RWANDA NATIONAL IMMUNISATION TECHNICAL ADVISORY GROUP

(RWANDA-NITAG)

Recommendation on the switch from two doses to single dose of Human Papilloma Virus Vaccine

June 2024

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ACRONYMS

CI	Confidence Interval
DNA	Desoxyribonucleic Acid
FIG	Full Immunized Girl
HINARI	Health Internetwork Access to Research Initiative
HPV	Human Papilloma Virus
hr HPV	high risk Human Papilloma Virus
HSIL	High-grade Squamous Intraepithelial
LMIC	Low-Middle Income countries
MOH	Ministry of Health
NITAG	National Immunization Technical Advisory Group
PICO	Population Intervention Comparator Outcome
SSA	Sub-Saharan Africa
STI	Sexual Transmissible Infections
WHO	World Health Organization

EXECUTIVE SUMMARY

Human Papilloma Virus (HPV) is the most common viral infection of the reproductive tract and causes precancerous lesions that may progress to cancer. While most HPV infections are asymptomatic and resolve spontaneously, an estimate of 10% to 20% of infections among women persist and cause nearly 100% of cervical cancers. Globally, 660,000 cervical cancer were diagnosed and 350,000 related deaths were reported in 2022.

The global strategy to accelerate the elimination of cervical cancer prioritize HPV vaccination as primary prevention of cervical cancer. Since 2006, six HPV vaccines including three bivalent, two quadrivalent, and one nonavalent have been prequalified by WHO. All these vaccines are highly efficacious in preventing infection with virus types 16 and 18, which are responsible for approximately 70% of cervical cancer, and precancerous cervical lesions caused by these virus types. The quadrivalent vaccine is also highly efficacious in preventing anogenital warts caused by infection with HPV types 6 and 11. The nonavalent provides additional protection against HPV types 31, 33, 45, 52 and 58. Data from clinical trials and initial post-marketing surveillance conducted in several continents show HPV vaccines to be safe. The primary target group in most of the countries is young adolescent girls, aged 9-14.

Rwanda introduced Human Papillomavirus Vaccine (HPV) in 2011, targeting adolescent girls aged 12 years. The HPV vaccination program uses school approaches and all the girls in Primary 6 receive two doses of quadrivalent HPV with interval of six months between the doses. Although efforts have been made to ensure every adolescent girl is reached, significant drop out between two doses has been observed. Tracing defaulters is always challenging for adolescents who receive their first dose few months before they break from the last semester of Primary 6 and the risk of incomplete vaccination is high.

Current evidence suggests that a single dose of quadrivalent HPV may have comparable efficacy and duration of protection as a 2-dose schedule and may offer programme advantages, be more efficient and affordable, and contribute to improved coverage.

Introducing a single dose would address the challenge of high dropout rate and therefore prevent the immunity gaps, while improving efficiency in vaccine delivery.

In the framework of improving the performance of HPV vaccination, the Ministry of Health sent a letter to the Rwanda National Immunization Technical Advisory Group (Rwanda NITAG) on 30th Marc 2023, requesting Rwanda NITAG to review relevant evidence and to advise on the switch from two doses to single dose schedule of HPV in Rwanda.

To answer to the question: “Should Rwanda switch from HPV two doses to single dose”? Rwanda NITAG established and assigned task to collect and analyse available information to support the recommendation. From the available literature, relevant published and unpublished articles and reports related to the recommendation elements were analysed.

Findings from the available literature provide sufficient evidence on efficacy and effectiveness of single dose including protection against HPV, efficiency in vaccine delivery, and cost-

effectiveness of the HPV single dose versus two doses schedule. The NITAG considered that relevant information was obtained to support the recommendation and advised the switch from HPV two doses to single dose schedule.

1. INTRODUCTION

1.1. Context of the request

Rwanda introduced Human Papillomavirus Vaccine (HPV) in 2011. The HPV vaccination targets adolescent girls aged 12 years. The HPV vaccination program uses school approaches and all the girls in Primary 6 receive two doses of quadrivalent HPV with interval of six months between the doses. Current evidence suggests that a single dose of quadrivalent HPV may have comparable efficacy and duration of protection as a 2-dose schedule and may offer programme advantages, be more efficient and affordable, and contribute to improved coverage. Although efforts have been made to ensure every adolescent girl is reached, significant drop out between two doses has been observed and tracing defaulters has been challenging for adolescents who receive their first dose few months before they break from the last semester of Primary 6 after which they move to different schools. The risk of incomplete vaccination is high. Introducing a single dose would address the challenge of high dropout rate and therefore prevent the immunity gaps, while improving efficiency in vaccine delivery.

In the framework of improving efficiency in HPV vaccine delivery, the Ministry of Health sent a request to the Rwanda National Immunization Technical Advisory Group (Rwanda NITAG) on 30th Marc 2023, to review relevant evidence and to advise on the switch from two doses to a single dose schedule of HPV vaccine in Rwanda

1.2. Humana Papilloma Virus, Cervical Cancer and Vaccination

Human Papillomavirus (HPV) ranks among the most common sexually transmitted infections. About 15 strains of HPV are associated with cervical cancer[1]. An estimate of 10% to 20% of infections among women persist and cause nearly 100% of cervical cancers[2]. Cervical cancer is the most frequently diagnosed cancer and the fourth leading cause of cancer death in women globally. Approximately 660,000 new cases and 350,000 deaths were reported worldwide in 2022. About 94% of deaths occur in low and middle-income countries (LMIC), with the highest rate of cervical cancer incidence and mortality in Sub-Saharan Africa (SSA).[3] The HPV vaccines include the quadrivalent and bivalent HPV vaccines which were licensed in 2006 and 2007 respectively. The two HPV vaccines widely recommended and used target types 16 and 18, which cause approximately 71% of cervical cancer cases and the quadrivalent HPV vaccine on top of these

[1] Okunade, K. S. (2020). Human papillomavirus and cervical cancer. Journal of Obstetrics and Gynaecology, 40(5), 602-608.

[2] Scott-Wittenborn, N., & Fakhry, C. (2021, October). Epidemiology of HPV related malignancies. In Seminars in Radiation Oncology (Vol. 31, No. 4, pp. 286-296). WB Saunders

[3] https://www.who.int/news-room/fact-sheets/detail/cervical-cancer

strains, also targets HPV types 6 and 11 associated with 90% of cases of genital warts worldwide. The nonavalent HPV vaccine licensed in 2014 targets other five types most commonly responsible for cervical cancer including HPV 31/33/45/52/58 in addition to the four HPV types covered by the quadrivalent HPV vaccine.[4]

Studies have documented a tremendous decrease in cervical lesions after HPV vaccination. The high reductions were documented in younger age groups (14–17 years), with up to 73% reduction in cervical intraepithelial neoplasia among vaccinated females.[5]

The quadrivalent HPV vaccine was introduced in Rwanda in 2011. As of 2023, so far 1597821 adolescent girls had received two doses of HPV vaccine.[6] From 2013 to 2020, the prevalence of HPV types 6, 11, 16, and 18 decreased by 69% (from 13% to 4%) among women aged 17–23 years who had completed at least 6 years of school, where vaccine coverage was 63% (median age at vaccination of 14 years).[7]

2. METHODS

To respond to the MOH request on whether Rwanda should switch from 2 doses to a single dose of HPV vaccine, Rwanda NITAG established working groups to work on the recommendation. The Rwanda NITAG members, convened on 8th June 2024 after technical working group meetings to gather evidence from the technical working groups and finalize the recommendation.

The following steps guided the development of the recommendation:

1. Identify and define the basic elements guiding the elaboration of the recommendations
2. Frame the questions for the interventions which are part of the recommendation
3. Determine sources of evidence and apply literature search strategies
4. Identify publications, pertinent studies, published and unpublished reports/articles of interest
5. Assess the quality of articles retained considering the methods and materials used to conduct the study.

[4] Brown, D. R., Joura, E. A., Yen, G. P., Kothari, S., Luxembourg, A., Saah, A., ... & Stanley, M. (2021). Systematic literature review of cross-protective effect of HPV vaccines based on data from randomized clinical trials and real-world evidence. Vaccine, 39(16), 2224-2236.

[5] Wang, W., Kothari, S., Skufca, J., Giuliano, A. R., Sundström, K., Nygård, M., ... & Garland, S. M. (2022). Real-world impact and effectiveness of the quadrivalent HPV vaccine: an updated systematic literature review. Expert Review of Vaccines, 21(12), 1799-1817.

[6] WHO/UNICEF estimates, through JRF reports

[7] Sayinzoga, F., Tenet, V., Heideman, D. A., Sibomana, H., Umulisa, M. C., Franceschi, S., ... & Baussano, I. (2023). Human papillomavirus vaccine effect against human papillomavirus infection in Rwanda: evidence from repeated cross-sectional cervical-cell-based surveys. The Lancet Global Health.

Four elements were analysed and where applicable, PICO (Population, Intervention, Comparator, Outcome) methods were applied to frame the research question. The following elements served as a basic framework to develop the recommendation:

- Epidemiology of HPV infection and Cervical Cancer
- Immunogenicity, efficacy, and effectiveness of quadrivalent HPV single dose
- Vaccine characteristics, logistic, handling and administration
- Economic and operational considerations for the HPV single dose delivery

Based on the above-mentioned elements, ~~of~~ the questions were formulated as follow:

1. What is the burden of HPV and cervical cancer in the Region and Rwanda?
2. What is the efficacy and effectiveness of quadrivalent HPV single dose compared to two dose schedule?
3. What are the vaccine characteristics, logistic, cold chain, handling, and administration requirements?
4. What are the economic and operational considerations for the use of quadrivalent HPV single dose

2.1 Documentation sources of evidence and strategies used for the literature search

Different databases were consulted including Global NITAG Network website, Health Internetwork Access to Research Initiative (HINARI), Google Scholar, and WHO resources. The relevant articles published, and unpublished reports were selected for inclusion in the final methodological analysis. The key words used for the literature search are summarized in the table below:

Questions	**Key words**
1	Epidemiology of HPV Infection-Global-SSA-Rwanda
2	Epidemiology and risk factors for cervical cancer- Global-SSA-Rwanda
2	Stability-Immunogenicity-Efficacy-Safety-effectiveness of HPV single dose
3	Quadrivalent HPV single dose vaccine-Characteristics-storage conditions-administration
5	Price HPV vaccines

2.2 Identification of potential articles and relevant studies

The relevant published and unpublished articles as well as reports were selected for inclusion in the analysis of the evidence. The team reviewed and numbered the articles according to the questions listed above, and a summary of the findings of each article was made.

Question	Number of articles
Epidemiology of HPV infection and Cervical Cancer	14
Immunogenicity, efficacy, and effectiveness of quadrivalent HPV single dose	8
Vaccine characteristics, logistic, handling and administration	3
Economic and operational considerations for the introduction of HPV single dos	5

3. FINDINGS FROM THE EVIDENCE

The findings from the search are summarized in the following sections:

3.1 Epidemiology of HPV infection and Cervical Cancer

The HPV is the most common sexually transmissible infection (STI). More than 200 HPV types can be sexually transmitted, and 15 types are classified as high-risk (hr) HPV which are responsible for dysplasia and cancer.[8,9] The age distribution of HPV infection indicates an early peak in the teens and twenties, however, some countries reported second peak among older individuals. Most of affected women are aged below 25 years old, with the trends decreasing with the increasing

[8]McBride, A. A. (2017). Oncogenic human papillomaviruses. Philosophical Transactions of the Royal Society B: Biological Sciences, 372(1732), 20160273.

[9] Seyoum, A., Assefa, N., Gure, T., Seyoum, B., Mulu, A., & Mihret, A. (2022). Prevalence and genotype distribution of high-risk human papillomavirus infection among Sub-Saharan African women: a systematic review and meta-analysis. Frontiers in Public Health, 10, 890880.

age.[10,11] Early-onset of sexual activity was identified as a potential risk for cervical cancer in Africa. A review of the literature revealed an association between early sexual activity and cervical cancer with a pooled odds ratio of 2.95 (95% CI = 1.06, 4.83), indicating that women who began sexual intercourse before the age of 18 had a higher risk of getting cervical cancer than adult women.[12]

Globally, the prevalence of HPV infection is estimated at 11.7%, with the highest prevalence observed in Southern Africa and Caribbean.[13] This provided an estimate of 291 million women worldwide who were carriers of HPV DNA in 2007, of which 32% were infected with HPV type 16 or HPV type 18, or both.[14] A systematic review was conducted to estimate the prevalence of high-risk HPV (hrHPV) in Sub-Saharan African countries reporting a pooled prevalence of 34%.[15]

In Rwanda, the overall prevalence of HPV infection was estimated at 34%. The crude and age-standardized prevalence of hrHPV types was 22 %, the prevalence of possible hrHPV was 10%, and low risk HPV was 15 %. Both HPV type 16 and 18 represented 7% of all hrHPV with HPV type 16 being the most prevalent type in women with normal cytology (4 %), low-grade squamous intraepithelial lesions (11 %), and high-grade squamous intraepithelial lesions (29 %).[16] Though

[10] Franceschi, S., Herrero, R., Clifford, G. M., Snijders, P. J., Arslan, A., Anh, P. T. H., ... & IARC HPV Prevalence Surveys Study Group. (2006). Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. International journal of cancer, 119(11), 2677-2684.

[11] Smith, J. S., Melendy, A., Rana, R. K., & Pimenta, J. M. (2008). Age-specific prevalence of infection with human papillomavirus in females: a global review. Journal of Adolescent Health, 43(4), S5-e1.

[12] Mekonnen, A. G., & Mittiku, Y. M. (2023). Early-onset of sexual activity as a potential risk of cervical cancer in Africa: A review of literature. PLOS Global Public Health, 3(3), e0000941

[13] Soheili, M., Keyvani, H., Soheili, M., & Nasseri, S. (2021). Human papilloma virus: A review study of epidemiology, carcinogenesis, diagnostic methods, and treatment of all HPV-related cancers. Medical journal of the Islamic Republic of Iran, 35, 65. https://doi.org/10.47176/mjiri.35.65

[14] De Sanjosé, S., Diaz, M., Castellsagué, X., Clifford, G., Bruni, L., Muñoz, N., & Bosch, F. X. (2007). Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. The Lancet infectious diseases, 7(7), 453-459.

[15] Seyoum, A., Assefa, N., Gure, T., Seyoum, B., Mulu, A., & Mihret, A. (2022). Prevalence and genotype distribution of high-risk human papillomavirus infection among Sub-Saharan African women: a systematic review and meta-analysis. Frontiers in Public Health, 10, 890880.

[16] Ngabo, F., Franceschi, S., Baussano, I., Umulisa, M. C., Snijders, P. J., Uyterlinde, A. M., ... & Clifford, G. M. (2016). Human papillomavirus infection in Rwanda at the moment of implementation of a national HPV vaccination programme. BMC infectious diseases, 16(1), 1-10.

12 hrHPV types are highly related to malignant neoplasms, HPV 16 and 18 are most incriminated in causing approximatively 70% of cervical cancer.[17, 18]

Globally, 660,000 cervical cancer cases and 350,000 deaths were reported in 2022, with the highest rates of cervical cancer incidence and mortality reported from Sub-Saharan Africa (SSA), Central America and South-East Asia. The global age-standardized incidence and mortality rates were estimated at 14.1% and 7.1% respectively. In the African Region, the age standardized incidence and mortality rate ranged from 40.4 to 26.9 cases, and 28.9 to 16.5 deaths per 100 000 population respectively.[19] The increase in age-specific incidence rate of cervical cancer begins after the age of 25 years, and the average age at death was 59 years, ranging from 45 to 76 years.[20] [21,22,23,24]

Findings from a study conducted in Rwanda between July 2013 and May 2014, estimated the HPV prevalence among women aged of 18 to 69 years at 34%. The highest prevalence (54%) was observed in women ≤19 years, decreasing to 20 % at among women aged 50 years and beyond. The prevalence of high risk (hr) HPV and cytological abnormalities was 22 and 11 % respectively. Age-standardized prevalence of hr HPV was 22 % and HPV16 was the most common type isolated. HPV 16/18 were associated with 40 % of high-grade squamous intraepithelial lesions (HSIL).[25]In 2023, Rwanda reported 1229 new cases of cervical cancer and 829 deaths from the disease.[26]

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[17] Sammarco, M. L., Tamburro, M., Pulliero, A., Izzotti, A., & Ripabelli, G. (2020). Human papillomavirus infections, cervical cancer and MicroRNAs: an overview and implications for public health. MicroRNA, 9(3), 174-186.

[18] Lekoane, K. M., Kuupiel, D., Mashamba-Thompson, T. P., & Ginindza, T. G. (2019). Evidence on the prevalence, incidence, mortality and trends of human papilloma virus-associated cancers in sub-Saharan Africa: systematic scoping review. BMC cancer, 19, 1-10.

[19] ME, J. F., Siegel, R. L., Isabelle Soerjomataram, M. D., & Ahmedin Jemal, D. V. M. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries

[20] Arbyn, M., Weiderpass, E., Bruni, L., de Sanjosé, S., Saraiya, M., Ferlay, J., & Bray, F. (2020). Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global Health, 8(2), e191-e203

[21] Arbyn, M., Weiderpass, E., Bruni, L., de Sanjosé, S., Saraiya, M., Ferlay, J., & Bray, F. (2020). Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global Health, 8(2), e191-e203

[22] Sammarco, M. L., Tamburro, M., Pulliero, A., Izzotti, A., & Ripabelli, G. (2020). Human papillomavirus infections, cervical cancer and MicroRNAs: an overview and implications for public health. MicroRNA, 9(3), 174-186.

[23] Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians, 71(3), 209–249. https://doi.org/10.3322/caac.21660

[24] Singh, D., Vignat, J., Lorenzoni, V., Eslahi, M., Ginsburg, O., Lauby-Secretan, B., ... & Vaccarella, S. (2023). Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. The Lancet Global Health, 11(2), e197-e206.

[25] Ngabo, F., Franceschi, S., Baussano, I., Umulisa, M. C., Snijders, P. J., Uyterlinde, A. M., ... & Clifford, G. M. (2016). Human papillomavirus infection in Rwanda at the moment of implementation of a national HPV vaccination programme. BMC infectious diseases, 16, 1-10.

[26] ICO/IARC Information Centre on HPV and Cancer, https://hpvcentre.net/statistics/reports/RWA_FS.pdf

3.2 Immunogenicity, efficacy, and effectiveness of quadrivalent HPV single dose vs double and triple doses

HPV vaccines have been found to be highly immunogenic and effective for preventing HPV infection. A systematic review was conducted to compare the efficacy of HPV single dose versus no vaccination, as well as two and three doses. The review aimed to answer two questions: whether one dose of HPV vaccine can provide non-inferior efficacy against HPV infection and associated clinical outcomes, and whether it can produce non-inferior immune responses compared to a two-dose or three-dose schedule. The literature consistently showed a low frequency of HPV type16/18 infection in vaccinated participants up to seven years after vaccination, regardless of the number of doses. One-dose recipients had significantly lower infection rates compared to those who were not vaccinated. The seropositivity rates of HPV types 16/18 were high in all HPV vaccine recipients, though antibody levels were lower with one compared to two or three doses.[27]

A recent systematic review of 15 clinical trials also found was conducted to appraise evidence of HPV vaccine single dose evidence from 15 clinical trials. All efficacy studies reported very a low incidence or prevalence of HPV type 16/18 infection among HPV-vaccinated participants, regardless of the number of doses received. In immunogenicity studies, HPV type 16/18 antibody seropositivity rates were high among all HPV-vaccinated participants. Antibody levels were significantly lower with one dose compared to two or three doses, but levels with one dose were stable and sustained up to 11 years post-vaccination.[28]

The findings from efficacy studies conducted in India, Mongolia, Tanzania and Kenya showed indicated consistently similar and uniformly low frequencies of cumulative incident and persistent HPV 16 and 18 infections in all the vaccinated study groups with different regimen in Indian studies.[29,30] About 99% and 98% of Tanzanian girls who received one dose of HPV vaccine had

[27] Whitworth, H. S., Gallagher, K. E., Howard, N., Mounier-Jack, S., Mbwanji, G., Kreimer, A. R., ... & 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), 1302-1314.

[28] Whitworth, H. S., Mounier-Jack, S., Choi, E. M., Gallagher, K. E., Howard, N., Kelly, H., ... & Watson-Jones, D. (2024). Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to multidose vaccination regimens or no vaccination: An updated systematic review of evidence from clinical trials. Vaccine: X, 100486.

[29] Sankaranarayanan, R., Joshi, S., Muwonge, R., Esmy, P. O., Basu, P., Prabhu, P., ... & Indian HPV vaccine study group. (2018). Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. Vaccine, 36(32), 4783-4791

[30] Basu, P., Malvi, S. G., Joshi, S., Bhatla, N., Muwonge, R., Lucas, E., ... & Sankaranarayanan, R. (2021). Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. The Lancet Oncology, 22(11), 1518-1529

high HPV 16 and 18 antibodies. Overall, All the studies concluded that a single dose of the HPV vaccine regimen is as efficacious and immunogenic as two or three doses schedule.[31]

3.3 Cost-effectiveness, Economic and Operational considerations of introducing single dose schedule in routine program

A modeling study including 188 countries in different scenarios reported that one-dose of the vaccine providing lifelong protection at 80% vaccine efficacy (over 30 years) would prevent an estimate of 147.8 million of cervical cancer cases. If higher coverage can be achieved with and protection is a longstanding protection , the one-dose HPV vaccination schedule would resulted in cost-savings compared to no vaccination and could be cost-effective compared to two-dose vaccination.[32] If higher coverage can be achieved with and protection is a longstanding protection, the one-dose HPV vaccination schedule would resulted in cost-savings compared to no vaccination and could be cost-effective compared to two-dose vaccination.[33]

Studies conducted in countries with similar programmatic environment as Rwanda, have shown significant monetary savings with a single dose scheme compared to two dose strategy. In Tanzania, using the World Health Organization's (WHO) Cervical Cancer Prevention and Control Costing (C4P) micro-costing tool, financial and economic costs of the national HPV vaccination program were estimated. The study found that the financial costs per dose and per Fully Immunized Girl (FIG) would be $2.51 in one dose scenario compared to $5.17 for two doses. The economic cost was estimated at $12.18 compared to $23.34 in two doses scenario. The one dose schedule results in a reduction of 51 % and 48 % in financial and economic costs respectively. Large reductions are observed in costs to vaccine and injection supplies (-57 %), service delivery (-56 %), and cold chain (-25 %).[34]

[31] Watson-Jones, D., Changalucha, J., Whitworth, H., Pinto, L., Mutani, P., Indangasi, J., ... & Baisley, K. (2022). Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial. The Lancet Global Health, 10(10), e1473-e1484.

[32] Prem, K., Choi, Y. H., Bénard, É., Burger, E. A., Hadley, L., Laprise, J. F., ... & Jit, M. (2023). Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. BMC medicine, 21(1), 313.

[33] Burger, E. A., Campos, N. G., Sy, S., Regan, C., & Kim, J. J. (2018). Health and economic benefits of single-dose HPV vaccination in a Gavi-eligible country. Vaccine, 36(32), 4823-4829.

[34] Hsiao, A., Struckmann, V., Stephani, V., Mmbando, D., Changalucha, J., Baisley, K., ... & Quentin, W. (2023). Costs of delivering human papillomavirus vaccination using a one-or two-dose strategy in Tanzania. Vaccine, 41(2), 372-379.

Acceptability studies reported preferences of fewer doses among providers, mothers, and adolescent girls, as it would reduce the clinic visits and injection pains.[35]

However, there There is currently no study conducted done in Rwandan settings, to demonstrate the economic gains from a single dose of HPV vaccination schedule compared to two doses. Given Considering that, Rwanda the country has already introduced HPV vaccine since 2011 in the routine program with a two dose schedule, it is obvious that the switching from two to one dose schedule would significantly will remarkably reduce the cost related to the vaccine and supplies, service delivery, cold chain and waste management. The cost-saving from one-dose strategy could be used to address disparities by making more vaccine doses available and increasing vaccine delivery capacity to better serve hard-to-reach groups of girls[36]

As part of the process that the country has undertaken to introduce the HPV single dose schedule in the routine vaccination programme, the economic impact and the operational change implications of the new schedule must be carefully appraised, determining the new overall cost and the incremental cost, looking at the short and long term. This is critical to ensure acceptability by the decision makers and the potential partners and the long-term sustainability of the program.

3.4 Vaccine characteristics, logistic, handling and administration

The quadrivalent HPV vaccine (Gardasil) is currently used in Rwanda, and the same product will be used for the single dose. The vaccine is packed in one dose vial, the cold chain requirements, and administration methods are not different from the two doses regimen vaccines.

4. CONCLUSION AND RECOMMENDATION

In conclusion, Human Papilloma Virus infection is the most common sexual transmissible infection with some of the strains leading to cervical cancer, particularly HPV type 16 and HPV type 18. Vaccinating adolescent girls at an early age is critical for controlling and eliminating cervical cancer. Rwanda introduced HPV vaccination in 2011 using school-based vaccination strategy. A two dose vaccine schedule was adopted for girls in primary six, where most of the adolescent are 12 years old. However, achieving high coverage for the second dose has been challenging, as tracing defaulters is complicated given that girls move to schools different from their primary locations after primary six. The delivery of two doses of HPV vaccine has been affected by factors such as COVID-19, change in school exam calendars among others. Studies

[35] Islam, J. Y., Hoyt, A. M., Ramos, S., Morgan, K., Kim, C. J., de Sanjose, S., ... & Smith, J. S. (2018). Acceptability of two- versus three-dose human papillomavirus vaccination schedule among providers and mothers of adolescent girls: a mixed-methods study in five countries. Cancer Causes & Control, 29, 1115-1130

[36] World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. 2020. https://www.who.int/publications/i/item/9789240014107

have demonstrated the efficacy and cost-effectiveness of HPV single dose, and showed that adolescent, caregivers, and health providers would prefer reduced number of the doses, as long as it is efficacious.

The economic cost for introducing HPV single dose in the routine program, is significantly reduced while the programmatic process are facilitated and prone to yield a higher coverage compared to the current program based on a two dose schedule.

Based on the evidence above, Rwanda NITAG recommends the following actions:

1. Switch from HPV two dose to one dose vaccine schedule to increase efficiency in HPV vaccine delivery and enhance HPV vaccine coverage
2. Enhance risk communication and community engagement activities to increase demand for HPV vaccination
3. Establish mechanisms to trace and vaccinate defaulters and adolescent girls who drop from school
4. Plan and implement HPV vaccination catch up to reach missed adolescent girls less than 20 years old.
5. Design and implement operational research to assess the cost-effectiveness of HPV single dose.

Implementing these recommendations will contribute to the control and elimination of cervical cancer in Rwanda by optimizing HPV vaccine delivery, increasing coverage, and improving program sustainability.

Appendix2: Recommendation framework

EVIDENCE TO RECOMMENDATION FRAMEWORK
Question: Should Rwanda switch from HPV two doses to single dose? **Population:** 12 years and above **Intervention:** One dose of HPV **Comparison:** Two or more HPV doses **Outcome:** Efficacy and effectiveness of HPV single dose
Background Human Papilloma virus (HPV) ranks among the most common sexually transmitted infections. About 15 strains of HPV are associated with cervical cancer. An estimate 10% to 20% of infections among women persist and cause nearly 100% of cervical cancers. Cervical cancer is the most frequently diagnosed cancer and the fourth leading cause of cancer death in women globally. The HPV vaccines include the quadrivalent and bivalent HPV vaccines which were licensed in 2006 and 2007 respectively. The nonavalent HPV vaccine, licensed in 2014, targets other five types most commonly responsible for cervical cancer including HPV 31/33/45/52/58 in addition to the four HPV types covered by the quadrivalent HPV vaccine.[37] The quadrivalent HPV vaccine was introduced in Rwanda in 2011. As of 2023, 1,597,821 adolescent girls had received two doses of HPV vaccine. From 2013 to 2020, the prevalence of HPV types 6, 11, 16, and 18 decreased by 69% (from 13% to 4%) among women aged 17–23 years who had completed at least 6 years of school, where vaccine coverage was 63% (median age at vaccination of 14 years). [38] In the framework of improving efficiency in HPV delivery, the Ministry of Health requested the Rwanda National Immunization Technical Advisory Group (Rwanda NITAG) to review relevant evidence and advise on the switch from two doses to single dose schedule of HPV in Rwanda.

[37] Kim, J., Choe, Y. J., Park, J., Cho, J., Cheong, C., Oh, J. K., ... & Yu, S. Y. (2024). Comparative Effects of Bivalent, Quadrivalent, and Nonavalent Human Papillomavirus Vaccines in The Prevention of Genotype-Specific Infection: A Systematic Review and Network Meta-Analysis. Infection & Chemotherapy, 56(1), 37.

[38] Sayinzoga, F., Tenet, V., Heideman, D. A., Sibomana, H., Umulisa, M. C., Franceschi, S., ... & Baussano, I. (2023). Human papillomavirus vaccine effect against human papillomavirus infection in Rwanda: evidence from repeated cross-sectional cervical-cell-based surveys. The Lancet Global Health.

Element	Specific data	Evidence	Ranking	Additional information
1. Disease	Epidemiology of HPV	Globally, the prevalence of HPV infection is estimated at 11.7%, with the highest prevalence observed in Southern Africa and Caribbean. Sub-Saharan Africa countries reported the high burden with a pooled prevalence of 34%.[39] In Rwanda, the overall prevalence of HPV infection was estimated at 34%. Both HPV16 and 18 represented 7% of all high-risk HPV with HPV 16 being the most prevalent type in women. HPV 16 and 18 are responsible of approximately 71% of cervical cancer cases and the quadrivalent HPV vaccine on top of these strains, also targets HPV types 6 and 11 associated with 90% of cases of genital warts worldwide. [40] Globally, 660,000 cervical cancer cases and 350,000 deaths were reported in 2022, with the highest rates of incidence and mortality reported from Sub-Saharan Africa (SSA), Central America and South-East Asia. The increase of age-specific incidence rate of cervical cancer begins after the age of 25 years, and	**Critical**	The prevalence of pre-cancer and invasive cervical cancer was 5.9% (95% CI 4.5, 7.5) and 1.7% (95% CI 0.9, 2.5), respectively. Risk factors associated with cervical cancer in multivariate analysis included initiation of sexual activity at less than 20 years (OR=1.75; 95% CI=(1.01, 3.03); being unmarried (single, divorced and widowed) (OR=3.29; 95% CI=(1.26, 8.60)); Older age of participants (OR= 0.52; 95% CI= (0.28, 0.97)), older age at the first pregnancy (OR=2.10; 95% CI=(1.20, 3.67) and higher number of children born (OR=0.42; 95%CI =(0.23, 0.76)) were protective[44] In Rwanda, 1229 new cases cervical cancer and 829 deaths were reported in 2023, and cervical cancer is ranked at the first position in women.

[39] Scott-Wittenborn, N., & Fakhry, C. (2021, October). Epidemiology of HPV related malignancies. In Seminars in radiation oncology (Vol. 31, No. 4, pp. 286-296). WB Saunders

[40] Ngabo, F., Franceschi, S., Baussano, I., Umulisa, M. C., Snijders, P. J., Uyterlinde, A. M., ... & Clifford, G. M. (2016). Human papillomavirus infection in Rwanda at the moment of implementation of a national HPV vaccination programme. BMC infectious diseases, 16, 1-10.

[44] Makuza, J. D., Nsanzimana, S., Muhimpundu, M. A., Pace, L. E., Ntaganira, J., & Riedel, D. J. (2015). Prevalence and risk factors for cervical cancer and pre-cancerous lesions in Rwanda. Pan African Medical Journal, 22(1).

		the average age at death was 59 years, ranging from 45 to 76 years.[41] The age-standardized incidence rate of cervical cancer in Rwanda, was estimated at 28.2/100,000 in 2020. [42] The introduction of HPV vaccine is recommended for the control of HPV infection and one of the key strategies for cervical cancer elimination.[43]		
1. Vaccine Safety and efficacy	Type, consequences and frequency of short and long-term adverse events following vaccination	Reports on Adverse Events (AEs) following quadrivalent HPV doses were monitored by the Australia's national regulator, the Therapeutic Goods Administration, from April 2007 and December 2017. Age and sex-specific rates, using denominator data from the national HPV vaccination register, were determined. Pre-specified AESI were identified using Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms and examined in detail. The findings from the document 4551 AE reports and the crude reporting rate of 39.8 per 100 000 doses. The reported rate of syncope in 12 to 13-year-old males and females was 29.6 per 100 000 doses during enhanced surveillance and 7.1 per 100	**Critical**	Data from immunogenicity trials, post-hoc analyses of efficacy trials, and post-licensure observational studies among females have demonstrated that a single dose of HPV vaccine is sufficient to elicit an immune response that provides similar protection as a multidose regimen against initial and persistent HPV infection. These data include results from a high quality RCT80 in which 2250 sexually active 15–20-year-old females were

[41] Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 74(3), 229-263.

[42] Bangura, M. S., Zhao, Y., Gonzalez Mendez, M. J., Wang, Y., Didier Sama, S., Xu, K., ... & Qiao, Y. L. (2022). Case study of cervical cancer prevention in two sub-Saharan African countries: Rwanda and Sierra Leone. Frontiers in Medicine, 9, 928685.

[43] World Health Organization. (2020). Global strategy to accelerate the elimination of cervical cancer as a public health problem. World Health Organization.

		000 doses during the remaining study period; rates of syncope were higher in younger compared to older adolescents. The rate of anaphylaxis (0.32 per 100 000 doses) was consistent with published rates. Other AESI including autoimmune disease, postural orthostatic tachycardia syndrome, primary ovarian insufficiency, Guillain-Barré syndrome, complex regional pain syndrome and venous thromboembolism, were reported at low rates and analysis did not reveal unexpected patterns that would suggest causal association. The Analysis of this large, longitudinal dataset in a country with high vaccine uptake, including a period of enhanced surveillance, affirms the safety profile of quadrivalent HPV.[45] A systematic review and meta-analysis evaluated post licensure safety studies related to HPV vaccination and autoimmune adverse events from inception to April 16, 2019. The meta-analysis was conducted on 35 diseases corresponding to 48 pooled risk estimates. Majority of the pooled estimates showed no significant effect (n = 43). Three negative (paralysis, immune thrombocytopenia purpura and chronic fatigue syndrome) and 2 positive (Hashimoto		randomized to receive either bivalent (Cervarix) or nonavalent (Gardasil-9) vaccine or to a control group. At 24 months postvaccination, over 97.5% of participants in all dose groups for both vaccines were seropositive. Immunobridging showed that a single dose of HPV16/18 produced antibody responses that were non-inferior to those in studies where single-dose efficacy was observed.[47]

[45] Phillips, A., Hickie, M., Totterdell, J., Brotherton, J., Dey, A., Hill, R., ... & Macartney, K. (2020). Adverse events following HPV vaccination: 11 years of surveillance in Australia. Vaccine, 38(38), 6038-6046.

[47] World Health Organization. (2022). Human papillomavirus vaccines: WHO position paper (2022 update)–Vaccins contre les papillomavirus humains: note de synthèse de l'OMS (mise à jour de 2022). Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire, 97(50), 645-672.

		and Raynaud diseases) associations were detected. The review reported an absence of clear association between HPV vaccines and autoimmune and other rare diseases.[46]		
	Risk groups or risk factors for adverse events	A cohort study was done in Korea and involved 441 399 girls aged 11-14 years who had been vaccinated in 2017including 382 020 who received HPV vaccine and 59 379 who received vaccinated other vaccines. In total, 33 predefined serious adverse events were assessed. No evidence was found to support an association between HPV vaccination and serious adverse events using both cohort analysis and self-controlled risk interval analysis and no associations were found with HPV vaccination in the cohort analysis.[48]	**Important**	The WHO's Global Advisory Committee on Vaccine Safety (GACVS) frequently reviews the safety of HPV vaccine, based on the available data. The committee has concluded that the benefit-risk profile remains favourable.[49]
	Contraindications	The quadrivalent HPV vaccine is produced in a yeast-based (Saccharomyces cerevisiae) system and use of this vaccine is contraindicated in persons with a history of immediate hypersensitivity to yeast. Overall, the evidence from post-licensure surveillance suggests that anaphylaxis and serious allergic reactions following HPV vaccination are rare and manageable, consistent with that found for other	**Important**	The use of Gardasil® is contraindicated in those individuals who have known hypersensitivity to any active component or excipient of the vaccine, including yeast. Individuals who develop hypersensitivity reactions after receiving a dose of Gardasil®

[46] Willame, C., Gadroen, K., Bramer, W., Weibel, D., & Sturkenboom, M. (2020). Systematic review and meta-analysis of postlicensure observational studies on human papillomavirus vaccination and autoimmune and other rare adverse events. The Pediatric infectious disease journal, 39(4), 287-293

[48] Yoon, D., Lee, J. H., Lee, H., & Shin, J. Y. (2021). Association between human papillomavirus vaccination and serious adverse events in South Korean adolescent girls: nationwide cohort study. Bmj, 372

[49] World Health Organization. (2019). Global Advisory Committee on Vaccine Safety, 5–6 June 2019–Comité consultatif mondial pour la sécurité des vaccins, 5-6 juin 2019. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire, 94(28), 309-316.

		vaccines. In two retrospective cohort studies in females from Australia, only a proportion of those reported as 'suspected' anaphylaxis cases were classified as anaphylaxis on clinical review, and even fewer (1/19) were found to have probable hypersensitivity after skin prick. Most of girls with a history of suspected anaphylaxis who were re-vaccinated under close medical observation had no subsequent adverse reactions.[50]		should not receive any further doses of the vaccine. As with other intramuscular vaccines, Gardasil® should not be administered to individuals with bleeding disorders (e.g., hemophilia or thrombocytopenia) or patients on anticoagulant therapy unless the benefits outweigh the risk for hematoma.
	Immunogenicity and effectiveness of HPV Single Dose	The efficacy of three doses, two doses and single dose of Quadrivalent HPV vaccine was tested among girls aged 10 t0 18 years old in India. The study involved 4348 participants who had three doses, 4980 had two doses (0 and 6 months), and 4949 had a single dose. Vaccine efficacy against persistent HPV 16 and 18 infections among participants evaluable for the endpoint was 95·4% (95% CI 85·0–99·9) in the single-dose default cohort (2135 women assessed), 93·1% (77·3–99·8) in the two-dose cohort (1452 women assessed), and 93·3% (77·5–99·7) in three-dose recipients (1460 women assessed). [51]	**Critical**	HPV vaccine was introduced in 2011, and the target population is 12 years old girls in Rwanda, vaccinated using quadrivalent HPV vaccine (Gardasil). Effectiveness study evaluated the In December 2020. The study found that HPV6, 11, 16, and 18 in HPV decreased from 12% (173 of 1501) among women aged 17–29 years baseline survey to 5% (crude reduction of 53%, (95% CI 40–63).[53]

[50] Macartney, K. K., Chiu, C., Georgousakis, M., & Brotherton, J. M. (2013). Safety of human papillomavirus vaccines: a review. Drug safety, 36, 393-412.

[51] Basu, P., Malvi, S. G., Joshi, S., Bhatla, N., Muwonge, R., Lucas, E., ... & Sankaranarayanan, R. (2021). Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. The Lancet Oncology, 22(11), 1518-1529.

[53] Sayinzoga, F., Tenet, V., Heideman, D. A., Sibomana, H., Umulisa, M. C., Franceschi, S., ... & Baussano, I. (2023). Human papillomavirus vaccine effect against human papillomavirus infection in Rwanda: evidence from repeated cross-sectional cervical-cell-based surveys. The Lancet Global Health, 11(7), e1096-e1104.

		Clinical trials evidenced that single dose of bivalent and nanovalent HPV vaccines where vaccines were each highly effective in preventing incident persistent oncogenic HPV infection, similar to multidose regimens. A randomized, multicenter, double-blind, controlled trial of single dose nonavalent (HPV 16/18/31/33/45/52/58/6/11 infection) or bivalent (HPV 16/18 infection) HPV vaccination compared with meningococcal vaccination among Kenyan women 15 to 20 years of age. Overall, 2275 women were randomly assigned and followed. A total of 758 participants received the nonavalent HPV vaccine, 760 received the bivalent HPV vaccine, and 757 received the meningococcal vaccine; retention was 98%. Thirty-eight incident persistent infections were detected in the HPV 16/18 modified intent-to-treat (mITT) cohort: one each among participants assigned to the bivalent and nonavalent groups and 36 among those assigned to the meningococcal group. Nonavalent vaccine efficacy (VE) was 97.5% (95% confidence interval [CI], 81.7 to 99.7%; P≤0.0001), and bivalent VE was 97.5% (95% CI, 81.6 to 99.7%; P≤0.0001). Thirty-three incident persistent infections were detected in the HPV 16/18/31/33/45/52/58 mITT cohort: four in the nonavalent group and 29 in the meningococcal group. Nonavalent VE for HPV		It should be stressed that completing the dosing schedule of Gardasil® may not confer total immunity in some vaccine recipients and will not provide protection for diseases caused by HPV types other than 6, 11, 16, and 18. Individuals, also who have reduced immune function such as genetic disorder or HIV, or are on immunosuppressive therapy may not sufficiently mount an immune response to the vaccine.[54]

[54] Anderson, J. Prophylaxis Against Human Papillomavirus Infections with Gardasil® Vaccine

		16/18/31/33/45/52/58 was 88.9% (95% CI, 68.5 to 96.1; P<0.0001). The rate of serious adverse events was 4.5% to 5.2% by group. [52]		
3. Economic and operational considerations	Direct and indirect costs to procure, store, distribute and administer the vaccine	Evidence on monetary saving with a single dose compared with the two doses schedules was documented in similar programmatic environment as Rwanda. Using the World Health Organization's (WHO) Cervical Cancer Prevention and Control Costing (C4P) micro-costing tool, financial and economic costs of the national HPV vaccination program were estimated in Tanzania in 2022. The study found that the financial costs per dose and per Fully Immunized Girl (FIG) would be $2.51 in one dose scenario compared to $5.17 for two doses. The economic cost was estimated at $12.18 compared to $23.34 in two doses scenario. The one dose schedule results in a reduction of 51 % and 48 % in financial and economic costs respectively. Large reductions are observed in costs to vaccine and injection supplies (-57 %), service delivery (-56 %), and cold chain (-25 %).[55]	**Very important**	There is no study done in Rwandan settings, to demonstrate the economic gains from a single dose of HPV vaccination schedule compared to two doses. Considering that, the country has already introduced HPV vaccine since 2011 in the routine program with a two dose schedule, it is obvious that the switch from two to one dose will remarkably reduce the cost related to the vaccine and supplies, service delivery, cold chain and waste management. The cost-saving from one-dose strategy could be used to address disparities by making more vaccine doses available and increasing vaccine delivery capacity to better serve hard-to-reach groups of girls

[52] Barnabas, R. V., Brown, E. R., Onono, M. A., Bukusi, E. A., Njoroge, B., Winer, R. L., ... & Mugo, N. (2022). Efficacy of single-dose human papillomavirus vaccination among young African women. NEJM evidence, 1(5), EVIDoa2100056.

[55] Hsiao, A., Struckmann, V., Stephani, V., Mmbando, D., Changalucha, J., Baisley, K., ... & Quentin, W. (2023). Costs of delivering human papillomavirus vaccination using a one-or two-dose strategy in Tanzania. Vaccine, 41(2), 372-379.

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