REVIEW ARTICLE

Adverse events following human papillomavirus vaccine in adolescents: systematic review of the literature

Eventos adversos pós-vacina contra o papilomavírus humano em adolescentes: revisão sistemática da literatura

Eventos adversos tras la vacuna contra el virus del papiloma humano en adolescentes: revisión sistemática de la literatura

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ABSTRACT

Objective: The objective of this study was to investigate the occurrence of Events Supposedly Attributable to Vaccination and/or Immunization associated with the Human Papillomavirus vaccine among adolescents of both sexes. **Methods:** This is a systematic review carried out according to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). **Results:** Initially, 11,016 articles were identified, of which 6,824 remained after removing duplicates, and 59 of these were selected for full reading. The sample comprised nine studies. The results indicate that most Events Supposedly Attributable to Vaccination and/or Immunization were mild and moderate, and events at the injection site, such as pain and edema, prevailed. The most common systemic Events Supposedly Attributable to Vaccination and/or Immunization were fever, headache, fatigue and dizziness. **Conclusion:** The Human Papillomavirus vaccine for adolescents is safe, reinforcing its importance as a strategy to reduce the incidence rates of Human Papillomavirus associated cancers.

Descriptors: Vaccination; Human Papillomavirus Viruses; Adolescent; Drug-Related Side Effects and Adverse Reactions; Injection Site Reaction.

RESUMO

Objetivo: *O objetivo desse estudo foi investigar a ocorrência de Eventos Supostamente Atribuídos a Vacinação e/ou Imunização associados à vacina Papilomavírus Humano entre adolescentes de ambos os sexos.* ***Métodos:*** *Trata-se de uma revisão sistemática, realizada segundo os preceitos do Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).* ***Resultados:*** *Inicialmente, foram identificados 11.016 artigos e, após a remoção de duplicidades, restaram 6.824. Destes, 59 foram selecionados para leitura na íntegra. Ao final, nove estudos compuseram a amostra. Os resultados indicam que a maioria dos Eventos Supostamente Atribuídos a Vacinação e/ou Imunização foram leves e moderados, prevalecendo eventos no local da injeção, como a dor e edema. Os Eventos Supostamente Atribuídos a Vacinação e/ou Imunização sistêmicos mais frequentes foram a febre, cefaleia, fadiga e tontura.* ***Conclusão:*** *A vacina contra o Papilomavírus Humano para os adolescentes é segura, reforçando-se sua importância como estratégia para diminuir as taxas de incidência dos cânceres associados ao Papilomavírus Humano.*

Descritores: *Vacinação; Papilomavírus Humano; Adolescente; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Reação no Local da Injeção*

RESUMEN

Objetivo: *El objetivo de este estudio fue investigar la ocurrencia de Eventos Supuestamente Atribuibles a la Vacunación o Inmunización asociados a la Vacuna contra el Virus del Papiloma Humano entre adolescentes de ambos sexos.* ***Métodos:*** *Se trata de una revisión sistemática realizada según la declaración Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).* ***Resultados:*** *Se identificaron 11.016 artículos y, tras eliminar duplicados, quedaron 6.824. De ellos, 59 fueron seleccionados para lectura completa. La muestra estuvo compuesta por nueve estudios. Los resultados indican que la mayoría de los Eventos Supuestamente Atribuibles a la Vacunación o Inmunización fueron leves y moderados, prevaleciendo los eventos en el lugar de la inyección, como dolor y edema. Los Eventos Supuestamente Atribuibles a la Vacunación o Inmunización sistémicos más comunes fueron fiebre, dolor de cabeza, fatiga y mareos.* ***Conclusión:*** *La vacuna contra el Virus del Papiloma Humano para adolescentes es segura, lo que refuerza su importancia como estrategia para reducir las tasas de incidencia de cánceres asociados al Virus del Papiloma Humano.*

Descriptores: *Vacunación; Virus del Papiloma Humano; Adolescente; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Reacción en el Punto de Inyección.*

INTRODUCTION

Human Papillomavirus (HPV) infection is a Sexually Transmitted Infection (STI) with high prevalence worldwide[1]. Although it is not restricted to females, as men can also become infected, this infection affects most sexually active women at some point in their lives[2,3].

Most HPV infections occur transiently and asymptomatically. However, persistent infections with HPV characterized by high oncogenic risk, called HPV 6, HPV 11, HPV 16 and HPV 18, can lead to the development of cervical cancer, oral cavity cancer and anogenital cancers[4-6]. Cervical cancer is the fourth most common type of cancer in the female population, with approximately half a million new cases and 266,000 deaths annually[1].

Studies show that the earlier the start of sexual life the greater the risk of exposure to HPV[7,8]. In view of this, public health strategies to reduce the rates of infections caused by this virus began to be sought. One of the measures was the development of a specific vaccine for HPV, which began to be sold in 2006[9-12]. Vaccination stands out as an effective strategy in the context of public health due to its positive impact on reducing morbidity and mortality from vaccine-preventable diseases, such as diseases caused by HPV.

The World Health Organization (WHO) recognizes cervical cancer and HPV-related diseases as a global public health problem, and recommends including the vaccine in national vaccination programs[12].

One of the biggest challenges for health services in relation to vaccination is to ensure safe vaccination practices, avoiding Events Supposedly Attributable to Vaccination or Immunization (ESAVI) as much as possible[1,2]. These are characterized as any unwanted or unintentional occurrences after vaccination that do not necessarily have a causal relationship with the use of a vaccine or other immunobiological, but may be related, for example, to the application technique, etc. Events Supposedly Attributable to Vaccination or Immunization can be classified according to severity and causality[3,4].

As for causality, ESAVI may be related to the vaccine or some of its components, such as adjuvants, for example; the quality of the vaccine; anxiety or stress triggered by vaccination; to immunization errors; or they may be coincidental events, in which the event is not related to the vaccine or any product thereof, nor to anxiety or stress triggered by vaccination[5], but rather to an unclear cause. In coincidental events, a temporal association between the occurrence of the adverse event and the vaccination is observed, but without proof of a causal link between them[5].

Immunization errors can be avoided through the adoption of good practices in immunization and periodic training of health professionals who work in vaccination services[6].

The ESAVI can exert important influence in individuals' decisions of being vaccinated or not. In Brazil, the HPV vaccine is currently available in the Brazilian Unified Health System through the National Immunization Program. The quadrivalent HPV vaccine is offered in the health network for female and male individuals aged nine to 14 years; and for the immunosuppressed population aged nine to 45 years, with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS), solid organ or bone marrow transplant recipients and oncology patients[12].

The challenges affecting the implementation and adoption of HPV vaccination in the adolescent population are highlighted in the literature as individual and environmental factors strongly linked to health. Studies show that individual factors refer to the acceptability and adherence to the HPV vaccine, which are linked to values, beliefs, and information about the epidemiology of HPV, cancer and the vaccine[1,13,14].

In the context of adolescents, the HPV vaccine was the target of numerous fallacies inadvertently associating it with ESAVI, such as events related to early sexualization and taboos associated with culture and fake news, which caused fear among young people and their families, and increased refusal to the HPV vaccine in this population[7,8]. In addition to these factors, the dissemination of ESAVI associated with this vaccine in the media and social networks, such as cases of teenagers fainting while taking the vaccine, are important influencers in the decision-making process of teenagers and those responsible for them in relation to getting vaccinated[2,13].

Therefore, it is relevant to synthesize knowledge about the occurrence of ESAVI, as this will certainly contribute to discuss issues about the safety and acceptability of the HPV vaccine and reflect on cultural aspects and the source of vaccination knowledge acquisition for better adherence and consequently, increased vaccination coverage.

Considering the high incidence of HPV infections, the free availability of the vaccine in Brazil and the low adherence to vaccination, the aim of this study was to identify in the literature the occurrence of Events Supposedly Attributable to Vaccination and/or Immunization associated with the Human Papillomavirus vaccine among adolescents of both sexes.

METHODS

This is a systematic review study conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions(15) and reported according to the steps recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement(16). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) identified by registration number CRD42020182349.

Search strategy

This review sought to answer the following research question: "What is the prevalence and types of ESAVI in adolescents who received the HPV vaccine?" For the systematic search, the research question was adjusted to the PECOS strategy[17] (Population, Exposure, Comparison, Outcomes, Study type) (Table 1).

The search strategy was carried out in the Embase and MEDLINE (Medical Literature Analysis and Retrieval System) databases via PubMed, which are among three search bases considered essential by Cochrane Collaboration. The search was carried out in April 2023. The terms chosen for the search were based on the keywords identified in a preliminary analysis of the literature, and included: "HPV", "vaccine", "immunization", "adolescent", "adverse reactions", "errors" and their associated terms. No language or period restrictions were adopted.

Table 1 - Description of the PECOS strategy[17]

Acronym	Definition	Description
P	Patient/ Population	Female and male adolescents aged 9 to 19 years
E	Exposure	*HPV vaccine
C	Comparison	Not applicable
O	Outcomes	**ESAVI
S	Study type	Observational studies

Note: * HPV - Human Papillomavirus; ** ESAVI - Events Supposedly Attributable to Vaccination or Immunization.

- Search Strategy in MEDLINE (*Medical Literature Analysis and Retrieval System*)

(((*"hpv" OR "human papilloma virus" OR "human papilloma virus" OR "papilloma viruses" OR "hpv, human papillomavirus viruses" OR "human papillomavirus viruses" OR "human papillomavirus virus" OR "human papillomavirus virus infection" OR "Papillomavirus Vaccines" OR "HPV Vaccines" OR "Papillomaviridae" OR "Human Papilloma Virus" OR "Human Papilloma Viruses" OR "Papilloma Virus, Human" OR "Papilloma Viruses, Human" OR "Virus, Human Papilloma" OR "Viruses, Human Papilloma" OR "HPV, Human Papillomavirus Viruses" OR "Human Papillomavirus Viruses" OR "Human Papillomavirus Virus" OR "Papillomavirus Virus, Human" OR "Papillomavirus Viruses, Human" OR "Virus, Human Papillomavirus" OR "Viruses, Human Papillomavirus")) AND (("Vaccination" OR "Vaccination" OR "Vaccination Coverage" OR "Immunization Programs" OR "Vaccination Refusal" OR "Adverse Reactions" OR "Medication Errors")) AND (("Adolescent" OR "Adolescent" OR "Adolescents" OR "Adolescence" OR "Teens" OR "Teen" OR "Teenagers" OR "Teenager" OR "Youth" OR "Youths" OR "Adolescents, Female" OR "Adolescent, Female" OR "Female Adolescent" OR "Female Adolescents" OR "Adolescents, Male" OR "Adolescent, Male" OR "Male Adolescent" OR "Male Adolescents")))) AND (("Prevalence"[Mesh] OR "Prevalence" OR "Prevalences"*))

- Search Strategy in Embase

#1 #1 AND #2 AND #3 AND #4

#3 'adolescent'/syn

#2 'vaccine'/syn OR 'vaccination'/syn OR 'immunization'/syn OR 'vaccination refusal'/syn OR 'adverse reactions' OR 'medication error'/syn

#1 'papillomavirus-transformed cell line'/syn OR 'wart virus'/syn OR 'papillomaviridae'/syn ('prevalence'/syn)

Eligibility criteria

The following were considered for the inclusion of studies: studies investigating ESAVI after the administration of any type of HPV vaccine with complete doses in adolescents aged nine to 19 years for the inclusion of the entire population from the beginning of application of the vaccine in different countries.

Studies evaluating populations with autoimmune diseases, immunocompromised people, pregnant women, people with inflammatory diseases, and those that presented insufficient information about the study population were excluded, in addition to reviews, case reports, abstracts presented at congresses and conferences, study protocols, letter to the editor, personal opinions, dissertation, thesis, institutional analysis and manuals.

If the study covered a population beyond the defined age group, but did not present segregated data, it was excluded from the analysis.

Study selection and data extraction

The selection of studies and data extraction were carried out independently by two pairs of reviewers who studied the topic covered, with use of the Rayyan software[18]. After excluding duplicates, the titles and abstracts were individually examined. The selected studies were read in full by the same pairs and eligibility criteria were checked. Discrepancies were resolved by consensus between members of the pair and in case of disagreements, the opinion of a third reviewer was requested.

Relevant characteristics were extracted from all included studies, such as: general characteristics of the study (title and authors, year of study, geographic location); methods (study design, participant allocation, reported measured outcomes, variables); participant characteristics (age) and outcomes (Adverse Events Following Immunization - AEFI). In case of duplicate studies, the one published previously or with more detailed information was included.

Bias risk assessment

The methodological quality of the studies was assessed using the Newcastle-Ottawa scale[19] from the Ottawa Hospital Research Institute. In cohort studies, the instrument evaluates seven study items divided into three domains: selection (sample representativeness, sample size, non-respondents and exposure investigation), comparability (adjustment for confounding factors) and outcome (outcome assessment and statistical test). In turn, the instrument for control case studies has seven domains. The Newcastle-Ottawa assessment scale for cohort studies was adapted by Wells et al.[19] to allow assessment of the quality of cross-sectional studies. This scale is explained through the number of stars that the article receives, the higher the number of stars, the lower the risk of bias.

RESULTS

The systematic literature search identified 11,016 scientific articles. After removing duplicates, 6,824 works with the potential to answer the research question remained. No additional studies were identified by manual search of reference lists. Initially, titles and abstracts were evaluated and 59 studies were selected for full reading. At the end of this process, nine studies[20-28] met all eligibility criteria and were included in this review (Figure 1).

Characteristics of the studies

The characteristics of studies included are presented in Table 2

The articles were published between 2013 and 2021. Regarding the country of origin, two were developed in the United States of America[20,21]; one study was carried out in each of the countries, Australia, Denmark, Vietnam/Uganda, Brazil, South Korea and Japan[22,25-28]; and one study had a multicenter sample[22].

Regarding the design, seven studies were cross-sectional[20-25,28], one a case-control[26] and one was a cohort study[27].

Regarding methodological quality, there were studies with a higher risk of bias[21,23] and studies with a lower risk of bias[20,22,24-28], indicating worse and better methodological quality, respectively, as shown in Table 3.

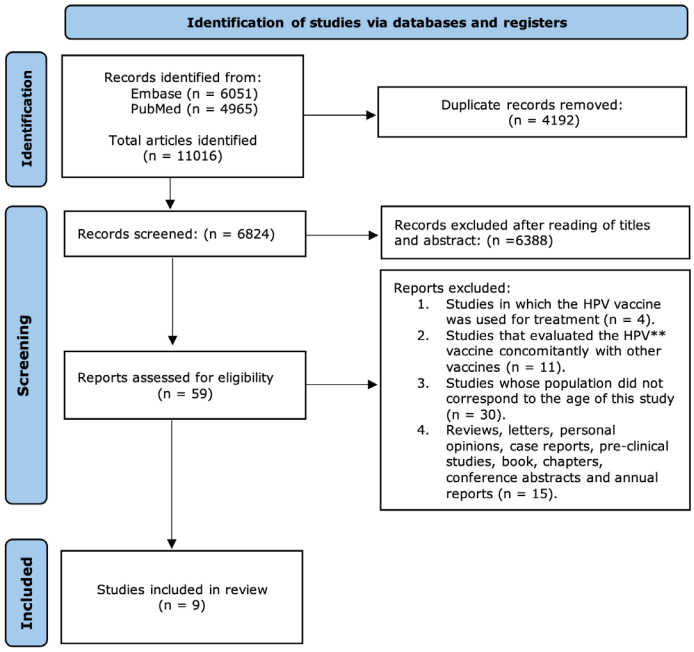
Events Supposedly Attributable to Vaccination or Immunization

Among the studies included in the analysis, five were aimed at evaluating all types of ESAVI after the HPV vaccine[21,23-26], three analyzed all ESAVI reported to the notification system in their country of origin[20,22,28] and one study reported ESAVI related only to systemic reactions to the HPV vaccine[27].

Six studies evaluated only the ESAVI related to the quadrivalent HPV vaccine[20-22,25-28] and one study evaluated the ESAVI regarding the bivalent and quadrivalent vaccine[24]. Although the type of vaccine evaluated was not reported in a study[23], it was related to the HPV vaccine.

The ESAVI reported were summarized in a table according to the division of these events into local and systemic reactions and as adverse events caused by Immunization Errors (Table 4).

Figure 1 - Flow diagram of bibliographic search and data extraction from the systematic review, prepared according to the PRISMA 2020* model



Note: * PRISMA 2020 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses, 2020; ** HPV - Human Papillomavirus.

Table 2 - Studies included in the review according to author, year, country, design, age, type of vaccine and outcome/ Events Supposedly Attributable to Vaccination or Immunization

Author	Year	Country	Design	Age of participants	Type of [a]HPV vaccine	Outcome/[b]ESAVI
Naleway et al.[21]	2012	[c]USA	Cross-sectional	*11 to 17 years	[d]4vHPV	Pain, bruising, angioedema, syncope and pre-syncope
Jain et al.[24]	2013	Vietnam and Uganda	Cross-sectional	10 to 15 years	[d]4vHPV [e]2vHPV	Fever, pain, local angioedema, tiredness, dizziness
Martínez-Lavín et al.[23]	2015	13 countries	Cross-sectional	Mean of 14 years	[d]4vHPV [e]2vHPV	Musculoskeletal pain, fatigue, headache, dizziness, paresthesia and nausea, vomiting, fibromyalgia
Crawford et al.[25]	2016	Australia	Cross-sectional	12 to 16 years	[d]4vHPV	Rash; local urticaria/angioedema; anaphylaxis; syncope and other neurological events
Jacobsen et al.[26]	2018	Denmark	Cross-sectional	*12 to 17 years	[d]4vHPV	Rash; local urticaria/angioedema; syncope, pain; nausea; fatigue
Neha et al.[20]	2019	USA	Cohort	*9 to 26 years	[d]4vHPV	Medication error; local reactions (pain, redness, swelling and itching at the injection site), pyrexia, nausea, dizziness, diarrhea, vomiting, fatigue, upper respiratory tract infections, oropharyngeal pain, myalgia and headache
Mauro et al.[22]	2019	Brazil	Cross-sectional	9 to 15 years	[d]4vHPV	Syncope, dizziness, malaise, headache and nausea. Pain and/or erythema
Yooh et al.[27]	2021	South Korea	Cohort	11 to 14 years	[d]4vHPV	Migraine
Hineno et al.[28]	2021	Japan	Transversal	*11 to 19 years	[d]4vHPV	Headache; generalized pain; dysautonomia symptoms

Note: * The samples evaluated in the studies were mostly composed of female individuals aged between 9 and 19 years. However, some studies (18,19,24,26) included a population older than that defined in this review. As they presented segregated data, they were included in this study; [a] HPV- Human papillomavirus; [b] Events Supposedly Attributable to Vaccination and/or Immunization; [c] The United State of American; [d] 4vHPV- Quadrivalent human papillomavirus vaccine; [e] 2vHPV- Bivalent human papillomavirus vaccine.

Table 3 - Evaluation of the methodological quality of studies - Newcastle-Ottawa[19]

Studies	Selection (maximum four stars)	Comparison (maximum two stars)	Outcome evaluation (maximum three stars)	Final score (maximum nine stars)*
Neha, et al.[20]	**	*	***	6
Naleway, et al.[21]	*	*	**	4
Mauro, et al.[22]	*	*	***	5
Martínez, et al.[23]	*	*	*	3
Jain, et al.[24]	**	*	***	6
Crawford, et al.[25]	**	*	***	6
Jacobsen, et al.[26]	**	*	**	5
Yooh, et al.[27]	***	*	***	7
Hileno et al.[28]	***	*	***	7

Note: * Strong evidence - consistent findings across multiple high-quality studies 6/9; Moderate evidence - consistent findings between several low-quality studies and/or one high-quality study 4-5/9; Limited evidence - one lower quality study < 4; Conflicting evidence - inconsistent findings between multiple studies; No evidence - no evidence across studies.

Table 4 - Adverse events reported in studies according to local and systemic reactions and immunization errors

Study	Adverse Events: Local Reactions	Adverse Events: Systemic Reactions	Events caused by errors in the preparation, handling or administration of the vaccine
Neha, et al.[20]	Not reported	Syncope and abdominal pain	Wrong vaccine administered; inadequate scheduling and storage errors
Naleway, et al.[21]	Pain, angioedema, bruising	Syncope	Not reported
Mauro et al.[22]	Pain and erythema	Syncope	Not reported
Martínez et al.[23]	Pain	Fatigue, Headache, chronic neuropathic pain	Not reported
Jain et al.[24]	Pain and angioedema	Fever	Not reported
Crawford et al.[25]	Angioedema and urticaria	Syncope, anxiety and anaphylaxis	Not reported
Jacobsen et al.[26]	Pain, angioedema, urticaria	Fainting, dizziness, fatigue	Not reported
Yooh, et al.[27]	Not reported	Migraine	Not reported
Hileno, et al.[28]	Pain	Headache, tremors	Not reported

DISCUSSION

Based on the evidence identified in the literature, most ESAVI referred to events at the injection site, such as pain and edema[20-26]. The most common systemic ESAVI were fever, headache, fatigue and dizziness[20,21,23,28]. The results of this study regarding ESAVI associated with the HPV vaccine do not raise concerns regarding the safety of vaccination in adolescents, since these types of events are commonly expected.

Local adverse events of the HPV vaccine, pain and edema, are considered common and expected in the adolescent population and characterized as a temporary and non-life-threatening condition[20]. These events must be notified and monitored through the surveillance system by the healthcare team for better management and monitoring. If any of them evolve into a more serious or chronic consequence, it must be reported as well.

Furthermore, the possible ESAVI of the HPV vaccine, both local and systemic, must be informed to patients in advance. This is of paramount importance in relation to adolescents and their parents/guardians, since prior information allows better attention on the part of both and allows them to report any occurrence of these events to the health service, thereby eliminating possible events associated with "fake news" and the stigma surrounding them[21,29].

Regarding immunization errs, one study showed a relationship with incorrect administration, inadequate scheduling and storage errors of the HPV vaccine[20]. According to the WHO Global Advisory Committee on Vaccine Safety, the use of expired vaccines or those that have been exposed to extreme temperatures, the inadvertent application of the vaccine to individuals who have any clinical or pharmacological contraindications,

the use of inappropriate diluents, incorrect technique or route of vaccine administration, and the administration of an inadequate dose or after the recommended deadline constitute immunization errs that can cause local or systemic reactions in the vaccinated individual[12]. These errors can have a negative impact on the population and health services. Among the losses associated with them, the highlights are the impairment of the immune response to the immunobiological, higher costs for health services and the reduction in the population's confidence, which directly impacts on vaccination coverage[4,5,29].

Immunization errors can be avoided through the adoption of strategies aimed at ensuring the proper functioning of the cold chain and good practices in immunization[4,6], such as: continuous monitoring of the temperature of the immunobiological at all stages of the cold chain, from the production laboratory to vaccination rooms; when reconstitution of the vaccine is necessary, it must be done using the diluent provided by the manufacturer; the reconstituted vaccine must be used within a maximum period of six hours, and discarded at the end of each working day; the immunobiological must be stored in exclusive cold chambers; workers must be trained and supervised during immunization practice; adverse events must be reported, investigated and monitored for the identification of their causes and establishment of strategies to correct the processes related to their occurrence[4].

Some studies indicate that Adverse Events Following Immunization can be explained by the complexity of the immunization schedule, increase in the number of immunobiologicals included in the vaccination schedule in recent decades, in addition to the awareness of health professionals regarding the importance of reporting these events[6,30,31].

Furthermore, the fear of possible adverse events is one of the main determinants of HPV vaccine hesitancy and the undermining of public confidence in vaccines. Therefore, studies that evaluate pharmacovigilance and adverse events of this vaccine in the adolescent population are extremely important, as events such as those mentioned above can influence adherence and, in turn, coverage rates of the HPV vaccine[28,32].

Some possible limitations should be considered in this study. Despite extensive research carried out, a small number of articles was found for each result, implying a limited representation of the global scenario. Despite this fact, a rigorous methodology based on the Cochrane Collaboration guidelines was used in this study, and with the results presented, it was possible to identify the main causes of ESAVI with the HPV vaccine among adolescents aged 9 to 19 years.

CONCLUSION

The HPV vaccine is safe for the adolescent population, since the reported ESAVI were only those already predicted for this type of vaccine and no new or unexpected events that would raise concerns about the safety of this vaccine were identified. The HPV vaccine is an important strategy to reduce the global morbidity and mortality of HPV-associated cancers.

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Conflicts of interest

None.

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Author's contributions - CRediT

BMOL: conceptualization; data curation; formal analysis; investigation; methodology; validation; writing - original draft and writing - review & editing.
TPRS: conceptualization; data curation; formal analysis; investigation; methodology; validation; writing - original draft and writing - review & editing.
APVF: conceptualization; data curation; formal analysis; investigation; methodology; validation; and writing - review & editing.
CKD: conceptualization; supervision; validation; and writing - review & editing.
TMRS: conceptualization; supervision; validation; and writing - review & editing.
AESN: conceptualization; data curation; formal analysis; investigation; methodology; validation; writing - original draft and writing - review & editing.
NSC: conceptualization; data curation; formal analysis; investigation; methodology; validation; writing - original draft and writing - review & editing.
FPM: conceptualization; project administration; supervision; validation; and writing - review & editing.

REFERENCES

1. Howard N, Gallagher KE, Mounier-Jack S, Burchett HED, Kabakama S, LaMontagne DS, et al. What works for human papillomavirus vaccine introduction in low and middle-income countries? Papillomavirus Res. 2017 Dec 4;22-5. https://doi.org/10.1016/j.pvr.2017.06.003
2. Ferrer HB, Trotter C, Hickman M, Audrey S. Barriers and facilitators to HPV vaccination of young women in high-

income countries: a qualitative systematic review and evidence synthesis. BMC Public Health 2014;14:700. https://doi.org/10.1186/1471-2458-14-700

3. Freeman LK. Adverse events following immunization. Can Fam Physician [Internet]. 2019 Mar [cited 2023 Jan 10];65(3):163. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6515964/

4. World Health Organization. How do vaccines work? Definition and Application of Terms for Vaccine Pharmacovigilance This report from the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with WHO covers the activities and outputs of the CIOMS/WHO. [Internet]. 2020 Dec 8 [cited 2023 Jan 11]. Available from: https://www.who.int/news-room/feature-stories/detail/how-do-vaccines-work

5. World Health Organization. Global manual on surveillance of adverse events following immunization [Internet]. 2016 [cited 2023 Jan 14]. Available from: https://www.who.int/publications/i/item/10665206144

6. Bisetto LH, Ciosak SI. Análise da ocorrência de evento adverso pós-vacinação decorrente de erro de imunização. Rev Bras Enferm. 2017 Jan-Feb;70(1):87-95. https://doi.org/10.1590/0034-7167-2016-0034

7. Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, Sundman J, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS One [Internet]. 2012 Mar 28 [cited 2023 Feb 28];7(3):e33536. Available from: https://pubmed.ncbi.nlm.nih.gov/22470453/

8. Laz TH, Rahman M, Berenson AB. An update on human papillomavirus vaccine uptake among 11-17 year old girls in the United States: National Health Interview Survey, 2010. Vaccine. 2012 Apr 2;30(24):3534-40. https://doi.org/10.1016/j.vaccine.2012.03.067

9. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: A pooled analysis. Lancet Glob Health. 2016 July;4(7):e453-63. https://doi.org/10.1016/S2214-109X(16)30099-7

10. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019 Aug 16;68(32):698-702. https://doi.org/10.15585/mmwr.mm6832a3

11. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2014 Sept 13;136(5):E359-86. https://doi.org/10.1002/ijc.29210

12. World Health Organization. Guide to introducing HPV vaccine into national immunization programmes [Internet]. 2016 [cited 2023 Abr 14]. Available from: https://apps.who.int/iris/handle/10665/253123

13. Lobão WM, Duarte FG, Burns JD, Santos CAST, Almeida MCC, Reingold A, et al. Low coverage of HPV vaccination in the national immunization programme in Brazil: Parental vaccine refusal or barriers in health-service based vaccine delivery? PLoS One [Internet]. 2018 Nov 12 [cited 2023 Jan 14];13(11):e0206726. Available from: https://pubmed.ncbi.nlm.nih.gov/30418980/

14. Sundaram N, Voo TC, Tam CC. Adolescent HPV vaccination: empowerment, equity and ethics. Hum Vaccin Immunother. 2020 Aug 2;16(8):1835-40. https://doi.org/10.1080/21645515.2019.1697596

15. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane [Internet]. 2022 [cited 2023 Apr 16]. Available from: https://training.cochrane.org/handbook

16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. https://doi.org/10.1136/bmj.n71

17. Ministério da Saúde, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia. Diretrizes metodológicas - Elaboração de revisão sistemática e metanálise dos estudos observacionais comparativos sobre fatores de risco e prognóstico [Internet]. Brasília: Ministério da Saúde. 2014 [cited 2023 Dec 20]. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_metodologicas_fatores_risco_prognostico.pdf

18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan — a web and mobile app for systematic reviews. Systematic Reviews. 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4

19. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis [Internet]. 2000 [cited 2023 Jan 10]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

20. Neha R, Subeesh V, Beulah E, Gouri N, Maheswari E. Postlicensure surveillance of human papillomavirus vaccine using the Vaccine Adverse Event Reporting System, 2006-2017. Perspect Clin Res. 2020 Jan-Mar;11(1):24-30. https://doi.org/10.4103/picr.PICR_140_18

21. Naleway AL, Gold R, Drew L, Riedlinger K, Henninger ML, Gee J. Reported adverse events in young women following quadrivalent human papillomavirus vaccination. J Womens Health (Larchmt) [Internet]. 2012 Apr 13;21(4):425-32. https://doi.org/10.1089/jwh.2011.2895

22. Mauro AB, Fernandes EG, Miyaji KT, Arantes BA, Valente MG, Sato HK, et al. Adverse events following

Quadrivalent HPV vaccination reported in Sao Paulo State, Brazil, in the first three years after introducing the vaccine for routine immunization (March 2014 to December 2016). Rev. Inst. Med. trop. S. Paulo. 2019 Sept 12;61. https://doi.org/10.1590/S1678-9946201961043

23. Martínez-Lavín M, Martínez-Martínez LA, Reyes-Loyola P. HPV vaccination syndrome. A questionnaire-based study. Clin Rheumatol. 2015 Sept 10;34(11):1981-3. https://doi.org/10.1007/s10067-015-3070-3

24. Jain KM, Paul P, LaMontagne DS. Monitoring adverse events following immunisation in developing countries: experience from human papillomavirus vaccination demonstration projects. Sex Health. 2013 Dec 14;(1):57-63. https://doi.org/10.1071/SH11161

25. Crawford NW, Hodgson K, Gold M, Buttery J, Wood N, AEFI-CAN network. Adverse events following HPV immunization in Australia: Establishment of a clinical network. Hum Vaccin Immunother. 2016 July 26;12(10):2662-5. https://doi.org/10.1080/21645515.2016.1192737

26. Jacobsen SU, Valentiner-Branth P, Mølbak K. Examining determinants for reporting suspected adverse events following HPV vaccination in Denmark. Vaccine. 2018 Sept 7;36(41):6158-62. https://doi.org/10.1016/j.vaccine.2018.08.061

27. Yoon D, Lee JH, Lee H, Shin JY. Association between human papillomavirus vaccination and serious adverse events in South Korean adolescent girls: nationwide cohort study. BMJ. 2021 Jan 29;372:m4931. https://doi.org/10.1136/bmj.m4931

28. Hineno A, Ikeda SI. A Long-Term Observation on the Possible Adverse Effects in Japanese Adolescent Girls after Human Papillomavirus Vaccination. Vaccines (Basel). 2021 Aug 4;9(8):856. https://doi.org/10.3390/vaccines9080856

29. Hibbs BF, Moro PL, Lewis P, Miller ER, Shimabukuro TT. Vaccination errors reported to the Vaccine Adverse Event Reporting System, (VAERS) United States, 2000-2013. Vaccine. 2015 May 14;33(28):3171-8. https://doi.org/10.1016/j.vaccine.2015.05.006

30. Leroy Z, Broder K, Menschik D, Shimabukuro T, Martin D. Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system. Vaccine. 2012 Feb 20;30(11):2020-3. https://doi.org/10.1016/j.vaccine.2011.12.042

31. Moro PL, Broder K, Zheteyeva Y, Revzina N, Tepper N, Kissin D, et al. Adverse events following administration to pregnant women of influenza A (H1N1) 2009 monovalent vaccine reported to the Vaccine Adverse Event Reporting System. Am J Obstet Gynecol. 2011 June 21;205(5):473.e1-9. https://doi.org/10.1016/j.ajog.2011.06.047

32. Moura LD L, Codeço CT, Luz PM. Cobertura da vacina papilomavírus humano (HPV) no Brasil: heterogeneidade espacial e entre coortes etárias. Rev. bras. epidemiol. 2020 Dec 18;24:1-12. https://doi.org/10.1590/1980-549720210001