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ORIGINAL

Events supposedly attributable to vaccination or immunization recommended for pregnant women: time series analysis

Eventos supostamente atribuíveis à vacinação ou imunização preconizadas às gestantes: análise de série temporal

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ABSTRACT

Objective: To analyze the events supposedly attributable to vaccination or immunization (ESAVI) associated with the Diphtheria-Tetanus Vaccine, Adult Diphtheria-Tetanus-Pertussis Vaccine (Tdap), Hepatitis B, and Influenza vaccines and their severity in pregnant women in Minas Gerais. **Methods:** Epidemiological, time series study on ESAVI registered in the Information System of the Brazilian National Immunization Program from 2015 to 2020. Four hundred and nine ESAVI were analyzed in pregnant women according to the kind of event, need for medical care, and evolution of the case. **Results:** The Tdap vaccine showed a higher proportion of ESAVI in this period (56.86%), followed by the Hepatitis B vaccine (29.41%), Influenza vaccine (20.04%), and adult Diphtheria-Tetanus Vaccine (16.00%). Local manifestations were more prevalent, and pain at the injection site was mostly reported. Notably, pregnant women vaccinated with the Adult Diphtheria-Tetanus-Pertussis Vaccine (Tdap) and / or Hepatitis B vaccine had a higher proportion of events classified as Immunization Error. There was a significant trend towards an increase in the rate of ESAVI because of the Diphtheria-Tetanus Vaccine (p=0.024). **Conclusion:** The ESAVI incidence rate during pregnancy was low and there was no increase in the risk of pregnant women presenting any serious adverse event after the administration of the recommended vaccines during pregnancy.

Descriptores: Vaccination; Drug-Related Side Effects and Adverse Reactions; Pregnant Women.

RESUMO

Objetivo: Analisar os eventos supostamente atribuíveis à vacinação ou imunização (ESAVI) associados às vacinas Dupla adulto, Tríplice bacteriana acelular adulto, Hepatite B e Influenza e sua gravidade em gestantes de Minas Gerais. **Métodos:** Estudo epidemiológico, de série temporal sobre ESAVI registrados no Sistema de Informação do Programa Nacional de Imunizações no período de 2015 a 2020. Analisou-se 459 ESAVI em gestantes segundo tipo do evento, necessidade de atendimento médico e evolução do caso. **Resultados:** A vacina dTpa apresentou maior proporção de ESAVI nesse período (56,86%), seguida da vacina contra Hepatite B (29,41%), vacina contra Influenza (20,04%) e vacina Dupla adulto (16,00%). As manifestações locais foram mais prevalentes, sendo a dor no local da injeção a mais relatada. Destaca-se que gestantes vacinadas com a vacina Tríplice bacteriana acelular adulto e/ou com vacina contra Hepatite B tiveram uma maior proporção de eventos classificados como Erro de Imunização. Observou-se tendência significativa de aumento da taxa de ESAVI em decorrência da vacina Dupla adulto (p=0,024). **Conclusão:** Evidencia que a taxa de incidência ESAVI durante a gestação do estado foi baixa e que não houve um aumento no risco da gestante de apresentar algum evento adverso grave após a administração das vacinas recomendadas durante a gestação.

Descritores: Vacinação; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Gestantes.

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INTRODUCTION

Immunization is essential in public health programs because it efficiently combats vaccine-preventable diseases in Brazil and worldwide, and such actions have been coordinated by the Brazilian National Immunization Program (PNI) since 1973[1]. The PNI is recognized worldwide because of the many vaccines made available for free and for all age groups and population groups, such as older adults, adolescents, children, and pregnant women[1-2].

Despite its proven efficacy and safety, vaccination is not a risk-free practice. After administration, unwanted and unintended clinical changes may occur and are called Events Supposedly Attributable to Vaccination or Immunization (ESAVI)[3-5] that may be related to the vaccine administered and the vaccination process. In addition, these ESAVI can range from low-grade fever and pain at the site of administration to anaphylactic shock. To monitor and investigate the cases that occurred in 1992, the PNI started to structure the Information System called Adverse Event Following Immunization (SI-EAPV), a tool of the ESAVI National Surveillance System, which was deactivated in 2014. In 2014, notifications/investigations/closures started to be inserted in the EAPV module of the PNI Information System (SIPNI). Additionally, in 2005, this type of adverse event became a compulsory notification problem in Brazil, contributing to the identification of predictors and risk groups[3-5].

In the context of vaccination in pregnant women, the Brazilian Ministry of Health (MS) currently recommends 4 vaccines, namely: Adult Diphtheria, Tetanus, and Pertussis) – Tdap; (Diphtheria and Tetanus) – Td; Influenza, and the Hepatitis B vaccine for all susceptible pregnant women. Those with a complete 3-dose schedule were considered immunized against Hepatitis B[1,6-8].

Such vaccines are extremely important for maternal and child health. Influenza virus infection, for example, is associated with several complications during pregnancy, such as spontaneous abortion[9-10] and more severe clinical conditions[11-12], which significantly contributes to increased hospitalization, morbidity, and maternal-infant mortality[9-12]. In addition, both infections with the Hepatitis B virus and the bacterium *Bordetella pertussis* (which causes pertussis) substantially increase the risks of hospitalization of the child at birth, lifelong complications, and even death since they present severe clinical manifestations, such as cirrhosis and acute respiratory symptoms, respectively[9-12].

Several studies in the international literature[13-17] prove the safety of the administration of vaccines in pregnant women and their benefits for mother-infant, showing a low percentage of associated serious adverse events (0.8%, 6.3%, and 4.5% for influenza, hepatitis B, and Tdap vaccines, respectively). Despite this, many women choose not to be vaccinated for fear of ESAVI[8-10, 13-17]. It is noteworthy that many of the ESAVI caused by these vaccines are classified as non-serious and present themselves as: pain, heat, and edema at the injection site[8-10, 13-17].

Considering the importance of vaccination for mom and child protection during pregnancy and the scarcity of studies on this subject in the Brazilian literature, this study aimed to analyze the ESAVI associated with the Td, Tdap, Hepatitis B, and Influenza vaccines and their severity in pregnant women in the state of Minas Gerais (MG).

METHOD

Ethical aspects

This study was approved in 2020 by the Research Ethics Committee (CEP) of the Federal University of Minas Gerais (UFMG) under opinion number 4,134,126.

Study design, period, and location

This is an epidemiological time series study guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) tool, carried out with the ESAVI secondary database registered with SIPNI in the state of MG, Brazil, from January 1, 2015 to December 31, 2020.

Only ESAVI notifications, registered as of January 1, 2015, were considered in this study. This methodological decision was made as a result of the implementation period of the SI-EAPV, which took place from July 2014, and its respective coverage, which took place only from 2015, in some municipalities, thus avoiding information bias.

Population, inclusion, and exclusion criteria

The study was conducted based on the notifications registered in this period regarding the recommended vaccines during pregnancy, totaling 314 ESAVI due to the administration of these vaccines. The cases of ESAVI with and without closure that occurred in the period were analyzed.

Data sources

Data were collected in the Adverse Event Following Immunization Surveillance Information System (SI-EAPV) and the SI-EAPV module of the Information System of the online Brazilian National Immunization Program (SIPNI). The SIPNI is an online tool to collect, process, analyze, and transmit information, made available by the General Coordination of the PNI, regarding the ESAVI of individuals from the public and private health networks[4, 16].

The ESAVI analyzed were based on the national vaccination schedule recommended by the PNI for the pregnant population of Brazil, so the following vaccines were analyzed: Tdap, Td, Influenza, and the Hepatitis B vaccine.

Study variables

The variables related to the ESAVI reported were: period, year of notification of ESAVI; vaccine administered; need for medical care, evolution of the case, and the type of ESAVI. The types of ESAVI were classified as follows: serious, non-serious, immunization error, and immunization error with adverse events [18]. To calculate the incidence rate of adverse events (IR) per 100,000 doses applied, the number of ESAVI in pregnant women (numerator) per 100,000 doses applied for each vaccine administered in pregnant women (denominator) was used. The number of doses of vaccines applied to pregnant women was obtained from the Ministry of Health website, at '<pni.datasus.gov.br>' and used as a denominator. In 2015, for the Tdap vaccine, the number of doses applied in pregnant women was informed together with the Td vaccine; therefore, the number of doses applied plus the doses of Tdap with the Td was used and the IR of ESAVI resulting from the two vaccines was calculated.

Analysis of results and statistics

For data analysis, the Stata statistical package, version 14.0, was used. The ESAVI were presented in percentage (%), according to the year of occurrence and vaccine recommended/administered during pregnancy.

To identify the existence of a trend in the adverse events of incidence rate (100,000 doses applied) of ESAVI, the Prais-Winsten generalized linear analysis models were used – to estimate the annual rates of change and confidence intervals (95% CI). The IR of ESAVI (number of ESAVI divided by the total number of doses applied) was used as the dependent variable and the year of ESAVI occurrence (2015 to 2019) was used as the independent variable. It should be noted that, for IRs related to influenza and Td/Tdap vaccines, the year 2020 was excluded because the number of doses applied to pregnant women available on the website < pni.datasus.gov.br > has not been included so far. It should also be noted that the Hepatitis B vaccine was also excluded - for the same reason. The Prais-Winsten model is suggested to correct serial autocorrelation in time series[19].

To perform the Prais-Winsten regression, the IR of ESAVI was transformed into the logarithmic scale to reduce the heterogeneity of the variance of residuals of the analysis from the regression and, in addition, the average annual percentage change (APC) was calculated[19].

The calculation of the APC followed the formula: APC = (-1+10[b1]*100%), with beta 1 being the Prais-Winsten regression coefficient. The 95% confidence intervals (95% CI) of the APC were also calculated using the formula: minimum 95% CI (-1+10 [b1-t *e]*100%) and maximum 95% CI (-1+10 [b1+t*e]*100%).

The regression trend was classified as follows: increasing trend (p significant value and positive regression coefficient), decreasing trend (p significant value and negative regression coefficient), and stationary trend (non-significant p value).

RESULTS

Between 2015 and 2020, 1,025 ESAVI were registered in the state of MG in pregnant women, of which 459 (44.78%) occurred with vaccines recommended to be administered during pregnancy: Tdap, Td, Influenza, and the Hepatitis B vaccine. The other notifications referred to other vaccines not evaluated in this study.

Table 1 shows the frequency of adverse events reported after the administration of the recommended vaccines during pregnancy. The Tdap vaccine was responsible for the highest proportion of ESAVI in this period, being associated with 261 adverse events (56.86%), followed by the Hepatitis B vaccine (29.41%), the Influenza vaccine (20.04%), and the Td vaccine (16.00%). Notably, a pregnant woman may have received more than one vaccine in the same period.

Table 1 – Frequency of Events Supposedly Attributable to Vaccination or Immunization in pregnant women according to the vaccine administered (n=459). Belo Horizonte, MG, Brazil, 2015 to 2020

Recommended vaccines during pregnancy	n (%) *
Diphtheria-Tetanus	164(16.00)
Influenza	92(20.04)
Hepatitis B	135(29.41)
Adult Diphtheria-Tetanus-Pertussis Vaccine (Tdap)	261(56.86)

Note: * It is noteworthy that a pregnant woman may have received more than one vaccine or more than one ESAVI at the same time; n= sample number.

Local manifestations were more prevalent when compared to systemic manifestations (28.10% and 9.80%, respectively). Regarding local manifestations, the highest percentage was pain at the injection site (82.31%), followed by erythema and flushing (56.15% both). Regarding systemic manifestations, headache was the most frequent (73.33%) (Table 2).

Table 2 – Frequency of local and systemic manifestations resulting from Events Supposedly Attributable to Vaccination or Immunization in pregnant women according to the vaccine administered (n=459). Belo Horizonte, MG, Brazil, 2015 to 2020

TYPE OF MANIFESTATION	n (%)*
Local manifestations	129(28.10)
Heat	75(57.69)
Erythema	73(56.15)
Flushing	73(56.15)
Pain	107(82.31)
Edema	60(46.15)
Hot abscess	19(14.62)
Cold abscess	1(0.77)
Nodule	1(1.54)
Itching	10(7.69)
Systemic Manifestation	45(9.80)
Nausea/Vomiting	16(35.56)
Headache	33(73.33)
Myalgia	10(22.22)
Fever	13(28.89)

Table 3 shows the proportion of the kinds of ESAVI reported that occurred in vaccinated pregnant women, according to the recommendation of the Ministry of Health regarding the kind of event, the need for medical care, and the evolution of the case. Pregnant women receiving the Tdap vaccine and/or Hepatitis B vaccine had a higher proportion of events classified as "Immunization Error" (61.69% and 57.78%, respectively). Pregnant women vaccinated with the Td vaccines obtained a higher proportion of the kind of events classified as "non-serious events" (53.66%).

Regarding the need for medical care due to ESAVI, the information about the medical care was not filled in or was ignored (44.51%, 67.43%, 57.61%, and 62.22%, respectively) for most pregnant women who had an ESAVI associated with the four vaccines recommended during pregnancy: Td, Tdap, Influenza, and Hepatitis B (Table 3).

Regarding the evolution of cases, most pregnant women with ESAVI associated with the Td vaccine had no such information (44.51%), followed by a cure without sequelae (41.46%). In addition, no information was found about the evolution of cases for pregnant women who presented ESAVI associated with Tdap, Hepatitis B, and influenza vaccines (67.43%, 62.22%, and 57.61%, respectively) (Table 3).

Table 3 – Frequency of Events Supposedly Attributable to Vaccination or Immunization in pregnant women according to vaccine, kind of event, and severity (n=459). Belo Horizonte, MG, Brazil, 2015 to 2020

	Diphtheria-Tetanus (Td)	Adult Diphtheria-Tetanus-Pertussis Vaccine (Tdap)	Influenza	Hepatitis B
	Yes n (%)	Yes n (%)	Yes n (%)	Yes n (%)
Kind of event				
Immunization Error	71(43.29)	161(61.69)	51(55.43)	78(57.78)
Immunization Error with adverse event	4(2.44)	7(2.68)	-	4(2.96)
Serious (SAE)	1(0.61)	2(0.77)	1(1.09)	1(0.74)
Non-Serious (NSAE)	88(53.66)	91(34.87)	40(43.48)	52(38.52)
Medical care				
Yes	47(28.66)	48(18.39)	24(26.09)	29(21.48)
No	38(23.17)	30(11.49)	12(13.04)	20(14.81)
Ignored	79(48.17)	183(70.11)	56(60.87)	86(63.70)
Case evolution				
Cure with sequelae	-	2(0.77)	1(1.09)	-
Cure without sequelae	68 (41.46)	62(23.75)	27(29.35)	39(28.89)
Under follow-up	21(12.80)	18(6.90)	10(10.87)	11(8.15)
It was not AEFI	1(0.61)	2(0.77)	1(1.09)	1(0.74)
Withdrawals	1(0.61)	1(0.38)	-	-
No information	73(44.51)	176(67.43)	53(57.61)	84(62.22)

Note: n = sample number.

Table 4 shows the trend of the IR of ESAVI, according to the recommendation of the Brazilian Ministry of Health for the pregnancy and vaccination period (Table 4).

In 2015, 47 ESAVI due to the Td and Tdap vaccines were reported in 137,221 doses applied, corresponding to an incidence rate of 34.25 cases of ESAVI for every 100,000 doses. In 2019, 37 ESAVI of Tdap were reported in 162,267 doses applied and 18 adverse events of Td in 15,630 doses applied, corresponding to a rate of 22.80 and 115.16 cases of ESAVI, respectively, for every 100,000 doses administered to pregnant women. In the trend regression analysis of the IR of ESAVI, an increasing trend was observed since 2015 for the Td vaccine in pregnant women, with a statistically significant difference (Table 4).

Regarding the influenza vaccine in pregnant women, the year with the highest ESAVI was 2019, with an IR of 9.35 cases of ESAVI for every 100,000 doses applied. In the regression analysis, a stationary trend was observed in the rate of ESAVI for the influenza vaccine in pregnant women in the period studied (Table 4).

Table 4 – Trend of the incidence rate of Events Supposedly Attributable to Vaccination or Immunization, according to the recommendation of the Ministry of Health, for the pregnancy and vaccination period (n=459). Belo Horizonte, MG, Brazil, 2015 to 2019

			Vaccines		
			Tdap	Td	Influenza
YEARS	2015	n	18	29	7
		AD*	0	137,221	171,126
		IR**	-	21.13	4.09

YEARS	**2016**	**n**	12	10	6
		AD*	66,617	26,304	151,624
		IR**	18.01	38.02	3.96
	2017	**n**	22	20	5
		AD*	98,865	22,609	165,055
		IR**	22.26	88.46	3.03
	2018	**n**	30	12	10
		AD*	182,968	20,187	161,919
		IR**	16.4	59.45	6.18
	2019	**n**	37	18	15
		AD*	162,267	15,630	160,453
		IR**	22.8	115.16	9.35
TREND ANALYSIS FROM 2015 TO 2019		**% annual average percentage change (95% CI)**	-	44.22(13.64;83.03)	23.35(-8.02; 65.43)
	p-value		-	0.024	0
	Trend		-	**Increasing**	Stationary

DISCUSSION

The results of this study showed that the proportions of ESAVI in pregnant women in the state of MG due to vaccines recommended during pregnancy were mostly low from 2015 to 2020, compared to other vaccines, such as the COVID-19 vaccine, which had an ESAVI rate in the state of MG of about 83.4% of ESAVI associated with women in 2020[8-10, 13-17,20].

There was a significant trend towards an increase in the rate of ESAVI because of the Diphtheria-Tetanus vaccine. In 2015, it went from 34.25 to 115.16 in 2019, with an average annual percentage change of 44.22% over the years. With the introduction of the Tdap vaccine and completion of the tetanus vaccine schedule, the number of doses of Tdap applied is expected to decrease and, consequently, its adverse events. However, the disparity found in 2015 about the others may have been influenced by the recent implementation of the online module of the SI-EAPV, which occurred in 2014, which required some adaptation of vaccinators to the new way of filling in the data, in addition to the failure to identify doses administered to pregnant women or women of childbearing age, for example[18].

The results shown in Table 4 demonstrate an increase in administered doses of Tdap at the expense of reducing doses of Td. And, summing up, 66.41% of the ESAVI occurred in pregnant women. These results are consistent with other findings in the literature that showed a higher incidence of ESAVI in pregnant women vaccinated with the Adult Diphtheria-Tetanus vaccine[8,13,21-22].

Regarding the Hepatitis B vaccine, no significant associations were found in this study between its administration and the increased risk of serious adverse events and/or need for medical care, corroborating what was found in the literature regarding the safety in the administration of this vaccine and its efficacy[10,16,23].

According to estimates, more than 70% of newborns infected with hepatitis B will develop a chronic infection of the disease, increasing the risk of developing cirrhosis, hepatocellular carcinoma, and, consequently, infant mortality. These are some of the reasons why the Hepatitis B vaccine is extremely important during pregnancy, as it contributes to the reduction of vertical transmission of the disease[10].

Regarding Influenza virus infection, it is known that pregnant women are classified as a high-risk group for this infection[24] and, therefore, the Influenza vaccine should be administered throughout pregnancy. The results found in this study show us an incidence of 20.04% of ESAVI, 43.48% of which are classified as non-serious, associated with the administration of this vaccine. This proportion is below what was found in the literature [9] and may be associated with the underreporting of Adverse Effects Following

Immunization (AEFI) in the evaluated period.
This study also revealed that most pregnant women who had some type of ESAVI associated with the influenza vaccine had their medical care information not filled in or ignored (60.87%), but had a cure without sequelae (29.35%) - or this information was not available in the medical record (57.61%).
Given its importance, several international studies[12,25-26] evaluated the adverse events caused by the administration of this vaccine, including its association with spontaneous abortion[12,25-26] and with long-term harm to the child, such as the development of asthma[9,12,25-26]. Both had no significant associations between its administration and severe ESAVI, corroborating that it is safe to administer this vaccine to pregnant women[9,12,25-26].
It is noteworthy that the early identification of possible adverse events associated with these vaccines, as well as the proper management of ESAVI with timely and adequate therapeutic intervention, help to reduce the risks of aggravation and death[18].
Finally, the completion of ESAVI notifications has an issue, since most ESAVI were closed without the evolution of the case. The incompleteness of the fields makes it difficult to conclude the factors related to ESAVI in pregnant women. Therefore, the need for supervision and monitoring of the healthcare providers who notify the ESAVI in the SI-EAPV by the Nurse professional is concluded, in addition to the adequate training of these providers, which would possibly reduce the missing data in the database[4].
Finally, the importance of continuing education of the team responsible for vaccination is emphasized, focusing on actions against AEFI and avoiding avoidable IE or, if in case they occur, what would be the most appropriate actions the team should take[27].

Limitations of the study

As the limitations of this work, it is noteworthy that it was developed based on data from secondary bases, limited to specific information. The SI-EAPV is configured as a passive surveillance system of ESAVI. Thus, it is subject to inherent limitations on its use. Despite this, it proves to be an important instrument for the evaluation of ESAVI. It also reinforces that, as previously mentioned, the same pregnant woman may have received more than one vaccine in the same period, which makes it difficult to know which vaccine caused AEFI. In addition, the quality of the data filled in and the fact that some forms in the system were not filled in properly due to the low completeness of the data and inconsistencies found stand out.

CONCLUSION

The results of this study showed that the ESAVI incidence rate in pregnant women in the state of MG due to vaccines recommended during pregnancy was low from 2015 to 2020. It was also evidenced that there was no increase in the risk of the pregnant woman presenting some type of serious adverse event after the administration of the recommended vaccines during pregnancy, although there was an increase in the rate of ESAVI due to the Diphtheria Tetanus vaccine in pregnant women.
The potential of the results presented in this research to support the safe administration of the vaccines recommended during pregnancy is noteworthy, since there are few studies with such specificity in the current national literature, in addition to reinforcing the fundamental role of nurses in the implementation of actions related to vaccination and the correct use of the instruments provided by the Brazilian National Immunization Program (PNI).
In addition, it should be noted that it is necessary to take some measures to increase vaccination coverage of these vaccines, such as spreading information on the safety of vaccines and training providers concerning their administration.

CONFLICT OF INTERESTS

The authors have declared that there is no conflict of interests.

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