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# NEED OF A STANDARD METRIC FOR QUANTIFYING ANTIBIOTIC USE IN HOSPITALS; A CLINICAL PHARMACIST'S VIEW

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## ABSTRACT
The burden of bacterial infections is huge and grossly under-represented in the current health-care system. Antibiotics are widely used in clinical practice globally and their irrational use could lead to antimicrobial resistance which further can result in increased morbidity, mortality and economic burden. As there is a growing need for quantitative insight into antibiotic consumption in order to improve the rationality of antibiotic use, Drug utilisation studies can act as a powerful tool for the study of prescribing of drugs, as well as to measure the consumption of drugs. The WHO has determined that Anatomical Therapeutic Chemical classification and Defined Daily Dose (ATC/DDD) system is an international drug classification method, serves as a tool for drug utilization monitoring and research in order to improve the quality of drug use. This review summarizes about the link between antibiotic resistance and antibiotic consumption, thereby the importance of antibiotic consumption data in hospitals and also gives a concise overview of ATC/DDD system and its significance as a standard metric for quantifying antibiotic use in hospitals.

**KEYWORDS:** Antibiotic resistance, Antibiotic consumption, Drug utilization studies, Anatomical Therapeutic Chemical classification (ATC), Defined Daily Dose (DDD).

## INTRODUCTION
Infectious diseases contribute to most common cause of curable morbidity and mortality in the world. Discovery of antibiotics since 1928 has been a boon to treat and prevent infections. Antimicrobial agents are "Magic bullets" which prevent millions of deaths each year and remain the primary treatment for potentially fatal bacterial infection. In the absence of the development of new generations of antibiotic drugs, appropriate use of existing antibiotics is needed to ensure the long term availability of effective treatment for bacterial infections.[1] Excessive and inappropriate use of antibiotics in hospitals, health care facilities and the community contributes to the development of bacterial resistance. High infectious disease burden, poor living conditions and easy availability of antibiotics are some of the major drivers of rising Antimicrobial Resistance (AMR) in India. AMR has emerged as a major risk to public health estimated to cause 10 million deaths annually by 2050. India carries one of the largest burdens of drug-resistant pathogens worldwide.[2]

The in-hospital use of antibiotic drugs has been a major concern in the last few decades for several reasons. For the purchasers of health care services and administrators, antibiotic drugs account for a major proportion of the escalating drug budget, especially in hospitals. The overuse and misuse of antibiotic drugs is considered to be one of the reasons for increasing resistance among various pathogens. These worries have led to the implementation of strict antibiotic policies in hospitals in many countries, with different strategies and different outcomes. Thus, one of the possible measures to reduce the inappropriate use is the rationalization. Unfortunately, India represents the country with highest antimicrobial consumption.[3]

Measuring the quantity of antibiotic use is one of the key strategies in antimicrobial stewardship programmes since measurement of antibiotic use is the first step that leads to control and eventually to an improvement of use. Quantity metrics may reflect the volume or costs of antibiotic use and proper comparison of antibiotic consumption is enabled only by standardization of its quantification.[4] Access to standardised and validated information on drug use is essential to allow audit of patterns of drug utilization, identification of problems, educational or other interventions and monitoring of the outcomes of the interventions.

Drug utilisation studies are a powerful tool that can be used to study the prescribing of drugs, as well as to measure the consumption of drugs. In order to measure drug use, it is important to have both a classification system and a unit of measurement. To deal with the objections against traditional units of measurement, a technical unit of measurement called the Defined Daily Dose (DDD) was developed for use in drug utilization studies.[5]

**Link Between Antibiotic Resistance and Antibiotic Consumption**

The increasing prevalence of antibiotic-resistant bacteria poses a major threat to the health of hospitalized patients. The development of AMR is a normal evolutionary process for microorganisms but it is accelerated by the selective pressure exerted by widespread use of antimicrobials. The relationship between emergence of resistance and antibiotic use and misuse is well recognized in individual health care facilities, communities and countries. There is a strong association between AMR and levels of antimicrobial use, implying that a reduction in unnecessary consumption of antimicrobials could affect resistance.[6]

Antibiotic consumption is defined as quantities of antimicrobials used in a specific setting (total, community, hospital) during a specific period of time (e.g. days, months, and year). It is an important parameter in the study of antibiotic use.[7] The term antibiotic use refers to data on antibiotics taken by the individual patients. Data's are collected at the patient level, which allows a more comprehensive set of data to be gathered, such as information on indication, treatment schemes and patient characteristics. Antimicrobial consumption in hospitals is a key factor in the emergence of antimicrobial-resistant hospital pathogens, such as meticillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), Clostridium difficile and multiple-resistant Gram-negative bacteria. Use of certain broad spectrum antibiotic classes appears to be particularly strongly associated with the emergence of such pathogens. It is evident that antibiotics affect not only the microorganism and the individual patient, but also the population as a whole.[6]

At the hospital population level, three factors are important with respect to the selection pressure exerted by antibiotics. First, the total amount of an antibiotic used in a particular geographical area (i.e. the entire hospital or a ward or unit) over a certain period of time. Secondly, the number of patients treated with the antibiotic (because they serve as the major 'sources' of resistant bacteria). Thirdly, the density of these patients, i.e. the proportion of patients on antibiotics in the hospital. Together these factors represent the selection density in the hospital environment. As the selection density increases, the number of resistant strains in the hospital environment increases and the number of susceptible strains able to survive in this environment decreases. This may facilitate the spread of resistant bacteria and resistance genes.[8]

Historically, the development and use of each new antibiotic have been followed by the emergence of resistance. The available evidence suggests that the global consumption of antibiotics in humans has risen in the past two decades, primarily driven by an increased use in low- and middle-income countries. Considering this issue new treatments for infections need to be developed to counteract emerging AMR, antibiotics must also be used appropriately, made accessible to those who need them, and meet international standards of quality.(6)

**Role of Antibiotic Consumption Data In Hospital Settings**

The surveillance of antimicrobial consumption is one of the most important issues that must be considered to improve the quality of antimicrobial use. Data on antimicrobial consumption provide information on which antimicrobials are used and in what quantities and allow for the assessment of trends over time at global, country or health facility levels. Data on the consumption of antimicrobial medicines in the hospital can be used to:

- Link antimicrobial exposure to the development of AMR;
- Identify and provide an early warning of problems related to changes in antimicrobial exposure and use, and develop interventions to address the problems identified;
- Monitor the outcomes of interventions;
- Assess the quality of prescribing in terms of adherence to practice guidelines;
- Raise awareness among health professionals and policy-makers about the problems of the inappropriate use of antimicrobials and its contribution to AMR.[6]

**ATC/DDD SYSTEM**

The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) as a measuring unit are tools for exchanging and comparing data on drug use at international, national or local levels. The purpose of the ATC/DDD system is to serve as a tool for drug utilization monitoring and research in order to improve quality of drug use. There is a need for such system of classification and standard metrics to facilitate comparisons of antimicrobial consumption between health facilities, between countries and between regions. The ATC/DDD system can also provide a basis for the evaluation of long-term trends in drug use. It is the prominent method and universal parameter suggested by WHO which can be used to standardise the data collection and reporting of antimicrobial consumption.[5]

**Historical Development of Atc/Ddd System**

The field of Drug Utilization Research (DUR) began attracting attention in the 1960's. This followed the publication of a breakthrough study on drug consumption from 1966-1967 (pioneered by the WHO Regional Office for Europe) which further exemplified the importance and applicability of DUR. In addition, the WHO symposium in 1969 entitled "The Consumption of Drugs", in Oslo, was determined that an international system of drug consumption measurement was needed and highlighted the need for an internationally accepted classification system for drug utilization studies. As a result the Drug Utilization Research Group (DURG) was established and entrusted with the development of internationally applicable methods for DUR. Inspired by this interest, the Anatomical Therapeutic Chemical (ATC) classification was developed in Norway as a modification and extension of the European Pharmaceutical Market Research Association (EphMRA) classification system.

The DDD was introduced as a unit of measurement in drug utilisation studies by the Norwegian Medicinal Depot in the early 1970s. The DDD was first mentioned in print in 1975, when a list of DDDs of drugs registered for sale in Norway was prepared.[9] International interests in the ATC/DDD methodology rapidly expanded, largely through the activity of the DURG. In 1981, the WHO Regional Office for Europe formally recognized the ATC/DDD system for drug utilization studies and recommended its use in Europe. In 1982 the WHO Collaborating Centre for Drug Statistics Methodology was established and assigned the responsibility to coordinate the development and use of the ATC/DDD methodology. In 1996, World Health Organization (WHO) recommended the global use of the ATC/DDD methodology.[5]

**Anatomical Therapeutic Chemical (Atc) Classification**

The Anatomical Therapeutic Chemical (ATC) classification system is the most commonly used method for aggregation of medicines data and allows flexibility in reporting by medicine or groups of medicines. In this system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Each drug is assigned at least one ATC code, which are classified into groups at five different levels. Only one ATC code will be assigned for each drug. Besides, ATC codes are often assigned according to the mechanism of action rather than therapy. An ATC group may therefore include drugs with many different indications, and drugs with similar therapeutic use may be classified in different groups. Table 1 is given with an illustration using amoxicillin.

**Table 1: Classification of amoxicillin of the ATC classification system.[5]**

| ATC classification | ATC category | Description |
|---|---|---|
| J | General anti-infectives for systemic use | 1st level, anatomical main group |
| J01 | Antibacterials for systemic use | 2nd level, therapeutic main group |
| J01C | Beta-lactam antibacterials, penicillins | 3rd level, therapeutic/pharmacological subgroup |
| J01C A | Penicillins with extended spectrum | 4th level, chemical/therapeutic/pharmacological subgroup |
| J01C A04 | Amoxicillin | 5th level, subgroup for chemical substance |

**Defined Daily Dose (DDD)**

The defined daily dose is an artificially and arbitrarily created statistical measurement used for research purposes in comparing the utilization of drugs. To facilitate the ability to compare consumption information across time and geography, a technical unit of measurement was created for use in conjunction with the ATC classification. It is referred to as that DDD are assigned to each drug at the 5th level (chemical substance) of classification. It is defined by the ATC as "the assumed average maintenance dose per day for a drug used for its main indication in adults". DDD's are assigned only to drugs that have already been provided with an ATC code. It is important to note that the DDD is not equivalent to the prescribed daily dose (PDD) or, the average amount of a specific drug prescribed to an adult patient for the drug's main indication per day. Different DDDs may be assigned for different drug formulations (i.e. parenteral versus oral). Table 2 is given with some examples of DDDs for antibiotics.

**Table 2: Examples of Defined Daily Doses (DDD).[5]**

| ATC classification | ATC drugs | DDD (Oral) | DDD (Parenteral) |
|---|---|---|---|
| J01C A04 | Amoxicillin | 1.5 g | 3g |
| J01C A01 | Ampicillin | 2g | 6g |
| J01M A02 | Ciprofloxacin | 1g | 0.8g |
| J01D D04 | Ceftriaxone | - | 2g |
| J01F A10 | Azithromycin | 0.3g | 0.5g |
| J01F F01 | Clindamycin | 1.2g | 1.8g |

**DDD INDICATORS**

Drug utilization figures expressed in DDDs are generally reported in units that control for population size differences. This provides a measure of exposure or therapeutic intensity in a defined population, allowing comparisons across various time periods and population groups. Drug Utilization figures should ideally be presented using a relevant denominator for the health context such as numbers of DDDs per 1000 inhabitants per day, DDD per inhabitant per year, or as DDDs per 100 bed days. These parameters can be very useful for evaluating drug utilization at every level of health-care system.

1) **DDD per 1000 inhabitants per day:** Sales or prescription data presented in DDDs per 1000 inhabitants per day may provide a rough estimate of the proportion of the study population treated daily with a particular drug or group of drugs.
2) **DDDs per inhabitant per year:** This indicator is often considered useful to present the figures for antiinfectives (or other drugs normally used in short periods). It will give an estimate of the number of days for which each inhabitant is, on average, treated annually.
3) **DDD per 100 bed days:** The DDDs per 100 bed days may be applied when drug use by inpatients is considered. A bed day is a day during which a person is confined to a bed and in which the patient stays overnight in a hospital. This measure is applied in analyses of in-hospital drug use. This indicator is quite useful for benchmarking in and between hospitals.
4) **DDD/patient:** This indicator is often calculated in pharmacoepidemiological databases and expresses the treatment intensity/total exposure according to a defined study period. If the actual dose used is equivalent to the DDD, the DDD/patient would also express number of treatment days in a specific period.(5)

**EXPRESSING DDD USE**

DDD use is a measure and should not be confused with a dose. The DDD is indicated in terms of the weight of active substance using the most appropriate units, for example, g (gram), mg (milligram), ug (microgram), mmol (millimol), E (unit), TE (thousand units) or ME (million units). Two basic assumptions underlie the use of the DDD, namely that patients take the medication (that is, that patients are compliant); and the doses used for the major indication are the average maintenance doses.

For practical reasons, the DDD is based on use in adults, except for certain preparations exclusively used in children. Where dosage is normally related to body weight, the daily dose is calculated on the assumption that the adult weighs 70 kg and the child 25 kg. For drugs administered in an initial loading dose that differs from the maintenance dose, the latter is chosen as a basis for the DDD. If a drug can be used for prophylaxis as well as for therapy, the therapeutic dose is generally chosen, except where the main indication is clearly prophylactic. The system has also been developed to allow for a number of problematic and fringe situations:

- For drugs used in different dosages according to the route of administration, for example, different daily doses may be established: one DDD may be used for the oral route and another for the parenteral route.
- For fixed combinations, where the defined dose cannot be expressed in weight of active substance, it is expressed as the number of single doses (such as the number of tablets, capsules or suppositories) normally used per day to obtain the desired therapeutic effect, following the same sources of information as those used to establish the DDD.

All DDDs for plain substances are based on monotherapy treatment. In some drug groups no DDDs are established since it is difficult to find appropriate DDDs, for example Dermatologicals. All assigned DDDs are regularly reviewed because dosages may change over time due to, for instance, new main indications or newer research, and it may be necessary to make some alterations.[10]

➢ **DDD as a metric for quantifying antibiotic consumption**

**a) In general population**

Consumption in a given geographical area is usually expressed in DDD per 1000 inhabitants per day. This parameter provides a rough idea of the proportion of the population receiving a standard drug treatment every day. For example, a consumption level for an antibiotic of 15 DDD per 1000 inhabitants per day theoretically corresponds to 1.5% of the population on continuous treatment; but such drugs are more generally used over short periods, and the reality is probably closer to 15% of the population taking the drug for a month or 60% for a week. In such cases, consumption is better expressed as DDD per inhabitant per year, making it easier to visualize what the figures mean in real terms.

DDD per 1000 inhabitants per day is calculated by using the formula;

$$\text{DDD/1000 Inhabitants/day} = \frac{\text{Utilization in DDDs} \times 1000}{(\text{No. of inhabitants}) \times (\text{No. of days in the period of data collection})}$$

Where,

Utilization in DDD = (Number of packages used) × (Number of DDD in a package)

**b) In hospital settings**

Consumption in hospitals is calculated in the same way as consumption in the general population, but it is usually expressed as the number of DDD per 100 bed days. Although there is no official standardized definition of a bed day it usually reflects a patient who is confined to bed and remains in the facility overnight. As more patients undergo medical procedures or surgery as "day" patients, the definition will need to be clarified. In making the calculation, the days of admission and discharge are usually counted together as one bed-day.

The recommended standard unit for measuring antibiotic consumption in hospitals is DDD per 100 bed-days. It has been used internationally in the comparison of in-hospital and outpatient to antibiotic use. Expressing antibiotic consumption in DDD/100 bed-days unit allows hospitals to compare their consumption with other hospitals, regardless of differences in quality and quantity of antibiotics. The DDDs for most antiinfectives are based on treatment of moderately severe infections. In hospital care, much higher doses are frequently used and this must be considered when using the DDD as a unit of measurement.(10) DDD per 100 bed days is calculated by using the formula;

$$\text{DDD/100 bed-days} = \frac{\text{No. of units administered in a given period} \times 100}{\text{DDD} \times \text{number of day's} \times \text{number of beds} \times \text{occupancy index}}$$

Where,

Number of DDDs = Total grams used / DDD value in grams

$$\text{Occupancy index} = \frac{\text{Total inpatient service days for a period} \times 100}{\text{Total inpatient bed count} \times \text{number of days in the period}}$$

## SIGNIFICANCE OF DDD

DDDs provide a fixed unit of measurement independent of price, currencies, package size and strength enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups. The calculation of DDDs makes it possible to study national and international data retrospectively and it is a relatively easy and inexpensive method of calculating drug consumption. By applying the DDD to a defined population, it is possible to:

- Examine changes in drug consumption over time;
- Make international comparisons;
- Evaluate the effect of educational programs directed either at the prescriber or patient level;
- Document the relative therapy intensity with various groups of drugs;
- Follow changes in the use of a class of drugs;
- Evaluate regulatory effects on prescribing patterns.[10]

## APPLICATIONS OF ATC/DDD METHODOLOGY

The purpose of the ATC/DDD methodology is to serve as a tool for producing good quality, usable and comparable drug utilization statistics. The methodology can be used in:

- **National Standard for Medicinal Products:** The ATC classification has been adopted in various countries as a national standard for classification of medicinal products. ATC codes can be used consistently by producers, wholesalers, pharmacies and the regulatory authorities to identify an active substance or a combination of active substances.
- **International Classification:** A drug classification system represents a common language for describing the drugs available in a country or region and is a prerequisite for national and international comparisons of drug use data.
- **Health Policy:** Drug utilization statistics is an important tool in the planning, monitoring and evaluation of national drug policies. Availability of local or national data on drug use represents the first step in improving the quality of drug use in the population.
- **Drug Utilization Research:** Follow trends and patterns in drug use. Applications of a specific set of ATC codes and DDDs to drug use information over time allow trends in drug utilization to be studied.
- **Pharmacovigilance:** The ATC classification can be used in the monitoring of Adverse Drug Reactions (ADRs) as the system helps to link ADRs to drug classes. Moreover, since DDDs can provide information on volume of medicines used, it can also help determine ADR rates.
- **Assisting procurement agencies and payer organizations:** To ensure a better overview of the availability of drugs. For example, identification of main drug costs to ensure no drug shortages.[5]

### Atc/Ddd In Drug Utilization Studies

Drug utilization studies are normally done in hospital or ambulatory care settings. Use of the ATC/DDD system allows standardisation of drug groups and represents a stable drug utilization metric to enable comparisons of drug use between countries, regions, and other health care settings, and to examine trends in drug use over time and in different settings. In Drug utilization studies, ATC/DDD system can helps to;

- Study patterns of use and changes over time.
- Evaluate the impact of information efforts, regulatory changes etc.
- Study drug exposure in relation to adverse drug reactions.
- Indicate over-use, under-use and misuse/abuse of drugs.
- Define need for further Pharmacoepidemiology studies.

Collecting and publishing drug utilization statistics are critical elements in the process of improving the prescribing and dispensing of medicines. For drug utilization statistics to have the best possible impact on drug use, the statistics need to be used in a focused and active manner. The WHO Centre has illuminated several specific examples of how the drug utilization statistics based on ATC and DDDs can be used to improve drug use:

- National publications, which provide clinicians, pharmacists and others with a profile of drug consumption in the country (with or without comparisons between countries or between areas within the country).
- Publications providing feedback within health services to individual health facilities, groups of health care providers, or individual health providers.
- Use of drug utilization statistics by national health systems, universities, drug information centres, and others to identify possible over use, underuse or misuse of individual drugs or therapeutic groups. Depending on the situation, this information can then be used to initiate specific studies or specific educational interventions. Educational interventions may include articles in drug bulletins, articles in scientific journals, letters to clinicians, etc.[5]

## LIMITATIONS OF DDD

- Drug utilization data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use, because it is based on the assumption that all drugs that are sold are actually consumed. Furthermore, many drugs are used in different dosages and this must be taken into account when drug consumption figures are evaluated.
- For some types of drugs, DDDs are not applicable. Examples are sera and vaccines, antineoplastic drugs and general and local anaesthetics.
- A DDD is not necessarily equivalent to the average doses actually prescribed or to the average dose actually ingested every day. The doses prescribed and taken in a particular community will vary with the actual predominating indications, national or regional therapeutic traditions and the attitude of patients.
- The DDD has limited potential for the evaluation of the effectiveness of the drugs consumed.

  Although the DDD is recognised internationally, the inherent limitations of the DDD as a unit for the measurement of drug consumption must be realised and taken into account when calculating and comparing drug consumption data. Despite its limitations, the DDD methodology is a valuable first step in overall drug use measurement.[9]

## CONCLUSION

The quality of life can be improved by enhancing standards of medical treatment at all levels of the health care delivery system. Drug utilization studies can provide useful information for improvement of the appropriate and effective use of pharmaceuticals in populations. ATC/DDD system is the “gold standard” for international drug utilisation research. The DDD metric along with the ATC drug classification form a system which can be a powerful tool for analysing patterns of drug utilization and the quality of drug use and health outcomes.

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