug use in children using the unrefined sales data found in DDDs. When available, paediatric prescribed daily dosages and indications should be checked with the DDD values. The general DDD should be used as a benchmark for general comparisons if it is challenging to identify the paediatric subpopulation.

## ADVANTAGES OF DDD

The drug usage information found in DDDs provides an approximation of consumption of its actual use. DDDs give researchers a fixed unit of measurement unaffected by factors like price, currency, package size, and strength. This allows them to compare various population groups and analyse drug usage trends. The following are its benefits.<sup>32</sup>

1. Analyse how drug use has changed throughout time.
2. Compare drug use internationally.

3. Assess how an intervention affects drug usage.
4. Pay attention to modifications in a drug class's usage.
5. Assess how interventions and regulations affect prescribing behaviors.

## LIMITATIONS OF THE DDD

The limitations of the usage of DDD are as follows.<sup>28</sup>

1. DDDs are based on the premise that all drugs supplied are consumed; measuring drug consumption in terms of DDDs only provides a general estimate of consumption rather than an accurate picture of actual use. Moreover, it is essential to consider that different medicines are consumed at varying dosages when analysing drug consumption data.
2. It is crucial to consider the size of the population utilised as a denominator and make any necessary adjustments. The population as a whole (all age groups) is typically used to determine general consumption. However, drug usage is frequently concentrated within particular categories, such as adults only using hypertension medications and women only using oral contraceptives (ages 18 to 44).
3. DDDs do not cover certain drug types. Sera, vaccinations, antineoplastic medications, and local and general anaesthetics are some examples.
4. The drug consumption reported in the DDD per population may be roughly in line with morbidity statistics if the pharmaceuticals are taken consistently and for a single indication.
5. There is no way to profile how often fixed combinations are used using the DDD methodology. While a particular unit (EO) has been established for combined preparations, it is unsuitable for comparing drug consumption across nations that employ various fixed combination types and dosages.
6. A DDD is not always equal to the average daily dose eaten or the average dose prescribed. The accurate predominating indications, local or national therapeutic customs, and patient attitudes will all influence the doses prescribed and taken in a given society.
7. The DDD's capacity to assess the medication's efficacy is restricted.

## CONCLUSIONS

DDD is a widely accepted metric worldwide and is a useful step in measuring total drug consumption as part of the larger gambit of AMSP for optimising antimicrobial therapy. It can and should be combined with other drug consumption methodologies, such as the prescribed daily dosage (PDD), for more accurate

estimates of drug use. However, when calculating and comparing drug consumption data, one must be aware of the inherent limitations of the DDD as a unit of measurement and must be used judiciously in AMSP.

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## CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

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Not applicable

## AUTHORS' CONTRIBUTIONS

**AM:** Conceptualization, Manuscript Writing and Review

**SS:** Review

**SR:** Review

**MC:** Manuscript Writing

**GR:** Manuscript Writing

**SRK:** Review

**LVS:** Manuscript Writing

**TV:** Manuscript Writing

**SR:** Manuscript Writing

## AI DECLARATION

No AI tool was used to generate research data, perform data analysis, interpret findings, formulate scientific conclusions, or make editorial decisions. All AI-assisted content was critically reviewed, verified, and revised by the authors. The authors take full responsibility for the accuracy, originality, integrity, and final content of the manuscript.

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