Research Article

Antibiotic Consumption in the State Sector of Sri Lanka Over 25 Years:
1994 - 2018 Using the GAP Methodology

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ABSTRACT

Purpose: Surveillance of antibiotic consumption is one of the five pillars of the World Health Organizations global action plan to combat antimicrobial resistance. This study determined the feasibility of using the WHO-GAP methodology to develop a sustainable Antimicrobial Medicines Consumption (AMC) monitoring system in Sri Lanka. The aggregated distribution data (1994 – 2018) in the State sector was used to test feasibility and incite interest. Methods: Aggregated data on J01 defined as antibacterials for systemic use, distributed to the State sector from 1994 to 2018 were extracted from the database of the Medical Supplies Division, Ministry of Health. The Anatomical Therapeutic Chemical (ATC) classification and the Defined Daily Dose methodology was used to calculate the total consumption as DDDs per 1000 inhabitants per day (DID), relative use measures (percentages), and extent of use of WHO Access, Watch and Reserve group antibiotics. Results: Antibiotic consumption increased from 6.79 DID in 1994 to 13.89 DID in 2018 with the number of chemical substances increasing from 19 to 41 respectively. The most consumed was J01C (beta-lactam antibacterials) while the largest increase in rate of consumption was seen in J01D (other beta-lactam antibacterials). From 2008 the top ten oral and parenteral antibiotics showed a significant shift to broad spectrum from narrow spectrum with their ratio increasing from 0.19 to 2.37, due to predominant consumption of cefuroxime, ceftriaxone and co-amoxiclav. Consumption of the RESERVE group though low is rapidly increasing with time. Conclusion: This paper provides the Ministry of Health the impetus and direction to begin a sustainable monitoring system to track trends and drivers of AMC in Sri Lanka.

Key words: Antibiotics consumption; Antimicrobial resistance; Global action plan; Sri Lanka

INTRODUCTION

The “Global Action Plan (GAP)” to reduce Antimicrobial Resistance (AMR) was introduced by the World Health Organization (WHO) in 2015. Within the identified five pillars, strengthening the evidence base through surveillance of AMR and monitoring antimicrobial medicines consumption (AMC) which is the main driver of AMR are two of their main objectives.(1) As a member
state of the WHO, the Ministry of Health, Sri Lanka launched its strategic plan to curb AMR in 2017 using the “One Health” approach (2) which includes both humans and animals.

To implement the objectives of GAP, in 2016 the WHO developed a standardized global methodology for the measurement of AMC, based on the Anatomical Therapeutic Chemical (ATC)/ Defined Daily Dose (DDD)-methodology of WHO, and the methodologies established by ESAC-Net and the WHO Regional Office for Europe so that data can be easily compared and exchanged globally. To test its feasibility, the WHO conducted a pilot study in the African region, region of the Americas, South-East Asia region, and European region. Although, South-East Asia region (SEAR) was selected for the pilot study, due to the lack of data, SEAR was excluded in the WHO report on surveillance of antibiotic consumption from 2016 – 2018.(3)

In Sri Lanka, the Ministry of Health takes the full responsibility of providing free health at point of delivery to all its inhabitants. Medicines are distributed to all parts of the country through the Medical Supplies Division (MSD) and as its strength has a good documentation system of medicines distributed to the State sector which predated GAP. Documentation was initially done by the maintenance of order control cards and books (1987–2000) followed by computerized databases. Hence studying aggregated antimicrobial distribution data was considered as a valid first step strategy to describe usage patterns over time in order to implement policies to contain AMR.

The aim of our study was to determine the feasibility of adopting the WHO GAP methodology to develop a sustainable monitoring system by analyzing the aggregated distribution data of antibacterials for systemic use (J01) from 1994 to 2018 at the Medical Supplies Division (MSD) of the Ministry of Health.

The specific objectives were to describe the trends in antibacterials for systemic use (J01) consumption (over the last 25 years, 1994 – 2018) and assess quality against selected indicators. For the purpose of this paper AMC denotes J01 consumption.

METHODS

Aggregate data from 1994 to 2018 (both years inclusive) on antibacterials for systemic use (J01) distributed to the State sector hospitals were extracted from the handwritten documents and computerized databases of the Medical Supplies Division (MSD) of the Ministry of Health, Nutrition and Indigenous Medicine of Sri Lanka. Following a series of discussions, the authors came to an agreement that the aggregate data of the distributed medicines gave a more accurate estimation of consumption than the procurement. Data was collected according to the WHO protocol which included data at the product level (proprietary and generic products), information on the active substance(s) of the product, route of administration, strength per unit, number of units per package, and total number of packages distributed. Data collection was facilitated by means of an Excel template with functions to calculate volume and consumption for each product.

Antibiotics were classified according to the year of study version of the Anatomical Therapeutic Chemical (ATC) classification and was quantified in Defined Daily Doses (DDDs).(4) All distributed antibiotics were assumed to have been consumed. The data
were expressed as absolute values, percentage increase or decrease and graphs using Microsoft Office Excel 2010. All datasets were validated through functions in the Excel template and through manual row-by-row review of the antibiotic products in order to detect inconsistencies. The analyzed data were revised or justified (gaps or drops and increases overtime) following cross checking with senior pharmacists at the MSD to ensure the quality of the data. As there are delays between annual estimations and procurement and spillover of the excess stock to the next year, the consumption was categorized into five-year blocks from 1994 to 2018.

The metrics and indicators reported in the study are as follows.

1. Population adjusted estimates of AMC expressed as DDDs per 1000 inhabitants per day (DID) using the Mid-year population in Sri Lanka published in census and statistics reports within the study period as it is the international recommendation to calculate the DID. (5)

2. Consumption at the 3rd and 5th level of the ATC index expressed as DID.

3. The most frequently used antibiotics comprising 75% of the total consumption stratified into 5-year blocks and route of administration – Drug utilization 75 (DU75).

4. At any point of significant change in AMC the data will be further analyzed according to the quality indicators based on European Surveillance of Antimicrobial Consumption (ESAC) recommendations (6) and World Health Organization (WHO), AWaRe categories (Access, Watch and Reserve). (7)

The indicators were calculated as follows.

4.1 Consumption of J01 group expressed in DID.

4.2 Consumption of beta-lactamase sensitive penicillins expressed as percentage of the total consumption of J01 (J01CE%).

4.3 Consumption of combination of penicillins, including beta-lactamase inhibitor expressed as percentage of the total consumption of J01 (J01CR%).

4.4 Consumption of third and fourth generation cephalosporins expressed as percentage of the total consumption of J01 (J01(DD+DE)%).

4.5 Consumption of fluoroquinolones expressed as a percentage of the total consumption of J01 (J01MA%).

4.6 Ratio of the consumption of broad-spectrum (J01(CR+DC+DD+(F-FA01))) to the consumption of narrow spectrum penicillins, cephalosporins and macrolides (J01(CE+DB+FA01)) indicated as (B/N).

As this is the first study using the ATC/DDD system the classification levels of amoxicillin is illustrated below. (4)

**J:** General anti-infectives for systemic use (1st level, ATC main group)

**J01:** Antibacterials for systemic use (2nd level, therapeutic main group)

**J01C:** Beta-lactam antibacterials, penicillins (3rd level, therapeutic/pharmacological subgroup)

**J01C A:** Penicillins with extended spectrum (4th level, chemical/therapeutic/pharmacological subgroup)

**J01C A04:** Amoxicillin (5th level, subgroup for chemical substance)

Ethical approval was sought from the Ethics Review Committee of Faculty of Medicine, General Sir John Kotelawala Defence University and permission was granted to conduct the analysis with exemption from ethical review as the study was done using data retrieved from the database of the MSD.
RESULTS

Trends and drivers of consumption of J01

Between 1994 and 2018 AMC expressed in Defined Daily Doses (DDDs), increased by 143% (44.4 – 108.2 million DDDs). The highest increase (19084%) was in J01D (other beta-lactam antibacterials) from 0.1 million DDDs to 18.4 million DDDs followed by J01M (quinolones), 579% (0.6 – 4.3 million DDDs), J01C (beta-lactam antibacterials), 201% (21.8 – 65.7 million DDDs), J01X (other antibacterials), 112% (3.3 – 7.0 million DDDs) and J01F (macrolides and lincosamides), 93% (3.9 – 7.7 million DDDs). In contrast, consumption of J01B (amphenicol), J01E (sulphonamides and trimethoprim), J01G (aminoglycoside) and J01A (tetracyclines) had decreased by 96% (0.1 – 0.004 million DDDs), 94% (7.6 – 0.4 million DDDs), 47% (0.4 – 0.2 million DDDs) and 30% (6.3 – 4.3 million DDDs) respectively. Of the total antibiotic consumption in 1994, J01C accounted for 49%, followed by J01E (17.2%), J01A (14.3%), J01F (9.0%) and J01X (7.4%). J01M, J01G, J01B and J01D accounted for 1.4%, 1.0%, 0.3% and 0.2% respectively. In contrast, in 2018 the J01C accounted for 60.6% followed by J01D (17.0%), J01F (7.1%), J01X (6.6%), J01A (4.1%), and J01M (4.0%) whereas consumption of J01E and J01G had dropped to 0.4% and 0.2% respectively.

In order to interpret the findings more accurately by considering the population size within the country, the rate of AMC is also expressed as DDD/ 1000 inhabitants/ day (DID). The rate of AMC between 1994 and 2018 increased by 104%. As shown in Figure 1, the rate of consumption had almost doubled from 6.8 DID in 1994 to 11.9 DID in 2009 and further increased to 13.9 DID by 2018. The increase over time was mainly driven by the groups, J01C, J01D, J01M and J01X. The predominantly consumed group throughout was J01C with the consumption doubling from 3.3 DID in 1994 to 6.5 DID in 2003 and increased to 8.4 DID by 2018. The major driver of increasing consumption over time was J01D which increased by 16685% from 1994 (0.014 DID) to 2018 (2.4 DID). J01M consumption increased by 485% (0.1 DID to 0.6 DID) while J01X consumption increased by 80% (0.5 DID to 0.9 DID) from 1994 to 2018. In contrast, total consumption of J01A, J01B, J01E and J01G decreased from 1.0, 0.02, 1.2 and 0.06 DID in 1994 to 0.6, 0.001, 0.06 and 0.03 DID in 2018 respectively.

The total number of chemical substances in the J01 had doubled between 1994 and 2018 from 19 to 41 respectively. It was driven by J01D (other beta-lactam antibacterials, 7 new) followed by J01M (quinolones, 4 new), J01C (beta-lactam antibacterials, 3 new), J01F (macrolides and lincosamides, 3 new) and J01X (other antibacterials, 3 new). A similar picture is evident in the parenterals, from 1994 to 1998 only eight substances were included, and increased thereafter to 28 by 2018 which included many broad-spectrum antibiotics.

From J01C, amoxicillin was the most consumed throughout, increasing from 2.1 DID in 1994 to 5.3 DID in 2018. Others consumed from J01C were ampicillin, benzylpenicillin, phenoxymethylpenicillin, benzathine benzylpenicillin, pivmecillinam and mecillinam with inclusion of new broad-spectrum antibiotics like co-amoxiclav, ticarcillin and flucloxacillin over time.
Clindamycin consumption increased from 2006 to 2018 (0.0005 DID to 0.05 DID). Clindamycin parenteral preparation was consumed more than the clarithromycin parenteral preparation from 2016 to 2018.

In J01G, gentamicin was the most consumed throughout, but its consumption has decreased from 0.05 DID in 1994 to 0.02 DID in 2018. Streptomycin, kanamycin, neomycin, amikacin, netilmicin were the other consumed aminoglycosides.

Consumption of J01M increased until 2012 (0.1 in 1994 to 0.9 DID in 2012) and decreased by 2018 (0.6 DID). The most commonly used quinolone was ciprofloxacin over time. Levofloxacin introduced in 2008 (0.00002 DID) rapidly increased to 0.03 in 2018 which included both oral and parenteral preparations. Consumption of nalidixic acid decreased from 0.1 DID in 1994 to 0.01 DID.
in 2018. Others available in J01M were ofloxacin and norfloxacin.

Among the J01X, metronidazole consumption increased from 1994 to 2018 (0.4 to 0.7 DID). The consumption of vancomycin introduced in 2002 showed a dramatic increase (24400%) by 2018 (0.00002 DID - 0.0049 DID). Consumption of nitrofurantoin had increased over time (0.1 DID in 1994 to 0.2 DID in 2018). Fusidic acid, teicoplanin and linesolid were the other antibiotics used from this group. Linesolid, introduced in 2011 showed a consumption of 0.000001 DID and in 2018 its consumption was 0.00058 DID with a dramatic increase during the period (57900%).

**Antibiotics that made up 75% of total AMC**

Amoxicillin was the highest used oral antibiotic over the 25 years. As shown in Table 1, number of antibiotics which contributed to the 75% of the AMC has increased over the time in both oral and parenteral preparations.

**Table 1: Antibiotics that made up 75% of total antibiotic consumption**

| Year          | Oral                      | Parenteral                |
|---------------|---------------------------|---------------------------|
| 1994–1998     | Amoxicillin, Amoxicillin  | Benzylpenicillin          |
| 1999–2003     | Co-trimoxazole, Erythromycin | Ampicillin               |
| 2004–2008     | Erythromycin, Cloxacillin | Cloxacillin, Cefuroxime   |
| 2009–2013     | -                         | Metronidazole, Cefuroxime |
| 2014–2018     | -                         | Benzylpenicillin          |

**Measurements of quality indicators of AMC**

Pettitt’s test was conducted using XLSTAT and results showed a significant change (p<0.0001) in total AMC from 2008 onwards (Figure 2). As the AMC pattern showed a significant change from 2008 onwards, analysis of the quality indicators was undertaken from 2008 to 2018. As shown in Table 2, from 2008 to 2018, J01CE% reduced from 5.7% to 1.5% while J01CR% increased from 1.4 to 15.2% respectively. Further, J01DD+J01DE% and J01MA% also increased over time. The ratio J01(CR+DC+DD+(F-FA01)) to J01(CE+DB +FA01) increased from 0.19 in 2008 to 2.4 in 2018 indicating increasing consumption of broad-spectrum antibiotics.
Figure 2: Total Antimicrobial Medicine Consumption (AMC) over the 25 years

Table 2: Measurement of quality indicators from 2008 to 2018

| Year | Total (J01) (DID) | Penicillin (J01C) (DID) | Cephalosporin (J01D) (DID) | Macrolides (J01F) (DID) | Quinolones (J01M) (DID) | Beta lactamase sensitive penicillin (J01CE)% | Combinations of penicillins incl. beta lactamase inhibitor (J01 CR)% | Third & fourth generation cephalosporins (J01 DD + J01 DE)% | Fluoroquinolones (J01 MA)% | Ratio B/N | B/N |
|------|------------------|------------------------|--------------------------|------------------------|------------------------|------------------------------------------|-------------------------------|-----------------------------|-----------------------------|----------------|-----|
| 2008 | 9.84             | 6.51                   | 0.46                     | 1.04                   | 0.47                   | 5.66                                     | 1.37                          | 0.42                          | 3.98                        | 0.19           |     |
| 2009 | 11.50            | 8.11                   | 0.54                     | 1.22                   | 0.43                   | 3.84                                     | 1.10                          | 0.39                          | 2.99                        | 0.21           |     |
| 2010 | 12.77            | 8.77                   | 0.86                     | 0.96                   | 0.61                   | 3.07                                     | 1.88                          | 0.38                          | 4.37                        | 0.31           |     |
| 2011 | 14.99            | 10.21                  | 1.38                     | 0.67                   | 0.96                   | 3.02                                     | 4.03                          | 0.57                          | 5.74                        | 0.66           |     |
| 2012 | 14.79            | 8.92                   | 1.42                     | 1.36                   | 0.87                   | 2.71                                     | 4.72                          | 0.44                          | 5.36                        | 0.55           |     |
| 2013 | 12.04            | 7.92                   | 1.28                     | 0.83                   | 0.76                   | 3.14                                     | 6.91                          | 0.67                          | 6.07                        | 0.92           |     |
| 2014 | 11.93            | 7.44                   | 1.42                     | 0.75                   | 0.99                   | 3.11                                     | 6.85                          | 0.87                          | 8.05                        | 0.85           |     |
| 2015 | 14.26            | 8.91                   | 2.15                     | 0.91                   | 0.66                   | 2.15                                     | 8.73                          | 0.70                          | 4.56                        | 1.15           |     |
| 2016 | 16.10            | 9.69                   | 2.53                     | 1.14                   | 0.92                   | 2.42                                     | 12.15                         | 0.91                          | 5.54                        | 1.47           |     |
| 2017 | 11.05            | 5.57                   | 1.83                     | 0.99                   | 0.89                   | 1.87                                     | 12.92                         | 0.86                          | 7.91                        | 2.29           |     |
| 2018 | 12.57            | 7.17                   | 2.36                     | 0.99                   | 0.56                   | 1.54                                     | 15.23                         | 1.00                          | 4.34                        | 2.37           |     |

DID, DDDs per 1000 inhabitants per day; B/N, Ratio of the consumption of broad-spectrum antibiotics to the consumption of narrow spectrum penicillins, cephalosporins, and macrolides.
Figure 3: Consumption of ACCESS, WATCH and RESERVE groups of antibiotics

**DISSCUSSION**

The key issues identified in this study using the longitudinal aggregated distribution data of the MSD which serves as a proxy for actual use of antibiotics over the past 25 years as defined by the WHO are highlighted and discussed. (3) The consumption of antibiotics expressed in both DDDs and DID have dramatically increased by 143% and 104% between 1994 and 2018 respectively. The likely drivers are an increase in outdoor and indoor attendance by 30.9% and 81.9% respectively and increased access to State sector doctors by 337.4% over time (8) as the Sri Lankan population increased only by 26% over the same time.

In comparison, global AMC (n=76 countries) DDDs and DID increased by 65% and 39% respectively between 2000 and 2001. The main driver was low and middle-income countries (LMICs) where mean consumption rates had increased by 77%.

The drivers in Asia were India (63%), China (65%) and Pakistan (21%).(9) Sri Lanka was not represented in this study. Our findings reveal that in the State sector of Sri Lanka alone during this same period of time, DDDs had increased by 62% and DID by 42%. The public sector consumption of antibiotics in Sri Lanka in the year 2015 (14.32 DID) was also higher than the average in low and lower-middle income countries (LMICs-LM) which was 13.5 DID.(9)

In Sri Lanka, a paradigm shift from narrow spectrum to broad-spectrum antibiotics was observed from 2008 onwards where the ratio increased from 0.19 to 2.37 (2018). A relative
increase in the consumption of second and third generation cephalosporins, quinolones, macrolides, glycopeptides (vancomycin), and carbapenems that are included in the WATCH group of medicines were observed over time. This is important to note for implementation of action as broad-spectrum antibiotics such as third generation cephalosporins, quinolones and carbapenems are categorized as WATCH antibiotics to be used with caution because of their high potential to cause AMR and/or their side effects. AMC consumption in the RESERVE which was almost zero in 2008 has increased by approximately 600% by 2018. The DID (0.00089) for the RESERVE group in 2018 suggests that at least 18 persons per day are on antibiotics included in this group in the State sector alone. The highest consumption was from the access category with amoxicillin been the highest use over the study period. Since 2014 co-amoxiclav, cephalexin, cefuroxime, ciprofloxacin, ceftriaxone, cefotaxime, and meropenem were within the 75% utilization category.

Studies published on AMR in Sri Lanka illustrate the relationship of high AMC consumption observed in our study with reported AMR. Between 2014 and 2016 the majority of coliform isolates showed very high resistance rates for ampicillin (85%), moderate resistance to cefalexin (44.8%), cefotaxime (36.6%), co-amoxiclav (36.3%) ciprofloxacin (46.2%) and gentamicin (23%).(10) In keeping with existing knowledge on AMR, nitrofurantoin which showed low resistance of 9% in 2016 had reduced consumption patterns over the last ten years.(10) Another study done in a State tertiary care hospital in 2009 showed that Acinetobacter spp responsible for Ventilator Associated Pneumonia (VAP) were multidrug resistant with resistance rates of 90% to cefotaxime, 73.3% to ceftazidime, 70% to imipenem, and 53% to cefoperazone-sulbactam.(11)

Concerns with AMR are further exacerbated in Sri Lanka as there is no functioning of an official surveillance system although the strategic plan to curb AMR was officially launched with celebrations in 2017. Thailand developed its national strategic plan on AMR around the same time as Sri Lanka but unlike us, has gone further to set targets one of which is for a reduction in AMC in humans by 20% in 2021.(12) Hence, the results of this study are an important first step for the Ministry of Health to initiate policy decisions as the data captures both indoor and outdoor aggregate AMC.

The main strength of this study is that this is the first study which presents the antibiotic consumption over time in the State sector hospitals of Sri Lanka. In addition, our study methodology is in keeping with the methodology designed to capture data for the implementation of the World Health Organizations GAP to combat antimicrobial resistance and is valid for inter-country comparison of AMC.

A limitation of this study is that only State sector data is included whereas it is well documented that approximately 50% of the population seek outpatient treatment from the private sector.(13) Another limitation is that the MSD aggregated distribution of antibiotics was assumed to be equal to the consumption of antibiotics in the State sector.

CONCLUSION
This paper highlights key issues on AMC to inform policies, regulations and interventions to optimize antibiotic consumption in the State sector and provides the impetus and
direction to the Ministry of Health to start a sustainable AMC monitoring system using the already available databases in the MSD. To capture the landscape of AMC in Sri Lanka we also recommend that the National Medicines Regulatory Authority (NMRA) enforces effective measures to capture the distribution data of the active pharmaceutical ingredients by importers, local manufacturers and pharmacies as done in Thailand and other developed countries.(12)

Competing interests: The authors declare that they have no competing interests to disclose.

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