









## ADVERSE EVENTS FOLLOWING HUMAN PAPILLOMAVIRUS VACCINE IN ADOLESCENTS IN THE STATE OF MINAS GERAIS

EVENTOS ADVERSOS APÓS A VACINA PAPILOMAVÍRUS HUMANO EM ADOLESCENTES NO ESTADO DE MINAS GERAIS

EVENTOS ADVERSOS DESPUÉS DE LA VACUNACIÓN CONTRA EL VIRUS DEL PAPILOMA HUMANO, EN ADOLESCENTES EN EL ESTADO DE MINAS GERAIS

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**Supervisão:** Fernanda P. Matozinhos.

**Funding:** No funding.

**Submitted on:** 09/11/2021  
**Approved on:** 09/12/2022

### Responsible Editors:

 Bruna Figueiredo Manzo  
 Tânia Couto Machado Chianca

### ABSTRACT

**Objective:** to investigate reports of adverse events following human papillomavirus vaccination in the state of Minas Gerais, according to the location of notification, causality, severity, and evolution of cases. **Methods:** epidemiological study carried out with data from 2015-2019, reported in the Adverse Event Surveillance Information System. Data were analyzed and presented in proportions, according to health macro-regions and years of study. **Results:** in 2015, 26.41% of adverse events were reported, being the year with the highest number of notifications. In the analysis of health macro-regions, Vale do Jequitinhonha had the lowest prevalence of registration (0.43%), and the Center had the highest prevalence of notification (30.95%). The most prevalent local adverse events were pain (56.48%) and edema (38.89%). As for systemic events, headache (29.69%) and gastroenteritis (29.69%) had the highest number of cases. Events classified as non-serious adverse events (59.82%) were the most prevalent, and regarding the cause, 35.94% of them were attributed to immunization errors. **Conclusion:** this study reinforces that adverse events following HPV vaccination were, for the most part, non-serious events, thus demonstrating the safety of the HPV vaccine for the adolescent public, contributing to the increase in vaccine coverage rates.

**Keywords:** Vaccination; Adolescent; Epidemiology; Drug-Related Side Effects and Adverse Reactions; Information Systems.

### RESUMO

**Objetivo:** investigar as notificações dos eventos adversos pós-vacinação papilomavírus humano no estado de Minas Gerais, de acordo com a localidade de notificação, a causalidade, a gravidade e a evolução dos casos. **Métodos:** estudo epidemiológico realizado com os dados de 2015-2019, notificados no Sistema de Informação de Vigilância de Eventos Adversos. Os dados foram analisados e apresentados em proporções, segundo as macrorregiões de saúde e os anos do estudo. **Resultados:** em 2015, foram notificados 26,41% eventos adversos, sendo o ano com maior notificação. Na análise das macrorregiões de saúde, Vale do Jequitinhonha apresentou a menor prevalência de registro (0,43%), e a Centro a maior prevalência de notificação (30,95%). Os eventos adversos locais mais prevalentes foram: dor (56,48%) e edema (38,89%). Já quanto aos eventos sistêmicos, a cefaleia (29,69%) e a gastroenterite (29,69%) tiveram os maiores registros de casos. Os eventos classificados como adversos não graves (59,82%) foram os mais prevalentes, e quanto à causa, 35,94% deles foram atribuídos aos erros de imunização. **Conclusão:** este estudo reforça que os eventos adversos pós-vacina de HPV foram, em sua maioria, eventos não graves, demonstrando, portanto, a segurança da vacina HPV para o público adolescente, contribuindo para o aumento das taxas de cobertura vacinal.

**Palavras-chave:** Vacinação; Adolescente; Epidemiologia; Efeitos Colaterais e Reações Adversas Relacionadas a Medicamentos; Sistemas de informação.

### RESUMEN

**Objetivo:** investigar las notificaciones de eventos adversos de papilomavirus humano en el Estado de Minas Gerais, según la localidad de notificación, la causalidad, la gravedad y la evolución de los casos. **Métodos:** estudio epidemiológico realizado con datos de 2015-2019, notificados en el Sistema de Información de Vigilancia de Eventos Adversos. Los datos fueron analizados y presentados en proporciones, según las macrorregiones sanitarias y los años del estudio. **Resultados:** en 2015 se notificaron un 26,41% de eventos adversos, siendo el año con mayor notificación. Al analizar las macrorregiones sanitarias, el Valle de Jequitinhonha tuvo la menor prevalencia de registro, con un 0,43%, y el Centro tuvo la mayor prevalencia de notificación (30,95%). Los efectos adversos locales más frecuentes fueron el dolor (56,48%) y el edema (38,89%). En cuanto a los eventos sistémicos, la cefalea (29,69%) y la gastroenteritis (29,69%) presentaron el mayor número de casos. Los eventos clasificados como adversos no graves (59,82%) fueron los más prevalentes y, en cuanto a la causa, el 35,94% de ellos se atribuyeron a los errores de inmunización. **Conclusión:** este estudio refuerza que los eventos adversos posteriores a la vacuna contra el VPH fueron en su mayoría eventos no graves, demostrando así la seguridad de la vacuna contra el VPH para el público adolescente y contribuyendo al aumento de las tasas de cobertura de vacunación.

**Palabras clave:** Vacunación; Adolescente; Epidemiología; Efectos Colaterales y Reacciones Adversas Relacionadas con Medicamentos; Sistemas de Información.

### How to cite this article:

Luvisaro BMO, Silva TPR, Felisbino-Mendes MS, Silva TMR, Silva RB, Lachtim SAF, Freitas GL, Matozinhos FP. Adverse events following human papillomavirus vaccine in adolescents in the state of Minas Gerais. REME - Rev Min Enferm. 2022[cited \_\_\_\_\_];26:e-1477. Available from: \_\_\_\_\_ DOI: 10.35699/2316-9389.2022.40892

## INTRODUCTION

Vaccination programs are considered fundamental for the control and eradication of several vaccine-preventable diseases and infections in the world, becoming fundamental strategies for public health.<sup>1,2</sup> Added to this is the fact that immunobiologicals are among the most pharmaceutical products considered safer for use in the human population, meeting strict quality parameters throughout the process.<sup>1,2</sup>

In Brazil, since the National Immunization Program (PNI, *Programa Nacional de Imunizações*) was created in 1973, it has been responsible for managing immunization in the country. Among its attributions are the financing and acquisition of vaccines, management and logistics, the provision of vaccination services up to the notification and investigation of adverse events following immunization (AEFI).<sup>2-4</sup>

AEFI are characterized as any occurrence that requires medical attention or surveillance after the administration of any immunobiological,<sup>3</sup> and may be related to the vaccine itself, the vaccinated and the administration.<sup>3,4</sup> The AEFI notification, followed by its investigation steps and communication, are essential for pharmacovigilance.<sup>3,5</sup> During the investigation step, the possible link between the adverse event and the administration of an immunobiological agent is established, with AEFI classified according to its location (local or systemic), its severity (serious or not serious) and its causality.<sup>3,4</sup>

Since 2014, the year in which the HPV vaccine was included in the Brazilian vaccination schedule for adolescents, in the Unified Health System (SUS, *Sistema Único de Saúde*), by the PNI - first for girls aged 11-14 years -, it has been observed that coverage is below of the goal recommended by the Ministry of Health (MoH), which is 80% for both doses.<sup>4</sup> Over the years, it is observed that the coverage rates of this vaccine continue to fall short of the estimated goals, and in 2020, the first dose was given to approximately 70% of girls aged 9 to 15 years and only 40% of boys aged 11 to 14 years.<sup>3</sup> In the same period, these rates were even lower for the second dose of the vaccine, and only 40% of girls and 30% of boys, on average, were immunized.<sup>3</sup>

The AEFI associated with the human papillomavirus (HPV) vaccine, publicized in the media since its introduction in health programs, may have compromised the acceptability and adherence of adolescents to this vaccine.<sup>5-9</sup> It is noteworthy that these were infrequent events and which were not recurrent over time, but their wide reproduction in mass communication

vehicles caused great commotion and much damage to the introduction of the vaccine in the country.<sup>6,8-10</sup>

Therefore, AEFI classified as severe are rare and the dissemination of information and epidemiological data can contribute to greater adherence and acceptance of adolescents to the HPV vaccine,<sup>5</sup> favoring the achievement of coverage targets and contributing to the achievement of elimination of the disease.<sup>11-13</sup>

This study aimed to investigate reports of adverse events after human papillomavirus vaccination in the state of *Minas Gerais* (MG), Brazil, according to the location of notification, causality, severity, and evolution of cases in the years 2015 to 2019.

## METHOD

Epidemiological, descriptive study, carried out with secondary AEFI data, collected in the second half of 2021, and registered in the years 2015 to 2019 in the Information System for the Surveillance of Adverse Events Following Immunization (ISS-AEFI) and in the module IS-AEFI from the online National Immunization Program Information System (PNI-IS).

For data collection, AEFI associated with the HPV vaccine (quadrivalent), notified monthly, in adolescents aged 9 to 15 years in the period evaluated, totaling 462 notifications in 5,058,214 doses of the vaccine applied, were organized. The cut-off age established by this study was adequate to cover all age groups contemplated with the HPV vaccine.<sup>14</sup> The number of doses of the HPV vaccine applied from January 2015 to December 2019 was obtained from the PNI-IS website, (<http://sipni.datasus.gov.br/>), using the available filters, which are: age group, macro-region and applied doses.

The state of *Minas Gerais* is composed of 853 municipalities, currently distributed in 14 health macro-regions, namely: South; Center-south; Center; *Jequitinhonha*; West; East; Southeast; North; Northwest; Southwest; Northeast; *Triângulo do Sul*; *Triângulo do Norte*; and *Vale do Aço*. These macro-regions were defined according to demographic, socioeconomic, geographic, sanitary, epidemiological, and healthcare service provision characteristics, taking into account each municipality.<sup>15</sup> It is important to emphasize that the Vale do Aço macro-region was later added to the others, but this did not bring damage to our study, as the municipalities were added to the macro-regions, one by one.

The following variables were extracted from the IS-AEFI online notifications associated with the HPV vaccine: year of occurrence; health macro-region;

route of administration (intramuscular; subcutaneous; and no information); application site (deltoid; gluteous; and no information); local and/or systemic manifestations; severity (not severe, severe); cause (immunization error, immunization error with adverse event); need for medical care (yes, no, ignored); and evolution of the case (cure without sequelae, cure with sequelae, in follow-up, not AEFI, death, others). It is noteworthy that local and systemic manifestations can be presented in more than one, that is, the number of reactions can vary from one to another.

In order to avoid information bias, only notifications registered from July 2014, period of implementation of the online system, were analyzed. This criterion was adopted in order to prevent municipalities that subsequently implemented the IS-AEFI from having low notifications when compared to those that already had the system implemented in the period. Completeness and consistency of records were assessed only for closed notifications. The exclusion criterion refers to data that were not complete.

Descriptive statistics were used for data analysis; subsequently, the Incidence Rate (IR) of AEFI associated with the HPV vaccine was calculated, through the number of AEFI associated with the administration of the vaccine in the period from 2015 to 2019, in the age group of 9 to 15 years, by health macro-region of the state of Minas Gerais / Number of doses of HPV vaccine given to individuals aged 9 to 15 years, from January 2015 to December 2019. The result was multiplied by 100,000. Data related to AEFI were presented in proportions (%), with their respective 95% confidence intervals (95%CI), according to year and health macro-region. For this study, the statistical package Statistical Software for Professional (Stata), version 16.0, was used.

Due to the nature of this study, using open access data, it was not necessary to submit the project to the Research Ethics Committee, according to Resolution 466/2012 of the National Health Council.<sup>16</sup>

## RESULTS

In the period from 2015 to 2019, 17,355 AEFI were notified in the state of Minas Gerais, of which 462 (2.63%) were associated with the HPV vaccine. When analyzing the data segregated by year of notification, the year 2015 showed the highest prevalence of AEFI notifications associated with this vaccine (26.41% - 95%CI: 22.57-30.62) followed by the year 2017 (22.94% - 95% CI: 19.31-27.01) (Figure 1).

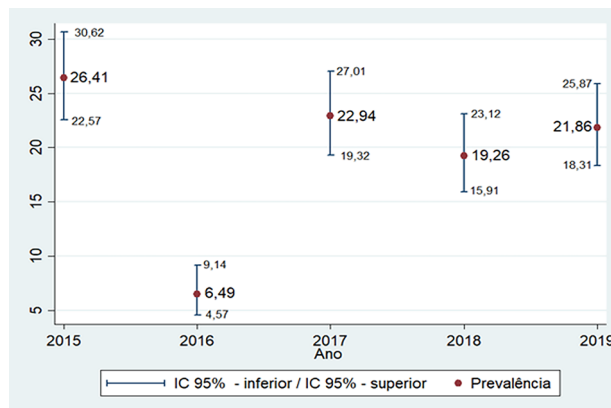


Figure 1 - Adverse events following immunization in adolescents resulting from the Quadrivalent HPV vaccine (%) and 95%CI, according to year of occurrence in the state of Minas Gerais, from 2015 to 2019

AEFI associated with the HPV vaccine were more prevalent in female adolescents (294; 63.64%), with a mean age of 11.07 years (SD: 1.38). The mean age among vaccinated female adolescents was 10.66 years (SD: 1.34) and, among male adolescents, 11.77 years (SD: 1.16).

The *Triângulo do Norte* macro-region had the highest AEFI IR, corresponding to 25.18 reported cases for every 100,000 applied doses of the aforementioned vaccine. The *Jequitinhonha* macro-region had the lowest IR, corresponding to 1.80 reported cases for every 100,000 doses (Table 1).

Table 1 - Incidence rate of adverse events after HPV vaccination per 100,000 applied doses, according to health macro-regions in Minas Gerais, 2015 to 2019

Health Macro-regions	Total of applied doses <sup>a</sup>	n <sup>b</sup>	IR <sup>c</sup>	% <sup>d</sup> total AEFI
<i>Jequitinhonha</i>	110,848	2	1.8	0.43
<b>Northeast</b>	226,732		2.21	1.08
Southeast	377,656	12	3.18	2.6
Center-south	202,512	11	5.43	2.38
Northwest	156,644	9	5.75	1.95
Southwest	174,828	11	6.29	2.38
East	182,356	12	6.58	2.6
North	437,882	29	6.62	6.28
<i>Vale do Aço</i>	206,822	18	8.7	3.9
<b>Total</b>	5,058,214	462	9.13	100.00
Center	1,535,724	143	9.31	30.95
West	280,718	29	10.33	6.28
South	665,350	70	10.52	15.15
Southern triangle	178,454	30	16.81	6.49
<b>Total</b>	5,058,214	462	9.13	100.00

Notes:

<sup>a</sup>Vaccine doses Applied in adolescents

<sup>b</sup>Sample number

<sup>c</sup>IR - Incidence rate of adverse events following immunization in adolescents per 100,00 applied doses

<sup>d</sup>Relative frequency

As for the types of AEFI, the most frequent events that occurred at the site of application of the HPV vaccine were pain (56.48%) and edema (38.89%), while headache (29.69%), gastroenteritis (29.69%) and syncope (16.67%) stood out among the systemic manifestations. It is also noteworthy that both local (76.62%) and systemic manifestations (58.44%) had a high prevalence in the “no information” field (Table 2).

Regarding the severity of AEFI, it was observed that 59.82% were classified as non-serious adverse events (NSAE); regarding the cause, 35.94% of them were attributed to immunization errors (IE). As for the medical care of notified AEFI, 33.26% reported medical care and, in 49.11% of the cases, filling in this field was ignored. As for the evolution of reported AEFIs, 40.85% were healed without sequelae and 45.31% of reported cases did not have an answer to this question (Table 3).

## DISCUSSION

The findings of this study indicate that the incidence rate of AEFI associated with the HPV vaccine in the state of Minas Gerais during the study period was very low. In addition, pain, edema, headache, and gastroenteritis prevailed, while the most frequent AEFIs are considered non-serious adverse events. Another important result was the regional differences in AEFI IR, being higher in *Triângulo do Norte* and lower in *Jequitinhonha*.

Table 2 - Adverse events following immunization in adolescents due to the HPV vaccine reported to the Immunization Surveillance System in the state of Minas Gerais, Brazil, 2015 to 2019

	n	%
<b>Administration Route</b>		
Intramuscular	392	84.85
Subcutaneous	2	0.43
<b>No information</b>	68	14.72
<b>Administration Site</b>		
Deltoid	386	83.55
Gluteous	1	0.22
No information	75	16.23
<b>Local Manifestations</b>		
No information	354	76.62
Pain	61	56.48
Edema	42	38.89
Erythema	37	34.26
Heat	31	28.70
Hot abscess	5	4.63
Nodule	8	7.41
Prurido	15	13.89
<b>Systemic Manifestations</b>		
No information	270	58.44
Fever	20	10.42
Migraine	57	29.69
Gastroenteritis	57	29.69
Syncope	32	16.67

Note: N: sample number; %: relative frequency

Table 3 - Characteristics of adverse events following immunization resulting from the HPV vaccine among adolescents, according to year of occurrence in the state of Minas Gerais from 2015 to 2019

	Year					Total
	2015	2016	2017	2018	2019	
<b>Type of event</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
Immunization Error	21(17.21)	12(40.0)	42(39.62)	50(56.18)	36(35.64)	161(35.94)
Immunization error with adverse event	1(0.82)	-	3(2.83)	-	2(1.98)	6(1.34)
Severe	5(4.10)	1(3.33)	-	3(3.37)	4(3.96)	13(2.90)
Not severe	95(77.87)	17(56.67)	61(57.55)	36(40.45)	59(58.42)	268(59.82)
<b>Medical care</b>						
Ignored	27(22.13)	16(53.33)	53(50.00)	56(62.92)	68(67.33)	220(49.11)
No	37(30.33)	5(16.67)	14(13.21)	11(12.36)	12(11.88)	79(17.63)
Yes	58(47.54)	9(30.00)	39(36.79)	22(24.72)	21(20.79)	149(33.26)
<b>Case evolution</b>						
Healing with sequelae	-	-	3(2.83)	2(2.25)	-	5(1.12)
Cure with no sequelae	81(66.39)	14(46.67)	40(37.74)	26(29.21)	22(21.78)	183(40.85)
In follow-up	12(9.84)	3(10.00)	13(12.26)	6(6.74)	14(13.86)	48(10.71)
It is not AEFI	8(6.56)	-	-	1(1.12)	-	9(2.01)
No information	21(17.21)	13(43.33)	50(47.17)	54(60.67)	65(64.36)	203(45.31)

Notes: N: sample number; %: relative frequency; AEFI: adverse event following immunization.

In 2015, one year after the introduction of the HPV vaccine, a higher AEFI IR was recorded. This behavior was expected, since, in a passive surveillance system,<sup>17,18</sup> there is an intensification of strategies for identifying and reporting healthcare problems after the inclusion of a new drug, immunobiological or technology.<sup>3</sup> This behavior may even be related to the sensitivity of the system with the implementation of the new AEFI-IS.

The high prevalence of fields such as “no information”, “ignored” or “not completed” was also identified by other studies.<sup>18,19</sup> Despite the mandatory reporting of AEFI, low adherence by healthcare professionals and institutions is observed when completing AEFI notifications. Also noteworthy is the presence of structural problems and access to health services, which offer barriers to the definitive establishment of AEFI notifications.<sup>19</sup>

The variation in AEFI IR in the macro-regions of the state of *Minas Gerais* identified in this study may be related to regional inequalities in investment in the healthcare sector, which impacts both the structure and access to services.<sup>20</sup> In the state of *Minas Gerais*, the *Jequitinhonha* macro-region it has the worst indicator of human and social development in the state and one of the worst in the country, with a historical and remarkable scarcity of resources and investments in the healthcare sector in this region.<sup>21</sup>

The lack of investment in the healthcare sector and in healthcare technologies can impact the availability of personnel to record notifications in the AEFI-IS online module.<sup>19</sup> In addition, the lack of adequately trained human resources to record notifications in the AEFI-IS, the lack of computers or in insufficient quantity and the unstable or non-existent access to the internet<sup>22</sup> also pose barriers to the notification of AEFI, since the AEFI-IS online module, established by the PNI in 2014, requires the registration of AEFI on computers connected to the internet network.<sup>19</sup>

The IR of AEFI associated with the HPV vaccine in the state of *Minas Gerais* found in the present study was lower than the average IR found in developed countries, such as the United States (32.7 cases per 100,000 vaccine doses)<sup>18</sup>; Alberta (province of Canada)<sup>23</sup> (37.4 cases per 100,000 doses of vaccine), Ontario (province of Canada)<sup>24</sup> (19.2 cases per 100,000 doses of vaccine) and Australia (34.8 cases per 100,000 doses of vaccine).<sup>25</sup> It is worth mentioning that the efficiency of pharmacovigilance in these countries and localities may have favored the identification, notification and communication of AEFI associated with this vaccine.<sup>26</sup>

Regarding the severity of adverse events, studies indicate the safety and quality of the HPV vaccine, as well as the prevalence of adverse events classified as non-serious (NSAE) (94.2%),<sup>18</sup> a result similar to that presented by this study. As for the clinical manifestations of AEFI, local reactions (such as pain and edema) and systemic reactions (such as headache and gastroenteritis) were pointed out by other studies and were among the most frequent clinical findings,<sup>13,18,25</sup> corroborating the results of the present study. Furthermore, regarding systemic manifestations, previous studies<sup>13,18,25,27</sup> reported a high prevalence of cases of syncope, which may be a psychogenic reaction to the vaccine. However, this was not the most prevalent systemic manifestation in this study.

It is noteworthy that the AEFI associated with the HPV vaccine in the state of *Minas Gerais* were temporary, self-limited, and classified as non-serious. Although no immunobiological is exempt from causing adverse events, studies indicate that the HPV vaccine is safe and that the chances of a vaccinated individual presenting an adverse event after this vaccine are small.<sup>18,25,27</sup>

It is also known that after notification of an AEFI, it is imperative that the investigation of the case be initiated, with a clinical evaluation being carried out and laboratory and complementary tests requested, in order to establish or rule out a link between the occurrence of the event and vaccination, so that sequelae or death are not inappropriately attributed to the vaccine.<sup>28</sup>

The limitation of this study refers to the possibility of underreporting, presence of missing/incomplete data and problems related to the quality of information. These aspects highlight the need for continuous assessment of AEFI surveillance, training and updating of professionals who enter data from Notification Forms in the AEFI-IS. They also highlight the need to adapt healthcare services that offer vaccination, availability of computers connected to the internet for the launch of AEFI. It is also noteworthy that AEFI notifications in Health Surveillance Notification System (NOTIVISA, *Sistema de Notificação em Vigilância Sanitária*), used for private vaccination services, were not included in this study. However, notifications on the public network cover most cases.

## CONCLUSION

Globally, HPV vaccine programs were affected, for the most part, by concerns and issues related to the safety of this vaccine and the manifestations of AEFI disseminated in various information vehicles, which had a negative impact on their coverage rates.

Thus, this study reinforces that AEFI caused by HPV were mostly non-serious events and in adolescents of both sexes. This is, therefore, a study that reinforces the safety of the HPV vaccine and may contribute to the increase in vaccine coverage rates. Also noteworthy is the importance of this vaccine and its coverage in high proportions in order to achieve the goals proposed by the World Health Organization (WHO) to eliminate cervical cancer and even its associated cancers.

## ACKNOWLEDGMENT

To the Núcleo de Estudo e Pesquisa em Vacinação of the Nursing School of the *Universidade Federal de Minas Gerais* (NUPESV) and the State Department of Health of *Minas Gerais* (SES, *Secretaria Estadual de Saúde*), for their support in carrying out this study.

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