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ANTIMICROBIAL CONSUMPTION AT THE HOSPITAL LEVEL IN LATIN AMERICA. SIMILARITIES AND DIFFERENCES ACCORDING TO EACH COUNTRY.

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ABSTRACT

One of the main problems for health service around the world is the antimicrobial resistance (AMR).
Objective: to describe the antimicrobial consumption (AMC) at hospital level in Latin American countries and compare the amount and type of antibiotics usage among them in order to guide local public health actions towards AMR prevention.
Design: A descriptive study of antimicrobial consumption at hospital level among six health institution in Latin America with an analytical comparative stage. Antimicrobials included corresponded to the WHO Anatomical Therapeutic Chemical (ATC) classification system subgroups: J01, A07A and P01AB.
Methods: WHO GLASS methodology was applied for surveillance of AMC, using the ATC classification based on Defined Daily Dose (DDD) and DDD/100 hospital discharges as standard unit of measurement. Antimicrobials consumed were also classified according to the WHO Access-Watch-Reserve (AWaRe) classification.
Results: The quantitative data, measured in DDD/100 hospital discharges, showed a wide range of consumption (182.48 - 2260.95). Qualitative analysis according to the AWaRe classification also showed a wide range in terms of consumption of Access (38.14% - 73.64%), Watch (24.93% - 60 .53%) and Reserve (0.31% - 3.55%) groups expressed as a percentage of the total consumption.

Conclusion: Great heterogeneity and arbitrariness exist in the selection of antimicrobials for hospital use. Although this situation might be explained on local antimicrobial resistance, the history of prescription, local pharmaceutical promotion, and pharmacological education of health professional in each country, particular habits and distinctive culture may justify the differential consumption patterns observed in each institution in this study.

Key Words: antimicrobials, consumption, Latin America, Hospital, AWaRe, WHO

INTRODUCTION

One of the main problems for health service around the world is the antimicrobial resistance (AMR)[1]. The overuse of antimicrobials has accelerated the emergence and spread of AMR[2]. At least half of the prescriptions of antimicrobials are related to an irrational or unnecessary use[3], whereby the diagnostic tests have discordant results[4] or even when the clinical presentation does not require any antibiotics. Bacteria have developed complex AMR mechanisms to resist the antimicrobial aggression and have left health professionals without new tools to control these situations.

AMR causes failure of empirical treatments, aggravates morbidity, increases mortality, and has negative impact on the costs of care because of ineffective antimicrobial treatment[5]. In addition to this global AMR situation, during the past three decades, no new family of antibiotics has been discovered[2]. The lack of new drug development by the pharmaceutical industry is due to the reduction of economic incentives and challenging regulatory requirements. Thus, AMR has become a serious and increasingly concerning public health threat, with enormous global health, social and political repercussions[1]. In 2015, the World Health Assembly (WHO) approved a global action plan to combat AMR, recognizing it as a global health priority[6] and the Pan American Health Organization (PAHO) Member States, highlighted the importance of raising awareness about AMR, optimizing the use of antimicrobials, reducing the incidence of infection and the spread of resistant microorganisms, and ensuring a sustainable investment in the fight against AMR[7].

For this reason, the WHO proposed in 2017 an antimicrobial classification that considered several therapeutical groups as "access", "watch" or "reserve" groups according to their risk of AMR[8]. The last two groups should be considered for certain situations, mostly at hospital level. Hospitals are special cases to be analyzed for antimicrobial consumption (AMC) since the use of antimicrobials at this level can explain most of the AMR situations observed in the countries.

It is well known that AMC depends on several variables such as level of training of health professionals, the drug use "culture" in each country, the pharmaceutical lobbying that companies exert on governments, the availability of different drugs on the local market, among others.

The aim of this study is to describe the antimicrobial consumption at hospital level in six Latin American countries: Argentina, Chile, Colombia, Costa Rica, Paraguay and Peru and compare the amount and type of antibiotics consumed, using the WHO GLASS AMC methodology for hospitals, in order to guide local public health actions towards AMR prevention in the region.

METHODS

Type of study: Descriptive study of antimicrobial consumption at hospital level with analytical comparative stage among six health institution.

Universe of analysis: General Level III Hospitals in Latin America with similar profiles.

Unit of analysis: Each of the hospitals enrolled in the study.

Sample: From the total number of hospitals in each country, local authorities randomly selected one Level III hospital with similar profile that better represents their health system according to the highest local health authority.

Study Period: The study was conducted from 1st January 2019 to 12th December 2019.

Antimicrobials studied: Antimicrobials included in the study corresponded to subgroups: J01, A07A and P01AB of the WHO Anatomical Therapeutic Chemical (ATC) classification system[10], where J01 constitutes "antibacterial for systemic use", A07A "intestinal anti-infectives", and P01AB "nitro-

imidazole derivatives for diseases caused by protozoa". Sub-groups included in this research are described in Table 1.

Table 1. Antimicrobials evaluated according to the WHO Anatomical Therapeutical Chemical (ATC) Classification.

Subgroup	Antimicrobial
J01A	Tetracyclines
J01B	Amphenicols
J01C	Beta-lactams, penicillins
J01D	Other beta-lactams
J01E	Sulfamides and trimethoprim
J01F	Macrolides, lincosamines
J01G	Aminoglycosides
J01M	Quinolones
J01X	Otherantibacterials
A07A	Neomicine, nistantine, rifamixine, vancomicine
P01AB	Metronidazole, ornidazole, tinidazole

[1] WHO Anatomical Therapeutical Chemical (ATC) Classification.

AMC measurement methodology: Data was evaluated using the WHO GLASS methodology for a global program on AMC surveillance. The ATC classification and Daily Defined Dose (DDD) as a standard unit of measurement to express the average maintenance dose per day for a drug used for its main indication in adults were used[10,11]. DDDs were then transformed in DDD/100 hospital discharges. Antimicrobials consumed were also classified according to the WHO Access-Watch-Reserve (AWaRe) classification[12].

Source of information: AMC data was obtained from sources available in each institution and country in agreement with the local authorities. Sources included pharmaceutical dispensation to each of the hospital areas and interview with the head hospital pharmacists.

Data collection tools: In order to obtain consumption data at the hospital level for subsequent analysis including comparisons over time and between different countries, a common methodology proposed by the World Health Organization (WHO) called "WHO Methodology for the surveillance of antimicrobial consumption in hospitals" was applied in all countries[9].
This tool allows the necessary standardization to make comparisons. The methodological tools that allow this data homogenization were: the ATC classification system for active ingredients; the unit of measure: Defined Daily Dose (DDD), which allows for the standardization of the content of each container[10]; the denominator data: number of hospital discharges ; and the standardized AMC measurement at the hospital level: expressed as DDD/100 hospital discharges.

The antimicrobials prioritized for analysis were antibiotics for systemic use (group J01).

Study Variables: Data obtained from the different institutions consisted in the number of antimicrobials used during the period of study, drug concentration, formulations and pharmaceutical presentations for each antimicrobial on the national market available, area of the hospital where the antimicrobial was used, Defined Daily Dose (DDD) for each antimicrobial, total number of hospital discharges in the study period; and, DDD/100 hospital discharges.

Ethical considerations*:* Nominal patient data were not requested. All the extracted data correspond to consultation of primary sources of each institution regarding the amounts of antimicrobials consumed during the study period. The protocol of study was validated by Pan American Health Organization Ethical Committee (PAHOERC). Ref. No: PAHOERC.0317.01

RESULTS

Six hospitals of equal complexity and level were selected by the health authorities of these countries in order to evaluate the consumption of antimicrobials in these health institutions. The characteristics of these hospitals can be seen in Table 2.

Table 2. Hospital features

Variable	ARG	CHILE	COL	CR	PAR	PERU
Level of Health Care	III	III	III	III	III	III
Number of Beds	156	403	102	413	570	590
Critical Care Unit	Yes	Yes	Yes	Yes	Yes	Yes
Paedriatric Area	Yes	Yes	Yes	Yes	Yes	Yes
Nº of hospital discharges/year	6732	49465	10638	33715	19268	21562

The consumption of antimicrobials corresponding to groups J01, A07A and P01AB was evaluated. In order to obtain comparable data, these consumptions were expressed in relation to the beds used and the patients seen in the period (Table 3).

According to the therapeutic group, overall, it was determined that penicillin and other beta-lactams were the most used antimicrobials followed by sulfonamides and quinolones.

Table 3. Antimicrobial consumption according to ATC Group

ATC	GROUP	ANTIMICROBIAL	ATC5	VIA	ARG	CHILE	COL	CR	PAR	PERU
J01A	Tetraciclines	Doxicicline	J01AA02	O	1,14	0	9,05	137,76	0,13	221,54
		Minocicline	J01AA08	O	1,68	0	0	0	0	0
		Tigecicline	J01AA12	P	1,78	1,21	1,8	0,36	0	0
J01B	Amphenicols	Cloranfenicol	J01BA01	O	0	0	0	0	0	0,27
		Cloranfenicol	J01BA01	P	0	0	0	0	0	1,12
J01C	Beta-lactamics, penicilins	Ampicilin	J01CA01	P	20,24	1,9	4,78	15,73	16,46	6,53
		Amoxicilin	J01CA04	O	7,37	3,03	1,17	140,21	110,9	103,81
		Bencilpenicilin	J01CE01	P	4,18	0,67	17,47	33,48	3,25	0,62
		Bencilpenicilin (Benza)	J01CE08	P	0,35	0,04	0	0,08	2,21	1,56
		Fenoximetilpenicilina	J01CE02	O	0,22	0	0	0	0	0
		Dicloxaciline	J01CF01	O	0	0	0	0	0	0
		Cloxacicline	J01CF02	P	0	3,09	0	0	0	0
		Oxaciline	J01CF04	P	0	0	116,07	32,11	12,32	0,5
		Ampicilina + IBL	J01CR01	P	27,43	4,83	25,62	0	0,26	5,38
		Amoxiciline + IBL	J01CR02	O	19,19	7,68	0,34	0	304,88	148,67
		Piperaciline + IBL	J01CR05	P	23,24	8,49	84,52	1,05	39,47	8,76

J01D	beta-lactamics (other)	Cefalexin	J01DB01	O	10,9	0	1,22	96,47	96,12	29,09
		Cefalotine	J01DB03	P	0	0	4,53	33,83	0	0
		Cefazoline	J01DB04	P	47,42	13,45	91,13	0	0	47,84
		Cefuroxime	J01DC02	O	0	0	0,07	0	0	99,45
		Cefuroxime	J01DC02	P	0	0	2,08	0	0	0
		Cefotaxime	J01DD01	P	0,22	3,82	0	71,99	34,77	1
		Ceftazidime	J01DD02	P	4,11	1,24	0,74	23,34	9,97	43,92
		Ceftriaxona	J01DD04	P	17,11	42,16	9,98	0,04	49,81	162,64
		Cefoperazone + IBL	J01DD62	P	0	0,001	0	0	0,28	0
		Cefepime	J01DE01	P	0	0,34	19,76	0	53,8	0
		Aztreonam	J01DF01	P	0	0,001	0,65	0	0	0
		Meropenem	J01DH02	P	6,97	2,33	41,9	12,53	9,01	89,33
		Ertapenem	J01DH03	P	0	0,71	3,06	4,73	0	2,12
		Imipenem + cilastatina	J01DH51	P	8,46	0,34	0	0,36	39,58	32,09
		Ceftolozane + IBL	J01DI54	P	0	0,002	0	0	0	0
J01E	Sulfonamides / trimetoprime	Sulphadiazine	J01EC02	O	19,16	0	0	0	0	0
		Sulphaametoxazole	J01EC02	O	0	0	0	13,13	0	0
		Sulphametoxazole/trim	J01EE01	O	12,81	6,22	13,03	224,75	18,09	161,03
		Sulphametoxazole/trim	J01EE01	P	22,65	1,03	3,69	0,09	0,2	2,73
J01F	Macrolides& lincosamides	Eritromicine	J01FA01	O	4,4	0	0,65	0	0	2,49
		Espiramicine	J01FA02	O	0	0	0,2	2,9	0	0
		Claritromicin	J01FA09	O	8,3	2,77	1,86	77,55	89,15	77,95
		Claritromicin	J01FA09	P	5,79	0	2,65	0	0	0
		Azitromicin	J01FA10	O	0	8,6	5,04	0,87	244,68	252,23
		Azitromicin	J01FA10	P	0	0,06	0	0	0	0
		Clindamicine	J01FF01	O	5,01	0	0,1	0,8	0	35,39
		Clindamicine	J01FF01	P	24,54	6,68	32,66	33,94	25,21	68,95
J01G	Aminoglucosides	Gentamicine	J01GB03	P	16,38	0,79	9,73	14,04	37	12,12
		Amikacine	J01GB06	P	3,68	4,04	11,17	5,93	19,62	34,41
J01M	Quinolones	Ciprofloxacin	J01MA02	O	25,4	13,88	3,13	53,69	293,28	207,98
		Ciprofloxacin	J01MA02	P	25,07	2,11	11,73	0	56,15	23,35
		Norfloxacin	J01MA06	O	0	0	0,53	0	0	0
		Levofloxacin	J01MA12	O	0	0,34	0	0	63,54	94,28
		Levofloxacin	J01MA12	P	0	0,25	0	4	19,14	0
		Moxifloxacin	J01MA14	O	0	0,32	0	0	0	10,89
		Moxifloxacin	J01MA14	P	0	0,002	0,26	0	0	0
J01XA	Glucopeptides	Vancomicin	J01XA01	P	11,66	10,21	0,59	38,09	69,71	70,5

J01XB	Polimixineas	Colistin	J01XB01	P	3,86	3,46	2,62	0,11	14,48	7,03
		Polimixina B	J01XB02	P	0	0	2,62	0	0	0
J01XD	Imidazoles	Metronidazol	J01XD01	P	42,07	16,14	15,75	17,78	0	38,42
J01XE	Nitrofurane	Nitrofurantoina	J01XE01	O	0,73	0	0	73,01	0	48,8
J01XX	Otherantibacterials	Fosfomicine	J01XX01	O	0	0	0,26	0	0	0
		Linezolid	J01XX08	O	0	0,13	4,17	1,07	0	33,6
		Linezolid	J01XX08	P	0,15	1,66	0	2,1	0	3,27
		Daptomicine	J01XX09	P	0	0	0,69	0	0	0
TOTAL					**433,7**	**182,48**	**599,93**	**1167,91**	**1771,61**	**2260,95**

In relation to the routes of administration, it is possible to establish that in Argentina, Chile and Colombia, the predominant route of administration for antimicrobials was parenteral; while in Costa Rica, Paraguay and Peru, the predominant route was oral (table 4).

Table 4. Antimicrobial consumption according to the route of administration

	Consumption (DDD/100 hospital discharges)	**Analysis According to route of administration** (% overall global consumption)	
		Oral	**Parenteral**
ARGENTINA (Hospital SR)	433.68	26.82	73.18
CHILE (Hospital NN)	182.48	23.55	76.45
COLOMBIA (Hospital La Samaritana)	599.93	6.80	93.20
COSTA RICA (Hospital RCG)	1167.91	70.40	29.60
PARAGUAY (Hospital NI)	1771.61	71.94	28.06
PERU (Hospital DM)	2260.95	70.62	29.38

Interview conducted with head pharmacists in each hospital sustained that the main reasons for antimicrobials prescription profile disparities was the pharmaceutical industry promotion among prescribers (100%), local antimicrobial resistance (83.3%), prescription history/habit (83.3%), pharmacological training of health professionals at university, and culture of the institution (66.6%).

Utilizing the WHO AWaRe classification, which emphasizes the importance of their optimal use and potential for antimicrobial resistance, it is observed that there is a predominance of the use of drugs from the Access group, with the exception of hospitals in Chile, Paraguay and Peru.

All hospitals in the countries have had a low consumption of antimicrobials from the Reserve group (Table 5).

Table 5. Antimicrobial consumption according to AWaRe Classification

	Consumption (DDD/100 hospital discharges)	**Global analysis according to AWaRe classification** (% overall global consumption)			
		Access	**Watch**	**Reserve**	**Without classification**
ARGENTINA (Hospital SR)	433.68	61.41	32.84	1.33	4.42
CHILE (Hospital NN)	182.48	38.14	58.31	3.55	0.0005
COLOMBIA (Hospital La Samaritana)	599.93	59.69	38.56	1.75	-
COSTA RICA (Hospital RCG)	1167.91	73.64	24.93	0.31	1.12
PARAGUAY (Hospital NI)	1771.61	38.66	60.53	0.82	-
PERU (Hospital DM)	2260.95	45.91	52.15	1.94	-

DISCUSSION

Knowing the consumption of antimicrobials in a health institution is the first step to improve the rational use and reduce bacterial resistance of these drugs. To determine this consumption, it is necessary that the measurement instruments are standardized and validated to be able to compare within the institution and with other institutions. The WHO GLASS methodology for AMC monitoring is an excellent tool that fulfills these functions and allows for data to be collected on an aggregated level[10]. The flexibility in the data sources for AMC enables each hospital to use pre-existing data to build up sustainable systems for AMC surveillance. This approach builds upon the long-term practice developed by the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) of the European Centre for Disease Prevention and Control (ECDC) to monitor hospital national trends in AMC over time[11]. Hospitals are encouraged to link AMC data with clinical and microbiological data to learn about the indications for antimicrobial use and improve practices in each area.

Results from this study showed wide variations in the quantity and types of antimicrobials consumed among the hospitals. This is likely reflection of actual differences in AMC culture in each country and each hospital but might also be partially attributed to differences in data coverage in each health system.

At the time of data analysis of this heterogeneity, it was important to keep in mind that some of the hospitals collected ATM consumption data only for hospitalized patients, while others have included consumption for hospitalized patients and for patients in outpatient treatment, this being a cause of the great dispersion in the results obtained for each one of the hospitals.

On the type of antimicrobial consumed, the majority of antimicrobials consumed in all countries, belonged to the "Access" and "Watch" groups, which is the expected/logical situation concerning the former group and a yellow alert flag in the case of the latter[12].

The limitations of the study and the potential problems in obtaining regular AMC information from hospitals are related to the absence of local information[13], the fluctuation of local manager engagement, the lack of resources, the lack of rules and regulations, and the limited staff assigned to this work [14].

The evaluation of AMC at hospital level is not yet a well-developed and standardized process in countries of the Americas. One of the main problems, especially in pediatric hospitals, is the lack of a reference DDD for the child population. However, it should be remembered that the data obtained is used to compare the evolution of consumption within the same institution and with other institutions. Therefore, if consumption is always measured with the same tool and in the same way, the data will be useful to meet these objectives. This study has set a path for standardization and systematization of a methodology for this purpose.

Knowing the current situation is the first step to identify the elements that must be improved; therefore, consumption studies will be the basis for future incorporation in the hospitals for projects to optimize the Use of Antimicrobials, such as PROA, or the enrollment of the institution in a WHO GLASS-AMC project[15]. Studies like this one will encourage the authorities of other hospitals, which in turn will allow them to make the right decisions not only with regards to improving use of these medicines, but also avoiding resistance to antibiotics.

CONCLUSION

Data provided in this study shows a hospital quantitative and qualitative reality in the six hospitals in the Latin American countries. The selected hospitals reflect the situation exhibited by some of the institutions, which, as observed, is heterogeneous in terms of the antimicrobial consumption, as well as the amount and the type of antibiotic used according to its bacterial resistance risk classification.

The quantitative data, measured in DDD/100 hospital discharges, show that there is a consumption with a wide range (182.48 - 2260.95). In a qualitative point of view, according to the AWaRe classification there was also a wide range in terms of consumption of the groups Access (38.14% - 73.64%), Watch (24.93% - 60 .53%) and Reserve (0.31% - 3.55%), expressed as a percentage of total antimicrobial consumption.

The enrolled institutions presented great heterogeneity and arbitrariness in the selection of antimicrobials for hospital use. While some countries prefer some drugs from certain therapeutic groups, others hardly utilize these, despite the consumption of large amounts of another drug from the same group. Although this situation might be explained on local antimicrobial resistance, it is clear that the history of prescription, pharmaceutical industry promotion, and pharmacological education of health professional in each territory, has developed particular habits and distinctive culture that justify the differential consumption patterns observed in each institution.

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CONFLICTS OF INTEREST:

Authors are either Health ministry staff of each country, WHO and PAHO members or independent consultants and declare no conflict of interest.

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