Antimicrobial Use in Humans

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Abstract

Antimicrobial agents, as a major milestone in the history of medicine and human health, have saved millions of lives. Antimicrobial use is the key driver for the development of resistance. Misuse and overuse of antimicrobials accelerate this problem further. As the resistance increases, prescribers are forced to use a higher-generation, broad-spectrum antimicrobials resulting in the development of resistance to these drugs as well.

Considerable variation exists between countries in the volumes of antimicrobial use depending upon socioeconomic factors, cultural differences, and remuneration incentives. Important factors influencing antimicrobial use are disease burden, access to antimicrobials, prevalence of resistance, and local healthcare

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service issues such as availability of medicines, pricing, affordability, infrastructure, and human resource for health. In order to rationalize antimicrobial use, their consumption needs to be measured and compared over time within and across other settings and countries. Surveillance data is also essential to establish epidemiological association between use of antimicrobials and emergence of resistance over time. The data must be collected using standard methodology and expressed in the comparable units of measurement. Besides assessing the quantum of antimicrobials used, there is a need to study the drivers of use, i.e., reasons for inappropriate prescribing. This chapter aims to provide a broad overview of the relationship between antimicrobial use and resistance and surveillance methodologies for antimicrobial consumption.

Keywords

Antimicrobial use · Antimicrobial consumption · Defined daily dose · Surveillance · Qualitative data

1 Introduction

Antimicrobials are the most important discovery of the past century. They have contributed immensely to reduce morbidity and mortality due to infectious diseases. The serendipitous discovery of penicillin, in 1928 by Alexander Fleming, and subsequent purification, mass production, and distribution in the 1940s for clinical use were a triumph for medical sciences in the war against infectious diseases (Aminov, 2010). However, Fleming, at that time itself, recognized the phenomenon of resistance and its associated dangers. He cautioned that unresponsiveness to penicillin was imminent, if penicillin was not used optimally. This warning has been largely ignored till date.

The discovery of penicillin established a prototype for research, development, and discovery of a large number of antimicrobial agents. Many novel antimicrobial classes were discovered and licensed from the 1940s to the 1960s, and this period came to be known as the "golden era" for discovery of new classes (Gould, 2016). Figure 1 depicts the timeline of antimicrobials finding their way to clinics (Hutchings et al., 2019; Durand et al., 2019; Taneja et al., 2019).

The discovery of new antimicrobial agents, along with improved sanitation, vaccinations, and access to safe water changed the practice of medicine and significantly reduced morbidity and mortality from infectious diseases, thereby doubling lifespan with substantial cost saving by early cure and reduced hospitalization days. Most achievements in medicine such as organ transplants, cancer treatment, and complex surgeries are, in fact, attributed to the use of antimicrobials, but unfortunately misuse came along with their use. Use of antimicrobials gradually extended beyond prophylactic and therapeutic application in human and animal health to unjustified overuse in mild self-limited trivial illnesses along with use for growth promotion in the animal sector to increase the yield for animal protein. The

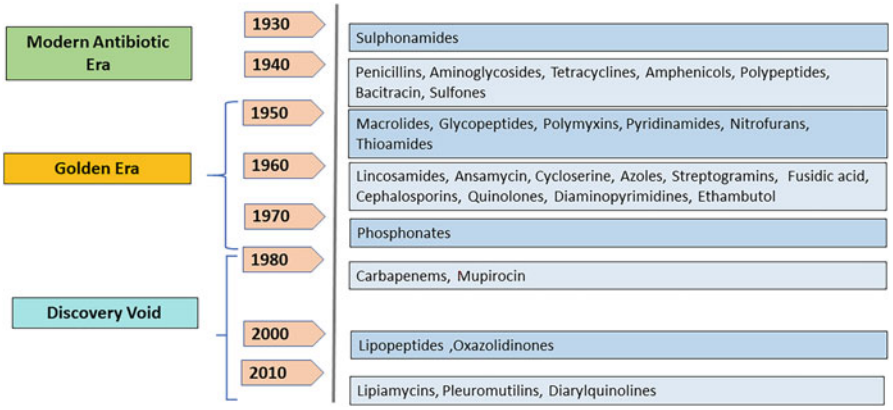

Fig. 1 Brief history of introduction of antimicrobials for clinical use

inappropriate use of antimicrobials resulted in the emergence of antimicrobial resistance (AMR) among the pathogens; the organisms which were being killed earlier started finding mechanisms to thwart the action of antimicrobials in their quest for survival and propagation.

Penicillin-resistant *Staphylococcus aureus* was observed as early as the 1940s, and to combat this, the first penicillinase-resistant β-lactam antimicrobial (methicillin) was developed in 1959 followed by ampicillin in 1961 and other derivatives with improved spectrum of activity and pharmacokinetics (Cunha et al., 2019). Within few years of use of methicillin, methicillin-resistant *Staphylococcus aureus* (MRSA) emerged to destroy methicillin.

The antimicrobial discovery slowed down considerably after the 1970s with very few new antimicrobial classes passing approval along with simultaneous increase in AMR (Durand et al., 2019; Taneja et al., 2019). The period after the 1990s is considered as "discovery void" as no major antimicrobials entered the market during this period (Hutchings et al., 2019). The overall rate of antibacterial approval has become extremely slow with one or two drugs entering the market every year from 2004 onwards which are largely optimization, modification, or combination of already known molecules (WHO, 2019a).

The pipeline for the discovery, and the development of new antimicrobials, has virtually dried out, and pharmaceutical industry is not interested in the development of novel antimicrobials as it is a resource-intensive exercise with cost of development of new drugs being very high (~$1.5–2 billion). Besides, it takes 10–12 years for market approval with no guarantee of return on capital invested in their development since resistance to new agent emerges in a short time frame (Cunha et al., 2019; WHO, 2019a). Antimicrobials are used for shorter durations, compared to drugs for chronic lifestyle diseases such as hypertension, diabetes, etc. In addition, even if new antimicrobials are developed, there is insistence to conserve the newly discovered antimicrobials for seriously ill patients, thereby further shrinking profit margins for the companies (Cunha et al., 2019).

With the dwindling antimicrobial discovery coupled with expanding magnitude of AMR, the "post-antimicrobial era" is imminent when easily curable illness will become incurable, necessitating safe and effective use of antimicrobials (Reardon, 2014; Draenert et al., 2015). The growing issue of AMR is directly linked with antimicrobial use (AMU). The administration (overuse or misuse) of antimicrobials for prophylactic, therapeutic, and non-therapeutic purposes in all sectors including humans, animals, horticulture, fisheries, and agriculture results in survival pressure on microbes, and hence they become resistant to antimicrobials used. Preserving the power of existing antimicrobials by rationalizing their use with investments in finding new innovative antimicrobials/solutions is the need of the hour.

2 Magnitude of Consumption/Use

The global human antimicrobial consumption has soared in the last two decades, mainly due to improved access and affordability in lower middle-income countries (LMICs) as a result of economic development (Van Boeckel et al., 2014). Consumption in developing countries is rapidly converging with high-income countries (HICs). A recent report from the Center for Disease Dynamics, Economics & Policy (CDDEP, 2021) has summarized antimicrobial consumption across nations and shown a 65% rise in overall global antimicrobial consumption between 2000 and 2015, in humans. Consumption in LMICs has increased two- to threefold from 2000 to 2015 with simultaneous increase in defined daily dose (DDDs) per 1,000 inhabitants, with Brazil, China, Africa, Saudi Arabia, and India being the main contributors (CDDEP, 2021). The rate of antimicrobial consumption increased from 11.3 to 15.7 DDDs per 1,000 people (39% increase) in the same period (Klein et al., 2018; CDDEP, 2021). There was a wide variation in consumption rates between LMICs ranging from 4 to 64 DDD per 1000 inhabitants per day probably due to access vs. excess paradox (some countries do not have sufficient access, whereas others are overusing) (WHO, 2018). The total consumption has also increased in high-income countries between 2000 and 2015, but DDDs per 1,000 inhabitants has increased marginally or even declined. However, per capita antimicrobial consumption in LMICs is still lower than HICs (CDDEP, 2021).

India was reported to be the highest consumer of antimicrobials in 2010, and the total consumption increased by 47.4% from 2010 (5411 million DDD) to 2020 (7976 million DDD) (CDDEP, 2021). India alone contributed to 75% of the global average of percentage change in total use from 2010 to 2020 (Klein et al., 2020). The per capita DDD has increased by 1.35 per person from 2010 to 2020 in India (CDDEP, 2021).

The World Health Organization (WHO) is advocating the Access, Watch, Reserve ("AWaRe") tool to streamline the consumption of antibiotics with relaxation to use the *Access* group of antibiotics over *Watch* and *Reserve* group in order to reduce AMR ("AWaRe" discussed later in targeted antibiotics). The global per capita consumption of *Watch* group of antibiotics has risen by 91% from 2000 to 2015 and is largely driven by increased consumption in LMICs (165% increase from 2.0

to 5.3 DDDs per 1,000 people) compared to HICs (27.9% increase from 6.1 to 7.8 DDDs per 1,000 people) (Klein et al., 2020). However, use of *Access* antibiotics has only marginally increased by 26.2% globally during the same period. The use of critically important antimicrobials like oxazolidinones, glycylcyclines, carbapenems, and polymyxins has rapidly increased in all countries (Klein et al., 2020). At the existing rate of consumption, the global antimicrobial consumption could double by 2030 (CDDEP, 2021).

3 Factors Driving Consumption in Humans

Globally antimicrobials are used inappropriately, and nearly half of those used in human healthcare is inappropriate with variation across regions (Laxminarayan et al., 2016). AMU is governed by several patient-related, prescriber-related, system-related, regulatory, supply chain factors, and rationality of their use depends on the context (Cockburn et al., 2005; Castro-Sánchez et al., 2016; Laxminarayan et al., 2016). The major factors for irresponsible antimicrobial use are summarized in Table 1.

In LMICs, enhanced access to antimicrobials, distinct national disease burden, seasonal patterns, and misuse of antimicrobials are largely responsible for increased consumption (Ayukekbong et al., 2017). Antimicrobial prescribing, a complex process, is seen in all clinical settings by all prescribers. A large variation in the rigor of training and knowledge of AMR combined with high workload, poor or limited accessibility to the infectious disease specialists, and nonavailability/non-utilization of point-of-care diagnostic tests further contributes to misuse of

Table 1 The major factors for irresponsible antimicrobial use

Patient related factors	Prescriber related factors	Drug related	Health system related factors
• Anxiety to get well soon • Misconceptions about magic power of antimicrobials • Social, economic and behavioral factors • Self-medication • Non compliance • Not completing prescribed course of antimicrobials • Poor adherence of dosage regimen • Saving antimicrobials for later use	• Informal prescribers • Economic concern due to patient loss • Lack of knowledge and training • Diagnostic uncertainty • Lack of opportunity for patient follow-up • Cognitive dissonance (i.e., knowledge but failure to act on it) • Pressure from pharmaceutical companies • Misleading or erroneous advertising	• Non adherence to regulatory requirements • Over the counter availability • Irrational fixed dose combination • Wrong compounds • Counterfeit and substandard drug • Sub-optimum storage conditions	• Governance and leadership • Overcrowding • Inadequately equipped diagnostic laboratories • Cost-saving pressure to substitute therapy for diagnostic tests • Sub optimum insertion devices • Poor infection prevention and control • Inadequate vaccination

antimicrobials. Very often the nature and severity of the illness, diagnostic uncertainty, high workload, difficulty in follow-up, availability, number of choices, defensive practice, and economic considerations are the deciding factors in real-life setting. A higher antimicrobial use is observed in winter months coinciding with influenza season both for appropriate (e.g., to treat secondary bacterial infections) and inappropriate (e.g., to treat viral infections caused by influenza or other viruses) indications. During COVID-19 pandemic, overuse of antimicrobials has been reported, partly because of concerns regarding bacterial co-infection and misinformation about benefits of antimicrobials for treating COVID-19 patients (Miranda et al., 2020; Beović et al., 2020). Empirical use of broad-spectrum and last-resort antimicrobials also increased in order to improve prognosis in serious illness. A low threshold for prescribing; selection of wrong choice, dose, route of administration, and duration for empirical use; delayed initiation of treatment when indicated; failure to de-escalate after 48–72 hours once the patient stabilizes to narrower-spectrum antimicrobials; and switch from parenteral to oral route due to a lack of awareness of the standard treatment guidelines are among the major prescribing errors (Ayukekbong et al., 2017). Often inappropriate, AMU has been reported in the peri-surgical prophylaxis for prevention of surgical site infections in the form of wrong timing of the first antimicrobial dose, choice, route of administration, and excessive duration despite clear established peri-surgical prophylaxis guidelines (Miliani et al., 2009).

Surveillance data on AMU is limited worldwide, but emerging evidence suggests that overuse and misuse are higher in certain clinical settings, clinical indications, patient demographics, and LMICs (Farooqui et al., 2018; CDDEP, 2021; CDDEP et al., 2021). Despite antimicrobials being prescription drugs, they can be easily accessed over the counter without a valid prescription because of poor enforcement of the laws (Morgan et al., 2011). As a result, patients bypass clinicians and self-medicate by directly purchasing it from the pharmacy and often do not take in adequate doses or complete the entire antimicrobial course. Moreover, private sector healthcare providers, pharmacies, and informal prescribers may advocate prolonged or shorter regimen for economic, rather than clinical, reasons. A higher AMU and misuse are also reported in the primary care setting and acute care wards and for clinicians treating neonatal and pediatric patients or specific infections or syndromes (CDDEP, 2021; CDDEP et al., 2021).

4 Relationship Between Use and Resistance

The development of AMR is a natural biological event but is expedited by the selection pressure exerted by excessive use of antimicrobials (Barboss & Levy, 2000; WHO, 2012; Holmes et al., 2015). Both excessive use and underuse (even when these are indicated) are responsible for the emergence of AMR. Quantum of antimicrobials used and the prescribing practices contribute to the selection of AMR strains.

Several studies conducted across many HICs and LMICs at individual level, healthcare facility level, community level, and country level have found a direct correlation with the amount of antimicrobial use and the development of AMR across spatial and temporal scales (Bronzwaer et al., 2002; Goossens et al., 2005, Goossens, 2009; Costelloe et al., 2010; Bell et al., 2014; Olesen et al., 2018).

Inadequate treatment resulting from limited access, substandard, or falsified agents with poor affordability to complete the full course of treatment also contributes to the emergence of drug-resistant pathogens (Cockburn et al., 2005). In LMICs, treatable infectious diseases currently cause five million deaths due to the lack of access to antimicrobials (CDDEP, 2021).

India and China are among the highest AMR prevalence countries in the world with alarming rates of resistance to almost all the microbes and also to the newer and more expensive drugs (Van Boeckel et al., 2014). Understanding the factors driving AMR in countries with *access* vs. *excess* paradox is highly challenging. Also, deciphering the complex interplay between a myriad of pathogens and antimicrobials in itself is extremely challenging as one microorganism may be resistant to one antimicrobial and susceptible to another and vice versa. To overcome this, the Drug Resistance Index (DRI) has been proposed to measure the average effectiveness of a group of antimicrobials used to treat a given bacterial infection (Klein et al., 2019). The DRI is a composite measure that combines the ability of antibiotics to treat infections with the extent of their use in clinical practice (CDDEP, 2021). It provides a better insight into the complex relationship between antimicrobial use and underuse with AMR in the context of geographical variation and underlying factors (Klein et al., 2020). Some studies identified that HICs like Sweden, Canada, Norway, Finland, and Denmark had the lowest DRIs (despite high use) vs. LMICs which had the highest DRI, reflecting the very low effectiveness of antimicrobial therapy in these countries (Klein et al., 2020).

5 Surveillance of Consumption/Use

Antimicrobial stewardship (AMS) to optimize AMU (reduce the unnecessary consumption with appropriate usage when indicated) can bring back susceptibility among microorganisms over several years (WHO, 2019b). It is imperative that before initiation of any AMS activities, the magnitude of antimicrobial use is measured and analyzed to understand the causes of irrational prescribing practices followed by designing of interventions to rationalize and reduce the AMU. Thus, surveillance for monitoring consumption/use is critical for implementation of a sustainable AMS program.

The data on consumption/use allows knowing the extent of the AMU in countries, regions, healthcare facilities, and departments within facilities to understand the amount and trends of antimicrobial use to guide interventions to regulate the use of antimicrobials and save cost. The AMU data can serve as a benchmark for risk-adjusted inter- and intra-facility use and to understand the quality of use and determinants leading to antimicrobial misuse/overuse at the population/patient

level; to identify the targets for developing strategies/interventions to stop its misuse; to motivate healthcare providers; and to monitor the effect of interventions. Besides, surveillance data is essential to establish epidemiological relationships between antimicrobial use and resistance (WHO, 2018).

The importance of data collection on antimicrobial consumption and analysis was realized by the European Union much before the rollout of the WHO Global Action Plan to combat AMR in 2015 (European Centre for Disease Prevention and Control, 2013). A regional surveillance system, namely, European Surveillance of Antimicrobial Consumption Network (ESAC-Net), was established in 2001 in the European Union/European Economic Area (EU/EEA), which was subsequently expanded to the rest of Europe. Currently, the WHO is providing ongoing support to improve and expand the network with facilitation in analysis and data sharing (ECDC, 2014; WHO, 2017a).

To capture standardized data for consumption, the WHO initiated the global program on surveillance of antimicrobial consumption for LMICs. A common methodology for the measurement of antimicrobial consumption was developed in 2016, based on existing international monitoring systems as reference, such as ESAC-Net and the WHO (ECDC, 2014; WHO, 2017a). The WHO started data collection on consumption for 2014–2016 in selected countries, followed by other countries across the world (WHO, 2017b).

6 Consumption and Use

Antimicrobial consumption (AMC) refers to aggregated data of antimicrobials procured/used at population level (country/hospital/clinical area), whereas antimicrobial use data is patient-level data which is based on indication, treatment regimen, and patient characteristics. AMC data provides the total quantum of antimicrobials consumed and trends for comparison between countries, state, facilities, and wards, whereas AMU data allows assessment of appropriateness of therapy in the context of diagnosis, suspected pathogens, and patient outcomes (WHO, 2017b), though AMC and AMU are two interrelated entities with subtle differences but are often used interchangeably (WHO, 2017b). AMC data is relatively easily accessible and can be collected quickly in comparison with patient-level data which is quite laborious and time-consuming especially in the absence of computerized databases to allow data retrieval.

Both these data are important and serve specific purposes and complement each other. Capturing consumption can be a starting point for resource-limited settings. This consumption data can be used as a proxy for AMU at the patient level.

7 AMU Surveillance Methodologies

Several methods have been employed to measure the magnitude of AMU, but none of the methods is a complete package to garner all the information required (Morris, 2014). The choice of the methodology depends upon the purpose of data collection,

specific objectives of the study, availability of manpower, technical expertise, and infrastructure. Similarly, strategy for data collection can be retrospective (backward), prospective (forward), or concurrent (during treatment) depending on the objective, feasibility in terms of available resources, and time to collect data. It is important to collect data randomly irrespective of the method used in order to draw valid conclusions and generalize results (Sharma, 2017).

The data for consumption/use can be collected quantitatively or qualitatively. Countries or hospitals should define their problems and find methods which are best suited to describe the antimicrobial consumption and link to resistance data (Morris, 2014). Quantitative methods allow estimation of the total volume of antimicrobials consumed/used in particular settings and measurement of any particular antimicrobial used and their trends. These include aggregate data methods, indicator studies, prescription audits, and point prevalence surveys and are useful to give an overall picture of the problem areas.

Qualitative methods allow investigation into the cause of the problem of inappropriate antimicrobial use and include focused discussions, detailed interview, structured observation, and surveys. The different methods to capture quantitative and qualitative data highlighting basic principles, advantages, and disadvantages are discussed below.

7.1 Quantitative Methods

7.1.1 Aggregate Data Methods

Aggregate data gives an overview of the consumption and can be collected relatively with ease from records (WHO, 2017b). Aggregate data on consumption is useful as it provides a broad picture on the quantities of antimicrobials used, the most frequently and infrequently used antimicrobials, and per capita use of specific products at the national, regional, facility, clinical area, or unit level (WHO, 2017b). The consumption can also be matched with the expected consumption based on the morbidity records and is also useful to manage hospital formulary by identifying the most expensive antimicrobials, utilization of Watch or Reserve antimicrobials, etc. Some of the aggregate data methods commonly used for capturing AMU are briefly discussed below.

ABC Analysis

ABC analysis is a selective inventory management tool in which items are classified on the basis of the healthcare cost consumed based on Pareto's 80/20 rule. *A* items are those which consume the maximum budget (either as they are high-cost or high-volume items), and control of these items has a great potential of cost saving with reduced irrational use. *B* items incur a moderate cost, and their use needs to be carefully watched. *C* items are low-cost items and constitute the majority of inventory and do not warrant tight controlling. ABC tool helps in identifying the costliest medicines, those consuming a major proportion of the budget, and designing strategies to rationalize their use (Sharma, et al., 2020). Since antimicrobials usually

consume considerable budget, the ABC principle can be used to identify as to which antimicrobial needs greater attention for control (Anand et al., 2013). Access group antimicrobials are usually low-cost items whose supply must be uninterrupted, whereas tighter control is required for purchase and use of high-cost/high-volume Watch and Reserve group antimicrobials. Similarly, newer-generation broad-spectrum antimicrobials are expensive, and regulating their access can limit their inappropriate use as well as significant cost saving. However, ABC analysis has its limitations. It cannot be used for benchmarking between countries or hospitals due to variability in costs. Also, it does not allow comparison of efficacy between antimicrobials.

Vital, Essential, and Nonessential/Desirable (VEN/D) Analysis

Vital, Essential, and Nonessential/Desirable (VEN (D)) analysis allows for prioritizing selection, procurement, and use of antimicrobials based on their necessity as vital (life-saving or crucial), essential (required for certain significant number of diseases), and nonessential or desirable categories (minor or self-limited illnesses). The VEN analysis must be based on the level of healthcare keeping in view the epidemiology and infectious disease morbidity statistics. A vital for a super-specialty hospital may be nonessential for a primary healthcare center and vice versa.

Using ABC analysis alone may leave out some low-cost and high-consumption antimicrobials which may be essential or lifesaving as they do not appear in category A. Similarly, VEN analysis alone also carries a risk of some nonessential but expensive drugs to get included as category A (Anand et al., 2013). Therefore, a combination matrix of ABC and VEN could be used to control the supply or usage of Group AD items requiring stringent control of critically important antimicrobials or by finding alternatives (such as replacing *Reserve* antimicrobials among A category with *Watch* antimicrobials; switching from broad-spectrum to narrow-spectrum antimicrobials; switching from *Watch* group antimicrobials to *Access* group antimicrobials) while ensuring availability of V and E items (such as *Access* antimicrobials) (Mathew et al., 2016).

Defined Daily Dose

Defined daily dose (DDD) is a WHO standardized reference methodology for measuring the consumption to allow benchmarking across countries, hospitals, and wards (WHO, 2017b). DDD is the assumed average maintenance dose per day for an antimicrobial used for its main indication in adult patients. DDD is defined globally for each medicine by the WHO Collaborating Centre for Drug Statistics in Oslo, Norway, and is regularly updated. The DDD reflects global dosage, and a single DDD is assigned per ATC code irrespective of genetic variations and administration routes (oral/parenteral).

DDD is most frequently expressed as DDD per 1,000 inhabitants per day for total antimicrobial consumption and gives general utilization for the total population (country, hospital). For hospital in-patient use, the WHO recommends DDDs per 100 bed-days for measuring antimicrobial use, and the difference in number of beds between hospitals is adjusted by using the occupancy rate (WHO, 2021). The DDD

utilizes consideration of the WHO Anatomical Therapeutic Chemical (ATC) classification system. User-friendly tools/software are available for calculation of DDD by entering the name of antimicrobial, pack size, and strength in grams (WHO, 2021). However, manual calculation using Microsoft Excel can also be done for calculating DDD.

DDD allows for comparing trends in the utilization of antimicrobials between countries and population groups as it does not take into consideration price, package size, and formulations (Muller et al., 2006). The DDD method elucidates the quantitative and ecological relationship between AMU and resistance (Goosen, 2009). However, it does not give an idea of the intensity of AMU in a particular patient and cannot differentiate between few patients prescribed with many antimicrobials and many patients getting few antimicrobials nor between antimicrobials used in some long-stay patients vs. many short-stay patients (Berrington, 2010). Also, this method has not been standardized to measure antimicrobial use in the pediatric population (Morris, 2014).

7.1.2 Prescribed Daily Dose

The prescribed daily dose (PDD) is the average dose prescribed as determined by a random sample of prescriptions and medical or pharmacy records. The PDD gives the average daily dose prescribed for a particular disease. The PDD varies according to the disease, clinical spectrum, patient demographics, pharmacokinetic/pharmacodynamic considerations, and national treatment guidelines. The PDDs may vary from one setting to another depending upon demography and ethnic differences and thus are not suitable for making national and international comparisons. DDD and PDD do not correspond frequently, and PDD is generally higher than DDD for most of the antimicrobial treatments (Muller et al., 2006).

7.1.3 Days of Therapy

Days of therapy (DOT) are the total number of days any antimicrobial agent is administered to individual patients irrespective of the dose or formulation (CDC, 2021). DOT is more clinically relevant compared to DDDs as it tells the actual treatment received vis-a-vis hypothetical consumption measured by DDD. DOT/patient days can also be used to benchmark consumption within and between institutions and can be used for the pediatric population (including neonates) unlike DDD.

The disadvantages with the use of DOT as a metric is that it only reflects antimicrobial use and cannot distinguish between single dose, multiple dose, or continuous infusion. For example, use of single antimicrobial for 14 days and use of two broad-spectrum antimicrobials in any dosage for 7 days both contribute to 14 DOTs (Morris, 2014).

7.1.4 Targeted Antibiotics (Access, Watch, Reserve Tool)

Antimicrobial stewardship (AMS) is much more required for some antibiotics which are more expensive, more toxic, broad spectrum, and critically important for human use. Reserving these targeted antibiotics for use for correct indications can bring

reduction in AMU. The WHO advocates "AWaRe" to promote the usage of narrow-spectrum antibiotics while reserving broad-spectrum antibiotics for "hardest to treat" infections (WHO, 2019c).

"AWaRe" tool classifies antibiotics into three groups:

1. The Access group consisting of narrow-spectrum antibiotics for common infections/specified infectious syndrome which should be easily accessible. It includes 48 antibiotics such as amoxicillin, cloxacillin, amoxicillin-clavulanic acid, etc. (WHO, 2019c).
2. The Watch group comprises broader-spectrum antibiotics which have potential for development of resistance. It includes 110 antibiotics such as ciprofloxacin, azithromycin, vancomycin, teicoplanin, etc. (WHO, 2019c).
3. The Reserve group consists of last-resort antimicrobials for targeted use in multidrug-resistant infections. It includes 22 antibiotics, viz., oxazolidinones, glycylcyclines, carbapenems, polymyxins, etc. (WHO, 2019c).

Absolute antimicrobial use can be measured by using total consumption data, and then relative use can be determined according to "AWaRe" categories. Patterns of antimicrobial use can be further studied by drug utilization percentage (i.e., number of antimicrobials that constitute 90% of the total use); proportion of antibiotic use (DDDs per 1000 admissions) in each "AWaRe" category over time; the ratio of *Access to Watch* antibiotics; etc. This may allow for designing AMS interventions to reduce the use of *Watch* or *Reserve* group of antibiotics as appropriate to the facility.

Adopting the "AWaRe" categorization also leads to improving availability and accessibility to antibiotics on the *Access* list and reducing the use of those on Watch and Reserve lists. The "AWaRe" classification provides an opportunity to set targets for measuring and reporting progress but may lead to shifting of selection pressure to cheaper agents. The countries should strive to reach a 60% target for antibiotic consumption from the essential category (WHO, 2019c).

One of the limitations of "AWaRe" classification is that some of the antibiotics have not been classified into this category as these are not listed on the WHO Essential Medicine List. There is a need to develop and evaluate pediatric AMS programs based on the "AWaRe" index (Hsia et al., 2019).

7.1.5 Indicator Study Methods

Indicator study methods allow us to explore the factors which drive AMU decisions. The WHO has developed "core drug use indicators" to measure performance or assess drug use practices in various settings over time in three related areas of prescribing practices, patient care, and facility-specific factors (WHO, 1993). The core drug use indicators are objective measures to describe the drug use situation in a country, region, or individual health facility. The core drug use indicators and other commonly used complimentary indicators are listed in Table 2.

These drugs use indicators that are highly specific, consistent, reliable, and representative and can be easily measured without the requirement of specially trained data collectors. Percent encounters with antimicrobial data provide

Table 2 Drug use indicators

Core drug use indicators	Complimentary indicators
Prescribing indicators: • Average number of drugs per encounter • Percentage of drugs prescribed by generic name • Percentage of encounters with an antimicrobial prescribed • Percentage of encounters with an injection prescribed • Percentage of drugs prescribed from Essential Medicines List or formulary	***Complementary drug use indicators*:** • Percentage of patients treated without drugs • Average drug cost per encounter • Percentage of drug cost spent on antimicrobials • Percentage of drug cost spent on injections • Percentage of prescriptions in accordance with treatment guidelines • Percentage of surgical patients who receive appropriate surgical prophylaxis • Number of antimicrobial sensitivity tests reported per hospital admission • Percentage of cases of malaria treated with recommended antimicrobials • Percentage of cases of diarrhea treated with oral rehydration therapy • Percentage of patients receiving medicines without prescription
Patient care indicators: • Average consultation time • Average dispensing time • Percentage of drugs actually dispensed • Percentage of drugs adequately labeled • Patients' knowledge of correct doses	
Facility indicators: • Availability of Essential Medicines List or formulary to practitioners • Availability of standard treatment guidelines • Availability of key drugs	-

Adapted from: World Health Organization (1993). How to investigate drug use in health facilities Selected drug use indicators. WHO/DAP/93.1

information about problem areas in medicine use at facility level and prescriber level and to evaluate the impact of interventions for corrective actions. These indicators are indicative of drug use problem only and are influenced by prescriber type and the disease pattern. These are most useful at primary healthcare facilities and to monitor trends over time. Encounters with antimicrobials indicate the extent of use problem only as reference value or the yardstick for antimicrobial use for a facility type or prescriber type and may vary depending on the clinical case mix presenting with infectious diseases.

These indicators do not provide sufficient information about drug appropriateness or the exact nature of the drug use problem as diagnosis is not considered. Further, drug use is influenced by complex interplay of factors. Core drug use indicators along with the morbidity pattern in a given setting can be used for developing and testing implementation of therapeutic guidelines for treatment of the various disease entities.

7.1.6 Prescription Audit

Prescription audit aids in analyzing the adequacy of the clinical prescription based on specific diagnosis as the number and type of antimicrobials prescribed, their dose, route of administration, timing of administration, etc. (Zhen et al., 2018). These audits allow to study the determinants of prescription like influence of patient

demand, industry interference (pressure from medical representatives), publicity campaigns, prevalent infectious diseases, adherence to standard treatment guidelines (such as use of ORS in diarrhea), and prescriptions for contraindicated or banned drugs.

7.1.7 Point Prevalence Survey

The WHO point prevalence survey (PPS) methodology is an adaptation of the EU and the US CDC protocol for healthcare-associated infections and AMU (WHO, 2019d). The PPS is a practical surveillance tool that reflects on the quality of antimicrobials prescribed. This is cross-sectional data collection method gathering information from patients' chart review in a short span of time (preferably 1 day, a few days up to weeks, may be a month for large national surveys) across the whole hospital (Versporten et al., 2015). The PPS can be repeated after a time interval to monitor trends and assess the impact of interventions. It is a practical alternative to continuous data collection which may not be possible due to the high workload and resource limitations.

The PPS allows for selection of variables (core and optional) at the country level, hospital level, and patient level. Selection of same variables across countries and hospitals allows for better comparability and interpretation of results (WHO, 2019d). Hospitals and countries may also include additional variables (e.g., microbiology results) to improve the understanding of antimicrobial use in hospitals.

By applying the PPS, it is possible to:

- Identify differences among prescribing rates between hospitals, hospital departments, regions, and countries in hospitalized patients.
- Determine variation in antimicrobials, dose, and indication across locations.
- Understand the quality of antimicrobial use, and identify targets for improvement.
- Assess the implementation of treatment guidelines (if indication for treatment available).
- Plan on interventions to promote stewardship.
- Evaluate the effectiveness of interventions through repeated surveys.

The major limitation of the PPS is that information on antimicrobial prescribing is collected from cross-section of all patients hospitalized for infectious disease management irrespective of their being on antimicrobial treatment at the time of data collection.

7.2 Qualitative Methods

Qualitative data is useful to determine the appropriateness of AMU and links antimicrobial usage to reasons (indications) for prescribing at a particular patient or community level. Several cultural and social determinants have been described as barriers to appropriate use such as patient-doctor relationship, perception of the

problem (consulting time, counseling), time constraint due to high workload (explaining antimicrobials prescribed is not necessary as it is time-consuming and unrewarding, decision fatigue, want to appease patient), treatment characteristics (frequency of drug administration), attitudes (perceived risk, fear, anxiety, patient demand or pressure, expecting antimicrobials especially in ambulatory setting and pediatrics), access to treatment (nonavailability of a medicine and patients' direct costs), characteristics and severity of the illness for which the antimicrobial was prescribed (severity at presentation and duration of symptoms), and knowledge (regarding illness and its treatment) (Krockow et al., 2019). Also, when developing any quality intervention, it is important to understand the attitudes, motivations, and intentions of those behaviors determining antimicrobial use as well as local social and environmental context. Qualitative studies in the community provide an understanding of the underlying issues and context of antimicrobial misuse as patient is an important decision-maker for use of antimicrobials. These qualitative methods help to describe the extent and variability in usage and to identify problems deserving more detailed studies. If therapy is identified to be inappropriate, interventions are designed to optimize antimicrobial therapy. Understanding of the social dynamics also helps in characterizing the optimal way of doing stewardship.

8 Conclusions

There is a general trend of rising AMC globally. AMC is directly related to the emergence of AMR. The variability in AMR within and across countries depends on the magnitude and patterns of AMU which is influenced by several socioeconomic, prescriber-related, regulatory, and system-related factors. Controlling global AMC is essential to reduce the menace of rising AMR. To rationalize AMU, it is essential to measure and compare consumption over time and understand drivers for excessive use, particularly the last-resort and *Watch* group antimicrobials.

Trends in AMU and AMR are being monitored in several HICs in humans and livestock, but data are scarce from LMICs. Time series analysis of AMC patterns across all settings and countries could aid in decisions to optimize antimicrobial prescribing and minimizing AMR. For this to be possible, the data must be collected using appropriate indicators, standardized methodologies, and measuring units using adequate sample size.

The choice of indicators to quantify AMU must take into consideration specific objectives of study, level of healthcare and resources, time available, etc. Stepwise approach to capture AMU data is generally recommended as no single indicator is adequate to address all aspects of AMU (Patel et al., 2019). One possible way is to start with capturing aggregate data of consumption at a population/facility level to identify broad issues followed by individual-level data collection and by detailed investigations using "qualitative methods." The impact of interventions can also be evaluated by using these tools.

9 Glossary

AMC	Antimicrobial consumption
AMR	Antimicrobial resistance
AMU	Antimicrobial use
AWaRe	Access, Watch, Reserve
DDD	Defined daily dose
DoT	Days of therapy
HICs	High-income countries
LMICs	Low- to middle-income countries
PDD	Prescribed daily dose
PPS	Point Prevalence Survey
VEN (D)	Vital, Essential, Nonessential (Desirable)
WHO	World Health Organization

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