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## **Original Research Article**

# Trend analysis of antibiotics consumption using WHO AWaRe classification in tertiary care hospital

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#### **ABSTRACT**

**Background:** Aim of the study was to assess trend in antibiotics consumption pattern from 2016 to 2019 using AWaRe classification, ATC and Defined daily dose methodology (DDD) in a tertiary care hospital. Antibiotics are crucial for treating infectious diseases and have significantly improved the prognosis of patients with infectious diseases, reducing morbidity and mortality. The aim of the study is to classify the antibiotic based on WHO AWaRe classification and compare their four-year consumption trends. The study was conducted at a tertiary care center, Pilakhuwa, Hapur. Antibiotic procurement data for a period of 4 years (2016-2019) was collected from the Central medical store.

**Methods:** This is a retrospective time series analysis of systemic antibiotics with no intervention at patient level. Antibiotic procurement was taken as proxy for consumption assuming that same has been used. ATC for systemic use (ATC code J01) antibacterial was used and defined daily dose (DDD) per 100 bed days was calculated. Antibiotics were further classified as Access, Watch, and Reserve (WHO AWaRe classification). Antibiotics consumption was ranked based on their volume of DDD i.e., drug utilization (DU90%) was calculated. Non-parametric Pearson's correlation coefficient was used for the comparison of consumption.

**Results:** Mean antibiotic procurement increased 1.25 folds from 140.3 DDD in 2016 to 201 DDD in 2018. A significant fall was seen in total DDDs in year 2019 (p value <0.05). A total of 41 antibiotics agents (Access 12, Watch 21, Reserve 6 and Not recommended 2) were procured. Reserve category antibiotics were procured from 2017 onwards. Out of 41 antibiotics procured 11 antibiotics (Access 3 and watch 8) accounted for DU 90%.

**Conclusions:** Antibiotics consumption of watch group was high and increasing antibiotic consumption trend was observed. Hospital antimicrobial stewardship program should be implemented to shift to use of Access group antibiotics and restrict use of Watch antibiotics.

Keywords: Antibiotics, AWaRe classification, ATC Classification, Defined daily dose

#### INTRODUCTION

Antibiotics consumption in India is among the highest in the world. Antibiotic procured in India increased from 3.<sup>2</sup> billion DDDs (defined daily doses) in 2000 to 6.5 billion DDDs in 2015. Although per-capita procurement of antibiotics in India is low when compared to several other countries Klein et al 2018.<sup>1</sup> In the year 2019, India has scored highest of 41 countries on the drug resistance index, a measure combining both antibiotic use and

resistance levels and by 2050, antimicrobial resistance has been forecast to claim on additional two million lives per year. Antimicrobial stewardship is recommended as a means of preserve effectiveness of last resort antibiotics, reducing antimicrobial resistance, along with lowering the risk of adverse drug events, treatment complications, and institutional costs. McElny et al, MacDougal et al 2005.<sup>2,3</sup> To optimize the use of antimicrobials, the world health organization (WHO) in 2019 updated the essential medicine list (EML) and categorized the antibiotics into

three groups- Access, Watch, Reserve and Not recommended (AWaRe) Sharlend et al 2018.<sup>4</sup> It is important for institutions to understand their patterns of antimicrobial use to identify and design appropriate stewardship interventions that have the greatest likelihood of impacting institutional antimicrobial utilization and the consequences of antimicrobial resistance.

In this study we assessed the antibiotics consumption in our institute using AWaRe classification to identify issues of inappropriate antibiotic use and develop more specific guidelines for antibiotic stewardship activities.

#### **METHODS**

#### Study design

This is a retrospective time series analysis of systemic antimicrobial (J01) procured in a 500 bedded tertiary care hospital in Pilakhuwa, Hapur. Trends analysis of antimicrobial procured was done from 2016-2019. The procurement data for antibiotics was obtained from the Central medical store for the years 2016 -2019. Antimicrobial procurement was used as a proxy for antimicrobial consumption assuming that the same has been dispensed to patients.

Antimicrobials drugs were coded on the basis of Anatomical Therapeutic Chemical (ATC) classification and antibiotics for systemic use (ATC code J01) were considered. These were further classified as Access, Watch and Reserve (AWaRe classification) (WHO EMLc 2019).8 The amount of antimicrobial drug in grams was converted into the number of defined daily (DDDs)/100 bed-days using AMC Tool 2019.

To test the quality of use, antibiotics procured was ranked based on their volume of DDD and accounted for drug utilization 90% (DU 90%) of total antibiotics procured. Proportion of DDD spent on according to AWaRe classification was determined.

No ethical committee approval was required for the work done.

#### **RESULTS**

#### Statistical analysis

Aggregated data that have been used were limited to systemic antibiotics (J01) only. Each antibiotic procured were explored for trend over time using linear regression and p value ( $r^2>0.3$ ,  $p\leq0.05$ ) consider statistically significant.

Table 1: AWaRe classification with DDD/100 bed-days in procured antibiotics over the year 2016-19.

Access	ATC	AWaRe	WHO DDD	2016	2017	2018	2019	Aver- age	Percent -age	DU- 90%
Amoxycillin	J01CA04	Access	1	22.11	25.33	39.50	14.76	25.43	16.15	16.15
Azithromycin	J01FA10	Watch	0.3	12.24	19.98	27.52	21.78	20.38	12.94	29.09
Ciprofloxacin	J01MA02	Watch	1	18.63	20.37	22.27	19.81	20.27	12.88	41.97
Amoxycillin Clavulanic acid	J01CR02	Access	1.5	22.35	15.71	25.85	14.55	19.61	12.46	54.43
Doxycycline	J01AA02	Access	1	15.24	15.85	19.45	12.12	15.66	9.95	64.38
Cefixime	J01DD08	Watch	4	11.27	14.63	15.54	13.45	13.72	8.72	73.09
Ceftriaxone	J01DD04	Watch	3	10.65	11.34	15.40	14.73	13.03	8.28	81.37
Erythromycin (as Stearate)	JO1FA08	Watch	1	3.22	3.55	5.83	3.74	4.09	2.60	83.97
Ofloxacin	J01MA01	Watch	0.4	4.89	4.17	3.58	2.62	3.82	2.42	86.39
Norfloxacin	J01MA06	Watch	0.8	2.12	4.18	5.38	2.22	3.48	2.21	88.60
Levofloxacin	J01MA12	Watch	0.5	2.42	3.01	5.08	1.16	2.92	1.85	90.45
Cloxacillin	J01CF02	Access	1	2.67	3.88	1.09	0.78	2.11	1.34	91.79
Ampicillin	J01CA01	Access	2	2.64	3.09	1.71	0.73	2.04	1.30	93.09
Metronidazole	J01XD01	Access	1.5	1.45	2.16	1.82	1.69	1.78	1.13	94.22
Ciprofloxacin + Tinidazole	J01RA11	Watch	1.2	1.62	1.74	1.54	1.46	1.59	1.01	95.23
Ofloxacin + Ornidazole	J01RA09	Watch	0	1.53	1.34	1.53	1.34	1.44	0.91	96.14
cefuroxime axetil	J01DC02	Watch	4	0.93	1.15	2.39	0.22	1.17	0.75	96.88
Nitrofurantoin	J01XE01	Access	1.2	0.96	1.21	0.96	1.44	1.14	0.72	97.61
Clindamycin	JO1SA02	Access	1.2	0.85	1.01	1.52	0.92	1.08	0.68	98.29
Sulfamethoxaz ole+ Trimethoprim	J01EC01	Access	2	0.97	0.80	1.30	0.65	0.93	0.59	98.88

Continued.

Access	ATC	AWaRe	WHO DDD	2016	2017	2018	2019	Aver- age	Percent -age	DU- 90%
Amikacin	J01GB06	Access	1	0.45	0.41	0.65	0.61	0.53	0.34	99.22
Clarithromycin	J01FA09	Watch	1	0.53	0.51	0.41	0.15	0.40	0.25	99.47
Rifaximin	A07aa11	Watch	0.4	0.14	0.12	0.18	0.14	0.15	0.09	99.57
Gentamicin	J01GB03	Access	0.24	0.10	0.09	0.15	0.13	0.12	0.07	99.64
Linezolid	JO1XX08	Reserve	0.5	0.00	0.05	0.26	0.11	0.11	0.07	99.71
Imipenem /Celestin	J01DH51	Watch	2	0.10	0.10	0.10	0.11	0.10	0.06	99.77
Vancomycin	J01XA01	Watch	1	0.06	0.04	0.19	0.11	0.10	0.06	99.83
Cephalexin	J01DB01	Watch	1	0.07	0.06	0.08	0.07	0.07	0.05	99.88
Teicoplanin	J01XA02	Watch	0.2	0.01	0.06	0.12	0.06	0.06	0.04	99.92
Meropenem	J01DH02	Watch	3	0.03	0.06	0.05	0.10	0.06	0.04	99.96
Cefpodoxime	J01DB03	Watch	1	0.02	0.03	0.01	0.05	0.03	0.02	99.97
Cefotaxime	J01DD01	Watch	1	0.00	0.00	0.04	0.03	0.02	0.01	99.99
Cefazolin	J001DB02	Watch	3	0.00	0.02	0.00	0.00	0.01	0.00	99.99
Ceftazidime	J01DD02	Watch	1	0.00	0.00	0.01	0.01	0.01	0.00	99.99
Tigecycline	J01AA12	Reserve	0.2	0.00	0.00	0.01	0.01	0.00	0.00	100.0 0
Cefoperazone +sulbactam	J01DD62	Reserve	1	0.00	0.00	0.01	0.00	0.00	0.00	100.0 0
Netilmicin Sulphate	JO1GH31	Watch	4	0.00	0.00	0.00	0.01	0.00	0.00	100
Minocycline	J01AA08	Reserve	0.2	0.00	0.00	0.00	0.00	0.00	0.00	100
Chloramphenic ol	J01BA01	Access	1	0.00	0.00	0.00	0.00	0.00	0.00	100
Colistimethate Sodium powder	A07AA10	Reserve	1	0.00	0.00	0.00	0.00	0.00	0.00	100
Polymyxin B	A07AA05	Reserve	0	0.00	0.00	0.00	0.00	0.00	0.00	100
Total			52.34	140.29	156.07	201.55	131.8	157.44		

# Drug utilization 90% (DU 90%) using DDD methodology

Here, (Table 1) depicts the antibiotics (J01) procurement pattern using DDD and DU90% methodology to interpret the change in utilization pattern over the year 2016-2019. (Figure 1). depicts mean antibiotic procurement increased 1.25 folds from 140.3 DDD in 2016 to 201 DDD in 2018. A significant fall was seen in total DDDs in year 2019 (p value <0.05). A total of 41 antibiotics agents (Access 12, Watch 21, Reserve 6 and Not recommended 2) were procured. Reserve category antibiotics were procured from 2017 onwards. Out of 41 antibiotics procured 11 antibiotics (Access 3 and watch 8) accounted for DU 90%. In Figure 2 order of procurement was highest for Amoxycillin (16.15%),azithromycin (12.94%),ciprofloxacin (12.88%), combination of amoxicillin and clavulanic acid (12.46%), doxycycline (9.95%), Cefixime (8.72%), ceftriaxone (8.28%), erythromycin (as Stearate) (2.60%), ofloxacin (2.42%), norfloxacin (2.21%), levofloxacin (1.85%).

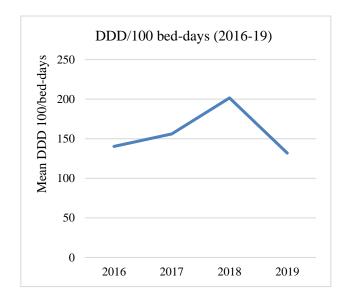


Figure 1: Antibiotic Consumption rate in wards from 2016 to 2019 in mean DDD/100 bed-days.

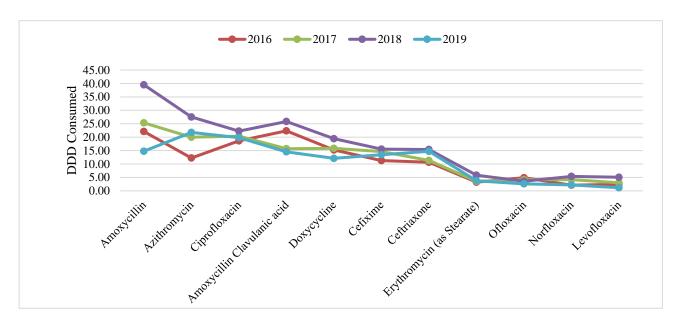


Figure 2: Drug utilization 90% based on DDD consumed.

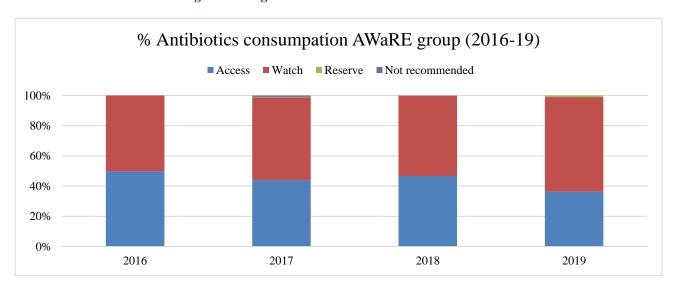


Figure 3: Percentage DDD consumption.

#### **AWaRe**

Figure 3. depicts the percentage of antibiotic procurement trend by DDD and AWaRe classification showing a significant increase in the use of Watch group antibiotics 63.23% (average 44.2%) in 2019 from 50.57% in 2016  $(R^2=0.78, p=0.043)$ , while a decrease in the use of access group from 49.43% (average=55.2) in 2016 to 35.6% in 2019 ( $R^2$ =0.74, p=0.031) was observed. A significant rise in procurement of a reserve group antibiotic was seen from 0.11% in 2017 to 1.47% in the year 2018. Three Not-recommended fixed dose combination antibiotics namely combination of ciprofloxacin and tinidazole, ofloxacin and ornidazole, cefoperazone and sulbactam, were also procured in the 2017. No DDD was assigned by WHO for Not-recommended fixed dose combination in EML list 2019. However, their procurement declined in 2018 to 0.19% from 2.01% in 2017.

#### **DISCUSSION**

The antibiotic procured was classified using AWaRe classification and there DDD is calculated using DDD methodology and then DU90% measured using average DDD of 4-year in tertiary care center.

During our 4-year analysis we observed a significant 1.25 times increase in the DDD of antibiotics. Our figures are higher than the 108.<sup>5</sup> DDDs/ 100 bed-days & 113.<sup>9</sup> DDDs/ 100 bed days reported by Shankar et al 2015, Handayal et al. 2019.<sup>5,6</sup>

In the present study, it was found that most of the prescribed antibiotics in DU-90% had 8 drugs from Watch group and have a DDD much higher than the DDD recommended by WHO. Glycopeptides, penicillin like antibiotics and carbapenems had a DDD lower than the

recommended DDD. These findings of the current study are comparable to results of other previous studies. Gidamudi et al and Sharma et al. 2018.<sup>7,8</sup>

Over the years procurement of Access group antibiotics declined by 20% and there was an increase watch group consumption. WHO goal is to target that 60% of all antibiotic's procurement should be from access group,9 but unfortunately in our study, that trend is going in opposite direction. Focus of this aware tool is to guide prescribers to prescribe narrower spectrum antibiotics compared to other watch and reserve AWaRe categories to prevent resistance. <sup>10</sup>

Our access-to-watch index is less<1 in 2019. Reserve antibiotics were introduced lately and their use is very limited but increasing trend was observed. Similar finding was found in a study by Hsia et al.11

One limitation in the measurement of antibiotic procured in DDDs/100 bed-days is its inability to adjust antibiotic use according to variations in the case mix over time. The high antibiotic procurement rate in our hospital is possibly due to a higher case mix index (CMI). CMI is an economic parameter that is calculated using diagnosis related groups, a measure that is today routinely used in various countries as a basis for hospital reimbursement. Kuster et al.<sup>12</sup>

The other reason for high antibiotic procurement may be because of high antimicrobial resistance and thus the tendency to treat infection with broad spectrum antibiotics from watch and reserve group. There is variable situation regarding antibiotics prescribing and emergent of important opportunistic pathogens in every institute. Increase in antibiotic procurement is associated with significant antimicrobial resistance and increase number of blood cultures performed over the year and thus increase in isolation rate.

A significantly high rising trend of third-generation cephalosporin, fluoroquinolones and macrolides antibiotics was seen in procurement from watch category. Penicillin, a narrow spectrum antibiotic is a better option but is not being used because of poor availability. Similar patterns in antibiotics procurement found in study of Barker et al, Gandara S et al Our result show parallel rise in resistance pattern (100 % in pseudomonas & 87% in klebsiella). Similar trend of high resistance was reported by NCDC, Walia et al. 2019.

The carbapenem class of antibiotics is one of the widely used antibiotics to treat serious bacterial infections. Our results showed no significant changes in procurement pattern.

Antibiotic FDCs are prevalent although there is no evidence to justify use of these combinations. Injudicious use of antibiotic FDCs could lead to emergence of bacterial strains resistant to multiple antibiotics.

Approximately 118 antibiotic FDCs are available in India (Ahmad et al 2016; Shankar et al 2016). <sup>16,17</sup> The use of the fixed-dose combinations of multiple broad-spectrum antibiotics listed in not-recommended group of WHO essential drug list is not evidence-based, nor recommended in high-quality international guidelines. WHO does not recommend their use in clinical practice. <sup>18</sup>

Our finding indicates that the use of watch antibiotic consumption shows a significant increase in consumption than access group over 4 years, which reflects changes in antibiotic selection and challenges in improving antibiotics use. Prescribers should follow the published treatment guidelines by national center for disease control (NCDC) and IndiaCLEN taskforce, recommending more use of Access group of antibiotics in outpatients and inpatients settings.19 Third generation cephalosporins and carbapenems belong to watch group should be reserved for sick patients or patients admitted to ICU or clinical deterioration on first line agents belonging to Access group.

#### Limitation

Procurement data is used as proxy for consumption considering that same has been dispensed to the patient this might not always reflect the actual amount consumed by the patients. However, in this inherent limitation of the study, we believe that the methodology adopted would be more than adequate to give a clue to the antibiotic consumption rate using a standardized metrics.

#### **CONCLUSION**

Antibiotics consumption of Watch group was high and increasing antibiotic consumption trend was observed. Hospital antimicrobial stewardship program should be implemented to shift to use of Access group antibiotics and restrict use of Watch antibiotics. Further studies which focus on antibiotics categorization and consumption patterns need to be conduct, which would be instrumental in setting up a antibiotic's stewardship at

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