Immunopreventable Diseases: Differences Between Genders in Brazil

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Abstract

Immunopreventable diseases are a public health reality in Brazil and worldwide. The international literature defined that there is difference between sexes at the answer to the infectious diseases. Objective: to discriminate the hospitalizations associated with immunopreventable diseases in Brazil and their care costs, within the scope of the SUS, between 2008 and 2018, differentiating the data by gender. Methods: A population, observational, descriptive, retrospective study was conducted with secondary information from DATASUS. Results: A total of 457,479 hospitalizations were evaluated, totaling a direct cost of R\$389,243,264.85, 53.17% in males and 46.83% in the female group (p-value 0.036). The trend analysis showed 6 diseases in decreasing situation (with statistical significance) and 4 in stationary tendency in the number of hospitalizations in the analyzed period. The direct costs of these hospitalizations were predominantly stationary for both sexes. Conclusions: the number of hospitalizations varied during the period analyzed, however the care costs of Immunopreventable diseases hospitalizations remained high, regardless of gender.

Introduction

The World Health Organization (WHO) estimated that a quarter of deaths in children under 5 years are caused by immunopreventable diseases¹⁻⁷. According to international literature⁸⁻¹⁰, a considerable proportion of health care is attributed to communicable diseases: one in six cases attended by primary care and about 128,000 hospitalizations (84% in public hospitals) were related to these conditions, data from 2010. Vaccination is important in the care of these diseases, since it makes possible both avoiding their incidence, their complications and their sequels⁸. Only basic sanitation and drinking water have greater public health benefits than vaccination^{5,6}. Vaccines prevent between 2 and 3 million deaths per year worldwide¹⁰.

The international literature has already evidenced the existence of a difference not only genetic between the sexes, but hormonal and immune in the response to infectious pathogens, vaccines and autoimmune diseases¹¹⁻¹³. Both sexes have the same cells, however, the innate humoral immunological response and mediated cell is different between the sexes, with different responses to the same stimuli (both pathogenic and vaccine), caused mainly by the interactions of sex hormones to the immune system, and by the specific genetic determinants for each sex¹⁴⁻¹⁸ (besides the socio-cultural-economic determinants that also interfere in the individual response to infections).

In this context, the main objective of this manuscript will be to discriminate the direct costs of hospitalizations under the Unified Health System, immunopreventable diseases (diphtheria, tetanus, pertussis, mumps, rubella, measles, hepatitis B, yellow fever, influenza virus respiratory syndrome, meningococcal disease, chickenpox), through DATASUS data, from 2008 to 2018, understanding the impact of gender difference by preventable diseases in Brazil. This analysis is important in the sense that it can guide specific public health policies for each gender or population group.

Methods

AREA OF STUDY

In this manuscript, data referring to Brazil were chosen for analysis. According to data from the Brazilian Institute of Geography and Statistics (IBGE, 2019/2020 - <https://cidades.ibge.gov.br/brasil/panorama> and <https://cidades.ibge.gov.br/brasil/pesquisa/53/0?ano=2020>), Brazil has an estimated population in 2020 of 211,755,692 people, with a population density of 22.43 inhabitants/km², with a predominance of the population in the age groups of 10 to 29 years, a predominance of the female population, with a life expectancy at birth of 7 years more for females. It has a predominantly urban population, with GDP per capita of R\$31,833.50 (year 2017) and Human Development Index (HDI) of 0.761 (79th position in the world in 2019 - <http://hdr.undp.org/en/content/2019-human-development-index-ranking>).

STUDY DESIGN

A population, observational, descriptive, retrospective study was conducted with multiple groups and time series, with aggregated secondary data, through information provided by the information system website of the Department of the Unified Health System (DATASUS - <http://www2.datasus.gov.br/DATASUS/index.php?area=02>). The research methodology on the DATASUS website was established according to the tools available in the consultation system: through the following links: "Health Information (TABNET)", "Epidemiological and Morbidity"; "Hospital Morbidity of the SUS (SIH/SUS)"; "General with place of hospitalization - from 2008"; "Brazil by Region and Federation Units"; Line = "Sex"; Column = "not active", content = "Hospitalizations; Hospital Admission Authorizations (AIH) approved; Total value; Value of hospital services; Value of professional services; Average AIH value; Average hospitalization value; Days stay; Average permanence; Deaths; Mortality rate"; available period from January 2008 to December 2018; Chapter of ICD 10 = "I Infectious and parasitic diseases"; list of morbidities / ICD 10 = "Neonatal tetanus and other tetanus; Diphtheria; Whooping. Yellow Fever; Meningococcal infections; Measles; Rubella; Mumps; Chickenpox / Herpes Zoster; Acute hepatitis B" (diseases chosen because they have preventive vaccines available in the National Vaccination Calendar of the Brazilian Ministry of Health). The data were updated at the DATASUS system in 2021.

The variables analyzed were the immunopreventable diseases mentioned above, year, age group, gender and economic variables. The socio-demographic data were tabulated and evaluated by descriptive statistics (mean, standard deviation, median and percentages) and probability associated with the student t test, by the Excel® (Microsoft Corp., United States version 2007) and Stata® (StataCorpLP, College Station, United States version 14.0), by the research team itself. For the continuous (numerical) variables, linear regression analysis was used in the cases of verification of the correlations of the economic variables of each immunopreventable disease. The time trends (Yt) of the economic variables in relation to hospitalizations, age groups and genders were also analyzed, defined by the equation of linear regression given by $Y_t = b_0 + b_1t + \text{and}_t$. In this expression, parameter b_0 corresponds to a constant, b_1 corresponds to the slope of the line, by the Prais-Winsten method, specific for time series analysis. When the Beta parameter was positive, the time series was considered increasing; when negative, was considered descending; and stationary when there was no significant difference between its value and zero. To measure the

rate of variation of the line that adjusts the points of the time series, the basic logarithmic transformation 10 of the coefficients (Y) was performed, as it contributes to the reduction of the heterogeneity of the variance of the residuals of the linear regression analysis¹⁹⁻²¹.

Results

Data were analyzed for 457,479 hospitalizations recorded in the DATASUS public system, in the period from 2008 to 2018, in all age groups (from under 1 year to over 80 years). Of these, 51.47% were in people identified with males (235,483 hospitalizations, with minimum of 134, maximum of 145,346, average of 21,407,54, median of 2,515, standard deviation - SD - of +/-43,438.13, 95% confidence interval - 95% CI - of +/-175.44) and 48.53% with females (221,996 hospitalizations, with a minimum of 141, maximum of 146,863, average of 20,181.45, median of 1,582, SD of +/-43,953.26, 95% CI of +/-182.83) (p-value 0.088), according to Table 1. Among the immunopreventable diseases evaluated, 55.69% of hospitalizations were associated with influenza disease, being the main cause observed, with 145,346 hospitalizations associated with males and 146,863 with females. The disease with fewer hospitalizations observed in this analysis was rubella, with 275 hospitalizations in the analyzed period (134 hospitalizations reported to males and 141 to females).

Table 1
Description of the data related to hospitalizations, by immunopreventable disease and gender, in Brazil, in the period surveyed from 2008 to 2018

IMMUNOPREVENTABLE DISEASES											
HOSPITALIZATIONS BY GENDER	Mumps		Whooping cough		Meningococcal disease		Diphtheria		Yellow fever		
MALE	2515	61.39%	9953	46.94%	13775	57.34%	753	55.61%	1546	77.57%	
FEMALE	1582	38.61%	11249	53.06%	10247	42.66%	601	44.39%	447	22.43%	
TOTAL	4097		21202		24022		1354		1993		
HOSPITALIZATIONS BY GENDER	Influenza		Hepatitis B		Rubella		Measles		Neonatal and accidental tetanus		Chick / Herp Zoste
MALE	145346	49.74%	10103	65.54%	134	48.73%	825	52.68%	1743	78.94%	48790
FEMALE	146863	50.26%	5312	34.46%	141	51.27%	741	47.32%	465	21.06%	44348
TOTAL	292209		15415		275		1566		2208		93138
Source: Unique Health System Information (DATASUS - TABNET). Period of the collected data from 2008 to 2018.											

These 457,479 hospitalizations recorded in the system, in the period from 2008 to 2018, totalled a direct cost of R\$389,243,264.85. Of these, 53.17% were in people identified as males (R\$206,943,642.06 direct costs with hospitalizations, with a minimum of R\$35,156.59, a maximum of R\$108,903,219.60, average of R\$18,813,058.37, median of R\$8,596,673.05, SD of +/-R\$32,021,390.25, 95% CI of +/-R\$4,362.76) and 46.83% for females (R\$182,299,622.79 direct costs from hospitalizations, with a minimum of R\$109,836.23, maximum of R\$107,882,552.40, an average of R\$16,572,692.98, median of R\$1,921,686.50, SD of +/-R\$31,942,325.80, 95% CI of +/-R\$4,636.83) (p-value 0.036), according to Table 2. Among the hospitalizations evaluated, 55.69% of hospitalizations were associated with influenza disease, with the main hospitalization in direct costs observed, with R\$108,903,219.58 in costs associated with males and R\$107,882,552.40 to females. The lower direct cost problem associated with hospitalizations observed in this analysis was rubella, with a value of R\$144,992.82 (R\$35,156.59 associated with males and R\$109,836.23 for females).

Table 2

Description of the data referring to the total values of hospitalizations, by immunopreventable disease and gender, in Brazil, in the period surveyed from 2008 to 2018

IMMUNOPREVENTABLE DISEASES						
HOSPITALIZATIONS' TOTAL COSTS BY GENDER	Mumps	Whooping cough	Meningococcal disease	Diphtheria	Yellow fever	
MALE	R\$ 602,007.64	R\$ 13,067,748.44	R\$ 27,001,578.56	R\$ 1,762,543.93	R\$ 2,256,943.37	
FEMALE	R\$ 359,811.01	R\$ 14,892,761.64	R\$ 20,155,155.93	R\$ 1,378,157.60	R\$ 411,065.27	
TOTAL	R\$ 961,818.65	R\$ 27,960,510.08	R\$ 47,156,734.49	R\$ 3,140,701.53	R\$ 2,668,008.64	
HOSPITALIZATIONS' TOTAL COSTS BY GENDER	Influenza	Hepatitis B	Rubella	Measles	Neonatal and accidental tetanus	Chickenpox / Herpes Zoster
MALE	R\$ 108,903,219.58	R\$ 8,596,673.05	R\$ 35,156.59	R\$ 278,720.19	R\$ 9,625,567.84	R\$ 34,813,482.87
FEMALE	R\$ 107,882,552.40	R\$ 4,441,529.31	R\$ 109,836.23	R\$ 218,884.97	R\$ 1,921,686.50	R\$ 30,528,181.93
TOTAL	R\$ 216,785,771.98	R\$ 13,038,202.36	R\$ 144,992.82	R\$ 497,605.16	R\$ 11,547,254.34	R\$ 65,341,664.80
Source: Unique Health System Information (DATASUS - TABNET). Period of the collected data from 2008 to 2018.						

Regarding the distribution of hospitalizations related to immunopreventable diseases studied in Brazil, the time series analyses were presented in Table 3, demonstrating, mostly, a stationary or decreasing trend in relation to the total number of hospitalizations, for both sexes, without differences in trends between the male and female groups. Some particularities were observed, as in the case of mumps disease that presented an increasing trend in the country, with statistical significance (p-value 0.005 in the male group and 0.000 in the female group).

Table 3

Temporal trend analysis of hospitalization data, by immunopreventable disease and gender, in Brazil, in the period surveyed from 2008 to 2018

HOSPITALIZATIONS BY DISEASE (2008-2018)	MALE					FEMALE				
	BETA	P-value	Confidence interval of 95%		Tendency	BETA	P-value	Confidence interval of 95%		Tendency
Mumps	0.049	0.005	0.019	0.078	growing	0.058	0.000	0.038	0.078	growing
Whooping cough	0.026	0.547	-0.069	0.123	stationary	0.026	0.561	-0.072	0.124	stationary
Meningococcal disease	-0.046	0.010	-0.079	-0.014	decreasing	-0.04	0.012	-0.068	-0.011	decreasing
Diphtheria	-0.031	0.010	-0.053	-0.0094	decreasing	-0.027	0.047	-0.055	-0.00049	decreasing
Yellow fever	0.123	0.306	-0.133	0.380	stationary	0.110	0.188	-0.065	0.285	stationary
Influenza	-0.026	0.000	-0.035	-0.017	decreasing	-0.024	0.000	-0.034	-0.014	decreasing
Hepatitis B	-0.042	0.007	-0.071	-0.014	decreasing	-0.037	0.004	-0.060	-0.015	decreasing
Rubella	-0.063	0.002	-0.097	-0.029	decreasing	-0.049	0.004	-0.078	-0.019	decreasing
Measles	0.035	0.248	-0.029	0.100	stationary	0.044	0.376	-0.063	0.152	stationary
Neonatal and accidental tetanus	0.000	0.962	-0.005	0.005	stationary	-0.014	0.050	-0.029	0.000	stationary
Chickenpox/Herpes Zoster	-0.039	0.000	-0.047	-0.031	decreasing	-0.035	0.000	-0.042	-0.028	decreasing
Source: Unique Health System Information (DATASUS - TABNET). Period of the collected data from 2008 to 2018.										

Regarding the distribution of total direct costs related to hospitalizations related to immunopreventable diseases researched in Brazil, the time series analyses were presented in Table 4, demonstrating, for the most part, a stationary or decreasing trend for both sexes, without differences in trends between the groups. Some particularities were observed, as in the case of mumps disease that presented an increasing trend in the country, with statistical significance (p-value of 0.000 for both sexes). And the case of rubella disease, which showed a decreasing trend in the male group (p-value of 0.008) and stationary in the female group (p-value of 0.480).

Table 4

Temporal trend analysis of data regarding total hospitalization values, by immunopreventable disease and gender, in Brazil, in the period surveyed from 2008 to 2018

HOSPITALIZATIONS' TOTAL COSTS BY DISEASE (2008-2018)	MALE					FEMALE				
	BETA	P-value	Confidence interval of 95%		Tendency	BETA	P-value	Confidence interval of 95%		Tendency
Mumps	0.063	0.000	0.036	0.090	growing	0.073	0.000	0.050	0.095	growing
Whooping cough	0.032	0.494	-0.069	0.133	stationary	0.034	0.446	-0.063	0.132	stationary
Meningococcal disease	-0.031	0.086	-0.069	0.0055	stationary	-0.027	0.115	-0.062	0.0081	stationary
Diphtheria	-0.023	0.166	-0.059	0.011	stationary	-0.021	0.388	-0.076	0.032	stationary
Yellow fever	0.178	0.282	-0.174	0.532	stationary	0.174	0.123	-0.057	0.406	stationary
Influenza	-0.022	0.003	-0.034	-0.009	decreasing	-0.020	0.006	-0.034	-0.007	decreasing
Hepatitis B	-0.0097	0.549	-0.045	0.025	stationary	-0.019	0.053	-0.038	0.00034	stationary
Rubella	-0.069	0.008	-0.115	-0.02	decreasing	-0.032	0.48	-0.133	0.067	stationary
Measles	0.056	0.077	-0.007	0.119	stationary	0.035	0.301	-0.038	0.109	stationary
Neonatal and accidental tetanus	0.016	0.067	-0.001	0.035	stationary	0.0039	0.725	-0.020	0.028	stationary
Chickenpox/Herpes Zoster	-0.022	0.010	-0.038	-0.0068	decreasing	-0.019	0.015	-0.034	-0.0049	decreasing
Source: Unique Health System Information (DATASUS - TABNET). Period of the collected data from 2008 to 2018.										

Discussion

The international literature¹¹⁻¹³ has already shown greater intensity and efficacy in the immune response in females, against pathogens, in developing autoimmune diseases and at responding to different vaccine agents (immune response and post-vaccine adverse events)¹⁴⁻¹⁸. As IBGE data, based on the population estimate for 2020, the population projected for females (108,228,003) is higher than for males (103,527,689). However, what was presented in 10 years of records was a discrete predominance of hospitalizations for immunopreventable diseases in the male group. This situation was also observed in the analysis of the total direct values related to these hospitalizations, also with statistical significance of 0.036. There is a need for public health policies aimed at the male population, regarding the importance of immunopreventable diseases and awareness of the importance of vaccination coverage to remain high in this group. Recent studies²², reiterate the importance of vaccines for the global population: it was estimated that vaccination for 10 pathogens would prevent 69 million deaths between 2000 and 2030. Adequate vaccination coverage and a complete vaccination schedule for major immunopreventable diseases have the power to reduce mortality of populations born from 2019 by 72%.

An interesting situation was verified in this study, through trend analysis: the number of hospitalizations for immunopreventable diseases was decreasing to 6 diseases (meningococcal disease, diphtheria, influenza, hepatitis B, rubella and varicella/ herpes zoster), with statistical significance (p-values < 0.005) in all cases. However, when the trend analysis was made for the total values related to these hospitalizations, the trends were stationary, i.e., there was no change for of the data analyzed (except for rubella disease in the male group that presented a decreasing trend with statistical significance). Thus, we observed that the costs related to these hospitalizations remain stable, even with the decrease in the total number of hospitalizations. In other words, immunopreventable diseases continue to financially impact the health system of the Brazilian population, even with the decrease in hospitalizations. This situation could be attributed to several causes, such as the increase in the costs of medical-hospital services and materials, the greater severity of hospitalizations, the increase in the age group affected by diseases, decreased vaccination coverage of the population, change in the quality of care provided to the population, delay in the care of suspected cases, increased comorbidities, worsening of social conditions that impact on the health of the population, among many other causes that could be listed here.

The main objective of this manuscript is not to determine the causal relationship for hospital costs for preventable diseases. The merit of this study is that it signals a reality that often goes unnoticed to the managers of the health system and the population: that diseases effectively preventable by vaccines still affect the Brazilian population, in a relevant amount, adding financial costs also relevant to the public health system of the country, regardless of gender and age (because here in this analysis we observe cases of immunopreventable diseases not only in children, but also in adults and the elderly, a reality observed internationally²³). These costs are not showing downward trends, but rather, they are proving stable over the time studied, even though vaccines are available free of charge to the entire population through the National Immunization Program for many years.

These direct financial costs signaled here that they could be employed in other health needs of the female and male populations. An opportunity for improvement that is observed is importance of employing awareness campaigns for the importance of specific vaccination of each population group. This awareness gains even more importance when observing the drop-in vaccination coverage globally during the 2020/2021 pandemic, predisposing to the resurgence and increase in the incidence of immunopreventable diseases²⁴, a reality that is not exclusive to children, but affects the entire world population, regardless of age group or gender. This is a commitment that must be made by all countries, because immunizing the population is an investment to create a healthier, safer and more prosperous future for all, as the WHO²⁵⁻²⁶ guides.

Limitations Of The Study

All studies based on public secondary databases have the limitation, already known, of underreporting and underreporting of the analyzed system itself, because these are dependent on the databases being fed by the employees responsible for the system. In the case of the SUS, these data are feeders in a decentralized manner and regionalized by States and Municipalities, that could update the data in any time even after the data had been publicized at the DATASUS site. However, despite the notorious underutilization of the system, these are the official data that are used for the development of public health policies in Brazil.

Declarations

1. Ethics approval and consent to participate: This study was approved by the Ethical Committee by the Federal University of Paraná, at the number CAAE 15102619.6.0000.0102
2. Consent for publication: Not applicable.
3. Availability of data and material: The data that support the findings of this study are openly available in the information system website of the Department of the Unified Health System (DATASUS - <http://www2.datasus.gov.br/DATASUS/index.php?area=02>).
4. Competing interests: There are not competing interests by the authors.
5. Funding: The authors didn't receive any funding sources.
6. Authors' contributions: The authors (ESMC; AD; EMCMP) are responsible for the study data, the methodology, the data analysis, the literature revision, and the study conclusions.
7. No acknowledgements to declare.

References

1. World Health Organization (WHO). International travel and health. Chapter 6. Disponível em: <https://www.who.int/ith/ith-chapter6.pdf>.
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Manual de normas e procedimentos para vacinação / Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis. – Brasília: Ministério da Saúde; 2014.
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Manual de rede de frio do Programa Nacional de Imunizações / Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis. – 5. ed. – Brasília: Ministério da Saúde; 2017.
4. Bloom DE, Canning D, Weston M. The value of vaccination. *World Economics*; 2005; 6(3): 15-39.
5. Andre FE, Booy R, Bock HL, Clemens J, Datta SK, John TJ, et al. Vaccination greatly reduces disease, disability, death and inequity worldwide. *Bulletin of the World Health Organization*; 2008;86:140–146.
6. Plotkin SL, Plotkin SA. A short history of vaccination. In: plotkin sa, orenstein wa, eds. *Vaccines*, 4th edn. Philadelphia: WB Saunders; 2004: 1-15.
7. Dabbagh A, Eggers R, Cochi S, Dietz V, Strebel P, Cherian T. World Health Organization. A new global framework for immunization monitoring and surveillance. Disponível em: <http://www.who.int/bulletin/volumes/85/12/07-048223/en/>.
8. Omer SB, Salmon DA, Orenstein WA, Dehart P, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. *N Engl J Med*; 2009;360:1981-8.
9. Pezzotti P, Bellino S, Prestinaci F, Iacchini S, Lucaroni F, Camoni L, et al. The impact of immunization programs on 10 vaccine preventable diseases in Italy: 1900- 2015. *Vaccine*; 2018;36(11):1435-1443.
10. World Health Organization (WHO). Surveillance standards for vaccine- preventable diseases, second edition. Geneva: World Health Organization; 2018. Disponível em: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/standards/en
11. Ruggieri A, Anticoli S, D'Ambrosio A, Giordani L, Viora M. The influence of sex and gender on immunity, infection and vaccination. *Ann Ist Super Sanità* 2016 | Vol. 52, No. 2: 198-204. DOI: 10.4415/ANN_16_02_11
12. Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. *Lancet Infect Dis* 2010;10(5):338-49. DOI: 10.1016/S1473-3099(10)70049-9
13. Klein SL, Roberts CW (Eds). *Sex hormones and immunity to infection*. Berlin: Springer Verlag; 2010. DOI:10.1007/978-3-642-02155-8
14. Engler RJ, Nelson MR, Klote MM, VanRaden MJ, Huang CY, Cox NJ, Klimov A, Keitel WA, Nichol KL, Carr WW, Treanor JJ; Walter Reed Health Care System Influenza Vaccine Consortium. Half- vs full-dose trivalent inactivated influenza vaccine (2004-2005): age, dose, and sex effects on immune responses. *Arch Intern Med* 2008;168(22):2405-14. DOI: 10.1001/archinternmed.2008.513
15. Furman D, Hejblum BP, Simon N, Jojic V, Dekker CL, Thiébaud R, et al. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. *Proc Natl Acad Sci US A* 2014;111(2):869-74. DOI: 10.1073/pnas.1321060111
16. Cook IF. Sexual dimorphism of humoral immunity with human vaccines. *Vaccine* 2008;26(29-30):3551-5. DOI:10.1016/j.vaccine.2008.04.054
17. Green MS, Shohat T, Lerman Y, Cohen D, Slepon R, Duvdevani P, et al. Sex differences in the humoral antibody response to live measles vaccine in young adults. *Int J Epidemiol* 1994;23(5):1078-81. DOI: 10.1093/ije/23.5.1078
18. Veit O, Niedrig M, Chapuis-Taillard C, Cavassini M, Mossdorf E, Schmid P, Bae HG, Litzba N, Staub T, Hatz C, Furrer H; Swiss HIV Cohort Study. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. *Clin Infect Dis* 2009;48(5):659-66. DOI:10.1086/597006

19. Antunes JLF & Cardoso MRA. Uso da análise de séries temporais em estudos epidemiológicos. Epidemiol. Serv. Saúde, Brasília, 24(3):565-576, jul-set 2015.
20. Franco GC. Apostila de modelos lineares em séries temporais. Universidade Federal De Minas Gerais – UFMG. Instituto De Ciências Exatas – ICEx. Departamento De Estatística – EST. Belo Horizonte. 2016. Disponível em:
<ftp://est.ufmg.br/pub/glaura/MLST/Modelos%20Lineares%20em%20S%20E9ries%20Temporais.pdf>
21. Fávero LP. Métodos quantitativos com stata: procedimentos, rotinas e análise de resultados. 1. ed. - Rio de Janeiro: Elsevier, 2014. ISBN 978-85-352-5157-9. Edição do Kindle.
22. Li X, Mukandavire C, Cucunubá ZM, Londono SE, Abbas K, Clapham HE, et al. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. Lancet 2021; 397: 398–408.
23. Wu Q, Zaid M, Xuan Z, Wang C, Gu H, Shi M, et al. Changes in epidemiological features of vaccine preventable infectious diseases among three eras of national vaccination strategies from 1953 to 2018 in Shanghai, China. The Lancet Regional Health - Western Pacific 7 (2021) 100092.
24. Cohen AL, Patel MK, Cherian T. Vaccines work: a reason for celebration and renewed commitment. Lancet 2021; 397: 351-352.
25. World Health Organization (WHO). Immunization agenda 2030: a global strategy to leave no one behind. April 1, 2020. Disponível em:
https://www.who.int/immunization/immunization_agenda_2030/en
26. World Health Organization (WHO). Global strategy for comprehensive vaccine-preventable disease (VPD) surveillance. June 19, 2020. Disponível em
[https://www.who.int/publications/m/item/global-strategy-for-comprehensive-vaccine-preventable-disease-\(vpd\)-surveillance](https://www.who.int/publications/m/item/global-strategy-for-comprehensive-vaccine-preventable-disease-(vpd)-surveillance)