# Nigeria Immunization Technical Advisory Group (NGI-TAG)

## Updated HPV Technical Dossier on Quadrivalent HPV (Gardasil-4valent) 1 -dose Regimen

*Given the prevailing HPV vaccine Shortages and the subsisting NGI-TAG recommendation of Gardasil-4valent HPV vaccine as the choice for Nigeria,* ***" Should Quadrivalent HPV (Gardasil-4valent) 1- dose schedule be introduced into Nigeria's Routine Immunization (RI) schedule for children aged 9-14 as against the previous 2 dose schedule recommended?"***

Contents

## 1. Executive Summary

Human Papillomavirus causes almost all cases of cervical cancer and the burden is disproportionate with 90% of deaths occurring in low- and middle-income countries. Around 13% of girls under 15 years of age have access to the HPV vaccine, which is relatively poor and an area of concern worldwide.

Cervical cancer stands as the second most common disease among women in Nigeria. There are 14089 new cases of cervical cancer each year, and 8240 females pass away from the disease. Due to limited access to reliable screening, delayed diagnosis and inadequate treatment, cervical cancer has a high fatality rate.

In Nigeria cervical cancer is associated with a high mortality rate because of poor access to effective screening, late presentation, and inadequate treatment services. Capacity for prevention, early detection, diagnosis and treatment of precancerous and cancerous lesions of the cervix in Nigeria remains weak. Cancer of the Cervix screening campaigns are currently conducted mainly by individual stakeholders and community based organizations. Hpv infection and subsequent cervical cancer is preventable with HPV vaccines and is most effective before a person becomes sexually active.

Guided by the NGI-TAG's recommendation, Nigeria's plan for HPV introduction in 2021 adopted the quadrivalent HPV recombinant vaccine (Gardasil) as the preferred vaccine candidate.

Amidst subsisting global HPV vaccine shortages, SAGE has recently provided additional evidence to the effect that a one dose regiment of the vaccine is as good as the two dose regimen; having considered evidence from updated systematic reviews on the immunogenicity, efficacy, and effectiveness of single-dose vaccination schedules compared with no vaccination, and multidose schedules. Overall, the review showed comparable efficacy and effectiveness between single- and multidose schedules in preventing persistent infection with HPV serotypes 16 and 18, lasting up to 10 years following vaccination.

Furthermore Nigeria has recently received a vaccine supply commitment from MERK of 8 million doses of Gardasil in 2023 and an additional 11 million doses in 2024 towards introduction in RI.

Against this backdrop, the NPHCDA requested NGI-TAG to provide guidance as to Nigeria introducing a one dose HPV vaccine schedule in 2023.

SAGE also recommended optimizing the vaccine schedule in older age cohorts. Those aged 15–20 years may receive one or 2 doses, while those aged ≥21 years should receive 2 doses with a 6-month interval. A single-dose schedule should be considered for those HPV vaccine

products for which data on efficacy or immuno-bridging to vaccines with proven single-dose efficacy are available.

immunocompromised persons ≥9 years should receive at least 2 doses and ideally 3 doses of HPV.

SAGE also recommended that further evidence should be collected on long-term immunogenicity, efficacy, and duration of protection of single-dose HPV schedules in girls aged 9–14 years, older females and males, and children below 9 years of age.

**Reference**: Weekly epidemiological record 17 JUNE 2022, ANNÉE No 24, 2022, 97, 261–276 http://www.who.int/we

**In accordance with NGI-TAG standard operating procedure, the Nigeria Immunization Technical Advisory Group (NGITAG) which was established in 2015 was assigned the responsibility of reviewing the previous recommendation on HPV vaccine dosing (consideration of the 1-dose regimen as against the 2-dose schedule). The HPV Working Group was assigned the responsibility to systematically analyze all relevant scientific information to aid the nation in decision-making about the introduction of the HPV vaccination.**

**"Should the single dose of Gardasil-4 HPV vaccine be introduced into Nigeria's routine immunization (RI) schedule rather than the previously advised two doses?".**

The following individuals make up the NGI-TAG HPV Disease Working Group (with areas of expertise indicated):

i. Prof. Mairo Hassan – Chairman. (Professor of OBGYN. Core member)
ii. Prof. Augustine Omoigberale – Vice Chairman. (Professor of Paediatrics. Core member)
iii. Dr. Abubakar D Tswanya, mni (International Health; Policy and Strategy. Non-core member)

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## 2. Introduction

HPV types 16 and 18 cause approximately 70% of cervical cancer worldwide [1]. The NGI-TAG Recommendations on HPV Vaccine Introduction into Routine Immunization (2019) document the most common high-risk HPV types in Nigeria as 16,18,31,35,51,52, with serotypes 16 and 18 accounting for 66.9 percent of invasive cervical cancer prevalence in Nigeria [2, 3]. Similarly, a cross-sectional study on the prevalence and distribution of high-risk HPV serotypes in invasive cancer in south west Nigeria discovered that serotypes 16 and 18 were responsible for 69.4 percent of cases [4]. Ano-genital warts are common among men and women in Nigeria, according to studies [5, 6].

Gavi opened the funding window for HPV vaccines in 2011, followed by the launch of the Gavi HPV program, which launched pilots in several countries and allowed for the collection of lessons learned on HPV vaccine delivery. By 2015, the first million girls had been vaccinated [11].The Gavi board approved the New Gavi HPV programme in December 2016, with the goal of reaching 40 million girls by 2020, and a focus on national introductions with multi-age

cohorts (9-14 years of age). The strong momentum that characterized the new HPV strategy was quickly jeopardized due to supply issues, with suppliers informing Gavi in June 2017 that the volume for the new strategy was not planned for.

To date, the WHO has prequalified t vaccines for use against HPV infection, namely [7-9]: Cerverix (Bivalent, 16/18), Gardasil-4 (Tetravalent, 16/18 and for anogenital warts 6/11), and Gardasil-9 (Nonavalent 16/18/31/33/45/52/58 and for anogenital warts 6/11).WHO prequalification of a fourth vaccine - Innovax-Cecolin (Bivalent, 16/18) - was expected in 2021, with at least ten other pipeline vaccines identified in various stages of phase 2 and phase 3 clinical trials [10].

Global HPV vaccine supply is currently insufficient to meet demand, but this is expected to improve by 2023 [12]. The three vaccines currently available in the Gavi portfolio are Gardasil, Cervarix, and Innovax-Cecolin; with tentative supply timelines (2021-2025) for the three vaccines show: -

➔ Gardasil will be more widely available by 2023, but prudent planning is required.

➔ Cervarix will not be available in the short term, and improvements in the medium term may not be sufficient to meet Nigeria's needs.

➔ Innovax- Cecolin is expected to be available in 2021 if and when it is prequalified by WHO.

- However, the non-valent vaccine (Gardasil 9) is not available through UNICEF and is not part of the Gavi portfolio.

Given the constrained global HPV vaccine supply situation, SAGE recommended in October 2019 that the introduction of multiple-age cohort vaccinations be postponed until all countries have been able to introduce HPV vaccination in at least 1 age/single age- cohort of the WHO recommended primary target population of 9-14 years. Gavi is already implementing the single age-cohort strategy .

### 2.1.1. Context of the question

Nigeria's proposal for HPV introduction which was developed and shared with Gavi in June 2020 was essentially guided by NGI-TAG's recommendation of the quadrivalent HPV recombinant vaccine (Gardasil) as the candidate of choice, with a two-pronged implementation strategy comprising facility- based interventions and outreaches, primarily targeting girls 9-14 years. Nationwide introduction is scheduled for a two-phased plan, to be implemented first in 20 states and FCT from March 2021 while the second phase covers the remaining 16 states, from September 2021.

However, due to the global shortage of HPV vaccine including the Countries choice (Gardasil-4valent) and the introduction of a new vaccine into the global market (Innovax Cecolin) the group was asked to review the recommendation in 2021 in light of the circumstances. The HPV working group after reviewing all available evidence reaffirmed the recommendation of the Quadrivalent-Gardasil HPV vaccine which was recommended by the NGI-TAG. As the Global shortage of HPV vaccines persists including Gardasil, the new recommendation by SAGE on the efficacy of a single dose of HPV vaccine has prompted the Country to consider the 1-dose schedule as ideal for Nigeria hence the request to the NGI-TAG for consideration.

In April, 2022, SAGE evaluated the evidence that has been emerging over past years that single-dose schedules provide comparable efficacy to the two or three-dose regimens. SAGE's review concluded that a single-dose Human Papillomavirus (HPV) vaccine delivers solid protection against HPV, the virus that causes cervical cancer, that is comparable to 2-dose schedules. This could be a game-changer for the prevention of the disease; ensuring more doses of the life-saving jab reach more girls.

### 2.2 General Information on the subject (here information on Gardasil 4-Valent (Quadrivalent) vaccine

Gardasil 4-Valent HPV vaccine is an Immunogen (Recombinant L1 proteins from HPV types):6, 11, 16, 18 and is Manufacturer by Merck Canada Inc. the Quadrivalent HPV vaccine is authorized for :females 9-45 years and males 9-26 years.

The Quadrivalent HPV vaccine Adjuvant is the 225 µg amorphous aluminum hydroxyphosphate sulfate (AAHS)

The HPV vaccine; Gardasil (Merck & Co., Kenilworth, NJ, USA), is the first commercially available HPV vaccine licensed by the United States Food and Drug Administration (FDA), in 2006.Gardasil, in addition to HPV16 and 18, also targets HPV6 and 11, which cause around 90% of genital warts .

## 3. Methodology

### 3.1 Establishment and functioning of a Working Group

In line with NGITAG SOP, the HPV working group was tasked with the responsibility of reviewing the HPV recommendation and making a proposal to NGI-TAG. The Working Group was mainly tasked to develop the recommendation framework, conduct a systematic search and data assessment and propose an updated recommendation on HPV vaccine dose schedule into the routine imuunization considering new information made available.

The working group is chaired by Prof. Mairo Hassan, Prof. Augustine Omoigberale as co-chair and Dr. A. D Tswanya who has various expertise: Public health, Gynecology, Pediatrics etc.

The group is supported by 10 committee secretaries; Dr. Amina Abdul-One (NPHCDA), Dr. Bakunawa Garba (NPHCDA),Muhammad Mashin(NPHCDA), Dr. Koko Ipuragboma (WHO), Dr Omotayo Giya (CHAI), Dr. Adeyelu Asekun (CDC), Lauretta Akin-John (Consultant), Funmi Oguntimehin(Coronams), Grace Erekosima (SYDANI) and Somto Keluo- Udeke. The working group TORs is attached to this document as Annex 1. To be able to deliver on the assignment, the HPV working group with support from the secretariat organized 2 Meetings. In addition to this, other coordination activities were constantly performed by the secretariat through regular emails and phone calls.

### 3.2 Recommendation framework (list issues and elements that were considered to inform the recommendation; full recommendation framework will be found in the annexes)

In order to guide the evidence, search, the working group developed a recommendation framework, outlining the issues and specific data needed to inform the decision on the NPHCDA request. The recommendation framework considered 4 categories of issues. Specific elements and data to search were identified and ranked for each issue. The main issues highlighted by the recommendation framework are as follows: 1) Vaccine and immunization characteristics; 2) Disease; 3) Economic and operational considerations; 4) Health policy and programmatic issues. Key elements considered for each issue are listed below:

- Vaccine and immunization characteristics: Efficacy and effectiveness; Vaccine characteristics
- Disease: Burden of disease; Regional and international considerations
- Economic and operational considerations: Vaccine related costs and resource use; Vaccine availability; Vaccine affordability; Socio-economic and social impact of disease; Economic impact on immunization programme
- Health policy and programmatic issues: Interaction with other existing strategies; A detailed recommendation framework is attached as Annex 2

## 4. Evidence search and assessment

Following the development of the recommendation framework, the working group has taken different steps in order to gather, assess and select evidence that will support the recommendation on the Cecolin HPV vaccine. Below is a brief description of the method used by the group:

### Step 1: Framing queries and data ranking

In order to enable a systematic and rigorous data search, for each specific data identified in the recommendation framework, specific queries were formulated, using the PICO format where appropriate. Data needed through these queries were then screened and ranked as critical, important and not important. Only data ranked as Critical and Important were

selected for literature search. Selected queries were categorized as those requiring a systematic search in databases and those for which information could be found in grey literature and reference documents such as unpublished NPHCDA reports and local data, WHO position papers, vaccine manufacturers' websites.

**Step 2: Searching relevant peer-reviewed articles**

For queries requiring systematic search, a clear search strategy has been formulated. Depending on the queries, one or more searches were performed mainly on Pubmed database. Articles obtained were screened (titles and abstracts) for relevance to the question and those available in full text were retrieved and qualified for the next step of quality assessment. The search process and results were documented and attached to this document as Annex XXX (table 1 and 2)

**Step 3: Quality Assessment of selected articles**

Extracted full articles went through a more detailed assessment using well-known quality check tools SIGN a CASP. The appropriate checklist was depending on the study design type. Each appraisal exercise looked at the methodological quality, the results' relevance to the specific query as well as its applicability in local settings. Articles were qualified for use or rejected based on the scoring and other considerations such as scarcity of studies dealing with a specific issue. Assessment outcomes are also recorded in Table 3 and 4 of Annex XXX.

**Step 4: Synthetizing and making sense of the evidence**

Qualified articles were first summarized, focusing on presenting findings to specific queries without providing any judgment. Secondly, a comprehensive analysis of the overall body of the evidence guided by the policy question was done to enable the decision and options to be presented to NGITAG members.

## 5. Presentation of Evidence

In this section each query related to specific data (it may have more than one query for a specific data) is indicated.

in the NGI-TAG recommendation framework will be indicated and the source of evidence on the same will be mentioned alongside. It will be in bullet points to facilitate the reporting but afterwards the working group will

put it in prose form. Note this section only presents the findings, the discussion (e-g judgment/sense -making in the country context) takes place in the next section. In light of the issues outlined in the discussion, recommendations/options are then proposed in the subsequent section.

### 5.1 Efficacy and Effectiveness

***Query 1: What is the antibody response of Gardasil-4 one dose in comparison with 2 dose in girls 9-14 years? {Systematic Search]***

***Paper 1***

**Title of Article:** Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: A systematic review of evidence from clinical trials

Whitworth, H.S., Gallagher, K.E., Howard, N., Mounier-Jack, S., Mbwanji, G., Kreimer, A.R., Basu, P., Kelly, H., Drolet, M., Brisson, M. and Watson-Jones, D., 2020. Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: a systematic review of evidence from clinical trials. Vaccine, 38(6), pp.1302-1314.

**Objective of Article:** This study aimed to systematically review the literature on the efficacy and immunogenicity of single-dose HPV vaccination compared to no vaccination or multi-dose schedules among vaccine trial participants

**Link of Article:** https://www.sciencedirect.com/science/article/pii/S0264410X19316597.

**Appraisal (Casp): 10**

**Type of Article: Systematic Review**

**Result:** Our systematic review presents strong epidemiological evidence that a single dose of HPV vaccine may be protective against HPV16 and HPV18 infection. The five included studies that evaluated efficacy endpoints found that HPV16/18 infection was rare (0% to <5% for one-time incident infection, and 0% to <1% for 12- month persistent infection) among participants who received any HPV vaccination up to four or seven years after dose one, regardless of the number of doses received [24–28]. Infection rates were significantly lower in all HPV vaccine arms than in study participants who were either unvaccinated or received control vaccines. Furthermore, no study found any difference in HPV16/18 infection incidence, persistence or prevalence between participants who received one versus two versus three HPV vaccine doses by year four or year seven. Our findings contrast with the conclusions of a previous systematic review of data from national HPV vaccination programmes, which included two studies evaluating efficacy of Cervarix against HPV16/18 prevalence at 4–5 years post vaccination [17]. One study reported statistically significant effectiveness for one, two and three doses of HPV vaccine compared to no vaccination, but effectiveness was lower for one-dose than for multidose schedules [33]. The other study found statistically significant effectiveness for three, but not one or two, vaccine doses compared to no vaccination [34].

Other studies included in the same review reported either no efficacy of single-dose HPV vaccination, or reduced efficacy compared to two- or three-dose schedules, for other clinical endpoints including anogenital warts and cervical abnormalities [17]. However, as reported by the review authors, several features of the included studies could have led to an underestimation of the effectiveness of one or two-dose schedules. In particular, recipients of one- or two-doses in national programmes where three-dose schedules were recommended proved to be, on average, older at vaccination, of lower socioeconomic status, and younger at first sexual exposure. These factors may be associated with higher risk of HPV infection at vaccination and exposure post-vaccination, both of which would adversely impact vaccine effectiveness estimates of one or two doses.

**Summary/Conclusion:**Our systematic review of the literature on single-dose HPV vaccination from clinical trials supports the premise that one dose may be as effective in preventing HPV infection as two or three doses in healthy young females up to seven years post vaccination. Seropositivity rates were high among all HPV vaccine recipients, also up to seven years post-vaccination. However, sustained durability of the immune response will be fundamental to longer-term protection, so further follow up of participants who received different dosing schedules is important. Whilst producing promising results, our systematic review also highlights the existing paucity of available evidence appropriate for informing policies and guidelines on HPV vaccination strategies. Ongoing clinical trials [14,18] assessing the efficacy and immunogenicity of single-dose HPV vaccination compared to currently-recommended schedules will go a long way towards addressing this knowledge gap for the target populations in those trials. However, research on the efficacy of, and immune responses to, single-dose HPV vaccination may need to be expanded to other target groups such as boys, alternative age groups and HIV-positive individuals, and should evaluate all licensed HPV vaccines, as well as promising new vaccines currently in development.

**Paper 2**

**Title of Article/Author:** B Cell Responses upon Human Papillomavirus (HPV) Infection and Vaccination

Prabhu PR, Carter JJ, Galloway DA. B Cell Responses upon Human Papillomavirus (HPV) Infection and Vaccination. Vaccines. 2022; 10(6): 837.

**Link:** B Cell Responses upon Human Papillomavirus (HPV) Infection and Vaccination | HTML.

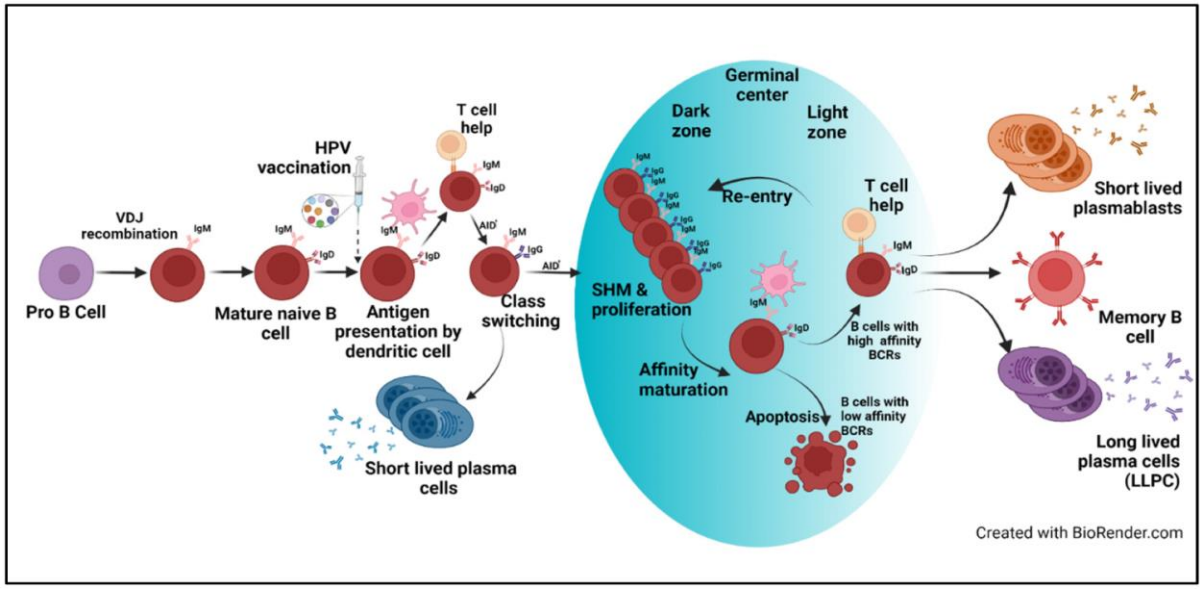
**type of article:**

**Objective:** This review summarizes current knowledge of B-cell responses following HPV vaccination and natural infection, including molecular signatures associated with these responses.

**Appraisal:** 10

**Result:** The fact that human papillomavirus (HPV) is a necessary cause of cervical cancer and that there are effective vaccines against HPV, makes cervical cancer a highly preventable disease through vaccination. The three HPV vaccines available to date, Cervarix™ (bivalent-2vHPV), Gardasil-4™ (quadrivalent-4vHPV), and Gardasil-9™ (nonavalent-9vHPV) , are all widely studied and confer >90% (2v-and 4vHPV) and >95% (9vHPV) protection when administered prior to HPV exposure.

The World Health Assembly passed a resolution calling for elimination of cervical cancer in August 2020 and WHO has launched a global strategy to accelerate the elimination of cervical cancer as a public health problem .
Effective vaccines confer protection that either prevents infection (sterilizing immunity) or reduces disease through induction of immune memory mediated by B and T cells. Following primary vaccination, naïve B cells encounter an antigen that is recognized by the B cell surface receptor. Together with follicular dendritic cells and T cells, B cells form germinal centers in draining lymph nodes. In the germinal center, activation-induced cytidine deaminase (AID) is expressed, an enzyme that mediates somatic hypermutation of immunoglobulin genes and class switching. Affinity maturation occurs as cells with higher affinity receptors replicate while cells with low-affinity receptors undergo apoptosis. This process results in short-lived, immunoglobulin-secreting plasmablasts, that are largely responsible for the peak of antibodies in the serum that occurs a week or two after infection/vaccination and long-lived plasma cells (LLPCs) that home to the bone marrow and secrete antibodies that can last for years to a lifetime (Figure 1). While most of the vaccines follow a similar process, some vaccines are much better than others at inducing long-lasting immunity.




B cell activation, maturation, and proliferation upon exposure to antigens included in the HPV. Dendritic cells present HPV antigens included in the vaccine to naïve B cells. Binding to HPV antigens by B cell receptors results in B-cell activation and proliferation. Some B cells rapidly differentiate into plasma cells that secrete antibodies. B cells that receive additional signals from CD4+ T-follicular helper cells (TfH) express AID which is required for antibody class switching and somatic hypermutation (SHM) of antibody gene sequences. Germinal centers develop, containing activated B cells, activated TfH and dendric cells. It is in the light region of the germinal center that B cells compete for interaction with TfH, B cells with higher affinity receptors bind antigen and present peptides to TfH which in turn provide survival signals that promote further proliferation and continued SHM which takes place in the dark zone. B cells with low affinity receptors that do not receive survival signals undergo apoptosis. B cells can go through repeated rounds of SHM resulting in affinity maturation of the antibody genes, until cells exit as either short-lived plasmablasts, long-lived plasma cells, or memory B cells

**Conclusion:**There are several factors that have contributed to the remarkable success of the HPV vaccine. The VLP is highly immunogenic and likely presents an array of epitopes that are closely packed for B cells to recognize. Additionally, most antibodies induced by VLPs are of high affinity and are neutralizing and, lastly, anti-HPV antibody titers persist many years after vaccination. While there are indications suggesting a single dose of a HPV vaccine provides good efficacy in preventing premalignant lesions, the titer of the vaccine-specific antibodies is lower than that elicited by two or three doses. Protection following one dose might be more dependent upon the Bmem response following exposure. However, there is no data available so far on Bmem response after a single dose of HPV vaccine. Neither have there been enough studies of local anamnestic responses following exposure. It would be a

remarkable achievement in vaccinology if a single dose of an HPV vaccine is proven to generate a protective Bmem response upon re-exposure to the HPV antigens.

***Paper 3***

**Title of Article/Author:** Human papillomavirus vaccines: an updated review

Cheng, L., Wang, Y. and Du, J., 2020. Human papillomavirus vaccines: an updated review. Vaccines, 8(3), p.391.

**Link:** https://www.mdpi.com/770978.

**Type of Article:**

**Objective:** To present the updated information about current HPV vaccines, focusing on vaccine coverage and efficacy.

**Appraisal**:10

**Result:**

**HPV Vaccine Efficacy**

Quadrivalent Gardasil shows excellent efficacy against cervical HPV infection, cervical cancer precursor lesions, and genital warts caused by the HPV types covered by Gardasil. In addition, studies demonstrated that Gardasil significantly decreases HPV infections in the anus, vulva, and penis, as well as in the oral cavity related to HPV vaccine types. Gardasil has a strong prevention rate (>90%, injection prior to HPV exposure) against CIN 2 or worse (CIN 2+), CIN 3+ and vulvar/vaginal intraepithelial neoplasia grade 2 or worse (VIN/VaIN 2+), caused by HPV 16 and 18 [6,41]. However, the inhibition on CIN 2 + and CIN 3 + caused by any HPV types was lower (20-50%) . Comparatively, Gardasil demonstrated less cross-protection effect than Cervarix and the protection efficacy for HPV31, 33, 45, 52, and 58 were 46%, 29%, 7%, 18%, and 6%, respectively.

A recent systematic meta-analysis including 60 million individuals from 14 high-income countries showed that HPV vaccines significantly reduced the prevalence of HPV-related endpoints (genital HPV infections, anogenital wart diagnoses, or histologically confirmed CIN2+) among girls, women, and boys . The most common HPV type, HPV16 and 18, significantly decreased by 83%, and HPV31, 33, and 45 decreased by 54%, among girls aged 13–19 years. The prevalence of anogenital warts decreased by 67%, and CIN2+ decreased by 51%, among girls aged 15–19 years. In addition to the significant decrease of HPV-related endpoints, herd effects among boys and older women were also observed in this meta-analysis

**Effects That Influence the Vaccine Coverage and Efficacy**

There are many potential effects that influence vaccine coverage and efficacy, such as vaccine age, geographical regions, and education. The ideal time for the best protection against HPV-related diseases is prior to HPV exposure.

**Male Vaccination**

WHO guidelines recommend HPV vaccination focusing primarily on young girls, as females have 10 times higher risk of HPV-related cancers than males, and heterosexual males will be protected owing to herd immunity caused by high female vaccine coverage

**Vaccine Safety and Adverse Effects**

Gardasil is immunogenic, clinically effective, and generally well-tolerated in preadolescents and adolescents.The most frequent adverse effects (AEs) ,Gardasil were injection-site reactions, such as pain and swelling, possibly due to the VLP-related inflammation process

**Conclusion:** HPV vaccines significantly decreased HPV infection and HPV related diseases. With the improvement in vaccine coverage and the introduction of pan-gender vaccination programs, better protection against HPV infections and fewer HPV-related cancer cases are expected. To achieve this, educational interventions introducing the risk of HPV and the benefits of vaccines are essential, especially in low- and middle- income countries. Decreased side effects with alternative adjuvants or other designs of vaccines will assist the acceptance and provision of vaccines at a young age. Another crucial problem is that the HPV types not covered by the vaccines are still at a high prevalence among young females. The next-generation HPV vaccines should focus on high-valent vaccines with broad-protection spectrum. In addition, studies or clinical trials are essential to evaluate the impact of HPV vaccination on all HPV-related cancers. Therapeutic vaccines for cancer treatments are of great importance and entail a promising future aimed at combating HPV infection and related diseases from prevention to clearance.

**Paper 4**

**Title of Article:**Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases

Garland, S.M., Hernandez-Avila, M., Wheeler, C.M., Perez, G., Harper, D.M., Leodolter, S., Tang, G.W., Ferris, D.G., Steben, M., Bryan, J. and Taddeo, F.J., 2007. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. New England Journal of Medicine, 356(19), pp.1928-1943.

**Objective of Article:** A phase 3 trial was conducted to evaluate the efficacy of a prophylactic quadrivalent vaccine in preventing anogenital diseases associated with human papillomavirus (HPV) types 6, 11, 16, and 18.

Link of Article:https://www.nejm.org/doi/full/10.1056/nejmoa061760.

**Appraisal (Casp):**10

**Type of Article:** RCT

**Result:**
In this randomized, placebo-controlled, double-blind trial involving 5455 women between the ages of 16 and 24 years, we assigned 2723 women to receive vaccine and 2732 to receive placebo at day 1, month 2, and month 6. The coprimary composite end points were the incidence of genital warts, vulvar or vaginal intraepithelial neoplasia, or cancer and the incidence of cervical intraepithelial neoplasia, adenocarcinoma in situ, or cancer associated with HPV type 6, 11, 16, or 18. Data for the primary analysis were collected for a per-protocol susceptible population of women who had no virologic evidence of HPV type 6, 11, 16, or 18 through 1 month after administration of the third dose.
The women were followed for an average of 3 years after administration of the first dose. In the per-protocol population, those followed for vulvar, vaginal, or perianal disease included 2261 women (83%) in the vaccine group and 2279 (83%) in the placebo group. Those followed for cervical disease included 2241 women (82%) in the vaccine group and 2258 (83%) in the placebo group. Vaccine efficacy was 100% for each of the coprimary endpoints. In an intention-to-treat analysis, including those with prevalent infection or disease caused by vaccine-type and non–vaccine-type HPV, vaccination reduced the rate of any vulvar or vaginal perianal lesions regardless of the causal HPV type by 34% (95% confidence interval [CI], 15 to 49), and the rate of cervical lesions regardless of the causal HPV type by 20% (95% CI, 8 to 31).
Summary/Conclusion:The quadrivalent vaccine significantly reduced the incidence of HPV-associated anogenital diseases in young women.

**Paper5**
**Title of Article:** Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study.

Sankaranarayanan, R., Prabhu, P.R., Pawlita, M., Gheit, T., Bhatla, N., Muwonge, R., Nene, B.M., Esmy, P.O., Joshi, S., Poli, U.R.R. and Jivarajani, P., 2016. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. The Lancet Oncology, 17(1), pp.67-77.

**Objective of Article:** We originally aimed to compare the immunogenicity and frequency of persistent infection and cervical precancerous lesions caused by vaccine-targeted HPV after vaccination with two doses of quadrivalent vaccine on days 1 and 180 or later, with three doses on days 1, 60, and 180 or later, in a cluster-randomized trial.

Link of Article: https://www.sciencedirect.com/science/article/pii/S1470204515004143.

**Appraisal (Casp):** 7

Type of Article: Cohort Study

**Result:** Our study was designed to be done in nine locations (188 clusters) in India. Participants were unmarried girls aged 10–18 years vaccinated in four cohorts: girls who received three doses of vaccine on days 1, 60, and 180 or later, two doses on days 1 and 180 or later, two doses on days 1 and 60 by default, and one dose by default. The primary outcomes were immunogenicity in terms of L1 genotype-specific binding antibody titres, neutralising antibody titres, and antibody avidity after vaccination for the vaccine-targeted HPV types 16, 18, 6, and 11 and incident and persistent infections with these HPVs. Analysis was per actual number of vaccine doses received.
Findings
Vaccination of eligible girls was initiated on Sept 1, 2009, and continued until April 8, 2010. Of 21 258 eligible girls identified at 188 clusters, 17 729 girls were recruited from 178 clusters before suspension. 4348 (25%) girls received three doses, 4979 (28%) received two doses on days 1 and 180 or later, 3452 (19%) received two doses at days 1 and 60, and 4950 (28%) received one dose. Immune response in the two-dose HPV vaccine group was non-inferior to the three-dose group (median fluorescence intensity ratio for HPV 16 1·12 [95% CI 1·02–1·23] and for HPV 18 1·04 [0·92–1·19]) at 7 months, but was inferior in the two-dose default (0·33 [0·29–0·38] for HPV 16 and 0·51 [0·43–0·59] for HPV 18) and one-dose default (0·09 [0·08–0·11] for HPV 16 and 0·12 [0·10–0·14] for HPV 18) groups at 18 months. The geometric mean avidity indices after fewer than three doses by design or default were non-inferior to those after three doses of vaccine. Fewer than three doses by design and default induced detectable concentrations of neutralizing antibodies to all four vaccine-targeted HPV types, but at much lower concentrations after one dose. Cervical samples from 2649 participants were tested and the frequency of incident HPV 16, 18, 6, and 11 infections was similar irrespective of the number of vaccine doses received. The testing of at least two samples from 838 participants showed that there was no persistent HPV 16 or 18 infections in any study group at a median follow-up of 4·7 years (IQR 4·2–5·1).

**Summary/Conclusion:**Despite the limitations imposed by the suspension of the HPV vaccination, our findings lend support to the WHO recommendation of two doses, at least 6 months apart, for routine vaccination of young girls. The short-term protection afforded by one dose of HPV vaccine against persistent infection with HPV 16, 18, 6, and 11 is similar to that afforded by two or three doses of vaccine and merits further assessment.

***Query 2: . What is the rate of seroconversion of Gardasil- 4 single dose in comparison to Gardasil-4 2 doses in girls 9-14 years[Systematic Search]***

***Paper 1***

**Title of Article/Author:** Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: A systematic review of evidence from clinical trials

Hilary S. Whitworth, Katherine E. Gallagher, Natasha Howard, Sandra Mounier-Jack, Gladys Mbwanji, Aimée R. Kreimer, Partha Basu, Helen Kelly, Mélanie Drolet, Marc Brisson, Deborah Watson-Jones, 2020. Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: A systematic review of evidence from clinical trials. Vaccine 38 (6), pp.1302-1314

**Link:** https://www.sciencedirect.com/science/article/pii/S0264410X19316597.

**Type of Article: Systematic Review**

**Objective:** This study aimed to systematically review the literature on the efficacy and immunogenicity of single-dose HPV vaccination compared to no vaccination or multi-dose schedules among vaccine trial participants

**Conclusion:** Our systematic review of the literature on single-dose HPV vaccination from clinical trials supports the premise that one dose may be as effective in preventing HPV infection as two or three doses in healthy young females up to seven years post vaccination. Seropositivity rates were high among all HPV vaccine recipients, also up to seven years post-vaccination. However, sustained durability of the immune response will be fundamental to longer-term protection, so further follow up of participants who received different dosing schedules is important. Whilst producing promising results, our systematic review also highlights the existing paucity of available evidence appropriate for informing policies and guidelines on HPV vaccination strategies. Ongoing clinical trials [14,18] assessing the efficacy and immunogenicity of single-dose HPV vaccination compared to currently-recommended

schedules will go a long way towards addressing this knowledge gap for the target populations in those trials. However, research on the efficacy of, and immune responses to, single-dose HPV vaccination may need to be expanded to other target groups such as boys, alternative age groups and HIV-positive individuals, and should evaluate all licensed HPV vaccines, as well as promising new vaccines currently in development.

***Paper 2***

**Title of Article/Author:** sustained Antibody Responses 6 Years Following 1, 2, or 3 Doses of Quadrivalent Human Papillomavirus (HPV) Vaccine in Adolescent Fijian Girls, and Subsequent Responses to a Single Dose of Bivalent HPV Vaccine: A Prospective Cohort Study

Toh ZQ, Russell FM, Reyburn R, Fong J, Tuivaga E, Ratu T, Nguyen CD, Devi R, Kama M, Matanitobua S, Tabrizi SN, Garland SM, Sinha R, Frazer I, Tikoduadua L, Kado J, Rafai E, Mulholland EK, Licciardi PV, 2017. Sustained Antibody Responses 6 Years Following 1, 2, or 3 Doses of Quadrivalent Human Papillomavirus (HPV) Vaccine in Adolescent Fijian Girls, and Subsequent Responses to a Single Dose of Bivalent HPV Vaccine: A Prospective Cohort Study. Clinical Infectious Disease 64(7), pp.852-859.

**Link:** https://pubmed.ncbi.nlm.nih.gov/28034886/

**Type of Article: Prospective cohort study**

**Objective:** To compare the antibody responses in girls previously vaccinated with zero, 1, 2, or 3 doses of quadrivalent HPV vaccine (4vHPV; Gardasil, Merck) 6 years previously.

**Result:** After 6 years (before a dose of 2vHPV was given), the geometric mean NAb titers for all 4 HPV types were not statistically different between 2-dose (2D) and 3-dose (3D) recipients: HPV-6 (3D: 2216 [95% confidence interval {CI},1695–2896]; 2D: 1476 [95% CI, 1019–2137]; P = .07), HPV-11 (3D: 4431 [95% CI, 3396–5783]; 2D: 2951 [95% CI, 1984–4390]; P = .09), HPV-16 (3D: 3373 [95% CI, 2511–4530]; 2D: 3275 [95% CI, 2452–4373]; P = .89); HPV-18 (3D: 628 [95% CI: 445–888]; 2D: 606 [95% CI, 462–862]; P = .89), and were higher in FID than iTaukei girls. Although 1-dose recipients had significantly lower NAb titers than 2-/3-dose recipients, their NAb titers were 5- to 30-fold higher than unvaccinated girls. Post-2vHPV NAb titers against HPV-16 and -18 were not statistically different between girls who received 1, 2, or 3 doses of 4vHPV previously

**Conclusion:** Results lend support to the WHO recommendation of 2 doses of HPV vaccine for young girls, and contribute to the growing evidence of the possibility of long-term protection against HPV following 1 dose of HPV vaccine. Furthermore, it would seem safe to use both vaccines within an individual. Further studies that specifically address the issue of single-dose

HPV schedules and long-term protection are warranted. In terms of how these immunogenicity findings translate into preventing HPV infection, we currently have a follow-up study in young pregnant women to determine HPV detection rates by HPV dosage group. Fiji has since moved to a 2-dose 2vHPV schedule, with a gap of 6 months between doses.

Article 3:

**Title of Article/ Author: Immunogenicity of quadrivalent HPV and combined hepatitis A and B vaccine when co-administered or administered one month apart to 9–10 year-old girls according to 0–6 month schedule** – Vladimir Gilca, Chantal Sauvageau, Nicole Boulianne, Gaston De Serres, Michel Couillard, Mel Kradjen et al.

**Link to article:** https://www.tandfonline.com/doi/full/10.4161/hv.29617

**Type of article:** Randomized clinical trial.

Vladimir Gilca, Chantal Sauvageau, Nicole Boulianne, Gaston De Serres, Michel Couillard, Mel Krajden, Manale Ouakki, Donald Murphy, Andrea Trevisan & Marc Dionne (2014) Immunogenicity of quadrivalent HPV and combined hepatitis A and B vaccine when co-administered or administered one month apart to 9–10 year-old girls according to 0–6 month schedule, Human Vaccines & Immunotherapeutics, 10:8, 2438-2445

**Objective:** To assess the immunogenicity of the qHPV and HAV/HBV vaccine when co-administered (Group-Co-adm) or given one month apart (Group-Sep) and to measure the persistence of HPV antibodies three years post-second dose of qHPV vaccine in both study groups.

**Results:** Six months post-first dose of qHPV vaccine administration (Group Co-adm) and before the second dose, 94%, 100%, 99% and 96% had detectable antibodies and 87%, 100%, 99%, and 86% had an anti-HPV titer ≥ 3 LU to HPV 6, 11, 16 and 18, respectively. The GMTs were 11, 71, 42 and 12 LU for HPV 6, HPV 11, HPV 16 and HPV 18, respectively.One month post-second dose of qHPV vaccine, all subjects (100%) in both study groups had an antibody titer ≥ 3 LU to all 4 HPV types included in the vaccine. A 55 to 100-fold increase of GMTs was observed post-second dose administration when compared with pre-second dose (6 mo post-first dose). No statistically significant difference was observed in anti-HPV seropositivity rates or GMTs in the two study groups.

**Conclusion:** Post-second dose administration of qHPV and HAV/HBV, no meaningful difference was observed in the immune response in the two study groups to any component of vaccines. A one-dose schedule for pre-adolescents might be a reasonable alternative to the currently approved two-dose schedules since differences in immune response were negligible in the short term.

Article 4

**Title of Article/Author: Immunogenicity and persistence of immunity of a quadrivalent Human Papillomavirus (HPV) vaccine in immunocompromised children** – C. Raina MacIntyre, Peter Shaw, Fiona E. Mackie, Christina Boros, Helen Marshall, Michelle Barnes, Holly Seale, Sean E. Kennedy, Aye Moa, Andrew Hayen, Abrar Ahmad Chughtai, Edward V. O'Loughlin, Michael Stormon

**Link to article:** https://www.sciencedirect.com/science/article/pii/S0264410X1630473X#!
**Type of article:** Multi-centre clinical trial.

C. Raina MacIntyre, Peter Shaw, Fiona E. Mackie, Christina Boros, Helen Marshall, Michelle Barnes, Holly Seale, Sean E. Kennedy, Aye Moa, Andrew Hayen, Abrar Ahmad Chughtai, Edward V. O'Loughlin, Michael Stormon, 2016. Immunogenicity and persistence of immunity of a quadrivalent Human Papillomavirus (HPV) vaccine in immunocompromised children, Vaccine 34(36), pp.4343-4350.

**Objective:** To determine the immunogenicity and reactogenicity of HPV vaccine in immunocompromised children.
**Results:** Fifty-nine participants were enrolled across the three paediatric hospitals and among those one was seropositive to types 6, 11 and 16 at baseline. Seven months after the first dose, seroconversion rates were 93.3%, 100%, 100% and 88.9% for type 6, 11, 16 and 18 respectively. The corresponding rates at 24 month follow up were 82.2%, 91.1%, 91.1% and 68.9%. The greatest increase in geometric mean titre (GMT) was for type 16, followed by type 11. GMTs declined over the following months, but remained more than fourfold higher for all serotypes compared to baseline titres at 24 months post vaccination.
**Conclusion:** One dose of the quadrivalent HPV vaccine elicited an adequate immunogenic response in immunosuppressed children regardless of age and the cause of immunosuppression.

Article 5:
**Title of Articleh/Author**: One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer.
Link to article: **https://www.who.int/news/item/11-04-2022-one-dose-human-papillomavirus-(hpv)-vaccine-offers-solid-protection-against-cervical-cancer**
**Type of article:** WHO news item.

WHO Strategic Advisory Group of Experts on Immunization (SAGE). 11 April 2022. One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer

**Objective:** To evaluate emerging evidence on the efficacy of single-dose vaccine in comparison to two or three-doses.
**Results:** WHO Strategic Advisory Group of Experts on Immunization (SAGE) after reviewing emerging evidences on the efficacy of the single-dose HPV vaccine when compared to the two or three-dose regimen of the HPV vaccine has concluded that the single dose regimen is highly effective for the prevention of HPV serotypes 16 & 18, which cause 70% of cervical cancer and has urged all countries to introduce HPV vaccines and prioritize multi-age cohort catch up of missed and older cohorts of girls.
**Conclusion:** The option for the single-dose vaccine is less expensive, less resource intensive and easier to administer which facilitates implementing catch-up campaigns for multiple age groups,

reduces the challenges linked to tracing girls for their second dose and allows for financial and human resources to be redirected to other health priorities.

### *Query 3: What is the immune response of Gardasil- 4 single dose in comparison to Gardasil-4 2-doses in girls 9-14 years [Systematic Search]*

Paper 1
**Title of Article/Author: Immunogenicity and persistence of immunity of a quadrivalent Human Papillomavirus (HPV) vaccine in immunocompromised children** – C. Raina MacIntyre, Peter Shaw, Fiona E. Mackie, Christina Boros, Helen Marshall, Michelle Barnes, Holly Seale, Sean E. Kennedy, Aye Moa, Andrew Hayen, Abrar Ahmad Chughtai, Edward V. O'Loughlin, Michael Stormon
**Link to article:** https://www.sciencedirect.com/science/article/pii/S0264410X1630473X#!
**Type of article:** Multi-centre clinical trial.

C. Raina MacIntyre, Peter Shaw, Fiona E. Mackie, Christina Boros, Helen Marshall, Michelle Barnes, Holly Seale, Sean E. Kennedy, Aye Moa, Andrew Hayen, Abrar Ahmad Chughtai, Edward V. O'Loughlin, Michael Stormon, 2016. Immunogenicity and persistence of immunity of a quadrivalent Human Papillomavirus (HPV) vaccine in immunocompromised children, Vaccine 34(36), pp.4343-4350.

**Objective:** To determine the immunogenicity and reactogenicity of HPV vaccine in immunocompromised children.
**Results:** Fifty-nine participants were enrolled across the three paediatric hospitals and among those one was seropositive to types 6, 11 and 16 at baseline. Seven months after the first dose, seroconversion rates were 93.3%, 100%, 100% and 88.9% for type 6, 11, 16 and 18 respectively. The corresponding rates at 24 month follow-up were 82.2%, 91.1%, 91.1% and 68.9%. The greatest increase in geometric mean titre (GMT) was for type 16, followed by type 11. GMTs declined over the following months, but remained more than fourfold higher for all serotypes compared to baseline titers at 24 months post vaccination.
**Conclusion:** One dose of the quadrivalent HPV vaccine elicited an adequate immunogenic response in immunosuppressed children regardless of age and the cause of immunosuppression.

### *Query 4: What is the duration of protection of Gardasil- 4 single dose in comparison to Gardasil-4 double (2) doses in girls 9-14 years? [Systematic Search]*

***Paper 1***
**Title of Article:** *Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study*

Rengaswamy Sankaranarayanan, Smita Joshi, Richard Muwonge, Pulikottil Okkuru Esmy, Partha Basu, Priya Prabhu, Neerja Bhatla, Bhagwan M. Nene, Janmesh Shaw, Usha Rani Reddy Poli, Yogesh Verma, Eric Zomawia, Sharmila Pimple, Massimo Tommasino, Michael Pawlita, Tarik Gheit, Tim Waterboer, Peter Sehr, Madhavan Radhakrishna Pillai, 2018. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. Vaccine 36 (32), pp.4783-4791

**Objective of Article:** *Human papillomavirus (HPV) vaccination is a major strategy for preventing cervical and other ano-genital cancers. Worldwide HPV vaccination introduction and coverage will be facilitated if a single dose of vaccine is as effective as two or three doses or demonstrates significant protective effect compared to 'no vaccination'.*

**Type of Article:** *Journal*

**Link to Article:** *https://www.sciencedirect.com/science/article/pii/S0264410X1830286X.*

**Result:** *The MFI threshold values for seroconversion for HPV 16 and 18 L1 were 100 and 41, respectively. All vaccinated girls in the study groups seroconverted against HPV 16 and HPV 18 after vaccination and all remained seropositive at 48 months regardless of the number of doses. Girls receiving one dose of HPV vaccine demonstrated a robust and sustained immune response by generating antibodies against HPV 16 and 18, albeit with antibody concentrations (mean MFI values) inferior to those generated after two or three doses*
*Our current results indicate that the frequencies of cumulative incident HPV 16 and 18 infections over 7 years from vaccination were similar and uniformly low in all the vaccinated groups; the frequencies of HPV 16 and 18 infections were higher in 1481 unvaccinated women (age standardized proportion 10.8%) than among the vaccine recipients (Table 5, age-standardized proportion 1.3% in 1180 three-dose, 0.9% in 1179 two-dose, 2.2% in 1473 two-dose (default) and 1.5% among 1823 one dose recipients). The age-standardized proportions of vaccine non-targeted HPV types were similar between three-, two- (including the default group) and one-dose groups, but higher in the unvaccinated control women*

***Conclusion:*** *A single dose of quadrivalent HPV vaccine is immunogenic and provides lasting protection against HPV 16 and 18 infections similar to the three- and two-dose vaccine schedules, although the study suffer from some limitations. A one-dose HPV vaccination schedule will have substantial cost saving and policy and programmatic advantages over multiple doses that will facilitate logistics of vaccine delivery, wider implementation and high coverage of target girls. One-dose vaccination is particularly conducive to wider implementation in the LMICs where four-fifths of the global burden of cervical cancer occurs.*

***Paper 2***

**Title of Article:** *The public health impact of a single-dose HPV vaccination schedule*

***Objective of Article:*** *A single-dose HPV vaccination schedule could alleviate financial and logistical barriers, accelerate HPV vaccine introduction into national immunization schedules, and achieve higher coverage in current country programs. Based on the available evidence, SAGE advised that countries may now choose between a one- or two-dose schedule for 9–14-year-old girls and women aged 15 to 20. This is a major step toward reaching the WHO's global strategy to accelerate the elimination of cervical cancer.*

Monica Graham, April 11, 2022. The public health impact of a single-dose HPV vaccination schedule, culled from *https://www.path.org/articles/single-dose-hpv-vaccine-cervical-cancer/*

**Type of Article:** *Commentary*

**Link to Article:** *https://www.path.org/articles/single-dose-hpv-vaccine-cervical-cancer/*.

**Result:** *Over the last four years, the Single-Dose HPV Vaccine Evaluation Consortium, coordinated by PATH, has gathered and evaluated data from clinical trials, observational studies and modeling analyses regarding the value of a single-dose HPV vaccination schedule. Results are emerging from several clinical trials that have been evaluating a single dose of HPV vaccine. In Kenya, a randomized controlled clinical trial demonstrated that a single dose of HPV vaccine was about 98 percent effective in preventing persistent HPV infections caused by HPV-16/18, the most common HPV types responsible for 70% of cervical cancers. Two high-quality observational studies in India and Costa Rica show protection against HPV infections after a single dose to be similar to two or three doses and last up to at least 10 years after vaccination. Another study in Tanzania showed that efficacy in young girls ages 9-14 years can be inferred based on bridging the immune response to studies conducted in India and Costa Rica. A single-dose HPV vaccination schedule is further supported by model-based evidence which consistently shows that single-dose vaccination, in settings that have not yet introduced HPV vaccines, will lead to substantial reduction in cervical cancer cases. Additionally, reaching more girls with a single dose will avert many more cervical cancer cases than vaccinating fewer girls with a second dose.*

**Conclusion:** *After review and evaluation by the Consortium, the current evidence supports the conclusion that single-dose HPV vaccination of the bivalent (Cervarix®), quadrivalent (Gardasil®), and nonavalent (Gardasil® 9) vaccines gives equivalent or near-equivalent protection to two-dose vaccination.*

**Paper 3**

**Title of Article:** *Single Dose of HPV Vaccine Yields Long-Term Protection from Many Cancer-Causing Types*

National Cancer Institute Blog, April 10, 2020. Single Dose of HPV Vaccine Yields Long-Term Protection from Many Cancer-Causing Types. culled from *https://www.cancer.gov/news-events/cancer-currents-blog/2020/hpv-vaccine-single-dose-long-term-protection*

**Objective of Article:** *Cervical cancer is a leading cause of cancer and cancer deaths in women worldwide. A combination of HPV vaccination and cervical cancer screening can greatly reduce cervical cancer incidence and deaths. But global HPV vaccination rates remain low, and many low-resource countries do not have HPV vaccination programs or routine screening.*

**Type of Article:** *National Cancer Institute Report*

**Link to Article:**
*https://www.cancer.gov/news-events/cancer-currents-blog/2020/hpv-vaccine-single-dose-long-term-protection*.

**Result:** *More than a decade after vaccination, women who had received a single dose of human papillomavirus (HPV) vaccine continued to be protected against cervical infection with the two cancer-causing HPV types targeted by the vaccine, HPV16 and 18. The new findings are from an extended follow-up of the NCI-sponsored Costa Rica HPV Vaccine Trial. In a second, related analysis, the trial's researchers found that a single vaccine dose also provided long-lasting protection against three other cancer-causing HPV types not targeted by the vaccine—a phenomenon known as cross-protection The vaccine also provided lesser cross-protection against two additional cancer-causing HPV types. The reduction in HPV infections was similar no matter how many vaccine doses were received, with an estimated vaccine efficacy of 82%, 84 %, and 80%, respectively, for one, two, and three doses.*
*Consistent with previous findings from this study, which had 7 years of follow-up, the updated analysis showed that women who received three doses experienced protection against new infections with HPV types 31, 33, and 45, with an average vaccine efficacy of 64% that remained stable over 11 years. Although limited by sample size, the data suggested that vaccine efficacy against these three HPV types was similar in women who received only one vaccine dose. The vaccine also provided a lesser degree of cross-protection against HPV types 35 and 58.*

**Conclusion:** *The ability to protect against many cancer-causing HPV infections with just one vaccine dose—rather than the two or three doses currently recommended—"would make a very big difference" in preventing the more than half a million new cervical cancer cases and more than 300,000 deaths from the disease worldwide each year.*

***Query 5: What is the Gardasil- 4valent single dose coverage threshold required for herd immunity? [Systematic Search]***

**Title of Article:** The WHO Strategic Advisory Group of Experts on Immunization (SAGE), between April 4-7, 2022, Accessed on the 9th of July,2022.

Basu P., Brisson M., Campos N., Clarke E., Drolet M., Gallagher K., Gebreselassie R., Graham M., Howard N., Jit M., Kelly H., Kim J., Kreimer A., Lewis R., Markowitz L., Ogilvie G., Schiller J., Schuind A., Simpson E., Watson-Jones D., and Whitworth H. S. May 30, 2022. Review of the current published evidence on single-dose HPV vaccination. 4th Edition.

**Objective of Article:** Recommended single-dose schedules provide comparable efficacy to the two or three-dose regimens.

**Link of Article:**
**https://media.path.org/documents/20220328_SDHPV_Evidence_Review_Edition_4_Final_L2.pdf?_gl=1*w2blrr*_ga*MTM4ODc2ODE2OC4xNjQ0NTc2MzE4*_ga_YBSE7ZKDQM*MTY1NzM2MDQ0MC4xLjEuMTY1NzM2MTA5MS4w.**

**Appraisal (Casp): NA**

**Type of Article: WHO Report**

**Result:** The WHO Strategic Advisory Group of Experts on Immunization (SAGE), between April 4-7, 2022, evaluated the evidence that has been emerging over past years that single-dose schedules provide comparable efficacy to the two or three-dose regimens. The SAGE's review concluded that a single-dose Human Papillomavirus (HPV) vaccine delivers solid protection against HPV, the virus that causes cervical cancer, comparable to 2-dose schedules.
Modeling studies are emerging from several clinical trials evaluating the impact of a single dose of HPV vaccine to inform decision-making.
A US analysis explored the epidemiologic impact of single-dose vaccination under varied assumptions of the duration of single-dose protection (10 years, 15 years, and lifetime) and achievable vaccination coverage (70% and 90%) (1). This analysis also assumed lower vaccine efficacy for one dose (80% against HPV 16 and 18 infections) than for two doses (100%). The analysis projected that both one-dose and two-dose vaccination provide substantial reductions in population HPV 16 prevalence over time, even when protection with one dose is not lifelong. When no waning of protection after one dose vaccination was assumed, HPV 16 prevalence reductions over time were lower for one-dose vaccination than two-dose vaccination, as expected with the lower efficacy; however, this loss in benefit was almost completely offset when there was an increase in one-dose vaccination coverage from 70% to 90%. The ability for increased coverage to compensate for decreased efficacy was diminished under assumptions of waning protection.

Using calibrated HPV-ADVISE models with country-specific data for 4 LMIC (India, Vietnam, Uganda, and Nigeria), Bénard et al. focused on evaluating the potential benefit of extended-dose schedules for HPV vaccination and explored the impact of varying vaccination coverage of the second dose, as well as one-dose efficacy and durability (2). They found that even with lower efficacy of a single dose, vaccination with an extended interval between doses was nearly equivalent to the current two-dose vaccination schedule, provided coverage of the second dose five years later was not low (e.g., 30% coverage). Furthermore, reaching 70% vaccination of 14-year-old girls irrespective of vaccination status would be even more effective than the current two-dose schedule.

Burger et al. estimated the impact of delayed implementation of single-dose HPV vaccination using two independent models calibrated to a setting with a high cervical cancer burden (3). With clinical trials underway and expected to report final results on the (non-) inferior efficacy of one-dose vaccination within five years, the authors examined two scenarios: (1) assuming non-inferiority of a single dose compared to two doses (i.e., 100% lifelong efficacy), single-dose vaccination implemented in the year 2021 compared to delayed implementation of single-dose vaccination in 2026; and (2) assuming an inferior vaccine efficacy of a single dose (80% lifelong efficacy), single-dose vaccination implemented in the year 2021, reverting to a two-dose schedule in 2026 (presumed year in which trial results show assumed inferiority). In the second scenario, different assumptions regarding re-vaccination of those who had received one dose in 2021 were explored, including 100% re-vaccination, 0% re-vaccination, and a multi-age cohort campaign assuming 70% of girls aged 10 to 14 years in 2026 received the vaccination, either as a first dose or second dose. In all scenarios, vaccination coverage was assumed to be 70% of girls aged 9 years, with a one-year campaign of girls ages 10 to 14 years. Both models demonstrated that immediate use of single-dose vaccine increased the number of averted cervical cancers from 2021 to 2120, compared to waiting 5 years (2026). Thus, immediate vaccination can benefit the health of individuals soon aging out of vaccine eligibility.

Another study evaluated the long-term health and economic impacts of routine one-dose HPV vaccination compared to (1) no vaccination and (2) two-dose HPV vaccination in Uganda (4). They used a three-tiered hybrid modeling approach that captured HPV transmission, cervical carcinogenesis, and population demographics to project long-term health and economic outcomes associated with one-dose HPV vaccination (assuming 80% efficacy against HPV-16/18 infections under three waning scenarios) and two-dose HPV vaccination (assuming 100% efficacy over the lifetime) in Uganda. Forty years after initiating routine vaccination and depending on assumptions of vaccine waning, one-dose HPV vaccination with equivalent coverage (70%) averted 15–16% of cervical cancer cases versus 21% with two-dose vaccination but required only half the upfront economic investment. Vaccination with two doses had an attractive cost-effectiveness profile except if one-dose vaccination enabled

higher coverage (90% vs. 70%) and did not wane. The authors concluded that one-dose HPV vaccination resulted in cost-savings compared to no vaccination and could be cost-effective compared to two-dose vaccination if protection is longstanding and higher coverage can be achieved.
Conclusion: One dose of Gardasil-4 had comparable effectiveness and health benefits as two or three doses in preventing high–grade cervical cancer under achievable vaccination coverage of 70% and 90% (1-4). Evidence has also shown that any loss due to decreased efficacy or durability with single-dose vaccination could be offset by reasonable coverage of a second dose, even five years later, and by focusing on reaching girls and young women before they age out of vaccine eligibility (5). These findings support the importance of reducing delays in implementing HPV vaccination programs in countries that have not yet introduced them.

**Summary/Conclusion:**

### 5.2 Vaccine Characteristics

**Query 6*: In what presentation and formulations are Gardasil-4 1-dose made available?* [Manufacturer's Website, WHO PP, Unicef, gavi]**

**Paper 1**

**Title of Article:** GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant], Updated June, 2022. Accessed 9th of July,2022.

**Objective of Article:** GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine. This study highlights do not include all the information needed to use GARDASIL safely and effectively.

NA, Highlights of Prescribing Information for Gardasil [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant], Suspension for intramuscular injection. No date.

**Appraisal (Casp):N/A**

**Type of Article: FDA Report**

**Link to Article:** https://www.fda.gov/media/74350/download.

**Result:** GARDASIL, Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant, is a non-infectious recombinant quadrivalent vaccine prepared from the

purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant Saccharomyces cerevisiae and self-assembled into VLPs. The fermentation process involves growth of S. cerevisiae on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate). The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.
Summary/Conclusion: GARDASIL is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein. Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate.

***Query 7: What is the dose and route of administration of Gardasil-4 1-dose vaccines?* [Manufacturer's Website, WHO PP, Unicef, gavi]**

**Paper 1**
**Title of Article:** GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant], Updated June, 2022. Accessed 9th of July,2022.

NA, Highlights of Prescribing Information for Gardasil [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant], Suspension for intramuscular injection. No date.

**Objective of Article:** GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine. This study highlights do not include all the information needed to use
GARDASIL safely and effectively.
**Link to Article:** https://www.fda.gov/media/74350/download.
**Appraisal (Casp): NA**
**Type of Article: FDA report**
**Result:** Method of Administration For intramuscular use only. Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension

of the vaccine. GARDASIL should not be diluted or mixed with other vaccines. After thorough agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the product if particulates are present or if it appears discolored. GARDASIL should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh. Syncope has been reported following vaccination with GARDASIL and may result in falling with injury; observation for 15 minutes after administration is recommended. [See Warnings and Precautions (5.1).] Single-Dose Vial Use Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly. Prefilled Syringe Use This package does not contain a needle. Shake well before use. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.
Summary/Conclusion: DOSAGE FORMS AND STRENGTHS GARDASIL is a suspension for intramuscular administration available in 0.5-mL single dose vials and prefilled syringes.

***Paper* 2**

**Title of Article:** Independent report: JCVI interim advice on a one-dose schedule for the routine HPV immunization programme; Published 10 February 2022. Accessed 9th of July,2022.

Joint Committee on Vaccination and Immunisation (JCVI). 10 February 2022. JCVI Interim Advice on a one-dose schedule for the routine HPV immunisation programme, An Independent Report.

**Objective of Article:** The JCVI has been considering the issue of a potential move to one dose of the HPV vaccine for several years. Indeed, the committee was aware of the potential for one dose as far back as 2018 and makes the evidence found.

**Link of Article**: https://www.gov.uk/government/publications/single-dose-of-hpv-vaccine-jcvi-interim-advice/jcvi-interim-advice-on-a-one-dose-schedule-for-the-routine-hpv-immunisation-programme.

**Appraisal (Casp):NA**

**Type of Article: Website report**

**Result**: The evidence considered included published and unpublished data on the immunogenicity and efficacy of a single dose of bivalent, quadrivalent and 9-valent HPV vaccine, and the duration of antibody response following vaccination. The evidence strongly indicated that one dose of the bivalent or quadrivalent vaccine will provide protection against infection and clinical endpoints for more than 10 years. Modelling evidence considered also showed that a one-dose schedule was likely to provide almost as much health benefit as a 2-dose schedule even in pessimistic scenarios where the one-dose schedule has lower efficacy

or duration of protection. Evidence regarding the durability of the antibody response to the 9-valent vaccine was more limited given that this was a more recently introduced vaccine.
**Summary/Conclusion:**

***Query 8: What is the recommended schedule of administering Gardasil- 4valent HPV vaccine***
**Paper 1**
**Title of Article:** One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer.
WHO Strategic Advisory Group of Experts on Immunization (SAGE). 11 April 2022. One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer.
**Objective of Article:** SAGE's review concluded that a single-dose Human Papillomavirus (HPV) vaccine delivers solid protection against HPV, the virus that causes cervical cancer, that is comparable to 2-dose schedules.
**Link of Article:** https://www.who.int/news/item/11-04-2022-one-dose-human-papillomavirus-(hpv)-vaccine-offers-solid-protection-against-cervical-cancer.
**Appraisal (Casp):** N/A
**Type of Article:** WHO report
**Result:** The option for a single dose of the vaccine is less costly, less resource intensive and easier to administer. It facilitates implementing catch-up campaigns for multiple age groups, reduces the challenges linked to tracing girls for their second/continuation of dose and allows for financial and human resources to be redirected to other health priorities."
SAGE recommends updating dose schedules for HPV as follows

- One or two-dose schedule for the primary target of girls aged 9-14
- One or two-dose schedule for young women aged 15-20
- Two doses with a 6-month interval for women older than 21

Summary/Conclusion:

***Query 9:* What are the cold chain requirements for Gardasil 4 single dose in comparison to Gardasil-4 double (2) dose HPV vaccines? *[*Manufacture's Website, WHO PP, Unicef, gavi, NPHCDA]**

**Title of Article: NPHCDA**
**Objective of Article: NA**
**Link of Article:NA**
**Appraisal (Casp):NA**
**Type of Article: NPHCDA**
**Result:**

- Gaps in cold chain adequacy exists in the country particularly at the national level and all zonal cold stores except for the SWZ cold store which has adequate capacity to store both 1 dose and 2 dose HPV vaccines
- At national level, the gap at the NSCC is about 237,119 liters and 348,182 liters for 1 dose and 2 dose of HPV vaccines respectively
- This highlights the urgent need for cold chain capacity expansion before the introduction of the vaccine

**Summary/Conclusion**

### 5.3 Disease

***Query 10:*** **Can Gardasil- 4 single dose prevent genital warts in women and men?**

**Paper 1:**

**Title of document/date:** Effectiveness of HPV vaccines against genital warts in women from Valencia, Spain Author: EstherNavarro-Illana et al /5th June 2017

**Link:** https://pubmed.ncbi.nlm.nih.gov/28499554/

Navarro-Illana E, López-Lacort M, Navarro-Illana P, Vilata JJ, Diez-Domingo J. Effectiveness of HPV vaccines against genital warts in women from Valencia, Spain. 2017 June 5, Vaccine 35(25), pp.3342-3346.

**Objective:** To assess the effectiveness of the HPV vaccines in preventing genital warts in young women.

**Result:**

Methodology: A Population-based study using health databases, carried out in the Valencian Community (Spain). Participants were girls and women aged 14–19 years who were registered in the Valencian Community between January 2009 and December 2014 (n = 279,787).

Main outcome measures

Incident cases of genital warts were defined as the first activation of diagnosis code ICD-9-CM 078.11 (Condyloma acuminatum) in primary care and outpatient clinics during the study period.

There were 612 cases of genital warts. The overall incidence rate was 75.8/100,000 person-years (95% CrI 69.7–81.8). There was a decrease in genital warts when female candidates to be vaccinated with quadrivalent HPV vaccine reached the age of 18 (in 2012), compared to previous years. Incidence of genital warts in unvaccinated women and those who received the bivalent vaccine was higher than in girls and women who received the quadrivalent HPV vaccine. The effectiveness of a three-dose regimen of the quadrivalent HPV vaccine was 77%

(95 CrI: 66–85%), whereas that of a single dose was 61% (95 CrI: 20–87%). No effectiveness was seen with a full vaccination course with the bivalent HPV vaccine.

**Conclusions**

Three doses of the quadrivalent HPV vaccine were effective against genital warts in our population. Moreover, with low vaccine coverage the incidence of genital warts decreased only in the vaccinated.

**Paper 2:**

**Title of Article/Author/Date:** One-Dose Human Papillomavirus Vaccination and the Risk of Genital Warts: A Danish Nationwide Population-based Study/Louise Baandrup, Christian Dehlendorff, Susanne K Kjaer/November 2021.

**Type of Article:** Cohort study

**Link:** https://pubmed.ncbi.nlm.nih.gov/33048118/

Baandrup L, Dehlendorff C, Kjaer SK. One-Dose Human Papillomavirus Vaccination and the Risk of Genital Warts: A Danish Nationwide Population-based Study. 2021 Nov 2; Clinical Infectious Disease 73(9), pp. e3220-e3226.

**Appraisal (Casp): 7**

**Methodology:** Complete enumeration of all women born within the period: 1985–2003 was made and individual-level vaccination data were retrieved. The cohort was followed up for the first occurrence of GWs up-to 31 December 2016. The study used Poisson regression to calculated incidence rates (IRs) of GWs per 100,000 person-years and IR ratios (IRRs) with corresponding 95% confidence intervals (CIs) for GWs, according to vaccination status, age at first dose, and calendar time.

**Result:** The study consisted 1,076,945 participants of which 485,408 were vaccinated. 1-dose vaccine effectiveness was 71% (IRR = 0.29; 95% CI, .22-.38) and 62% (0.38; .29-.49) for and girls initiating vaccination at age 12-14 years and 15-16 years respectively, compared with unvaccinated girls. whereas 2-dose vaccine effectiveness was 78% (IRR, 0.22; 95% CI, .18-.26) and 68% (0.32; .26-.38) for the same age groups respectively. Between 2009 and 2016, the IRRs for 3-dose versus 1-dose and 2-dose versus 1-dose increased towards unity over calendar time, being 0.69 (95% CI, .57-.84) and 0.86 (.68-1.08).

**Conclusions:** The study found that 1-dose or 2-dose of quadrivalent HPV vaccine was associated with substantial protection against GWs in girls vaccinated at age ≤16 years. The 1-dose vaccine effectiveness approached that of 3-dose or 2-dose over calendar time, probably reflecting the impact of herd protection.

## 5.4 Vaccine related costs and resource use

***Query 11: How much would the Gardasil-4 single dose cost in comparison to Gardasil-4 double (2) doses in the routine immunization of girls age 9-14? [Manufacture's Website, WHO PP, Unicef, Gavi]***

**Title of Article:**
**Objective of Article:**
**Link of Article:**
**Appraisal (Casp):**
**Type of Article:**
**Result:**
**Summary/Conclusion:**

***Query 12: What is the cost benefit of introducing Gardasil 4valent single dose in comparison to Gardasil 4 double (2) doses HPV vaccines in girls 9-14 years? {NPHCDA, Manufacture's Website, WHO PP, Unicef, gavi]***

**Title of Article:** Costs of introducing and delivering HPV vaccines in low and lower middle income countries: inputs for GAVI policy on introduction grant support to countries.

**Objective of Article:** This paper describes the data and analysis shared with GAVI policymakers for this decision regarding GAVI HPV vaccine support. The paper reviews why strategies and costs for HPV vaccine delivery are different from other vaccines and what is known about the cost components from available data that originated primarily from HPV vaccine delivery costing studies in low and middle income-countries.

Levin A, Wang SA, Levin C, Tsu V, Hutubessy R (2014) Costs of Introducing and Delivering HPV Vaccines in Low and Lower Middle Income Countries: Inputs for GAVI Policy on Introduction Grant Support to Countries. PLoS ONE 9(6): e101114.

**Link of Article:**
http://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC4072768&blobtype=pdf
**Appraisal (Casp):**
**Type of Article:**
**Result:** Costs varied among pilot projects and estimates of national programs due to differences in scale and service delivery strategy. The average introduction costs per fully immunized girl ranged from $1.49 to $18.94 while recurrent costs per girl ranged from $1.00 to $15.69, with both types of costs varying by delivery strategy and country. Evaluating delivery costs along programme characteristics as well as country characteristics (population

density, income/cost level, existing service delivery infrastructure) are likely the most informative and useful for anticipating costs for HPV vaccine delivery.

**Summary/Conclusion:**

An analysis conducted by PATH gave a breakdown of the cost effectiveness of a single dose to multi-dose HPV vaccination as highlighted on the table below.

***Query 13: What is the cost effectiveness of introducing Gardasil- 4valent single dose in comparison to Gardasil 4 double (2) doses into RI for girls 9-14 years?***

**Paper 1:**

**Title of Article:** Health and economic benefits of single-dose HPV vaccination in a Gavi-eligible country

**Name of Authors:** Emily A. Burger, Nicole G. Campos, Stephen Sy, Catherine Regan, Jane J. Kim

**Objective of Article:** The objective was to evaluate the long-term health and economic impacts of routine one-dose HPV vaccination compared to (1) no vaccination and (2) two-dose HPV vaccination in a low-income country.

Emily A. Burger, Nicole G. Campos, Stephen Sy, Catherine Regan, Jane J. Kim; 2018. Health and economic benefits of single-dose HPV vaccination in a Gavi-eligible country, Vaccine 36(32), pp. 4823-4829

**LinkofArticle:**

**https://www.sciencedirect.com/science/article/pii/S0264410X18305589?via%3Dihub#!**

**Appraisal (Casp):**

**Type of Article:** Peer-reviewed

**Result:** Routine one-dose HPV vaccination of 9-year-old girls required substantial upfront investment but was cost-saving compared to no vaccination when accounting for the cost-offsets from future cancers averted. Forty years after initiating routine vaccination and depending on assumptions of vaccine waning, one-dose HPV vaccination with equivalent coverage (70%) averted 15–16% of cervical cancer cases versus 21% with two-dose vaccination but required only half the upfront economic investment.

**Paper 2:**

**Title of Article:** Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis.

**Objective of Article:** The objective of the study was to estimated the long-term health benefits and cost-effectiveness of one-dose versus two-dose HPV vaccination, in 192

countries, assuming that one dose of the vaccine gives either a shorter duration of full protection (20 or 30 years) or lifelong protection but lower vaccine efficacy (e.g., 80%) compared to two doses.

Kiesha Prem, Yoon Hong Choi, Élodie Bénard, Emily A Burger, Liza Hadley, Jean-François Laprise, Catherine Regan, Mélanie Drolet, Stephen Sy, Kaja Abbas, Jane J Kim, Marc Brisson and Mark Jit. 2021; Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis

**Link of Article:** https://www.medrxiv.org/content/10.1101/2021.02.08.21251186v1.full.pdf
**Appraisal (Casp):**
**Type of Article:** A comparative modelling analysis.
**Result:** Findings Over the next century, one-dose vaccination at 80% coverage could avert 64 million (80%UI 62·2–64·8) and 66·6 million (80%UI 63·4–69·1) cervical cancer cases should one dose of the vaccine confer 20 and 30 years of protection, respectively. Should one dose of the vaccine provide lifelong protection at 80% vaccine efficacy, 68·4 million (80%UI 63·8–69·4) cervical cancer cases could be prevented. Across all country income groups, two-dose schedules conferring lifelong protection would avert only slightly more cases (2·1–8·7 million) than the one-dose scenarios explored.

**Summary/Conclusion:**

Limited evidence on cost effectiveness of one dose protocol. Available evidence points to potential cost savings from the one dose schedule. A one-dose vaccination program has been considered to have lower durability (i.e number of years of protection) in some cases but if the program can achieve higher coverage (up to 90%), the prevalence of HPV16/18 can be reduced by 85%, similar to what the two-dose regimen achieves. Given the high number of countries that have yet to adopt an HPV vaccination program – and paired with its inherently lower cost and greater feasibility – one-dose HPV vaccination has the potential to boost HPV vaccine impact globally.

Data accumulated to date from clinical trials and high-quality observational clinical studies provide strong evidence that single-dose HPV vaccination could substantially reduce the incidence of HPV-attributable cervical precancer and cancer. With greatly reduced costs and simplified implementation potentially allowing more countries to introduce HPV vaccination or increase coverage, health and economic impact analyses show that single-dose HPV vaccination could be a high-value public health intervention. A single-dose HPV vaccination schedule is further supported by model-based evidence which consistently shows that single-dose vaccination in settings that have not yet introduced HPV vaccines will lead to substantial reduction in cervical cancer cases. Additionally, reaching more girls with a single dose will avert many more cervical cancer cases than vaccinating fewer girls with a second dose

### 5.5 Vaccine availability

***Query 14: Is there sufficient production capacity of Gardasil 1- dose?*** **[Manufacture's Website, WHO PP, unicef, gavi]**

**Paper 1**

**Title of Article:** Human-papillomavirus-vaccine-HPV-supply-and-demand-update

**Objective of Article:**

UNICEF, 2019. Human Papillomavirus Vaccine: Supply and Demand Update. culled from human-papillomavirus-vaccine-HPV-supply-and-demand-update.pdf (unicef.org)

**Link of Article:**

https://www.unicef.org/supply/sites/unicef.org.supply/files/2020-03/human-papillomavirus-vaccine-HPV-supply-and-demand-update.pdf.

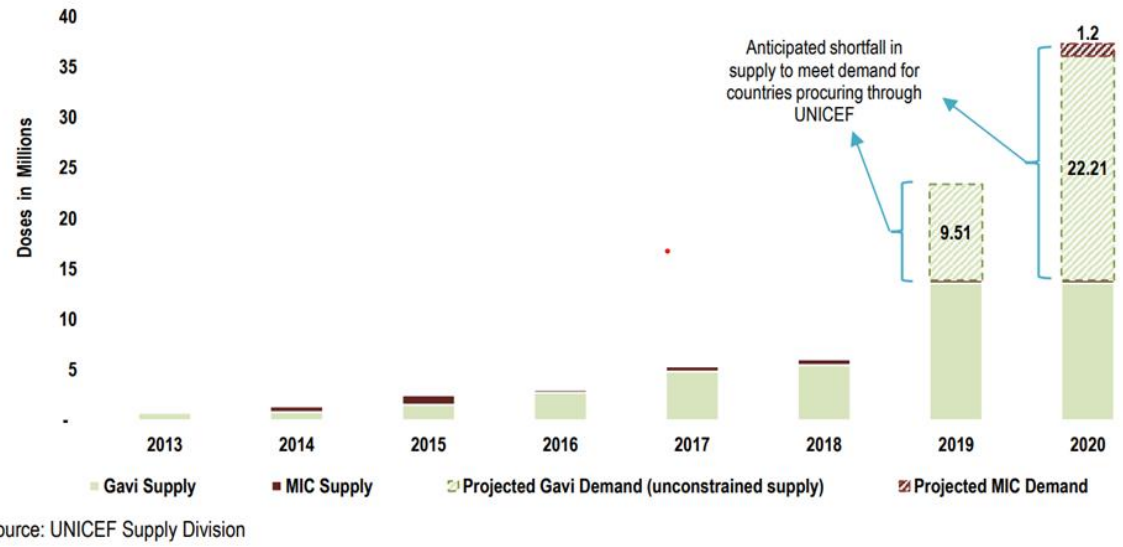
**Appraisal (Casp): NA**

**Type of Article: UNICEF REPORT**

**Result:**

From 2013 to 2018, UNICEF procured 18.9 million doses of bivalent and tetravalent HPV vaccines for both Gavi-supported countries and self-financing MICs totalling USD 105.7 million.18 In 2018, UNICEF procured six million doses at a value of USD 30 million, which represents a market share of approximately 14 per cent of the global volume and 1.4 per cent of the value. Countries have not yet procured any nonavalent vaccine through UNICEF to date (Figure 5). UNICEF's current total projected demand for 2019 and 2020 could reach up to 60.8 million doses, mostly (97 per cent) on behalf of Gavi-supported countries, with 23 million doses for 2019, and 35.8 million for 2020. However, based on suppliers' indications on short-term supply availability, UNICEF was only able to secure 13.58 million doses a year for 2019 and 2020, resulting in an anticipated shortfall of 31.7 million doses, which is more than half of the projected demand (Figure 5).

Figure 5 UNICEF HPV Supply and Projected Demand 2013-2020




Source: UNICEF Supply Division

**Summary/Conclusion:**

**Paper 2**

**Title of document/date: World Health Organization/Global Market Study Hpv Vaccines**

**Link:** **https://cdn.who.int/media/docs/default-source/immunization/mi4a/who-hpv-vaccine-global-market-study-april-2022.pdf?sfvrsn=6acb4c98_1&download=true**

WHO, March 2022. Global Market Study: HPV Vaccine, WHO working, culled from who-hpv-vaccine-global-market-study-april-2022.pdf

GLOBAL MARKET STUDY HPV

**Result:**

Global Supply (Available Supply for Commercialization)

Consultations with manufacturers and experts, as well as a review of publicly available information on HPV vaccines, provided the basis for an assessment of the current and future global supply of HPV vaccine. Since the last update, one new HPV vaccine – Cecolin, a bivalent HPV vaccine produced by Innovax – has received WHO prequalification, expanding the global supplier base from two to three suppliers. In addition, Walvax Biotechnology's product received marketing authorization and existing manufacturers are continuing investments to increase manufacturing capacity. Supply has already increased on average by 15% annually in recent years, and new investments are expected to translate into continuing and increased growth in available supply, with significant increases anticipated in the short and medium term (2023–2025). Two quadrivalent HPV vaccines are currently in Phase 3 clinical development: one from Serum Institute of India and one from the China National Biotec Group (CNBG). All use aluminium-containing adjuvants and are likely to be licensed with an indication for girls 9–14 years old for two- and/or three-dose schedules. The success, timing and capacity of these pipeline vaccine efforts will have a significant impact on the long-term outlook for HPV vaccine supply.

**Paper 3**
**Title of Article:**
**Objective of Article:**
**Link of Article:**
**Appraisal (Casp):**
**Type of Article:**
**Result:**

**Summary/Conclusion:**

**Title of document/date:** Press Release- Gardasil pulls in $1.5bn, driving vaccine business for Merck

**Link:** https://bioprocessintl.com/bioprocess-insider/facilities-capacity/gardasil-pulls-in-1-5bn-driving-vaccine-business-for-merck/

Dan Stanton, 14 February 2022. Gardasil pulls in $1.5bn, driving vaccine business for Merck, A press release of the BioProcess Insider

**Result:**
For the full year, 2021, vaccines pulled in around $9.7 billion in sales revenues for Merck. The division was driven by Gardasil and Gardasil 9, which saw sales of $5.7 billion for the 12 months, up 44% on the year prior.

As CFO Caroline Litchfield said during the firm's end-of-year conference call, "underlying global demand for Gardasil remains strong, as it is increasingly being recognized as a vaccine that can help prevent certain HPV-related cancers in both, females and males."

With continued demand, Merck predicts sales could potentially double by 2030 as a host of new facilities come online.

"We are making significant investments in production capacity for our HPV vaccines, with an urgency to increase supply to meet the growing global demand," a Merck spokesperson told *BioProcess Insider*. "As we announced in late 2018, we are investing $16 billion in capital projects over the next five years, with a sizable portion dedicated to vaccine expansion. The overall investment is unprecedented in the company's history in terms of size and scope. These efforts include $1.7 billion expansions of our vaccines production capabilities, including our HPV vaccines, at our sites in Elkton, Virginia, and Durham, North Carolina.
Between 2017-2020, Merck nearly doubled Gardasil supply, the spokesperson said, and these further expansion programs are expected to double capacity again when they come online from 2023.

"Despite the pandemic, we have continued to expand capacity and increase supply," we were told. "We are fully committed to our significant manufacturing expansion efforts to meet growing global demand. This remains a top priority for Merck and is central to our goal of reducing the number of women and men affected by vaccine-preventable HPV-related cancers and diseases."

For the full year 2021, Merck reported total sales of $48.7 billion, $17.2 billion of which came from a 20% year-on-year increase in sales of cancer drug Keytruda (pembrolizumab).

**Paper 4**
**Title of Article:**
**Objective of Article:**
**Link of Article:**
**Appraisal (Casp):**
**Type of Article:**

**Result:**
**Summary/Conclusion:**

**Title of document/date:** Press Release- HPV Vaccine Manufacturing Increases to Meet Growing Global Demand

**Link:** https://www.precisionvaccinations.com/2022/04/04/hpv-vaccine-manufacturing-increases-meet-growing-global-demand

Precision Vaccinations, 14 April 2022. Press Release- HPV Vaccine Manufacturing Increases to Meet Growing Global Demand, https://www.precisionvaccinations.com/2022/04/04/hpv-vaccine-manufacturing-increases-meet-growing-global-demand

**Result:**

New Jersey-based Merck today reaffirmed its commitment to enable broad equitable access to its human papillomavirus (HPV) vaccines. The company has invested significantly in vaccine manufacturing and recently expanded its facility in Elkton, VA, to support this commitment.

Merck expects the supply of its HPV vaccines to double between 2020-2023 as the company continues to expand capacity at existing facilities and as new facilities come online.

Merck previously committed to expand production capacity at existing manufacturing facilities and build new facilities to address the unprecedented global demand for its HPV vaccines.

"As we continue to increase production of our HPV vaccines, we are prioritizing access in countries with a high burden of disease, including countries eligible for support from Gavi and UNICEF," commented Dr. Priya Agrawal, global lead for HPV Vaccines at Merck, in a press statement issued on April 4, 2022.

"Through our long-term agreement with UNICEF, we plan to provide 91.5 million doses of our HPV vaccines in Gavi-supported countries from 2021-2025."

"And we have offered additional doses beyond that agreement as needed to help meet growing demand."

Merck's leading U.S. FDA Approved HPV vaccine, GARDASIL 9, is indicated for:

- females 9 through 45 years of age for the prevention of cervical, vulvar, vaginal, anal, oropharyngeal, and other head and neck cancers caused by HPV Types 16, 18, 31, 33, 45, 52, and 58; cervical, vulvar, vaginal, and anal precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV Types 6 and 11,
- males 9 through 45 years of age for the prevention of anal, oropharyngeal, and other head and neck cancers caused by HPV Types 16, 18, 31, 33, 45, 52, and 58; anal precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV Types 6 and 11.

The oropharyngeal and head and neck cancer indication is approved under accelerated approval based on effectiveness in preventing HPV-related anogenital disease.

According to Merck, continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Furthermore, GARDASIL 9 vaccination does not eliminate the necessity for vaccine recipients to undergo screening for cervical, vulvar, vaginal, anal, oropharyngeal, and other head and neck cancers as recommended by a health care provider.

Previous HPV vaccines news is posted at PrecisionVaccinations.com/HPV.

Note: The press release was edited for clarity and manually curated for mobile readers.

**Regional and international considerations**

***Query 15:*** dates and content of last SAGE recommendations 2.WHO position paper

**Title of document/date:** WHO Weekly epidemiological record/ 17 June 2022, ANNÉE No 24, 2022, 97, 261–276

**Link:** **The Weekly Epidemiological Record (WER) (who.int)**

**Result:** Given the high incidence of HPV-related cancers in immunocompromised persons, those living with HIV, and children or adolescents who face sexual abuse, **SAGE** recommends

that these groups be considered for vaccination even if they are outside the standard eligible age range.
SAGE considered the evidence from an updated systematic review on the immunogenicity, efficacy, and effectiveness of single-dose vaccination schedules compared with no vaccination, and multidose schedules. The review included 55 studies, 20 of which were new studies not included in a review conducted in 2019. The review showed comparable efficacy and effectiveness between single- and multidose schedules in preventing persistent infection with HPV serotypes 16 and 18, lasting up to 10 years following vaccination. The estimates come predominantly from observational studies that are at serious risk of bias due to confounding. However, a high-quality randomized clinical trial in Kenya included in the review also showed high efficacy of a single dose of HPV vaccine (97.5%) in girls up to 20 years of age. While there is no known antibody correlate for protection from infection or disease, antibody levels following a single dose were lower than those following multidose schedules. However, they remained stable and seropositivity against HPV 16 and 18 persisted up to 11 years following a single dose. Further evidence on single-dose schedules from efficacy trials, including trials for which interim results were reviewed by SAGE, will become available during the next 3 years. On the basis of the recent data on efficacy and effectiveness, SAGE endorsed the optimization of the HPV vaccine schedules. For 9–14-year-olds, national immunization programmes can use either a single-dose or a 2-dose vaccination schedule with an interval between doses of at least 6 months.

SAGE also recommended optimizing the vaccine schedule in older age cohorts. Those aged 15–20 years may receive one or 2 doses, while those aged ≥21 years should receive 2 doses with a 6-month interval. A single-dose schedule should be considered for those HPV vaccine products for which data on efficacy or immuno-bridging of vaccines with proven single-dose efficacy are available.
immunocompromised persons ≥9 years should receive at least 2 doses and ideally 3 doses of HPV.
Further evidence should be collected on long-term immunogenicity, efficacy, and duration of protection of single-dose HPV schedules in girls aged 9–14 years, older females and males, and children below 9 years of age.

## Discussions

## Proposed Recommendation (s)/Options

▪

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