Pharmaceutical Sciences Asia

Pharm Sci Asia 2024; 51(4), 301-313

DOI:10.29090/psa.2024.04.24.AP0730

Research Article

Measurement of DDD and DOT metrics for optimizing antimicrobial surveillance in two tertiary hospitals in Viet Nam: A four-year retrospective study

Nhien Phan-thuy Nguyen[1], Quynh Thuy Truong[2], Thao Phuong Huynh[2], Hien Thi-thu Pham[3], Thanh Dinh Le[4], Yen Thi-hai Nguyen[1], Nga Thi-quynh Nguyen[1,*]

1 Department of Pharmaceutical Administration, Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam
2 Department of Pharmacy, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam
3 Department of Pharmacy, Thong Nhat Hospital, Ho Chi Minh City, Vietnam
4 Board of Directors, Thong Nhat Hospital, Ho Chi Minh City, Vietnam

ABSTRACT

Monitoring antimicrobial consumption is essential for evaluating antibiotic stewardship programs and controlling resistance. In Vietnam, Defined Daily Dose (DDD) is prioritized over Day of Therapy (DOT) for antimicrobial surveillance due to resource constraints and hospital data retrieval challenges. However, compared to DOT, DDD has been criticized due to its unrepresentativeness when relying on pre-defined values and undefined in pediatric patients. This study aimed to compare DDD and DOT metrics of antimicrobials for determining the optimal metric for resource allocation. We retrospectively analyzed clinical and administrative data of inpatients receiving antimicrobials at two tertiary hospitals from 01/2017 to 12/2020. Our primary outcome was the differences between antimicrobial use measured by DDDs per 1000 patient-days (DDD/1000PDs) and DOTs per 1000 patient-days (DOT/1000PDs) across periods and age-specific groups. We assessed the relationship between DDD- and DOT-based metrics over time using linear regression. Cohen's d was used to evaluate the standardized mean differences between DDDs and DOTs among pediatric and adult inpatients. Two hospitals recorded 1011.68 and 1036.76 DDD/1000PDs, exceeding DOT estimates (920.87 and 838.44 DOT/1000PDs, respectively). DDD- and DOT- metrics showed significant linear relationships for most antimicrobials, except for cefuroxime, ceftriaxone, and linezolid. DDD/1000PDs of fluoroquinolone use surpassed DOT/1000PDs ($p < 0.001$), indicating the administered daily doses often greater than the DDD value assigned by the World Health Organization (WHO-DDD). Carbapenem use showed comparable results between DOT and DDD because the daily dose aligned with WHO-DDD and these antibiotics were mainly used in adult inpatients. Pediatric and adult inpatients displayed DDD and DOT differences, particularly in glycopeptides, with a small effect size of d=0.18 in children and a large one of d=0.96 in adults. We suggest using DDD to measure the consumption of last-resort antibiotics efficiently. Additionally, DOT should be prioritized to prevent overestimating consumption levels in frequently used antimicrobial groups like fluoroquinolones.

Keywords:
Antimicrobial consumption, Defined Daily Dose, Day of Therapy, DDD, DOT, Vietnam

1. INTRODUCTION

The discovery of antibiotics in the 1940s has increased the average life expectancy and revolutionized healthcare, paving the way for medical advances in treating infectious diseases and modern clinical procedures, including organ transplantation, cancer treatment, and open surgery[1].

***Corresponding author:**
* Nga Thi-quynh Nguyen Email: nguyenthiquynhnga@ump.edu.vn

However, the inappropriate use of antibiotics has triggered the emergence of resistant strains, which create selective pressure for future usage of antibiotics, as well as high healthcare costs, morbidity, and mortality[2]. By 2050, unless we strengthen the prominent policy plans and initiatives, it is expected that there will be an average of 10 million deaths annually due to antibiotic resistance, equivalent to one death every 3 seconds from one resistant infection[3]. Therefore, implementing antibiotic stewardship programs (ASP) for optimizing antibiotic usage is essential, especially in the inpatient setting where the risk of the emergence and spread of bacterial resistance is sharply accelerated, along with nosocomial pathogens reported with the highest rates of resistance[4,5]. One of the main pillars of an ASP is to monitor antibiotic consumption and use this information to evaluate targeted ASP interventions as well as provide recommendations for limiting antibiotic misuse[6].

Antibiotic consumption is often quantified using a ratio, where the numerator reflecting antibiotic usage per defined denominator (e.g., patient days, admissions, discharges) to standardize for the differences in hospital census and allow for comparisons within the same setting or other settings over time[7]. Two commonly utilized numerator metrics include (1) DDD (Defined Daily Dose) and (2) DOT (Day of Therapy)[8,9]. According to the World Health Organization (WHO), the Defined Daily Dose (DDD) represents the assumed average daily maintenance dosage for a drug when utilized for its primary indication in adults[7]. Meanwhile, as the Centers for Disease Control and Prevention (CDC) documented, one DOT is the administration of a specific antibiotic agent to a patient, irrespective of the dose, on a given day[10]. Each metric has its own set of strengths and weaknesses. While DDD can be computed from various data sources like inpatient discharges or hospital billing records, extracting the DOT metric depends solely on patient-level prescription data, posing challenges in estimating antibiotic consumption at healthcare facilities having limited information technology capabilities. However, compared to DOT, DDD has been criticized due to its unrepresentativeness when relying on pre-defined values and undefined in some populations, especially pediatric patients and individuals with impaired liver and kidney function[8,9]

In Vietnam, 47% of 655 hospitals have implemented ASPs since the introduction of the Guideline for Implementing ASP in Hospitals (Decision 772) in March 2016, followed by the enactment of new legislation for implementing an ASP (Decision 5631) in December 2020 by the Ministry of Health (MoH)[11]. However, there is still no official antibiotic usage surveillance system in hospital settings, and each healthcare facility has to submit annual reports on these data to the Ministry of Health (MoH) without sharing them with stakeholders, making it difficult to measure the overall performance of current integrated ASP activities and develop evidence-informed policy from the policymaker perspective[12]. Limited resources and inadequate information technology (IT) infrastructure were two major barriers to constructing antibiotic consumption surveillance[13]. Besides, technological limitations often prevent the measurement of DOTs which is required patient-level prescription data in most healthcare facilities. Therefore, the current landscape involves a mixture of both metrics, with DDD prioritizing DOT due to resource constraints and hospital data retrieval challenges[14]

We hypothesize that, given the similarities between DDD and DOT estimates across periods and age-specific groups, the DDD method can be a good alternative to the DOT method to quantify antibiotic use in most hospitals with limited resources and collected in the data form for the first release of antibiotic usage surveillance system. We conducted a pilot study in two tertiary hospitals in Ho Chi Minh City to test this hypothesis as these two hospitals have had strong health information system to support the ASP activities such as making decisions for support and review, extracting patient-level data for monitoring antibiotic usages as well as the early implementation of antibiotic stewardship program.

We ultimately aimed to compare DDD and DOT metrics to determine the optimal metric for measuring antibiotic consumption levels. Our specific objectives included: (1) estimating antibiotic consumption by DOTs per 1000 patient-days (DOT/1000PDs) and DDDs per 1000 patient-days (DDD/1000PDs), (2) assessing the linear relationship between DDDs and DOTs by months, (3) comparing antibiotic use metrics between children and adults.

2. MATERIALS AND METHODS

2.1. Study settings and design

This retrospective observational study was conducted at the Hospital for Tropical Diseases and Thong Nhat Hospital from 2017 to 2020. Hospital for Tropical Diseases has been a 660-bed tertiary hospital specializing in tropical infectious diseases for patients in southern Vietnam, with 19 wards, two intensive care units (ICU), and one emergency department. Thong Nhat Hospital has been known as the largest geriatric national hospitals in southern Vietnam, with a capacity of 1200 beds. These hospitals have adopted the ASP guidance on monitoring antibiotic use with strong IT capabilities since April 2016 and July 2017 respectively, as soon as Decision 772 of the Vietnamese Ministry of Health was released (March 2016)[15,16].

The two hospitals involved in the study were identified as Hospital 1 and Hospital 2 without indicating any specific order to ensure anonymity in the data.

This study explored the differences between antimicrobial use measured by DDD/1000PDsand DOT/1000PDs via two main factors: periods and age-specific groups. Regarding the time factor, as the WHO adopted new DDD values of seven antibiotics in 2019, our study examined the linear relationship between monthly DDD/1000PDs and DOT/1000PDs whether the WHO's 2019 DDD updates impacted consumption measurement. Furthermore, we compared antibiotic consumption using DDD/1000PDs and DOT/1000PDs among pediatric and adult inpatients to identify considerations for DDD measurement in this special population.

2.2. Data source and study population

We obtained antibiotic consumption data from inpatient electronic medical records for patients hospitalized at two hospitals between January 1, 2017, and December 31, 2020. We included all inpatients using systemic antibiotics (Anatomical Therapeutic Chemical (ATC) code "J01") during hospitalization with antibiotic treatment time ≥ 72 hours. Patients who only used topical antibiotic therapies (i.e., eye ointments and ear drops), indicated for surgical treatments, or had missing/incorrect information related to treatment (e.g., missing data related to admission and discharge dates or timing of administration, the administration time with numbers of drugs less than 0[i]) were excluded from the analysis. In this study, we also included the pediatric inpatients to provide a thorough overview of antibiotic inpatient use in Vietnamese hospitals.

Information retrieval from electronic medical records could be classified into three main groups, including demographic information (e.g., age, gender, date of hospitalization and discharge, admission wards), drug information (e.g., the generic name of each antibiotic drug, ATC code, dosage form, unit of measurement, the route of administration, the time of administration, the total grams of antibiotic dispensed, the number of doses), clinical outcomes (infection episodes, treatment outcomes and length of stays). We identified treatment outcomes based on the classification recorded in the data. The treatment outcome classification was determined by clinical evaluations conducted by physicians with five levels (Recovered, Improved, Unchanged, Worsen, and Deceased).

2.3. Study Outcomes

Our primary outcome was the differences between antimicrobial use measured by DDDs per 1000 patient-days (DDD/1000PDs) and DOTs per 1000 patient-days (DOT/1000PDs) across periods and age-specific groups. DDDs and DOTs were calculated as below:

- Each antibiotic's DDD was calculated separately by dividing the total grams administered by WHO-DDD in grams[9]. All WHO-DDD values were taken from the 2017-2020 version of the ATC Classification system, incorporating the updates from the WHO's 2019 revision of DDDs for seven antibiotics[17,18].

- The DOT metric was equal to the total number of days of all antibiotics regardless of the dose strength, usually calculated for one infection episode[9]. For example, if one patient was administered ceftriaxone 500mg q12hr or ceftriaxone 750mg q24hr, both would represent 1 DOT[9]. Moreover, if this patient received both meropenem and vancomycin, two DOTs were counted.

DDDs and DOTs were then adjusted per 1,000 patient days by dividing these metrics by "patient days" and multiplying by 1,000 to account for variations in the hospital census[19]. The term "patient-days" referred to the total number of days patients were admitted to the hospital[20].

2.4. Statistical analysis

All statistical analyses were carried out by R software, version 4.1.3. For continuous variable, mean and standard deviation were calculated if the data follow a normal distribution, otherwise, continuous variable with non-normal distribution was reported as median (interquartile range [IQR]). Categorical variables were presented as Number (%).

The study assessed continuous variable distributions for normality using the one-sample Kolmogorov-Smirnov test. To compare means between two normally distributed continuous variables, we employed the independent samples Student's t-test. Otherwise, the Mann-Whitney U test and Kruskal-Wallis test were performed to compare means among two and three or more groups for non-normally distributed variables. Categorical variable frequencies were compared with Pearson's $\chi 2$ test (for 2×2 tables) or Fisher's exact test (for low expected values) with a significance level of 0.05.

Quantifying the differences between DOT/1000PDs and DDD/1000PDs

We calculated the difference between mean monthly DDD/1000PDs and DOT/1000PDs of top 13 most prescribed antibiotics in two hospitals by the following formula:

$$\% \text{ difference between DOT/1000PDs and DDD/1000PDs} = \frac{(DDD/1000PDs - DOT/1000PDs)}{DDD/1000PDs} \; x \; 100$$

According to the previous studies, we categorized the differences between DDD/1000PDs and DOT/1000PDs with three magnitude thresholds: "major difference" (≥25%), "moderate difference" (≥5% and <25%), "minor difference" (< 5%)[19,21].

Assessment of the linear relationship between DDD/1000PDs and DOT/1000PDs by months

We decided to include those antibiotics belonged to three commonly used groups or antibiotics requiring priority management in hospitals following the national legislation regarding to management of the antibiotic use in hospitals (Decision No. 5631) to explore the linear relationship between DDDs and DOTs[22]. These antibiotics were also classified as Watch/ Reserve Antibiotics according to the 2023 update of AWaRe Classification[23].

Univariate linear regression model was used to assess the linear relationship between DDD/1000PDs (independent variable) and DOT/1000PDs measurements (dependent variable) of each antibiotic by month. The regression model results included 95% confidence intervals for the slope coefficients. If the 95% confidence interval for the slope coefficient did not encompass 0, it signified a statistically significant relationship between the DOT/1000PDs and DDD/1000PDs, or the observed association between these metrics was unlikely to be attributed to random variation. Adjusted R-squared was applied to indicate the model's goodness-of-fit.

Comparison of antibiotic use metrics between children and adults

This study examined the difference between the DOT/1000PDs and DDD/1000PDs metrics of each antibiotic in two patient groups (pediatric patients (under 18 years old) and adult patients (over 18 years old)) by employing Cohen's d effect size. Cohen's d quantified the effect size by measuring the difference between two group means in terms of the pooled standard deviation[24].

Under the assumption that the two independent groups have roughly equal standard deviations, a positive value of Cohen's d indicated that the mean antibiotic use measured by the DOT method was greater than the mean antibiotic use measured by the DDD method and in reverse. The interpretation of the effect size in absolute terms was referred to three thresholds (0.2 (small), 0.5 (medium) and 0.8 (large)[25]. By Cohen's d effect size, the study can also evaluate the probability of overlapping distributions between DOT/1000PDs and DDD/1000PDs based on the assumption of normal distribution. The higher the value of Cohen's d gained, the lower the probability of overlapping was and vice versa)[26].

3. RESULTS

3.1. Characteristics of study population

Of the 124,438 patients admitted during the study period (January 2017 – December 2020) at the Hospital 1, the percentage of patients using antibiotics accounted for 47.11%. Of these, the percentage of patients receiving antibiotics for at least 72 hours was 87.46% (51,273 inpatients). At the Hospital 2, a total of 49,427 (52.87%) patients out of 93,488 patients admitted during the study period received antibiotics, and 92.26% of them (45,602 inpatients) had an antibiotic treatment time of 72 hours or more. The demographic characteristics of the study population are shown in **Table 1** The majority (59,061, 60.97%) of inpatients enrolled in the study were men. The median age of the patients was 47 years old (IQR: 18 - 69). During the study period, nearly half of the patients (46.32%) at the Hospital 1 were children whereas Hospital 2 primarily served elderly patients with a median age of 66. The rate of patients having one infection episode in the Hospital 1 and Hospital 2 was very high, with 95.81% and 81.33% of patients, respectively. There were statistically significant differences in all demographic characteristics, including gender, age, number of infection episodes, length of stay, and treatment outcomes between the two hospitals ($p < 0.001$).

3.2. Total antibiotic consumption in two hospitals from 2017 to 2020

Table 2 presents the total consumption of antibiotics by antibiotic groups and agents in the study period. The analysis showed that the total antibiotic consumption using the DDD metric from 2017 to 2020 at the two hospitals (1011.68 DDD/1000PDs and 1036.76 DDD/1000PDs, respectively) were higher than when applying the DOT one, specifically up to 8.91% and 19.1% differences between these metrics in Hospitals 1 and 2. Cephalosporins, fluoroquinolones, and penicillins were the most frequently prescribed antibiotic groups. Among the cephalosporin group, third- and second-generation cephalosporins had the highest percentage of use, with 69.4% (213.68 DDD/1000PDs) and 30.5% (93.68 DDD/1000PDs) in the Hospital 1 and 57.0% (188.07 DDD/1000PDs) and 34.8% (114.84 DDD/1000PDs) in the Hospital 2. Glycopeptides showed an alarming consumption pattern with a DDD/1000PDs value of 92.94 (making up 8.97% of total consumption) in Hospital 2.

Table 1. Demographic characteristics of the study population in the study

		Hospital	
Characteristics	**Overall**, N = 96,875	**Hospital 1**, N = 51,273	**Hospital 2**, N = 45,602	**p-value**
Gender				<0.001[a]
Male	59,061 (60.97%)	29,685 (57.90%)	29,376 (64.42%)	
Female	37,814 (39.03%)	21,588 (42.10%)	16,226 (35.58%)	
Age				
Median (Q1- Q3)	47 (18 - 69)	24 (3 - 47)	66 (50 - 79)	<0.001[b]
Children (0-17)	23,935 (24.71%)	23,751 (46.32%)	184 (0.40%)	<0.001[a]
Adults (18-59)	37,521 (38.73%)	20,439 (39.86%)	17,082 (37.46%)	
Elderly (≥ 60)	35,419 (36.56%)	7,083 (13.81%)	28,336 (62.14%)	
Numbers of infection episodes				<0.001[a]
1	86,213 (88.99%)	49,124 (95.81%)	37,089 (81.33%)	
2	9,195 (9.49%)	1,911 (3.73%)	7,284 (15.97%)	
≥ 3	1,467 (1.52%)	238 (0.43%)	1,229 (2.70%)	
Year Of Hospitalization				<0.001[a]
2017	27,488 (28.37%)	13,839 (26.99%)	13,649 (29.93%)	
2018	24,433 (25.22%)	14,339 (27.97%)	10,094 (22.13%)	
2019	25,183 (26.00%)	14,169 (27.63%)	11,014 (24.15%)	
2020	19,771 (20.41%)	8,926 (17.41%)	10,845 (23.78%)	
Length of stays (LOS)				
Median (Q1 - Q3)	8 (5 - 12)	7 (5 - 10)	9 (6 - 15)	<0.001[b]
3 days	5,998 (6.19%)	2,877 (5.61%)	3,121 (6.84%)	<0.001[a]
4-7 days	28,200 (29.11%)	18,922 (36.90%)	9,278 (20.35%)	
8-14 days	42,496 (43.87%)	22,910 (44.68%)	19,586 (42.95%)	
15-29 days	16,615 (17.15%)	5,377 (10.49%)	11,238 (24.64%)	
≥30 days	3,566 (3.68%)	1,187 (2.32%)	2,379 (5.22%)	
Treatment Outcomes				<0.001[a]
Recovered	29,101 (30.04%)	23,870 (46.55%)	5,231 (11.47%)	
Improved	60,062 (62.00%)	21,913 (42.74%)	38,149 (83.66%)	
Unchanged	5,089 (5.25%)	4,259 (8.31%)	830 (1.82%)	
Worsen	2,301 (2.38%)	1,169 (2.28%)	1,132 (2.48%)	
Deceased	322 (0.33%)	62 (0.12%)	260 (0.57%)	

[a] p-value calculation for the Pearson's $\chi 2$ test ; [b] p-value calculation for the Mann-Whitney U test

Table 2. Total antibiotic consumption in two hospitals over four-year period

Antibiotics	**ATC code**	**Adm. R**[a]	**Hospital 1**		**Hospital 2**	
			DDD/ 1000PDs (% of total consumption)	**DOT/1000PDs (% of total consumption)**	**DDD/ 1000PDs (% of total consumption)**	**DOT/1000PDs (% of total consumption)**
Penicillins						
Penicillins with extended spectrum						
Ampicillin	J01CA01	P	1.19 (0.12%)	0.99 (0.11%)		
Amoxicillin	J01CA04	O	0.85 (0.08%)	0.68 (0.07%)	2.40 (0.23%)	1.70 (0.20%)
Piperacillin	J01CA12	P			0.12 (0.01%)	0.15 (0.02%)
Beta-lactamase sensitive penicillins						
Benzylpenicillin	J01CE01	P	1.22 (0.12%)	0.63 (0.07%)		
Phenoxymethylpenicillin	J01CE02	O	0.14 (0.01%)	0.08 (0.01%)		
Beta-lactamase resistant penicillins						
Cloxacillin	J01CF02	O	2.45 (0.24%)	2.77 (0.30%)		
Oxacillin	J01CF04	P	53.26 (5.26%)	16.42 (1.78%)	0.99 (0.10%)	0.58 (0.07%)
		O	4.12 (0.41%)	3.57 (0.39%)		
Combinations of penicillins and beta-lactamase inhibitors						
Ampicillin + sulbactam	J01CR01	P	1.15 (0.11%)	1.10 (0.12%)	3.90 (0.38%)	10.12 (1.21%)
		O	0.01 (0.00%)	0.01 (0.00%)	0.08 (0.01%)	0.05 (0.01%)
Amoxicillin + sulbactam	J01CR02	P			6.05 (0.58%)	7.98 (0.95%)
Amoxicillin + clavulanic acid	J01CR02	P	0.03 (0.00%)	0.03 (0.00%)	2.03 (0.20%)	2.71 (0.32%)
		O	49.35 (4.88%)	73.24 (7.95%)	120.45 (11.62%)	73.28 (8.74%)
Ticarcillin + clavulanic acid	J01CR03	P	0.02 (0.00%)	0.09 (0.01%)	0.73 (0.07%)	1.71 (0.20%)
Piperacillin + tazobactam	J01CR05	P	55.66 (5.50%)	58.64 (6.37%)	15.47 (1.49%)	16.34 (1.95%)
Cephalosporins						
First-generation cephalosporins						
Cefalexin	J01DB01	O	0.26 (0.03%)	36 (0.04%)		
Cefalotin	J01DB03	P			8.53 (0.82%)	6.70 (0.80%)

Table 2. Total antibiotic consumption in two hospitals over four-year period

Antibiotics	ATC code	Adm. R[a]	Hospital 1		Hospital 2	
			DDD/ 1000PDs (% of total consumption)	DOT/1000PDs (% of total consumption)	DDD/ 1000PDs (% of total consumption)	DOT/1000PDs (% of total consumption)
Cefazolin	J01DB04	P			3.77 (0.36%)	4.86 (0.58%)
Second-generation cephalosporins						
Cefoxitin	J01DC01	P			38.64 (3.73%)	72.61 (8.66%)
Cefuroxime	J01DC02	P			8.74 (0.84%)	10.49 (1.25%)
		O	93.59 (9.25%)	95.88 (10.41%)	118.62 (11.44%)	39.22 (4.68%)
Cefaclor	J01DC04	O	0.09 (0.01%)	0.27 (0.03%)	17.57 (1.69%)	14.53 (1.73%)
Cefmetazole	J01DC09	P			4.50 (0.43%)	3.79 (0.45%)
Third-generation cephalosporins						
Cefotaxime	J01DD01	P	0.33 (0.03%)	0.57 (0.06%)	0.38 (0.04%)	0.34 (0.04%)
Ceftazidime	J01DD02	P	4.46 (0.44%)	3.83 (0.42%)	15.30 (1.48%)	14.89 (1.78%)
Ceftriaxone	J01DD04	P	204.53 (20.22%)	204.19 (22.17%)	56.38 (5.44%)	47.45 (5.66%)
Ceftizoxime	J01DD07	P			2.97 (0.29%)	4.60 (0.55%)
Cefixime	J01DD08	O	1.30 (0.13%)	2.15 (0.23%)	0.16 (0.02%)	0.10 (0.01%)
Cefoperazone	J01DD12	P			8.19 (0.79%)	7.74 (0.92%)
Cefpodoxime	J01DD13	O	1.66 (0.16%)	2.23 (0.24%)		
Ceftazidime + avibactam	J01DD52	P	0.02 (0.00%)	0.03 (0.00%)		
Cefoperazone + sulbactam	J01DD62	P	1.08 (0.11%)	3.37 (0.37%)	31.46 (3.03%)	53.95 (6.43%)
Fourth-generation cephalosporins						
Cefepime	J01DE01	P	0.13 (0.01%)	0.19 (0.02%)	7.75 (0.75%)	7.18 (0.86%)
Cefpirome	J01DE02	P			7.07 (0.68%)	10.77 (1.28%)
Fifth-generation cephalosporins						
Ceftolozane + tazobactam	J01DI54	P	0.03 (0.00%)	0.06 (0.01%)		
Carbapenems						
Meropenem	J01DH02	P	23.32 (2.31%)	24.02 (2.61%)	26.31 (2.54%)	24.71 (2.95%)
Ertapenem	J01DH03	P	28.3 (2.80%)	27.88 (3.03%)	7.79 (0.75%)	5.37 (0.64%)
Doripenem	J01DH04	P			5.17 (0.50%)	3.28 (0.39%)
Imipenem + cilastatin	J01DH51	P	56.79 (5.61%)	59.73 (6.49%)	46.7 (4.50%)	54.08 (6.45%)
Aminoglycosides						
Tobramycin	J01GB01	P			0.23 (0.02%)	0.32 (0.04%)
Gentamicin	J01GB03	P	1.10 (0.11%)	1.04 (0.11%)	2.40 (0.23%)	3.51 (0.42%)
Amikacin	J01GB06	P	2.26 (0.22%)	2.68 (0.29%)	22.27 (2.15%)	23.18 (2.76%)
Neltimicin	J01GB07	P			3.58 (0.35%)	4.84 (0.58%)
Phosphonics						
Fosfomycin	J01XX01	P	0.03 (0.00%)	0.03 (0.00%)	10.31 (0.98%)	19.04 (2.27%)
		O	0.10 (0.01%)	0.14 (0.02%)	2.47 (0.26%)	3.69 (0.44%)
Tetracyclines						
Doxycycline	J01AA02	O	9.40 (0.93%)	4.25 (0.46%)	0.05 (0.01%)	0.02 (0.00%)
Tetracycline	J01AA07	O			0.18 (0.02%)	0.09 (0.01%)
Glycylcyclines						
Tigecycline	J01AA12	P			0.86 (0.08%)	0.72 (0.09%)
Macrolides						
Erythromycin	J01FA01	O	4.10 (0.41%)	1.29 (0.14%)		
Spiramycin	J01FA02	O	0.07 (0.01%)	0.20 (0.02%)	0.01 (0.00%)	0.01 (0.00%)
Clarithromycin	J01FA09	O	10.88 (1.08%)	5.14 (0.56%)	9.24 (0.89%)	4.25 (0.51%)
Azithromycin	J01FA10	O	83.22 (8.23%)	83.06 (9.02%)	7.83 (0.75%)	2.70 (0.32%)
Lincosamides						
Clindamycin	J01FF01	P	1.34 (0.13%)	1.49 (0.16%)	1.92 (0.18%)	2.80 (0.33%)
		O	2.56 (0.25%)	2.91 (0.32%)	2.14 (0.21%)	2.57 (0.30%)
Fluoroquinolones						
Ofloxacin	J01MA01	P			0.13 (0.01%)	0.13 (0.02%)
		O	0.33 (0.13%)	0.09 (0.01%)	3.77 (0.36%)	2.77 (0.33%)
Ciprofloxacin	J01MA02	P	2.24 (0.22%)	2.19 (0.24%)	25.80 (2.49%)	28.40 (3.39%)
		O	2.28 (0.23%)	2.45 (0.27%)	24.10 (2.32%)	18.94 (2.26%)
Norfloxacin	J01MA06	O	19.33 (1.91%)	32.94 (3.58%)	0.07 (0.01%)	0.06 (0.01%)
Levofloxacin	J01MA12	P	14.28 (1.41%)	9.69 (1.05%)	61.46 (5.93%)	31.64 (3.77%)
		O	54.05 (5.34%)	31.48 (3.42%)	66.93 (6.46%)	34.50 (4.12%)
Moxifloxacin	J01MA14	P	0.41 (0.04%)	1.40 (0.15%)	51.50 (4.97%)	34.98 (4.17%)
		O	0.52 (0.05%)	0.44 (0.05%)	32.32 (3.12%)	16.07 (1.92%)
Glycopeptides						

Table 2. Total antibiotic consumption in two hospitals over four-year period

Antibiotics	ATC code	Adm. R[a]	Hospital 1		Hospital 2	
			DDD/ 1000PDs (% of total consumption)	DOT/1000PDs (% of total consumption)	DDD/ 1000PDs (% of total consumption)	DOT/1000PDs (% of total consumption)
Teicoplanin	J01XA02	P	1.01 (0.10%)	1.84 (0.20%)	81.56 (7.87%)	30.04 (3.58%)
Vancomycin	J01XA01	P	35.66 (3.52%)	33.83 (3.67%)	11.38 (1.10%)	12.49 (1.49%)
Polymyxins						
Colistin	J01XB01	P	2.48 (0.25%)	6.10 (0.66%)	10.91 (1.02%)	13.52 (1.61%)
Imidazoles						
Metronidazol	J01XD01	P	4.02 (0.41%)	3.40 (0.37%)	5.55 (0.54%)	9.72 (1.16%)
		O	21.53 (2.13%)	41.31 (4.49%)	20.49 (1.98%)	23.92 (2.85%)
Nitrofurans						
Nitrofurantoin	J01XE01	O	6.37 (0.63%)	3.05 (0.33%)		
Oxadiazones						
Linezolid	J01XX08	P	1.95 (0.19%)	1.79 (0.19%)	6.09 (0.59%)	9.45 (1.13%)
		O	1.13 (0.11%)	0.83 (0.09%)	2.34 (0.23%)	1.93 (0.24%)
Combinations of antibacterials						
Spiramycin + metronidazole	J01RA04	O	1.87 (0.18%)	0.87 (0.09%)	0.65 (0.06%)	0.86 (0.10%)
Sulfamethoxazole + trimethoprim	J01EE01	P	0.01 (0.00%)	0.01 (0.00%)		
		O	141.81 (14.02%)	61.9 (6.72%)		
Total			**1011.68 (100%)**	**920.87 (100%)**	**1036.76 (100%)**	**838.44 (100%)**

[a] P: Parenteral Route, O: Oral Route

3.3. Comparison of antibiotic consumptions measured by DDD/1000PDs and DOT/1000PDs for the most frequently prescribed antibiotics in two hospitals

Table 3 summarizes the measurement results by DOT and DDD of the 13 most commonly used antibiotics at two hospitals over four years. At Hospital 1, 5/13 antibiotics showed "major" differences between mean monthly DDD/1000PDs and DOT/1000PDs, in which four antibiotics under the Access Group according to AWaRe classification (metronidazole (by oral route (O)), oxacillin (by parenteral route (P)), sulfamethoxazole + trimethoprim (O), amoxicillin-clavulanic acid (O)). Among six antibiotics that gave "minor" differences in DDD- and DOT- metrics, we could observe that most of the antibiotic groups were prescribed at a specific limited dose 1-2 times a day, such as azithromycin (O) and vancomycin (P). Besides, at Hospital 2, most of the commonly used antibiotics had "major" differences between DDD/1000PDs and DOT/1000PDs (8/13 antibiotics) except meropenem, with "minor" differences between these metrics (4.24%). In addition, 76.9% of antibiotics in Hospital 2 were indicated with daily doses higher than the DDD value provided by WHO. Meanwhile, for antibiotics classified by the Ministry of Health to require priority in management, such as aminoglycosides, carbapenems, the process of prescribing, approving, and dispensing was strictly required, limiting errors in prescribing and minimizing the differences between DOT and DDD (<5%) in both hospitals[22]

Table 3. Comparison of antibiotic consumptions measured by DDD/1000PDs and DOT/1000PDs for the 13 most frequently prescribed antibiotics at two hospitals over 4 years

Antibiotics	Antibiotic Group	Percent-age of usage	DDD/1000PDs Mean (SD)	DOT/1000PDs Mean (SD)	p-Value	% differences between DOT and DDD		WHO DDD (g)	Average daily dose (g/day)
						%	Classifi--cation[a]		
Hospital 1									
Ceftriaxone (P)	Cephalosporins	20.22%	214.34 (24.51)	212.98 (22.09)	<0.001	0.63%	(1)	2	2.003
Sulfamethoxazole + trimethprim (O)	Combinations of antibacterials	14.02%	154.87 (56.89)	67.32 (25.76)	<0.001	56.53%	(3)	4UD[c]	4.483 - 23.132
Cefuroxime (O)	Cephalosporins	9.25%	94.10 (44.90)	95.98 (40.47)	0.170	-2.00%	(1)	0.5	0.488
Azithromycin (O)	Macrolides	8.23%	85.89 (17.89)	84.53 (22.18)	<0.001	1.59%	(1)	0.3	0.301
IMI[b] (P)	Carbapenems	5.61%	60.78 (15.75)	64.03 (18.85)	<0.001	-5.35%	(2)	2	1.901
PTZ[b] (P)	Penicillins	5.50%	62.02 (56.94)	65.44 (60.68)	<0.01	-5.51%	(2)	14	13.289
Oxacillin (P)	Penicillins	5.26%	55.72 (20.60)	17.02 (5.84)	<0.001	69.46%	(3)	2	6.488
Levofloxacin (O)	Fluoroquinolones	5.34%	55.97 (28.40)	32.59 (14.80)	<0.001	41.77%	(3)	0.5	0.859
AMX/CLA[b] (O)	Penicillins	4.88%	49.34 (24.12)	73.73 (36.30)	<0.001	-49.42%	(3)	1.5	1.011
Vancomycin (P)	Glycopeptides	3.52%	38.43 (11.31)	37.35 (10.90)	<0.001	2.81%	(1)	2	2.051
Ertapenem (P)	Carbapenems	2.80%	29.77 (11.01)	29.31 (10.21)	0.236	1.55%	(1)	1	1.015
Meropenem (P)	Carbapenems	2.31%	25.09 (8.06)	25.83 (7.28)	0.352	-2.93%	(1)	2 – 3[d]	2.912
Metronidazol (O)	Imidazoles	2.13%	23.34 (8.20)	44.68 (14.36)	<0.001	-91.39%	(3)	2	1.042
Hospital 2									
AMX/CLA[b] (O)	Penicillins	11.62%	132.46 (30.59)	81.73 (13.96)	<0.001	38.30%	(3)	1.5	2.234
Cefuroxim (O)	Cephalosporins	11.44%	130.29 (72.35)	43.75 (17.72)	<0.001	66.42%	(3)	0.5	1.693
Teicoplanin (P)	Glycopeptides	7.87%	88.69 (112.42)	33.95 (20.81)	<0.001	61.72%	(3)	0.4	1.064
Levofloxacin (O)	Fluoroquinolones	6.46%	77.99 (45.13)	47.66 (33.89)	<0.001	38.89%	(3)	0.5	0.834
Levofloxacin (P)	Fluoroquinolones	5.93%	58.10 (58.53)	48.30 (37.83)	<0.001	16.87%	(2)	0.5	0.607
Ceftriaxone (P)	Cephalosporins	5.44%	60.53 (26.14)	51.62 (24.28)	<0.001	14.72%	(2)	2	2.329
Moxifloxacin (P)	Fluoroquinolones	4.97%	54.88 (34.98)	37.55 (24.04)	<0.001	31.58%	(3)	0.4	0.652
IMI[b] (P)	Carbapenems	4.50%	58.10 (58.53)	48.30 (37.83)	<0.001	-18.11%	(2)	2	1.684
Cefoxitin (P)	Cephalosporins	3.73%	45.10 (28.05)	86.74 (50.89)	<0.001	-92.31%	(3)	6	4.220
Moxifloxacin (O)	Fluoroquinolones	3.12%	39.31 (24.39)	19.38 (10.86)	<0.001	50.69%	(3)	0.4	0.795
CEF/SUL[b] (P)	Cephalosporins	3.03%	34.97 (17.16)	60.60 (28.63)	<0.001	-73.30%	(3)	2	2.284
Meropenem (P)	Carbapenems	2.54%	29.25 (10.56)	28.01 (9.69)	0.189	4.24%	(1)	2 – 3[d]	3.114
Ciprofloxacin (P)	Fluoroquinolones	2.49%	27.93 (8.74)	32.31 (8.38)	0.04	-15.66%	(2)	0.5 - 0.8[d]	0.689

[a] Percentage differences between DDD/1000PDs and DOT/1000PDs were classified into three groups: Group 1 ("minor difference" (< 5%)), Group 2 ("moderate difference" (≥5% and <25%)), Group 3 ("major difference" (≥25%))

[b] IMI: Imipenem + cilastatin, PTZ: Piperacillin + tazobactam, AMX/CLA: Amoxicillin + clavulanic acid, CEF/SUL: Cefoperazone + sulbactam

[c] UD = Unit Dose. Since combination products such as sulfamethoxazole + trimethprim that do not adhere to the main principles, their DDDs are listed separately in the cited reference[27].

[d] Each of these antibiotic had two WHO-DDD values following the adjustments in the WHO's 2019 update on DDD measurement[17].

3.4. Assessment of the linear relationship between DDDs and DOTs

Figure 1. visually depicts the relationship using univariate linear regression between DDD/1000 PDs and DOT/1000PDs per each antibiotic within three commonly used groups and prioritized antibiotics in management. The majority of the models (69.2%) had the values of slope coefficient less than 1, showing that the mean prescribed daily doses were greater than WHO-recommended dose in almost antibiotics. Most of the estimated 95% confidence interval of slope coefficient in these models were consistently greater than zero and did not include zero, indicating a statistically significant positive linear relationship between DOT/1000PDs and DDD/1000PDs. However, residual analysis revealed that the relationship between these variables for the antibiotics cefuroxime (O), ceftriaxone (P), and linezolid (P) violated the hypothesis as the residuals were not normally distributed. The study also found that fluoroquinolones often had DDD/1000PDs values greater than DOT/1000 PDs, showing that this group's daily doses were often greater than the DDD values recommended by WHO. Considering ciprofloxacin (by parenteral route) with the DDD alteration from 0.5g to 0.8g in 2019, most of the monthly ciprofloxacin use values in the pre-update DDD period (before 2019) were in the plane to the right of the x = y line, or monthly DDD/1000PDs were greater than DOT/1000PDs. In other ways, the mean daily actual dose of ciprofloxacin in the period 2017 to 2018 was more significant than WHO-recommended DDD values (0.5g). Regarding amoxicillin + clavulanic acid under the Access Group, the study showed the differences between DDD and DOT metrics among hospitals. Meanwhile, DOT/1000PDs values of carbapenems belonging to the list of antibiotics for priority in strict management were approximately equal to DDD/1000 PDs. Colistin, regarded as a last-resort antibiotic, was always prescribed at a smaller dose than the dose prescribed by the WHO (change from 3MIU to 9MIU in 2019

Figure 1. The association between DOT/1000PDs and DDD/1000PDs per antibiotic. Each data point was represented one monthly antibiotic consumption point with x-axis expressed by DDD/1000PDs and y-axis expressed by DOT/1000PDs. The study symbolized the blue and orange color as the monthly consumption measured in Hospital 1 and Hospital 2, respectively. The figure contained the straight line x = y (black line) means that DOT/1000PDs was approximately equal to the value DDD/1000PDs. Therefore, the plane to the left of the x = y line will include data points with DOT/1000PDs values greater than DDD/1000PDs and vice versa

3.5. Comparison of antibiotic use metrics between children and adults

When examining the difference between DOT and DDD variables in pediatric patients, the antibiotic consumed usually has the Cohen's d value > 0.5, meaning the standardized mean difference between DOT and DDD ranged from medium to large. This can be interpreted as children often being indicated to have lower daily doses of antibiotics compared to the recommended dose by WHO. Most antibiotics used for adults had a small-medium differences, especially carbapenems with $|d| < 0.19$ (sample size (n) for meropenem (P), imipenem-cilastatin (P), and ertapenem (P) were equal to 2,662, 7,044, 2,385, respectively) and aminoglycosides with $|d|_{aminoglycoside}$ equal to 0.06 (n for amikacin (P) and gentamicin (P) were equal to 2,716 and 546, respectively) . For glycopeptides, pediatric and adult inpatients displayed DDD and DOT differences, especially in vancomycin, with a small effect size of d=0.18 (n = 198) in children and a large one of d=0.96 (n=3,468) in adults.

4. DISCUSSION

Given the resource constraints and lack of IT infrastructure in Vietnamese hospitals, it is crucial to identify and select the most feasible metric for all hospitals to coordinate and synchronize toward an antibiotic usage surveillance system. In this study, we provided a general comparison of two measures of antibiotic use, including DDDs and DOTs, by periods and age-specific groups to determine the optimal metric for monitoring antibiotic-tailored consumption and develop potential applications for the hospitals in the same context. The study found that the total inpatient antibiotic consumption at the two hospitals (1011.68 DDD/1000PDs and 1036.76 DDD/1000PDs, respectively) were slightly lower than in other hospitals in Vietnam[28,29].This can be explained by the underestimation of antibiotic consumption when the study also included the pediatric population. Moreover, it might be as these two hospitals started early implementation of ASP and initiated effective ASP interventions, the ASPs had the potential impacts to reduce antibiotic consumption of the study population estimated by DDD- and DOT-metrics in comparison to ASPs in other hospitals located in small provinces[30]. Although the Hospital 2 did not specialize in tropical infectious diseases like Hospital 1, the total antibiotic consumption of patients in Hospital 2 expressed by DDD/1000PDs was quite similar to that of Hospital 1, showing that these hospitals used nearly the same amount of antibiotics. This result can be explained by patient characteristics as Hospital 2 was the central hospital where critically ill geriatric patients with combined comorbidities and an increased risk of acquiring multidrug-resistant infections were regularly treated. This particular population might need careful considerations of receiving combinations of antibiotics and last-resort antibiotic use, resulting in high antibiotic consumption compared to other populations.

Moreover, the total antibiotic consumption was higher when indicated by the DDD metric compared to the DOT one, specifically up to 8.91% and 19.1% differences between these metrics in Hospitals 1 and 2, respectively. Another study conducted in an ICU at a hospital in Spain also showed that antibiotic consumption measured by the DDD metric was 36.7% higher than when measured by the DOT metric[21]. This could reflect that the average daily dose of most antibiotics of the study population at the two hospitals, as well as in the reference study, was higher than the dose assigned by WHO. This difference may be due to different antibiotic use guidelines in different regions and countries, depending on patient characteristics and the distribution of antibiotic resistance patterns in different regions or countries. However, the percentage differences between these two metrics in our study (8.91% and 19.1% differences) were much lower than the study conducted in Spain (36.7% difference) because we collected data entirely from electronic medical records, whereas the DDD and DOT values of the reference study were calculated from two different data sources (from physicians' self-collection data and pharmacy records)[21]. Each data source had a different data entry form and extraction process, which might lead to errors when calculating the metrics from the combined data[31]. For example, the prescription data provided insights into the disposal practices for unused drugs, whereas the billing data did not capture this information. Besides, although the pediatric patients who were hypothesized that the daily dose should be much lower than the WHO-DDD covered 46.32% of the patients in Hospital 1, the actual dose of all prescribed antibiotics in Hospital 1 was still higher than the dose assigned by WHO. This can be explained by the remaining adult patient populations being prescribed doses much higher than WHO-DDD or the actual dose of pediatric patients contradicting the given hypothesis, leading to the pooled patients having higher prescribed antibiotic doses than WHO-DDD. To test the hypothesis on pediatric patients, we evaluated the standardized mean differences between DOT and DDD metrics among pediatric patients by Cohen's d. The Cohen's d values between DOT and DDD metrics in antibiotics frequently used for children were larger than 0.5, which was concordant with our hypothesis that children's daily administered doses were often below the WHO-recommended doses.

There was a similar finding between this study and other antibiotic utilization studies in other settings where cephalosporins, fluoroquinolones, and penicillin were the most frequently prescribed antibiotic groups. Within the cephalosporin group, third- and second-generation cephalosporins accounted for the highest percentage of use, with 69.4% (213.68 DDD/1000PDs) and 30.5% (93.68 DDD/1000PDs) in the Hospital 1 and 57.0% (188.07 DDD/1000PDs) and 34.8% (114.84 DDD/1000PDs) in the Hospital 2. The explanation for this result might be that third-generation cephalosporins group was a broad-spectrum antibiotic group with activities against many Gram (-) strains, which have been considered as the main causative agents of hospital-acquired infections nowadays. However, the increase in third-cephalosporin consumption can lead to a high risk of resistance among these bacteria, specifically extended-spectrum beta-lactamase (ESBL)--producing bacteria[32]. The DDD/1000PDs value of glycopeptides (92.94 DDD/1000PDs, accounting for 8.97% of total consumption) revealed a concerning consumption trend in Hospital 2. As this antimicrobial group belongs to the Reserve Group of the AWaRe classification, misuse and continuous use of this group as empirical therapy would emerge as antimicrobial resistance in the future

Among four Access antibiotics showing "major" differences between mean monthly DDD/1000PDs and DOT/1000PDs, especially for the sulfamethoxazole + trimethoprim combination, the study found that the DDD/1000PDs value of this antibiotic was 1.5 times as much as the DOT/1000 value, which was similar to the study by Nguyen. et al in Dong Thap Hospital[28]. Another way that can be interpreted is that the actual dose of the patient using the sulfamethoxazole + trimethoprim combination was 1.5 times as much as the WHO-recommended dose (4UD = 1,600mg + 320mg) and equaled 2,400mg + 480 mg. This dose was the maximum dose recommendation following the product information, and not all patients were indicated for this dose (depending on infection type and age groups). In this case, for patients indicated a combination of antibiotics such as sulfamethoxazole + trimethoprim, the DOT method cannot reflect the current practice as accurately as the DDD method. Moreover, taking an example in Hospital 1, if we ranked the antibiotic consumption by DOT/1000PDs, it would be much different from those measured by DDD/1000PDs as sulfamethoxazole + trimethoprim accounted for a significant amount in antibiotic consumption (ranked second by DDD measurement), and we estimated this antibiotic's consumption not precisely. For benchmarking antibiotic use purposes with the inclusion of combination therapies as the example above, DDD method provided more helpful tool than DOT method.

Regarding the differences between DDD and DOT metrics by age-specific groups, it was observed that most antibiotics used for adults had small-medium differences, especially antibiotics for priority in strict management (aminoglycosides, carbapenems). By yielding insight into the different effect sizes between antibiotic use metrics (DDD and DOT) among pediatric and adult patients, the hospitals can evaluate their current target ASP interventions to enhance the ASPs and facilitate evidence-based policy-making to improve antibiotic usage surveillance systems. For example, small effect sizes between carbapenem uses measured by DDD and DOT in adults can reveal that the daily doses of the carbapenem group were equivalent to WHO-DDD, illustrating that DDD can surrogate DOT in monitoring adult carbapenem use as the DDD method is more feasible than the DOT one. Besides, some antibiotics in which pediatrics showed smaller effect sizes compared to adults, such as levofloxacin (oral route), may suggest the demand for more stringent prescribing guidelines for adults. However, hospitals should also consider the sample size to evaluate the strength of evidence in the decision-making process.

The study has several strengths. We analyzed the four-year longitudinal antibiotic usage data, and both hospitals were in the early stages of ASPs in 2017, so our study could estimate the antibiotic use in the inpatient setting with the impact of early implementations of ASP initiatives. As information extraction from the patient-level prescription data was fully computerized, it might not only reduce data retrieval errors due to missing datasets and misinterpreting physicians's prescriptions but also maintain consistency compared to calculating the metrics from two different data sources.

The limitation of the study was that only two hospitals located in Ho Chi Minh City participated in this study, which could limit generalizability due to local formulary decisions, prescription practices, and patient characteristics.

However, we would like to provide a proposed methodology to compare DDD- and DOT- metrics and some considerations when measured by these metrics in a particular population for investigating further multicentre studies in Vietnam. Besides, we included all pediatric and adult inpatients in the included population to offer a comprehensive overview of antibiotic use in hospitals, which might hinder the application of the outcomes, and readers should take into consideration when benchmarking the usability of the combined data on antibiotic use in children and adult patients in this study. Moreover, the study period of this study lasted from 2017 to 2020, which was still not updated in comparison to the current situation. However, if we continued to collect data during the COVID pandemic, the measurement

results might be calculated inaccurately as one of two hospitals emerged as the primary unit that prevented, rapidly tested, and treated COVID-19 patients. In future research, we will take a deep dive into the impact of COVID-19 on antimicrobial measurement by DDD/1000PDs and DOT/1000PDs in many healthcare facilities in Vietnam.

5. CONCLUSION

Two hospitals reported that the total consumption measured by DDD/1000PDs exceeded those measured by DOT/1000PDs, indicating the average daily dose of most antibiotics was higher than the dose assigned by WHO. The DDD method was recommended as a potential alternative to the DOT methodfor efficiently measuring last-resort antibiotic consumption in adult patients. For benchmarking, DDD was better for combination therapies, while DOT should be preferred to avoid overestimating the use of common antimicrobials such as fluoroquinolones.

6. ACKNOWLEDGMENT

The authors would like to express the deepest gratitude to Nguyen Le (University of Texas at Austin) for the statistical knowledge support for this study.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This research received no external funding

Ethics approval

None to declare

Article info:

Received May 18, 2024
Received in revised form June 03, 2024
Accepted July 25, 2024

REFERENCES

1. Hutchings MI, Truman AW, Wilkinson B. Antibiotics: Past, present and future. Curr Opin Microbiol.2019;51:72-80. doi:https://doi.org/10.1016/j.mib.2019.10.008
2. Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022;399(10325):629-55. doi:10.1016/S0140-6736(21)02724-0
3. Jim O'Neill. Antimicrobial resistance: tackling a crisis for the health and wealth of nations.; 2014. https://amr-eview.org/sites/default/files/AMR Review Paper - Tackling a crisis for the health and wealth of nations_1.pdf
4. Honda H, Ohmagari N, Tokuda Y, Mattar C, Warren D. Antimicrobial stewardship in inpatient settings in the asia pacific region: A systematic review and meta-analysis. Clin Infect Dis. 2017;64:S119-S126. doi:10.1093/cid/cix017
5. Wagner B, Filice GA, Drekonja D, Greer N, MacDonald R, Rutks I, et al. Antimicrobial stewardship programs in inpatient hospital settings: A systematic review. Infect Control Hosp Epidemiol. 2014;35(10):1209-28. doi:DOI: 10.1086/678057
6. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. Clinical Infectious Diseases.2016;62(10):e51-e77. doi:10.1093/cid/ciw118
7. World Health Organization (WHO). Antimicrobial stewardship programmes in health-care facilities in low-and middle-income countries: A WHO practical toolkit. Published 2019. https://iris.who.int/bitstream/handle/10665/329404/9789241515481-eng.pdf
8. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementingan antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. Clinical Infectious Diseases.2016;62(10):e51-e77. doi:10.1093/cid/ciw118
9. Morris AM. Antimicrobial stewardship programs: appropriate measures and metrics to study their impact. Curr Treat Options Infect Dis. 2014;6(2):101-12. doi:10.1007/s40506-014-0015-3
10. Centers For Disease Control And Prevention. The core elements of hospital antibiotic stewardship programs.; 2014. https://www.cdc.gov/antibioticuse/healthcare/pdfs/coreelements.pdf
11. Ngan TTD, Quan TA, Quang LM, Vinh VH, Duc CM, Nguyet HT, et al. Review of antibiotic prescriptions as part of antimicrobial stewardship programmes: results from a pilot implementation at two provincial-level hospitals in Viet Nam. JAC Antimicrob Resist. 2023;5(1):dlac144. doi:10.1093/jacamr/dlac144
12. OUCRU. Assessment of antimicrobial stewardship implementation at the national level.; 2023. https://www.oucru.org/antimicrobial-stewardship/
13. Vong S, Anciaux A, Hulth A, Stelling J, Thamlikitkul V, Gupta S, et al. Using information technology to improve surveillance of antimicrobial resistance in South East Asia. BMJ. 2017;358:j3781. doi:10.1136/bmj.j3781
14. Nguyen Thi Hai Yen, Huynh Phuong Thao NVVC. The situation of implementation of the management program guidelines of the Ministry Of Health in health facilities in Ho Chi Min City. Vietnam Medical Journal. Published online 2012. doi:https://doi.org/10.51298/vmj.v507i1.1360
15. Phan QTN, Le TD, Do QK, Pham HTT, Tran MTP, Vo TD, et al. Impact of antimicrobial stewardship intervention in clean and clean-contaminated surgical procedures at a Vietnamese national hospital. Tropical Medicine & International Health. 2022;27(4):454-62. doi:https://doi.org/10.1111/tmi.13738
16. Nguyen-Thi HY, Nguyen DA, Huynh PT, Le NDT. Impact of antimicrobial stewardship program on vancomycin usage: costs and outcomes at hospital for tropical diseases in Ho Chi Minh City, Vietnam. Risk Manag Healthc Policy. 2021;14:2637-46. doi:10.2147/RMHP.S307744
17. World Health Organization. DDD alterations from 2005-2024. Published 2024. Accessed May 18, 2024. https://atcddd.fhi.no/atc_ddd_alterations__cumulative/ddd_alterations/
18. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2024. Accessed May 16, 2024. https://atcddd.fhi.no/atc_ddd_index/

19. Polk RE, Fox C, Mahoney A, Letcavage J, MacDougall C. Measurement of adult antibacterial drug use in 130 US hospitals: Comparison of defined daily dose and days of therapy. Clinical Infectious Diseases. 2007;44(5):664-70. doi:10.1086/511640
20. Momattin H, Al-Ali AY, Mohammed K, Al-Tawfiq JA.Benchmarking of antibiotic usage: An adjustment to reflect antibiotic stewardship program outcome in a hospital in Saudi Arabia. J Infect Public Health. 2018;11(3):310-13. doi:10.1016/j.jiph.2017.08.008
21. Vallès J, Fernández S, Cortés E, Morón A, Fondevilla E, Oliva JC, et al. Comparison of the defined daily dose and days of treatment methods for evaluating the consumption of antibiotics and antifungals in the intensive care unit. Med Intensiva. 2020;44(5):294-300. doi:10.1016/j.medin.2019.06.008
22. Ministry of Health. Decision No. 5631/QD-BYT 2020 Guidance on Management of the Antibiotic Use in Hospitals.; 2020.
23. World Health Organization. AWaRe classification of antibiotics for evaluation and monitoring of use, 2023. Published 2023. Accessed May 23, 2024. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04
24. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol. 2013;4:863. doi:10.3389/fpsyg.2013.00863
25. Bakker A, Cai J, English L, Kaiser G, Mesa V, Van Dooren W. Beyond small, medium, or large: points of consideration when interpreting effect sizes. Educational Studies in Mathematics. 2019;102(1):1-8. doi:10.1007/s10649-019-09908-4
26. Kristoffer Magnusson. Interpreting Cohen's d Effect Size: An Interac.tive Visualization. Published 2023. Accessed May 16, 2024. https://rpsychologist.com/cohend/
27. World Health Organization. List of DDDs combined products. Published 2024. Accessed May 16,2024. https://atcddd.fhi.no/ddd/list_of_ddds_combined_products/
28. Nguyen-Thi H-Y, Bui TV, Tran-Thi H-N, Minh Le AD, Gia Nguyen BD, Tran-Thi H-N, et al. Evaluation of the impact before and after the application of an antimicrobial stewardship program at Dong Thap General Hospital, Vietnam, from 2017 to 2021. Infection prevention in practice. 2023;5(4):100311. doi:10.1016/j.infpip.2023.100311
29. Nguyen K Van, Thi Do NT, Chandna A, Nguyen TV, Pham C Van, Doan PM, et al. Antibiotic use and resistance in emerging economies: a situation analysis for Viet Nam. BMC Public Health. 2013;13:1158. doi:10.1186/1471-2458-13-1158
30. Nguyen HQ, Nguyen-Thi HY, Huynh PT, Le NDT, NguyenNTQ, Hsia Y. Effectiveness of an enhanced antibiotic stewardship programme among paediatric patients in a tertiary hospital in Vietnam. J Hosp Infect. 2022;127:121-28.doi:10.1016/j.jhin.2022.06.002
31. Kallen MC, Natsch S, Opmeer BC, et al. How to measure quantitative antibiotic use in order to support antimicrobial stewardship in acute care hospitals: A retrospective observational study. Eur J Clin Microbiol Infect Dis. 019;38(2):347-55. doi:10.1007/s10096-018-3434-0
32. Rohde AM, Zweigner J, Wiese-Posselt M, et al. Incidence of infections due to third generation cephalosporin-resistant Enterobacteriaceae - a prospective multicentre cohort study in six German university hospitals. Antimicrob Resist InfectControl. 2018;7(1):159. doi:10.1186/s13756-018-0452-8