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REVIEW ARTICLE

Evaluation of the Effectiveness and Durability of Anti-Hpv Vaccine in Different Vaccination Schedules:
A Systematic Review

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Highlights
(1) 1 ou 2 doses schedules maintain immunogenicity and efficacy comparable to 3 doses.
(2) Lasting vaccine protection, without significative diferences between the dose groups.
(3) Younger age and obesity influence then vaccine immunogenity and the imune response.

INTRODUCTION

HPV is the etiological agent of cervical cancer. It is the second leading neoplasm among women, when less developed and low-income countries are considered. Despite the development of three vaccines that are effective in preventing HPV-related infections and lesions, complete compliance with the vaccination schedule is not always observed. It is believed that the number of doses may be a major factor in low adherence. To this end, the objective of the study was to verify whether the reduced dose schedule has comparable efficacy and durability to the expanded schedule. This is a matter of systematic literature review whose bibliographic research strategy included consultation of the PubMed and SciELO research bases in the first half of 2022. The inclusion criteria were randomized clinical studies published in English, Portuguese, or Spanish; Publications from the last five years; Publications in which the intervention is the application of the vaccine to the adolescent or adult population; Publications that evaluate different vaccination schedules and Publications with an outcome related to the effectiveness and durability of vaccination schedules. The criteria were assessed by two independent reviewers and the risk of bias in the publications was analyzed using the CONSORT checklist. 54 articles were gathered, of which 12 were eligible. The results of this study showed that reduced regimens of one or two doses have satisfactory immunogenicity, efficacy, and durability of anti-HPV protection, without any disadvantages in relation to three-dose regimens. Therefore, reduced schedules become an immunization strategy, especially with regard to developing countries, which would have their vaccination programs strengthened and vaccination coverage expanded.

Keywords: HPV vaccine; vaccine effectiveness; immunogenicity of the vaccine; immunization schedule

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INTRODUCTION

The Human Papillomavirus (HPV) is the etiological agent of cervical cancer[1]. It is a virus composed of double-stranded DNA, epitheliotropic, capable of infecting skin and oral, genital, and anal mucous membranes[2]. HPV, when in contact with the epithelium, infects basal cells that have high mitogenic capacity and little differentiation, resulting in uncontrolled proliferation through tissue microlesions. This proliferative stimulation culminates in pre-neoplastic lesions that can eventually become invasive with the persistence of the viral infection[2]. In some cases, when HPV infects the transition zone between the endocervical canal and the cervical canal, it directly reaches the target cells[3]. Viral transmission occurs through direct contact with infected skin or mucous membrane, the most common form being through sexual transmission: oral-genital, genital-genital or even manual-genital. Vertical transmission is also possible[4].

Regarding risk factors, it is believed that immunological, genetic, and sexual behavioral factors may have an impact on the mechanisms that determine the regression or persistence of HPV infection and the possible development of precursor or malignant lesions. Thus, smoking and early initiation of sexual life, especially before the age of 16, are key elements[5]. Multiplicity of sexual partners, contraceptive pills and immunosuppressive factors are risk factors for cervical cancer. Age is also considered a risk factor, as younger women are more susceptible to infection with HPV types with high oncogenic risk[6], despite this, it is known that the majority of women under 30 years of age experience regression of the infection, while persistence is more common in older age[7,8,9].

There are more than 250 types of HPV currently described[1]. According to their oncogenic capacity, they can be classified into high, low, and probable high-risk groups. The high-risk HPV types are: 16, 18 (these being the most related to high-grade lesions, that is, precursor lesions of cervical cancer), as well as other less common types that were found worldwide such as 31, 33 , 35, 39, 45, 51, 52, 56, 58, 59, 73 and 82[10]. There is also the probable high-risk classification, which includes type 68[11]. In turn, the low-risk HPV types are : 6, 11, 40, 42, 43, 44, 54, 61, 70, 72 and 81[10], less associated with the development of malignant neoplasms, but related to benign proliferations, condylomas and anogenital warts[2].

Worldwide, cervical cancer is the fourth leading neoplasm that affects women, responsible for around 311,000 deaths in 2018. This scenario is more worrying in low-income countries, where cervical cancer occupies the second position in this population. Around 80% of women who die from this neoplasm are found in these countries[1].

In Brazil, cervical cancer is the third most common type in females, with the exception of non-melanoma skin tumors. Moreover, it is estimated that there will be 16,710 new cases by 2022, which represents a considered risk of 15.38 cases per 100 thousand women[12]. In addition to this, HPV-related neoplasms also significantly affect the male population. Penile cancer, for example, represents, in Brazil, around 2% of cancers in men[2].

In view of the high incidence and global morbidity and mortality of HPV infection, prophylactic vaccines were developed, which activate the humoral and cellular immune system and induce the production of antibodies, generating effective protection against HPV infection[13]. There are, until now, three types of immunizers: bivalent (Cervarix®, GlaxoSmithKline®), which protects against types 16 and 18; the quadrivalent (Gardasil, Merck Sharp & Dohme) effective against types 6, 11, 16 and 18 and the nonavalent (Gardasil-9®), which includes the types covered by the quadrivalent vaccine, in addition to types 31, 33, 45, 52 and 58[14], but in Brazil it is not yet available on the national market, although already being approved by the National Health Surveillance Agency (Anvisa)[15].

The prophylactic anti-HPV vaccine was first implemented in Australia, in 2007, when female adolescents aged 12 and 13 were immunized with 3 doses of the quadrivalent vaccine. In Brazil, the

quadrivalent anti-HPV vaccine was added to public health in 2014, in a program for female adolescents aged 11 to 13 years. In 2015, the vaccination program began to include girls aged 9 to 13 and, from 2017, the female population aged 9 to 14 years old. In 2017, boys aged 11 to 14 years and populations at increased risk for infection were included, such as immunocompromised and cancer patients, a rule currently in force[16]. Recently, in 2022, the expansion included boys aged 9 and 10. As a result, vaccination is now available to anyone aged 9 to 14, regardless of gender[17]. Initially, a three-dose schedule was recommended, however, since 2016, in Brazil, a vaccination schedule with just two doses was instituted, with the second dose administered six months after the first one[17].

Data from the National Immunization Program point out that, from 2013 to 2016, coverage achieved nationally in the first dose was 74.5% for girls aged 9 to 15 years, while for the second dose coverage was lower, around 45.1 %[18]. Some of the factors associated with non-compliance with the complete schedule were ethnicity, difficulty accessing healthcare and countries with few resources. Therefore, reducing the number of doses in the vaccination schedule could potentially reduce transport and infrastructure costs and facilitate the implementation of the vaccine in schools, for example[19], promoting an increase in anti-HPV vaccination coverage in the target population.

In this regard, it is necessary to systematize the data present in the literature, in order to explore the viability of alternative vaccination schedules, comparing them with the initially recommended program. The objective of the study was to evaluate the immunogenicity, efficacy, and durability of anti-HPV protection in reduced vaccination schedules and discuss the health and economic advantages of its implementation in the target population.

METHODOLOGY

The present study is a systematic review of the literature as a method for synthesizing data related to reduced vaccination schedules against HPV. Its development happened following the steps: definition of the research question, choice of databases, definition of inclusion and exclusion criteria, search for articles, collection of information from selected articles, data tabulation, discussion of results and writing of the review.

The titles were analyzed based on the PICO20 strategy, whose acronym represents Population of interest, Intervention or phenomenon of interest, Comparison and Outcomes to define the outcome. These four components are the essential elements for developing the research question and question construction to optimize the bibliographic search for evidence. The guiding question was defined: What is the effectiveness and durability of protection of the HPV vaccine when administered in reduced dose schedules in the target population?

The review was carried out in the first half of 2022. The bibliographic research strategy included consulting the PubMed (Medline) and Scielo search bases and, to carry out these searches, the following keywords combined with Boolean operators were used: HPV vaccine AND single dose; HPV vaccine AND different schedules; HPV vaccine AND two doses. The filters Clinical Trial and the time frame of the last five years were applied. The inclusion criteria were: Randomized clinical studies published in English, Portuguese or Spanish; Publications from the last five years; Publications in which the intervention is the application of the vaccine to the adolescent or adult population; Publications that evaluate different vaccination schedules and Publications with an outcome related to the effectiveness and durability of vaccination schedules; grey literature was included, as government documents and documents from large health institutions were used. The exclusion criteria: Review studies; Publications prior to 2018; Publications without the full article available. Publications that considered other variations of the vaccination schedule (interval between doses) or even those that contained a population with specific diseases.

The titles were transferred and archived in the research and bibliographic reference assistant, the ZOTERO® software. The articles were analyzed according to their fulfillment of the PICO strategy criteria by a pair of reviewers independently. Initially, exclusion was made through the title and reading of the abstracts and, if there were still doubts, the next step was to read the full text.

RESULTS

As a result, 54 articles were gathered which, after analysis, resulted in a final sample of 12 articles that met the inclusion criteria established for the review, as shown in Figure 1, adapted from Main Items for Reporting Systematic Reviews and Meta-Analyses (Prisma), a recommendation consisting of 27 items and a four-step flowchart that aims to improve systematic review reports and increase the transparency of the research process[21]. They were found in the PubMed database, published from 2018 onwards, the year with the highest number of publications among the articles reviewed (n=6).

All publications were in English, with no publications found in Portuguese or Spanish. Countries in which studies were carried out include: Costa Rica (n=3), Canada (n=3), India (n=3) Colombia (n=2), Panama (n=2), Mexico (n=2), Hong Kong (n=1), Singapore (n=1), France (n=1) and Sweden (n=1). The age range of the study population was not uniform, ranging from girls aged 4 to 6 years old to women aged 26 years old, as minimum, and maximum limits.

Regarding the data present in the articles, all were obtained from clinical studies carried out in humans and, in all of them, the intervention was the vaccination of the target population with different anti-HPV vaccination schedules. All types of vaccines were considered, bivalent, quadrivalent and nonavalent.

EVALUATION OF THE EFFECTIVENESS AND DURABILITY OF ANTI-HPV VACCINE IN DIFFERENT VACCINATION SCHEDULES: A SYSTEMATIC REVIEW

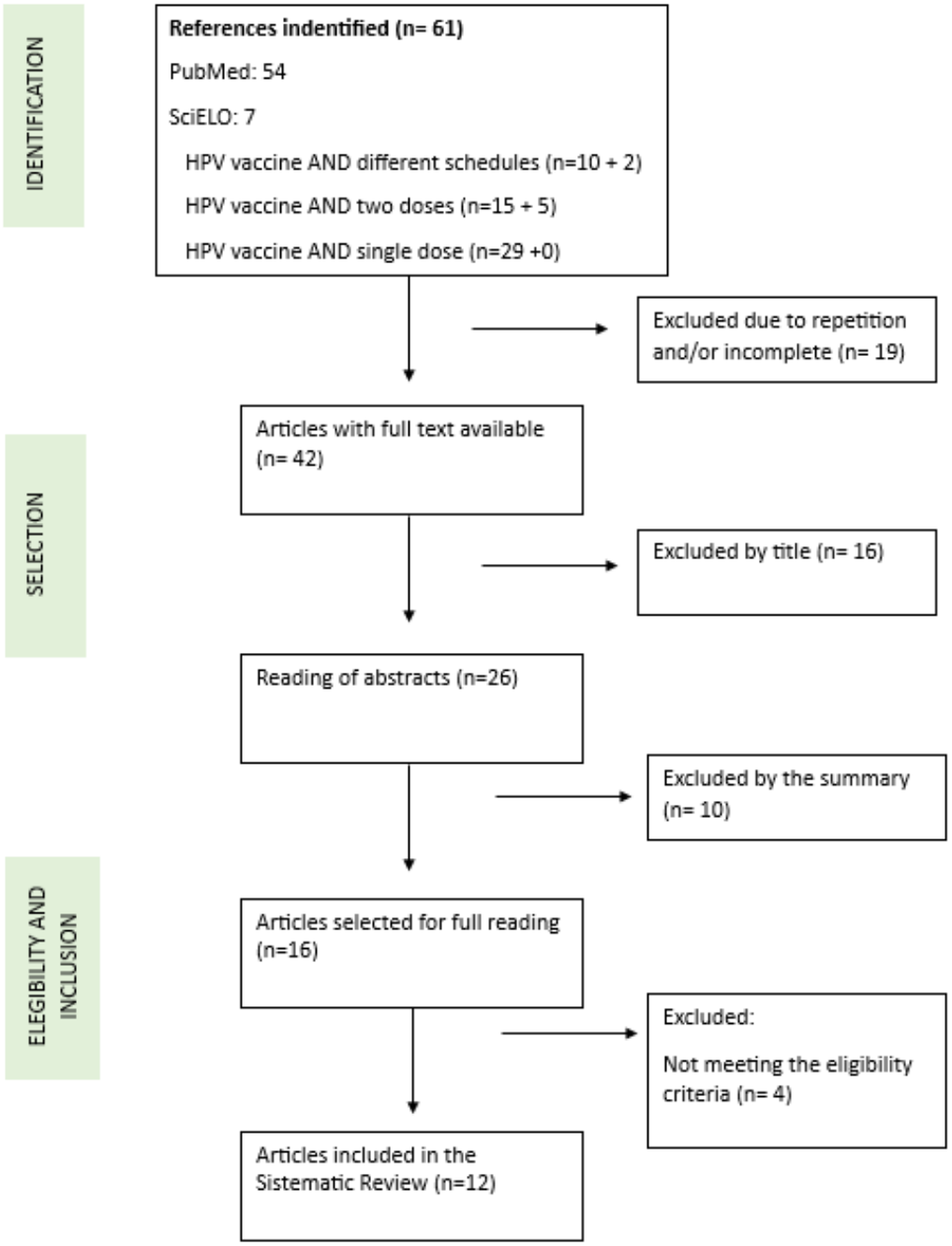

Figure 1 – Graphic representation of the selection process of studies resulting from the search

Source: Adapted from Prisma[21].

The studies were also analyzed for risk of bias using the CONSORT – Outcomes[22], presented in Table 1.

Table 1 – Analysis of bias and quality of studies

	Tsang et al.[23] 2020	Donken et al.[34] 2020	Bhatla et al.[25] 2018	Kreimer et al.[26] 2020	Sankaranarayanan et al.[27] 2018	Lin et al.[28], 2019	Ting Fan Leung et al.[29], 2018	Safaiean et al.[30] 2018	Gilca et. al.[31], 2018	Partha Basu et al[32] 2019	Sauvageau et al.[34] 2019	Lin et al.[33], 2018
1a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3a	No	No	No	No	No	No	No	No	No	No	No	No
3b	Yes	No	No	No	Yes	Yes	No	Yes	No	No	No	No
4a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4b	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a.1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a.2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a.3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a.4	No	No	Yes	No	Yes	No	No	No	Yes	Nao	No	No
6a.5	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
6a.6	No	No	No	No	No	Yes	No	Yes	No	No	Yes	No
6a.7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a.8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a.9	No	No	No	No	No	Yes	No	No	No	No	No	No
6a.10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6b	No	No	No	No	No	No	No	Yes	Yes	No	No	No
7a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7a.1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7b	NA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A
8a	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
8b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
9	No	No	No	No	No	No	No	No	No	No	No	No
10	No	No	No	No	No	No	No	No	No	No	No	No
11a	No	Yes	Yes	No	No	No	No	No	Yes	No	Yes	No
11b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
12a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12a.1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12a.2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12a.3	No	No	No	No	Yes	No	Yes	No	No	No	Yes	Yes
12a.4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14b	No	No	No	No	No	No	No	No	No	No	No	No
15	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
16	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
17a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

17b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes
18.1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
19	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
20	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
24	No	Yes	No	Yes	No	No	Yes	No	No	No	Yes	Yes
25	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total	34	38	37	37	39	40	38	40	40	35	40	36

Source: Elaborated by the authors, adapted from CONSORT[2].

For the analysis and description of the data, immunogenicity was considered as the property of the immunizer to stimulate seroconversion, that is, antibody titers higher than those obtained in the baseline analysis, in addition to taking into consideration the average antibody titers in response to each type and vaccination schedule. In turn, efficacy was determined as the capacity of the immunizer to prevent prevalent and incident HPV infections and neoplasms associated with them[23].

Data regarding the year of publication, authors, objectives and methods, main results and conclusion of the reviewed studies can be consulted in Table 2.

Table 2 – Description of the studies resulting from the inclusion criteria, according to authorship, year, population evaluated, time and evaluation measure, main results and conclusion

AUTHOR/YEAR	EVALUATED POPULATION/ EVALUATION TIME	EVALUATION MEASURE	MAIN RESULTS – Efficiency – Immunogenicity – Durability	CONCLUSIONS
Tsang et al.[23] 2020	Women aged 18-25 years (n=7466) received 1, 2 or 3d of bivalent vaccine or placebo. Follow-up for 4 years and then for 7 years	Annual follow-up with collection of blood and cervical mucus samples, for those who were sexually active.	**Efficacy:** 54.4% with 1d (HPV 31/33/45- no statistical difference from those who received 3d) **Durability:** 33.4% (after 2 to 4 years) 69.3% (after 7 to 11 years) Potential for protection against up to 7% HPV-related cancers (HPV 16/18) even after 11 years	Evidence of efficacy with 1 dose is growing, showing that the vaccine is effective and long-lasting for protection against HPV-associated cancers. Important cross protection.
Donken et al.[24] 2020	Girls aged 9-13 years (n=210) received 2 or 3d. Girls aged 16-26 received 3 doses of quadrivalent vaccine. Follow-up for 120 months.	Measurement of antibodies against HPV6, 11, 16 and 18 of all participants on day 1, at 7, 24 and 120 months of study, using cLIA and IgG.	**Immunogenicity:** 95% antibody response across all types and vaccination schedules. – Rate of titer decline after 120 months: HPV18 in girls 3d: log 1.11 HPV18 in girls 2d: log 0.93 HPV16 in girls 3d: 0.95 HPV16 in girls 2d: 0.81	2d of the quadrivalent vaccine can be immunogenic and have a sustained response for 10 years.
Bhatla et al.[25], 2018	Single girls aged 10-18 (n= 6017). They received 2 or 3d. Follow-up after 7, 18, 36 and 48 months after vaccination.	Blood samples. L1 binding antibody titers, antibody avidity for the HPV types targeted by the vaccine, and neutralizing antibody EC50 titers against HPV were measured.	**Immunogenicity:** Proportion of median fluorescence intensity between 2d/3d at 7/ 36/ 48 months: HPV18: 0.92/ 0.69/ 0.94 HPV16: 1.05/ 0.82/ 1.07 HPV 6: 0.99/ 0.87/ 0.95 HPV 11: 1.10/ 1.20/ 1.40	Adolescent girls, vaccinated between 15 and 18 years of age, with 2d of the quadrivalent have antibody profiles similar to those who receive 3d.
Kreimer et al.[26], 2020	Young people between 18-25 years of age who received 1 (n=112), 2 (n= 62) or 3d (n=1365). Evaluated after 4 years and after 11 years of vaccination.	Patients were visited every two years and cervical and blood samples were collected and, subsequently, HPV DNA genotyping. Antibody levels were measured by ELISA and the seropositivity cutoff points were 8EU/mL (HPV 16) and 7EU/mL (HPV18).	**Efficacy:** anti-HPV16 and 18 was 80.2% for 3d, 83.8% for 2d and 82.1% for 1d for prevention of prevalent HPV infections. **Durability:** seropositivity after 11 years: 1d: 96.7% HPV16 92.9% HPV18 2d: 98.7% HPV16 and 100% for HPV18	A single dose protects against HPV for 10 years after vaccination and antibodies remain stable. The effectiveness of the 1d schedule is greater than non-vaccination.

Sankaranarayanan[27], 2018	Single girls aged 10-18 years (n= 20.000) who received 2 or 3 days of the quadrivalent vaccine.	Blood samples were collected, the last one at month 60. Antibody concentration was measured by immunofluorescence; Specific antibodies to the HPV-L1 protein were measured by PBNA. Cervical samples were also collected for genotyping.	**Efficacy:** Cumulative incident HPV infections in vaccinated women in study: 3d: 14.4%; 2d: 13.2%; 1d: 13.8% **Durability:** The percentage change in geometric mean antibody levels at 36 and 48 months 3d: -13% for HPV 16 and -23% for HPV 18 2d: +14% e +9% 1d: +18% e -9%	Single dose of quadrivalent HPV vaccine is immunogenic and offers long-lasting protection against HPV 16 and 18.
Lin et al.[28], 2019	Girls between 4-6 years of age (n= 148) who received 2 days of bivalent vaccine or placebo. Follow-up was carried out for 36 months.	Blood samples were collected at baseline, month 7, 12, 18, 24 and 36. Antibodies to HPV 16 and 18 were measured by ELISA, with cutoff values being 19EU/mL and 18EU/mL for HPV 16 and 18.	**Efficacy:** By month 36, all participants had seroconverted to HPV 16 e 18. **Immunogenicity:** Antibody levels: 1680.6 for HPV16 and 536.4 for HPV18. **Durability:** Antibodies peak at month 7, and decline at month 12, reaching a plateau by month 36.	Vaccination of girls aged 4 to 6 years with 2d of bivalent induced high immunogenicity and maintained sustained antibodies until at least 36 months.
Ting Fan Leung et al.[29], 2018	Girls aged 9 to 14 years received 2 doses of 2v (n=259) or 2 of 4v (n=358) or 3 of 4v (n=358).	Samples were collected before and in months 7, 12, 18, 24 and 36 and measured by ELISA and PBNA. HPV-specific memory lymphocytes were measured by ELISA.	**Immunogenicity**: Group 2d (99.3%) and 3d (99.7%) had seroconversion for anti-HPV-16 antibodies. Some individuals remained seronegative during the study, that is, without protection against HPV 13.9% with 2d and 7.2% with 3d.	Superior HPV16/18 antibody responses were induced by 2d of the bivalent compared with 2 or 3d of the quadrivalent vaccine.
Mahboobeh Safaeian et al.[30], 2018	Women between 18-25 allocated to groups: 1d (n= 134), 2d (month 0 and month 1) (n=193), 2d (month 0 and month 6) (n=79) and 3d (n=2043) and compared to non-vaccinated women (n=2382) Follow-up for 7 years.	Home visits with collection of blood and cervical mucus samples. HPV detection and genotyping was done by PCR and anti-HPV antibodies were measured by ELISA.	**Efficacy and Durability:** Incident infections were, after 7 years, uniformly low and equal between dose groups. 100% remained producing antibodies to HPV16 and 18. Decreasing in average HPV16 (4 and 7 years) in the 3d group: -10.8%; 2d (0/6 months): -17.3% , 2d (0/1 month): -6.9%, and 1d: -5.5%; (not significant) – Similar results for HPV18	Over 7 years, low rates of HPV16/18 infections were observed and small reductions, if any, in antibodies levels against HPV16/18.
Gilca et. al[31], 2018	Girls and boys between 9-10 years of age (n=371) who received 2d of nonavalent or mixed regimen (1d bivalent + 1d nonavalent) Follow-up for up to 6 months after the 1st dose.	Blood samples were collected, and antibodies were measured using IgG ELISA.	**Immunogenicity:** -1d of 9v: 1 person did not seroconvert to HPV45, the rest seroconverted to the 9 types. Titers ranged from 4.4 to 75.1 according to the HPV type; 1d of 2v: 100% seroconverted to HPV16 and 18. Titers of 16.7 (HPV16) and 11.7 (HPV18) – 2nd dose: 100% seroconversion for the 9 types, increase in titers from 1.2 to 143x – Levels for HPV16 and 18 significantly higher for 2v as the first dose. Antibodies to HPV6, 11, 31, 33, 45, 52 and 58 higher in 2d of 9v	Bivalent + nonavalent scheme induces response to all types of 9v and higher antibodies to HPV16 and 18.

Partha Basu et al.[32], 2019	Single girls between 10-18 years of age. Group of 10-14 received 2d (n=611); group 15-18 received 2d (n=901) or 3d (n=860)	Immunogenicity included measurement of genotype-specific antibody titers and antibody avidity. Genotyping was done by PCR	**Efficacy:** Incident HPV16 and/or 18 infections: 1.6% of those who received 2d (15–18); 0.8% of those who received 3d (15-18) – 0.5% for those with 2d (10-14) – 7% unvaccinated – No CIN 2 or worse lesions in the cohorts that received 2 or 3d (15-18). – Unvaccinated: 2 lesions CIN 2 and two CIN 3; both CIN 2 lesions and one of the CIN 3 positive for HPV16 and/or 18	The 2d protection of the quadrivalent vaccine in recipients aged 15 to 18 years is comparable to that observed in 3d recipients of the same age.
Sauvageau[34] et. al 2019	Girls between 9-13 years old (n= 253) randomized into groups: (1) 9-13 years old who received 2d; (2) 9-13 years who received 3d. They were followed in months 0, 7 and 24.	Antibody titers were measured at months 7 and 24 of the study using a Luminex competitive immunoassay (cLIA).	**Immunogenicity:** 100% of girls seroconverted to HPV6, 11, 16 and 18 and 89% to HPV18 – Similar average titles between age groups when comparing 9-10 years with 11-13. – Significantly lower antibody level in obese girls (month 7). HPV 6: IMC adequate (2252); obese (1396) HPV 11: IMC adequate (2479); obese (1492) HPV 16: IMC adequate (7647); obese (4440) HPV 18: IMC adequate (1265); obese (559) – The same happened in month 24 – No difference observed among pre or post menarche girls	2d of the quadrivalent are highly immunogenic if applied 6 months apart in girls aged 9-13 years, regardless of menarche. Obesity can reduce titers over time.
Lin et al.[33], 2018	Girls between 4-6 years old who received 2d of the bivalent (n=74) or control. Follow-up until month 12.	Blood samples for analysis of HPV antibody responses were collected on day 0, M7 and M12 in both study groups. Serum anti-HPV-16/-18 antibodies were measured by an enzyme-linked immunosorbent assay (ELISA).	**Immunogenicity:** Test group: All girls seronegative for 16 and 18 developed antibodies and maintained until month 12: HPV16 titers: 20,080 (month 7); 3246 (month 12) HPV18 titers: 10621.8 (month 7); 1,216.6 (month 12) – Control group: Among the seronegative women, only 1 developed antibodies, for both types, which did not persist until month 12	Vaccination in 2 days of this population appears to be adequate due to the level of antibodies achieved.

Caption: n: number; d: dose; ELISA: Enzyme-Linked Immunosorbent Assay; PBNA: Pseudovirion-Based Neutralization Assay; PCR: Polymerase Chain Reaction

Source: Prepared by the authors.

DISCUSSION

This studies results demonstrated that reduced regimens of one or two doses have satisfactory immunogenicity, efficacy, and durability of anti-HPV protection, without any disadvantages in relation to three-dose regimens. Additionally, single-dose schemes, especially, have demonstrated promise and attracted attention due to the gain in practicality which this vaccination scheme proposes, without losing their protective potential against HPV infection. This finding is in line with what was discussed by the National Specialized Commission (CNE) on Vaccines of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo), which points out that reduced regimens can contribute to the prevention of pathologies linked to HPV and result in a true and significant impact, especially regarding to morbidity and mortality from cervical cancer, which is, after all, a problem facing women's health today in Brazil[35].

Regarding the implementation of the reduction in the number of doses, sources show that the adoption of a single dose strategy would be advantageous for public health. Among the preponderant factors are the establishment of consistent herd immunity, protecting the population from infection by a major cause of malignant neoplasms, reducing deaths linked to HPV infection, budget relief through cost reduction and greater ease of administration.[36-37]

As for the vaccine efficacy found in the scheme with just one dose of bivalent vaccine, an efficacy finding of 82.1% was observed, a value minimally lower than the value observed with the two-dose scheme of bivalent vaccine. The same is observed years after application of the vaccine when there is stable immunity against HPV, which strengthens the evidence that just one dose would be sufficient for adequate protection[26]. In contrast, there is evidence to suggest that the use of the second dose of the quadrivalent or nonavalent vaccine would function as a booster dose, which impacts the amplitude of the immunological response and can be implemented as a guarantee of vaccine efficacy.[31]

When comparing the two-dose and three-dose schedule, the response in terms of the production of anti-HPV antibodies was high in both vaccination schedules, thus there was no statistically important difference. Regarding the decline in geometric antibody titers over time, the finding was similar: the protection measured by antibody titers was maintained sufficiently for around 10 years in all vaccination schedules, showing great similarity between the durability of two and three doses of the quadrivalent vaccine. The same was seen in another panorama that evaluated whether the immune response of two and three doses can be compared, reaching the expected conclusion that antibody profiles are actually extremely similar[24-25]. Regarding the immunogenicity of the regimen with two doses of bivalent, it was demonstrated that, in approximately three years, almost all patients had shown sufficient seroconversion to protect against the virus, with a minimum portion of both the two-dose group and the of three doses that had not had an adequate immunological response. Other authors showed that regarding types HPV16 and 18, specifically, the data were reliable since both patients who received two and three doses of the bivalent vaccine managed to obtain high levels of seroconversion[28-29-33-30]. However, a lower titer of antibodies to HPV18 was also evidenced in patients who received only 2 doses of the vaccine, compared to those who received 3 doses. Further studies are needed to better understand how this would affect the effectiveness against HPV infection.[24.]

Contrary to what is observed for populations of healthy young girls, immunocompromised individuals, including people living with HIV, should receive 2 or, preferably 3 doses, given the small amount of evidence available regarding this population[38].

Considering the number of women who became infected with HPV after vaccination with the two- and three-dose schemes, there was an important finding, because although both schemes had low rates of subsequent infection, those vaccinated with two doses had twice as many HPV infections.

HPV in the study in question, therefore, there was greater protection offered by the three doses of quadrivalent vaccine[32].

The results obtained are in line with the cohort observed by Brotherton et. al[39], in 2019, in which the efficacy of a single-dose anti-HPV vaccine was demonstrated by comparing disease rates between those vaccinated with 1 and those who received 2 or 3 doses.

There were also some unexpected findings when constructing the results, these were in relation to BMI, in which the level of antibodies was significantly lower for HPV 11 and 18 in obese girls, compared to those with adequate BMI[34]. The same occurred after 24 months of vaccination[34]. This can be justified, as a high lipid profile has a considerable impact on the immune system, triggering metabolic and inflammatory disorders and these changes are related to the progression of chronic disease, changes in immunity and vaccine efficacy[40]. Furthermore, a cross-protection offered by the single dose of the bivalent vaccine was noticed. The protection found was related to HPV31, 33 and 35 types and was numerically similar to patients who received three doses. This evidence corroborates the promising efficacy of the single dose of the vaccine and adds the finding of important cross-protection[23].

Regarding the applicability of the reduced scheme, with emphasis on the single dose of the bivalent or quadrivalent vaccine, its effectiveness comparable to other schemes is reinforced, in addition, the sufficiency of a single anti-HPV dose for prevention has been increasingly well demonstrated. of HPV-related diseases. The vaccine has high immunogenicity and maintains a plateau of antibody titers capable of guaranteeing protection even with just 1 dose.

The cost-benefit, in the case of the anti-HPV vaccine, is obtained when there is at least 70% coverage of the target population[39]. It is known that this is not a reality in all countries, especially in those with fewer resources. In this sense, a single dose program would increase the number of women vaccinated. Another advantage of the 1-dose schedule is the expansion of vaccination of male adolescents, which offered protection for this population, in addition to favoring an increase in vaccination coverage and, consequently, herd immunity[39].

The implementation of this model of vaccination schedule is capable of reducing costs and facilitating the logistics of distributing doses, consequently strengthening vaccination programs in countries where it is most fragile. When the public health system is called into question, financial savings and savings in time and labor resources are important advantages, in addition to the possibility of redirecting investments to other deficient health areas[41]. It is not ignored, however, the possible need for a next dose a few years after the first, in order to maintain the longevity of protection[1], but favoring a greater number of vaccinated people in the short term is an important step towards preventing HPV-related in women and men.

Despite the interesting cost advantage, it should be noted that just as one dose of vaccine appears to induce protection against the included HPV types, the administration of the second dose of any vaccine increases the amplitude of the immune response and can be seen as a guarantee of safety. to obtain the desired protection[31]. In this sense, the durability of vaccine protection is considered: if a single dose provides less than 20 years of protection, the application of the second dose has a positive impact on public health. On the other hand, if protection is prolonged, the cost-benefit of applying a second dose becomes lower. [37]

In fact, even with suggestive results, a clear determination of the ideal minimum number of doses in a randomized and controlled study must be the way to achieve the due level of evidence desired by the main recommending bodies, and thus be sufficient to support a change in current recommendations.[26]

This article has some limitations, which are worth mentioning, the review articles were checked by only two different reviewers, the methodology used in each of the tests to analyze the parameters studied was not the same, in addition to the number of randomized studies with this theme is still small.

The results obtained emphasize the need for more studies to be carried out in order to enhance data regarding the application of fewer anti-HPV doses and cover them for populations such as Brazil. Moreover, the literature is still scarce regarding the use of a single dose, even though its indicators are promising, which demonstrates the need for more clinical trials that enable its application.

CONCLUSION

The present article demonstrated similar protection efficacy against HPV between the reduced two- and single-dose vaccination schedule and the three-dose schedule. The patients' anti-HPV antibody titers were satisfactory after years of vaccination, with a small decline in the reduced regimens; however, this decline for the most relevant types, HPV16 and 18, did not differ significantly from the extended regimen. The promising potential of reduced schedules was proven, especially with regard to developing countries, which would have their vaccination programs strengthened and vaccination coverage expanded. However, studies are still needed to confirm and expand the population coverage of these findings with a view to their practical application.

REFERENCES

[1] Gallant D, Tummers P, Weyers S, Merckx M. Single-Dose Human Papillomavirus Vaccination in Low – and Middle--Income Countries – Time for Implementation? J Pediatr Adolesc Gynecol. 2021;34(5):586-590.

[2] Sichero L, Picconi MA, Villa LL. The contribution of Latin American research to HPV epidemiology and natural history knowledge. Brazilian J Med Biol Res. 2020;53(2):1-10.

[3] Kombe AJK, Li B, Zahid A, Mengist HM, Bounda GA, Zhou Y, et al. Epidemiology and Burden of Human Papillomavirus and Related Diseases, Molecular Pathogenesis, and Vaccine Evaluation. Front Public Heal. 2021;8:1-19.

[4] Carvalho NS de, Silva RJ de C da, Val IC do, Bazzo ML, Silveira MF da. Protocolo Brasileiro para Infecções Sexualmente Transmissíveis 2020: infecção pelo papilomavírus humano (HPV). Epidemiol e Serviços Saúde. 2021;30(spe1):1-10.

[5] Ribeiro AA, Costa MC, Alves RRF, Villa LL, Saddi VA, Carneiro MADS, et al. HPV infection and cervical neoplasia: Associated risk factors. Infect Agent Cancer. 2015;10(1):1-7.

[6] McHome BL, Kjaer SK, Manongi R, Swai P, Waldstroem M, Iftner T, et al. HPV types, cervical high-grade lesions and risk factors for oncogenic human papillomavirus infection among 3416 Tanzanian women. Sex Transm Infect. 2021;97(1):56-62.

[7] Collaboration I, Studies E, Cancer C. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16 573 women with cervical cancer and 35 509 women without cervical cancer from 24 epidemiological studies. Lancet. 2007;370(9599):1.609-1.621.

[8] Appleby P, Beral V, De González AB, Colin D, Franceschi S, Green J, et al. Cervical carcinoma and sexual behavior: Collaborative reanalysis of individual data on 15,461 women with cervical carcinoma and 29,164 women without cervical carcinoma from 21 epidemiological studies. Cancer Epidemiol Biomarkers Prev. 2009;18(4):1.060-1.069.

[9] International Agency Of Research On Cancer (IARC). Lyon: WHO [Internet]. Working Group on the Evaluation of Carcinogenic Risks to Humans: Human papillomaviruses; 2007 [cited 2 Oct. 2022] 636p. Available at: https://monographs.iarc.who.int/wpcontent/uploads/2018/06/mono90.pdf

[10] Faria AJV, Barroso ACF, Lacerda APS, Mendes BMC, Partata CE, Araújo CL de, et al. HPV: a importância da vacinação para redução do surgimento de lesões pré-malignas do câncer de colo uterino. Rev Eletrônica Acervo Saúde. 2021;13(4):e6946.

[11] Schiffman M, Doorbar J, Wentzensen N, De Sanjosé S, Fakhry C, Monk BJ, et al. Carcinogenic human papillomavirus infection. Nat Rev Dis Prim. 2016;2:16086

[12] Ministério da Saúde, INCA. Estimativa 2020: incidência de câncer no Brasil 2019. [cited 2 Oct. 2022] 122p. Available at: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2020incidencia-de--cancer-no-brasil.pdf. Epub 2019. ISBN: 978-85-7318-389-4

[13] Yousefi Z, Aria H, Ghaedrahmati F, Bakhtiari T, Azizi M, Bastan R, et al. An Update on Human Papilloma Virus Vaccines: History, Types, Protection, and Efficacy. Front Immunol. 2022;12(Jan.):1-11.

[14] Patel C, Brotherton JML, Pillsbury A, Jayasinghe S, Donovan B, Macartney K, et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: What additional disease burden will a nonavalent vaccine prevent? Eurosurveillance. 2018;23(41):30-40.

[15] Fedrizzi EM. Why is the nonavalente HPV vaccine so important for Brazil? DTS- Jornal Brasileiro de Doenças Sexualmente Transmissíveis. 2019;31(2):39-42.

[16] Wendland EM, Kops NL, Bessel M, Comerlato J, Maranhão AGK, Souza FMA, et al. Effectiveness of a universal vaccination program with an HPV quadrivalent vaccine in young Brazilian women. Vaccine. 2021;39(13):1.840-1.845.

[17] Ministério da Saúde. Calendário nacional de vacinação. [Internet]. 2022. [cited 10 Oct. 2022]. Available at: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/c/calendario-nacionalde-vacinacao

[18] Coordenação Geral do Programa Nacional de Imunizações, Departamento de Vigilância das Doenças Transmissíveis, Secretaria de Vigilância em Saúde, Ministério da Saúde. PNI – Programa Nacional de Imunizações. Boletim Informativo do PNI-02/2016 Vacinação contra HPV [Internet]; 2016 [cited Oct. 2022] Available at: https://www.conasems.org.br/wp-content/uploads/2016/10/images_Boletim_informativo__HPV002-2016.pdf

[19] De Oliveira CM, Fregnani JHTG, Villa LL. HPV Vaccine: Updates and Highlights. Acta Cytol. 2019;63(2):159-168.

[20] Santos CMDC, Pimenta CADM, Nobre MRC. A estratégia PICO para a construção da pergunta de pesquisa e busca de evidências. Rev Lat Am Enfermagem. 2007;15(3):508-511.

[21] Moher D, Liberati A, Tetzlaff J, Altman DG. Principais itens para relatar Revisões sistemáticas e Meta-análises: A recomendação PRISMA. Epidemiol e Serviços Saúde. 2015;24(2):335-342.

[22] Butcher NJ, Monsour A, Mew EJ, et al. Guidelines for Reporting Outcomes in Trial Reports: The CONSORT-Outcomes 2022 Extension. JAMA [Internet] 2022 [cited 2023 Sept. 24];328(22):2.252. Available at: https://jamanetwork.com/journals/jama/fullarticle/2799401

[23] Tsang SH, Sampson JN, Schussler J, Porras C, Wagner S, Boland J, et al. Durability of cross-protection by different schedules of the bivalent HPV vaccine: The CVT Trial. J Natl Cancer Inst. 2020;112(10):1.030-1.037.

[24] Donken R, Dobson SRM, Marty KD, Cook D, Sauvageau C, Gilca V, et al. Immunogenicity of 2 and 3 doses of the quadrivalent human papillomavirus vaccine up to 120 months postvaccination: Follow-up of a randomized clinical trial. Clin Infect Dis. 2020;71(4):1.022-1.029.

[25] Bhatla N, Nene BM, Joshi S, Esmy PO, Poli URR, Joshi G, et al. Are two doses of human papillomavirus vaccine sufficient for girls aged 15-18 years? Results from a cohort study in India. Papillomavirus Res. 2018;5:163-171.

[26] Kreimer AR, Sampson JN, Porras C, Schiller JT, Kemp T, Herrero R, et al. Evaluation of durability of a single dose of the bivalent HPV vaccine: The CVT trial. J Natl Cancer Inst. 2020;112(10).

[27] Sankaranarayanan R, Joshi S, Muwonge R, Esmy PO, Basu P, Prabhu P, et al. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. Vaccine. 2018;36(32):4.783-4.791.

[28] Lin, Lan MD; Macias P, Mercedes MD; Sierra, Victor Y. MD; Salas C, Albino MD; Granados, Maria Angelica MD; Luque, Adriana MD; Karkada, Naveen MSc; Castrejon A, Maria Mercedes MD; Romano-Mazzotti, LMD; Borys, Dorota MD; Struyf, Frank MD. Long-term Immunogenicity and Safety of the AS04-adjuvanted Human Papillomavirus–16/18 Vaccine in Four- to Six-year-old Girls: Three-year Follow-up of a Randomized Phase III Trial. The Pediatric Infectious Disease Journal: Oct. 2019;30:1.061-1.067.

[29] Leung TF, Liu APY, Lim FS, Thollot F, Oh HML, Lee BW, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and 4vHPV vaccine administered according to two- or three-dose schedules in girls aged 9–14 years: Results to month 36 from a randomized trial. Vaccine. 2018;36(1):98-106.

[30] Safaeian M, Sampson JN, Pan Y, Porras C, Kemp TJ, Herrero R, et al. Durability of Protection Afforded by Fewer Doses of the HPV16/18 Vaccine: The CVT Trial. J Natl Cancer Inst. 2018;110(2):205-212.

[31] Gilca V, Sauvageau C, Panicker G, De Serres G, Ouakki M, Unger ER. Immunogenicity and safety of a mixed vaccination schedule with one dose of nonavalent and one dose of bivalent HPV vaccine versus two doses of nonavalent vaccine – A randomized clinical trial. Vaccine. 12 Nov. 2018;36(46):7.017-7.024.

[32] Basu P, Muwonge R, Bhatla N, Nene BM, Joshi S, Esmy PO, et al. Two-dose recommendation for Human Papillomavirus vaccine can be extended up to 18 years – updated evidence from Indian follow-up cohort study. Papillomavirus Res. 2019;7:75-81.

[33] Lin L, Parra MM, Sierra VY, Cespedes AS, Granados MA, Luque A, et al. Safety and Immunogenicity of the HPV-16/18 AS04-adjuvanted Vaccine in 4-6-year-old Girls: Results to Month 12 From a Randomized Trial. Pediatr Infect Dis J. Apr. 2018;37(4):e93-102.

[34] Sauvageau C, Gilca V, Donken R, Fan SY, Ogilvie G, Dobson S. The immune response to a two-dose schedule of quadrivalent HPV vaccine in 9-13 year-old girls: Is it influenced by age, menarche status or body mass index? Vaccine. 20 Nov. 2019;37(49):7.203-7.206.

[35] Carolina A, Cavalcanti D, Cristovão H, De Souza, Machado Martins G, Lima J, et al. Eficácia da dose única na imunização contra o HPV. Brazilian Journal of Surgery and Clinical Research BJSCR [Internet]. 2019 [cited 2022 Dec. 3];28(1):2.317-4.404. Available at: https://www.mastereditora.com.br/periodico/20190905_224513.pdf

[36] Watson-Jones, D., Changalucha, J., Whitworth, H., Pinto, L., Mutani, P., Indangasi, J., Kemp, T., Hashim, R., Kamala, B., Wiggins, R., Songoro, T., Connor, N., Mbwanji, G., Pavon, M. A., Lowe, B., Mmbando, D., Kapiga, S., Mayaud, P., de SanJosé, S., Dillner, J., Baisley, K. Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial. The Lancet. Global health. 2022;10(10):e1473-e1484. DOI: https://doi.org/10.1016/S2214-109X(22)00309-6

[37] Prem K., Choi YH., Bénard É et al. Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. BMC. Med. 2023;21(313).

[38] Villa LL, Richtmann R. HPV vaccination programs in LMIC: is it time to optimize schedules and recommendations? Jornal de Pediatria. 2023;99(1):57-56.

[39] Brotherton JML, Budd A, Rompotis C, Bartlett N, Malloy MJ, Andersen RL, et al. Is one dose of human papillomavirus vaccine as effective as three? A national cohort analysis. Papillomavirus Research. 2019;8:100177.

[40] Silva AT da, Ladeia Denise Neves, Ladeia Diana Neves, Zanotti ERV, Gazzoni GAS, Rodrigues GN, et al. Alterações da resposta imune em pacientes com obesidade. BJHR 2020;3:10.945-10.960.

[41] Cavalcanti ACD, Souza CH, Martins GM, Paula JLS, Rocha KNS, Souza JHK. Eficácia da dose única na imunização contra o HPV. Brazilian Journal of Surgery and Clinical Research. Nov. 2019;28(1):61-70.

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