



HOSPITAL ADMISSIONS DUE TO ADVERSE REACTIONS AND DRUG INTOXICATIONS IN PATIENTS UNDER 5 YEARS OF AGE IN BRAZIL: ANALYSIS FROM 2000 TO 2017

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ABSTRACT

The objective of this study was to analyze the trend of hospitalizations due to adverse reaction and drug poisoning in patients aged less than 5 years, in Brazil from 2000 to 2017. Data were from the Hospital Information System systems and the population was analyzed by sex and region of residence. The trend analysis of the historical series was performed using the Prais-Winsten method. The hospitalizations due to adverse reaction and drug poisoning presented a declining trend. The analysis by regions showed the Northeast and Southeast regions with a declining trend, and the North, Central West and South regions with a steady trend. The cases of MI and RAM contribute to the increase in the occurrence of hospitalizations of children under 5 years of age and information systems such as the SIH-SUS are extremely important for studies that monitor hospital morbidity.

KEYWORDS : poisoning, Drug-Related Side Effects and Adverse Reactions; Hospital Information Systems

INTRODUCTION

Deaths and injuries caused by intoxications among children remain at the beginning of the 21st century as important challenges to be faced by several countries^{1,2,3}. Although fatal events have declined substantially in the last decades⁴, thousands of cases are still reported annually in control centers around the world, with medicines being the main agents^{1,3}.

It is estimated that they are present in 42.7% of cases, with a regional variation of 30.0% to 80.0%³. In Brazil, in 2016 alone, 27,261 cases of drug poisoning were reported in the National Toxic-Pharmacological Information System (SINITOX), representing 34.0% of all registered poisonings and 32.0% of those with minor children of 5 years old⁵. A study conducted with data from the Hospital Information System (SIH) identified that between 2002 and 2013, 17,725 hospitalizations were reported for drug intoxications in children under 5 years of age⁶.

Despite the fact that Brazil has a national registry of toxic-pharmacological information and public-sector hospitalizations, it is believed that these data are underestimated, mainly by low participation of the Information and Assistance Centers (CIAT's).

Given this scenario, the Hospital Information System (SIH-SUS) is a great ally for the monitoring of these diseases. Despite its existence and recognized quality, few studies of national scope that bring data on hospitalizations due to drug intoxication in children under 5 years of age^{6,8,9,10,11}.

In this context, the objective of the present study was to analyze hospital admissions, due to adverse reaction to medication and drug intoxication, indicating its trend in the country, according to sex and region of residence, between 2000 and 2017.

METHODS

This is an ecological time series study. Data on hospital admissions are from the Hospital Information System of SUS (SIH-SUS) and data on the number of inhabitants are from the censuses of 2000 and 2010 and from intercensal estimates made by the Brazilian Institute of Geography and Statistics (IBGE).

The hospitalizations analyzed were those that present as the primary diagnosis of hospitalization the following codes of the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10): adverse effects related to adverse drug reactions (ADR) - T88.6, T88.7 and Y40 to Y57; (F11.0, F13.0, F15.0, F19.0, F55, T36 to T39, T40.2 to T40.4, T41 to T50, X40, X41, X43, X64, X60, X61, X63, X64, X85, Y10, Y11, Y13 and Y14. The codes X42, X62 and Y12 were suppressed to avoid the selection of codes that do not allow to differentiate the intoxications caused by drugs from those caused by licit and illicit drugs. Exposure conditions for MIs participating in the study were obtained by codes X40 to X44 (accidental condition), X60 to X64 (autointoxication), X85 (aggression) and Y10 to Y14 (circumstance not determined).

The analysis of hospitalizations for adverse reactions and drug intoxication was performed according to the sex (female and male) and the region of residence of the patient (North, Northeast, Midwest, Southeast and South of Brazil). The trend analysis of the historical series was performed using generalized linear regression using the Prais-Winsten method, with correction for the first order autocorrelation effect¹². The trend of hospital admissions was considered stationary when $p > 0.05$; declining when $p < 0.05$ and coefficient of negative regression; or ascending when $p < 0.05$ and coefficient of positive regression. To avoid roughness in the polygon delineated in the graphs caused by the random variation in the time series, the smoothing feature was used by moving averages of order 3¹³. The analyzes were performed in Stata 15.

RESULTS

Between 2000 and 2017, 25,877 hospital admissions for drug intoxication (MI) and 428 admissions for adverse drug reactions (ADR) were registered in children under 5 years of age in Brazil. The coefficient of hospitalizations for MI and ADR under the age of 5 years decreased by approximately 34.0%, from 11.8 hospitalizations / 100,000 inhabitants in 2000 for 7.8 hospitalizations / 100,000 inhabitants in 2017.

The mean rates of hospital admissions for MI and ADR in children under 5 years of age were slightly higher in males during the study period (Table 1).

Table 1 - Coeficientes médios de hospitalizações (por 100 mil hab.) Por medicamentos e intoxicações por medicamentos, segundo sexo, Brasil e regiões, 2000-2017.

Sex	Brazil	North	Northeast	Center-West	Southeast	South
Adverse reactions						
Male	0.15	0.08	0.10	0.18	0.19	0.19
Female	0.15	0.07	0.09	0.22	0.20	0.15
Both	0.15	0.07	0.10	0.20	0.19	0.17
Intoxications						
Male	9.38	4.30	6.40	13.65	10.98	13.43
Female	8.75	3.67	5.88	12.48	10.46	12.64
Both	9.07	3.99	6.14	13.07	10.72	13.04
Both						
Male	9.53	4.38	6.51	13.82	11.17	13.62
Female	8.50	3.74	5.97	12.70	10.65	12.79
Both	9.22	4.07	6.24	13.27	10.92	13.21

The prevalence of occurrences in the Central-South regions, above the national average, is observed in the historical series of hospitalization rates by MI and AMR in children under 5 years of age during the study period. The North and Northeast regions remained below this average. The Central-West region presented the highest averages and the North region, the lowest (Figure 1).

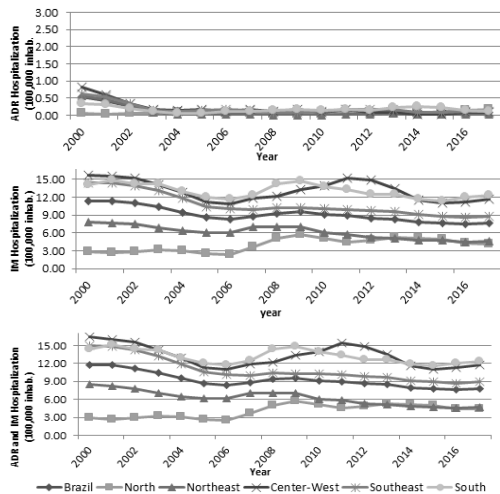


Figure 1 Historical series of hospitalization rates due to adverse reactions (ADR) and intoxications (IM) for drugs under 5 years, Brazil and regions, 2000-2017.

For IM, intoxication by diuretics and other drugs, drugs and biological substances (T50) ranked first in 2000 (45.0%), 2010 (30.4%) and 2017 (38.8%). For AMR, the main cause of hospitalization in 2000 was the adverse reaction to other drugs and medications and unspecified (Y57) (37.8%); as early as 2010 and 2017 was the unspecified adverse drug or drug effect (T88.7) (57.1% and 73.3%, respectively).

In the trend analysis for hospital admissions for MI and ADR in children under 5 years in Brazil, there was a decline in both sexes during the period studied. The analysis by regions shows the North, Center-West and South with stationary trends, and Northeast and Southeast with declining trends. There were differences between the sexes in the North and South regions. In the male sex, the first presented an upward trend and the second one declined (Table 2).

Table 2 - Total hospitalizations, regression coefficient and trend of hospitalizations due to adverse reactions and drug intoxications, according to sex, Brazil and regions, 2000-2017.

Sex	Hospitalizations	Coefficient	CI (95%)		p	TREND
			lower	upper		
Brazil						
Male	13,857	-0.23	-0.34	-0.11	0.001	Declining
Female	12,448	-0.23	-0.36	-0.09	0.003	Declining

Both	26,305	-0.23	-0.35	-0.10	0.001	Declining
Region North						
Male	669	0.17	0.00	0.34	0.044	Ascending
Female	551	0.09	-0.04	0.22	0.157	Stationary
Both	1,220	0.13	-0.02	0.28	0.089	Stationary
Region Northeast						
Male	2,934	-0.23	-0.30	-0.15	0.000	Declining
Female	2,592	-0.19	-0.29	-0.10	0.001	Declining
Both	5,526	-0.21	-0.29	-0.13	0.000	Declining
Region Center-West						
Male	1,482	-0.18	-0.42	0.05	0.118	Stationary
Female	1,304	-0.25	-0.64	0.14	0.194	Stationary
Both	2,786	-0.24	-0.54	0.07	0.119	Stationary
Region Southeast						
Male	6,216	-0.35	-0.52	-0.18	0.000	Declining
Female	5,708	-0.36	-0.54	-0.17	0.001	Declining
Both	11,924	-0.36	-0.54	-0.18	0.001	Declining
Region South						
Male	2,556	-0.19	-0.38	0.00	0.048	Declining
Female	2,293	-0.07	-0.24	0.10	0.420	Stationary
Both	4,849	-0.13	-0.30	0.04	0.132	Stationary

The trend analysis performed separately for IM and RAM by regions presented steady trends for the South region. The other regions showed differences between trends of each event, and the Northern region showed a steady trend for MI and ascending for ADR; the Northeast, declining for IM and stationary for RAM; and the Midwest, stationary for MI and declining for ADR (Table 3).

Table 3 - Total hospitalizations, regression coefficient and trend of hospitalizations due to adverse reactions (ADR) and intoxications (IM) by drugs under 5 years, according to the event of interest, Brazil and regions, 2000-2014.

	Hospitalizations	Coefficient	CI (95%)		p	Trend
			Lower	Upper		
Brazil						
ADR	428	-0.02	-0.04	0.00	0.049	Declining
IM	25,877	-0.21	-0.32	-0.09	0.001	Declining
Região Norte						
ADR	22	0.00	0.00	0.01	0.046	Ascending
IM	1,198	0.12	-0.04	0.28	0.122	Stationary
Região Nordeste						
ADR	89	-0.02	-0.05	0.00	0.064	Stationary
IM	5,437	-0.19	-0.27	-0.12	0.000	Declining
Região Centro-Oeste						
ADR	42	-0.03	-0.05	-0.01	0.018	Declining
IM	2,744	-0.20	-0.50	0.09	0.158	Stationary
Região Sudeste						
ADR	213	-0.02	-0.05	0.00	0.037	Declining
IM	11,711	-0.33	-0.49	-0.17	0.000	Declining
Região Sul						
ADR	62	0.00	-0.02	0.01	0.404	Stationary
IM	4,787	-0.12	-0.29	0.04	0.135	Stationary

DISCUSSION

The study identified a trend of declining hospitalizations due to adverse drug reaction (ADR) and drug intoxication (MI) in children under 5 in Brazil between 2000 and 2017. The coefficients ranged from 11.8 hospitalizations / 100,000 inhabitants. in the first year analyzed to 7.8 hospitalizations / 100,000 inhabitants. in 2017.

The American Association of Poison Control Centers reports that exposure to drugs in patients under 5 years of age has declined in the United States since in 2008 it accounted for 9.7% of cases of intoxication and ranged to 9.2% in 2016.¹⁴ data can be justified in Brazil by the implementation of regulations regulating the sale of several drugs, such as drugs under special control and antibiotics, and also by the greater restrictions on the sale of controlled drugs from 2007 through the National Management System of Controlled Products (SNGPC)^{15,16,17}.

The present study identified that cases of ADR and MI were more frequent in males. The greater freedom given by the parents and the

less zeal in relation to the boys, being able to engage in more activities, become more active and in search of more adventures and / or risks, can explain this difference between the sexes¹.

Among poisoning and adverse reactions, the most frequent therapeutic classes were biological ones, followed by systemic antibiotics and sedatives and hypnotics. A review conducted by Cliff-eribo, Sammons and Choonara (2016)¹⁸ identified that antibiotics were the drugs most frequently observed in most intoxication studies in Europe, North America, and South America, by the year 2015. However, another review on ADR that analyzed several bibliographic databases, with publications from 1966 to 2010, showed that the class of anti-infectious drugs was the most reported¹⁹. In Brazil, antimicrobial agents, decongestants, analgesics and bronchodilators were widely used in childhood, with the most reported in cases of intoxication.

As seen, many medications used for common childhood illnesses are responsible for poisoning and adverse reactions. It is important to note that, unlike adults, a considerable range of drugs used in children are of off-label use and end up having a greater chance of intoxication or adverse reactions^{21,22}. In 2007, WHO launched the Make Medicines Child Size campaign, highlighting the importance of studies on medicines for children, since many medicines were not developed for children and are used because there is no alternative available²³.

In relation to the tendency of increase in the hospitalizations of the North Region, only this tendency in sex was observed. However, cases reported by the Center for Toxicology in this region between 1999 and 2009 identified a gradual increase in the number of cases²⁴. But its magnitude is small. In the rest of the country, the trends are in decline, which may demonstrate a gradual improvement in the information provided by health professionals and services and the greater care with the safeguard of these inputs.

In addition, many of the poisonings occur in the victim's own home, most of them with the presence of adults²⁵. In a review study by Mayor and Oliveira (2012) found that another aggravating factor for intoxication at home is storage, since the medicines are not kept in places beyond the reach of children and / or without the proper boxes, as in medicine carriers, only with the loose tablets, which often appear to be bullet-shaped or candy-shaped²⁰. The fact that the drugs have sweeteners in their formulations to improve the taste and, in a way, improve adhesion, makes many children like to take medicines and take them hidden to eat, because they have a pleasant taste²⁶.

When analyzing the historical series of the regions of this study, it was observed that the Midwest, South and Southeast remained always above the national average, a scenario partially different from that found in studies in MI, where Silva et al. (2016)²⁴ analyzed the period between 1999 and 2009 and reported that the regions with the highest number of intoxication cases in children under 5 years were in descending order, Southeast, South, Northeast, Central West and North. However, in this study the number of cases in the Center-West region had increased considerably in the last years analyzed. Due to the difference between the methods and / or type of information analyzed, it should be pointed out that these studies are not satisfactory comparative sources, and no studies were found that presented values that were equally or partially comparative with the present study.

IM and RH trends in the country, when analyzed together, are declining; but analyzing them separately, we can see that the trend of RAM is stationary. As it is a factor that can hardly be avoided, since it occurs when there is the use of drugs in doses normally used, studies affirm that with the improvement of the prescriptions or prevention of the use of medicines without orientation, the ADRs could be avoided¹⁸. Differently, MIs represent more than 93.0% of the cases in the country and are of a more clearly avoidable nature, since their occurrence depends on an overdose of drugs. The

declining trend of MY cases in the country may occur through increased awareness of the rational use of medications, their correct prescription, dispensing, and storage²⁷.

Poisoning can happen at any time, in the prenatal period, in breastfeeding or as a child. It is estimated that about 50% of the drugs sold, prescribed and / or dispensed are inappropriately consumed. In Brazil, 35.0% of the medicines used are self-medication²⁰. One factor that would help to reduce MI cases would be the use of higher cupboards in drug storage houses in locked boxes with padlocks to avoid the intake of inappropriate and large amounts of medication, since many store medicines in the kitchen, preferably over microwave oven and refrigerator, facilitating access²⁹.

The present study has as a limitation the fact that the SIH-SUS covers only hospitalizations financed by the public power, being absent the data of particular institutions and also the incorrect underreporting and fulfillment.

Intoxication cases, even in a declining trend, should be seen and analyzed seriously as a public health problem, these hospitalizations compromise the lives of children and generate high and unnecessary costs for society.

REFERENCES

- World Health Organization (WHO). (2008). World report on child injury prevention. Geneva: World Health Organization.
- Mbeledogu CN, Cecil EV, Millett C, et al.(2015). Hospital admissions for unintentional poisoning in preschool children in England; 2000–2011. *Arch Dis Child*, 100:180–182.
- Mintegi S, Azkunaga B, Prego J, Qureshi N, Dalziel SR, Arana-Arri E, Acedo Y, Martinez-Indart L, Urkaregi A, Salmon N, Benito J, Kuppermann N. (2019). Pediatric Emergency Research Networks (PERN) Poisoning Working Group. International Epidemiological Differences in Acute Poisonings in Pediatric Emergency Departments. *Pediatr Emerg Care*, Jan;35(1):50-57.
- Mowry JB, Spyker DA, Cantilena LR Jr, et al. (2013). Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th annual report. *Clin Toxicol (Phila)*, 51:949–1229.
- SINITOX. (2016) Sistema Nacional de Informações Toxicológicas (SINITOX). Registro de intoxicações no Brasil. Retrieve in : <https://sinitox.icict.fiocruz.br/dados-de-agentes-toxicos> (acessado em 04/Jan/2019).
- Maior MDCLS, Osorio-de-Castro CGS, Andrade CLT. (2017). Hospitalizations due to drug poisoning in under-five-year-old children in Brazil, 2003-2012. *Epidemiol Serv Saude*.26(4):771-782.
- SINITOX. (2017): Sistema Nacional de Informações Tóxico-Farmacológicas. Retrieve in: <https://sinitox.icict.fiocruz.br/dados-nacionais>.
- Santos GAS, Boing AC. (2018). Hospitalizations and deaths from drug poisoning and adverse reactions in Brazil: an analysis from 2000 to 2014. *Cad Saude Publica*.Jun 25;34(6)
- Domingos SM, Borghesan NBA, Merino MFGL, Higarashi IH. Internações por intoxicação de crianças de zero a 14 anos em hospital de ensino no Sul do Brasil, 2006-2011. (2016). *Epidemiol Serv Saude*, 25 (2):343-350e
- Agência Nacional de Vigilância Sanitária. Farmacovigilância: glossário.(2019). Retrieve in: <http://sanvisa.gov.br/wps/sr/r/i/x>
- Antunes JLF, Cardoso MRA.(2015). Uso da análise de séries temporais em estudos epidemiológicos. *Epidemiol. Serv. Saude*, Jul-Set;24(3):565-576.
- Gaynor PE, Kirkpatrick RC. (1994). Introduction to time-series modeling and forecasting in business and economics. New York: McGraw-Hill.
- Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, Banner W. (2017). Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. *Clin Toxicol (Phila)*, Dec;55(10):1072-1252.
- Brasil. Ministério da Saúde. Portaria nº 344. (1998). Aprova o regulamento técnico sobre substâncias e medicamentos sujeitos a controle especial. *Diário Oficial da União da República Federativa do Brasil*, Brasília (DF).
- Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução RDC nº 44 (2010). Dispõe sobre o controle de medicamentos à base de substâncias classificadas como antimicrobianos, de uso sob prescrição médica, isoladas ou em associação e dá outras providências. *Diário Oficial da União da República Federativa do Brasil*, Brasília (DF).
- Brasil. (2007). Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução RDC nº 27, de 30 de março de 2007. Dispõe sobre o Sistema Nacional de Gerenciamento de Produtos Controlados - SNGPC, estabelece a implantação do módulo para drogarias e farmácias e dá outras providências. *Diário Oficial da União da República Federativa do Brasil*, Brasília (DF).
- Cliff-Erifo KO, Sammons H, Choonara I.(2016). Systematic review of paediatric studies of adverse drug reactions from pharmacovigilance databases. *Expert Opin Drug Saf*,15(10):1321-8.
- Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, Smyth R, Williamson P. 2012. Adverse drug reactions in children—a systematic review. *PLoS One*,7(3):e24061.
- Maior MCLS, Oliveira NVBV. (2012). Intoxicação medicamentosa infantil: um estudo das causas e ações preventivas possíveis. *Revista Brasileira de Farmácia*, 93(4): 422-430.
- Paula CS, Miguel MD, Miguel OG, Souza MN. (2011). *Rev Ciênc Farm Básica Apl*, 32(3): 217-223.
- Brasil. (2018). Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Uso Off-Label de medicamentos. Brasília.
- World Health Organization (WHO). (2007). Efforts on child-appropriate medicines intensify. Geneva/London: World Health Organization. Retrieve in: <http://www.who.int/mediacentre/news/releases/2007/pr63/en/>.

23. Silva FS, Oliveira DA, Augusto MA, Fernandes RL.(2016). Intoxicações Medicamentosas em Crianças de 0 a 4 anos atendidas pelos Centros de Informações Toxicológicas. *Catussaba*, 5(1):121-132.
24. Okuda ET, Buriola AA, Teixeira JAS; Silva TL, et al.(2013). Fatores associados à intoxicação infantil. *Escola Anna Nery*, 17(1):31-37.
25. Witter AA, Medeiros AISR, Teixeira L, et al.(2016). Intoxicação medicamentosa em crianças: uma revisão de literatura. *Revinter*, 9(3):64-71.
26. Brasil. (2012). Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Uso racional de medicamentos: temas selecionados. Série A. Normas e Manuais Técnicos. Brasília: Ministério da Saúde, 2012.
27. Beckhauser GC, Valgas C, Galato D. (2012). Perfil do estoque domiciliar de medicamentos em residências com crianças. *Revista de Ciências Farmacêuticas Básica e Aplicada*, 33(4):583-589.