

Consumption of benzylpenicillin as a syphilis control indicator

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Syphilis is a disease with compulsory and mandatory notification to the Notifiable Diseases Information System (SINAN), with benzathine benzylpenicillin being the treatment of choice. The aim of the study was to compare the consumption of benzylpenicillin benzathine, from the dispensation, between the health regions of a capital in the southern region of the country, according to the georeferencing of notified cases of syphilis. This is a descriptive, cross-sectional, retrospective study of the use of benzylpenicillin benzathine and of reported cases of syphilis. Data on syphilis cases were obtained from notifications made in SINAN, and drug consumption data were obtained from the Municipal Health Department computerized system for Drug Dispensing from January 1st, 2019 to December 31st, 2019. Notifications and drug consumption were georeferenced according to 8 health regions. From the compilation of data, the rates of cases and consumption in relation to the population of each region were calculated. A total of 3188 notifications and a total of 35191 vials of benzathine benzylpenicillin were analyzed. The ratio of vials by SINAN notifications showed that each patient took 11 vials of the drug, which is a higher value if we consider that the complete treatment is 2 to 6 vials per case.

Keywords: Pharmaceutical care. Syphilis. Georeferencing. Health surveillance.

INTRODUCTION

Syphilis is a Sexually Transmitted Infection (STI) caused by *Treponema pallidum* bacterium and can be classified as acquired, gestational and congenital. It demands compulsory and mandatory notification to the Notifiable Diseases Information System (SINAN). Syphilis infection is easily identifiable and treatable, yet infection rates continue to increase worldwide. (Brazil, 2015; Kojima, Klausner, 2018).

According to the World Health Organization (WHO), there are about 6 million new cases of syphilis every year worldwide, in people aged between 15 and 49 years. The rate for men and women is similar in the world context: 17.2 and 17.7 per 100,000 inhabitants, respectively. In Africa and Western Pacific, women have higher rates, whereas in

Europe, the rate is higher among men (Arando Lasagabaster, Otero Guerra, 2019; Kojima, Klausner, 2018).

The effective control of syphilis requires a broad effort combining health managers and national involvement to expand access to diagnosis and treatment for the population, seeking partnerships in order to overcome barriers such as the use of benzathine benzylpenicillin in primary care (Brazil, 2018a).

Penicillin, a beta-lactam antibiotic, is chosen for treating syphilis, with benzylpenicillin (Penicillin G Benzathine) included in the Municipal List of Essential Medicines (REMUME) and indicated for all classifications of syphilis (Brazil, 2018b).

Drug use studies are important epidemiological research strategies that can contribute to the understanding of drug use in different situations in order to establish information that helps in interventions that promote the Rational Use of Medicines (RUM), as well as improvement in health care services (Magarinos-Torres, Osório-de-Castro, Pepe, 2007).

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Another strategy to understand health relationships is georeferencing, which consists of a process where descriptive textual information of a location, such as the address related to a health event, is converted into geographic representations in the form of maps (Silveira *et al.*, 2017).

Health indicators related to syphilis serve to analyze the behavior of the disease, its exponential increase in the general population, as well as the impact on primary health care (Santos *et al.*, 2021).

The aim of this study was to compare the consumption of benzylpenicillin benzathine, from the dispensation, between the health regions of a capital in the southern region of the country, according to the georeferencing of notified cases of syphilis.

MATERIAL AND METHODS

This is a descriptive cross-sectional study with retrospective secondary data analysis of the use of benzylpenicillin benzathine for syphilis treatment in primary health care (PHC) and of syphilis cases reported from January 1st to December 31st, 2019.

Data on syphilis cases were obtained from notifications made to SINAN through the Business Intelligence (BI) system of health surveillance in a capital in the southern region of the country. For the analyses in this study, the database was composed of cases of acquired and gestational syphilis, excluding cases of congenital syphilis.

Data for consumption of benzathine benzylpenicillin were extracted from the Municipal Health Department computerized system for Drug Dispensing (DIS). As a metric for drug consumption, we used the number of dispensed vials. The consumption database was composed by the relationship of patients with the dispensations made and the number of vials dispensed in the period. Patients with up to 12 vials dispensed were included directly in the consumption calculation, and patients with 13 or more vials dispensed were included after confirming their names in the SINAN database.

According to the city's protocol, for primary, secondary and recent latent syphilis, the dose for treatment is 2,400,000 international units (IU) in a single dose (2 vials), and, for tertiary and late latent syphilis,

the dose is 2,400,000 IU for 3 weeks, totaling 7,200,000 IU (6 vials). For the treatment of gestational syphilis, the same dosages presented for acquired syphilis are used (2 vials) (Porto Alegre, 2018).

Data categorization for the development of descriptive statistics was performed using Microsoft Excel®. From the databases, notified cases and drug consumption were divided according to the health regions of the city, according to the address of the place where the notification was made and the drug was dispensed.

The municipality has an administrative division of 8 health regions that were used in the analysis of notified cases and drug consumption georeferencing. SINAN notifications were georeferenced according to the 8 health regions and divided into acquired and gestational syphilis according to the month of diagnosis. Drug consumption data were analyzed according to the 8 health regions of the city surveyed and by month. The rates of syphilis cases and drug consumption per 100,000 inhabitants and the relationship between dispensed vials and reported cases were then calculated.

The ethical criteria established by Resolution #466/2012 of the National Council of Ethics in Research Guidelines and Regulatory Norms for Research Involving Human Beings were adopted in the research, ensuring confidentiality of accessed data. The research project was submitted to the respective Municipal Health Department through a research authorization application and approved. The researchers signed the Term of Commitment to Use the Data. This project was submitted to the relevant Research Ethics Committee in and was approved via Plataforma Brasil under the number CAAE 31507620.2.0000.5329.

RESULTS

A total of 3188 notifications in SINAN were analyzed, 2222 (69.70%) of acquired syphilis and 966 (30.30%) of gestational syphilis. In relation to health regions, it was observed that region 6 had the highest number of notifications (20.23%), followed by regions 5 (15.65%) and 2 (13.64%) according to the georeferencing performed. The months with the highest frequencies of notifications were January (10.73%), followed by August (9.88%) and May (9.82%), as shown in Table I.

TABLE I - Syphilis notifications in SINAN in 2019 by health region and month

Health Region	Syphilis/ Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total partial	Total	%
1	A	31	25	20	17	38	26	18	18	14	24	22	16	269	322	10,10
	G	7	2	7	2	5	3	4	6	5	4	5	3	53		
2	A	41	30	18	27	35	23	20	25	22	12	20	10	283	435	13,64
	G	11	10	12	19	16	12	18	14	13	13	8	6	152		
3	A	15	14	23	17	25	26	20	18	15	14	20	18	225	356	11,17
	G	10	8	12	9	11	12	16	11	12	8	7	15	131		
4	A	38	30	21	21	28	30	26	20	18	22	12	15	281	352	11,04
	G	3	7	4	6	5	4	10	9	9	10	2	2	71		
5	A	39	23	40	27	45	23	28	30	18	20	20	22	335	499	15,65
	G	16	6	9	16	12	15	19	26	14	12	11	8	164		
6	A	59	37	33	32	36	34	37	46	41	34	40	26	455	645	20,23
	G	13	19	11	17	17	17	24	18	16	20	11	7	190		
7	A	20	11	13	16	12	10	8	18	7	16	9	10	150	257	8,06
	G	10	7	6	9	11	13	6	15	17	6	4	3	107		
8	A	25	23	18	19	12	20	15	24	16	23	16	13	224	322	10,10
	G	4	2	9	7	5	7	19	17	7	8	5	8	98		
Total		342	254	256	261	313	275	288	315	244	246	212	182		3188	
%		10,73	7,97	8,03	8,19	9,82	8,63	9,03	9,88	7,65	7,72	6,65	5,71			

Key: Acquired (A). Gestational (G).

A total of 35191 vials of benzathine benzylpenicillin were dispensed and registered in the DIS system in 2019. These records account for dispensing for 7633 users with up to 12 vials dispensed and 53 with 13 or more vials dispensed, for a total of 7686 people.

Region 6 had the highest number of dispensed vials, 5852 (16.63%), followed by region 1 with 5691 vials (16.17%) and region 5 with 4841 vials (13.76%). It was observed that the highest frequencies of dispensations were in the months of July (9.03%), followed by January (8.82%) and April (8.76%), as shown in Table II.

TABLE II - Number of benzathine benzylpenicillin vials dispensed in 2019 by health region and month

Health Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total	%
1	544	382	410	457	506	405	436	448	510	533	543	517	5691	16,17
2	363	316	296	354	363	312	450	504	368	293	257	255	4131	11,74

TABLE II - Number of benzathine benzylpenicillin vials dispensed in 2019 by health region and month

Health Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total	%
3	260	244	225	301	361	301	422	297	366	441	421	376	4015	11,41
4	302	275	193	304	313	272	346	308	355	350	283	239	3540	10,06
5	379	317	342	432	422	407	438	437	414	365	456	432	4841	13,76
6	624	580	391	456	544	376	522	508	437	500	463	451	5852	16,63
7	291	234	230	240	218	233	145	115	310	233	265	279	2793	7,94
8	340	361	267	538	247	435	419	443	311	333	359	275	4328	12,30
Total	3103	2709	2354	3082	2974	2741	3178	3060	3071	3048	3047	2824	35191	
%	8,82	7,70	6,69	8,76	8,45	7,79	9,03	8,70	8,73	8,66	8,66	8,02		

Source: Municipal Health Department.

When comparing the number of cases and the consumption of vials in the entire municipality, there is a variability in the consumption graphs that is not

accompanied by the case graphs (Figure 1). When analyzed separately by region, there is variability in all regions. Regions 7 and 8 show discrepancies between the graphs, in the 1st semester and in the 2nd semester respectively.



FIGURE 1 - Graphs of the number of vials dispensed and cases reported through the months of 2019.

The rates of cases and consumption (vials) per 100,000 inhabitants, as well as the consumption of vials per case of syphilis reported by health region, are shown in table III. Regions 6, 2 and 7 had the highest rates of

cases and consumption, and regions 1, 8 and 4 had the lowest. Regions 1, 8 and 3 had the highest consumption of vials for each notified case of syphilis, and regions 6, 2 and 5 had the lowest.

TABLE III - Syphilis case rates and benzathine benzylpenicillin consumption by health regions

Health Region	Population	Cases	Cases/ 100.000 hab	Bottles	Bottles/ 100.000 hab	Bottles/ case
1	291.047	322	111 (8 ^a)	5691	1955 (7 ^a)	17,7 (1 ^a)
2	157.031	435	277 (2 ^a)	4131	2631 (3 ^a)	9,5 (7 ^a)
3	158.549	356	225 (5 ^a)	4015	2532 (4 ^a)	11,3 (3 ^a)
4	192.285	352	183 (6 ^a)	3540	1841 (8 ^a)	10,1 (5 ^a)
5	199.757	499	250 (4 ^a)	4841	2423 (5 ^a)	9,7 (6 ^a)
6	181.710	645	355 (1 ^a)	5852	3221 (1 ^a)	9,1 (8 ^a)
7	98.438	257	261 (3 ^a)	2793	2837 (2 ^a)	10,9 (4 ^a)
8	200.284	322	161 (7 ^a)	4328	2161 (6 ^a)	13,4 (2 ^a)
Total	1.479.101	3.188	216	35.191		11,0

Source: IBGE 2018 Estimate, Competence Dec 2019.

DISCUSSION

This study compared the use of benzathine benzylpenicillin between health regions according to the georeferencing of notified cases of syphilis. The challenge of this study was to observe two public databases that address syphilis in the city — one from the perspective of diagnosis and the other from the perspective of treatment — and analyze the profile of this health problem. We identified differences between regions both with regard to cases and drug consumption and the rate of treatment (vials/case).

Syphilis is a health problem with compulsory notification, and this notification has the main function of providing data for the implementation of public health policies that promote, protect and control the health of the population. All identified cases need to be reported to the health services. The number of cases of the disease in Brazil continues to increase, and the occurrence of incomplete reports makes it difficult to develop public

policies to implement preventive strategies (Garbin *et al.*, 2019; Brazil, 2016).

Analyzing the place where syphilis patients live and recognizing the various factors that can contribute to the monitoring of this health problem can contribute to the quality of care for these users. The relationship established between the treatment provided and the pickup site can help evaluate how health actions can be planned. In our results we identified different case rates as well as different drug dispensing rates between different health regions.

Social determinants of health, such as living and working conditions of individuals and population groups, are related to their health situation. Among the challenges to understanding the relationship between social determinants and health are for health units to establish different approaches to factors of social, economic and political nature and to mediate how these factors affect the health situation of groups and people, without a simple direct cause-effect relationship. The organization and

the functioning of health services by managing social, economic, cultural, ethnic-racial, psychological and behavioral factors of users in their territory contribute to promoting the health of users in their assigned region (Buss, Pellegrini Filho, 2007).

In the Northeast region of Brazil from 2008 to 2015, an ecological study investigated the spatial distribution and analyzed the incidence of congenital syphilis, concluding that it is associated with social vulnerability (Souza *et al.*, 2020).

Another study, conducted in southern China, showed an uneven geographic distribution of reported syphilis cases between cities, with a higher number of notifications of acquired syphilis followed by congenital syphilis, which is in line with our data. This same study revealed a potential risk of syphilis transmission in rural areas, due to its lower accessibility to health services (Wong *et al.*, 2018).

In this context, another study carried out in a southern province of China showed that most cases of syphilis were among farmers or unemployed population, with less education in sexual health. This observation partly reflected lower accessibility to health services and to sexual health education among infected cases in the city, highlighting the importance of expanding public health interventions aimed at older adults in rural areas, such as sexual health education and promotion of use of condom (Peng *et al.*, 2021).

A study carried out in Poland reports that despite the availability of diagnostic tests and effective treatment, problems with surveillance and reporting of this infectious disease occur. Although notification to the epidemiological surveillance system is mandatory, health professionals' low awareness generates underreporting (Teter *et al.*, 2019).

According to Wong *et al.* (2018) sexual partners of positive cases are at higher risk of becoming infected, and effective partner notification and contact tracking are crucial for identifying syphilis cases possibly related to the same sexual network. In addition to expanding the coverage of screening and partner notification, it is necessary to implement actions to reduce the risk in the identified locations to intervene in continuous transmission in the community (Wong *et al.*, 2018).

A study published in 2021 evaluated the evolution of syphilis incidence in Sibiu County (Romania) over a period of 10 years (2009–2018). It concluded that patients with syphilis were mainly from urban areas (67.42%), where there is more access to the internet and sexual activity is more intense, with multiple partners, sometimes of the same sex, and without the use of condom (Iancu, Rotaru, 2021).

The theoretical framework establishes a relationship between syphilis and social determinants. The health regions of the analyzed municipality have social vulnerabilities that are characterized in different ways and this is demonstrated by the analyzed data. Access to health services, population profile, economic income and education are strongly present in geographic indicators associated with georeferencing and can influence the results of syphilis cases, both gestational and acquired.

Another aspect linked to syphilis is related to the differences between the way syphilis is treated in health care regions. When the rates per 100,000 inhabitants are analyzed, there is no great variability between the health regions, but there are differences in the rates of vials/cases treated. The region with the highest syphilis rates — region 6 — also presented the lowest treatment rate (9.1 vials/case), whereas region 1 had the lowest syphilis rates and the highest treatment rate (17.7 vials/case). Due to the characteristics of the study and the limitations of the databases, it is not possible to point out the differences between the health regions, but the analysis methodology indicated clear differences in the treatment of syphilis in the city studied and highlights the importance of evaluating these peculiarities.

The calculated rates serve as indicators to analyze how benzathine benzylpenicillin is used and can be an important strategy for monitoring the treatment of syphilis, since it is not possible to assess the effectiveness of the treatment in the real world as patients do not undergo the test to control the cure after treatment, even with the indication of the protocols.

Benzathinebenzylpenicillin 1,200,000 IU is mainly indicated for primary, secondary and recent latent syphilis, and in some situations to prevent the recurrence of rheumatic fever and acute bacterial pharyngitis in cases of non-adherence to first-line treatment with

amoxicillin. The National Policy of Pharmaceutical Assistance comprehends the expansion of access to medication through primary health care (Janier *et al.*, 2021; Brazil, 2018b).

In Brazil, the treatment for primary, secondary and recent latent syphilis consists of a single dose of 2,400,000 IU of benzathine benzylpenicillin, which should be favorable for controlling the disease; however, it does not reflect the consumption values found.

The relation of vials per case showed that each patient consumed 11 vials of the drug, which is a high value when we consider that the complete treatment would be 2 to 6 vials per case, even if the drug is used for other health problems. This study used a methodological approach that indicated significant differences in the regions evaluated: 9.1 vials per case in region 6 and 17.7 vials per case in region 1. Differentiated access can justify these values.

It is noteworthy that the medication can be dispensed at any health unit in the city, and the user can pick up the medication at any health unit in the city. The therapeutic itinerary in the search for medication in the health care network is a potential of the unified health system. The way in which this dynamic is established may limit the analysis of cases by drug pickup. Several factors can lead to the search for health services and dispensing. Geographic location and access to public transportation can be cited as barriers to accessing the drug (Demétrio, Santana, Pereira-Santos, 2019).

With this macroscopic analysis of consumption versus cases, we verified that the proposed methodology can indeed be used to assess differences and variations between health regions. We were able to point out that these differences are relevant and that the characteristics of the regions are decisive in the results. It is also necessary to reflect on the work processes and management of these services that may have some influence on the results and need to be researched and evaluated.

As limitations of this study, we can primarily mention that data on cure or relapse of syphilis were not used. Patients who picked up more than 12 vials of the drug, who had no notification in SINAN, who started treatment in December 2018 were not considered. Cases of congenital syphilis and the dispensing of benzylpenicillin for the treatment of other conditions were not included.

As a limitation of this study, we present that the results cannot be extrapolated to the use of this drug, as they are records of drug withdrawal in places where this drug is dispensed. The research carried out analyzed secondary data available in two independent databases, comparing data between health regions. The confirmation of the use of this drug and the effectiveness of the treatment needs more comprehensive studies so that the data can be extrapolated to other realities in the national territory.

CONCLUSION

The proposal to obtain an indicator for evaluating the control of syphilis using data on the consumption of benzathine benzylpenicillin, from dispensing records, compared with the reported cases and georeferencing health regions establishes assumptions for health management in PHC from the monitoring and follow-up of data processed with syphilis notifications and drug withdrawal at this level of health care.

With the visualization of the georeferencing of syphilis cases from the withdrawal of the drug, health management guidelines are established with data linked to social determinants that can impact public policies related to the drug. The recognition of the rational use of medication in different communities and related health services impacts the National Pharmaceutical Assistance Policy, enabling the establishment of effective lines of care for health users with syphilis

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