

Current HPV Vaccination Strategies in Brazil

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How to cite this paper: Filho, D.S.T., Rocha, C.M.R., Bacha, E., Andrade, Á.N.M., Pereira, D.D.P., Nunes, L.M., Passos, L.D., Braz, P.T.S., Braz, P.A.S., Bisneta, A.I.S. and Sobrinho, F.E.R.A. (2023) Current HPV Vaccination Strategies in Brazil. *Health*, 15, 107-121.

<https://doi.org/10.4236/health.2023.152009>

Received: January 2, 2023

Accepted: February 18, 2023

Published: February 21, 2023

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Abstract

Cervical cancer is one of the most preventable and treatable malignancies, however, it still has high incidence and mortality rates, especially in less developed countries. For Brazil, the estimate is more than 16,000 new cases and more than 6000 deaths annually. Despite this, vaccines against HPV (responsible for cervical cancer) are effective and promote a significant decrease in infections and neoplastic lesions of the cervix. As recommended by the World Health Organization, girls aged 9 to 14 should be vaccinated before becoming sexually active. Although the vaccine was developed in 2006, in Brazil immunization only started to be carried out in 2014, initially only for girls between 9 and 11 years old. The present work is an integrative review, with the objective of explaining the current situation of vaccination against HPV throughout the country. Using the PubMed, MED-LINE and Google Scholar databases, a search for scientific articles was carried out during the year 2022, using the descriptors “Vaccine”, “HPV” and “Brazil”, simultaneously selecting 17 articles. The Brazilian recommendations for vaccination against HPV have undergone several strategic changes over time, in the following points: age group and gender of the target population, major site of application of vaccines and number of doses to be applied. Currently, in Brazil, the recommendation for vaccination against HPV is neutral in gender, between 9 and 14 years old and in immunosuppressed people up to 45 years old, with a vaccination schedule of 2 doses with an interval of 6 months between them, and 3 doses for those from 15 years and immunocompromised individual (0 - 2 - 6 months). The tetravalent vaccine offered by public funding continues to be applied at health centers, despite several favorable criticisms of the return of application in schools. Even though the vaccine is available free of charge, studies point to the difficulty in achieving and maintaining vaccination cov-

erage, especially for the second dose. Among the factors that impede success, they cite illiteracy in health generated mainly by social inequality and the lack of educational actions by the government, demonstrating the need to plan effective strategies in this regard.

Keywords

Brazil, HPV, Vaccine Update, Cervical Cancer

1. Introduction

Human Papillomavirus (HPV) is mainly sexually transmitted and promotes abnormal proliferation of the mucosal epithelium and is responsible for the most frequent infections of the genital tract. But it can also affect the oral cavity, trachea, bronchi, esophagus, rectum and anus. HPV Subtypes 16, 18, 31, 33, 45, 52 and 58 are oncogenic and together represent more than 95% of cases of cervical-uterine cancers. HPV-6 and HPV-11 are the two primary non-cancerous types responsible for anogenital warts [1].

Cervical cancer is one of the most easily preventable and treatable malignancies, with primary prevention measures (vaccine and use of condoms), secondary prevention (screening tests to detect infection and pre-malignant) and tertiary prevention (early treatment of initial lesions) [1].

It is worth mentioning that cervical cancer is a disease of slow and silent development, and may be asymptomatic in the initial phase, or with precursor lesions, and evolve after 15 to 20 years [2]. However, cervical cancer still has high incidence and mortality rates, especially in less developed countries [2].

For Brazil, the estimate is more than 16,000 new cases and more than 6000 annual deaths resulting from cervical cancer. Despite this, vaccines against HPV are effective and promote a significant decrease in infections, consequently, in neoplastic lesions of the cervix [3].

As recommended by the World Health Organization (WHO), girls should be vaccinated before they become sexually active, between the ages of 9 and 14. There are three types of vaccine, according to the subtypes covered: bivalent (16 and 18), tetravalent (6, 8, 16 and 18), and nonvalent encompassing coverage for the other oncogenic subtypes (31, 33, 45, 52 and 58) [4].

Although the HPV vaccine has been implemented since 2006 in some developed countries, such as Canada, the United States and Australia, in Brazil, immunization only began to be carried out in 2014, through the Unified Health System (SUS), initially only for girls between 9 and 11 years old [5]. However, in 2017, the distribution of the vaccine to boys was also approved [5].

Brazil was the first country in South America to offer the vaccine to boys in national immunization programs; this change was supported by cross-protection for girls, in addition to protecting against cancers of other affected systems related to HPV [6].

Initially, in line with developed countries, vaccination in Brazil was carried out within schools, later it was carried out exclusively at UBS (Basic Health Units). It was found, then, that the immunization strategy within schools is one of the main guarantors of vaccine success, to the detriment of exclusive vaccination in the UBS (Basic Health Units) [7].

The COVID-19 pandemic enacted in early 2020 caused vaccination against HPV, along with other immunizations, to register vaccine rates far below the desired level [8].

Warning that cervical cancer is a preventable disease, but still has a high incidence and mortality, the WHO (World Health Organization) launched, in August 2020, a campaign for the eradication of cervical cancer in the world by the year 2030 and FEBRASGO (Brazilian Federation of Gynecology and Obstetrics Associations) joined the initiative [9]. WHO's proposed strategy to accelerate the elimination of cervical cancer is based on three goals: 1) to ensure that 90% of girls receive the HPV vaccine by the age of 15; 2) to ensure that 70% of women perform a screening test with effective test up to 35 years and another up to 45 years of age; and 3) to certify that 90% of women identified with precursor lesions or invasive cancer receive treatment [10].

In April 2022, the WHO SAGE (Immunization Strategies Advisory Group) compared the evidence of the efficacy of the single dose of HPV vaccines with evidence of the efficacy of two or three doses in the recommended regimens, and it was concluded that a single dose may offer significant and non-negligible protection against HPV, in some situations, it may be equivalent to the two doses that are currently recommended for adolescents [11]. These observations would also allow the two-dose regimen to be expanded to ages over 14 years. Therefore, adopting the single dose as a strategy may be an important step to increase coverage and provide protection for a greater number of girls who do not have access to HPV immunization [4].

SAGE's current recommendations for the HPV vaccine are:

A single dose or two doses for girls from 9 to 14 years of age;

A single dose or two doses for girls 15 to 20 years of age;

Two doses six months apart for women over 21 years of age.

Also, in relation to these recommendations, immunocompromised patients, including those living with HIV/AIDS, should continue to receive the three-dose regimen or, when this is not possible, at least two doses [12].

The single dose is more cost-effective and easier to administer and facilitates the implementation of catch-up campaigns at all ages [13]. Although to date, the efficacy of the two-dose regimen of HPV vaccine in adolescents for the various outcomes of the infection, for the single-dose regimen, there is still a lack of more consistent evidence, which can be obtained in the coming years with the results of ongoing studies [4].

Given the importance of immunization against common cancer and in view of all these difficulties presented, it is interesting to address the established strategies for vaccination against HPV at the national level, knowing their peculiarities.

The aim of this study is to summarize the current status of vaccination against HPV in Brazil.

2. Methods

The present work is an integrative review, aiming to explain the current situation of vaccination against HPV nationwide. Using the PubMed, MEDLINE and Google Scholar databases, a search for scientific articles was carried out during the second semester of the year 2022, in which the descriptors “Vaccine”, “HPV” and “Brazil” were used simultaneously.

Initially, the search resulted in a total of 299 articles, and then the use of the filters articles launched in the last five years, resulting in 195 articles; publications in either English or Portuguese, with 113 resulting papers; it was also considered access to the full text free of charge and only works carried out in the human species were considered, leaving 78 publications. After being selected, titles and abstracts were read, of which only 57 publications were adapted to the objective of the present study, and 30 articles were excluded due to inadequacy of the content. Finally, after the complete reading of the articles and analysis of the methodology, 17 publications were framed in the objective of the current systematic review (Figure 1).

3. Results

After all the methodological stages described were performed, 17 articles were considered appropriate to the proposed one. These works are identified as below.

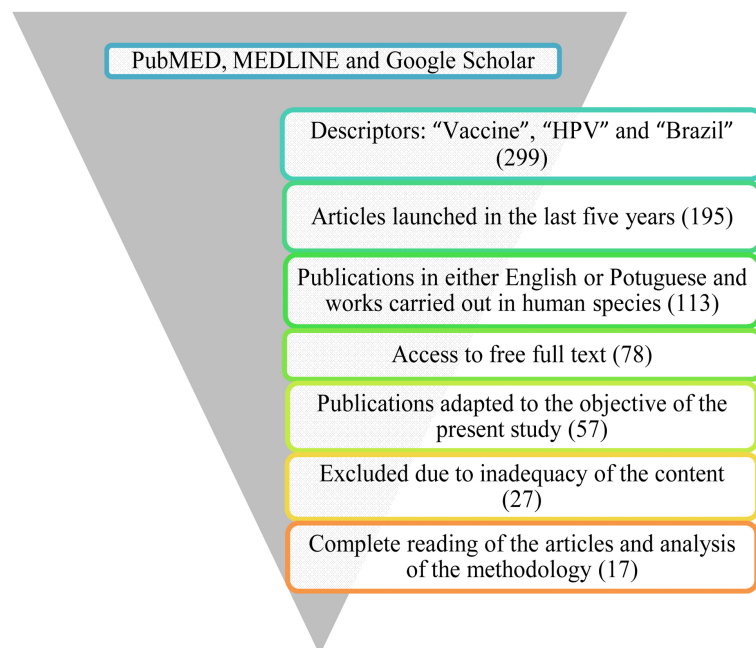


Figure 1. Flowchart representing the methodology used in the study. Source: authors.

1) Title: Cobertura da Vacina Papilomavírus Humano (HPV) No Brasil: Heterogeneidade Espacial e Entre Coortes Etárias. Year of publication: 2021 [7].

- Despite the vaccine being made available in the SUS, the authors point out a difficulty in achieving and maintaining coverage for the second dose. Among the factors that impede success, they mainly cite social inequality, demonstrating the need to plan specific strategies according to the difficulties encountered.

2) Title: Effect of Educational Intervention for Compliance of School Adolescents with the Human Papillomavirus Vaccine. Year of publication: 2022 [6].

- The authors concluded that educational intervention should be incorporated into the health education process, in different environments, as the effects of this measure were positive. They claim that because it is a low-cost and simple-to-apply measure, the logistical and financial barrier will have a minimal impact. The authors also argue that this intervention should occur mainly in the periods that precede the vaccination campaign.

3) Title: Evaluating the Quality of HPV Vaccine-Related Information on the Portuguese Internet. Year of publication: 2022 [10].

- The authors noticed that there is low adherence to vaccination in all age groups and genders, corroborating the data revealed by the PNI, and indicate multifactorial causes. As a way of overcoming these difficulties, they suggest that quality information should be offered and that it is within the reach of users, guaranteeing the public correct data that help to make the right decisions. The authors concluded that most users have access to content of low scientific value that can lead to wrong conclusions and decisions.

4) Title: HPV Vaccination and Screening with High-Performance Test: Brazilian Evidence. Year of publication: 2021 [11].

- The authors concluded that the scientific evidence is satisfactory and supported. However, the adherence of people with decision-making power over health actions (public managers and politicians) is still necessary.

5) Title: Human Papillomavirus (HPV) and the Quadrivalent HPV Vaccine among Brazilian Adolescents and Parents: Factors Associated with and Divergences in Knowledge and Acceptance. Year of publication: 2020 [13].

- The authors noticed that females (adolescents or parents/guardians) showed better knowledge about HPV and its vaccine. The authors indicated that the development of high-quality, gender-adapted educational materials should occur to provide detailed information about HPV and its potential health consequences. In addition, they highlighted the need for health actions that facilitate the exchange of knowledge between parents/guardians and children, with emphasis on adolescents, especially males with low education.

6) Title: Impact of the COVID-19 Pandemic on Human Papillomavirus Vaccination in Brazil. Year of publication: 2022 [14].

- The authors noted that the COVID-19 pandemic resulted in a reduction in the number of applied doses of the HPV vaccine as an effect of restrictive ac-

tions in an attempt to reduce the spread of the respiratory virus and suggested public health policies to guarantee immunization strategies against HPV during epidemic crises.

7) Title: Influence of Gender and Undergraduate Course on the Knowledge about HPV and HPV Vaccine, and Vaccination Rate among Students of a Public University. Year of publication: 2020 [15].

- The authors concluded that the rates of knowledge and vaccination against HPV are low among university students, demonstrating that greater knowledge is directly associated with greater acceptance of the vaccine. The authors also indicate that entering higher education is a good opportunity for awareness campaigns.

8) Title: Knowledge about Cervical Cancer and HPV Immunization Dropout Rate among Brazilian Adolescent Girls and Their Guardians. Year of publication: 2020 [16].

- The authors associated that higher education and higher family income are related to acceptance of the vaccine. They also indicated that low knowledge is observed in groups with a high rate of abandonment of vaccination among adolescents. With these conclusions, the authors suggest the need for more effective educational actions on HPV and cervical cancer, prioritizing the low-income population.

9) Title: Moving towards a Strategy to Accelerate Cervical Cancer Elimination in a High-Burden City—Lessons Learned from the Amazon City of Manaus, Brazil. Year of publication: 2021 [17].

- The authors demonstrated that to reduce the incidence and mortality from cervical cancer, the public health system must ensure high coverage. Furthermore, secondary prevention will be needed to avoid early deaths, as there are still gaps in primary prevention. They also stated that new screening programs should be organized based on risk, adapting strategies to confront social differences and reach women considered at high risk.

10) Title: School-Based HPV Vaccination: The Challenges in a Brazilian Initiative. Year of publication: 2021 [18].

- The authors observed that school vaccination against HPV significantly increased vaccination coverage, regardless of gender, however, it is necessary to create professional teams that prioritize the execution of the vaccination program, being essential this adequacy to achieve high coverage rates.

11) Title: The Family Health Strategy Influence on the Human Papillomavirus Vaccine Acceptance in a Peripheral Community of the Brazilian Amazon Region. Year of publication: 2022 [19].

- The authors concluded that non-acceptance is directly associated with knowledge, suggesting that public actors responsible for health education should maintain close and constant contact with families, to combat false information that underlies anti-vaccination campaigns. They suggest that the use of social media is one of the strategies that can be used in this fight, in addition

to educational interventions and continuing education.

12) Title: Vaccination against Human Papillomavirus in Brazilian School-children: National Survey of School Health, 2019. Year of publication: 2022 [20].

- The authors indicated that public policies and health strategies are essential to improve vaccination indicators in adolescents. They also highlighted that nursing professionals are central to health education, as they establish a communication channel that provides information about vaccination against the virus, contributing to increased vaccination adherence.

13) Title: Vaccination Coverage against Human Papillomavirus (HPV) and Associated Factors in Female Academics from a University in Southwestern Goiás, Brazil. Year of publication: 2021 [21].

- The authors revealed ample possibilities for interventions in the population, and that from the recognition of population subgroups with lower vaccination coverage, effective actions can be directed towards achieving greater vaccination coverage. They also emphasized that Brazil used vaccination in schools, with excellent results, recommending, therefore, the return of the offer of vaccines in schools, in association with health units, since the knowledge environment that the school promotes can better develop the integration between students, parents and teachers involved in vaccination.

14) Title: Vaccination Coverage Rates and Predictors of HPV Vaccination among Eligible and Non-Eligible Female Adolescents at the Brazilian HPV Vaccination Public Program. Year of publication: 2020 [22].

- The authors suggest that a public policy of vaccination against HPV for older adolescents would increase coverage, and consequently promote the reduction of diseases related to HPV.

15) Title: Quadrivalent HPV Vaccine is Expanded to Men Up to 45 Years Old with Immunosuppression. Year of publication: 2022 [23].

- The Department of Health made available, until mid-2022, the quadrivalent HPV vaccine for immunosuppressed people (living with HIV/AIDS, undergoing cancer treatment, hematopoietic stem cell transplants or solid organs) from 9 to 45 years for women and 9 to 26 years for men. In July 2020, the National Immunization Program/PNI recommended expanding the HPV vaccine for men aged 9 to 45 with immunosuppression, harmonizing recommendations and availability for immunosuppressed men and women.

16) Title: The National Immunization Program in Brazil Announces the Extension of the Offer of the HPV Vaccine for Boys Aged 9 and 10. Year of publication: 2022 [24].

- The Department of Health made available, until mid-2022, the quadrivalent HPV vaccine for girls aged 9 to 14 years, boys aged 11 to 14 years. Even more recently, in September 2022, the PNI expanded the age range for boys to 9 and 14 years old, equally for girls.

17) Title: WHO Recommendation on the Single Dose of the HPV Vaccine: The Reality in Brazil. Year of publication: 2022 [25].

- In April 2022, the WHO Immunization Strategies Advisory Group (SAGE) compared the evidence for the efficacy of a single dose of HPV vaccines with the evidence for the efficacy of two or three doses in the recommended schedules, and concluded that one dose of the vaccine can offer significant and non-negligible protection against HPV, in some situations, and may be equivalent to the two doses that are currently recommended for adolescents [26] [27]. Currently, there is a wide availability of vaccines against HPV in Brazil, in view of this, the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO) suggests, at this time, maintaining the recommendation of the two-dose vaccination schedule (with an interval of 6 to 12 months between doses), awaiting more scientific evidence for a change in the vaccination schedule that could encompass the single dose of the vaccine against HPV.

4. Discussion

4.1. Gender Neutral

In Brazil, public immunization against HPV started in 2014 only for girls. However, in 2017, the distribution of the vaccine to boys was also approved [6].

Parents or guardians of children had a high rate of vaccine hesitancy due to insufficient knowledge about the effects of HPV on men's health. In more developed countries, such as the United States, the low vaccination rate in boys is associated with parents' lack of knowledge about the impact of vaccination on boys. In this way, there is a need to emphasize the inclusion of the male public, emphasizing the benefits achieved for those who are immunized and for public health [10] [13].

Faisal-Cury *et al.* [22] demonstrated that the female public is more influenced by mothers regarding the act of getting vaccinated, which is reflected in better vaccination rates, including among those who are not covered by the public service. In the same study, the authors noticed that girls who live with only their father are less likely to be vaccinated.

In view of this, the recommendation for vaccination for both sexes is already very well established in the scientific literature, where gains have been demonstrated both for those who are immunized and for society [24].

4.2. Age

In March 2014, the HPV vaccine was incorporated into the SUS and began to be offered, at no direct cost, in basic health units, public and private schools for girls aged 11 to 13 years. In the work by Luvisaro *et al.* [9], the coverage achieved with the first and second doses indicated that younger cohorts had a greater chance of being vaccinated. Therefore, it is a relevant factor in vaccination against HPV, as the younger population benefits from this immunobiological, both due to a greater response to the vaccine and the presumption of non-exposure to

HPV, which makes the vaccine have greater power of efficacy and immunogenicity [9].

The age range was expanded to girls between 9 and 11 years old in 2015. In 2017, there were two changes in the therapeutic scheme: girls aged between nine and 14 years old and boys aged between 11 and 14 years old were now covered by national immunization. In the year 2022, the Brazilian Ministry of Health expanded the male public, equaling the female, and currently both sexes are eligible to be vaccinated between 9 and 14 years of age [7] [23].

4.3. Type of Vaccine

The vaccine currently used in the Brazilian public scheme is the tetravalent vaccine. The decision to choose this type of vaccine is best explained by the cost-effectiveness achieved, in which subtypes 16 and 18 are responsible for more than 70% of cervical cancers, in addition to providing protection against the subtypes responsible for anagenetic warts [26].

The nonvalent vaccine is also available in some countries, such as the United States and Australia. The higher cost of this type denotes that its choice is still restricted to more developed countries [3]. The additional types of HPV covered by this vaccine correspond to 15% of cases of cervical cancer and its adoption by the Brazilian government becomes plausible, as long as the current socioeconomic conditions are respected [26] [27].

The efficacy and safety of available vaccines have already been demonstrated all over the world and in several studies, and are already well established in the scientific community. Wendland *et al.* [8] highlighted that in Sweden, for example, vaccination with the tetravalent vaccine significantly reduced the prevalence of cervical cancer a decade after the introduction of the vaccine. In the same study, the authors demonstrated a significant reduction in HPV infection just four to five years after immunization.

4.4. Number of Doses

The number of doses of the vaccine against HPV has been a point of debate since the beginning of immunization, since, initially, the use of a therapeutic scheme with three doses (intervals of 6 and 60 months between doses) was recommended, but in 2016 it was verified that the effectiveness of vaccination with only 2 doses was similar to the extended three-dose scheme, which was then adopted by the SUS (Unified Health System). This change in the vaccination schedule allows for better immunization coverage by allocating the resources that would be used in the third dose to other target groups [28].

Although the HPV vaccine is available in the PNI (National Immunization Program) of Brazil, Moura, Codeço and Luz pointed to the difficulty of maintaining coverage for the second dose. The authors pointed to the success of vaccination coverage of the first dose [7]. On the other hand, for the second dose the opposite was observed, a low vaccination coverage. This suggests that, despite the greater

opportunity to perform the first dose, there may be discontinuity of vaccination, also called vaccine delay, demanding greater attention to the second dose. Vaccination discontinuity is recognized by the PNI as one of the recurrent factors, but not exclusive to the HPV vaccine, as well as to other vaccines [25].

In April 2022, the WHO Immunization Strategies Advisory Group (SAGE) suggest that single-dose scheme may be useful to achieve universal vaccine coverage in less developed countries, contributing to the goal of eliminating deaths from cervical cancer [27].

In Brazil, the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO) suggests, at this time, maintaining the recommendation of the two-dose vaccine schedule (with an interval of 6 to 12 months between doses), because there is no lack of vaccines against HPV and wait for more evidence to support a change in the calendar and, at the same time, to intensify the actions integrated measures to improve vaccination coverage for adolescents in our country, especially with school-based vaccination, combined with a national campaign to raise awareness among the population, in order to achieve the goals established by the WHO [27].

4.5. Place of Vaccination

In the 1st year (2014), the vaccination strategy in Brazil was based on immunization applications carried out in schools. However, there was a migration to health units, and later there was a significant drop in the coverage rate. Silva *et al.* [20] demonstrated adequate coverage when proposing to vaccinate young people in schools. The authors even noticed a three higher vaccination coverage when compared to the rates registered by the public service in the previous year (when it was already carried out in health centers). The increase in coverage observed in the months the study was carried out indicates the success of school vaccination [20].

In more developed countries, such as Australia, Canada and Sweden, which opted for the school strategy, vaccination coverage remained high and sustained [9].

For Teixeira *et al.* [11], the parents' difficulty in taking adolescents to be vaccinated at Health Units during business hours may be the main obstacle. A Brazilian study that surveyed 826 parents using an online questionnaire suggested that low coverage appeared to be due to challenges in vaccine administration and barriers to HPV vaccination at health centers rather than vaccine refusal. It also identified "Not vaccinating at school" as the most common reason for missing vaccines [12].

Geographical barriers can also influence the reduction of access to vaccination, which may be related, for example, to hesitation to vaccinate. Luvisaro *et al.* [9] demonstrated that the population was instructed to receive the vaccine, but hesitated when going to the health center or access was difficult, which is the most frequent reason among adolescents enrolled in public schools. This finding was

further reinforced when the goal of 80% vaccination coverage was achieved in just three months at the beginning of vaccination in schools. Therefore, the return of school-based vaccination becomes a necessary measure for adequate neighborhood coverage [9] [27].

4.6. Immunocompromised

The immunocompromised (immunosuppressed, people living with HIV/AIDS, patients with solid organ or bone marrow transplants and oncology patients) are part of a group at four times higher infectious risk and demand special attention, therefore, the recommendations for the immunization of this group differ [23]. However, the introduction of this population only occurred in the year following the start of immunization in the country (2015), being only for the female public aged between nine and 26 years, but in 2017 it was extended to the male public of the same age group [23].

In the year 2022, the PNI extended vaccination to immunocompromised men and currently they can be immunized from nine to 45 years of age, thus equaling the age group of women in the same risk conditions [23].

In addition to the increased age range, the vaccination schedule for people with immunosuppression is longer, with three doses (with intervals of two and six months between doses) (Figure 2). The maintenance of this scheme is based

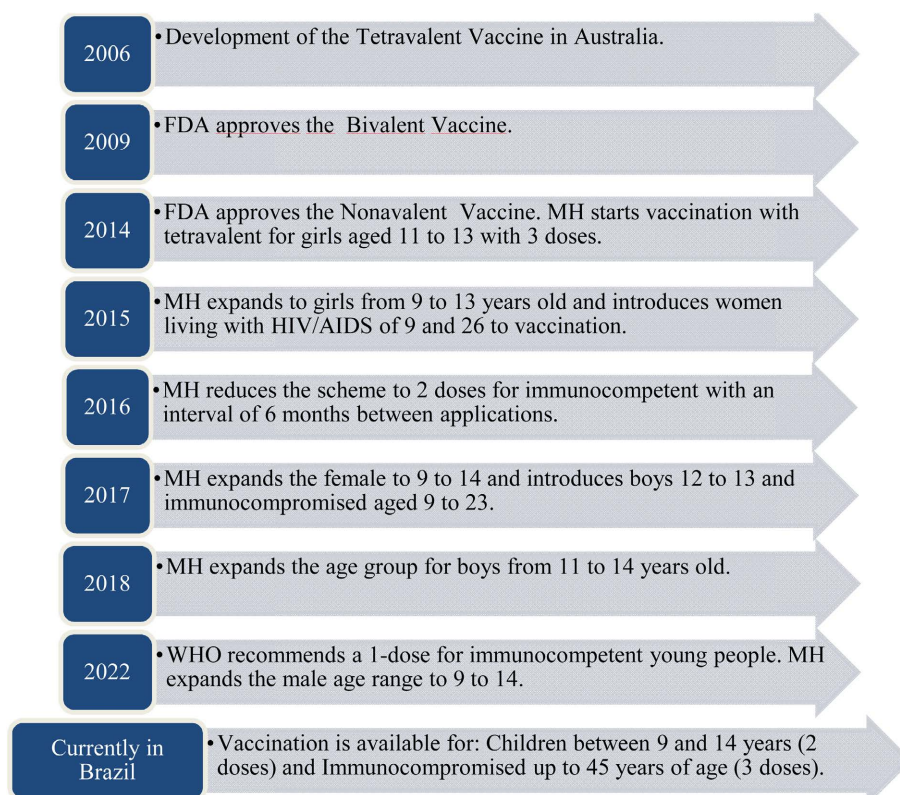


Figure 2. Timeline of changes in Brazilian vaccination recommendations against HPV. FDA: US Food and Drug Administration; MH: Ministry of Health of Brazil; WHO: World Health Organization. Source: authors.

on the lack of scientific evidence regarding the effectiveness of the single dose in this population so far [25].

4.7. Health Education

Several authors of this study concluded that educational intervention should be incorporated into the health education process, in different environments, noticed that adolescents or parents/guardians showed better knowledge about HPV and its vaccine [6]. They indicated that the development of high-quality, gender-adapted educational materials should occur to provide detailed information about HPV and its potential health consequences, appoint to a low-cost and simple-to-apply measure, and logistical and financial barrier will have a minimal impact [13].

The knowledge and vaccination against HPV are low among university students, demonstrating that greater knowledge is directly associated with greater acceptance of the vaccine [15]. Too Bacha *et al.* verified in a before-and-after clinical trial in order to assess the prior knowledge of medical students about HPV; the percentage of correct answers was 45.6% showing limited knowledge of the subject [2].

In summary, **Figure 2** shows the timeline of the most significant changes that occurred in vaccination against HPV in Brazil.

5. Conclusion

The impact of HPV vaccination rates in terms of public health will occur if 90% of vaccination coverage is achieved among adolescents. Effective operationalization towards this goal is extremely relevant and necessary. The effort to eliminate cervical cancer in Brazil requires a combination of multiple changes: public health measures and the evaluation of immunization strategies depend on recognizing the difficulties and limitations of factors associated with possible inequities in vaccine coverage, pervading inexorably through health literacy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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