Leveraging Single-Dose HPV Vaccination to Accelerate Cervical Cancer Elimination: Acceptability, Cost-Effectiveness, and Policy Considerations for Single-Dose Adoption in East Africa

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Abstract

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Every two minutes, a woman dies of cervical cancer, a disease that is highly preventable. Human papillomavirus (HPV) vaccines protect against high-risk HPV infections, which cause cervical cancer, but only 15% of eligible girls have been vaccinated globally. HPV vaccination uptake remains particularly low in low- and middle-income countries (LMICs) where most cervical cancer-related deaths occur. In 2020, the World Health Assembly (WHA) adopted a global strategy to eliminate cervical cancer that focused on three pillars to be achieved by 2030. These targets include having 90% of girls fully vaccinated with the HPV vaccine by age 15. Recent evidence on

the efficacy and effectiveness of a single-dose HPV vaccination led the World Health Organization (WHO) to recommend countries to consider a single-dose HPV vaccination schedule to improve coverage and catalyze progress towards achieving cervical cancer elimination. This dissertation sought to comprehensively assess implementation outcomes of single-dose HPV vaccination, focusing on acceptability, cost-effectiveness of single-dose HPV vaccination in Kenya, and policy considerations for single-dose HPV vaccination adoption in East Africa.

Using a mixed-methods study approach, we assessed the acceptability of a single-dose HPV vaccination schedule among healthcare providers (HCPs) in Kenya. We found that most HCPs thought that a single-dose schedule was acceptable, and the lack of information among HCPs was the main reason for disapproval. Additionally, HCPs based at rural facilities had higher acceptability likelihood compared to those based at urban facilities.

In chapter 3, we conducted a cost-effectiveness analysis to assess the potential health and economic impact of a single-dose HPV vaccination schedule in Kenya. We found that a two-dose HPV vaccination strategy at 90% coverage had a higher incremental cost-effectiveness ratio (ICER) compared to a one-dose strategy at the same coverage level (US$ $6,508.08/ DALY averted vs US$ $ 197.44/ DALY averted). Additionally, switching to a single-dose schedule would result in US$ $21.4 million in savings over five years, which could fund 2.75 million additional HPV vaccinations. This re-investment could fund catch-up vaccinations, and the greatest DALYs would be averted by supplementing a single-dose strategy with a 90% coverage with a catch-up vaccination for 11- 24-year-old girls (ICER: US$ $ 78.73 / DALY averted).

Finally, in chapter 4, we leveraged a rapid review to conduct a framework policy analysis on single-dose HPV vaccination adoption in three East African countries. We found that in Ethiopia, Uganda, and Tanzania, political will was crucial to prioritizing the revision of HPV vaccination policy, and

National Immunization Technical Advisory Groups (NITAGs) were central to the single-dose decision-making process. Additionally, across the three countries, the WHO endorsement and availability of key evidence on the burden of the disease, health, and economic benefits of a single-dose schedule played an important role in the policy revision process.

In conclusion, single-dose HPV vaccination has the potential to accelerate progress in cervical cancer elimination. Considering its acceptability even among HCPs in rural areas, potential health and economic benefits, a single-dose schedule could simplify logistics and inform policy revisions to improve coverage in Kenya and comparable settings. These findings also have the potential to inform future immunization policy revision initiatives.

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Chapter 1. Introduction

Cervical cancer is the fourth leading cause of death among women and most cases and deaths occur in low-and-middle income countries (LMICs). (1,2) Fortunately, human papillomavirus (HPV) vaccines are safe and efficacious in prevent high-risk HPV infections that lead to cervical cancer. This led the World Health Organization (WHO) to make HPV vaccination one of the pillars of its Global Cervical Cancer Elimination Strategy, but HPV coverage remains low in many LMICs. HPV vaccines were first licensed to use in a 3-dose vaccination schedule but a 2-dose schedule was proven to be effective and a recent trial showed that a single-dose of the HPV nonavalent or bivalent vaccine was 97.5 % efficacious (95% CI: 82 – 100) in preventing high-risk HPV infections (HPV16/18) among sexually active young Kenyan adolescent and women aged 15-20 years. (3) Similar results on the efficacy and effectiveness of the single-dose HPV vaccination were also reported in Tanzania, Costa Rica, India and Scotland. (4–8) These strong evidence on the health and economic benefit of the single-dose HPV resulted in the 2022 World Health Organization (WHO)'s recommendation for countries to leverage a single-dose schedule to reach the greatest number of adolescent girls and young women (AGYW). (9–14) To date, HPV vaccination have been introduced into national immunization program in only 146 countries. (15) In Sub-Saharan Africa (SSA) particularly, where HPV vaccination coverage remains low, countries have recorded high cervical cancer prevalence and mortality rates. In this setting, limited data are available on HPV vaccination implementation outcomes, a knowledge gap that complicates the designing and implementation of efficient strategies to improve HPV vaccination coverage.

In settings where HPV vaccination has been introduced into national immunization programs, delivery strategies have included school-based, facility-based, outreaches or mixed strategies. Existing evidence have shown that the cost of HPV vaccination delivery for adolescents is higher than the cost of immunization for infants. (16,17) Reason for this difference in operational

costs include the fact that HPV vaccination are delivered mainly to adolescents outside traditional immunization settings to achieve high coverage while infant immunization programs have lower operational costs since they deliver multiple vaccines targeting different pathogens at health facilities. (16) Furthermore, the cost of HPV vaccination delivery varies between settings depending on the delivery strategy used, characteristics of the setting and other factors (GAVI eligibility, etc). (16) By December 2024, only 19 SSA countries had adopted a single-dose HPV vaccination schedule following the 2022 WHO recommendation.(15) The field of implementation science (IS) has the potential to catalyze the systematic uptake of evidence-based practices (EBPs) into routine practice to improve the quality and effectiveness of health services. (18) While this field presents tremendous potential to improve public health practices and health outcomes, its application is still limited in LMICs. Beyond evidence generated from multiple-countries and global analyses, it is important for decision-makers to be equipped with findings on implementation outcomes specific to their setting to inform policy revision initiatives. This evidence is especially crucial for LMICs where there are competing priorities, and limited resources.

In Kenya, HPV vaccination was introduced in 2019 as a two-dose schedule targeting 10-year-old adolescent girls. In this setting, HPV vaccination is delivered at health facilities with communication and social mobilization interventions carried out in schools and the community (19,20). The suboptimal coverage in Kenya were reflected in data from 2020 where only a third of the targeted population had received the first dose and only 16% had received their second dose. Considering the potential of single-dose HPV vaccination to improve vaccination coverage and accelerate the attainment of cervical cancer elimination goals, this dissertation aimed to generate

evidence on implementation outcomes (acceptability and cost-effectiveness of single-dose) in Kenya, and policy considerations for single-dose adoption in East Africa.

In chapter 2, we assessed the acceptability of the single-dose schedule among healthcare providers (HCPs) in Kenya. Healthcare providers (HCPs) or healthcare workers (HCWs) play an important role as communicators and enablers of immunization. A systematic review of studies on the knowledge, awareness of the HPV vaccine and acceptability to get vaccinated in sub-Saharan Africa (SSA) reported that in South Africa, 46% of women (18-44 years) were more likely to get vaccinated based on their HCPs' recommendation. This was rated higher (more important) than effectiveness or cost of the vaccine. (21) Similar findings were reported among adults who had children aged 12-14 years and were seeking care at the Kenyatta National Hospital. (22) Additionally, systematic review on HCPs' perception of HPV vaccination reported that HCPs' recommendation had a considerable impact on patients' uptake across vaccines and populations. (23) While the field of IS has the potential to improve the uptake of EBPs, most implementation science theories and frameworks remain untested in LMICs. (24) To address these gaps and generate evidence to inform HPV vaccine delivery, in this chapter, we contributed to this body research by assessing the operationalization of an acceptability framework in the context of HPV vaccination in Kenya, evaluating the acceptability and predictors of acceptability of the single-dose HPV vaccination schedule among HCPs in Kenya.

A recent cost-effectiveness analysis, estimated the long-term health benefit and cost effectiveness of one-dose compared to two-dose HPV vaccination in 188 countries (12). This study reported that a one-dose schedule at 80% global coverage would provide a high level of population protection and be cost-effective. Additionally, this study highlighted that a one-dose schedule would accelerate high uptake across countries which would translate into significant public health

impact globally. Similar findings were reported by analyses from different LMICs, emphasizing the health and economic benefit of a single-dose HPV vaccination compared to a two-dose schedule. (10,25,26) In Kenya specifically, the most recent cost-effectiveness analysis assessed the impact of introducing the HPV vaccine for 10-year-old girls in Kenya focusing on the cost-effectiveness of bivalent and quadrivalent HPV vaccines. (27) In the mist of competing priorities and changing donor support, national HPV vaccination programs and especially those in LMICs need costing, cost-effectiveness, and budget impact evidence to inform their decision. Hence, in chapter 3 we conducted a cost-effectiveness to assess the potential health and economic impact of switching to a single-dose HPV vaccination schedule in Kenya. Considering the uncertainty over the duration of the single-dose vaccination beyond the 16 years reported by the Costa Rica HPV vaccine Trial, we sought to assess the potential waning of one-dose efficacy on health and economic outcomes.(5,28) Lastly, we assessed the potential health and economic impact of using five-year cost-savings of switching to a one-dose schedule to supplement vaccination for girls by age 10 with catch-up vaccination for multi-age cohorts (MAC) of girls and young women or vaccinate all 10-year-olds (vaccination for all).

Finally, in chapter 4, we performed a framework policy analysis to assess “the how” of policy revision on HPV vaccination in East Africa. We leveraged a policy framework to unpack what, who and how single-dose schedule was adopted in Ethiopia, Uganda and Tanzania. Considering the value of cross-country lessons, we also compiled factors that contribute to a single-dose HPV vaccination adoption across countries.

Chapter 2. Acceptability of Single-dose HPV Vaccination Schedule Among Healthcare Providers in Kenya: A Mixed-Methods Study

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Acceptability of Single-dose HPV Vaccination Schedule Among Healthcare Providers in Kenya: A Mixed-Methods Study

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Abstract

Background

The World Health Organization recommends a single-dose HPV vaccine schedule for girls and boys to accelerate progress towards cervical cancer elimination. We operationalized the Theoretical Framework of Acceptability (TFA) within the context of HPV vaccination to assess the acceptability of a single-dose schedule among healthcare providers (HCPs) in Kenya.

Methods

A REDCap survey was developed leveraging relevant TFA domains and validated with HCPs. Descriptive analyses and multivariate Poisson regression were conducted to assess factors associated with increased acceptability. Free text responses were analyzed using a rapid qualitative approach and findings were presented using a joint display.

Results

Among 385 responses, 74.2% of HCPs were female and 48.6% were nurses. On average, respondents had been in their position for 60 months, and a third (33.2%) were based at level 4 facilities. The majority (75.84%) thought that giving a single-dose of the HPV vaccine to adolescent girls and young women (AGYW) was either acceptable or very acceptable. Qualitative findings highlighted that lack of information among HCPs was the underlying reason for nonacceptance, and most HCPs thought that a single-dose schedule was less burdensome to providers and patients. Hospital directors had a non-statistically significant lower acceptability likelihood compared to nurses (IRR: 0.93; 95%CI: 0.45,1.71) and HCPs at urban facilities had a non-statistically significant lower acceptability likelihood compared to those in rural facilities (IRR:0.97; 95% CI: 0.83, 1.13).

Conclusion

While not statistically significant, predictors of increased acceptability provide information to tailor strategies to increase HPV vaccination coverage and accelerate progress toward cervical elimination.

Background

Cervical cancer (CC) is the fourth leading cause of death among women. Low- and middle-income countries (LMICs), where more than 85% of cervical cancer cases occur, are disproportionately impacted.(1,2,29) Human papillomavirus (HPV) infections are the primary cause of CC. HPV vaccines have high efficacy, preventing persistent HPV infections, a precursor for dysplastic lesions and CC.(30) Despite this, HPV vaccination coverage remains low in many LMICs including in Sub-Saharan Africa (SSA).(31,32) Health system challenges, stigma, fear of side effects, misinformation, and inadequate health education have been identified as barriers to HPV vaccination uptake in SSA.(33) In Kenya specifically, less than a third of girls aged 9-14 years had received one dose and only 16% had received 2 doses in 2020.(34) The strength of evidence for single-dose HPV vaccine effectiveness is substantial and irrefutable.(35) In a randomized trial in Kenya, single-dose of HPV vaccine was highly efficacious with a vaccine efficacy (VE) of 97.5% for the bivalent vaccine and 98.8% for the nonavalent vaccine to prevent incident persistent HPV 16/18 infection.(3,36,37) Similar results highlighting the efficacy of the single-dose of HPV vaccine in providing protection against persistent HPV 16 and 18 infections for more than a decade post vaccination were reported in other settings.(38,5,7,39) At population level, HPV vaccination of adolescent girls and young women (AGYW) conferred high protection against cervical cancer irrespective of the number of doses.(8) These findings supports the single-dose HPV vaccination schedule recommendations from the World Health Organization (WHO) to reach AGYW and accelerate progress towards cervical cancer elimination.(14) Evidence is needed to optimize HPV vaccination delivery approaches, especially in settings with low HPV vaccine coverage.

Healthcare providers (HCPs) play a vital role as communicators and enablers of immunization. A systematic review of studies on the knowledge, awareness of the HPV vaccine, and acceptability reported that in South Africa, 46% of women (18-44 years) were more likely to get vaccinated based on HCPs' recommendation. This was rated higher (more important) than effectiveness or cost.(21) Similar findings were highlighted in a recent study conducted among adults who had children aged 12-14 years and were seeking care at the Kenyatta National Hospital.(22) In this study, 86% of participants reported that doctor's recommendation was the main reason for their willingness to have their daughter vaccinated. Additionally, HCPs' perception and acceptability of HPV vaccination affect their recommendation regarding the vaccine which in turn impact vaccine uptake. HCPs who have vaccine confidence, driven by correct knowledge on the vaccine and the disease it prevents are more likely to recommend the vaccine to patients. HCPs' recommendations are known to have a considerable impact on patient uptake across vaccines and populations.(23) While the concept of acceptability has been defined differently in implementation research, these definitions are closely related to the definition of acceptability in the Theorical Framework of Acceptability (TFA).(40–44) The TFA has the advantage of allowing the assessment of the acceptability of an evidence-based intervention (EBI) before, during and after the delivery of the EBI.(40,43) Additionally, the TFA was developed leveraging both inductive (empirical) and deductive (theorical) approaches. Nevertheless, the TFA as several implementation research frameworks was informed by insights from high income countries (HICs). Most implementation science theories and frameworks remain untested in low-and-middle income countries (LMICs).(24) It is crucial to assess the relevance of implementation science frameworks in guiding implementation theories and frameworks for LMICs.

To address these gaps and generate evidence to inform HPV vaccine delivery, we assessed the operationalization of the TFA in the context of HPV vaccination in Kenya, evaluated the acceptability and predictors of acceptability of the single-dose HPV vaccination schedule among HCPs in Kenya.

Methods

This study was nested within the KEN SHE Study (ClinicalTrials.gov number NCT03675256). The KEN SHE Study is a randomized, multicenter, double-blind, three-arm, controlled trial that tested the efficacy of single-dose bivalent (HPV 16/18) and single-dose nonavalent (HPV 16/18/31/33/45/52/58/6/11) HPV vaccination among Kenyan women of 15 to 20 years of age.(36) The implementation science component of the KEN SHE study sought to generate insights on drivers of HPV vaccination and the acceptability of the single-dose schedule among healthcare providers (HCPs) in Kenya.(45)

Here, we share findings from our experience operationalizing the Theoretical Framework of Acceptability (TFA) in the context of HPV vaccination in Kenya to assess the relationship between different components of the TFA, assess the reported acceptability of the single-dose schedule among HCPs and predictors of acceptability among HCPs in Kenya.

Study design, sample size calculation, and participants

A concurrent mixed-methods approach was used to capture comprehensive insights to describe the perspective of HCPs and assess the acceptability of the single-dose schedule. A concurrent mixed-methods design prioritizes both qualitative and quantitative data equally, data on both components are collected concurrently, analyzed independently and results are mixed to interpret findings.(46,47) Targeted HCPs included nurses, clinical officers, pharmacists, pharmacy

technicians, medical officers, and other relevant HCPs. A sample size calculation was conducted focusing counties where KEN SHE study sites were based (Kiambu, Kisumu and Nairobi City).(45) Assuming that each health facility had at least one healthcare provider responsible for HPV vaccination with a total of 1,568 health facilities in the three KEN SHE counties (Kiambu: 364, Nairobi ~ 1,000, Kisumu ~200), we estimated the total number of healthcare providers responsible for HPV vaccination to be ~1,568. Thus, we estimated that responses were needed from at least 309 HCPs to be able to assess the acceptability of the single-dose schedule among HCPs with a 95% confidence interval that the real value is within ±5% of the survey results.

Implementation science framework and selection of appropriate constructs

To assess the acceptability of the single-dose HPV vaccination among HCPs, we leveraged the TFA to capture HCPs' insights on the acceptability of the single-dose schedule as well as other key aspects of acceptability relevant to single-dose HPV vaccination. To achieve this, we reviewed the TFA questionnaire to select and adapted ones that aligned with constructs and domains relevant to our topic and context (i.e. single-dose HPV vaccination in Kenya).(41) Additional information on this process is presented in the supplementary materials (Supplementary Methods 1).

Data collection and key study measures

Data were collected using a REDCap survey developed based on domains of the TFA relevant to the context of HPV vaccination in Kenya (Supplementary Methods 2).(48,40,41) Survey responses included qualitative data from free-text responses and quantitative data on participants' demographic characteristics, their perspectives on the acceptability of the single-dose schedule, and relevant TFA domains. The survey was validated by six HCPs and other KEN SHE research team members before being deployed. Given the structure of the healthcare system in

Kenya that has 6 levels from the community facilities (level 1) to national referral hospitals (level 6), we added an indicator to capture the level of the facility of respondents.(49,50) The survey was shared with HCPs via WhatsApp to facilitate the wide distribution of the survey among HCPs involved in HPV vaccine delivery at different levels of the healthcare system (urban vs rural, level 1 vs higher levels, etc.). Additional details on the study design and procedures has been described elsewhere.(45)

Analytic approach

Descriptive statics were generated to describe demographic characteristics of survey respondents as well as the distribution of response across counties. Chi-square tests for continuous variables and Kruskal-Wallis tests for categorical variables were used to assess the distribution of survey responses between the targeted counties. The distribution of key TFA items and the general acceptability was reported across the three counties and among all participants. Following previously published guidance on the analysis of TFA items; correlation analyses were performed to assess the relationship between 1) the reported general acceptability and scores of TFA items (relevant constructs of acceptability), and 2) the reported general acceptability and the total mean score of relevant TFA items (relevant constructs of acceptability).(41) Spearman correlation coefficients and p-values were reported. A multivariate regression analysis was conducted to assess the association between key TFA items and the reported general acceptability score.

Further, regression analyses were performed to describe factors associated with acceptability while accounting for confounding characteristics. The outcome of interest (reported general acceptability) was treated as a continuous variable. Factors associated with acceptability of the single-dose schedule that were examined include the county, geographic location of the facility (rural vs urban), level of the facility within the health system, job title (nurse vs pharmacist

vs clinical officer vs medical doctor vs other). Additionally, we adjusted for confounding characteristics including age, gender, religion, and duration at their job. Model selection analyses were run to assess the model assumptions and identify the best fitting model. The generalized linear model (glm) with log link function and family "poisson" was selected as the best fitting model. Incidence Rate Ratio (IRR) for the best fitting model and 95% Confidence Interval were reported. Quantitative analyses were performed in R-4.3.1.

For free text responses (qualitative data), a rapid qualitative approach was leveraged to identify themes that emerged from text responses.(51,52) An inductive approach was used by identifying codes emerging from responses and a deductive approach was used by identifying codes from the responses that were related to the TFA.(40) Codes were merged into broader themes that were paired with findings from the quantitative analysis to provide a comprehensive assessment of what providers thought about the single-dose strategy, how they learned about the single-dose schedule and factors that enable or impend their acceptability of a single-dose schedule of the HPV vaccination. Findings were presented using a joint display approach.

Ethics

This study was approved by the Kenya Medical Research Institute's (KEMRI) Scientific Ethics Review Unit, the Massachusetts General Hospital (MGH) and University of Washington (UW) institutional review boards. All participants underwent an informed consent process before completing the survey.

Results

Respondents' characteristics

Overall, five hundred and thirty-four responses from 35 counties were submitted to the REDCap survey. Since the survey was shared by Kenyan HCPs in different providers' WhatsApp groups, we could not estimate the response rate because we did not know the number of participants in these groups. Three hundred and eighty-five responses were included in the analysis after excluding duplicates (n=5), entries that did not have an answer for the general acceptability question (N=14), responses from non-HCPs respondents (drivers, data clerk, etc), and non-KEN SHE counties (n=130) (Figure 1). Among the 385 HCPs, 285 (74.2%) were women; 78.7% in Kiambu, 69% in Kisumu and 77.7% in Nairobi (Table 1). The median age was 32 years overall, but this was lower in Nairobi (28 years) (p-value= 0.004). Most respondents were Christian (97.1%) and 87.8% used a phone to complete the survey. The distribution of these characteristics was also consistent across counties.

Overall, most respondents were nurses (48.6%) or had other job titles (24.2%) such as community healthcare workers (CHWs), Community Health Volunteers (CHVs), and specialists such as pediatricians and Gynecologists. Other job titles included clinical officers (13.8%), medical officers (5.5%) and pharmacists (4.7%). Respondents had been in their job for an average of 60 months overall with a variation across counties where the lowest average duration of 36 months (~3 years) was reported among respondents from Nairobi. Additionally, referral levels where respondents were employed included level 4 facilities (33.2%), level 5 facilities (20.3%), and level 3 facilities (19.2%). This distribution differed across sites where in Kiambu 11.1% of respondents were based at health dispensaries (level 2) and in Nairobi where 14.6% were employed at level 6 facilities (p-value <0.05). Most respondents' facilities were in urban settings overall (75.8%) and this proportion varied across counties (92.2% in Nairobi, 78.7% in Kiambu and 64.4% in Kisumu) (Table 1).

Acceptability constructs and operationalization of the TFA

Overall, most HCPs reported that a single-dose HPV vaccination schedule for AGYW was acceptable (43.38%) or very acceptable (32.46%). Regarding domains of the TFA, in terms of burden, most HCPs thought that a single-dose schedule did not require a substantial effort (69.87%), a large amount of time (87.02%) or resources (77.41%). For ethicality, 32.38% of HCPs agreed or completely agreed that there were moral consequences to offering a single-dose schedule to AGYW while 83.07% of HCPs reported that giving a single-dose of HPV vaccination to AGYW was fair (Table 2). Most HCPs (89.29%) reported that the single-dose HPV vaccination schedule was effective in preventing cervical cancer, 86.94% were confident providing a single-dose schedule to AGYW while 23.75% of HCPs reported not having knowledge on the single-dose schedule for HPV vaccination. The distribution of responses on the general acceptability and relevant aspects of acceptability from the TFA were similar across the three counties (Supplementary Figures 1: a-f). Overall, free text responses highlighted that HCPs thought that the single-dose schedule was convenient, safe, effective, resource friendly and would result into increased uptake of HPV vaccination. Parental acceptability was reported as a major concern or "*the elephant in the house"* (Table 2). Some HCPs were misinformed since they thought that the HPV vaccine causes cancer, infertility and should not be given to AGYW. Other concerns reported related to the acceptability of the single-dose included their knowledge on the matter and ability to address concerns from AGYW or parents. Additionally, in terms of other key insights captured, 78.12% HCPs also reported that integrating the single-dose schedule within existing workflow would not require huge efforts, 89.52% were confident explaining benefits of HPV vaccination and 91.91% were confident addressing concerns on HPV vaccination from AGYW and their parents or guardians (Table 3). Free text responses underscored the gap in communication and

sensitization for HPV vaccination. This was raised in responses from HCPs who mentioned that: *there was no proper mobilization about HPV vaccines*; *they need more information and sensitization to the staff and parents* and they *need be able to explain the importance of vaccine to the guardian in local understandable language* and flagged that more training would equip them with appropriate skills (Table 3). Lastly, additional insight highlighted that despite many challenges that they thought might impend their ability to deliver the single-dose schedule, most HCPs consider the single-dose schedule to be *"a good thing to be implemented"* and the *"way forward."*

When assessing the relationship between the general acceptability measure and responses reported on relevant constructs of acceptability; all constructs had a weak or very weak correlation with the general acceptability measure. The resource and moral consequence constructs had a very weak negative correlation with the reported acceptability, spearman correlation coefficient of -0.007 and -0.056 respectively but these relationships were not statistically significant. On the other side, the fairness and effectiveness constructs had a positive correlation with acceptability with a Spearman correlation coefficient of 0.24 and 0.14 respectively (P value <0.05) (Table 4). When assessing the relationship between the reported general acceptability and the acceptability measurement calculated by getting an average of relevant constructs, the new acceptability scores were weakly correlated with the reported general acceptability and this relationship was statistically significant for the acceptability scores that was calculated including fairness as one of their constructs (Table 5 and Supplementary Table 1). When assessing the association between the constructs of acceptability with the general acceptability measure, most constructs were found to be weak predictors of acceptability except for the fairness construct (Beta: 0.23, 95% CI: 0.1, 0.36, p-value <0.001) (Supplementary Table 2). Lastly, all relevant constructs of acceptability remained

weakly correlated with the general acceptability measure when these variables were treated as categorical variables (Supplementary Table 3).

Model Selection

While the outputs from the multivariate logistics regression showed that no statistically significant association between characteristics of HCPs and the acceptability of the single-dose schedule, the linear multivariate model showed that other cadres had 0.37 higher acceptability (as a unit of the acceptability score) compared to nurses (95% CI: 0.01, 0.73; p-value =0.044) (Supplementary Table 4). When assessing the combined effect of the referral level and county as well as the job title and duration on the acceptability of the single-dose schedule, referral level had a linear, quadratic, and cubic effect on the acceptability of the single-dose where this effect resulted in an increased acceptability across referral levels in the linear and cubic trend (Supplementary Table 5). Additionally, outputs from this model revealed that HCPs from Nairobi had 0.43 lower acceptability of the single-dose schedule compared to those in Kiambu (95%CI: -0.84, -0.02; p-value=0.039).

To assess the linearity assumption of the multivariate linear regression model with and without interactions, we assessed the distribution of residuals compared to predicted values and found that residuals seemed to follow a pattern and were not random in nature. Thus, a logistic regression model was more appropriate for our data (Supplementary Table 6). Additionally, the Akaike Information (AIC) also revealed that the multivariate regression without interaction was indeed the best fitting model and most appropriate for our data (Supplementary Figure 2). Lastly, we assessed the possible effect of fairness on the acceptability of single-dose and found that while increased score of fairness was statistically significantly associated with higher acceptability of the single-dose schedule among HCPs, this variable had influence on the effect of HCPs'

characteristics on the acceptability of the single-dose schedule (Supplementary Figure 3). Based on these results, we reported findings from the simplest logistic regression (no interaction or constructs of acceptability added) to estimate the association between HCPs' characteristics and the acceptability of the single-dose HPV vaccination schedule.

Determinants of acceptability

When assessing the association between characteristics of HCPs and their acceptability of the single-dose schedule; while controlling for other factors we found that the acceptability was 1% higher among female HCPs compared to male HCPs (IRR: 1.01, 95% CI: 0.89, 1.16) and 20% higher among HCPs other religions compared to Christians (IRR: 1.2, 95% CI: 0.67, 1.98) (Table 5). Additionally, the acceptability of the single-dose was 13% higher among pharmacists technologist (IRR: 1.13, 05% CI: 0.87, 1.45), 10% higher among other cadres (IRR: 1.1, 95% CI: 0.96, 1.26) but 7 % lower among hospital directors (IRR: 0.93, 95% CI: 0.45, 1.71) compared to nurses. In terms of locations of their facilities, the acceptability of the single-dose schedule was 3% lower among HCPs based in urban settings compared to those in rural areas (IRR: 0.97, 95% CI: 0.83, 1.13) and the acceptability of the single-dose among HCPs in Kisumu and Nairobi was lower by a factor of 0.95 (IRR: 0.95, 95% CI: 0.83, 1.09) and 0.91 (IRR:0.91, 95% CI: 0.78, 1.06) respectively compared to Kiambu while holding other HCPs' characteristics constant (Table 6 and Figure 2). Lastly, no contrasts contributed significantly to explaining the difference between referral levels and the acceptability of the single-dose. We found a linear increasing trend in acceptability across referral levels but there was no significant effect of the referral level on the acceptability of the single-dose schedule (IRR: 1.1, 95% CI: 0.87, 1.42). A similar pattern was observed for the quadratic and cubic trend, but higher-level trends were associated with a

decreased trend in acceptability across referral levels. Overall, the referral level did not have a linear, quadratic, or cubic effect on the acceptability of the single-dose schedule among HCPs.

Discussion

In this study, we operationalized the TFA within the context of HPV vaccination to assess the acceptability of a single-dose schedule among healthcare providers (HCPs) across three Kenyan counties (Kiambu, Kisumu, and Nairobi). Overall, most HCPs (75.84%) reported that a single-dose HPV vaccination schedule for AGYW was acceptable or very acceptable. Most respondents were women, nurses, and had been in their job for an average of 60 months. Thirty-three percent were based at level 4 facilities and 75.8% were in urban settings. Close to a third of HCPs were not knowledgeable of the single-dose schedule while 93% of HCPs thought that HPV vaccination was effective in preventing cervical cancer, and a slightly lower proportion (89.3%) thought that a single-dose schedule was effective in preventing cervical cancer. This was also emphasized by insights reported qualitatively by HCPs where they mentioned that a single-dose HPV vaccination schedule was efficacious in preventing or protecting against cervical cancer. These findings converged with quantitative results and provided more insights into HCPs knowledge and beliefs on the single-dose schedule. Focusing on HCPs' characteristics, we found that hospital directors had 7% lower acceptability compared to nurses while pharmacists and other cadres had respectively 13% and 10% higher acceptability of the single-dose schedule compared to nurses. Additionally, HCPs based in urban settings had lower acceptability compared to those in rural settings. Constructs of the TFA were weakly correlated to and they were weak predictors of the general measure of acceptability, which have both practical and theoretical implications.

Practically, from a public health perspective, we identified areas to improve HPV vaccination uptake in Kenya. In a context where HCPs are considered a main source of information

when making health decisions; it is important to ensure that they are equipped with the latest evidence on cervical cancer prevention and control to accelerate uptake of HPV vaccination. Other studies previously reported that women obtained information on HPV vaccine from HCPs.(22,53) Similar results were also reported in Cameroon where a study conducted among 553 adolescent girls reported that 62.9% heard about HPV from a nurse. This was higher compared to other sources such as teachers (14.2%) or the public media (13.5%).(54) Irrespective of HPV vaccination schedule (1 vs 2 doses), in our study some HCPs reported that the HPV vaccine was not effective in preventing cervical cancer. This is concerning because a recent systematic review on HCPs' HPV vaccine perceptions, hesitancy and recommendation to patients highlighted that HCPs' recommendation had a considerable impact on patient uptake across vaccines and populations. Additionally, HCPs' confidence in or knowledge of the vaccine, the disease severity and risk of infection were associated with high likelihood to recommend the vaccine. Similar findings were reported in other settings where in Camerron where 44% of HCPs reported not believing that the HPV vaccine prevented cancer but high willingness to recommend the vaccine was reported among those who believed that it could prevent cancer.(21) HCPs play an important role in the promotion and delivery of immunization and preventive services in many SSA settings and they are trusted source of information in their communities thus they can hugely contribute to increasing uptake.

Theoretically, while the TFA has been used in other contexts, most study leveraged it to assess acceptability qualitatively. (55–58) Our use of the TFA to capture and assess acceptability quantitative highlighted that constructs of the TFA that were thought to capture aspects of acceptability might not be facets or constituents of acceptability. This raises a question about the TFA and suggests a need to re-assess if respondents' understanding of key components of

acceptability align with what was proposed during the designing and validation of the TFA. As previously reported, the TFA was developed focusing on insights from biomedical studies that were conducted in high income countries which might affect its relevance or appropriateness for LMICs.(40) Additionally, the TFA was designed with input from researchers from HIC with low representation from non-academic stakeholders which might have excluded important considerations from recipients of EBIs and perspectives from LMICs. While other theorical frameworks have been developed expanding on the TFA, it might be worth assessing the perspective of stakeholders beyond the research community on the relevance of constructs and domains that have been portrayed as key aspects or components of acceptability.(43,44,59)

Taking into consideration vaccination schedule, our study highlighted that over a third of the respondent were not knowledgeable about the single-dose schedule and a similar proportion thought that there were moral consequences to offering the single-dose schedule to AGYW. While results from the logistic regression were not statistically significant, they should be considered given their public health relevance which could contribute to increasing HPV vaccination uptake in these settings. If Kenya considers a single-dose schedule to accelerate progress on cervical cancer prevention, it will be crucial to leverage appropriate approaches to increase knowledge on single-dose among HCPs, address concerns that they might have on moral consequences of a single-dose schedule and engage key stakeholders such as hospital directors to get their buy-in and improve their acceptability of the single-dose schedule prior to roll-out. Other considerations for a successful implementation should include using appropriate strategies for HCPs based in urban settings as well as those that account for county-specific implementation context. In addition to equipping HCPs with the right education materials, communication training might also have an impact in making sure that HCPs appropriately address parents, AGYW and community concerns

regarding the HPV vaccines which would increase uptake.(23) We captured insights on the acceptability of HCPs but to ultimately achieve HPV vaccination and cervical cancer elimination goals; the perspective of two other key actors, their acceptability of the single-dose and other key contextual characteristics that might affect HPV vaccination delivery should be taken into consideration.(60)

One of the limitations is that HCPs who participated in the study may not be representative of all HCPs involved in HPV vaccination. To capture the most representative sample possible, we aimed to leverage HCPs WhatsApp groups to survey HCPs from different levels of the healthcare system and we might have been able to capture insights from those who are not on WhatsApp groups. Additionally, since contact information of all HCPs involved in HPV vaccination in the 3 counties was not widely available, we were not able to estimate the response rate. Furthermore, our findings might have not explored some aspects in depth, which for example could have included a further exploration of why some HCPs thought that there was a moral consequence to providing a single-dose HPV vaccination schedule to AGYW while a considerable proportion of HCPs thought that a single-dose HPV vaccination schedule for AGYW was fair. Despite these limitations, our findings they generated early insights on HCPs' perspective regarding the single-dose schedule in Kenya. Our findings also study provides insights on the operationalization of the TFA to capture data and assess acceptability quantitatively in the context of HPV vaccination in a LMIC. Additionally, these findings could provide insight that could be useful to the National Vaccine and Immunization Program and contribute to the designing and adaptation of approaches improve HPV vaccine uptake in Kenya.

Conclusion

Pairing tailored educational approaches for key stakeholders and removing limitation of multiple vaccination schedule would contribute to increasing acceptability. A single-dose schedule has the potential to address concerns related to financial burden and access, which would improve acceptability and ultimately contribute to increasing uptake. Given reduced logistics needed to deliver a single-dose schedule, this approach has the potential to catalyzed equitable access to HPV vaccination by reaching AGYW who might be in complicated situations due to their community livelihood such as nomad community or those who are in remote or conflict areas.

Authors' Contributions

All the listed authors contributions include the conception and design, drafting the article or revising it critically for important intellectual content, and final approval of the version published. Regarding responsibility for overall content, the lead author, Grace Umutesi is the guarantor.

GU led the designing, implementation, analysis, and manuscript drafting. BW provided input on the designing, analysis, and feedback on the manuscript. LO supported the designing and implementation of the project and provided input on the manuscript. EB, MO, BN, LM, KN, RVB and NRM provided input on the design of the project, contextualization of findings and feedback on the manuscript. All authors revised the article and approved the final version. As the guarantor, GU affirms that the manuscript provides an honest, accurate, and transparent account of the issues covered, that there are no important omissions, and that there are no discrepancies between what was planned and the final version. All authors accept full responsibility for the work and the decision to publish.

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Data Availability Statement

The raw data underlying this article cannot be shared due to ethical reasons to protect the identity of individuals who participated in the study. Facility level demographics can be shared as well as individual level data excluding information that could trace the responses back to study participants especially in small facilities. The data will be availed upon request via an online secure repository.

Figures and Tables

Table 1: Demographic characteristics of respondents, 385 HCPs from the 3 counties

	Kiambu (n=108)	**Kisumu** (n=174)	**Nairobi** (n=103)	**Overall** (n=385)	**P-value**
Sex					0.097$^{\alpha}$
Male	22 (20.4%)	54 (31%)	23 (22.3%)	99 (25.8%)	
Female	85 (78.7%)	120 (69%)	80 (77.7%)	285 (74.2%)	
Age					**0.004$^{\beta,*}$**
Median [IQR]	32.0 [12.5]	32.5 [9.0]	28.0 [8.0]	32 [10]	
Religion					0.38$^{\alpha}$
Christian	107 (99.1%)	165 (94.8%)	101 (98.1%)	374 (97.1%)	
Muslim	1 (0.9%)	6 (3.4%)	1 (1.0%)	8 (2.1%)	
Other	0 (0%)	2 (1.1%)	1 (1.0%)	3 (0.8%)	
Modality					0.29$^{\alpha}$
In-person	7 (6.5%)	11 (6.3%)	3 (2.9%)	21 (5.5%)	
Phone	94 (87.0%)	155 (89.1%)	89 (86.4%)	338 (87.8%)	
Computer/ Laptop	5 (4.6%)	8 (4.6%)	10 (9.7%)	23 (6.0%)	
Role/ Cadre					**0.029$^{\alpha}$**
Nurse	50 (46.3%)	76 (43.7%)	61 (59.2%)	187 (48.6%)	
Clinical Officer	21 (19.4%)	24 (13.8%)	8 (7.8%)	53 (13.8%)	
Medical Officer	4 (3.7%)	7 (4.0%)	10 (9.7%)	21 (5.5%)	
Pharmacist Technologist	3 (2.8%)	10 (5.7%)	5 (4.9%)	18 (4.7%)	
Pharmacist	2 (1.9%)	4 (2.3%)	3 (2.9%)	9 (2.3%)	
Hospital Director	2 (1.9%)	1 (0.6%)	0 (0%)	3 (0.8%)	
Other	25 (23.1%)	51 (29.3%)	16 (15.5%)	92 (24.2%)	
Duration at the job (Months)					0.052$^{\beta,*}$
Median [IQR]	48.0 [72]	60.0 [72]	36.0 [60]	60.0 [72]	
Level in the HS of the Health Facility					**<0.05$^{\alpha,*}$**
Community Facilities (level 1)	4 (3.7%)	3 (1.7%)	4 (3.9%)	11 (2.9%)	
Health dispensaries (level 2)	12 (11.1%)	8 (4.6%)	0 (0%)	20 (5.2%)	
Health center (level 3)	14 (13.0%)	37 (21.3%)	23 (22.3%)	74 (19.2%)	

County hospitals (level 4)	20 (18.5%)	84 (48.3%)	24 (23.3%)	128 (33.2%)	
County Referral (level 5)	31 (28.7%)	30 (17.2%)	17 (16.5%)	78 (20.3%)	
National Referral (level 6)	7 (6.5%)	1 (0.6%)	15 (14.6%)	23 (6.0%)	
Other	20 (18.5%)	11 (6.3%)	18 (17.5%)	49 (12.7%)	
Location of the Health Facility					**<0.05**[α,*]
Urban	85 (78.7%)	112 (64.4%)	95 (92.2%)	292 (75.8%)	
Rural	23 (21.3%)	61 (35.1%)	5 (4.9%)	89 (23.1%)	
Other	0 (0%)	0 (0%)	2 (1.9%)	2 (0.5%)	

[α]Kruskal-Wallis test

[β]Chi-square test

P-value compare characteristics across KEN SHE Counties

*P-value <0.05

Table 2: Responses of participants on the acceptability of a single-dose HPV vaccination schedule for AGYW (n= 385)

Domain		Question*	Completely Disagree n (%)	Disagree n (%)	Neutral n (%)	Agree n (%)	Completely Agree n (%)	Insights from HCPs
General Acceptability		Is a single-dose of HPV vaccination for AGYW acceptable?	52 (13.51)	9 (2.34)	32 (8.31)	167 (43.38)	125 (32.46)	• Believed that a single-dose schedule would be more acceptable compared to the 2-dose schedule. • Noted that it would result into an increased uptake and coverage. • Emphasized acceptability (among HCP and the community) as a factor that would enable their ability to deliver a single-dose schedule. • Acceptability among parents and caregivers was reported as the major concern or *"the elephant in the house"*.
Burden[a]	*Effort*	Is a huge effort needed to	52 (13.51)	217 (56.36)	63 (16.36)	37 (9.61)	16 (4.16)	• Noted that a single-dose schedule would require *minimal effort* and result in better compliance.

		provide single-dose HPV vaccination?						• Regarded the single-dose schedule as a good approach that was *efficient, less tedious and that would reduce workload*. • Flagged that a single-dose schedule would *reduce contact tracing or follow-up efforts that have challenging in the past*.
	Time	Is a huge amount of time needed to provide single-dose HPV vaccination?	11 (2.86)	324 (84.16)	25 (6.49)	22 (5.71)	3 (0.78)	• Stressed the efficiency and less time consumption of the single-dose schedule as a factor that would facilitate its delivery. • Pointed out that using less time to deliver the single-dose schedule would increase its acceptability among HCPs. ○ *it saves time and the turn out will be good* • Considered a single-dose schedule *"very easy and saves time since there is no need to come back".*

	Resource	Are huge resources needed to provide single-dose HPV vaccination?	14 (3.64)	284 (73.77)	26 (6.75)	47 (12.21)	14 (3.64)	• Reported the lack of required resources (cold chain, consumables, storage, transport, communication materials, adequate workforce) as a factor limiting their confidence in delivering the single-dose schedule. • Mentioned that a single-dose schedule will reduce financial resources needed and the rate of defaulters. • Believed that a single-dose schedule was *"resource friendly"*. • Recommended that the single-dose schedule be *adopted especially in government facilities*.
Ethicality	*Moral consequence*	Are there moral consequences to offering single-dose HPV	72 (18.80)	113 (29.50)	74 (19.32)	98 (25.59)	26 (6.79)	• Reported concerns of people who thought that the vaccine causes infertility and other who thought that it causes cancer. o *It can cause cancer*

		vaccination?						
	Fairness	Is it fair to give a single-dose HPV vaccination to AGYW?	19 (4.95)	15 (3.91)	31 (8.07)	147 (38.28)	172 (44.79)	• Believed that a single-dose schedule will be beneficial to AGYW. o *I t will offer many girls protection because not all girls receive second dose…*
Perceived Effectiveness	*Effectiveness of 1-dose*	Is a single-dose HPV vaccination effective in preventing cervical cancer?	5 (1.31)	23 (6.0)	13 (3.39)	157 (40.99)	185 (48.30)	• Many reported that a single-dose prevents HPV infection and cervical cancer. o *No significant different in its efficacy compared to multiple doses.* o *Single-dose for live immunity* • Reported that it might give partial protection. • Uncertainty in its effectiveness was also reported by some HCPs. o *Not sure if it is as effective as 2-dose.*

								○ *it's working but not sure of its effectiveness.*
Self-Efficacy		Are you confident providing single-dose of HPV vaccination?	22 (5.74)	12 (3.13)	16 (4.18)	91 (23.76)	242 (63.18)	• Reported confidence as an enabling factor in delivering a single-dose schedule. • Most HCPs reported being confident delivering the single-dose schedule. • Some mentioned that awareness will need to be done properly to preserve their confidence. ○ *If awareness creation will not be done properly then it might interfere with my confidence*
Intervention Coherence	Knowledge on the single-dose schedule	Are you knowledgeable about the single-dose schedule for HPV vaccination	34 (8.97)	56 (14.78)	25 (6.60)	190 (50.13)	74 (19.52)	• Reported minimal or little knowledge on the single-dose schedule. • Cited knowledge, skills, and training gaps as major barriers to delivering a single-dose schedule. ○ *Lack of knowledge on how to deal with adverse effects in case they occur.*

								• Noted that they knew details regarding the single-dose schedule delivery (frequency, mode of delivery, administration, and the target population)
								• Highlighted benefits (effectiveness, efficiency, potential to improve uptake and compliance)
								  ○ *Given once without a second dose.*
								  ○ *WHO approved.*
								  ○ *Same or simply efficacious to the double dose, better uptake.*

[*]Questions were reworded for brevity, Supplementary Methods 2 presents questions that were asked to operationalize the TFA and capture constructs and domains of acceptability relevant to this project.

[a]Constructs for the burden domain were reversed scored during analysis to make sure that the high score/ ranking corresponded to high acceptability ie if the EBI requires a little effort, it is more likely to be acceptable.

Table 3: Other insights related to the acceptability of the single-dose schedule reported by HCPs (n=385)

Domains/ Themes	Constructs/ sub-themes	Completely Disagree n (%)	Disagree n (%)	Neutral n (%)	Agree n (%)	Completely Agree n (%)	Insights from HCPs
Burden[a]	*Integration of single-dose vaccination into existing work*	29 (7.55)	271 (70.57)	24 (6.25)	50 (13.02)	10 (2.60)	• Reported the lack of integration into normal flow as an obstacle limiting their confidence to deliver the single-dose schedule
Perceived Effectiveness	Effectiveness of the HPV vaccine	2 (0.52)	15 (3.91)	9 (2.34)	154 (40.10)	204 (53.12)	• Voiced that the HPV vaccine was safe and effective. • Considered the effectiveness and efficacy of the vaccine as a factor that would facilitate the delivery of the single-dose schedule. o *I have had the shot, I know of the advantages of the vaccine, I know it will greatly reduce cervical cancer in our population*

Self-Efficacy	Confidence explaining benefits	10 (2.61)	18 (4.71)	12 (3.14)	79 (20.68)	263 (68.84)	• Mentioned that more training would empower them to communicate well advantages of HPV vaccination to AGYW, parents and the community. ○ *Need be able to explain the importance of vaccine to the guardian in local understandable language*
	Confidence addressing concerns	10 (2.61)	10 (2.61)	11 (2.87)	109 (28.46)	243 (63.45)	• Reported that capacity building would enhance their confidence in counselling and administering the HPV vaccine.
Additional insights reported							
Facilitators of single-dose delivery	• Availability of clear protocols, policy, and guidelines from MOH • Motivation (of AGYW and HPCs) • Proper planning • Efficacy, effectiveness, and safety of the HPV vaccine • Simplified school-based vaccination • Sensitization, awareness, engagement, and health education of AGYW, parents and the community • HCPs skills (including clinical, outreach and community engagement experience) • Availability of training and mentorship						

Barriers of single-dose delivery	• Vaccine hesitancy • Religious and cultural beliefs • Myths and misconceptions about the HPV vaccine • Community norms and traditions • Lack of information or update on the vaccine among HCPs and the community • Lack of support from MOH and parents • Refusal and lack of consent from parents or AGYW • Lack of knowledge, awareness, mobilization, and sensitization on the single-dose schedule in the community • Reported stigma as a concern that was still present; *"stigma is still there"*

Belief on single-dose schedule	• Considered the single-dose schedule *"a good thing to be implemented."*
	• Reported concerns on its protection or whether a boaster dose will be needed later.
	  ○ *Not very sure if the content is efficient to offer full protection compared to the recommended doses.*
	  ○ *I actually do not know if one will need a booster later*

Other Comments	• Learned about the single-dose schedule mostly from colleagues, the internet, training and CME or workshops.
	• Some reported that they were yet to learn about it.
	  ○ *I have not heard about it.*
	  ○ *I haven't learnt as yet*
	  ○ *Not yet updated*
	  ○ *Learned through this survey, now*

[a]Constructs for the burden domain were reversed scored during analysis to make sure that the high score/ ranking corresponded to high acceptability ie if the EBI requires a little effort, it is more likely to be acceptable.

Table 4: Correlation between the acceptability domains and general acceptability reported.

Domain	Constructs	Spearman Correlation	
		Coefficient	**P-value**
Burden*	Effort to provide single-dose	0.0011	0.98
	Time to provide single-dose	0.028	0.58
	Resource to provide single-dose	-0.007	0.89
Ethicality	Moral consequence to providing single-dose	-0.056	0.27
	Fairness to provide single-dose	**0.24**	**<0.01**[#]
Self-Efficacy	Confidence	0.069	0.18
Perceived Effectiveness	Effectiveness of single-dose	**0.14**	**<0.05**
Intervention Coherence	Knowledge on single-dose	0.034	0.51
Other insights captured that aligned with domains of acceptability			
Burden*	Effort required to integrate the HPV vaccine in existing workflow	0.013	0.8
Self-Efficacy	Confidence explaining benefits of the vaccine	0.059	0.25
	Confidence addressing concerns on the vaccine	0.05	0.33
Perceived Effectiveness	Effectiveness of the HPV vaccine	**0.12**	**<0.05**

*Constructs for the burned domain were reversed scored to make sure that the high score/ ranking corresponded to high acceptability ie if the EBI requires a little effort, it is more likely to be acceptable. [#]P-value <0.05, these constructs and general confidence are significantly correlated with low positive correlation coefficient and p-values < 0.05.

Table 5: Correlation between the reported general acceptability and the acceptability computed from relevant domains*

Item	Components	Distribution of Score Across Counties Mean (SD)[#]					Spearman Correlation	
		Kiambu	Kisumu	Nairobi	Overall	P-value[a]	Coefficient	P-value[b]
General acceptability (reported)	NA	4.01 (1.30)	3.74 (1.33)	3.65 (1.22)	3.79 (1.29)	0.1		
Acceptability mean score1[c]	• Effort • Moral consequence • Confidence • Effectiveness • Knowledge	3.76 (0.51)	3.71 (0.52)	3.70 (0.51)	3.72 (0.52)	0.69	0.052	0.31
Acceptability mean score2[d]	• Effort • Fairness • Confidence • Effectiveness • Knowledge	4.10 (0.59)	3.98 (0.62)	3.95 (0.51)	4.0 (0.58)	0.15	0.18	**<0.05**

*Full table available in the Supplementary Materials (Supplementary Table 1)

[#]Mean acceptability scores were calculated by summing the score for relevant constructs for each participant and dividing the total score by the number of constructs used for the calculation (5)

[a]P-value comparing scores across sites

[b]P-value of the correlation coefficient

[c]Using moral consequence as the measurement of burden; the newly computed acceptability score was very weakly positively correlated with the general acceptability score reported (rho= 0.052). This correlation was not statistically significant (p-value=0.3).

[d]Using Fairness to assess burden, the newly calculated acceptability score was weakly positively correlated with the general acceptability score reported (rho=0.18). This relationship was statistically significant (p-value<0.05).

Table 6: Determinants of acceptability among HCPs. Findings of the multivariate poisson regresion reporting incidence rate ratios (IRR) with 95 % confidence interval (CI)

	IRR[1]	95% CI[1]	p-value
Gender			
Male (Ref)	—	—	
Female	1.01	0.89, 1.16	0.8
Age	1	0.99, 1.01	0.6
Religion			
Christian (Ref)	—	—	
Muslim	0.99	0.66, 1.41	>0.9
Other	1.2	0.67, 1.98	0.5
Job title			
Nurse (Ref)	—	—	
Clinical Officer	1.02	0.86, 1.20	0.8
Medical Officer	1.07	0.83, 1.37	0.6
Pharmacist Technologist	1.13	0.87, 1.45	0.3
Pharmacist	1.08	0.74, 1.51	0.7
Hospital Director	0.93	0.45, 1.71	0.8
Other	1.1	0.96, 1.26	0.2
Job duration (in Months)	1	1.00, 1.00	0.8
Facility Level			
Facility_level.L	1.1	0.87, 1.42	0.4
Facility_level.Q	1.01	0.81, 1.26	>0.9
Facility_level.C	1.08	0.87, 1.35	0.5
Facility_level^4	0.92	0.75, 1.13	0.4
Facility_level^5	0.99	0.83, 1.18	0.9
Facility_level^6	0.96	0.85, 1.09	0.5

Geographic location			
Rural (Ref)	—	—	
Urban	0.97	0.83, 1.13	0.7
Other	1.02	0.46, 1.96	>0.9
County			
Kiambu (Ref)	—	—	
Kisumu	0.95	0.83, 1.09	0.5
Nairobi City	0.91	0.78, 1.06	0.2

[1] IRR = Incidence Rate Ratio, CI = Confidence Interval

Figures

Figure 1: Flow chart describing responses used to assess the acceptability of the single-dose schedule of HPV vaccination for AGYW among HCPs

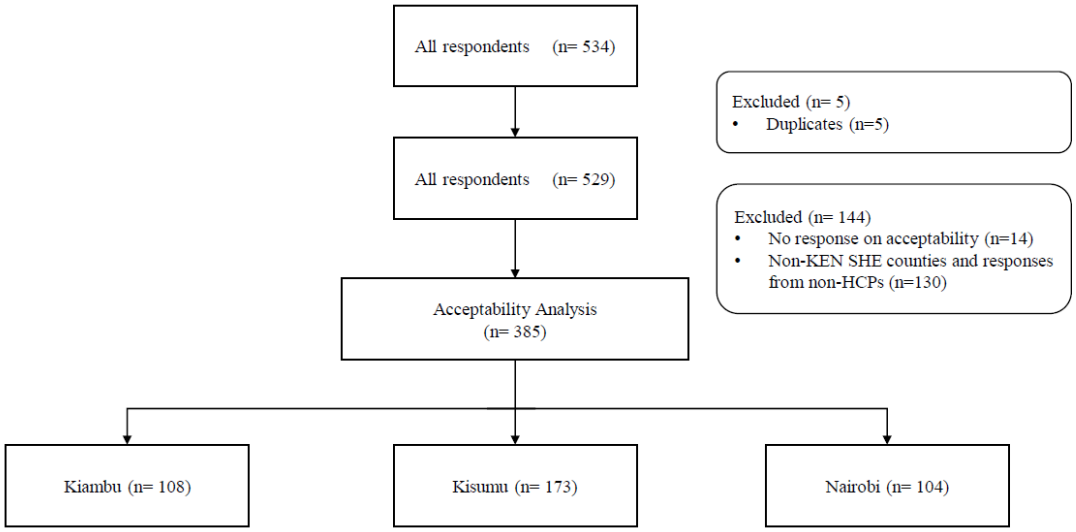
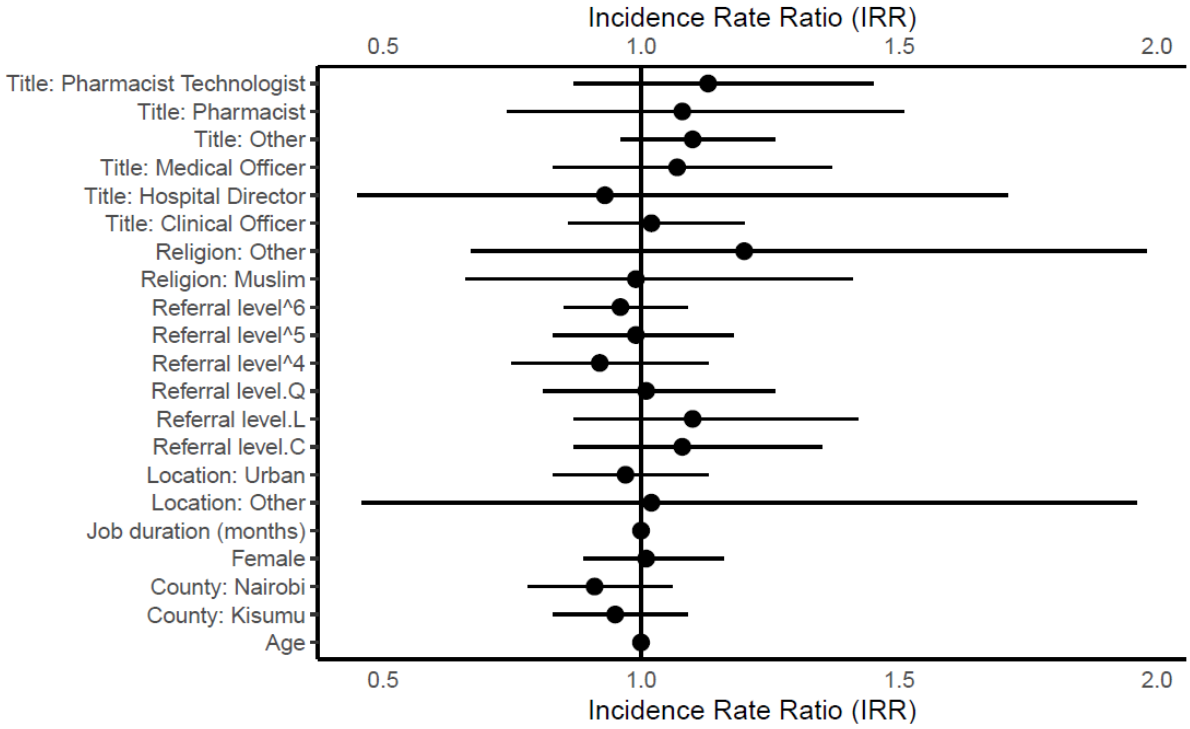


Figure 2: Determinants of acceptability among HCPs. Findings of a multivariate poisson regresion reporting incidence rate ratios (IRR) with 95 % confidence interval (CI)



Model equation: logit (Y_m)=α_m+ B1 job title +B2 religion + B3 referral level + B4 geographic location of the facility + B5 job duration + B6 gender + B7 county + B8 age

Chapter 3. The potential impact of a single dose HPV vaccination schedule on cervical cancer outcomes in Kenya: A mathematical modelling and health economic analysis

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The potential impact of a single dose HPV vaccination schedule on cervical cancer outcomes in Kenya: A mathematical modelling and health economic analysis

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Abstract

Background

Human Papillomavirus (HPV) is the primary cause of cervical cancer. Single-dose HPV vaccination can effectively prevent high-risk HPV infections that cause cervical cancer and accelerate progress toward achieving cervical cancer elimination goals. We modelled the potential impact of adopting single-dose HPV vaccination strategies on health and economic outcomes in Kenya, where a two-dose schedule is the current standard.

Methods

Using a validated compartmental transmission model of HPV and HIV in Kenya, we evaluated the costs from the payer's perspective to vaccinate girls by age 10 with either one or two doses and increasing coverage levels (0%, 70%, 77%, 90%). Additionally, we modelled single-dose strategies supplemented with either catch-up vaccination of adolescent girls and young women or vaccination for all by age 10, funded with the first five-years of cost savings of switching from a two- to one-dose schedule. Costs and outcomes were discounted at 3% annually, and incremental cost-effectiveness ratios (ICERs) were calculated per disability-adjusted-life-year (DALY) averted.

Results

All one-dose and the two-dose 90% coverage strategies were on the efficiency frontier, dominating the remaining two-dose strategies. The two-dose 90% coverage strategy had a substantially higher ICER (US$6,508.80/DALY averted) than the one-dose 90% coverage (US$197.44/DALY averted). Transitioning from a two- to one-dose schedule could result in US$21.4 Million saved over the first five years, which could potentially fund 2.75 million supplemental HPV vaccinations. With this re-investment, all two-dose HPV vaccination scenarios would be dominated. The greatest

DALYs were averted with the single-dose HPV vaccination schedule at 90% coverage supplemented with catch-up for 11-24-year-old girls, which had an ICER of US$78.73/DALYs averted.

Conclusion

Considering the logistical and cost burdens of a two-dose schedule, a one-dose schedule for girls by age 10 would generate savings that could be leveraged for catch-up vaccination for older girls and accelerate cervical cancer elimination in Kenya

Keywords: HPV vaccination; Single-dose; Cost-effectiveness analysis; Mathematical modelling; Low-and-middle income country; Kenya

1. Introduction

Human papillomavirus (HPV) is the primary cause of cervical cancer, the fourth leading cause of female cancer worldwide.(61) In Kenya, there are over 5,236 new cases and 3,211 deaths due to cervical cancer annually.(62) High-risk HPV infections are responsible for almost all cervical cancer cases and HPV vaccination is an efficacious prevention strategy.(63–65) To achieve Cervical Cancer Elimination by 2030, the World Health Organization (WHO) has set these goals: vaccinate 90% of girls by age 15, screen 70% of women by age 35 and again by age 45, and treat 90% of women diagnosed with pre- or invasive cancer.(66)

The Kenyan Ministry of Health (MoH) launched the national HPV vaccination program in 2019 through the National Vaccines and Immunization Program (NVIP). The program aimed to deliver two doses of the quadrivalent HPV vaccine in health facilities, six months apart, initially to 10-year-old girls, although provision was expanded in 2021 to a multi-age cohort of girls 10-14 years.(34,67) However, HPV vaccination uptake has remained low; in 2021, only 31% of 10-year-old girls received the recommended two doses of the vaccine, while 77% received one dose.(27) Additionally, Kenya is expected to graduate from Gavi support for the HPV vaccine over the next five years, which could result in costs exceeding US$10 Million per year.(27)

High-quality evidence supports the efficacy of a single dose HPV vaccination. Randomized trials, a meta-analysis, observational studies, and modelling analyses demonstrated the efficacy and population-level effectiveness of one-dose HPV vaccination in different contexts, including low- and middle-income countries (LMICs).(37,5,68,7,4,9,69,6,11,10,13,12,26) A recent study from Scotland also showed that no cervical cancer cases were detected in vaccinated women following HPV immunization at age 12-13, irrespective of the number of doses.(8) This body of evidence supports the WHO recommendation of a one or two-dose schedule for girls and boys

aged 9-20 years to increase coverage and catalyze progress toward cervical cancer elimination goals.(14) The WHO Africa regional office also recommended that countries transition to single-dose HPV vaccination schedule to reach more adolescent girls and young women.(70) In Kenya, the KEN SHE Study, a randomized trial conducted in 3 counties, has shown high efficacy of a single-dose of the HPV vaccine. (37) However, there is uncertainty over the duration of equivalent protection as the earliest single-dose study has not yet reached 20 years.(5) The Costa Rica HPV Vaccine Trial (CVT) has shown durable protection of a single-dose HPV vaccine for at least 16 years.(5,28)

As Kenya explores strategies to accelerate cervical cancer elimination, a modelling and health economic analysis would inform the potential implications of switching to a single-dose HPV vaccination schedule, including the long-term outcomes and cost. We leveraged modelling analyses to perform three evaluations: (1) the cost-effectiveness of one-dose delivered in health facilities compared to a two-dose HPV vaccination schedule under various coverage scenarios, (2) the impact of potential waning of one-dose HPV vaccine efficacy on cervical cancer and health economic outcomes, and (3) the added impact of using the five-year cost savings of switching from a two- to one-dose HPV vaccination schedule for either catch-up vaccination for multi-age cohorts (MAC) of girls and young women or vaccination for all by age 10 strategies (i.e. vaccination of both girls and boys).

2. Methods

2.1. Model Description

We used a validated compartmental, dynamic model of heterosexual HPV and HIV transmission calibrated to the Kenyan setting, which has been described previously.(71,72) The

model simulates HIV and HPV transmission, development of cervical intraepithelial neoplasia (CIN), and progression to cervical cancer. Interventions simulated in the model include HIV treatment, cervical cancer screening, and HPV vaccination. Simulating both HIV and HPV is important because Kenyan women have an HIV prevalence of approximately 6%, and women living with HIV have a six-fold higher risk of cervical cancer compared to women without HIV.(73–75)

*2.2. **Modelled Scenarios***

Beginning in 2019, we modelled two-dose HPV vaccination of girls by age 10 in Kenya with the quadrivalent HPV vaccine, and with coverage increasing linearly to present-day levels of 31% by 2023.(34) Starting in 2023, we simulated a baseline scenario of no further HPV vaccination and scenarios varying vaccine dose, durability, and coverage. Using methods described in previous publications, we simulated uncertainty in vaccine efficacy of one- and two-doses. Two-dose vaccine scenarios reflected the quadrivalent vaccine efficacy results from the FUTURE I and II trial of 100% (95% CI 88.4, 100), and one-dose vaccine scenarios reflected the bivalent vaccine efficacy results from the KEN SHE trial of 97.5% (95% CI 90.0, 99.4), which was similar to the results of the nonavalent vaccine against HPV 16 and 18 of 98.7% (95% CI 90.5, 99.8).(37,76,77) Although the KEN SHE trial did not study the efficacy of the quadrivalent vaccine, we assumed efficacy would be similar to the bivalent and nonavalent vaccines since high-risk types HPV16 and HPV18 are targeted by both vaccines, and the nonavalent vaccine is based on the quadrivalent vaccine technology. In the paired draws, we conservatively assumed that one-dose vaccine efficacy was always equal to or lower than two-dose efficacy for each parameter set.

For the first evaluation objective of the study, we assumed lifelong efficacy of both one- and two-dose vaccination and simulated scenarios of increasing vaccination coverage, including a

hypothetical baseline of 0% future coverage. We modelled two-dose scenarios with coverage remaining at current levels of 31%, and scenarios of increasing coverage of 50%, 70%, 77%, and 90%. Similarly, we ran one-dose scenarios with coverage remaining at current levels of 77%, as well as 70% and 90%.(34) These scenarios aimed to inform the health and financial trade-offs of achieving different coverage levels with different vaccination dosing schedules.

The second objective was to evaluate the potential impact of one-dose waning efficacy possibilities on cervical cancer outcomes. We modelled one-dose scenarios of combinations of an efficacy period between 20-30 years and a waning period of 10 or 20 years. The efficacy period (EP) is the duration of full vaccine efficacy, and the waning period (WP) is the duration of time in which vaccine efficacy declines linearly to 0%. We selected 20 years as the minimum EP because recent evidence suggests that one dose of the HPV vaccine maintains full efficacy up to at least 16 years.(28) We selected 30 years as an alternative EP since it would protect women against HPV acquisition and provide coverage through ages with high observed incidence of cervical cancer.(78) For these scenarios, we maintained vaccination coverage at 90%.

For the third objective, we calculated the expected five-year cost savings if Kenya switched from a two- to a one-dose HPV vaccination schedule, and simulated investing the savings into additional one-dose HPV vaccinations, including either i) vaccination for all by age 10 inclusive of boys and girls, ii) catch-up vaccination of 11 to 19 year-old girls to align with the current WHO recommendation for one-dose vaccination, or iii) catch-up vaccination of 11 to 24 year-old girls and young women to cover a wider age of women. We ran these alternative supplemental vaccination strategies alongside a primary strategy of one-dose HPV vaccination of girls by age 10 at 90% coverage. We modelled each vaccination strategy under three durability scenarios: lifelong vaccine efficacy, pessimistic waning efficacy (20 years EP, 10 years WP), and alternative

waning efficacy (30 years EP, 20 years WP). These scenarios aimed to identify whether cost-savings from reduced dosing can fund supplemental strategies capable of overcoming the potential effects of waning one-dose vaccine efficacy.(14)

For all scenarios, we modelled a constant one-time cervical cancer screening coverage at their current national averages of 14% for women without HIV and 56% for women with HIV, both at ages 35-39 years. Screening assumed visual inspection with acetic acid, triage with colposcopic biopsy, and those diagnosed with CIN2 or greater were modelled as treated with ablative therapy. To account for uncertainty in sexual behavior, HIV and HPV natural history, and HPV vaccine efficacy, we ran 25 parameter sets for each scenario.(62,79)

2.3. Epidemiologic Outcomes

To evaluate the impact of vaccination strategies on cervical cancer outcomes, we estimated annual age-adjusted cervical cancer incidence rates from 2023 to 2123, standardized using the WHO 2000-2025 Standard Population distribution.(80) We used the results from the "no additonal vaccination" scenario as a reference. We evaluated: (1) cumulative cancer cases averted, (2) percent reduction in incidence, and (3) mortality for each scenario compared to the reference. Finally, we calculated the total number of HPV vaccines administered, number of vaccines required to avert one case of cervical cancer, and the year at which the elimination threshold would be reached (incidence rate of 4 per 100,000 women).(66) Results were reported as a median of 25 parameter sets, and uncertainty as a 90% confidence interval (CI).

2.4. Costs and Economic Outcomes

Costing and economic analyses were conducted from the Kenyan Ministry of Health perspective, including only direct medical costs incurred and averted. Disability-adjusted life-

years (DALYs) were calculated from model outputs, disability weights for cervical cancer health states derived from the 2019 Global Burden of Disease, and life expectancy estimates from WHO life tables.(81,82) Cost estimates were extracted from published studies. HPV vaccination costs are described in Table 1, and account for the quadrivalent HPV vaccine (US $4.50 per dose), commodities including syringes and safety boxes, international handling (3%), delivery fees (10%) , and wastage (5%).(83,84) Additionally, we used an estimated cost to the health system of US $4.97 per dose for vaccine delivery within health facilities.(27) To account for Kenya's expected graduation from Gavi support for the HPV vaccine, we applied a cost per dose of US$0.50 in 2020, and, starting in 2021, increased the cost gradually from 20% of the vaccine price to 100% by 2027 (20% in 2021, 25% in 2022, 30% in 2023, 46% in 2024, 62% in 2025 and 80% in 2026).(27) Since our analysis accounted for a starting point after the launch of the HPV vaccination program in Kenya, we did not include a Gavi Vaccine introduction grant for routine immunization that would have been available to the country in the first year (2020) of the HPV vaccination program. We also accounted for aggregated costs of cervical cancer screening, triage, and cervical pre-cancer and cancer treatment. Costs were converted to 2023 US dollars (USD). Both costs and outcomes were projected over a 100-year time horizon from 2023 to 2123 and discounted at an annual rate of 3% following standard practice. (85)

Five-year cost-savings of switching from a two- to one-dose schedule were estimated by comparing all possible two-dose coverage levels with a switch to all possible one-dose coverage levels. These pairwise comparisons were made rather than only comparing two with one-dose schedules at equivalent coverage levels since changing the dosing could allow an expansion of HPV vaccination coverage. To be conservative, we used mean cost estimates for all one- and two-dose scenarios at each coverage level. The lowest possible five-year cost-savings of switching to

a single-dose schedule and the median discounted cost per vaccination (including costs of the vaccine, supplies, and to the health system for facility-based vaccination) were used to estimate the number of additional HPV vaccine doses that could be administered using a supplemental strategy. Supplemental catch-up strategies targeting girls over age 10 were modelled to happen once over the first five years (2023-2028) while vaccination for all by age 10 strategies were modelled to persist over the full-time horizon (2023-2123).

The comparative performance of each scenario was evaluated using the incremental cost-effectiveness ratio (ICER), calculated as the difference in cost divided by the difference in health (in DALYs) of one strategy compared with the next less costly strategy. Strategies that were more costly and less effective than an alternative (strongly dominated) or had higher ICERs compared to a more effective alternative (weakly or extended dominated) were considered inefficient and removed from the calculations in the analysis following standard practice.(85) For all non-dominated scenarios, we reported the median ICER between adjacent non-dominated scenarios from simulations using the 25 best-fitting parameter sets, along with the 90% confidence interval. The cost-effectiveness analyses were conducted using R (version 4.2.1) and Stata (version 18). We reported our results according to HPV-FRAME, a consensus statement and quality framework for modelled evaluations of HPV prevention, and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022, the guidance for reporting health economic evaluations (Appendix Section V).(86,87)

2.5. Cost Sensitivity Analysis

One-way sensitivity analyses were conducted for each scenario to assess the impact of changes in each economic parameter on ICERs using range estimates extracted from published literature (Table 1). The following cost categories were investigated: Gavi contribution,

procurement, health system delivery, supplies, screening, and treatment. Using in-country expert input, we increased Gavi contributions by 10% every year starting from a 30% contribution in 2023 (lower bound) or a 40% contribution in 2023 (upper bound) until the full cost of the vaccine to be covered by the country was reached. Results from one-way sensitivity analyses were presented using tornado diagrams to showcase changes in the ICERs compared to the no vaccination scenario.

Results

3.1. Assuming Single Dose Lifelong Efficacy

Maintaining a two-dose schedule and current coverage of 31% for girls by age 10 would result in a cervical cancer incidence of 14.6 per 100,000 women (5.6-23.8) compared to the no vaccination scenario of 26.0 per 100,000 women (12.3-39.2), a percent reduction in incidence of 33.4% (20.0-51.9) (Table 2). Increasing coverage levels will continue to reduce cervical cancer incidence, and similar trends are also observed for cervical cancer mortality rates. For the two-dose 90% scenario, cervical cancer incidence is expected to reach the elimination threshold of 4 per 100,000 women by 2094, and at our 100-year time horizon from 2023, the incidence is expected to fall to 2.9 per 100,000 women (1.6-4.9).

If Kenya switches to a one-dose HPV vaccination strategy for girls by age 10, maintaining a one-dose schedule at the current one-dose coverage of 77% is expected to reduce cervical cancer incidence to 4.1 per 100,000 women (1.7-8.0) by 2123. For a two-dose strategy at the same coverage level (77%), the cervical cancer incidence is expected to be slightly lower at 3.9 per 100,000 women (1.7-7.3). For the one-dose 90% scenario, cervical cancer incidence is expected to reach the elimination threshold of 4 per 100,000 women by 2096, and at our 100-year time

horizon from 2023, the cervical cancer incidence is expected to fall to 3.1 per 100,000 women (1.6-5.3). Figure 1 illustrates age-adjusted cervical cancer incidence for all one- and two-dose scenarios with varying coverage levels.

Despite one-dose scenarios having incidence levels slightly higher than two-dose scenarios at the same coverage level, all one-dose scenarios required roughly half the number of vaccines to avert one case of cervical cancer compared to two-dose scenarios. For example, the two-dose scenario at 90% coverage required 21.4 (14.6-45.0) thousand vaccines to avert one cervical cancer case, while the one-dose scenario at the same coverage level required 11.0 (7.4-22.7) thousand vaccines to avert one cervical cancer case (Table 2).

All one-dose scenarios and the two-dose 90% coverage scenario were considered efficient (non-dominated strategy on the efficiency frontier), as shown in Figure 2A. Compared to the next non-dominated strategy, the two-dose 90% coverage scenario had an ICER of US$6,508.80 per DALY averted, higher than the one-dose 90% coverage scenario that had an ICER of US$197.44 per DALY averted (Table 3).

3.2. Assuming Waning Efficacy for Single Dose Scenarios

Under various possible scenarios of single-dose HPV vaccine waning efficacy at 90% coverage, cervical cancer incidence after 100 years ranged from 3.1 (1.6-5.6) per 100,000 women for the 30EP/20WP scenario to 4.6 (1.7-10.2) per 100,000 women for the 20EP/10WP scenario. All waning scenarios of single-dose vaccination are expected to avert fewer cases of cervical cancer compared to a two-dose scenario at 90% coverage. However, the pessimistic waning efficacy scenario for one-dose (20EP/10WP) would still reduce the number of vaccines needed to avert one cervical cancer case to 12.6 (9.0-23.9) thousand vaccines, substantially lower than the

required number of vaccines (21.4 [14.6-45.0] thousand vaccines) to achieve a similar outcome for the two-dose scenario (Table 2).

The efficiency frontiers for the pessimistic (Figure 2B) and alternative (Figure 2C) waning scenarios were similar to the lifelong efficacy results; all the one-dose and the two-dose 90% coverage scenarios were on the efficiency frontier. Under the pessimistic and alternative waning assumptions, the ICERs of the two-dose 90% coverage scenario compared to the one-dose 90% coverage scenario were US$1,087.49 per DALY averted (pessimistic waning) and US$4,736.59 per DALY averted (alternative waning). Comparatively, the one-dose 90% coverage scenario for the pessimistic and alternative waning scenarios compared to the next lower cost and non-dominated strategy (one-dose 77% coverage scenario) had ICERs of US$168.55 per DALY averted (pessimistic waning) and US$191.95 per DALY averted (alternative waning).

3.3. Assessing the Impact of Supplemental Vaccination Strategies

When comparing the five-year cost savings of all potential transitions from a two-dose to one-dose HVP vaccination schedule, the lowest cost saving would result from switching from a two-dose strategy at 70% coverage to one-dose strategy at 90% coverage. This is estimated to result in a cost saving of US$21.4 Million over five years (Appendix Section II). Using the mean estimate of the discounted total cost of vaccination of $7.77 per vaccination, the 5-year cost saving could cover an additional 2.75 million doses of the quadrivalent HPV vaccine. These vaccinations could be leveraged to expand HPV vaccination to other age groups and young boys in addition to vaccinating girls by age 10 at 90% coverage. Supplemental expanded HPV vaccination strategies that could be conducted with the 5-year cost savings include a single-dose catch-up HPV vaccination of girls and young women ages 11-19 at 46% coverage, catch-up HPV vaccination of girls and young women ages 11-24 at 33% coverage, and vaccination for all by age 10 at 90%

coverage. Figure 3 and Table 2 show the impact of these additional strategies on cervical cancer incidence over 100 years.

If we assume pessimistic waning of single-dose vaccine efficacy (20EP/10WP), a vaccination program of girls by age 10 at 90% coverage would reduce cervical cancer incidence by 61.5% (44.8-85.9) compared to the reference scenario of no vaccination. In comparison, the current two-dose strategy would reduce incidence by 73.1% (59.7-88.8). However, adding catch-up or vaccination for all by age 10 strategies alongside a single-dose vaccination of girls by age 10 could reduce cervical cancer incidence by up to 72.4% (55.5-88.7). This is similar to the incidence reduction that could be achieved with a two-dose vaccination strategy at a 90% coverage for girls by age 10, but the single-dose strategy paired with a catch-up or vaccination for all by age 10 strategy would require fewer vaccines to reach more individuals.

Assuming the alternative waning scenario of 30EP/20WP and a single-dose, the percent reduction of cervical cancer incidence for vaccination of girls by age 10 would be similar between the one- and two-dose scenarios at 90% coverage. However, investing cost savings into an expanded single-dose vaccination strategy could reduce cervical cancer incidence even further to 75.9% (65.5-90.1), which is a greater reduction than that achieved with the current two-dose strategy at 90% coverage. Similarly, if we assume lifelong single-dose vaccine efficacy and supplemental vaccination, the percent reduction in cervical cancer incidence is predicted to reach 76.3% (66.6-90.2).

The cost-effectiveness analysis of the lifelong efficacy, pessimistic waning, and alternative waning of one-dose HPV vaccination alongside catch-up or vaccination for all by age 10 strategies show that the two-dose strategies are consistently dominated (Figure 4). Comparatively, the single-dose HPV vaccination strategies alongside catch-up of 11-24-year-old girls and young women

were consistently on the efficiency frontier, with ICERs ranging from US$75.47 (alternative waning) to US$86.16 (pessimistic waning). The single-dose HPV vaccination strategy at 70% coverage was also on the frontier for the lifelong efficacy and alternative waning assumptions. Vaccination for all by age 10 consistently averted the most cervical cancer cases, but at ICERS far off the efficiency frontier.

3.4. Sensitivity Analyses

When assessing ICERs of different scenarios compared to no additional vaccination, changes in health system delivery, treatment, and procurement cost had the greatest effect on the ICER across scenarios, while changes in the cost of supplies and screening had a lower effect on the ICER, followed by variations in Gavi contribution. For example, when comparing the two-dose HPV vaccination at 90% coverage to the no-vaccination scenario, a change in the cost of health system delivery resulted in a 13% change in the ICER while a change in the cost of supplies led to a 0.1% change in the ICER (Appendix –Section IV Figure S1, Table S6 and Table S7).

Discussion

HPV vaccination is a foundational strategy for cervical cancer elimination. Pairing robust HPV vaccination coverage with adequate and early cervical cancer screening and treatment services would significantly reduce the burden of cervical cancer in Kenya. While Kenya's current HPV vaccination strategy focuses on vaccinating 10-year-old girls with two doses delivered in health facilities, leveraging a one-dose HPV strategy could catalyze progress towards cervical cancer elimination given the high efficacy of single-dose vaccination. This could allow the country to reach higher vaccination coverage at lower costs than a two-dose HPV vaccination strategy. Considering logistical and cost-related burdens with a two-dose schedule, switching to a one-dose

schedule would accelerate progress towards increasing coverage of girls by age 10 and generate cost-savings that could be invested into catch-up vaccination for girls currently aged 11-24 or to expand HPV vaccination to young boys, which could further accelerate cervical cancer elimination efforts. Additionally, this switch would be strategic considering the anticipated graduation of Kenya from Gavi support in the next few years.(4) However, the impact of switching to a one-dose strategy needs to be evaluated, while also considering incorporating uncertainty around the durability of a single-dose.

Focusing on vaccination of girls by age 10, we found that single-dose HPV vaccination scenarios at coverage levels from 70-90% or a two-dose scenario at 90% coverage would be the most efficient strategies, and these results are consistent regardless of potential waning durability. While a two-dose vaccination strategy at 90% coverage would lead to the greatest DALYs averted, it is also important to recognize the considerable costs required for a two-dose strategy relative to local cost-effectiveness standards. The incremental benefits of a two-dose strategy are further reduced if we observe an alternative one-dose waning scenario of 30EP/20WP or lifetime durability. The cost implications of a two-dose strategy are crucial to optimizing health gains for available health resources.

Although there is uncertainty around HPV vaccine durability, the demonstrated durability for single and multiple doses is comparable. Further, a supplemental vaccination for all by age 10 or catch-up strategy could mitigate the effects of potential one-dose waning efficacy. Our findings show that a single-dose schedule with a supplemental strategy could avert more cases of cervical cancer at a lower cost and more accelerated timeframe compared to a two-dose schedule. In this study, we found that by investing five-year cost savings of switching from a two- to one-dose schedule into a catch-up or vaccination for all by age 10 strategy, all two-dose strategies were

dominated meaning that these strategies were both more expensive and resulted in the same or poorer health outcomes than alternative vaccination strategies. For the lifelong efficacy and alternative waning assumption, catch-up strategies resulted in better cervical cancer outcomes and more DALYs averted compared to the two-dose 90% coverage strategy and at significantly lower costs. In the scenario that one-dose durability follows the pessimistic waning assumption, catch-up of 11–24-year-old girls and young women would still result in the best health outcomes, with a 3.6% reduction in total DALYs compared to two-dose vaccination at 90% coverage, and a 33.3% reduction in total cost. The alternative waning and lifelong efficacy scenarios showed even greater reductions in total DALYs by 6.3% and 6.5%, respectively.

An important context to our results is our assumptions around vaccine efficacy. We imposed a conservative constraint that two-dose efficacy is equal to or greater than one-dose efficacy for all 25 parameter sets run. However, the trial results show significant overlap in confidence intervals in efficacy, and no evidence suggests that two-dose vaccination strategies are superior to one-dose strategies. As a sensitivity analysis, we ran the one-dose 90% coverage of girls by age 10 with a lifelong vaccine efficacy scenario without imposing this bound on vaccine efficacy. The results showed much closer alignment in cervical cancer outcomes, with a one-dose schedule resulting in roughly 899 thousand cervical cancer cases averted while the two-dose schedule resulted in 900 thousand cases averted.

As shown in Tables 2 and 3, modeling potential waning showed that more pessimistic waning assumptions resulted in slightly worse projected health outcomes for single-dose strategies, but that even the most pessimistic plausible assumptions resulted in only modest decrements to health that still clearly defined the cost-effectiveness efficiency frontier. Our findings showed that at 90% coverage, single-dose HPV vaccination with lifelong efficacy resulted

in a greater number of cervical cancer cases averted (971 thousand cases) compared to one-dose scenarios with waning efficacy where the single-dose (20 EP/10 WP) scenario had the lowest number of cervical cancer cases averted (862 thousand cases) but Figure 2 displays that this scenario none the less still comprises the efficiency frontier. Previous modelling studies have also explored the potential impact of single-dose HPV vaccination and waning efficacy in Kenya and other low- and middle-income countries (LMICs).(4,14,26) One study by Bénard and colleagues modelled the impact of single-dose vaccination in four LMICs and found that single-dose strategies could prevent 69% to 94% of cervical cancer cases averted by a two-dose strategy.(13) This finding aligns with our results for Kenya, in which we expect a one-dose strategy to avert 85% (pessimistic waning) to 96% (lifelong efficacy) of the cervical cancer cases averted by an equivalent two-dose strategy. Another modelling study in India by Carvalho and colleagues showed similar estimates for the ICER of two-dose vaccination versus one-dose vaccination of US$3,364 to US$15,530 for different vaccine efficacy and waning assumptions.(26) Finally, a recent modelling study in Kenya by Mwenda and colleagues compared the cost-effectiveness of different HPV vaccine products, and also found that switching to a single dose strategy could save US$50 Million in ten years.(27) While strong evidence from modelling studies and trials supports the durable efficacy of single-dose HPV vaccination, future studies should assess the long-term (>20years) efficacy of a single-dose, the efficacy of single-dose vaccination among people living with HIV, and economic evaluations of single-dose HPV vaccination accounting for HIV care costs given the association between HIV and HPV.

Our study explores the impact of using the five-year cost savings of switching from a two- to one-dose strategy to invest in an expanded catch-up or vaccination for all by age 10 program. It also expands on previous modelling studies with updated estimates of single-dose efficacy based

on the KEN SHE Study, a trial conducted in Kenya. Further, we designed and conducted this study in close collaboration with the National Vaccines and Immunizations Program of Kenya. Model inputs, scenarios, and cost assumptions were decided with colleagues with deep expertise in the HPV vaccination program in Kenya. Our study is also the first single-dose modelling study that accounts for the HIV epidemic in Kenya and the bidirectional interaction between HIV and HPV. Our findings, while specific to Kenya's context, could inform HPV vaccination in settings with similar vaccination delivery, screening and treatment costs as well as HIV and HPV epidemiologic profiles.

There are limitations of our study that could have an impact on the findings. To estimate the impact of vaccination alone on cervical cancer outcomes, we maintained cervical cancer screening using VIA and treatment at the same coverage levels as present day. However, Kenya is advancing capacity for HPV DNA screening and treatment access. We expect the expansion of screening to amplify the impact on cervical cancer cases and deaths averted. Future studies should also explore the impact of investing the cost savings of switching from a two- to one-dose vaccination strategy into expanded cervical cancer screening and treatment programs.

While the model accounts for differences in risk of HPV acquisition for women living with HIV, we do not model differences in vaccine doses, durability, or efficacy based on HIV status. To date, there have been no clinical trials that have studied single-dose efficacy for women living with HIV, so we kept vaccine parameters consistent regardless of HIV status. This emphasizes the need for studies that explore the impact of uncertainty of single-dose HPV schedules for women living with HIV. Since our focus was on HPV vaccination related costs, we did not include HIV-associated costs or disability weights in this study; rather, we chose to limit the study to evaluating costs associated with cervical cancer prevention, screening, and treatment. This study focused on

a facility-based delivery of HPV vaccination, but future studies should also explore comparisons with school-based and mixed-models. Finally, our study does not account for the benefits of HPV vaccination on preventing other HPV-related cancers for both males and females, such as vaginal, vulvar, anal, oropharyngeal, and penile cancers, or the quality-of-life impacts of preventing genital warts from HPV types 6 and 11. As a result, the health outcomes from vaccination strategies reported in this study are likely underestimations. Additionally, given the simplified logistics for a single-dose HPV vaccination schedule both for providers and the community, we believe that it would result in higher uptake and catalyze progress in achieving high HPV vaccination coverage. Evidence from a recent implementation research study highlighted that most providers surveyed in Kenya thought that a single-dose schedule is acceptable, but future research should assess the acceptability of a single-dose schedule in the community and identify factors that might affect uptake in the community.(88)

Conclusion

In conclusion, a single-dose HPV vaccination schedule, regardless of the uncertainty around waning vaccine efficacy, is more cost-effective than the current two-dose schedule, especially when the cost-savings of switching to one-dose vaccination are re-invested into a catch-up campaign. Catch-up of 11-24-year-old girls and young women alongside vaccination of girls by age 10 can overcome the possible effects of potential one-dose waning efficacy and could avert more cases of cervical cancer at a more accelerated timeframe and at a lower cost compared to a two-dose schedule. This could ultimately accelerate Kenya's efforts towards cervical cancer elimination.

Supplementary Materials: The following supporting information are available Section I: Additional modelling results; Section II: Additional economic results; Section III: Full Incremental

Cost Effectiveness Analysis results; Section IV: One-way sensitivity analysis; Section V: Reporting checklists.

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Tables and Figures

Table 1. Key model inputs and costs.

Key model inputs	*Inputs*		
HPV routine vaccination			
Doses	1-2		
Two-dose vaccine efficacy	Beta distribution (α=10.76 and β=0.15) to reflect 100% (95% CI 88.4, 100) (77)		
One-dose vaccine efficacy	Beta distribution (α=49.7 and β=1.6) to reflect 97.5% (95% CI 90.0, 99.4) (37)		
Historical two-dose coverage of girls by age 10	Linear scale-up of coverage from 0%-16% between 2019-2020, and then 16%-31% between 2020-2023 (34)		
Two-dose coverage of girls by age 10	31% (current two-dose coverage), 50%, 70%, 77%, 90% (34)		
One-dose coverage of girls by age 10	70%, 77% (current one-dose coverage), 90% (34)		
One-dose vaccine durability	Lifetime efficacy; combinations of EP 20, 25, 30 years and WP 10, 20 years		
Two-dose vaccine durability	Lifetime efficacy[a] (10,76)		
Additional vaccination strategies	Vaccination for all boys and girls by age 10 (90% coverage), age 11-19 catch-up of girls (46% coverage), age 11-24 catch-up of girls (33% coverage)		
Cervical cancer screening	Screening with VIA, triage with colposcopy, and treatment with cryotherapy (79,89,90)		
Costs[b]	***Estimate (Range) [Source]***	***Costs, continued[b]***	***Estimate (Range) [Source]***
HPV Vaccine		**Vaccine delivery**	
Cost of quadrivalent vaccine per dose (USD)	4.5 (4.5 – 4.5) (27,91)	Incremental health system costs (USD)	4.97 (3.98 – 5.98) (92)
Wastage (% of price)	5 (4 – 6) (27,91)	**Screening & Treatment**	
International handling fee (% of price)	3 (2 – 4) (27,91)	VIA (USD)	5 (5 – 5) (92)
International delivery fee (% of price)	10 (8 – 12) (27,93)	Colposcopy (USD)	33.92 (27.00 – 40.79) (93)

Syringes		Ablative therapy	50.56 (50.56 – 50.56) (92)
Price per dose[c] (USD)	0.07 (0.06 – 0.08) (27,84)	**Cervical Cancer**	
Wastage (% of price)	5 (4 – 6) (27,91)	Diagnostics (Biopsy and histopathology)	36.19 (36.19 – 36.19) (92)
International handling fee (% of price)	3 (2 – 4) (27)	Hysterectomy - radical	493.6 (493.6 – 493.6) (94)
International delivery fee (% of price)	10 (8 – 12) (27)	Local cervical cancer	1,279.10 (1,021.23 – 1,532.69) (27)
Safety boxes		Local cervical cancer (without hysterectomy)	391.31 (311.84, 469.44) (92)
Price per box (USD)	1.3 (1.3 – 1.3) (27,84)	Regional cervical cancer	6,447.33 (5,174.22 – 7,746.97) (27)
Total number of syringes per safety box	100 (27)	Regional cervical cancer (without hysterectomy)	5,086.06 (4,087.13 – 6,113.59) (92)
Price per syringe/dose (USD)	0.0103 (0.0103 – 0.0103) (27)	Distant cervical cancer	5,086.05 (4,084.71 – 6,096.59) (27)
Wastage (% of price)	5 (4 – 6) (27)	**Disability Weights**	
International handling fee (% of price)	3 (2 – 4) (27,95)	Local cervical cancer	0.288 (0.193 – 0.399) (81,93)
International delivery fee (% of price)	10 (8 – 12) (27,93)	Regional cervical cancer	0.451 (0.307 – 0.600) (81,93)
		Distant cervical cancer	0.540 (0.377 – 0.687) (81,93)

[a] Two-dose lifetime efficacy is a conservative assumption that was made for this study, although there is not enough longitudinal data yet to confirm the validity of this assumption.

[b] Costs are shown in U.S. Dollars (USD).

[c] Full cost after Gavi graduation.

Table 2. Projected cervical cancer incidence rates, cases averted, years to elimination (incidence below 4 per 100,000 women), and number of vaccines relative to a reference scenario of no vaccination from the years 2023 to 2123. Results are presented as a median and 90% confidence interval using 25 parameter sets**.**

Dose and durability	Coverage	Additional strategy[c]	Cervical cancer incidence, per 100,000[a]	Percent reduction in incidence	Cumulative cancer cases averted	Number of vaccines (millions)	Number of vaccines to avert 1 cervical cancer case (thousands)	Year elimination threshold reached[b]
One-dose, lifelong efficacy scenarios								
No vaccination	0%		26.0 (12.3-39.2)	Reference	Reference	0.0 (0.0-0.0)	Reference	X (X-X)
Two-dose	31%		14.6 (5.6-23.8)	33.4 (20.0-51.9)	460,516 (273,506- 637,270)	77.1 (69.7-79.4)	16.0 (11.9-28.0)	X (X-X)
	50%		9.1 (3.0-15.8)	51.5 (36.4-73.7)	705,734 (396,958-1,003,420)	125.7 (113.7-129.6)	17.0 (12.3-31.5)	X (2093-X)
	70%		4.9 (1.8-9.1)	66.4 (50.0-85.1)	900,106 (471,208-1,317,820)	177 (160.0-182.5)	18.7 (13.2-37.4)	X (2080-X)
	77%		3.9 (1.7-7.3)	70.4 (53.8-86.7)	949,784 (485,919-1,406,610)	194.9 (176.2-201.0)	19.6 (13.6-39.9)	2117 (2078-X)
	90%		2.9 (1.6-4.9)	73.1 (59.7-88.8)	1,009,341 (504,392-1,536,007)	228.2 (206.4-235.3)	21.4 (14.6-45.0)	2094 (2076-X)
One-dose, lifelong efficacy	70%		5.2 (1.8-9.9)	62.7 (46.5-83.7)	851,996 (466,220-1,281,876)	88.5 (80.0-91.2)	9.9 (6.8-18.9)	X (2081-X)
	77%		4.1 (1.7-8.0)	67.1 (50.5-86.1)	899,829 (481,815-1,372,771)	97.5 (88.1-100.5)	10.2 (7.0-20.1)	X (2079-X)
	90%		3.1 (1.6-5.3)	72.5 (56.9-88.5)	971,797 (501,399-1,509,509)	114.1 (103.2-117.6)	11.0 (7.4-22.7)	2096 (2076-X)
One-dose, waning efficacy scenarios								

One-dose, 20EP/20WP	90%		3.7 (1.6-7.8)	66.7 (49.5-87.2)	908,713 (486,397-1,360,152)	114.1 (103.2-117.6)	11.8 (8.3-23.4)	2112 (2078-X)
One-dose, 25EP/20WP	90%		3.3 (1.6-6.2)	70.7 (53.4-87.9)	940,727 (494,742-1,444,153)	114.1 (103.2-117.6)	11.3 (7.8-23.0)	2101 (2077-X)
One-dose, 30EP/20WP	90%		3.1 (1.6-5.6)	72.1 (55.7-88.4)	960,471 (498,985-1,485,883)	114.1 (103.2-117.6)	11.1 (7.6-22.8)	2098 (2076-X)
One-dose, 20EP/10WP	90%		4.6 (1.7-10.2)	61.5 (44.8-85.9)	862,768 (474,837-1,243,891)	114.1 (103.2-117.6)	12.6 (9.0-23.9)	X (2080-X)
One-dose, 25EP/10WP	90%		3.5 (1.6-7.1)	68.3 (51.0-87.4)	922,133 (490,080-1,394,175)	114.1 (103.2-117.6)	11.6 (8.1-23.2)	2106 (2078-X)
One-dose, 30EP/10WP	90%		3.2 (1.6-5.8)	71.8 (54.8-88.2)	952,911 (497,402-1,469,637)	114.1 (103.2-117.6)	11.2 (7.6-22.8)	2099 (2076-X)
One-dose, using cost savings to invest in an additional vaccination strategy, lifelong and waning efficacy scenarios								
One-dose, lifelong efficacy	46%	CU girls age 11-19	3.0 (1.6-5.3)	75.7 (63.6-88.7)	1,031,065 (532,160-1,596,335)	114.1 (103.2-117.7)	10.3 (7.0-21.3)	2092 (2072-X)
	33%	CU girls age 11-24	3.0 (1.6-5.3)	75.6 (63.2-88.6)	1,033,237 (535,074-1,598,068)	114.1 (103.2-117.7)	10.3 (7.0-21.2)	2093 (2072-X)
	90%	Vaccination for all by age 10	2.7 (1.6-3.8)	76.3 (66.6-90.2)	1,058,653 (526,325-1,656,407)	221.9 (200.7-228.8)	19.7 (13.2-42.0)	2085 (2072-2105)
One-dose, 30EP/20WP	46%	CU girls age 11-19	3.1 (1.6-5.6)	75.5 (63.0-88.5)	1,024,003 (531,228-1,580,671)	114.1 (103.2-117.7)	10.4 (7.1-21.4)	2094 (2072-X)
	33%	CU girls age 11-24	3.1 (1.6-5.6)	75.4 (62.6-88.5)	1,026,159 (534,146-1,582,341)	114.1 (103.2-117.7)	10.4 (7.1-21.3)	2094 (2072-X)
	90%	Vaccination for all by age 10	2.7 (1.6-3.8)	75.9 (65.5-90.1)	1,052,968 (524,145-1,643,371)	221.9 (200.7-228.8)	19.8 (13.3-42.1)	2086 (2073-2107)
One-dose, 20EP/10WP	46%	CU girls age 11-19	4.5 (1.7-10.1)	66.3 (54.0-86.3)	945,419 (517,625-1,366,675)	114.1 (103.2-117.7)	11.5 (8.2-21.9)	X (2075-X)

33%	CU girls age 11-24	4.5 (1.7-10.1)	66.2 (53.8-86.3)	948,401 (520,579-1,369,248)	114.1 (103.2-117.7)	11.5 (8.2-21.8)	X (2075-X)	
90%	Vaccination for all by age 10	3.0 (1.6-5.6)	72.4 (55.5-88.7)	979,871 (504,294-1,469,412)	221.9 (200.7-228.8)	21.2 (14.9-43.8)	2098 (2076-X)	

Abbreviations: EP, efficacy period; WP, waning period; CU, catch-up.
[a] Standardized to the 2000-2025 Standard Population distribution.
[b] X is used to show that the elimination threshold was not reached during the 100-year time horizon.
[c] All scenarios of additional strategies are HPV vaccination strategies that are pursued in addition to one-dose vaccination of girls by age 10 at a 90% coverage.

Table 3. Health and cost impact of vaccination strategies in Kenya. The analysis considers two possible decision scenarios – if the decision-maker considers only vaccination of girls by age 10, or if they would consider vaccination of girls by age 10 with additional strategies such as catch-up or vaccination for all by age 10.

Possible scenario	One-dose durability	Strategy	Total cost (Million 2023 USD); Median (90% CI)[a]	Total DALYs (Thousand); Median (90% CI)[a]	Incremental cost (Million 2023 USD); Median (90% CI)[a]	DALYs averted (Thousand); Median (90% CI)[a]	ICER ($ per DALY averted); Median (90% CI)[b]
Vaccination of girls by age 10 only	Lifelong	No vaccination	414.46 (230.62-606.00)	6,467.38 (3,526.16-9,180.60)	-	-	-
		1-dose, 70% coverage	532.50 (411.14-676.31)	4,689.55 (2,634.16-6,757.53)	122.38 (70.8-181.01)	1,625.58 (892-2,423.09)	74.60 (29.41-203.58)
		1-dose, 77% coverage	546.33 (433.32-687.94)	4,569.15 (2,592.00-6,568.43)	16.84 (11.63-22.18)	111.46 (42.16-189.1)	142.78 (61.72-527.97)
		2-dose, 31% coverage [c]	553.82 (403.54-730.33)	5,573.07 (3,039.92-8,036.84)	-	-	Dominated

	1-dose, 90% coverage	581.87 (475.74-713.27)	4,413.62 (2,531.41-6,270.33)	34.14 (25.33-42.58)	171.73 (60.6-298.11)	197.44 (85.15-702.24)
	2-dose, 50% coverage [c]	650.86 (522.48-814.85)	5,052.00 (2,791.19-7,317.65)	-	-	Dominated
	2-dose, 70% coverage [c]	769.83 (654.07-912.34)	4,645.83 (2,620.47-6,680.84)	-	-	Dominated
	2-dose, 77% coverage [c]	809.38 (701.45-948.99)	4,541.81 (2,579.57-6,493.85)	-	-	Dominated
	2-dose, 90% coverage [c]	885.85 (790.65-1,021.16)	4,391.11(2,520.83-6,205.23)	313.33 (284-325.23)	49.64 (6.16-115.54)	6,508.80 (2,527.55-51,541.03)
Alternative waning (30EP/20WP)	1-dose, 70% coverage	534.73 (411.73-680.77)	4,712.72 (2,640.58-6,805.54)	124.02 (75.71-181.1)	1,604.99 (885.57-2,375.06)	76.43 (31.67-205.15)
	1-dose, 77% coverage	548.46 (433.87-692.20)	4,590.55 (2,598.04-6,614.31)	16.71 (11.42-22.14)	112.74 (42.55-191.24)	140.23 (59.94-522.43)
	1-dose, 90% coverage	583.35(476.25-716.95)	4,430.33 (2,536.90-6,310.30)	33.9 (24.76-42.49)	174.06 (61.14-304.01)	191.95 (81.65-695.31)
	2-dose, 90% coverage	885.85 (790.65-1,021.16)	4,391.11 (2,520.83-6,205.23)	312.05 (283.11-324.95)	68.63 (15.86-146.08)	4,736.59 (2,053.19-20,027.37)
Pessimistic waning (20EP/10WP)	1-dose, 70% coverage	552.53 (417.44-714.83)	4,949.92 (2,713.50-7,235.11)	141.85 (120.03-187)	1,370.93 (807.36-1,827.14)	102.11 (66.41-232.15)
	1-dose, 77% coverage	566.41(439.30-726.91)	4,824.51 (2,667.34-7,051.80)	16.58 (13.32-23.97)	115.94 (46.16-183.31)	137.18 (66.12-475.72)

		1-dose, 90% coverage	598.16 (481.21-751.26)	4,624.61 (2,600.13-6,741.83)	32.67 (24.36-41.91)	184.17 (67.21-309.98)	168.55 (78.8-626.06)
		2-dose, 90% coverage	885.85 (790.65-1,021.16)	4,391.11 (2,520.83-6,205.23)	291.13 (257.27-316.5)	276.02 (79.3-536.6)	1,087.49 (503.03-3,908.66)
Vaccination of girls by age 10 + additional vaccination strategies	Lifelong	1-dose, 70% coverage	532.50 (411.14-676.31)	4,689.55 (2,634.16-6,757.53)	128.92 (99.49-183.61)	1,579.44 (839.55-2,061.36)	85.11 (48.29-236.32)
		1-dose, 11-24YO catch-up of girls [d]	580.44 (482.29-701.29)	4,108.85 (2,356.00-5,833.02)	58.75 (39.37-135.52)	603.47 (278.16-3,347.58)	78.73 (28.64-256.28)
		1-dose, 11-19YO catch-up of girls [e]	582.19 (483.80-703.48)	4,138.94 (2,378.70-5,864.55)	-	-	Dominated
		1-dose, Vaccination for all by age 10 [f]	862.35 (771.21-983.84)	4,203.98 (2,438.65-5,868.82)	279.07 (279.07-279.07)	120.51 (120.51-120.51)	Weakly Dominated
	Alternative waning (30EP/20WP)	1-dose, 70% coverage	534.73 (411.73-680.77)	4,712.72 (2,640.58-6,805.54)	142.54 (112.35-192.57)	1,402.52 (720.28-1,889.22)	97.89 (59.68-348.11)
		1-dose, 11-24YO catch-up of girls [d]	581.05 (482.42-703.09)	4,115.01 (2,357.46-5,852.30)	69.23 (44.66-159.32)	636.39 (283.12-3,328.31)	75.47 (29.35-250.21)
		1-dose, 11-19YO catch-up of girls [e]	582.80 (483.94-705.29)	4,145.09 (2,380.17-5,883.79)	-	-	Dominated

	1-dose, Vaccination for all by age 10 [f]	863.94 (771.74-986.70)	4,219.35 (2,444.50-5,900.54)	279.81 (279.81-279.81)	110.68 (110.68-110.68)	Weakly Dominated
Pessimistic waning (20EP/10WP)	1-dose, 70% coverage	534.73 (411.73-680.77)	4,712.72 (2,640.58-6,805.54)	-	-	-
	1-dose, 11-24YO catch-up of girls [d]	590.69 (484.67-729.11)	4,233.94 (2,385.33-6,174.27)	182.22 (126.04-254.05)	2,066.75 (1,140.82-3,006.33)	86.16 (41.12-223.31)
	1-dose, 11-19YO catch-up of girls [e]	592.52 (486.23-731.61)	4,265.01 (2,408.43-6,209.01)	-	-	Dominated
	1-dose, Vaccination for all by age 10 [f]	879.21 (776.54-1,016.81)	4,387.00 (2,505.77-6,278.66)	285.63 (285.63-285.63)	30.59 (30.59-30.59)	Weakly Dominated

Abbreviations: EP, efficacy period; WP, waning period; YO, year-old.

[a] Results are summarized as a median of all 25 parameter sets.

[b] ICERs are calculated for each parameter set, and results are summarized as the median ICER of the 25 parameter sets.

[c] Dominated two-dose strategies were included as part of the cost-effectiveness analysis but are not reported here for brevity since the results are the same as the vaccination of girls by age 10 lifelong efficacy results. Please see Appendix Section IV dii for an expanded table of these results.

[d] 11–24-year-old catch-up of girls and young women with one-dose at a coverage of 33%, in addition to vaccination of girls by age 10 at a coverage of 90%.

[e] 11–19-year-old catch-up of girls and young women with one-dose at a coverage of 46%, in addition to vaccination of girls by age 10 at a coverage of 90%.

[f] Vaccination of boys and girls by age 10 at a coverage of 90%

Figure 1. Projected cervical cancer incidence over 100 years under scenarios of no vaccination, two-dose vaccination with increasing coverage, and one-dose vaccination with increasing coverage. The plotted lines represent the median incidence from 25 parameter sets. The horizonal dotted line shows the cervical cancer elimination threshold of 4 per 100,000 women.

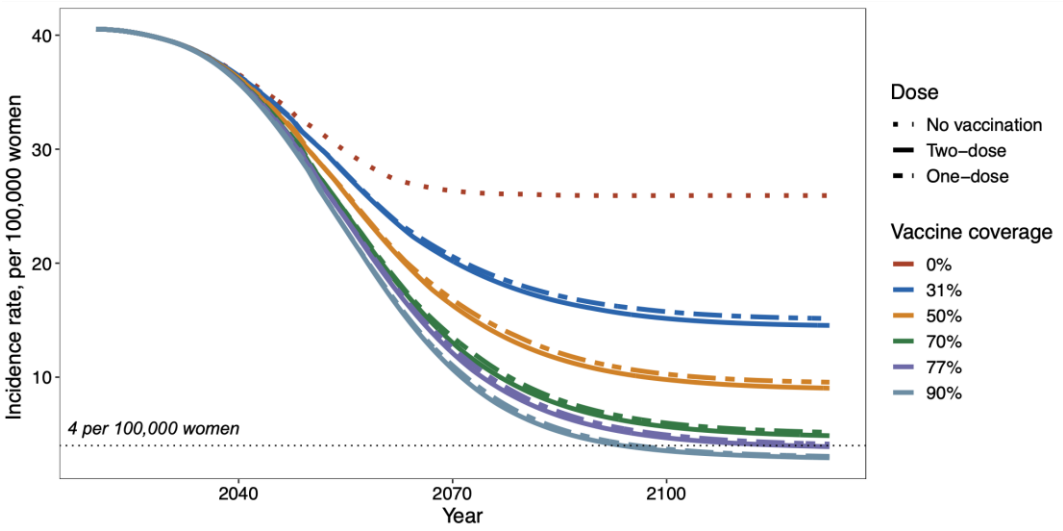


Figure 2. Cost-effectiveness analysis of 10-year-old girl vaccination at different coverage levels and HPV vaccine doses, with different assumptions for one-dose HPV vaccine durability of (A) lifelong efficacy, (B) pessimistic waning of 20 years of efficacy and 10 years of waning, and (C) alternative waning of 30 years of efficacy and 20 years of waning. The graphs display the discounted incremental costs (*x*-axis; in 2023 USD) and DALYs averted (*y*-axis) over a 100-year time horizon compared to no vaccination. The cost-effectiveness of changing from one strategy to a more costly alternative strategy is calculated by taking the difference in cost and dividing it by the difference in DALYs of the two strategies. The dotted line represents the strategies that are efficient because they are more effective and either cost less or have a more attractive cost-effectiveness ratio than less effective options. The ICER is the reciprocal of the slope of the line connecting the two strategies under comparison. All points represent the median of 25 parameter sets. Abbreviations: EP, efficacy period; WP, waning period.

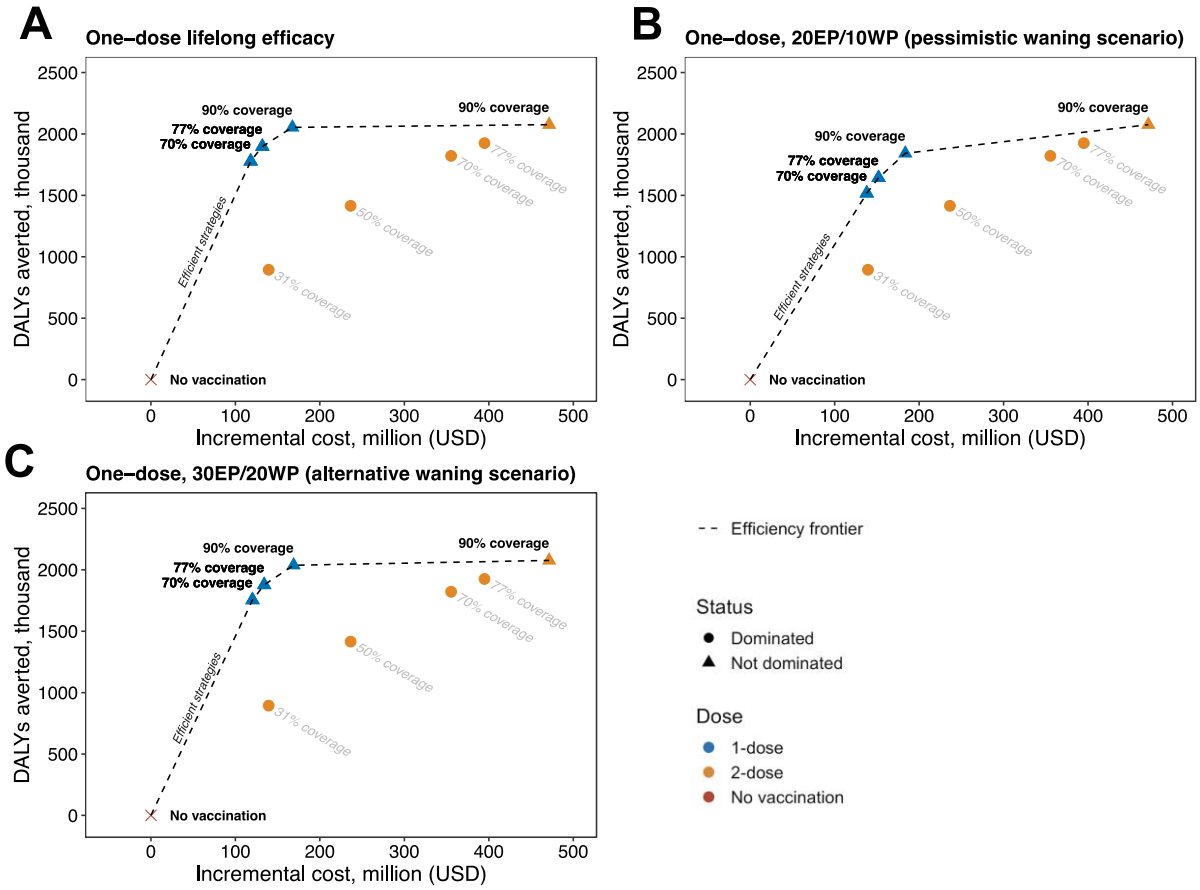


Figure 3. Projected cervical cancer cases averted (in thousands) over 100 years compared to a reference case of no vaccination. (A) Cervical cancer cases averted for a two-dose, 10-year-old girl vaccination strategy at 90% coverage. (B) Cervical cancer cases averted for one-dose strategies assuming a pessimistic waning scenario of 20 years of efficacy and 10 years of waning. (C) Cervical cancer cases averted for one-dose strategies assuming an alternative waning scenario of 30 years of efficacy and 20 years of waning. (D) Cervical cancer cases averted for one-dose strategies assuming lifelong efficacy. Dotted red lines represent the upper and lower quartiles of the two-dose 90% coverage results. Error bars are the 5th and 95th percentiles, vertical black horizontal lines are the median, and boxes are the 25th and 75th percentiles of 25 parameter sets. Abbreviations: 2D, two-dose; 1D, one-dose; EP, efficacy period; WP, waning period.

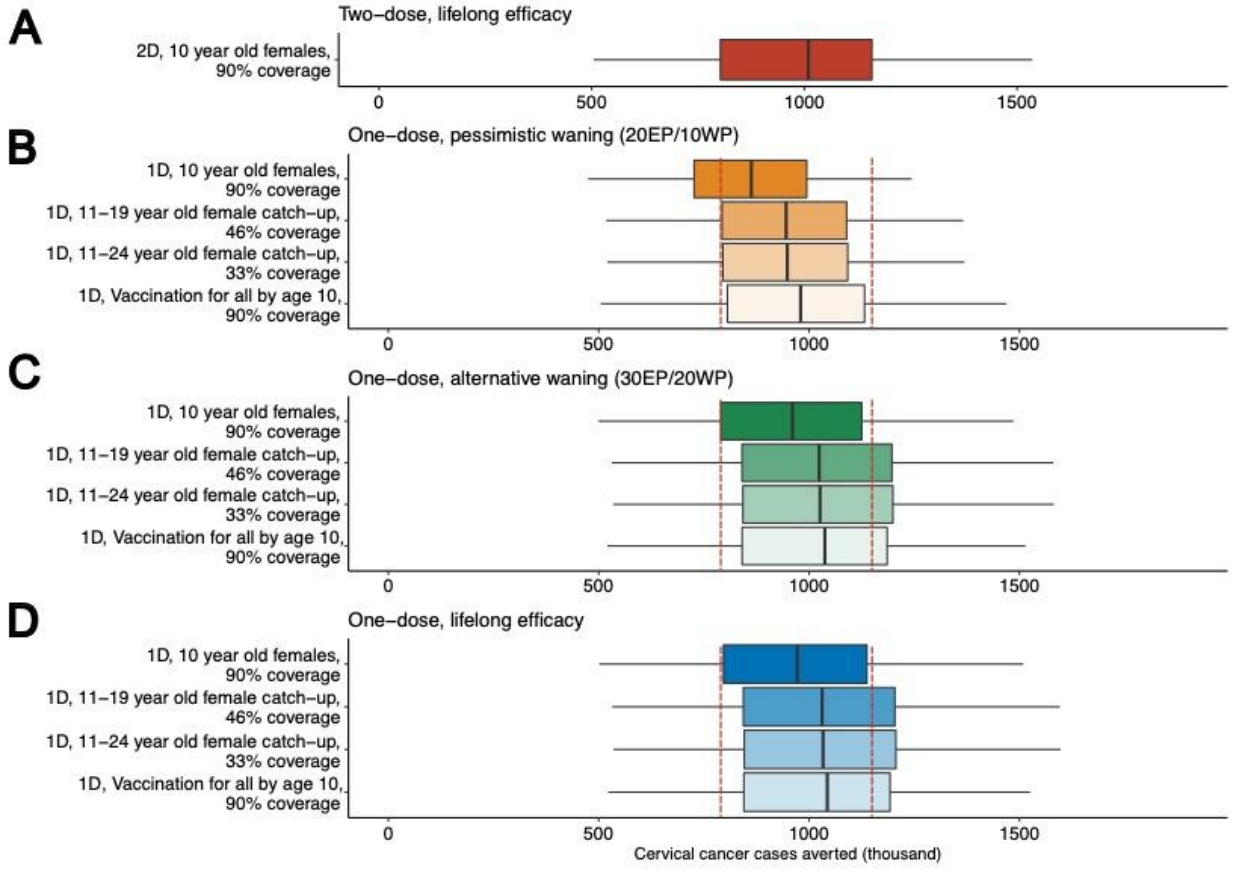
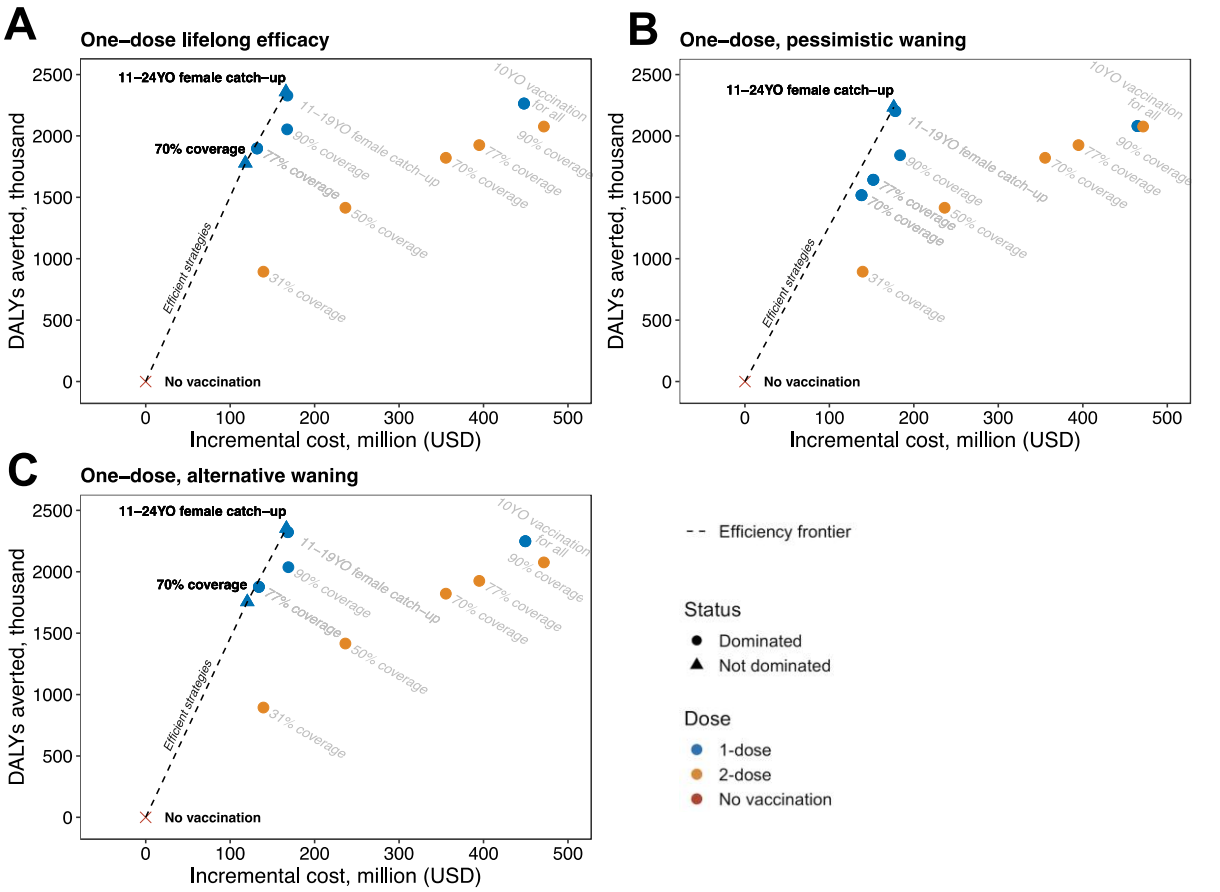


Figure 4. Cost-effectiveness analysis of vaccination of girls by age 10 at different coverage levels, or with additional catch-up or vaccination for all by age 10 strategies. Each panel considers different assumptions of one-dose HPV vaccine durability of (A) lifelong efficacy, (B) pessimistic waning of 20 years of efficacy and 10 years of waning, and (C) alternative waning of 30 years of efficacy and 20 years of waning. The graphs display the discounted incremental costs (*x*-axis; in 2023 USD) and DALYs averted (*y*-axis) over a 100-year time horizon compared to no vaccination. The cost-effectiveness of changing from one strategy to a more costly alternative strategy is calculated by taking the difference in cost and dividing it by the difference in DALYs of the two strategies. The dotted line represents the strategies that are efficient because they are more effective and either cost less or have a more attractive cost-effectiveness ratio than less effective options. The ICER is the reciprocal of the slope of the line connecting the two strategies under comparison. All points represent the median of 25 parameter sets. Abbreviations: EP, efficacy period; WP, waning period; YO, year-old; CU, catch-up.



Chapter 4. A framework policy analysis of single-dose HPV vaccination adoption in East Africa: a rapid review

A framework policy analysis of single-dose HPV vaccination adoption in East Africa: a rapid review

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Key words: HPV vaccination, single-dose schedule, Ethiopia, Uganda, Tanzania, policy, implementation science, cervical cancer elimination, sub-Saharan Africa, East Africa

Abstract

Background

Cervical cancer is a global public health problem. While HPV vaccination effectively prevents cervical cancer, vaccination coverage remains low in low -and-middle-income countries (LMICs) where around 94% of cervical cancer-related deaths occur. To improve coverage and accelerate progress toward achieving cervical cancer elimination, the World Health Organization (WHO) recommended countries to switch to a single-dose HPV vaccination schedule in 2022. Despite strong evidence of the health and economic benefits of a single-dose HPV vaccination schedule, its adoption has varied across countries. We sought to rapidly review existing evidence to assess the "how" of policy reform on HPV vaccination leveraging a policy analysis of single-dose HPV vaccination adoption in three East African countries.

Methods

We used the Health Policy Triangle Framework (HPF) to compile key considerations that led to the adoption of single-dose HPV vaccination in Ethiopia, Uganda and Tanzania. Relevant articles from peer-reviewed journals and grey literature published up to December 2024 were selected using pre-set inclusion and exclusion criteria. Data were extracted and summarized using a rapid qualitative analysis approach guided by the HPF.

Results

Twenty-four articles from academic and grey literature were examined. Beyond context-specific aspects, a few common themes emerged across the three countries. Political will was crucial to prioritize the revision of the HPV vaccination policy. The policy revision on the HPV vaccination schedule was undertaken building on existing evidence and the WHO endorsement.

Additionally, the availability of key evidence on the burden of the disease, the efficacy, and the economic benefit of the single-dose schedule played an important role in the policy revision process. At the national level, National Immunization Technical Advisory Groups (NITAGs) were central to the single-dose decision-making process.

Conclusion

Our findings highlighted key considerations for the policy revision process in three East African countries which could inform strategic policy decisions in these countries and comparable settings.

Background

Globally, cervical cancer is the fourth most common cancer among women and in 2022, 94% of cervical cancer-related deaths occurred in low-and-middle-income countries (LMICs).(96) Persistent infections with high-risk human papillomavirus (HPV) are the primary cause of cervical cancer but HPV vaccination is known to effectively prevent cervical cancer. Unfortunately, HPV vaccination coverage remains low. In 2023 first dose HPV vaccination coverage was only 27% globally and 46 countries were yet to introduce HPV vaccination in their immunization program as of December 2024. (97,15) In 2014, the World Health Organization (WHO) recommended countries to switch from a three to a two-dose schedule to improve HPV vaccination coverage. In 2022, the WHO updated the HPV vaccination recommendation to a single-dose HPV schedule to accelerate progress towards achieving cervical cancer elimination based on the strength of evidence of the health and economic benefits single-dose HPV vaccination.(98–100)

Despite this recommendation, the adoption of a single-dose HPV vaccination schedule has been slow where only 67 countries globally had adopted a single-dose HPV vaccination schedule by the end of 2024.(15) In East Africa specifically, HPV vaccination schedules vary across countries despite the high burden of cervical cancer in the region and the potential benefits of a single-dose HPV vaccination schedule to expand coverage. (15,101) In this setting, cervical cancer had the highest age-standardized incidence and mortality rate in 2022. (102) At country levels, cervical cancer was the 2nd most common and deadly cancer in Ethiopia while it had the highest incidence and mortality rate in Uganda and Tanzania. (103–105)

Several studies have shown the durability of the protection of single-dose HPV vaccination as well as its potential benefits on health outcomes, cost and implementation outcomes but gaps remain in the literature on why some countries decide to adopt this approach and others do not.

(4,37,106–108,88,109) Studies conducted on the diffusion of policies have reported that early adopters often implement policies for economic or political reasons, but that interaction with early adopters was also a primary influence on adoption. (110) They highlighted that behaviors or adoptions can spread through networks like a disease and the so-called "contagion model" could influence the adoption of policies between countries based on exposure to early adopters. Additionally, adoption decisions tend to be influenced by information from similar settings where policies have been adopted and implemented within a network.

Health policy analysis can address this gap by generating evidence underlining factors that influence policy changes to inform future policy strategic decisions or implementation and support decision-making in comparable settings. (111) Furthermore, considering diverse influencing parties involved in policy setting and revision, policy analysis cannot ignore the "how" of policy reforms on policy choices and implementation practices. (112) In this study, we sought to address the "how" of policy reform on HPV vaccination by leveraging a policy analysis of single-dose HPV vaccination adoption in three East African countries.

Methods

Study Approach

We used the Health Policy Triangle Framework (HPF) to unpack how, why and who was involved in the adoption of the single-dose HPV vaccination schedule in Ethiopia, Uganda and Tanzania . (112) While other frameworks such as the general diffusion model might be appropriate in assessing determinants of adoption, we used the HPF since it was more appropriate to address our research question and it can be used to conduct a policy analysis prospectively or retrospectively. (110) The HPF has been used elsewhere for health system analysis purposes in

LMICs and it offers the possibility to assess complex interrelationships in policy by separating the policy analysis into context, content, process and actors to explain how and why policies do or do not change over time. (113–115) Domains of the HPF are defined as follows: *context* refers to systemic factors including social, economic, political, cultural and other environmental conditions. *Content* speaks to policy objectives, operational policies, legislation, regulations and guidelines. *Process* refers to the way policies are initiated, developed or formulated, negotiated, communicated, implemented, and evaluated. Lastly, *actors* are defined as influential individuals (senior policy- and decision-makers), groups and organizations. (112,116)

Data Collection and Analysis

We identified relevant documents by searching PubMed, CINAHL Complete, African Journal Online, Global Index Medicus, ProQuest, Academic search complete, Google Scholar and grey literature from key evidence generating institutions (WHO, JSI, Jhpiego, PATH) as well as media and press releases from Ethiopia, Uganda and Tanzania to gather relevant literature. Additionally, we searched the Government and Ministry of Health websites of the three countries to compile important announcements and documents published by the Government. Table S1 in the supplementary materials summarizes details of the inclusion criteria. Search strategies were adjusted to fit different database settings and included search terms such as [‘HPV vaccine’ OR ‘HPV vaccination’] AND [‘Single-Dose Schedule’ OR ‘Reduced Dose Schedule’] AND [‘Ethiopia’ OR ‘Uganda’ OR ‘Tanzania’] (Table S2).

A librarian from the University of Washington (TJ) was consulted at different stages of the review to ensure that we searched relevant databases using appropriate search terms and that the review process was conducted appropriately. All compiled publications and documents were managed in Covidence where they were deduplicated and screened for relevance based on their

titles, abstracts and contents of the documents. (117) Prior to conducting the review, the protocol was published in Prospero (registration number CRD42024624104). After screening all compiled documents, relevant documents published up to December 2024 were analyzed using a rapid review approach guided by the HPF. (118) Key insights were compiled using domains the HPF to capture how policy on HPV vaccination evolved in East African countries that adopted a single-dose schedule.

Results

The search yielded 413 articles from database searches and other sources including the grey literature where relevant websites and reports were searched. After removing duplicates, 245 records were moved for a title and abstract review where 197 records were excluded, and 48 remaining articles were moved to a full-text review process. Of these, 24 articles were included in the review. Figure 1 presents the PRISMA flow of records selected through the review process and Table S3 in the supplementary materials summarizes key details of documents that were included in the review.

In the three countries, the HPV vaccination program was introduced using lessons from demonstration projects before updating the program to a single-dose schedule (Table 1). Uganda rolled out the demonstration project and its national HPV vaccination program earlier than Ethiopia and Tanzania where its demonstration project was implemented in 2008 and HPV vaccination was introduced nationally in 2015 while the demonstration project and national introduction did not happen until the mid-2010s and 2018 in Ethiopia and Tanzania. (119–124) (Figure 2) Additionally, the demonstration project was implemented using a three-dose schedule in Uganda while a two-dose schedule was used during the demonstration project conducted in Ethiopia and Tanzania, aligning with WHO recommendations that were in place at that time.

(98,120,122,125) Additionally, Uganda and Tanzania focused on a single age cohort throughout the evolution of the HPV vaccination program while Ethiopia targeted 9–13-year-old girls during the demonstration project, scaled back to a single age cohort of 14 year-old-girls before shifting to focus on 9-year-old girls. (126,127) Additionally, after the 2024 single-dose HPV multi-age cohort (MAC)campaigns targeting 9-14-year-old girls that were implemented in Ethiopia and Tanzania to increase access, a single-dose schedule was expected to be routinely delivered to 9-year-old girls. (127,128) School-based vaccination was the most common delivery strategy across the three countries throughout the different phases of the HPV vaccination program. (15,122–125) Table 1 summarizes key characteristics of HPV vaccination in the three countries during the demonstration projects, national introductions, and after switching to a single-dose schedule.

Policy Considerations for single-dose HPV vaccination adoption in Ethiopia

Context

Cervical cancer is a growing public health problem in Ethiopia. Building on lessons learned from the demonstration project, Ethiopia introduced the HPV vaccination program in 2018 targeting 14-year-old girls even if the initial plan was to deploy it to a multi-age cohort (MAC). This decision was driven by the global vaccine shortage that limited the number of vaccines that countries received. (124,129) In 2023, key immunization stakeholders from Ethiopia reported that a single-dose schedule was cost and logistically efficient but more scientific evidence supporting the benefit of the single-dose schedule was needed to support their country's decision. Additionally, political unrest and unreliable administrative data complicated the countries' decision-making process. (130)

Content

In addition to the WHO's position papers that were published in 2014, 2017, and 2022: Ethiopia published the National Cancer Control Plan and guidelines for cervical cancer control and prevention in 2015 which supported policy setting and revision for HPV vaccination. (98–100,120). In 2023, the WHO Africa Regional Immunization Technical Group (RITAG) endorsed WHO recommendations on the single-dose HPV vaccination schedule and encouraged African countries to leverage a single-dose schedule to accelerate cervical cancer prevention efforts. (131)

Actors

Key influencing parties involved in the adoption and delivery of the single-dose schedule included: the Ministry of Health (MOH), Inter-Agency Coordinating Committee (ICC), MOH's Expanded program on Immunization (EPI), the National Immunization Technical Advisory Group (NITAG), the WHO, Gavi, the Vaccine Alliance, and the United Nations Children's Fund (UNICEF).(132,133) The Ministry of Education and implementing partners such as the Clinton Health Access Initiative (CHAI), John Snow, Inc, PATH, the International Rescue Committee (IRC), the Christian Relief and Development Associations (CCRDA)/CORE Group Partners Project (CGPP), Family Health International (FHI360), and Girls Effect were also reported among key players. (129)

Process

In Ethiopia, the ICC was reported as the main decision-making body for all national vaccination programs both for introduction and updates on delivery strategies. NITAG members reported in 2017 that for a potential switch to single-dose, the NITAG would review evidence, drive the discussion on schedule change and advice the ICC for an informed decision-making process. (120) After the publication of the WHO's position paper in 2022, the NITAG was

requested to advise the MOH on their recommendation given the potential health and economic benefit of a single-dose schedule in Ethiopia. In March 2023, the NITAG recommended postponing the decision to switch to a single-dose schedule until sufficient evidence was compiled. (134) After additional consultations, Ethiopia's MOH approved the single-dose schedule and implemented a single-dose MAC campaign targeting 14-year-old girls in March 2024 to align with the WHO's SAGE recommendations. (129) This was followed by an expansion of the targeted age group to 9–14-year-old girls to increase coverage. The MAC campaign was a one-time activity after which HPV vaccination efforts were expected to be integrated into routine immunization schedules targeting 9-year-old girls. (127)

Policy Considerations for single-dose HPV vaccination adoption in Uganda

Context

In an assessment conducted in 2007 before the introduction of the HPV vaccination program, policymakers perceived HPV vaccination as a potential long-term solution to prevent cervical cancer. (135) The government of Uganda was committed to protecting women of reproductive age against vaccine-preventable diseases and the National Resistance Movement party had pledged to scale up HPV vaccination in its 2011-2016 manifesto. (136) Additionally, immunization and the introduction of new vaccines were identified among national MOH priorities. (137) During the introduction of the HPV vaccination program, a new policy was not deemed necessary since EPI policies and the MOH Reproductive Health division were expected to accommodate both primary and secondary cervical cancer prevention efforts (135) A focus group discussion conducted in 2023 with NITAG members highlighted the lack of adequate human resources for the delivery of school-based outreach services in Uganda. (130)

Content

In Uganda, policy guidelines that set up national standard for HPV vaccination and integrated them into existing policies were identified as key drivers of HPV introduction. (135) The Public Health Act 1935 (Ch 281), the 2000 revision, and the Local Government Act (CH243) mandated the government of Uganda to purchase and introduce vaccines for the public good. In 2007, the Uganda National Drug Authority registered bivalent (Cervarix) and quadrivalent (Gardasil) HPV vaccines. (136) Additionally, the cervical cancer strategic plan and the Uganda Cancer Society Strategic plan were published in 2010 and 2016 respectively. These policies and guidelines were supplemented by WHO recommendations on HPV vaccination schedule. (98–100,131)

Actors

In addition to global norm-setting bodies such as the WHO, Gavi and UNICEF; actors involved in single-dose adoption in Uganda included MOH, the Uganda National Expanded Program on Immunization (UNEPI), NITAG, Uganda National Immunization Technical Advisory Group (UNITAG), the Advisory Committee on Vaccines and Immunization (ACVI) and implementing partners such as PATH, and the USAID. (137)

Process

Political will and active support were reported as a crucial driver for policy change favorable to HPV vaccine adoption. (135) In Uganda, the decision to evaluate a schedule change depended on the recommendation of the WHO's SAGE on Immunization for the vaccine since the country was supported by Gavi. (138) In a study that assessed a potential switch to a single-dose schedule in 2017, NITAG members reported that the MOH and the Advisory Committee on

Vaccines and Immunization (ACVI) were the key decision-making bodies for the revision of the HPV vaccination schedule in Uganda. (120) In this study, the decision-making process was reported to consist of: 1) a NITAG consultation and review of the evidence, 2) a presentation to the MOH and ACVI and 3) an endorsement of the recommendation by the MOH and ACVI.(120) Recently, a document summarizing the policy revision process for HPV vaccination schedule in Uganda reported that the process might have followed the following steps: 1) the EPI manager notified the NITAG of new data and suggested an evaluation of existing policy; 2) NITAG evaluated the existing evidence focusing on aspects including the vaccine characteristics, single-dose effectiveness, the country's context and exiting challenges for vaccine delivery; 3) NITAG recommended the MOH to switch to a single-dose schedule; 4) the MOH adopted the recommendation as a policy revision and MOH guidelines were updated accordingly; 5) district health officers and other stakeholders communities, schools, etc) were notified and HPV vaccination materials were updated (vaccination cards and materials). (138)

For new vaccine introductions, the process was reported to be different where the Health Interagency Policy Advisory Committee (HIPAC) is involved and gives the final approval and monitors vaccine implementation. (137) When the WHO and Gavi recommend a new vaccine, the Uganda National Academy of Science (UNAS) elects a NITAG or an ACVI for the new vaccine. Then the NITAG collects and reviews evidence on the potential new vaccines and makes evidence-based recommendations to the UNAS. Based on their recommendations, UNAS advises the Technical Working Group (TWG) within the MoH (chaired by the EPI manager) and the MOH TWG makes the decision. Once the decision is made, the EPI manager develops a proposal and presents it to the senior management committee in the MoH where if approved, the proposal is

submitted to HIPAC. Depending on the availability of the vaccine, the vaccine is then procured at the national level and delivered to the districts. (137)

Policy Considerations for single-dose HPV vaccination adoption in Tanzania

Context

Tanzania decided to introduce the HPV vaccine due to the high burden of cervical cancer, strong political commitment, a successful demonstration project and widespread community acceptance of the vaccine. (121) The initial plan was to introduce the vaccine for 9-14-year-old girls but the focus shifted to a single cohort of 14-year-olds due to limited global vaccine supply. (125) Key stakeholders from the EPI and NITAG reported in 2023 that switching to a single-dose would help address cost challenges and simplify delivery. (130)

Content

Tanzania established its cervical cancer strategic plan in 2011 before implementing WHO recommendations on HPV vaccination. This was followed by the publication of the national cancer strategic plan in 2013 that built on the Ocean Road Cancer Institute Act from 1996 which established the Ocean Road Cancer Institute (ORCI), a major public institution under the MOH that provides comprehensive cancer care. (139)

Actors

Key actors who were involved in HPV vaccination policy revision included the Ministry of Health, Community Development, Gender, Elderly, and Children (MoHCDGEC), WHO, UNICEF, the Tanzania Immunization Technical Advisory Group (TAITAG), the EPI TWG, and the National Interagency Coordinating Committee (ICC). (125) Other key players involved in HPV

vaccination in Tanzania include the Ministry of Education and the President's Office of Reginal Administration and Local Government (PORALG) which supported coordination at sub-national regional and council levels. Additionally, community and religious organizations, professional associations, and technical partners such as the Clinton Health Access Initiative (CHAI), Jhpiego, PATH, and JSI were involved in HPV vaccination delivery. (125,140) The EPI TWG consists of immunization stakeholders from the MoHCDGEC, WHO, UNICEF, and technical partners. (125)

Process

Despite limited evidence in the literature of the process used for the policy revision of the HPV vaccination schedule, the decision-making process was similar to the process highlighted by key stakeholders from LMICs including those from Tanzania.(133) This process was also similar to the process used for the introduction of the HPV vaccination program in Tanzania. (125,133) In short, the EPI TWG consolidated existing evidence that was shared with the TAITAG for its review and recommendations. Once the recommendations from the TAITAG were approved by the MoHCDGEC, they were endorsed by the ICC and the recommendations on HPV vaccination schedule were updated accordingly. (125,133)

Table 2 summarizes key policy aspects of single-dose HPV vaccination adoption in the three countries across domains of the HPF.

Policy-making analysis of single-dose HPV vaccination adoption across countries based on domains of the HPF

Context

Some similarities emerged across the three countries in all 4 domains of the HPF. In 2018, many countries supported by Gavi, including Ethiopia and Tanzania launched the HPV vaccination

into their routine immunization program which stretched the global manufacturing capacity and complicated countries' ability to deliver the vaccine using a MAC approach as initially planned. (121) Before the WHO recommendation on single-dose HPV vaccination was published, NITAG members and EPI managers highlighted the need for strong political will to consider policy change despite the financial and logistics advantages of single-dose delivery. (119) This was reiterated in 2022 during a symposium that convened key stakeholders LMICs, who reported that ownership from the local government was the main driver of HPV vaccination delivery in their settings. (132) Additionally, previous assessments of HPV vaccination delivery in LMICs revealed that school-based vaccination was a better strategy to improve coverage. Unfortunately, this strategy was more expensive, considering the resources needed (e.g., time, transport, stipend), and stretched the capacity of healthcare providers (HCPs) to deliver other services at health facilities. (141)

Content

Evidence showing the impact of the vaccine and the burden of the disease was key to supporting decision-making for HPV vaccination programs in LMICs.(141) Interviews with NITAG members and EPI managers on a hypothetical switch to a single-dose schedule emphasized that WHO recommendations and evidence on the efficacy of the single-dose compared to two or three doses were crucial to initiate any discussion to change the HPV vaccine schedule in their countries. (120) The WHO's SAGE on Immunization recommended in 2014 a two-dose HPV vaccination schedule for girls younger than 15 years instead of 3 doses given the evidence that was available on the non-inferiority of immune responses after a 2-dose schedule.(98) This recommendation was updated in 2017 and later on in 2022 when the WHO urged countries to consider a single-dose HPV vaccination schedule to expand coverage considering strong evidence on the efficacy of the single-dose schedule. (100) This was followed by a regional recommendation

in November 2023 from the WHO Africa Regional Immunization Technical Group (RITAG) endorsing the adoption of a single-dose HPV vaccination schedule to accelerate cervical cancer prevention efforts. (131) Additionally, all three countries had published cervical cancer strategic plans and national cancer control, and prevention plans before launching HPV vaccination programs or updating their national policy on HPV vaccination schedule. (120,139)

Actors

Across countries, main actors who influenced the policy revision included the World Health Organization (WHO), UNICEF, Gavi, MOH and MOH's Expanded program on Immunization (EPI), the local government and NITAGs that were instrumental in HPV vaccine schedule decision-making. (132,133)

Process

An HPV Vaccination acceleration roadmap developed in 2023 by multiple SSA countries reported the need to review evidence to support decision-making to switch to single-dose and update national cervical cancer Elimination strategies. (130) Once WHO recommendations were published, in general, countries followed similar steps to update their HPV vaccination schedule: 1) review of the evidence on the HPV vaccine schedule by the NITAG, 2) submission of the NITAG's recommendation on vaccination schedule to the MOH, 3) upon MOH approval, final technical review and ratification of the MOH recommendation on the dose change by the ICC provides. (133) Figure 3 summarizes key policy aspects of single-dose HPV vaccination schedule adoption across the three countries based on domains of the HPF.

Discussion

This rapid review identified 24 articles that included relevant information regarding policy considerations for single-dose HPV vaccination adoption in Ethiopia, Uganda, and Tanzania. To our knowledge, this is the first study that leveraged a policy framework to better understand how, why, and who was involved in the HPV vaccination policy revision. While considerations for policy revision aligned with each country's context, they highlighted key aspects of the HPF that were common to all three countries during the policy revision process. First, political will played a crucial role in prioritizing HPV vaccination policy. Second, the existence of national cervical cancer prevention and control plans as well as the WHO endorsement of HPV vaccination schedule change and evidence on the health and economic impact of single-dose HPV vaccination played an important role during the HPV vaccination policy revision process. Third, the EPI and NITAGs drove the policy revision process with the support of implementing partners. Lastly, the publication of the WHO recommendation on the single-dose HPV vaccination schedule initiated the policy revision process which was similar to the steps taken during the introduction of the HPV vaccination program. These findings align with previous articles that emphasized the crucial role of political commitment, existing evidence and NITAGs in advancing evidence-based immunization policy and programmatic decisions. (133,142,143)

Political will has been reported as a pre-requite for health reforms among African countries and elsewhere.(144) While political will contributes and avails resources to achieve specific objectives, the literature stresses the need to be cognizant of political constraints and risks associated with reform processes that might influence policy changes or reforms.(145) In our review, an assessment conducted on a hypothetical switch to a single-dose schedule reported that key informants were concerned that a change in HPV vaccine schedule policy could fuel negatively media coverage of the national immunization program. (119) Previously published literature have

reiterated the complex nature of health policy reforms that require more than leaders decision to exercise their "will" or change the policy. (144) Additionally, a previous assessment of health policy analysis in LMICs highlighted that effective policy change requires an emphasis on processes by which the change is achieved to account for concerns of actors who might block the policy change.(111) In our review, we found a diversity of actors who were involved in the policy revision process which underlined the important role of multi-sectoral partnerships (other ministries, technical advisors, funders, norm-setting bodies, etc) in supporting policy revision initiatives. Additionally, we found that existing data on the burden of the disease, the efficacy and potential health and cost impact of a single-dose schedule played a crucial role in supporting the policy revision process in all three countries. This stresses the need to strengthen multidisciplinary and in-country operational research capacity to generate evidence that will catalyze progress to achieve immunization and cervical cancer elimination goals; a call that has been highlighted in recent studies. (146,147)

Findings from this review should be interpreted while accounting for some limitations. Our review only considered articles written in English which could have resulted in a language bias. Additionally, most articles were published before the three countries switched to a single-dose schedule which could have limited the documentation of policy-related events that occurred leading up to the countries' decision to switch to a single-dose schedule and limited our ability to assess with more granularity policy events that happened over time. Moreover, our review focused on three SSA countries that switched to a single-dose schedule at the time of our review which might have not captured key policy considerations in other SSA countries that switched afterward or those that decided to keep the two-dose schedule. Despite these limitations, findings from this review contribute evidence to the field of policy implementation research deepening the

understanding of the policy revision process on HPV vaccination schedule which could inform future strategic health policy decisions in these countries and comparable settings.

Conclusions

The policy revision on HPV vaccination schedule was facilitated by actors, evidence, and processes that were used to introduce the HPV vaccine in the three countries. While endorsements from the WHO and other evidence on single-dose were crucial during this process, NITAGs and the growing burden of cervical cancer in the region were key to achieving a policy change. Our findings highlighted key policy considerations for single-dose HPV vaccination adoption in three East African countries, the insight that could inform similar health reforms in these countries or decision-makers from comparable settings.

Supporting Information

- **Table S1:** Inclusion and exclusion criteria (PICOTS)
- **Table S2:** Search strategy and terms
- **Table S3:** Data Extraction Table from Academic and Grey Literature Sources

Authors Contributions

GU conceptualized the project, extracted and analyzed the data. She also led the drafting and revision of the manuscript. BJW contributed to the conceptualization of the project and validation of findings. TJ provided guidance during the data curation process. SK contributed to the validation of findings. BJW, TJ, SK, JL, NRM, and RVB reviewed and edited the manuscript.

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Conflict of interest

G.U. reports research funding from Sub-Saharan Africa L'Oréal-UNESCO for Women in Science Young Talent program outside this study. N.R.M. reports research funding from the Merck Investigator Studies Program, outside this study. R.V.B. reports that Regeneron Pharmaceuticals provided abstract and manuscript writing support outside this study.

Tables and Figures

Table 1: Key Characteristics of HPV vaccination in the Three Countries

Country	Demonstration Project			Two-dose HPV Vaccination Schedule (Vaccination schedule at introduction)				Single-dose HPV Vaccination Schedule			
	Year	Targeted age group	Delivery strategy	Year of introduction	Targeted age group	Delivery strategy	Coverage[a]	Year of switch	Targeted age group	Delivery strategy	Coverage[b]
Ethiopia	2015-2017	9 -13-year-old girls	School + Outreach	2018	14- year-old girls	School	84%	2023	9-year-old girls	School	60%
Uganda	2008-2011	10- year-old girls	School + HF+ Outreach	2015	10- year-old girls	School + Outreach	64%	2024	10-year-old girls	School	99%
Tanzania	2014-2016	9- year-old girls	School + HF (Year 1) and HF + Outreach (Year 2)	2018	14- year-old girls	HF+ Outreach[c]	49%	2024	9-year-old girls	HF+ Outreach[c]	99%

[a] Last dose HPV vaccination coverage in 2019; [b] First dose HPV vaccination in 2023; [c] Outreach sites include community outreach (>10km from the HF) and school sites (125) Abbreviations: HF: health facilities

Table 2: Determinants of single-dose HPV vaccination adoption in Ethiopia, Uganda and Tanzania based on the HPF

	Ethiopia	Uganda	Tanzania
Context	• Cervical cancer was the 2nd most common cancer and cause of cancer-related deaths in 2022 (103) • The HPV vaccination program was introduced in 2018 focusing on 14 year old school girls due to the global vaccine shortage. (124,129) • In 2023, single-dose schedule was reported as a cost and logistically efficient option but more scientific evidence supporting its benefit was needed to support the decision for its adoption. (130) • Local political unrests and unreliable administrative data challenged the decision-making process to increase coverage.(130)	• In 2022, cervical cancer had the highest age-standardized incidence and mortality rates. (104) • Policymakers perceived HPV vaccine as a potential long-term solution to cervical cancer prevention.(135) • The government was committed to protect women of reproductive age against vaccine preventable diseases. (136) • The lack of inadequate human resources challenged the delivery of HPV vaccination services during school outreaches. (130) • The demonstration project was conducted in 2 districts using a three-dose schedule. (122)	• Tanzania had the 9th highest number of new cervical cancer cases in the world in 2022. (148) • The HPV vaccination program introduced in 2018 targeted14-year-olds instead of 9-14 year olds as initially planned due to limited global vaccine supply. (125) • Poor multi-sectoral collaboration between the Ministries of Education and Health was reported as a main challenge that affect HPV vaccination. • A transition to single-dose vaccination schedule was considered as an approach to overcome costs and delivery challenges. (130)
Content	• The National Cancer Control Plan was published in 2015. • The guideline for cervical cancer control and prevention was published in the same year. (120) • The WHO recommendation on vaccination schedule was published in 2014 and updated in 2022 to inform decision-making. (98,100,131,133)	• The bivalent (Cervarix) and quadrivalent (Gardasil) HPV vaccines were registered by the Uganda National Drug Authority registered 2007. (136) • The Public Health Act 1935 (Ch 281) and 2000 revision as well as the local Gvt Act (CH243) mandated the government to	• The cervical cancer strategic plan was published in 2011. (139) • The National cancer strategic plan was published in 2013. (139) • The WHO recommendations on vaccination schedule was published in 2014 and

		purchase and introduce vaccines. (136) • The Cervical Cancer Strategic Plan was published in 2010. • The Uganda Cancer Society Strategic plan was published 2016. (139) • The WHO recommendations on vaccination schedule was published in 2014 and updated in 2022 to inform decision-making. (98,100,131,133)	updated in 2022 to inform decision-making. (98,100,131,133)
Actor	• MOH • Ministry of Education • NITAG (129) • WHO, UNICEF • Gavi, the Vaccine Alliance • ICC (120,133) • Implementing partners (129)	• MOH • WHO • UNICEF • Gavi • UNEPI • UNITAG • Implementing partners (137)	• MoHCDGEC • TAITAG • The EPI TWG • WHO, UNICEF, Gavi • ICC (125) • Implementing partners (140)
Process	• After WHO recommendation was published in 2022, the NITAG was requested to advise the MOH on their recommendation. (134) • In March 2023, NITAG recommended postponing the decision to switch to a single-dose schedule. (44) • In March 2024, Ethiopia endorsed the single-dose schedule. • A single-dose MAC campaign was implemented targeting 14-year-old girls. (38)	• After WHO recommendation was published in 2022, the EPI manager suggested an evaluation of existing policy. (45) • NITAG evaluated existing evidence • The NITAG presented its recommendations to the MOH and SIVAC to make the final decision. (120) • MOH adopted the recommendation as a policy revision, notified district health	• After WHO recommendation was published in 2022, the EPI TWG consolidated evidence on single-dose HPV vaccination. • The TAITAG reviewed the evidence and shared its recommendations with the MoHCDGEC. • The MoHCDGEC approved the single-dose recommendations

	• In November 2024, the targeted age-group was expanded to 9–14-year-old girls. (30) • Afterwards, HPV vaccination efforts were expected to be integrated into routine immunization schedule targeting 9-year-old girls. (30)	officers, other stakeholders, schools, etc) and updated HPV vaccination materials (vaccination cards and materials). (45)	• Interagency Coordinating Committee (ICC) ratified the MoHCDGEC decision. (125,133)

Figure 1: PRISMA Flow chart (149)

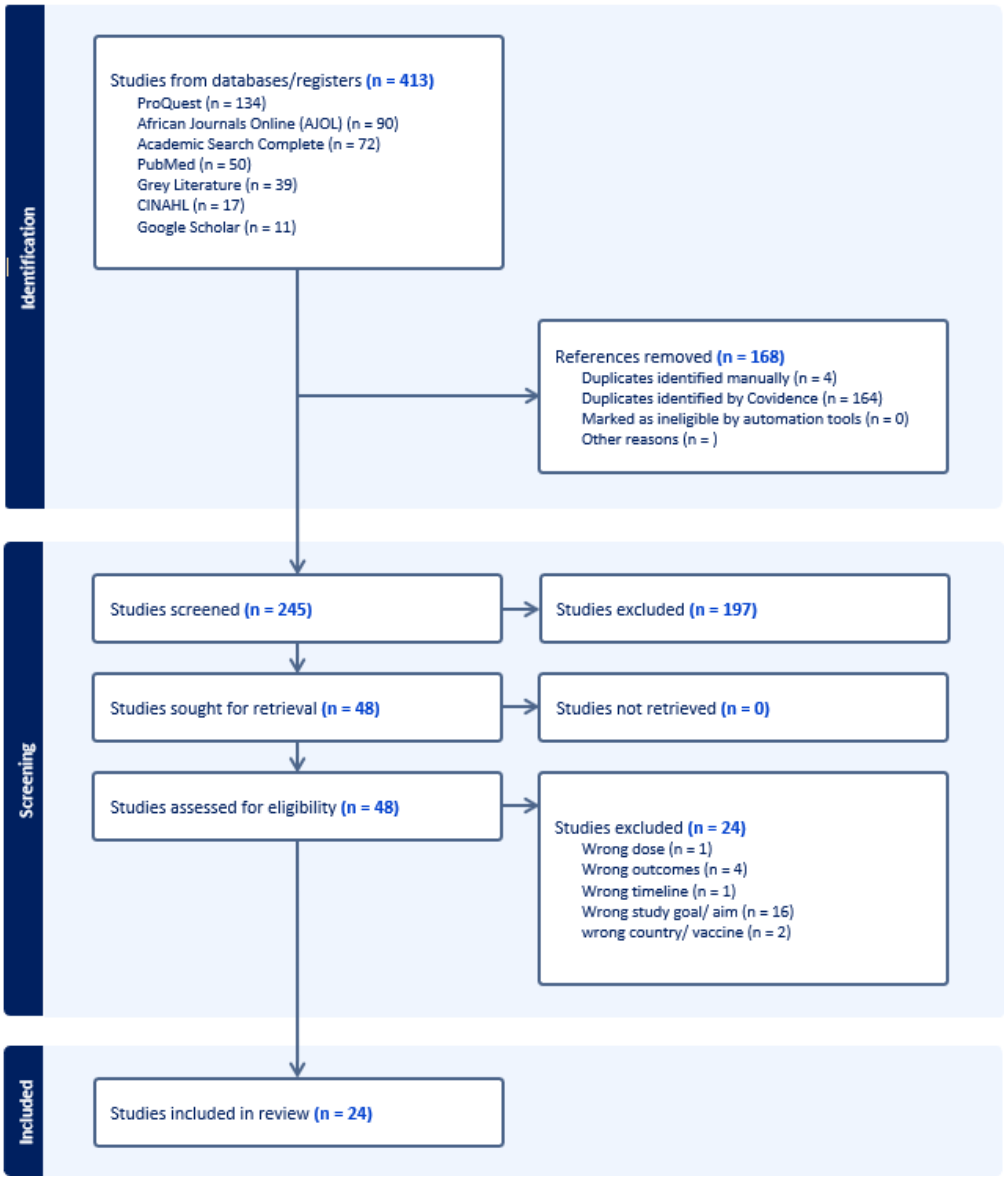


Figure 2: Timeline of Key Events Leading up to the Adoption of the Single-dose HPV Vaccination Schedule in Three East African Countries

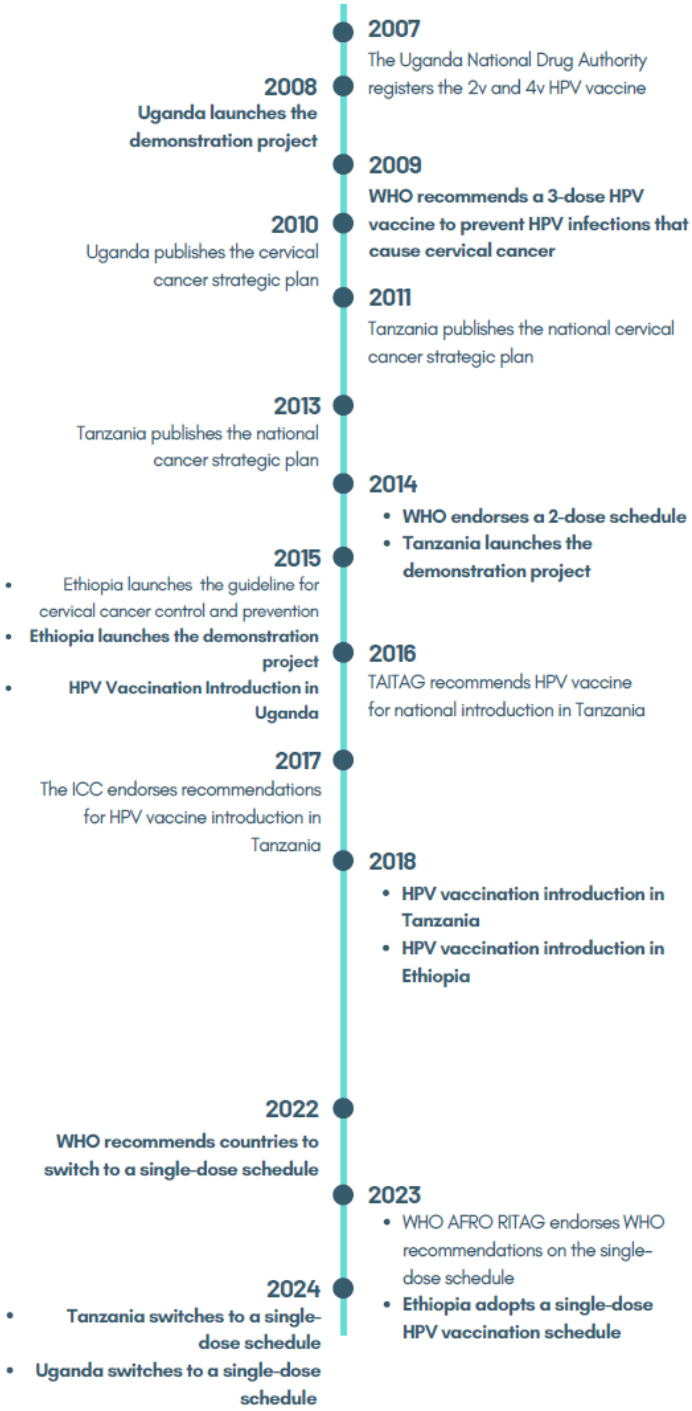
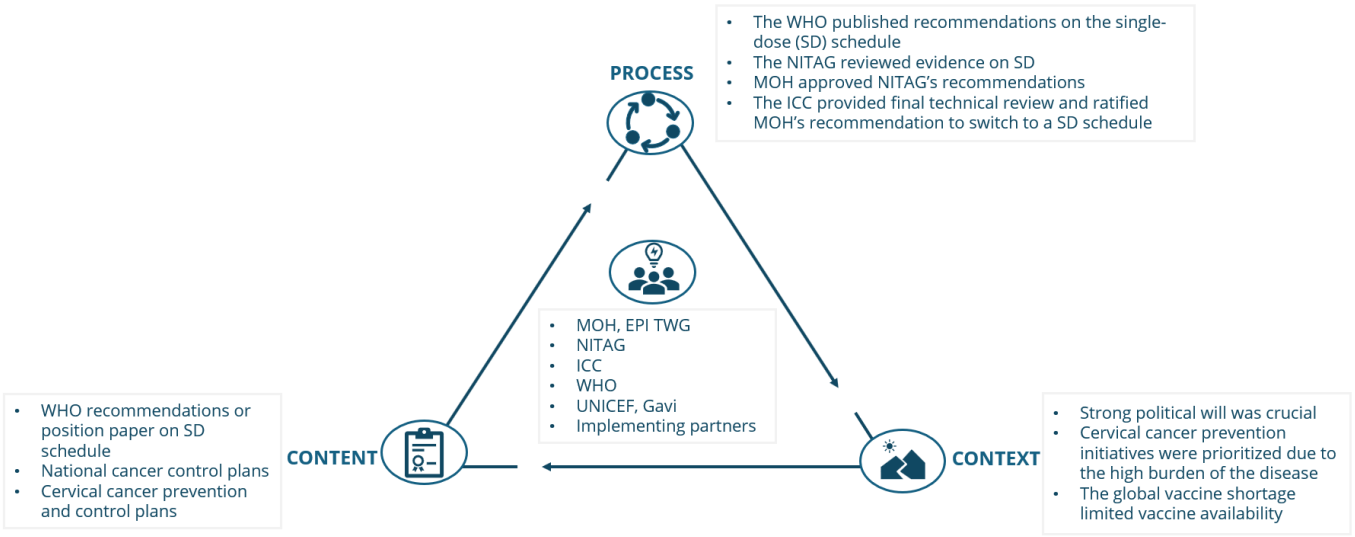


Figure 3: Policy Analysis of Single-dose HPV Vaccination schedule Adoption Across Three East African Countries Based on the HPF



Chapter 5. Discussion

One woman dies from cervical cancer every two minutes, a disease that is largely preventable.(150) In 2020, cervical cancer caused over 340, 000 cancer-related deaths among women globally and it was the largest cause of maternal orphanhood in Eastern and Southern Africa.(151) Additionally, a meta-analysis on HPV vaccination uptake reported that close to 47 million women were fully vaccinated from 2006 – 2020, but only 1% of them were from LMICs.(152) HPV vaccination is crucial to building a world free of cervical cancer and recent evidence on the efficacy and effectiveness of a single-dose schedule presents tremendous advantages to ensure that this life-saving protection reaches all.(5,8,37,37,39,106) A single-dose schedule presents multiple programmatic and economic benefits which would lead to an efficient use of resources and advance the equitable delivery of this important health innovation. Leveraging efficient approaches to protect and save as many lives as possible from cervical cancer is especially important now as recent changes are threating initiatives that support the delivery of vaccines in LMICs.(153,154) This dissertation leveraged implementation science to address knowledge gap in single-dose HPV vaccination adoption in East Africa focusing on the acceptability, cost-effectiveness of single-dose HPV vaccination in Kenya and policy considerations for single-dose adoption in Ethiopia, Uganda and Tanzania. Evidence generated by this dissertation informed decision-makers on Kenya's potential switch to a single-dose schedule and contributed a blueprint to inform future immunization policy revisions.

Previous research described implementation determinants of HPV vaccination in WHO African Region and highlighted interrelationships that existed within and across domain.(155) This study reported that successful HPV vaccine integration into national immunization schedule would expand vaccine delivery and improve uptake; but these effects were contingent on other implementation determinants including the knowledge and belief of healthcare workers (HCW)

and concerns about safety among vaccinators.(155) These individual level determinants are known to affect acceptability which in turn influences HCW and community attitude towards HPV vaccination. Considering pre-existing misinformation and disinformation on HPV vaccination and immunization programs in sub-Saharan Africa, it is crucial to assess implementation outcomes to ensure implementation effectiveness of single-dose HPV vaccination. The field of implementation science has the potential to generate evidence to address challenges with vaccine delivery that immunization programs face in the WHO African Region and catalyze the uptake of immunization services. (146)

In chapter two, we leveraged a mixed-methods study to assess the operationalization of an acceptability framework in the context of HPV vaccination, the acceptability of single-dose HPV vaccination among healthcare providers (HCPs) and predictors of increased acceptability of the single-dose schedule in Kenya. While the Theorical Framework for Acceptability (TFA) has been used in other settings, its use has mainly focused on a qualitative assessment of acceptability. (54,55,57,58) Our application of the Theorical Framework for Acceptability (TFA) to assess acceptability quantitatively revealed that constructs of acceptability were weakly correlated, and they were weak predictors of acceptability. These findings revealed that constructs of acceptability might not be considered or understood by respondents as aspects of acceptability. This reiterated the need to assess and account for the perspective of stakeholders in LMICs when developing implementation science frameworks to ensure their relevance for LMICs.

In chapter two, we found that most HCPs (75.8%) reported that a single-dose schedule was acceptable or very acceptable. Additionally, both qualitative and quantitative findings highlighted that HCPs thought that a single-dose schedule was efficacious in protecting against cervical cancer but a third of respondents were not knowledgeable about single-dose schedule and a similar

proportion reported that there were moral consequences to offering a single-dose schedule. Among HCPs, pharmacists and other cadres had 13% and 10% higher acceptability of the single-dose schedule compared to nurses while HCPs based in urban areas had lower acceptability compared to those in rural settings. Considering the recent switch to a single-dose schedule in Kenya, programmatic interventions should focus on increasing the knowledge on single-dose schedule among HCPs and address concerns that they might have about potential moral consequences of rolling out a single-dose schedule to ensure high acceptability among HCPs which will translate into increased uptake in the community.

Additionally, over three quarters of HCPs reported that a single-dose schedule would require less resources, save time and reduce the rate of defaulters. In chapter 3, we quantitatively estimated the potential health and economic impact of switching to a single-dose schedule in Kenya. Building on a previous research that assessed the potential impact of HPV vaccination accounting for the bidirectional interaction between HIV and HPV infection and a recent cost-effectiveness analysis that assessed the impact of different HPV vaccine regimens on health and economic outcomes in Kenya (27,71), we assessed the impact of switching to a single-dose schedule while accounting for uncertainty around the durability of a single-dose and estimating potential impact of additional vaccinations from a five-year cost-saving after switching to a single-dose schedule. First, we found that regardless of potential assumptions on waning durability of the HPV vaccine, a single-dose HPV vaccination at 70- 90% coverage and a two-dose schedule at 90% coverage were most efficient strategies. Even if a two-dose schedule at 90% resulted in the greatest disability-adjusted life years (DALYs) averted, it was more costly compared to alternative one-dose scenarios with 30EP/ 20 WP or lifetime durability assumption that resulted in high health benefits. Our findings aligned with a recent study that reported an expected reduction in the

estimated financial and economic cost for HPV vaccine delivery under a single-dose schedule compared to a two-dose schedule in Ethiopia, Rwanda and Uganda.(108)

We found that switching from a two-dose schedule for 10-year-old girls to a single-dose schedule would save the Kenyan Government over US $21 million which could fund additional vaccination to expanded age-group of girls or a vaccination for all strategy to increase coverage. By supplementing a single-dose HPV vaccination schedule with additional catch-up vaccinations, all two-dose schedule scenarios were less efficient since they were more expensive and translated into similar or poorer health outcomes compared to alternative single-dose strategies. Even by assuming a pessimistic waning assumption of a single-dose schedule, a single-dose schedule for girls aged 10 supplemented with a catch-up vaccination of 11–24-year-old girls still resulted into better health and economic outcomes compared to a two-dose schedule and it reduced the total DALYs averted by 3.6% and the total cost by 33% compared to a two-dose vaccination at 90% coverage. Our findings reinforced the benefit of leveraging a single-dose schedule to accelerate cervical cancer elimination goal by using resources efficiently while reaching and saving more lives.

Following the 2022 WHO recommendation for countries to switch to a single-dose schedule to increase coverage, countries had to review these recommendations and decide if a policy revision on HPV vaccination schedule was appropriate for their settings. In chapter 4, we used a policy framework analysis to assess the “how” of policy decision on single-dose adoption in Ethiopia, Uganda and Tanzania, three East African countries that had switched to a single-dose schedule by December 2024. Political will has previously been reported as an enabler of successful implementation HPV vaccination and other reforms in Africa.(144,155) Our rapid review revealed that in some settings, decision-makers were concerned about negative impact of a potential

schedule change on how the immunization program is perceived. Additionally, we highlighted other factors (actors, context, content, and process) that contributed to the adoption of the single-dose schedule in the three East African countries. A diversity of actors were involved in the policy revision process across countries, but National Immunization Technical Advisory Groups (NITAGs) were central to the single-dose decision-making process which reinforced the important role that multi-sectoral partnerships play in facilitating immunization policy revisions processes. Lastly, country specific implementation evidence played an important role in guiding the policy revision process. Thus, reiterating the need to invest in and reinforce local operational research capacity to continuously generate evidence to inform an efficient use of resource and health policy setting initiatives.

In conclusion, this dissertation generated important findings that informed the policy revision process on HPV vaccination schedule in Kenya and could serve as a blueprint for future policy revision initiatives on changes in immunization schedules. While a single-dose HPV vaccination would improve prevention of cervical cancer, future implementation research studies should contribute evidence to inform decision on emerging evidence on therapeutic HPV vaccination.(156,157) This promising approach to treat HPV infections and pre-cancers through vaccination could further accelerate cervical cancer elimination considering the logistics, cost and capacity limitations of existing cervical cancer treatment modalities. Ultimately, if we want to eliminate cervical cancer, we need to contribute to the fast translation and delivery of impactful preventive and treatment modalities that will leave no woman behind.

Supplementary Materials: Additional Methodology Details and Results for Chapter 2

Supplementary Materials

Supplementary Methods

- **Supplementary Methods 1:** Approach used to select relevant TFA constructs and adapt the TFA questionnaire
- **Supplementary Methods 2:** Data collection Tool

Supplementary Tables

- **Supplementary Table 1:** Correlation between the reported general acceptability and the computed acceptability varying constructs used to represent relevant domains (with all variables treated as continuous variable)
- **Supplementary Table 2:** Output from the regression model assessing the association between constructs of acceptability and the reported general acceptability.
- **Supplementary Table 3:** Correlation between the general acceptability and the different constructs of acceptability (Treated as categorical variables)
- **Supplementary Table 4:** Determinants of acceptability among HCPs. Findings of a multivariate linear regresion model (without interraction)
- **Supplementary Table 5:** Determinants of acceptability among HCPs. Findings of a multivariate linear regresion model (with interraction between referral level and county as well as job title and job duration)
- **Supplementary Table 6:** Model selection: Checking the best fitting model

Supplementary Figures

- **Supplementary Figures 1:** Distribution of responses on domains of acceptability overall and across counties
- **Supplementary Figure 2:** Model selection: Assessing the linearity assumption for the linear regression model with lowest AIC values**Supplementary Figure 3:** Comparison of estimates of determinants of acceptability among HCPs. Findings of a multivariate logistic regression with and without the fairness construct included in the model, reporting incidence rate ratios (IRR) with 95% Confidence Intervals (CI)
- **Supplementary Figure 4:** Determinants of acceptability among HCPs. Findings of a multivariate poisson regresion reporting incidence rate ratios (IRR) with robust standard errors (HC1)

Supplementary Methods

Supplementary Methods 1: Approach used to select relevant TFA constructs and adapt the TFA questionnaire

The theoretical framework for acceptability (TFA) has 7 components constructs as described by Sekhon and colleagues.[22,23] The TFA was leveraged to inform the design of the survey used in our study by focusing on questions that were relevant to the context of single-dose HPV vaccination in our setting. All constructs were included in our questionnaire except for the construct of "affective attitude" and "opportunity costs" since they were not deemed relevant to our context. Additional questions were added to capture other aspects of burden (time, effort or resources) that were crucial from HCPs' perspective to deliver a single-dose HPV vaccination. With input from local implementers, we adjusted the construct of intervention coherence to capture HCPs' knowledge of the single-dose HPV vaccination schedule. Additionally, with feedback from local partners, additional questions were added to the construct of "perceived effectiveness" to explore HCPs' perceived effectiveness of the HPV vaccine in preventing HPV infections in addtion to capturing their perceived effectiveness of the single-dose. Questions were also added to the construct of self-efficacy to assess HCPs' confidence in addressing concerns and explaining benefit of the HPV vaccine to parents and AGYW in addition to assesssing their confidence in providing the single-dose HPV vaccine to AGYW. Selected constructs and related questions were validated and pilot tested with HCPs in Kenya before launching the survey. Quantitative data from survey responses were analyzed following the guidance from Sekhon and colleagues while qualitative data from free text responses were analyzed using a rapid qualitative analysis approach.[23,34,35] The table below summarizes the 7 TFA constructs, their definition, the generic questionnaire items as well as related quantitative questions that were included in our adapted TFA questionnaire. A copy of the survey with all the questions that were asked HCPs is available in the Supplementary Methods 2.

<table>
<tr><th>TFA construct</th><th>Definition</th><th>Generic TFA questionnaire items</th><th>Questionnaire items from the survey</th></tr>
<tr><td>Affective attitude</td><td>How an individual feels about the intervention</td><td>Did you like or dislike [intervention]?
OR
How comfortable did you feel [behaviour i.e. to engage with] [intervention]?</td><td>NA</td></tr>
<tr><td>Burden</td><td>The amount of effort required to participate in the intervention</td><td>How much effort did it take [behaviour i.e. to engage with] [intervention]?
<table>
<tr><td>No effort at all</td><td>A little effort</td><td>No opinion</td><td>A lot of effort</td><td>Huge effort</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table></td><td>How much effort does it take you to provide one dose of the HPV vaccine to AGYW?[a]
<table>
<tr><td>No effort at all</td><td>A little effort</td><td>No opinion</td><td>A lot of effort</td><td>Huge effort</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table></td></tr>
</table>

			In your opinion, how much time does it/ will it take you to provide a single-dose of the HPV vaccine to AGYW?[a] No time at all | Little time | No opinion | A lot of time | Huge amount of time 1 | 2 | 3 | 4 | 5 In your opinion, how much resource does it/ will it take you to provide a single-dose of the HPV vaccine to AGYW?[a] No resource at all | Little resource | No opinion | A lot of resources | Huge resources 1 | 2 | 3 | 4 | 5 . How much effort does it take to incorporate the Single-dose into the existing workflow at your clinic/ facility?[b] No effort at all | A little effort | No opinion | A lot of effort | Huge effort 1 | 2 | 3 | 4 | 5

<table>
<tr>
<td>Ethicality</td>
<td>The extent to which the intervention has good fit with an individual's value system</td>
<td>How fair is [Intervention] for [people/ participants/ recipients] with [condition]?
<table>
<tr><td>Very unfair</td><td>Unfair</td><td>No opinion</td><td>Fair</td><td>Very fair</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
OR
There are moral or ethical consequences [behaviour i.e. to engage with] [intervention]
<table>
<tr><td>Strongly disagree</td><td>Disagree</td><td>No opinion</td><td>Agree</td><td>Strongly agree</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
</td>
<td>In your opinion, do you think there are moral or ethical consequences with offering one dose of the HPV vaccine to AGYW?[a]
<table>
<tr><td>Strongly disagree</td><td>Disagree</td><td>No opinion</td><td>Agree</td><td>Strongly agree</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
How fair is the reduced dose strategy for the AGYW?[a]
<table>
<tr><td>Very unfair</td><td>Unfair</td><td>No opinion</td><td>Fair</td><td>Very fair</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
</td>
</tr>
<tr>
<td>Perceived effectiveness</td>
<td>The extent to which the intervention is perceived to have achieved its objective</td>
<td>The [intervention] has improved [behaviour/ condition/ clinical outcome]:
<table>
<tr><td>Strongly disagree</td><td>Disagree</td><td>No opinion</td><td>Agree</td><td>Strongly agree</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
</td>
<td>To what extent do you think the HPV vaccine prevents HPV infection and cervical cancer?[b]
<table>
<tr><td>Not at all</td><td>Slight protection</td><td>No opinion</td><td>Moderate protection</td><td>Full protection</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
To what extent do you think the single-dose of the HPV vaccine would prevent HPV infection and cervical cancer?[a]
<table>
<tr><td>Not at all</td><td>Slight protection</td><td>No opinion</td><td>Moderate protection</td><td>Full protection</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Intervention coherence</td>
<td>The extent to which the participant understands how the intervention works</td>
<td>It is clear to me how [intervention] will help [manage/ improve] my [behaviour/ condition/clinical outcome]
<table>
<tr><td>Strongly disagree</td><td>Disagree</td><td>No opinion</td><td>Agree</td><td>Strongly agree</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
*Please tell us more about your views</td>
<td>How knowledgeable are you about the single-dose strategy of the HPV vaccine?[a]
<table>
<tr><td>Very unknowledgeable</td><td>Slightly unknowledgeable</td><td>No opinion</td><td>Moderately knowledgeable</td><td>Very knowledgeable</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table></td>
</tr>
<tr>
<td>Self - efficacy</td>
<td>A participant's confidence that they can perform behaviour(s) required to participate in the intervention</td>
<td>How confident did you feel about [behaviour i.e. engaging with] [intervention]?
<table>
<tr><td>Very unconfident</td><td>Unconfident</td><td>No opinion</td><td>Confident</td><td>Very confident</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table></td>
<td>How confident are you in providing (correctly) single-doses of HPV vaccines to AGYWs?[a]
<table>
<tr><td>Very unconfident</td><td>Unconfident</td><td>No opinion</td><td>Confident</td><td>Very confident</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
How confident are you in explaining the benefits of the HPV vaccine to AGYWs and/ or their parents/ guardians?[b]
<table>
<tr><td>Very unconfident</td><td>Unconfident</td><td>No opinion</td><td>Confident</td><td>Very confident</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
How confident are you in addressing concerns that AGYWs and/ or their parents/ guardians have on the HPV vaccine?[b]
<table>
<tr><td>Very unconfident</td><td>Unconfident</td><td>No opinion</td><td>Confident</td><td>Very confident</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table></td>
</tr>
</table>

<table>
<tr>
<td>Opportunity costs</td>
<td>The benefits, profits or values that would have to be given up to engage with the intervention</td>
<td>[Behaviour i.e. engaging in] [intervention] interfered with my other priorities
<table>
<tr><td>Strongly disagree</td><td>Disagree</td><td>No opinion</td><td>Agree</td><td>Strongly agree</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
</td>
<td>NA</td>
</tr>
<tr>
<td>General acceptability</td>
<td></td>
<td>How acceptable was the [intervention] to you?
<table>
<tr><td>Completely unacceptable</td><td>Unaccep table</td><td>No opinion</td><td>Acceptable</td><td>Completely acceptable</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
</td>
<td>In your opinion, how acceptable do you think it is to provide a single-dose of the HPV vaccine to AGYW?[a]
<table>
<tr><td>Very unacceptable</td><td>Unacceptable</td><td>No opinion</td><td>Acceptable</td><td>Very acceptable</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
</td>
</tr>
</table>

[a] Questions adapted from the TFA generic questionnaire | [b]Additional questions related to TFA constructs that were deemed important in influencing the acceptability of the single-dose schedule of HPV vaccination in Kenya among HCPs

Supplementary Methods 2: Data collection Tool

Acceptability of the Reduced Dose Strategy of HPV Vaccine

Thank you for taking the time to participate in this study and for completing this survey.

The Kenya Ministry of Health (MoH) recommendation for HPV vaccination is a two-dose schedule 0 and 6 months similar to the World Health Organization (WHO) Recommendations. Kenya currently has a national HPV vaccine program that was launched in 2019 based on evidence from a school-based vaccination for 9-10 years. GAVI has supported two HPV vaccination demonstration projects from 2013-2015 and 2016-present in Kitui county (outside of our proposed study areas). Both demonstration projects used the quadrivalent HPV 16/18/6/11 vaccine in a school-based strategy that targeted girls aged 9-10 years, and the first achieved 85% coverage.

Considering the recent endorsement of the WHO or the reduced dose strategy of the HPV vaccine for adolescent girls and young women (AGYWs), we are interested in your perceptions of how acceptable you think the reduced dose strategy is and what would make HPV vaccination a sustainable component of cervical cancer prevention among AGYW in our communities.

All your responses will be de-identified and this component of the study will not require any recording.

Do you have any questions please feel free to email or call the project PI Dr. Lynda Oluoch at lynda@pipsthika.org or 0736464299

Phone number

_____
(Please note that this number will not be shared outside the KEMRI study team)

Part I: Demographics Information

Date

_____

1. Modality used to complete the questionnaire
- ◯ In-person/ guided survey
- ◯ Phone
- ◯ Computer/ Laptop
- ◯ Other

(Please clarify how you are completing this survey)

1. a. Please specify

_____

2. Gender
- ◯ Male
- ◯ Female

3. Age (years)

_____

4. Religion
- ◯ Christian
- ◯ Muslim
- ◯ Hindu
- ◯ Other

4. a. Please specify

_____

5. County
- ◯ Mombasa
- ◯ Kwale
- ◯ Kilifi
- ◯ Tana River
- ◯ Lamu
- ◯ Taita/Taveta
- ◯ Garissa
- ◯ Wajir
- ◯ Mandera
- ◯ Marsabit
- ◯ Isiolo
- ◯ Meru
- ◯ Tharaka-Nithi
- ◯ Embu
- ◯ Kitui
- ◯ Machakos
- ◯ Makueni
- ◯ Nyandarua
- ◯ Nyeri
- ◯ Kirinyaga
- ◯ Murang'a
- ◯ Kiambu
- ◯ Turkana
- ◯ West Pokot
- ◯ Samburu
- ◯ Trans Nzoia
- ◯ Uasin Gishu
- ◯ Elgeyo/Marakwet
- ◯ Nandi
- ◯ Baringo
- ◯ Laikipia
- ◯ Nakuru
- ◯ Narok
- ◯ Kajiado
- ◯ Kericho
- ◯ Bomet
- ◯ Kakamega
- ◯ Vihiga
- ◯ Bungoma
- ◯ Busia
- ◯ Siaya
- ◯ Kisumu
- ◯ Homa Bay
- ◯ Migori
- ◯ Kisii
- ◯ Nyamira
- ◯ Nairobi City

(Please pick one)

6. Name of the facility where participant works

_____

7. Participant Job Title
- ◯ Nurse
- ◯ Clinical Officer
- ◯ Medical Officer
- ◯ Pharmacist Technologist
- ◯ Pharmacist
- ◯ Hospital Director
- ◯ Other

7. a. Please specify

_____

8. Duration at that job

_____

8. a. The duration at the job mentioned above is in
- ◯ Days
- ◯ Weeks
- ◯ Months
- ◯ Years

9. Level of the health system where the participant is employed
- ◯ National Referral (level 6)
- ◯ County Referral (level 5)
- ◯ County hospitals (level 4)
- ◯ Health center (level 3)
- ◯ Health dispensaries (level 2)
- ◯ Community Facilities (level 1)
- ◯ Other

9. a. Please specify

_____

10. Geographic location of the facility
- ◯ Rural
- ◯ Urban
- ◯ Other

10. a. Please specify

_____

Part II: Questions on the Acceptability of the HPV vaccine reduced dose strategy

1.General acceptability
In your opinion, how acceptable do you think it is to provide a single dose of the HPV vaccine to AGYW?
- ◯ Very unacceptable
- ◯ Unacceptable
- ◯ Neutral
- ◯ Acceptable
- ◯ Very acceptable

2. Burden

2.1 How much effort does it take you to provide one dose of the HPV vaccine to AGYW?
- ◯ No effort at all
- ◯ A little effort
- ◯ Neutral
- ◯ A lot of effort
- ◯ Huge effort

2.2. In your opinion, how much time does it/ will it take you to provide a single dose of the HPV vaccine to AGYW?
- ◯ No time at all
- ◯ Little time
- ◯ No opinion
- ◯ A lot of time
- ◯ A huge amount of time

2.3. In your opinion, how much resource does it/ will it take you to provide a single dose of the HPV vaccine to AGYW?
- ◯ No resource at all
- ◯ Little resource
- ◯ No opinion
- ◯ A lot of resources
- ◯ Huge resources

2.4 How much effort does it take to incorporate the single dose into the existing workflow at your clinic/ facility
- ◯ No effort at all
- ◯ A little effort
- ◯ No opinion
- ◯ A lot of effort
- ◯ Huge effort

3. Ethicality

3.1. In your opinion, do you think there are moral or ethical consequences with offering one dose of the HPV vaccine to AGYW?
- ◯ Strongly disagree
- ◯ Disagree
- ◯ Neutral
- ◯ Agree
- ◯ Strongly agree

3.2. How fair is the reduced dose strategy for the AGYWs?
- ◯ Very unfair
- ◯ Unfair
- ◯ No opinion
- ◯ Fair
- ◯ Very fair

4. Perceived effectiveness

4.1 To what extent do you think the HPV vaccine prevents HPV infection and cervical cancer?
- ◯ Not at all
- ◯ Slight protection
- ◯ Not really |No opinion
- ◯ Somehow Moderate protection
- ◯ Very much Full protection

4.2 To what extent do you think the single dose of the HPV vaccine would prevent HPV infection and cervical cancer?
- ◯ Not at all
- ◯ Slight protection
- ◯ Not really No opinion
- ◯ Somehow Moderate protection
- ◯ Very much Full protection

5. Self-efficacy

5.1 How confident are you in providing (administering correctly) single doses of HPV vaccines to AGYWs?
- ◯ Very unconfident
- ◯ Slightly unconfident
- ◯ No opinion
- ◯ Moderately confident
- ◯ Very confident

5.2 How confident are you in explaining the benefits of the HPV vaccine to AGYWs and/ or their parents/ guardians?
- ◯ Very unconfident
- ◯ Slightly unconfident
- ◯ No opinion
- ◯ Moderately confident
- ◯ Very confident

5.3 How confident are you in addressing concerns that AGYWs and/ or their parents/ guardians have on the HPV vaccine?
- ◯ Very unconfident
- ◯ Slightly unconfident
- ◯ No opinion
- ◯ Moderately confident
- ◯ Very confident

6. In your opinion, what factors enable your ability to confidently deliver a single dose of the HPV vaccine?

_____
(What has made you/ makes you confident?)

7. What limits your confidence in delivering a single dose of the HPV vaccine?

_____
(What has made you/ makes you less confident?)

8. Knowledge

8.1. How knowledgeable are you about the single-dose strategy of the HPV vaccine?
- ◯ Very unknowledgeable
- ◯ Slightly unknowledgeable
- ◯ No opinion
- ◯ Moderately knowledgeable
- ◯ Very knowledgeable

8.2. What do you know about the single-dose strategy of the HPV vaccine?

_____

8.3. How did you learn about the single-dose strategy of the HPV vaccine?

_____

9. What are your beliefs regarding the single-dose strategy of the HPV vaccine?

_____

General Comments

Other comments?

_____

Supplementary Tables

Supplementary Table 1: Correlation between the reported general acceptability and the computed acceptability varying constructs used to represent relevant domains (with all variables treated as continuous variable)

Item	Components	Distribution of Score Across Counties Mean (SD)					Spearman Correlation	
		Kiambu	Kisumu	Nairobi	Overall	P-value[1]	Coefficient	P-value[2]
General acceptability (reported)	NA	4.01 (1.30)	3.74 (1.33)	3.65 (1.22)	3.79 (1.29)	0.1		
Acceptability mean score1	• Effort • Moral consequence • Confidence • Effectiveness • Knowledge	3.76 (0.51)	3.71 (0.52)	3.70 (0.51)	3.72 (0.52)	0.69	0.052	0.31
Acceptability mean score2	• Time • Moral consequence • Confidence • Effectiveness • Knowledge	3.79 (0.49)	3.74 (0.53)	3.74 (0.51)	3.75 (0.51)	0.69	0.043	0.40
Acceptability mean score3	• Resource • Moral consequence • Confidence • Effectiveness • Knowledge	3.77 (0.48)	3.68 (0.52)	3.69 (0.52)	3.71 (0.51)	0.35	0.04	0.43

Acceptability mean score4	• Effort • Fairness • Confidence • Effectiveness • Knowledge	4.10 (0.59)	3.98 (0.62)	3.95 (0.51)	4.0 (0.58)	0.15	0.18	**<0.05***
Acceptability mean score5	• Time • Fairness • Confidence • Effectiveness • Knowledge	4.13 (0.54)	4.01 (0.62)	3.99 (0.52)	4.04 (0.57)	0.16	0.19	**<0.05***
Acceptability mean score6	• Resource • Fairness • Confidence • Effectiveness • Knowledge	4.11 (0.54)	3.95 (0.62)	3.93 (0.55)	3.99 (0.58)	0.055	0.17	**<0.05***

[1]P-value comparing scores across sites [2]P-value of the correlation coefficient *P-value <0.05

Supplementary Table 2: Output from the regression model assessing the association between constructs of acceptability and the reported general acceptability.

Construct	**Using the moral consequence construct for the ethicality domain**			**Using fairness construct for the ethicality domain**			**Accounting for all relevant constructs and domains of acceptability**		
	Beta	**95% CI[1]**	**P-value**	**Beta**	**95% CI[1]**	**P-value**	**Beta**	**95% CI[1]**	**P-value**
Effort*	-0.07	-0.21, 0.07	0.3	-0.07	-0.21, 0.06	0.3	-0.03	-0.19, 0.13	0.7
Moral consequence	0.05	-0.07, 0.16	0.4				0.06	-0.06, 0.17	0.3
Fairness				0.22	0.09, 0.35	**0.001***	0.23	0.10, 0.36	**<0.001***

Perceived effectiveness of 1-dose	0.12	-0.03, 0.28	0.12	0.05	-0.10, 0.21	0.5	0.08	-0.08, 0.24	0.3
Confidence giving 1-dose	0.03	-0.10, 0.16	0.6	-0.01	-0.14, 0.12	>0.9	0	-0.13, 0.13	>0.9
Knowledge on 1-dose	-0.06	-0.17, 0.06	0.3	-0.04	-0.16, 0.07	0.5	-0.06	-0.17, 0.06	0.3
Time							-0.02	-0.30, 0.25	0.9
Resources							-0.07	-0.25, 0.11	0.5
Effort to integrate 1-dose							0	-0.18, 0.18	>0.9

[1]CI = Confidence Interval *P-value< 0.05

Supplementary Table 3: Correlation between the general acceptability and the different constructs of acceptability (Treated as categorical variables)

		Polychronic Correlation Coefficient
Burden[#]	Effort to give 1 dose	-0.031
	Time to give 1 dose	0.013
	Resource to give 1 dose	-0.03
	Effort to integrate 1 dose into Existing work	-0.012
Ethicality	Moral consequences of giving 1 dose	-0.04
	Fair to give 1 dose	0.29
Perceived Effectiveness	Effectiveness of the HPV vaccine	0.16
	Effectiveness of 1 dose the HPV vaccine	0.15
Self-Efficacy	Confidence giving 1 dose	0.09
	Confidence explaining benefits of the vaccine	0.06
	Confidence addressing concerns on the vaccine	0.05
Intervention Coherence	Knowledge on 1 dose	0.006

*Excluded responses (n=11) that were missing data for acceptability domains and constructs of interest [#] The score of constructs of the burden domain were reversed before conducting the correlation analysis

Supplementary Table 4: Determinants of acceptability among HCPs. Findings of a multivariate linear regresion model (without interraction)

	Beta	95% CI[1]	p-value
Gender			
Male (Ref)	—	—	
Female	0.05	-0.28, 0.38	0.8
Age	-0.01	-0.04, 0.02	0.5
religion			
Christian	—	—	
Muslim	-0.07	-1.0, 0.89	0.9
Other	0.81	-0.70, 2.3	0.3
Job Title			
Nurse (Ref)	—	—	
Clinical Officer	-0.01	-0.45, 0.44	>0.9
Medical Officer	0.24	-0.41, 0.90	0.5
Pharmacist Technologist	0.46	-0.21, 1.1	0.2
Pharmacist	0.25	-0.66, 1.2	0.6
Hospital Director	-0.25	-1.8, 1.3	0.8
Other	0.37	0.01, 0.73	**0.044***
Job duration (Months)	0	0.00, 0.00	0.7
Facility Level			
Facility_level.L	0.39	-0.24, 1.0	0.2
Facility_level.Q	0.07	-0.49, 0.62	0.8
Facility_level.C	0.3	-0.26, 0.86	0.3
Facility_level^4	-0.34	-0.88, 0.21	0.2
Facility_level^5	-0.03	-0.48, 0.43	>0.9
Facility_level^6	-0.13	-0.46, 0.19	0.4
Geographic location			
Rural (Ref)	—	—	
Urban	-0.12	-0.52, 0.28	0.6
Other	0.09	-1.8, 2.0	>0.9
County			
Kiambu (Ref)	—	—	

Kisumu	-0.19	-0.55, 0.17	0.3
Nairobi City	-0.36	-0.76, 0.04	0.077

[1] CI = Confidence Interval *P-value <0.05
Model no interraction with complete data only (n=356)

Supplementary Table 5: Determinants of acceptability among HCPs. Findings of a multivariate linear regresion model (with interraction between referral level and county as well as job title and job duration)[#]

	Beta	95% CI[1]	p-value
Gender			
Male (Ref)	—	—	
Female	-0.02	-0.35, 0.31	>0.9
Age	-0.01	-0.04, 0.01	0.3
Religion			
Christian (Ref)	—	—	
Muslim	-0.09	-1.1, 0.87	0.9
Other	0.85	-0.67, 2.4	0.3
Job title			
Nurse (Ref)	—	—	
Clinical Officer	0.3	-0.36, 0.95	0.4
Medical Officer	-0.14	-1.2, 0.90	0.8
Pharmacist Technologist	0.66	-0.34, 1.7	0.2
Pharmacist	0.67	-0.93, 2.3	0.4
Hospital Director	-1	-3.2, 1.2	0.3
Other	0.3	-0.20, 0.81	0.2
County			
Kiambu (Ref)	—	—	
Kisumu	-0.19	-0.57, 0.19	0.3
Nairobi City	-0.43	-0.84, -0.02	**0.039**
Job title * Job duration (months)			
Clinical Officer * Job duration	0	-0.01, 0.00	0.3
Medical Officer * Job duration	0	-0.01, 0.02	0.4
Pharmacist Technologist * Job duration	0	-0.02, 0.01	0.5
Pharmacist * Job duration	0	-0.02, 0.01	0.6
Hospital Director * Job duration	0.03	-0.03, 0.09	0.3
Other * Job duration	0	0.00, 0.01	0.9
Facility level * geographic location			
Facility level.L * Urban	-17	-33, -1.1	**0.037**
Facility level.Q * Urban	18	2.3, 34	**0.025**
Facility level.C * Urban	-14	-26, -1.7	**0.026**
Facility level ^4 * Urban	5.5	-0.50, 12	0.072

Job duration (months)	0	0.00, 0.00	0.5	Facility level ^5 * Urban	-5.3	-9.3, -1.3	**0.009**
Facility level				Facility level ^6 * Urban			
Facility level.L	17	1.4, 33	**0.033**	Facility level.L * Other	3.9	-4.2, 12	0.3
Facility level.Q	-18	-33, -2.2	**0.025**	Facility level.Q * Other			
Facility level.C	14	2.1, 27	**0.022**	Facility level.C * Other			
Facility level ^4	-6.1	-12, 0.03	0.051	Facility level ^4 * Other			
facility_level^5	5.2	1.2, 9.3	**0.011**	Facility level ^5 * Other			
facility_level^6	-0.24	-0.67, 0.20	0.3	Facility level ^6 * Other			
Geographic location							
Rural (Ref)	—	—					
Urban	5	0.71, 9.3	**0.022**				
Other	-1	-3.7, 1.7	0.5				

[#]Complete data (n=356)
[1] CI = Confidence Interval
Numbers in bold= p-values < 0.05

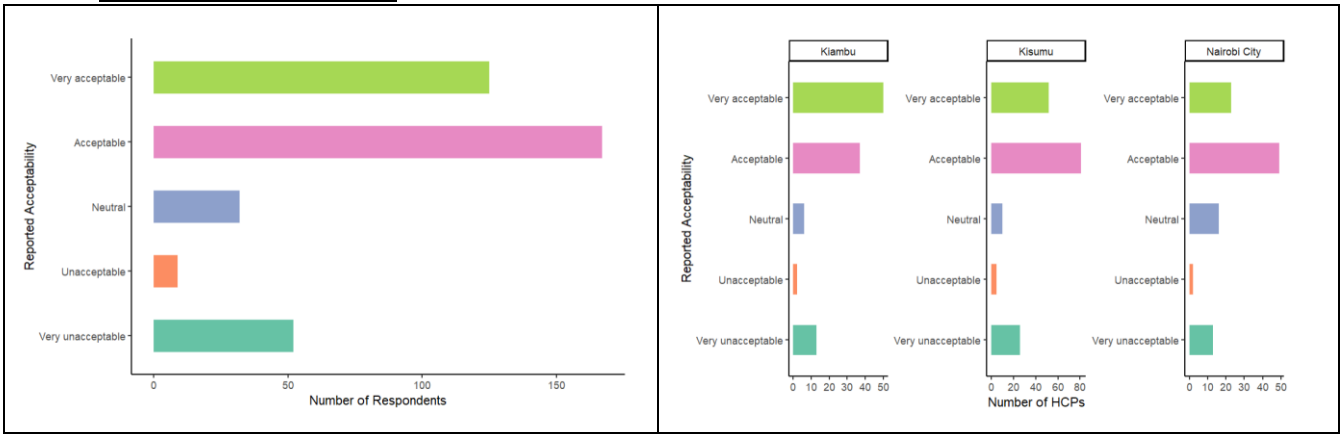
Supplementary Table 6: Model selection: Checking the best fitting model

Model	Description	AIC
model2	Linear multiregression model without interraction all data available (n=385)	1253.8
model2b	Linear multiregression model without interraction no NAs (n=356)	***1221.6***
model3	Linear multiregression model with interraction between job title and dutation as well as referral level and geographic location (n=385)	1262.3
model3b	Linear multiregression model with interraction between referral level and geographic location (n=385)	1254.3
model4	Linear multiregression model with interraction between job title and dutation as well as referral level and geographic location (n=356)	***1230.4***
model5	Multivariate poisson regression model without interraction (n=385)	**1383.7**
model6	Multivariate poisson regression model with interraction between job title and dutation as well as referral level and geographic location (n=385)	1400.5

Supplementary Figures

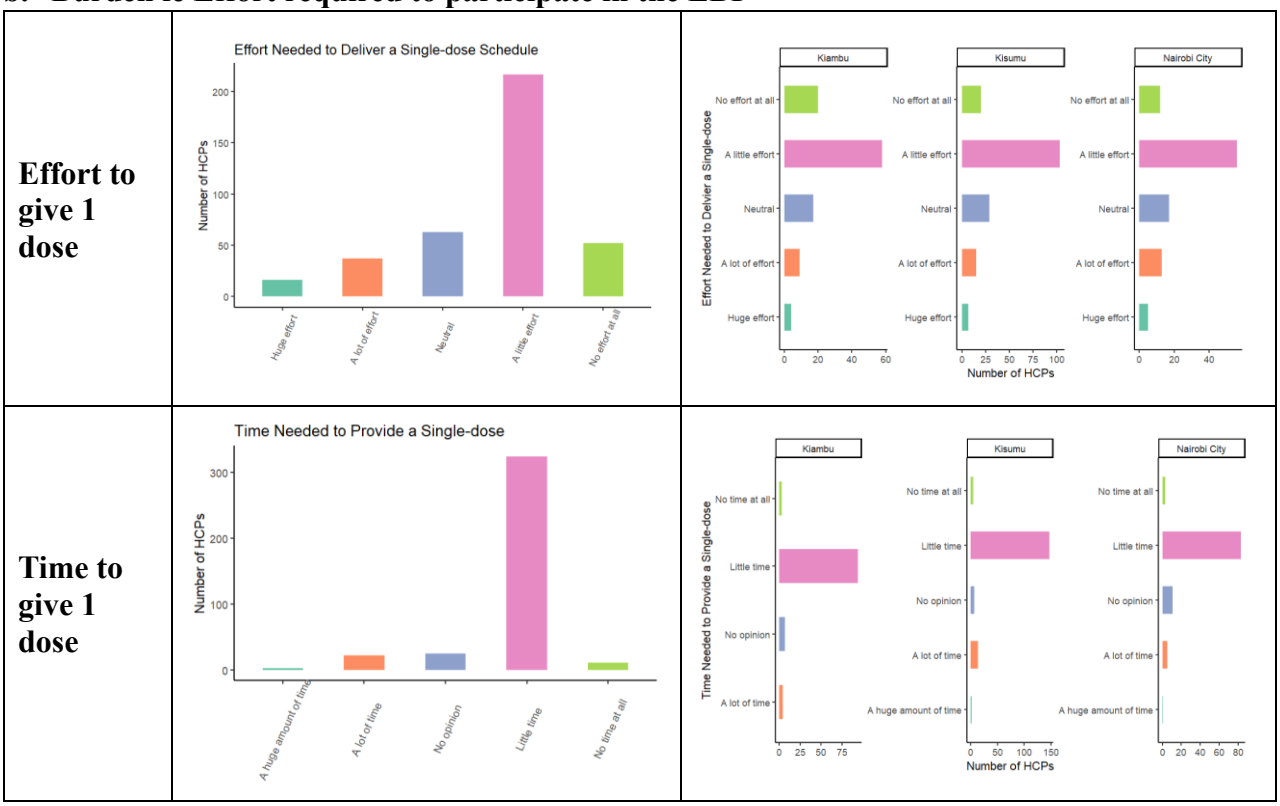
Supplementary Figures 1:: Distribution of responses on domains of acceptability overall and across counties

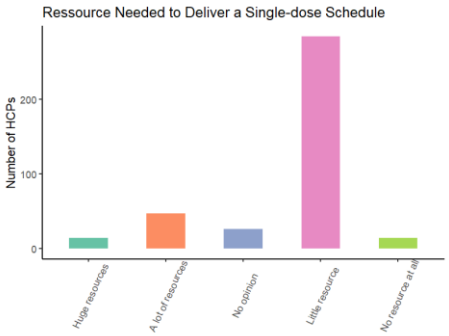
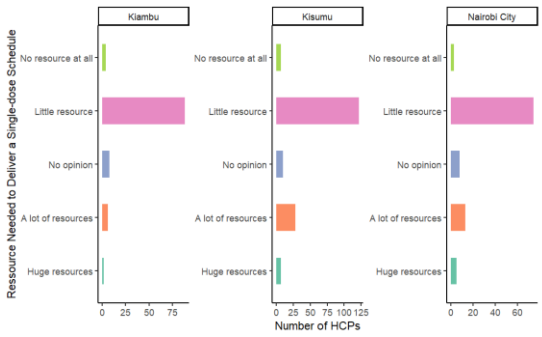
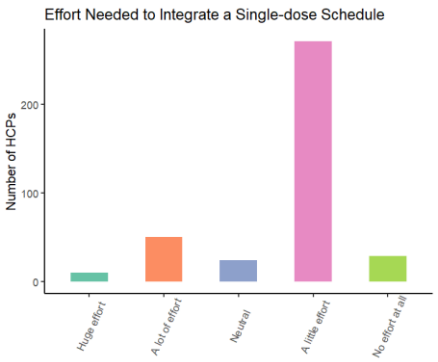
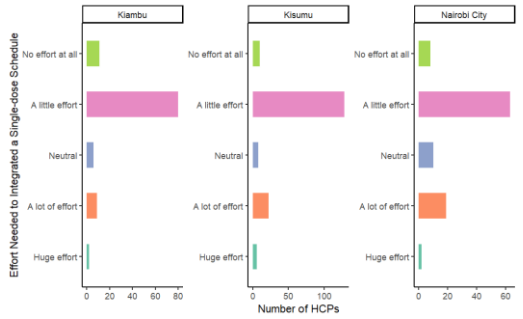
a. General Acceptability



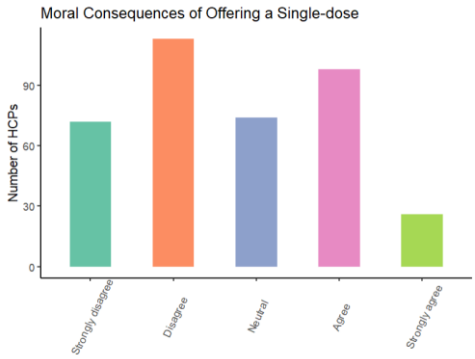
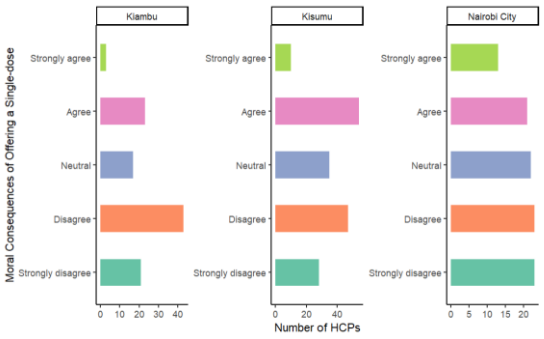
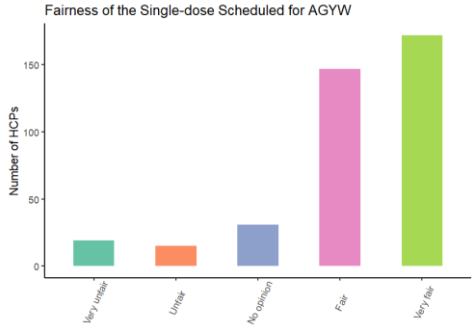
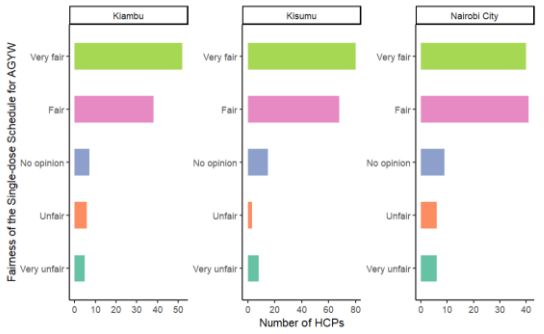
Constructs of Acceptability

b. Burden ie Effort required to participate in the EBI

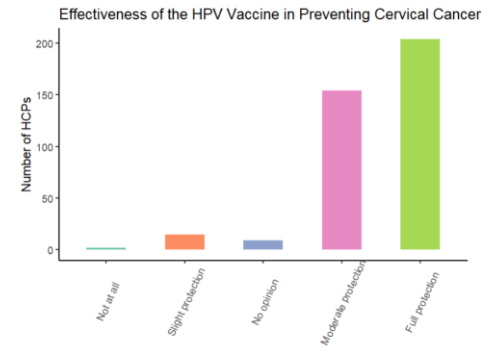
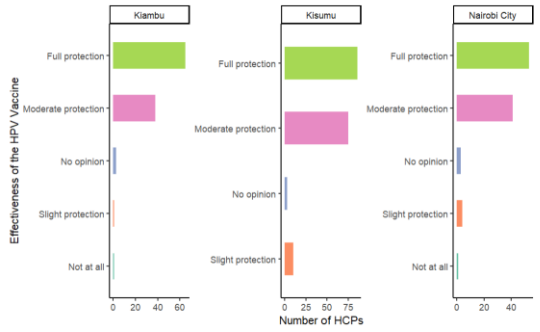
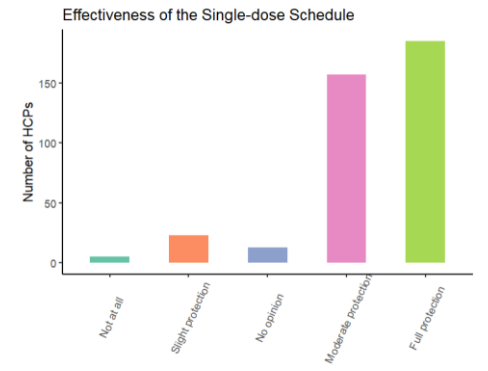
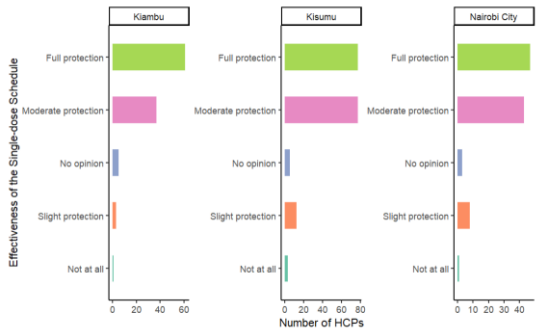


Resource to give 1 dose		
Effort to integrate 1 dose into existing work		

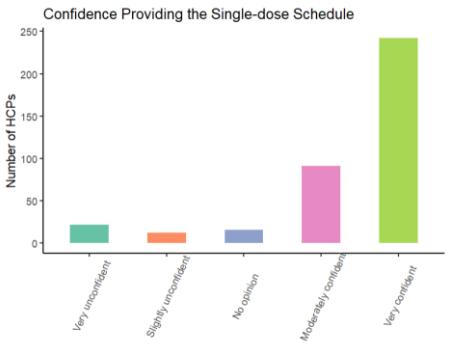
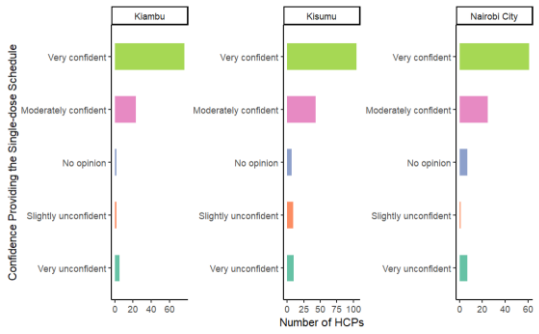
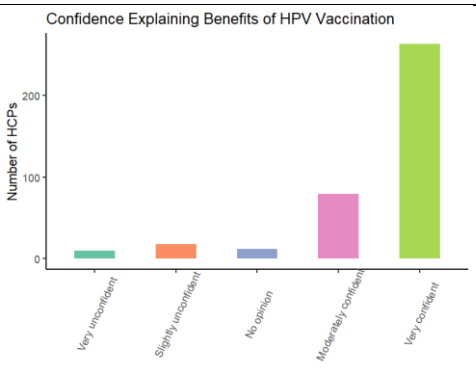
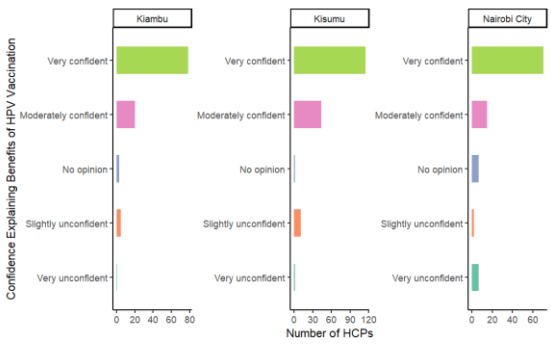
c. Ethicality ie Fair or moral consequences

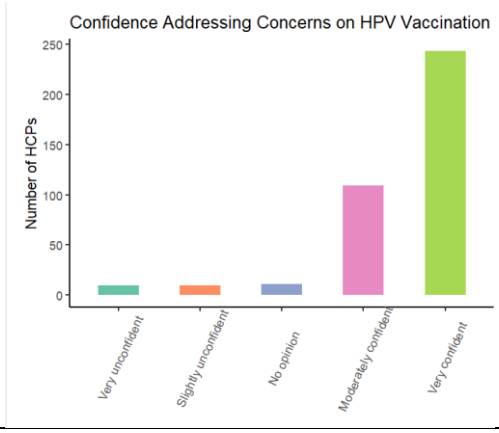
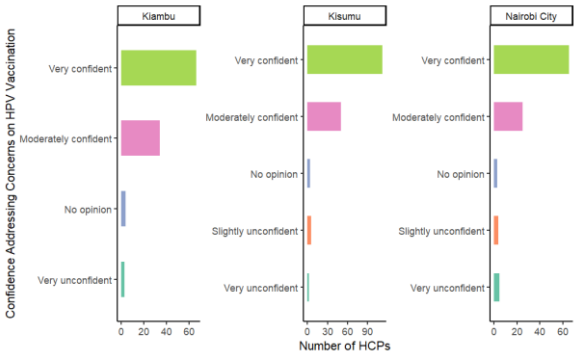
Moral Consequence of Giving 1 dose		
Fairness		

d. Perceived Effectiveness ie Extent to which the EBI is perceived to achieve its objective

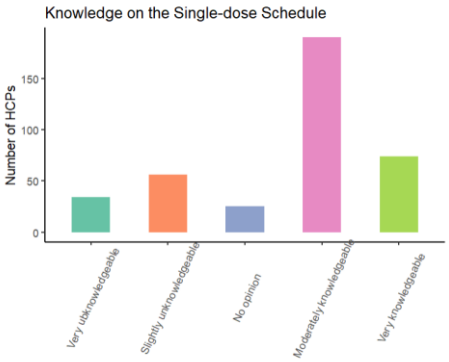
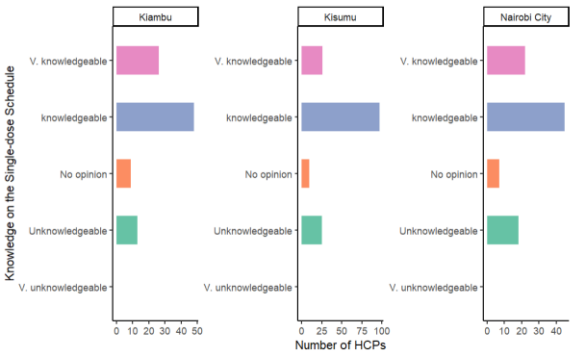
Effectiveness of the HPV vaccine		
Effectiveness of 1 dose		

e. Self-Efficacy – confidence participating in the EBI

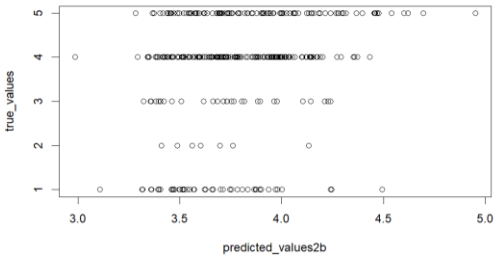
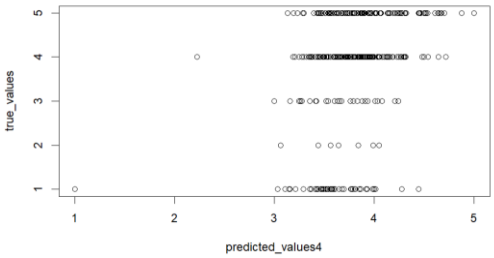
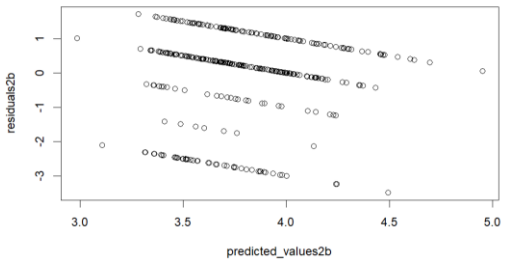
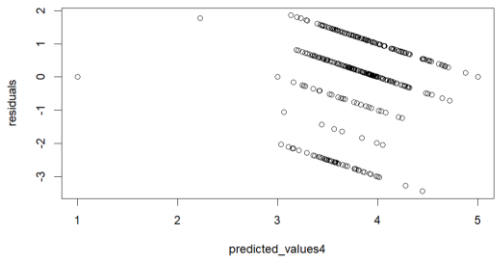
Confidence providing 1 dose		
Confidence explaining benefits of the vaccine		

Confidence addressing concerns on HPV vacine		

f. Knowledge/ Intervention coherence (ie understanding of how the EBI works)

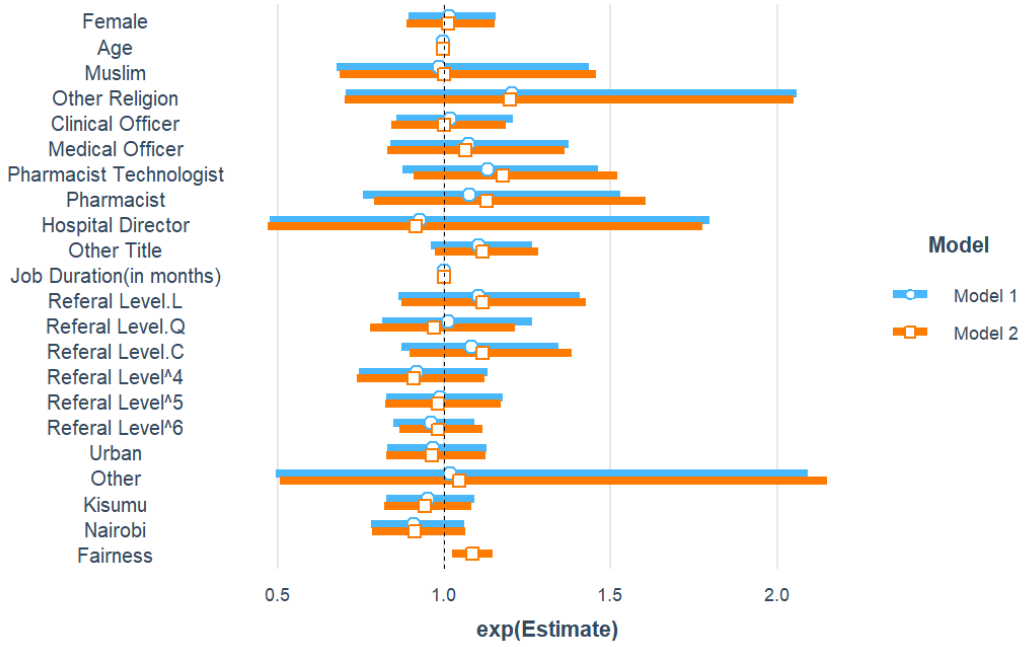
Knowledge on single-dose		

<u>Supplementary Figure 2</u>: Model Selection: Assessing the linearity assumption for the linear regression model

	Model 2b: Linear multiregression model without interraction no NAs (n=356)	**Model 4 : Linear multiregression model with interraction between job title and dutation as well as referral level and geographic location (n=356)**
Plot true vs precited values		
Plot of residuals vs predicted values		

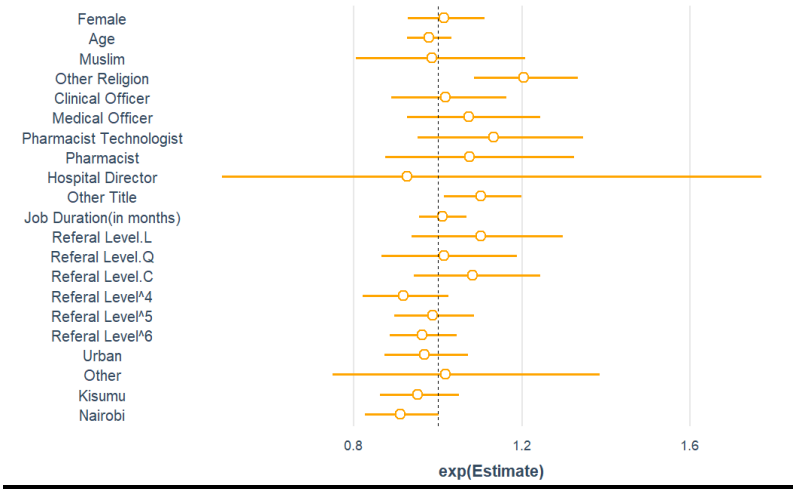
Residuals seem to be following a clear pattern and are not quite random in nature so a linear model is not the best model for this data. Thus a logistics regression model with the lowest AIC is more appropriate.

Supplementary Figure 3: Comparison of estimates of determinants of acceptability among HCPs. Findings of a multivariate logistic regression with and without the fairness construct included in the model, reporting incidence rate ratios (IRR) with 95% Confidence Intervals (CI)



Model 1: outputs from the multivariate logistic regression reported on table 5 (without the fairness score) Model 2: outputs from the multivariate logistic regression with the fairness construct

Supplementary Figure 4: Determinants of acceptability among HCPs. Findings of a multivariate poisson regresion reporting incidence rate ratios (IRR) with robust standard errors (HC1)



Supplementary Materials: Additional Methodology Details and Results for Chapter 3

Supplementary Materials

I. Additional Modelling Results

II. Additional Economic Results

III. Full Incremental Cost Effectiveness Analysis Results

IV. One-Way Sensitivity Analysis

V. Reporting

   a. HPV-FRAME Checklist

   b. CHEERS 2022 Checklist

I. Additional Modelling Results

In addition to evaluating the impact of vaccination strategies on cervical cancer incidence, cases averted, and DALYs averted, we also looked at the impact on cervical cancer mortality, shown in Table S1 below.

Table S1. Projected cervical cancer mortality rates from the years 2023 to 2123. Results are presented as a median and 90% confidence interval using 25 parameter sets.

Dose and durability	Cover	Additional strategy	Mortality rate, per 100,000	Percent reduction in mortality
One-dose, lifelong efficacy scenarios				
No vaccination	0%		3.8 (1.8-5.7)	Reference
Two-dose	31%		2.2 (0.9-3.6)	25.6 (23.3-29.3)
	50%		1.4 (0.5-2.4)	39.4 (36.4-43.4)
	70%		0.8 (0.3-1.5)	50.4 (46.5-53.3)
	77%		0.7 (0.3-1.2)	53.2 (49.1-55.8)
	90%		0.5 (0.3-0.9)	57.5 (52.7-58.8)
One-dose, lifelong efficacy	77%		0.9 (0.3-1.6)	49.2 (44-51.9)
	70%		0.7 (0.3-1.3)	51.9 (47.1-54.2)
	90%		0.6 (0.3-0.9)	56.3 (51.3-58)
One-dose, waning efficacy scenarios				
One-dose, 20EP/20WP	90%		0.6 (0.3-1.3)	52.5 (47.2-55)
One-dose, 25EP/20WP	90%		0.6 (0.3-1.1)	54.4 (49.7-56.5)
One-dose, 30EP/20WP	90%		0.6 (0.3-1)	55.5 (50.7-57.4)
One-dose, 20EP/10WP	90%		0.8 (0.3-1.6)	50 (42.8-53.4)
One-dose, 25EP/10WP	90%		0.6 (0.3-1.2)	53.5 (48.2-55.6)
One-dose, 30EP/10WP	90%		0.6 (0.3-1)	55 (50.3-57.1)
One-dose, using cost savings to invest in an additional vaccination strategy, lifelong and waning efficacy scenarios				
One-dose, lifelong efficacy	90%	CU females age 11-19	0.5 (0.3-0.9)	59.8 (54.8-61.5)
	90%	CU females age 11-24	0.5 (0.3-0.9)	59.9 (55-61.7)
	90%	Vaccination for all by age 10	0.5 (0.3-0.7)	61.2 (56-62.2)
One-dose, 30EP/20WP	90%	CU females age 11-19	0.6 (0.3-1)	59.4 (54.5-61.3)
	90%	CU females age 11-24	0.6 (0.3-1)	59.4 (54.7-61.4)

	90%	Vaccination for all by age 10	0.5 (0.3-0.7)	60.9 (55.6-61.8)
One-dose, 20EP/10WP	90%	CU females age 11-19	0.8 (0.3-1.6)	55.1 (47.4-58.4)
	90%	CU females age 11-24	0.8 (0.3-1.6)	55.2 (47.5-58.6)
	90%	Vaccination for all by age 10	0.5 (0.3-1)	56.1 (51.3-58.2)

II. Additional Economic Results

i. Pairwise Cost Effectiveness Analysis Results and Calculation of Five-Year Cost Savings

We evaluated the economic outcomes of all possible switches from two- to one-dose HPV vaccination schedule, as shown in Table S2 below. We used the mean to calculate the most conservative estimate for potential five-year cost savings if Kenya switches to a single dose strategy. We decided to evaluate cost savings over five years after consultation with experts from the National Vaccines and Immunizations Program within the Ministry of Health. Additionally, Table S3 below presents results from a similar analysis over a 100-year time horizon where we summarized the median of health and economic outcomes of all possible switches from a two- to a one-dose HPV vaccination schedule.

Table S2. DALYs averted over a 5-year time horizon, incremental costs over five-years, and ICERS if Kenya switches from various two-dose scenarios (columns) to one-dose scenarios (rows), with different waning assumptions. Orange signifies that the switch results into reduced cost and reduced DALYs averted, blue signifies that the switch would result into increased costs and increased DALYs averted, and green signifies that the switch would result into increased DALYs averted at lower costs.

		No Vaccination	**2-dose, 31%coverage**	**2-dose, 50%coverage**	**2-dose, 70%coverage**	**2-dose, 77%coverage**	**2-dose, 90%coverage**
		Mean	Mean	Mean	Mean	Mean	Mean
No Vaccination	DALYs Averted	0	-814,791	-1,291,100	-1,683,990	-1,791,966	-1,951,176
	Cost Increment	0	-$20,100,000	-$41,800,000	-$64,700,000	-$72,700,000	-$87,500,000
	ICER		29	39	47	50	56
2-dose, 31%coverage	DALYs Averted	814,791	0	-476,309	-869,199	-977,175	-1,136,385
	Cost Increment	$20,100,000	$0	-$21,700,000	-$44,600,000	-$52,600,000	-$67,500,000
	ICER	29		58	68	72	81
2-dose, 50%coverage	DALYs Averted	1,291,100	476,309	0	-392,890	-500,866	-660,076
	Cost Increment	$41,800,000	$21,700,000	$0	-$22,900,000	-$30,900,000	-$45,700,000
	ICER	39	58		82	88	100

2-dose, 70%coverage	DALYs Averted	1,683,990	869,199	392,890	0	-107,976	-267,186
	Cost Increment	$64,700,000	$44,600,000	$22,900,000	$0	-$8,003,008	-$22,900,000
	ICER	47	68	82		110	128
2-dose, 77%coverage	DALYs Averted	1,791,966	977,175	500,866	107,976	0	-159,210
	Cost Increment	$72,700,000	$52,600,000	$30,900,000	$8,003,008	$0	-$14,900,000
	ICER	50	72	88	110		139
2-dose, 90%coverage	DALYs Averted	1,951,176	1,136,385	660,076	267,186	159,210	0
	Cost Increment	$87,500,000	$67,500,000	$45,700,000	$22,900,000	$14,900,000	$0
	ICER	56	81	100	128	139	
1-dose, 77%coverage	DALYs Averted	1,731,319	916,528	440,218	47,328	-60,648	-219,857
	Cost Increment	$35,800,000	$15,800,000	-$5,955,062	-$28,800,000	-$36,800,000	-$51,700,000
	ICER	25	23	-19	-407	2,441	390
1-dose, 70%coverage	DALYs Averted	1,620,310	805,519	329,210	-63,680	-171,656	-330,866
	Cost Increment	$31,800,000	$11,800,000	-$9,956,564	-$32,800,000	-$40,800,000	-$55,700,000
	ICER	24	19	-41	2,042.93	413	268
1-dose, 90%coverage	DALYs Averted	1,899,385	1,084,594	608,284	215,394	107,418	-51,791
	Cost Increment	$43,300,000	$23,200,000	$1,476,299	- $21,400,000	-$29,400,000	-$44,300,000
	ICER	28	29	3	-141	-394	3359
1-dose, 90%coverage (20EP/20WP)	DALYs Averted	1,765,248	950,457	474,148	81,258	-26,718	-185,928
	Cost Increment	$43,300,000	$23,200,000	$1,476,301	-$21,400,000	-$29,400,000	-$44,300,000
	ICER	30	32	4	-311	-782	456
1-dose, 90%coverage (25EP/20WP)	DALYs Averted	1,841,715	1,026,924	550,615	157,725	49,749	-109,460
	Cost Increment	$43,300,000	$23,200,000	$1,476,299	-$21,400,000	-$29,400,000	-$44,300,000
	ICER	29	30	4	-185	-741	863
1-dose, 90%coverage (30EP/20WP)	DALYs Averted	1,880,297	1,065,506	589,196	196,306	88,330	-70,879
	Cost Increment	$43,300,000	$23,200,000	$1,476,299	-$21,400,000	-$29,400,000	-$44,300,000
	ICER	29	29	4	-153	-490	1646
1-dose, 90%coverage (20EP/10WP)	DALYs Averted	1,667,964	853,174	376,864	-16,026	-124,002	-283,211
	Cost Increment	$43,300,000	$23,200,000	$1,476,304	-$21,400,000	-$29,400,000	-$44,300,000
	ICER	31	35	5	1043	988	289
	DALYs Averted	1,800,967	986,176	509,867	116,977	9,001	-150,209

1-dose, 90%coverage (25EP/10WP)	Cost Increment	$43,300,000	$23,200,000	$1,476,299	-$21,400,000	-$29,400,000	-$44,300,000
	ICER	30	31	4	-245	-1029	591
1-dose, 90%coverage (30EP/10WP)	DALYs Averted	1,867,432	1,052,641	576,332	183,442	75,466	-83,744
	Cost Increment	$43,300,000	$23,200,000	$1,476,299	-$21,400,000	-$29,400,000	-$44,300,000
	ICER	29	29	4	-162	-639	1267

Table S3. DALYs averted over a 100-year time horizon, incremental costs over 100-years, and ICERS if Kenya switches from various two-dose scenarios (columns) to one-dose scenarios (rows), with different waning assumptions. Yellow signifies that the switch result into reduced cost and reduced DALYs averted, blue signifies that the switch would result into increased costs and increased DALYs averted, and green signifies that the switch would result into increased DALYs averted at lower costs.

		No Vaccination	**2-dose, 31%coverage**	**2-dose, 50%coverage**	**2-dose, 70%coverage**	**2-dose, 77%coverage**	**2-dose, 90%coverage**
		Median	Median	Median	Median	Median	Median
No Vaccination	DALYS Averted	0	-829397.50	-1315514.00	-1718444	-1829005	-1988002
	Cost Increment	$0	-$144,428,320	-$243,985,024	-$357,339,776	-$399,367,680	-$480,857,280
	ICER		171.17	182.27	203.83	213.81	236.081
2-dose, 31%coverage	DALYS Averted	829397.50	0	-486116.5	-883887.5	-989390	-1140014
	Cost Increment	$144,428,320	$0	-$99,738,560	-$213,093,312	-$255,121,216	-$336,610,816
	ICER	171.17		201.2473	234.34	249.25	282.55
2-dose, 50%coverage	DALYS Averted	1315514.00	486116.5	0	-395252.5	-500755	-651378.5
	Cost Increment	$243,985,024	$99,738,560	$0	-$113,354,752	-$155,382,656	-$236,783,040
	ICER	182.27	201.2473		274.30	294.73	341.21
2-dose, 70%coverage	DALYS Averted	1718444.0	883887.5	395252.5	0.0	-107257.5	-267078.5
	Cost Increment	$357,339,776	$213,093,312	$113,354,752	$0	-$41,974,528	-$122,498,816
	ICER	203.83	234.34	274.30		369.29	442.12
2-dose, 77%coverage	DALYS Averted	1829005	989390	500755	107257.5	0	-159821
	Cost Increment	$399,367,680	$255,121,216	$155,382,656	$41,974,528	$0	-$80,524,288
	ICER	213.81	249.25	294.73	369.29		493.59
2-dose, 90%coverage	DALYS Averted	1988002	1140014	651378.5	267078.5	159821	0
	Cost Increment	$480,857,280	$336,610,816	$236,783,040	$122,498,816	$80,524,288	$0
	ICER	236.08	282.55	341.21	442.12	493.59	

1-dose, 77%coverage	DALYS Averted	1731544	906631	417996	43525	-60913.5	-229956.5
	Cost Increment	$138,923,200	-$4,757,184	-$104,486,656	-$224,096,064	-$266,457,856	-$347,595,776
	ICER	78.52	-5.03	-230.50	-3928.61	4477.38	1529.083
1-dose, 70%coverage	DALYS Averted	1625570.00	795172.50	325207.50	-62662	-180545	-344841
	Cost Increment	$121,880,000	-$21,321,472	-$121,678,016	-$241,191,616	-$282,577,280	-$364,066,880
	ICER	74.3	-25.7	-362.5	3777.12	1564.675	1074.471
1-dose, 90%coverage	DALYS Averted	1887070	1072199	583564	207040.5	106800.5	-49639.5
	Cost Increment	$173,316,960	$28,456,576	-$68,994,048	-$187,920,192	-$231,852,032	-$313,827,136
	ICER	88.21	26.27	-114.26	-839.68	-2123.923	6519.192
1-dose, 90%coverage (15EP/20WP)	DALYS Averted	1630016	813222	340905.2	-56837.5	-173653.5	-326791.5
	Cost Increment	$192,827,072	$50,482,496	-$49,287,936	-$166,126,784	-$206,857,792	-$285,830,016
	ICER	117.59	60.37	-145.1789	2381.04	1216.12	908.08
1-dose, 90%coverage (20EP/20WP)	DALYS Averted	1767606	952906	464271	84606	-16946	-184965
	Cost Increment	$183,786,528	$39,262,720	-$59,576,000	-$178,086,784	-$220,696,192	-$302,185,792
	ICER	101.17	39.84	-123.01	-1998.88	2261.17	1654.124
1-dose, 90%coverage (25EP/20WP)	DALYS Averted	1836143	1021703	533067.5	160841	48702.5	-105595.5
	Cost Increment	$178,000,416	$33,029,952	-$64,820,992	-$183,996,480	-$227,167,168	-$308,656,768
	ICER	93.30	31.71	-116.98	-1107.42	-3787.04	2909.58
1-dose, 90%coverage (30EP/20WP)	DALYS Averted	1870361	1055736	567100.5	193460.2	93705.5	-68633.5
	Cost Increment	$174,989,984	$29,980,224	-$67,518,656	-$186,198,272	-$230,364,544	-$312,045,888
	ICER	89.92	28.11	-114.90	-915.71	-2500.77	4736.586
1-dose, 90%coverage (15EP/10WP)	DALYS Averted	1439535	621913	132839	-262413.5	-367916	-527245
	Cost Increment	$208,247,872	$65,158,624	-$35,556,416	-$149,091,904	-$191,119,808	-$272,609,408
	ICER	143.12	108.14	-246.33	587.09	538.02	525.77
1-dose, 90%coverage (20EP/10WP)	DALYS Averted	1678710	863996.5	380782	-2838	-117677.5	-276017
	Cost Increment	$190,303,552	$46,903,040	-$52,700,800	-$170,157,568	-$212,156,224	-$291,128,448
	ICER	112.20	52.70	-136.10	1709.28	1827.30	1087.495
1-dose, 90%coverage (25EP/10WP)	DALYS Averted	1800146	985934.5	497299.5	128500.2	18899.5	-147984
	Cost Increment	$181,255,776	$36,581,568	-$61,911,872	-$180,881,600	-$223,540,736	-$305,030,336
	ICER	97.54	35.96	-119.31	-1421.96	-5389.115	2085.597
	DALYS Averted	1859132	1044670	556034.5	184356.7	85873.8	-74696

1-dose, 90%coverage (30EP/10WP)	Cost Increment	$176,094,880	$30,987,200	-$66,543,680	-$185,513,408	-$229,286,144	-$310,775,744
	ICER	91.07	29.36	-115.38	-965.75	-2724.00	4307.366

III. Full Incremental Cost Effectiveness Analysis Results

Table S4. Health and cost impact of vaccination strategies in Kenya if decision-makers consider strategies of vaccinating girls by age 10. These are the full CEA results expanded from Table 3, which includes total DALYs, DALYs averted, and all strategies ordered by increasing total cost.

One-dose durability	Strategy	Total cost (Million 2023 USD)	Total DALYs (Thousand)	Incremental cost (Million 2023 USD)	DALYs averted (Thousand)	ICER ($ per DALY averted)
Lifelong	No vaccination	414.46 (230.62-606.00)	6,467.38 (3,526.16-9,180.60)	-	-	-
	1-dose, 70% coverage	532.50 (411.14-676.31)	4,689.55 (2,634.16-6,757.53)	122.38 (70.8-181.01)	1,625.58 (892-2,423.09)	74.60 (29.41-203.58)
	1-dose, 77% coverage	546.33 (433.32-687.94)	4,569.15 (2,592.00-6,568.43)	16.84 (11.63-22.18)	111.46 (42.16-189.1)	142.78 (61.72-527.97)
	2-dose, 31% coverage	553.82 (403.54-730.33)	5,573.07 (3,039.92-8,036.84)	-	-	Dominated
	1-dose, 90% coverage	581.87 (475.74-713.27)	4,413.62 (2,531.41-6,270.33)	34.14 (25.33-42.58)	171.73 (60.6-298.11)	197.44 (85.15-702.24)
	2-dose, 50% coverage	650.86 (522.48-814.85)	5,052.00 (2,791.19-7,317.65)	-	-	Dominated
	2-dose, 70% coverage	769.83 (654.07-912.34)	4,645.83 (2,620.47-6,680.84)	-	-	Dominated
	2-dose, 77% coverage	809.38 (701.45-948.99)	4,541.81 (2,579.57-6,493.85)	-	-	Dominated
	2-dose, 90% coverage	885.85 (790.65-1,021.16)	4,391.11 (2,520.83-6,205.23)	313.33 (284-325.23)	49.64 (6.16-115.54)	6,508.8 (2,527.55-51,541.03)
Alternative waning (30EP/20WP)	No vaccination	414.46 (230.62-606.00)	6,467.38 (3,526.16-9,180.60)	-	-	-
	1-dose, 70% coverage	534.73 (411.73-680.77)	4,712.72 (2,640.58-6,805.54)	124.02 (75.71-181.1)	1,604.99 (885.57-2,375.06)	76.43 (31.67-205.15)
	1-dose, 77% coverage	548.46 (433.87-692.20)	4,590.55 (2,598.04-6,614.31)	16.71 (11.42-22.14)	112.74 (42.55-191.24)	140.23 (59.94-522.43)
	2-dose, 31% coverage	553.82 (403.54-730.33)	5,573.07 (3,039.92-8,036.84)	-	-	Dominated
	1-dose, 90% coverage	583.35 (476.25-716.95)	4,430.33 (2,536.90-6,310.30)	33.9 (24.76-42.49)	174.06 (61.14-304.01)	191.95 (81.65-695.31)

	2-dose, 50% coverage	650.86 (522.48-814.85)	5,052.00 (2,791.19-7,317.65)	-	-	Dominated
	2-dose, 70% coverage	769.83 (654.07-912.34)	4,645.83 (2,620.47-6,680.84)	-	-	Dominated
	2-dose, 77% coverage	809.38 (701.45-948.99)	4,541.81 (2,579.57-6,493.85)	-	-	Dominated
	2-dose, 90% coverage	885.85 (790.65-1,021.16)	4,391.11 (2,520.83-6,205.23)	312.05 (283.11-324.95)	68.63 (15.86-146.08)	4,736.59 (2,053.19-20,027.37)
Pessimistic waning (20EP/10WP)	No vaccination	414.46 (230.62-606.00)	6,467.38 (3,526.16-9,180.60)	-	-	-
	1-dose, 70% coverage	552.53 (417.44-714.83)	4,949.92 (2,713.50-7,235.11)	141.85 (120.03-187)	1,370.93 (807.36-1,827.14)	102.11 (66.41-232.15)
	2-dose, 31% coverage	553.82 (403.54-730.33)	5,573.07 (3,039.92-8,036.84)	-	-	Dominated
	1-dose, 77% coverage	566.41 (439.30-726.91)	4,824.51 (2,667.34-7,051.80)	16.58 (13.32-23.97)	115.94 (46.16-183.31)	137.18 (66.12-475.72)
	1-dose, 90% coverage	598.16 (481.21-751.26)	4,624.61 (2,600.13-6,741.83)	32.67 (24.36-41.91)	184.17 (67.21-309.98)	168.55 (78.8-626.06)
	2-dose, 50% coverage	650.86 (522.48-814.85)	5,052.00 (2,791.19-7,317.65)	-	-	Dominated
	2-dose, 70% coverage	769.83 (654.07-912.34)	4,645.83 (2,620.47-6,680.84)	-	-	Dominated
	2-dose, 77% coverage	809.38 (701.45-948.99)	4,541.81 (2,579.57-6,493.85)	-	-	Dominated
	2-dose, 90% coverage	885.85 (790.65-1,021.16)	4,391.11 (2,520.83-6,205.23)	291.13 (257.27-316.5)	276.02 (79.3-536.6)	1,087.49 (503.03-3,908.66)

Table S5. Health and cost impact of vaccination strategies in Kenya if decision-makers consider vaccinating girls by age 10 or expanding the HPV vaccination strategy to include catch-up or vaccination for all by age 10 using the 5-year cost savings of switching from a two- to one-dose schedule. These are the full CEA results expanded from Table 3, which includes total DALYs, DALYs averted, and all strategies ordered by increasing total cost.

One-dose durability	Strategy	Total cost (Million 2023 USD)	Total DALYs (Thousand)	Incremental cost (Million 2023 USD)	DALYs averted (Thousand)	ICER ($ per DALY averted)
Lifelong efficacy	No vaccination	414.46 (230.62-606.00)	6,467.38 (3,526.16-9,180.60)	-	-	-
	1-dose, 70% coverage	532.50 (411.14-676.31)	4,689.55 (2,634.16-6,757.53)	128.92 (99.49-183.61)	1,579.44 (839.55-2,061.36)	85.11 (48.29-236.32)

	1-dose, 77% coverage	546.33 (433.32-687.94)	4,569.15 (2,592.00-6,568.43)	-	-	Dominated
	2-dose, 31% coverage	553.82 (403.54-730.33)	5,573.07 (3,039.92-8,036.84)	-	-	Dominated
	1-dose, 11-24YO female catch-up	580.44 (482.29-701.29)	4,108.85 (2,356.00-5,833.02)	58.75 (39.37-135.52)	603.47 (278.16-3,347.58)	78.73 (28.64-256.28)
	1-dose, 90% coverage	581.87 (475.74-713.27)	4,413.62 (2,531.41-6,270.33)	-	-	Dominated
	1-dose, 11-19YO female catch-up	582.19 (483.80-703.48)	4,138.94 (2,378.70-5,864.55)	-	-	Dominated
	2-dose, 50% coverage	650.86 (522.48-814.85)	5,052.00 (2,791.19-7,317.65)	-	-	Dominated
	2-dose, 70% coverage	769.83 (654.07-912.34)	4,645.83 (2,620.47-6,680.84)	-	-	Dominated
	2-dose, 77% coverage	809.38 (701.45-948.99)	4,541.81 (2,579.57-6,493.85)	-	-	Dominated
	1-dose, vaccination for all by age 10	862.35 (771.21-983.84)	4,203.98 (2,438.65-5,868.82)	279.07 (279.07-279.07)	120.51 (120.51-120.51)	Weakly Dominated
	2-dose, 90% coverage	885.85 (790.65-1,021.16)	4,391.11 (2,520.83-6,205.23)	-	-	Dominated
Alternative waning (30EP/20WP)	No vaccination	414.46 (230.62-606.00)	6,467.38 (3,526.16-9,180.60)	-	-	-
	1-dose, 70% coverage	534.73 (411.73-680.77)	4,712.72 (2,640.58-6,805.54)	142.54 (112.35-192.57)	1,402.52 (720.28-1,889.22)	97.89 (59.68-348.11)
	1-dose, 77% coverage	548.46 (433.87-692.20)	4,590.55 (2,598.04-6,614.31)	-	-	Dominated
	2-dose, 31% coverage	553.82 (403.54-730.33)	5,573.07 (3,039.92-8,036.84)	-	-	Dominated
	1-dose, 11-24YO female catch-up	581.05 (482.42-703.09)	4,115.01 (2,357.46-5,852.30)	69.23 (44.66-159.32)	636.39 (283.12-3,328.31)	75.47 (29.35-250.21)
	1-dose, 11-19YO female catch-up	582.80 (483.94-705.29)	4,145.09 (2,380.17-5,883.79)	-	-	Dominated
	1-dose, 90% coverage	583.35 (476.25-716.95)	4,430.33 (2,536.90-6,310.30)	-	-	Dominated
	2-dose, 50% coverage	650.86 (522.48-814.85)	5,052.00 (2,791.19-7,317.65)	-	-	Dominated
	2-dose, 70% coverage	769.83 (654.07-912.34)	4,645.83 (2,620.47-6,680.84)	-	-	Dominated
	2-dose, 77% coverage	809.38 (701.45-948.99)	4,541.81 (2,579.57-6,493.85)	-	-	Dominated

	1-dose, vaccination for all by age 10	863.94 (771.74-986.70)	4,219.35 (2,444.50-5,900.54)	279.81 (279.81-279.81)	110.68 (110.68-110.68)	Weakly Dominated
	2-dose, 90% coverage	885.85 (790.65-1,021.16)	4,391.11 (2,520.83-6,205.23)	-	-	Dominated
Pessimistic waning (20EP/10WP)	No vaccination	414.46 (230.62-606.00)	6,467.38 (3,526.16-9,180.60)	-	-	-
	1-dose, 70% coverage	552.53 (417.44-714.83)	4,949.92 (2,713.50-7,235.11)	-	-	Dominated
	2-dose, 31% coverage	553.82 (403.54-730.33)	5,573.07 (3,039.92-8,036.84)	-	-	Dominated
	1-dose, 77% coverage	566.41 (439.30-726.91)	4,824.51 (2,667.34-7,051.80)	-	-	Dominated
	1-dose, 11-24YO female catch-up	590.69 (484.67-729.11)	4,233.94 (2,385.33-6,174.27)	182.22 (126.04-254.05)	2,066.75 (1,140.82-3,006.33)	86.16 (41.12-223.31)
	1-dose, 11-19YO female catch-up	592.52 (486.23-731.61)	4,265.01 (2,408.43-6,209.01)	-	-	Dominated
	1-dose, 90% coverage	598.16 (481.21-751.26)	4,624.61 (2,600.13-6,741.83)	-	-	Dominated
	2-dose, 50% coverage	650.86 (522.48-814.85)	5,052.00 (2,791.19-7,317.65)	-	-	Dominated
	2-dose, 70% coverage	769.83 (654.07-912.34)	4,645.83 (2,620.47-6,680.84)	-	-	Dominated
	2-dose, 77% coverage	809.38 (701.45-948.99)	4,541.81 (2,579.57-6,493.85)	-	-	Dominated
	1-dose, vaccination for all by age 10	879.21 (776.54-1,016.81)	4,387.00 (2,505.77-6,278.66)	285.63 (285.63-285.63)	30.59 (30.59-30.59)	Weakly Dominated
	2-dose, 90% coverage	885.85 (790.65-1,021.16)	4,391.11 (2,520.83-6,205.23)	-	-	Dominated

IV. One-Way Sensitivity Analysis

One-way sensitivity analyses were conducted for each scenario to assess the impact of changes in each economic parameter on ICERs using alternative estimates using range estimates extracted from published literature (Table 1). The following cost categories were investigated: Gavi contribution and costs of procurement, health system delivery, supplies, screening, and treatment. Using in-country expert input, Gavi contributions increased by 10% every year starting from a 30% contribution in 2023 (lower bound) or a 40% contribution in 2023 (upper bound) until the full cost of the vaccine was covered by the country. Results from one-way sensitivity analyses were presented using tornado diagrams to showcase changes in ICER for selected

scenarios compared to the no vaccination scenario are presented on Figure S1, Table S6 and S7 summarize all median ICERs, and 95% CI of each scenario compared to the no vaccination scenario.

Figure S1. One Way sensitivity analyses of the ICER of selected scenarios compared to the no vaccination scenario

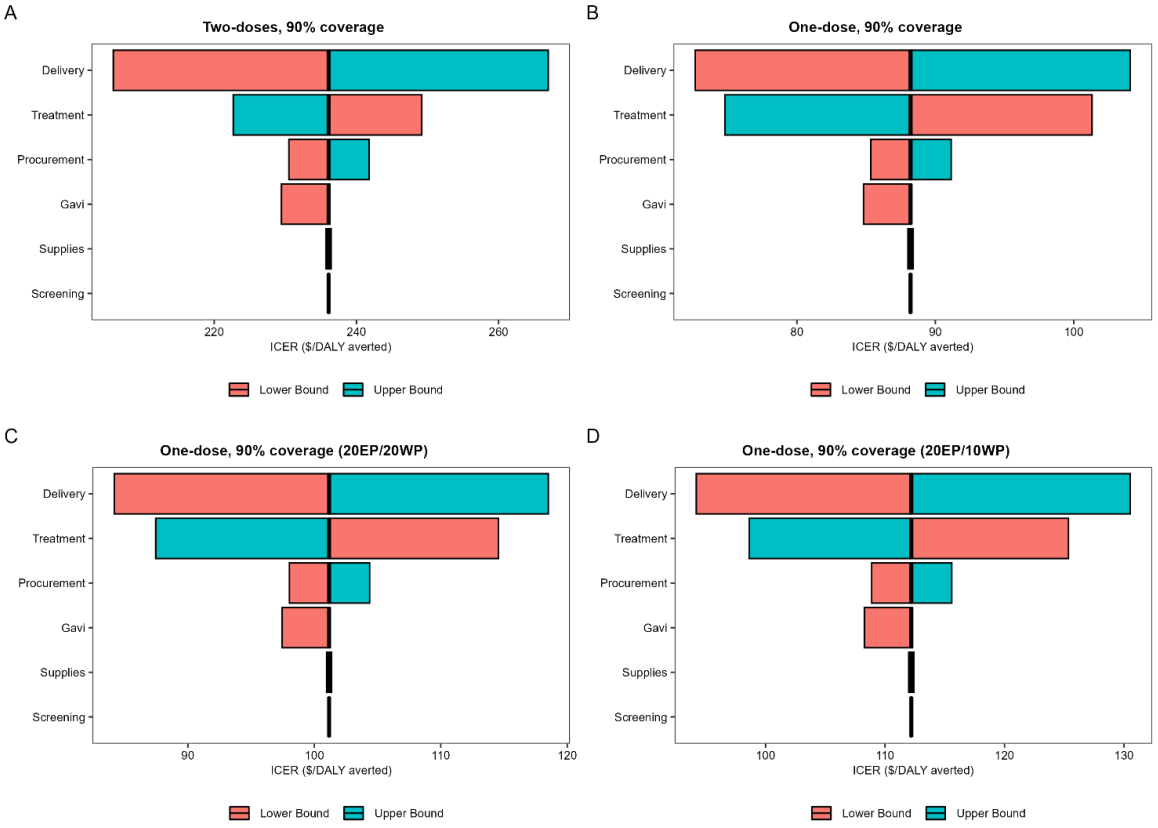


Table S6 Variation of the ICER estimates (median and 95% CI) comparing each scenario to the no vaccination scenario after adjusting GAVI contribution, Procurement and Delivery Costs. These are the full one-way sensitivity analysis expanded from Figure S1.

One-dose durability	Strategy	Initial Run	GAVI Contribution		Procurement		Delivery	
			Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
Lifelong efficacy	No vaccination	-	-	-	-	-	-	-
	2-dose 31% cov	171.2 (108.8-356.3)	166.2 (105.1-347.4)	170.4 (108.2-354.9)	166.7 (105.4-348.3)	175.8 (112.2-364.5)	147.9 (91.4-314.9)	194.9 (126.6-398.6)
	2-dose 50% cov	182.3 (112.2-398)	176.9 (108.3-388)	182 (112.1-397.6)	177.6 (108.9-389.4)	187 (115.7-406.9)	157.6 (94.3-351.9)	207.5 (130.6-445.1)

	2-dose 70% cov	203.8 (122.7-468.7)	197.9 (118.6-457.1)	203.8 (122.7-468.8)	198.8 (119.2-458.8)	208.9 (126.4-478.9)	176.9 (103.6-415.3)	231.4 (142.3-523.3)
	2-dose 77% cov	213.8 (127.9-498.7)	207.7 (123.6-486.4)	213.9 (127.9-498.8)	208.6 (124.2-488.2)	219.1 (131.6-509.4)	185.8 (108.2-442.2)	242.4 (147.9-556.3)
	2-dose 90% cov	236.1 (139.8-558.5)	229.5 (135.2-544.8)	236.3 (139.9-558.9)	230.5 (135.9-547)	241.8 (143.7-570.3)	205.8 (118.9-496)	267 (161.1-622.3)
	1-dose 77% cov	78.5 (31.6-217.7)	75.3 (29.4-211.4)	78.5 (31.6-217.7)	75.8 (29.7-212.4)	81.3 (33.5-223.1)	63.7 (21.5-189.1)	93.6 (41.9-246.8)
	1-dose 70% cov	74.3 (29.2-203)	71.2 (27.1-197.1)	74.3 (29.2-203)	71.6 (27.4-198)	77 (31.1-208.2)	60 (19.4-176)	88.9 (39.3-230.6)
	1-dose 90% cov	88.2 (37.1-247.2)	84.8 (34.7-240.3)	88.3 (37.1-247.3)	85.3 (35.1-241.4)	91.1 (39.1-253.1)	72.7 (26.4-215.6)	104.1 (47.9-279.4)
	1-dose, vaccination for all by age 10	204.7 (114.4-498.4)	198.7 (110.3-485.9)	205.1 (114.6-499.2)	199.7 (111-488)	209.8 (117.8-509)	177.4 (95.9-441.5)	232.5 (133.2-556.4)
	1-dose, 11-19YO female catch-up	76.7 (29.6-221.3)	73.4 (27.3-214.7)	77.4 (30.1-222.7)	74.1 (27.8-216.1)	79.3 (31.4-226.6)	61.9 (19.4-191.6)	91.7 (40-251.6)
	1-dose, 11-24YO female catch-up	74.9 (28.6-215.7)	71.7 (26.4-209.2)	75.6 (29.1-217.1)	72.4 (26.9-210.6)	77.5 (30.4-220.9)	60.3 (18.6-186.5)	89.8 (38.9-245.4)
	1-dose, 31% cov	59.7 (25.8-149.1)	57 (23.8-144.5)	59.2 (25.4-148.3)	57.3 (24-145)	62.1 (27.6-153.3)	47.3 (16.5-127.9)	72.3 (35.2-170.8)
	1-dose, 50% cov	64 (25-168.8)	61.1 (23-163.7)	63.8 (24.9-168.5)	61.5 (23.3-164.4)	66.5 (26.8-173.3)	51 (15.8-145.3)	77.2 (34.5-192.8)
Alternative waning (30EP/20WP)	1-dose 90% cov	89.9 (38.9-249.1)	86.5 (36.5-242.1)	90 (38.9-249.2)	87 (36.9-243.2)	92.9 (40.9-255)	74.2 (28-217.4)	105.9 (49.9-281.4)
	1-dose, 11-19YO female catch-up	77.2 (30.3-221.7)	73.9 (28-215.1)	77.9 (30.8-223.1)	74.6 (28.5-216.5)	79.9 (32.1-227)	62.4 (20.1-191.9)	92.4 (40.7-252.1)
	1-dose, vaccination for all by age 10	206.9 (116.3-501.6)	200.8 (112.2-489)	207.3 (116.6-502.4)	201.9 (112.9-491.2)	212 (119.8-512.3)	179.4 (97.7-444.4)	234.9 (135.4-559.9)
	1-dose, 11-24YO female catch-up	75.5 (29.3-216.1)	72.2 (27.1-209.6)	76.2 (29.8-217.5)	72.9 (27.6-211)	78.1 (31.2-221.3)	60.8 (19.2-186.9)	90.4 (39.7-245.9)
	1-dose, 70% cov	76.4 (31.7-205.2)	73.3 (29.5-199.2)	76.4 (31.7-205.1)	73.7 (29.8-200.1)	79.2 (33.6-210.3)	62 (21.6-177.9)	91.2 (41.9-232.9)
	1-dose, 77% cov	80.9 (33.8-219.7)	77.6 (31.5-213.4)	80.9 (33.8-219.7)	78.1 (31.9-214.4)	83.7 (35.7-225.1)	65.9 (23.5-191)	96.2 (44.3-249)
Pessimistic waning	1-dose 90% cov	112.2 (59.8-271.4)	108.3 (57-264)	112.3 (59.8-271.6)	108.9 (57.4-265.2)	115.6 (62.2-277.8)	94.2 (47-237.5)	130.5 (72.7-306)

(20EP/10WP)	1-dose, 11-19YO female catch-up	88.4 (42.4-229.3)	84.8 (39.9-222.5)	89.1 (43-230.8)	85.5 (40.5-224)	91.2 (44.5-234.8)	72.2 (31.1-198.8)	104.8 (54-260.5)
	1-dose, vaccination for all by age 10	232.8 (141.8-536.4)	226.2 (137.2-523.1)	233.2 (142.1-537.3)	227.3 (138-525.4)	238.4 (145.7-547.7)	202.7 (120.7-475.8)	263.4 (163.3-598.3)
	1-dose, 11-24YO female catch-up	86.2 (41.1-223.3)	82.6 (38.6-216.6)	86.9 (41.7-224.7)	83.4 (39.2-218.1)	89 (43.1-228.6)	70.3 (29.9-193.4)	102.4 (52.6-253.8)
	1-dose, 70% cov	100.3 (58-230.5)	96.7 (55.4-224.1)	100.2 (58-230.5)	97.2 (55.8-225)	103.4 (60.4-236.2)	83.7 (45.7-200.9)	117.1 (70.6-260.8)
	1-dose, 77% cov	103.5 (58.1-243.7)	99.8 (55.4-236.9)	103.5 (58.1-243.7)	100.3 (55.8-237.9)	106.7 (60.4-249.6)	86.5 (45.7-212.7)	120.9 (70.7-275.4)
15EP/20WP	1-dose 90% cov	117.6 (64.9-278)	113.5 (62-270.4)	117.7 (64.9-278.1)	114.2 (62.4-271.6)	121.1 (67.4-284.5)	99.1 (51.6-243.5)	136.5 (78.4-313.2)
20EP/20WP	1-dose 90% cov	101.2 (49.4-260.9)	97.5 (46.8-253.7)	101.2 (49.5-261.1)	98 (47.2-254.8)	104.4 (51.6-267.1)	84.2 (37.6-228)	118.5 (61.4-294.4)
25EP/20WP	1-dose 90% cov	93.3 (42.3-252.9)	89.8 (39.8-245.9)	93.4 (42.3-253.1)	90.3 (40.2-247)	96.4 (44.4-259)	77.3 (31.2-220.9)	109.9 (53.6-285.7)
15EP/10WP	1-dose 90% cov	143.1 (92.2-305.8)	138.5 (88.8-297.7)	143.2 (92.3-306)	139.3 (89.3-298.9)	147.1 (95.1-312.8)	122.2 (76.5-268.6)	164.5 (108.2-343.8)
25EP/10WP	1-dose 90% cov	97.5 (46.3-257)	93.9 (43.7-249.9)	97.6 (46.3-257.2)	94.5 (44.1-251)	100.7 (48.4-263.1)	80.9 (34.8-224.5)	114.5 (58-290.1)
30EP/10WP	1-dose 90% cov	91.1 (40.1-250.3)	87.6 (37.7-243.4)	91.1 (40.1-250.5)	88.2 (38.1-244.4)	94.1 (42.1-256.3)	75.3 (29.2-218.5)	107.2 (51.2-282.8)
Lifelong efficacy + change in testing, treatment strategy	1-dose,90%cov HPV DNA	88.1 (37-246.8)	84.7 (34.7-239.9)	88.1 (37-247)	85.2 (35-241)	91 (39-252.8)	72.5 (26.3-215.3)	103.9 (47.9-279)
	1-dose,90%cov HPV DNA + ablative therapy	86.8 (36.5-243.8)	83.5 (34.2-237)	86.9 (36.5-243.9)	84 (34.5-238)	89.7 (38.5-249.7)	71.4 (25.9-212.6)	102.5 (47.3-275.6)
	1-dose, 90%cov unbound efficacy	84.4 (36.7-252.1)	81.1 (34.4-245.1)	84.4 (36.7-252.3)	81.6 (34.7-246.2)	87.2 (38.7-258.1)	69.2 (26.1-220.1)	99.9 (47.5-284.8)

Results are summarized as a median and 95% CI of all 25 parameter sets.

Table S6 Variation of the ICER estimates (median and 95% CI) comparing each scenario to the no vaccination scenario after adjusting Supplies, Screening and Treatment Costs. These are the full one-way sensitivity analysis expanded from Figure S1.

One-dose durability	Strategy	Initial Run	Supplies		Screening		Treatment	
			Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
Lifelong efficacy	No vaccination	-	-	-	-	-	-	-
	2-dose 31% cov	171.2 (108.8-356.3)	170.9 (108.6-355.8)	171.4 (109-356.8)	171.2 (108.8-356.4)	171.1 (108.8-356.3)	184.3 (122.4-369.8)	157.7 (94.9-342.6)
	2-dose 50% cov	182.3 (112.2-398)	182 (112-397.5)	182.6(112.5-398.6)	182.3 (112.3-398)	182.3 (112.2-398)	195.4 (125.8-411.5)	168.9 (98.4-384.2)
	2-dose 70% cov	203.8 (122.7-468.7)	203.5 (122.5-468.1)	204.2 (123-469.4)	203.9 (122.7-468.8)	203.8 (122.7-468.7)	216.9 (136.2-482.2)	190.4 (108.9-455)
	2-dose 77% cov	213.8 (127.9-498.7)	213.5 (127.6-498)	214.1(128.1-499.4)	213.8 (127.9-498.7)	213.8 (127.8-498.7)	226.9 (141.4-512.1)	200.4 (114-484.9)
	2-dose 90% cov	236.1 (139.8-558.5)	235.7 (139.5-557.8)	236.4 (140-559.3)	236.1 (139.8-558.5)	236.1 (139.7-558.5)	249.2 (153.3-572)	222.7 (125.9-544.7)
	1-dose 77% cov	78.5 (31.6-217.7)	78.3 (31.4-217.3)	78.7 (31.7-218)	78.5 (31.6-217.7)	78.5 (31.5-217.7)	92.1 (45.1-231.1)	64.6 (17.7-203.9)
	1-dose 70% cov	74.3 (29.2-203)	74.1 (29.1-202.7)	74.5 (29.3-203.3)	74.3 (29.2-203)	74.3 (29.2-203)	87.7 (42.7-216.5)	60.6 (15.4-189.2)
	1-dose 90% cov	88.2 (37.1-247.2)	88 (36.9-246.8)	88.4 (37.2-247.6)	88.2 (37.1-247.2)	88.2 (37-247.2)	101.3 (50.6-260.6)	74.8 (23.2-233.4)
	1-dose, vaccination for all by age 10	204.7 (114.4-498.4)	204.3 (114.1-497.7)	205 (114.6-499.1)	204.7 (114.4-498.4)	204.7 (114.3-498.4)	217.8 (127.9-511.9)	191.3 (100.5-484.6)
	1-dose, 11-19YO female catch-up	76.7 (29.6-221.3)	76.5 (29.5-220.9)	76.8 (29.7-221.7)	76.7 (29.6-221.3)	76.6 (29.6-221.3)	89.7 (43.1-234.7)	63.3 (15.8-207.6)
	1-dose, 11-24YO female catch-up	74.9 (28.6-215.7)	74.7 (28.5-215.3)	75.1 (28.8-216)	74.9 (28.7-215.7)	74.9 (28.6-215.7)	88 (42.1-229.1)	61.5 (14.8-202)
	1-dose, 31% cov	59.7 (25.8-149.1)	59.5 (25.6-148.8)	59.8 (25.9-149.4)	59.7 (25.8-149.1)	59.7 (25.7-149.1)	72.8 (39.1-162.6)	46.2 (12.1-135.3)
	1-dose, 50% cov	64 (25-168.8)	63.8 (24.9-168.5)	64.1 (25.2-169.1)	64 (25.1-168.8)	63.9 (25-168.8)	77.1 (38.4-182.3)	50.5 (11.4-155)
Alternative waning	1-dose 90% cov	89.9 (38.9-249.1)	89.7 (38.7-248.7)	90.1 (39-249.4)	89.9 (38.9-249.1)	89.9 (38.8-249)	103 (52.3-262.5)	76.6 (25.1-235.3)

(30EP/20WP)	1-dose, 11-19YO female catch-up	77.2 (30.3-221.7)	77.1 (30.2-221.3)	77.4 (30.4-222.1)	77.3 (30.3-221.7)	77.2 (30.3-221.7)	90.3 (43.8-235.1)	63.9 (16.5-208)
	1-dose, vaccination for all by age 10	206.9 (116.3-501.6)	206.6 (116.1-500.9)	207.2(116.6-502.3)	206.9 (116.4-501.6)	206.9 (116.3-501.6)	220 (129.8-515)	193.5 (102.5-487.8)
	1-dose, 11-24YO female catch-up	75.5 (29.3-216.1)	75.3 (29.2-215.7)	75.6 (29.5-216.4)	75.5 (29.4-216.1)	75.5 (29.3-216.1)	88.5 (42.8-229.5)	62.1 (15.6-202.3)
	1-dose, 70% cov	76.4 (31.7-205.2)	76.3 (31.6-204.8)	76.6 (31.8-205.5)	76.5 (31.7-205.2)	76.4 (31.7-205.1)	89.8 (45.1-218.6)	62.8 (17.9-191.4)
	1-dose, 77% cov	80.9 (33.8-219.7)	80.7 (33.7-219.3)	81 (33.9-220)	80.9 (33.8-219.7)	80.8 (33.8-219.7)	94.4 (47.2-233.1)	67 (20-205.9)
Pessimistic waning (20EP/10WP)	1-dose 90% cov	112.2 (59.8-271.4)	112 (59.6-271)	112.4(59.9-271.8)	112.2 (59.8-271.4)	112.2 (59.7-271.4)	125.4 (72.9-284.7)	98.6 (46.3-257.8)
	1-dose, 11-19YO female catch-up	88.4 (42.4-229.3)	88.2 (42.3-229)	88.6 (42.6-229.7)	88.4 (42.5-229.4)	88.3 (42.4-229.3)	101.7 (55.7-242.7)	74.7 (28.9-215.7)
	1-dose, vaccination for all by age 10	232.8 (141.8-536.4)	232.4 (141.6-535.7)	233.1(142.1-537.2)	232.8 (141.8-536.5)	232.7 (141.8-536.4)	245.7 (155.1-549.8)	219.5 (128.3-522.8)
	1-dose, 11-24YO female catch-up	86.2 (41.1-223.3)	86 (41-222.9)	86.4 (41.3-223.7)	86.2 (41.1-223.3)	86.1 (41.1-223.3)	99.5 (54.4-236.7)	72.5 (27.6-209.6)
	1-dose, 70% cov	100.3 (58-230.5)	100.1 (57.9-230.2)	100.5(58.2-230.9)	100.3 (58.1-230.6)	100.2 (58-230.5)	113 (70.8-243.8)	87.2 (45-217)
	1-dose, 77% cov	103.5 (58.1-243.7)	103.3 (57.9-243.3)	103.7(58.2-244.1)	103.5 (58.1-243.7)	103.5 (58.1-243.7)	116.6 (70.8-257)	90.1 (45-230.1)
15EP/20WP	1-dose 90% cov	117.6 (64.9-278)	117.4 (64.7-277.6)	117.8 (65-278.4)	117.6 (64.9-278)	117.6 (64.8-278)	130.7 (78-291.3)	104.1 (51.6-264.4)
20EP/20WP	1-dose 90% cov	101.2 (49.4-260.9)	101 (49.3-260.5)	101.4(49.6-261.3)	101.2 (49.4-260.9)	101.1 (49.4-260.9)	114.6 (62.7-274.3)	87.5 (35.8-247.2)
25EP/20WP	1-dose 90% cov	93.3 (42.3-252.9)	93.1 (42.1-252.6)	93.5 (42.4-253.3)	93.3 (42.3-253)	93.3 (42.3-252.9)	106.8 (55.7-266.3)	80 (28.6-239.2)
15EP/10WP	1-dose 90% cov	143.1 (92.2-305.8)	142.9 (92-305.4)	143.4(92.4-306.3)	143.1 (92.2-305.8)	143.1 (92.2-305.8)	156.1 (104.8-319)	129.8 (79.3-292.3)
25EP/10WP	1-dose 90% cov	97.5 (46.3-257)	97.3 (46.1-256.6)	97.7 (46.4-257.4)	97.6 (46.3-257)	97.5 (46.2-257)	110.9 (59.6-270.4)	83.8 (32.6-243.3)
30EP/10WP	1-dose 90% cov	91.1 (40.1-250.3)	90.9 (40-249.9)	91.3 (40.2-250.7)	91.1 (40.1-250.3)	91.1 (40.1-250.3)	104.3 (53.5-263.7)	77.7 (26.4-236.6)
Lifelong efficacy + change in	1-dose,90%cov HPV DNA	88.1 (37-246.8)	87.9 (36.9-246.4)	88.2 (37.1-247.2)	88.1 (37-246.8)	88 (37-246.8)	101.2 (50.5-260.3)	74.7 (23.2-233.1)

testing, treatment strategy	1-dose,90%cov HPV DNA + ablative therapy	86.8 (36.5-243.8)	86.6 (36.4-243.4)	87 (36.6-244.2)	86.8 (36.5-243.8)	86.8 (36.5-243.8)	99.9 (50-257.2)	73.5 (22.7-230.1)
	1-dose,90%cov unbound efficacy	84.4 (36.7-252.1)	84.2 (36.6-251.7)	84.6 (36.8-252.5)	84.4 (36.7-252.1)	84.4 (36.7-252.1)	97.5 (50.2-265.6)	71 (22.9-238.3)

Results are summarized as a median and 95% CI of all 25 parameter set

V. Reporting

We conformed to published guidance for reporting modeling studies of HPV prevention and economic evaluations – HPV-FRAME and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022.

a. HPV-FRAME Checklist

Inputs	Reported by age? (Y/N)	Reported by sex?	Comments
Target population for intervention	Y	Y	Vaccination of girls by the age of 10. Additional scenarios explore catch-up vaccination of females age 10-19 or 10-24, as well as vaccination for all by age 10.
Sexual behavior	Y	Y	Sexual risk distribution reported by age in Table S4.
Cohort examined for evaluation / time horizon	Y	Y	100-year time horizon from 2023-2123. Intervention is given to cohorts, but we examine the outcome in the population.
Quality of life assumptions	N	Y	Disability weights were used for cervical cancer health state. Disability weights were only applied to women, but not stratified by age (see section Methods of the article).
Calibration	Y	Y	The model was calibrated with country-specific behavioral and epidemiological data (see section IIIa of the Appendix).
Validation (where possible)	Y	Y	The model was validated to HIV, HPV, and cervical cancer outcomes (see section IIIb of the Appendix).
Costs	N	Y	All costs were related to both cervical cancer (screening and treatment) and HPV vaccination, drawn from published literature and insights from in-country experts (see section Methods of the article).
Reporting standards for models of vaccination in adolescent individuals			
Vaccine coverage	Y	Y	See Methods section of the article for information on the vaccine coverages modelled.
Vaccine efficacy	Y	Y	See Methods section of the article for the assumptions around one- and two-dose efficacy.
Vaccine cross-protection	N	N	We do not account for cross-protection against additional HPV types.
Duration vaccine protection and waning	Y	Y	Waning assumptions are described in the Methods section of the article. We assume duration of protection is the same regardless of age or sex.
Vaccine and delivery costs	Y	Y	See Table 1 of the article for vaccine and delivery costs. We assume costs are the same across all ages and sexes.
Pre-vaccination disease burden	Y	Y	Pre-vaccination disease burden is reflected in the model validation, as shown in III of the Appendix.
Duration of natural immunity	Y	Y	See Section IIc of the Appendix.
Reporting standards for evaluations assessing alternative vaccine types or reduced-dose schedules			
Timing between doses	Not applicable	Not applicable	The model does not simulate timing between doses. The time at which an individual is fully vaccinated is when they receive the second dose.
Reporting standards for models of HPV prevention in LMIC			
HIV prevalence rates, if endemic in country	Y	Y	The model was calibrated to HIV prevalence data stratified by age and sex (see section IIIa of the Appendix).

Description of any opportunistic or pilot/demonstration screening projects ongoing	Y	Y	We ran scenarios reflecting current screening and vaccination coverage in Kenya (see section Methods of the article).
Costs	N	Y	Total costs of each strategy are reported in Table 3 of the section Results of the article.
Reporting standards for models of HPV-associated cancers among individuals living with HIV (ILWH)			
HPV prevalence, CIN prevalence, and cervical cancer incidence by HIV status	N	N	The purpose of the study was to evaluate cervical cancer outcomes nationally in Kenya so we did not stratify results by HIV status at this time.
HPV disease multipliers on HPV acquisition, progression from HPV infection to cancer for HIV-infected women/men	Y	Y	HPV acquisition multipliers for persons living with HIV is reported in Table S9 of the Appendix.
HPV-associated cancer mortality by HIV status	Y	Y	Cervical cancer-associated mortality rates by HIV health state are reported in Table S10 of the Appendix.
Relevant co-morbidities	Y	Y	Mortality rates account for HIV-associated mortality, cervical cancer-associated mortality, and background mortality due to other causes (see section II of the Appendix).
HPV-associated screening sensitivity/specificity by HIV status	N	Y	Screening test performance stratified by HIV status is reported in Section IIv of the Appendix. Test performance is assumed to be the same for all age groups.
Reporting standards for models of cervical screening			
Routine screening behavior	Y	Y	We model once-per lifetime cervical screening for women in the age range of 35-39 with VIA, colposcopy triage, and cryotherapy treatment (see section IIv of the Appendix).
Screening test(s) and colposcopy accuracies	N	Y	Accuracy of VIA and colposcopy is reported in section IIv of the Appendix. Accuracy is assumed to be the same for all age groups.
Abnormal test management	N	Y	Follow-up after an abnormal screening test is reported in section IIv of the Appendix. Follow-up tests are not stratified by age.
Diagnostic follow-up of abnormal tests	N	Y	Follow-up after an abnormal screening test is reported in section IIv of the Appendix. Follow-up tests are not stratified by age.
Management by disease grade	N	Y	Treatment is by cryotherapy. Management is consistent across all ages and disease grades. This is reported in section IIv of the Appendix.
Sources of information for screening structure and parameterization	Y	Y	Screening structure in the model is described in section IIv of the Appendix.
Reporting standards for integrated models of cervical screening and vaccination			
HPV type incidence, clearance, and progression rates	Y	Y	HPV natural history parameters stratified by age are reported in Table S9 of the Appendix.
Herd effect	Y	Y	The model is dynamic in natural history, so it captures population-level effects such as herd immunity.
Association between vaccination and screening uptake	Y	Y	The model assumes the same level of screening uptake by age regardless of vaccination status.
Screening test(s) and colposcopy accuracies	N	Y	Screening test performance and accuracy of colposcopy is reported in section IIv of the Appendix. It is not stratified by age.

Fixed-variable costs	N	Y	All cost assumptions are reported in Table 1 of the article. Costs are not stratified by age.
B. Outputs	**Reported by age? (Y/N)**	**Reported by sex?**	**Comments**
Core reporting standards			
Cancer incidence, mortality, life years, QALYs/DALYs (as appropriate)	N	Y	Cancer incidence is reported in Table 2, mortality in Table S17 (in the Appendix), life years in Table S19 and S20 (in the Appendix), and DALYs in Table S19 and S20 (in the Appendix).
HPV prevalence, pre-intervention	N	Y	HPV outcomes pre-intervention were reported in the previous modeling publication by Liu, et al.[2]
CIN2/3 detected	N	Y	CIN outcomes were reported during model calibration, shown in Figure S7 of the Appendix.
Sensitivity analysis on key inputs	N	Y	Results of sensitivity analyses are described in section IVdiii of the Appendix.
Incremental cost-effectiveness ratios and costs saved	N	Y	ICERs are reported in Table 3 of the article.
Reporting standards for models of vaccination in adolescent individuals			
Absolute reductions in HPV infections, and/or warts, post-vaccination	N	N	This was not presented since this study focuses on the impact of vaccination on the burden of cervical cancer.
Absolute reductions in CIN2+ post-vaccination	N	N	This was not presented since this study focuses on the impact of vaccination on the burden of cervical cancer.
Absolute reductions in invasive cancer (cervical and other HPV cancers, as relevant) post-vaccination	N	Y	We presented reduction in cervical cancer cases and incidence in Table 2 of the article. We do not present the results stratified by age.
Reporting standards for models of HPV-associated cancers among individuals living with HIV (ILWH)			
Reduction in cervical cancer incidence over time by HIV status (and CD4 count and ART status if modelled)	N	N	The purpose of this article was to explore the population-level health economic impact of HPV vaccination. Cervical cancer outcomes by HIV status are beyond the scope of this article.

b. CHEERS 2022 Checklist

Section/topic	Item No	Guidance for reporting	Reported in section
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Introduction
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract

Section/topic	Item No	Guidance for reporting	Reported in section
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Methods
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Methods
Setting and location	6	Provide relevant contextual information that may influence findings.	Introduction, Methods
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods, Discussion
Time horizon	9	State the time horizon for the study and why appropriate.	Methods, Discussion
Discount rate	10	Report the discount rate(s) and reason chosen.	Methods
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Methods
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods

Section/topic	Item No	Guidance for reporting	Reported in section
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Methods
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods, Appendix
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Not applicable
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Not applicable
Characterizing uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Methods
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Methods
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Results
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Appendix
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Not applicable
Discussion			

Section/topic	Item No	Guidance for reporting	Reported in section
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Funding disclosure
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Conflict of interest disclosure

Supplementary Materials: Additional Methodology Details and Results for Chapter 4

Supplementary Materials

Table S1: Inclusion and exclusion criteria (PICOTS)

	Include	**Priority/ Emphasize**	**Exclude**
Population	• Stakeholders involved in the adoption of single-dose HPV vaccination	• East Africa • Ethiopia, Tanzania and Uganda • Ministry of Health officials and technical advisors	• High income countries • Non- African countries
Intervention	Single-dose HPV vaccination	• National programs/ implementation	• Randomized control trials • Modelling and economic evaluation studies
Comparison	Any		
Outcomes (of the review)	Determinants of adoption of single-dose HPV vaccination		
Time Frame	2000-2024		
Setting	• Facility-based • School-based • Mixed delivery	• National Immunization Programs	• Controlled settings • Services delivered in public or private facilities only
Other [Study design]	• Quantitative OR • Qualitative OR • Mixed-Methods • Studies and reports that highlight determinants of single-dose adoption in East Africa	• Systematic reviews and meta-analyses • Implementation studies • Policy analysis	• Randomized control trials • Modelling and economic evaluation studies

PICOTS: P- Population, I – Intervention, C- Comparison, O – Outcome, T- Time frame, S – Setting

Table S2: Search strategy and terms

We identified relevant documents by searching PubMed, CINAHL Complete, African Journal Online, Global Index Medicus, ProQuest, Academic search complete, Google Scholar and grey literature from key evidence generating institutions (WHO, JSI, Jhpiego, PATH) as well as media

and press releases from Ethiopia, Uganda and Tanzania to gather relevant literature. Additionally, we searched the Government and Ministry of Health websites of the three countries to compile important announcements and documents published by the Government. The table below summarizes details of the inclusion criteria. Search strategies were adjusted to fit different databased setting and included search terms such as [‘HPV vaccine’ OR ‘HPV vaccination’] AND [‘Single-Dose Schedule’ OR ‘Reduced Dose Schedule’] AND [‘Ethiopia’ OR ‘Uganda’ OR ‘Tanzania’].

Search Component	**Search terms**
Single-dose vaccination	((Single-dose OR Single dose OR One dose OR Reduced dose) AND (Immunization OR Vaccin*)) OR Vaccination schedule OR Immunization schedule
AND	
Intervention	Cervical cancer prevention OR National HPV program OR Cervical cancer eliminat* OR ((HPV OR "human papillomavirus") AND (immunization OR vaccin*)) OR "Papillomavirus Vaccines" [Mesh]
AND	
setting	East* Africa* OR "Africa, Eastern"[Mesh] OR Ethiopia* OR "Ethiopia"[Mesh] OR Tanzania* OR "Tanzania"[Mesh] OR Uganda* OR "Uganda"[Mesh])
AND	
years	2000-2024

Table S3: Data Extraction Table from Academic and Grey Literature Sources

	Document	**Country**	**Relevant details extracted**
1	Gallagher et al., 2018 (119)	Ethiopia, Uganda and other LMICs	• Characteristics of the demonstration project and vaccine introduction
2	Gallagher et al., 2018 (120)	Ethiopia, Uganda and other LMICs	• Characteristics of the demonstration project and vaccine introduction • Key relevant policy that supported initiatives to improve HPV vaccine coverage • Details on decision-making bodies for a revision of the HPV vaccination schedule • Details on the expected process for the single-dose adoption in Uganda

3	Li et al., 2022 (121)	Tanzania	• Details on the HPV vaccine introduction in Tanzania
4	PATH, 2011 (122)	Uganda	• Details of the demonstration project in Uganda
5	Gallagher et al., 2017 (123)	All three countries and other LMICs	• Characteristics of the demonstration project and vaccine introduction
6	Tsu et al., 2021 (124)	All three countries and other LMICs	• Characteristics of the vaccine introduction • Context of HPV vaccination in Ethiopia
7	Mphuru et al., 2022 (125)	Tanzania	• Details on the HPV vaccine introduction in Tanzania • Process and actors involved in HPV vaccination and decision-making in Tanzania
8	WHO, 2016 (126)	Ethiopia	• Details of the demonstration project in Ethiopia
9	WHO,2025 (127)	Ethiopia	• Details on single-dose adoption in Ethiopia • Process of single-dose adoption in Ethiopia
10	WHO, 2024 (128)	Tanzania	• Details on single-dose vaccination in Tanzania
11	WHO, 2024 (129)	Ethiopia	• Details on single-dose vaccination in Ethiopia • Process and actors involved in single-dose adoption in Ethiopia
12	Adeyanju et al., 2024 (130)	All three countries and other LMICs	• Details on the country situation after WHO recommendations on single-dose HPV vaccination were published • NITAG members' position on single-dose adoption in Tanzania
13	WHO, 2024 (131)	WHO AFRO countries	• Regional endorsement of WHO recommendations on single-dose HPV vaccination
14	Bolio et al., 2024 (132)	All three countries and other LMICs	• Actors involved in single-dose adoption and HPV vaccination in LMICs

15	JSI, 2024 (133)	All three countries and other LMICs	• Actors and decision-making pathway for single-dose adoption in selected LMICs • Details on the decision-making process
16	E-NITAG, 2023 (134)	Ethiopia	• Process for decision making in Ethiopia, details on NITAG decision from 2023
17	Ra, 2008 (135)	Uganda	• Details on the context in Uganda before the HPV vaccine introduction
18	Banura et al., 2012 (136)	Uganda	• Details on the context in Uganda before the HPV vaccine introduction • Key relevant policy that supported initiatives to improve HPV vaccine coverage
19	Wallace et al., 2017 (137)	Uganda	• Details on HPV vaccination prioritization • Actors involved in the revision of immunization related policies in Uganda • Process for a new vaccine introduction in Uganda
20	PATH, 2021 (138)	Uganda	• Details on the process for single-dose adoption in Uganda • Anticipated process for a single-dose adoption in Uganda
21	Njuguna et al., 2020 (139)	Tanzania	• Policies and guidelines that contributed to the progress in HPV vaccination in Tanzania
22	JSI, (140)	Tanzania	• Actors involved in single-dose adoption in Tanzania
23	World Cancer Research Fund (148)	All three countries	• Statistics on the burden of cervical cancer in Tanzania
24	Guillaume et al., 2024 (141)	LMICs	• Insights from regional experts on the context and details needed for a policy revision

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